THE PYRAZINES

This is the Forty-First Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER AND EDWARD C. TAYLOR

Editors

THE PYRAZINES

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

This volume summarizes published pyrazine chemistry with emphasis on syntheses, properties, and reactions of pyrazines and pyrazine *N*-oxides (Chapters I–X). Treatment of theoretical aspects is minimal. Although not strictly relevant, Chapter XI is presented as a summary of earlier reviews and more recent literature of reduced pyrazines (including piperazines). The literature recorded in *Beilstein* to 1929 and *Chemical Abstracts* through 1978 (Volume 89) has been covered together with selected references to 1980. Whereas every reasonable effort has been made to incorporate most significant material, no attempt has been made to include all relevant data. Tables have been incorporated in the text to extend the range of examples.

The tables in the Appendix provide access to the literature, melting points, and some other physical data for most known simple pyrazines and pyrazine *N*-oxides.

I have been helped greatly in the collection of the data and in the preparation of this manuscript over several years by many people. Dr. D. J. Brown has generously provided constant advice, assistance, and encouragement, and he has carefully read and advised on the entire text. Professor A. Albert advised in many ways and provided unpublished data. Mrs. Y. Yap, Mrs. Z. Pakulska, Mr. I. Brown, Mr. K. McAndrew, and the late Miss V. Richardson assisted with the collection of published data. Drs. K. Ienaga, T. Nagamatsu, Y. Iwai, and K. Shinozuka helped with translations of Japanese, Dr. H. Stünzi with German, and Mrs. Z. Pakulska and Professor L. Strękowski with Polish papers. Drs. W. L. F. Armarego, W. V. Brown, M. D. Fenn, D. D. Perrin, E. Spinner, and Professor B. Stanovnik helped with the provision and interpretation of data. Mesdames S. Schenk, J. White, and D. Dick typed the manuscript and prepared the formulas. To these people, and others not mentioned, I express my gratitude and thanks for their assistance in so many ways.

G. B. BARLIN

Canberra, Australia
January 1982

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CHAPTER I

Introduction to Pyrazines

1. HISTORY

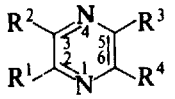
The first recorded synthesis of a pyrazine (1) was that of tetraphenylpyrazine by Laurent (1) in 1855. In this preparation α-phenyl-α-(benzylideneamino)acetonitrile, PhCH=NCHPhCN ("benzoylazotid," prepared from crude benzaldehyde, that is, benzaldehyde containing some hydrogen cyanide, by treatment with ammonia), was subjected to dry distillation to give (1, $R^1 = R^2 = R^3 = R^4 = Ph$), which Laurent called "amarone" [Table I.1 lists the names assigned by early workers (1–14) to some simple pyrazines]. Tetraphenylpyrazine was also prepared by Erdmann (11) from the reaction of ammonia on benzoin, but on this occasion it was named "benzoinimide."

TABLE I.1 NAMES ASSIGNED TO SOME SIMPLE PYRAZINES BY EARLY WORKERS

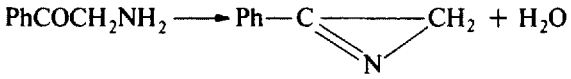
Pyrazine	Name	Refs.
Unsubstituted	Pyrazine	2, 3
	Aldine	4
	Piazine	5, 6
	Paradiazine	5, 6
2,5-Dimethyl	Ketine	7, 8
	Glycolin	9
2,5-Diphenyl	Isoindol	10
Tetraphenyl	Amarone	1
	Benzoinimide	11
	Ditolanazotide	12
	Tetraphenylazine	13
	Tetraphenylpyrazine	14

2,5-Diphenylpyrazine (1, $R^1 = R^3 = Ph$, $R^2 = R^4 = H$) was the second pyrazine synthesized, and it was prepared by Staedel and Rügheimer (10) in 1876 by the action of ammonia on ω-chloroacetophenone and was named "isoindol." These authors postulated the first structure for a pyrazine as an inner anhydride (2) of an amino ketone.

Alkylpyrazines were then described in a series of papers from Victor Meyer's laboratory at Zürich. Gutknecht (15, 16) examined the reduction of the monoxime of diacetyl (then thought to be a true nitroso derivative of ethyl methyl ketone,



(1)

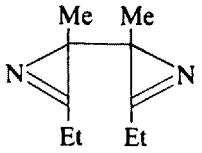


(2)
"Isoindol"

from which it was derived with nitrous acid) with tin and hydrochloric acid to give tetramethylpyrazine, which was also assigned the formula of an inner anhydride of the amino ketone. Treadwell (8) found from vapor density determinations on the analogous product from methyl propyl ketone that the molecular weight was about twice that which would be expected from an inner anhydride, and by analogy with the reduction of acetone to pinacol, Treadwell assigned the formula (3) to the product. He and Meyer (7, 8) also proposed the name "ketine" for the product (2,5-dimethylpyrazine) derived from acetone, and dimethylketine and diethylketine for those derived from ethyl methyl ketone and methyl propyl ketone, respectively.

Meanwhile Étard (9) in 1881 found that 2,5-dimethylpyrazine (which he termed "glycolin") could be isolated from the heating of a mixture of glycerol and an ammonium salt.

Meyer (17) in the following year then expressed the view that the products of the action of nitrous acid on the ketones were not true nitroso compounds (4) but isomeric oximes (5), and he considered their reduction to be analogous to the conversion of a nitro to amino group, rather than that of ketone to pinacol. Thereafter the Treadwell formulation of pyrazines was abandoned.



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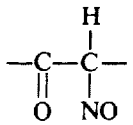

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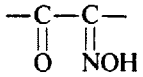
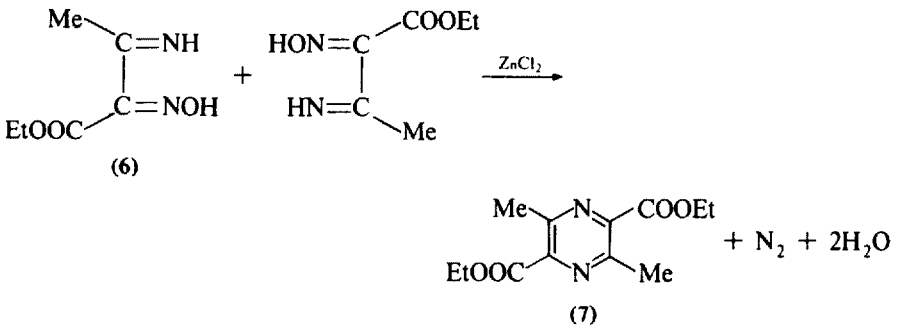


(5)

Wleügel (18), who examined the reduction of (iso) "nitrosoacetic acid" ester (from ethyl acetoacetate and nitrous acid) to the diethyl ester of dicarboxydimethylpyrazine ("ketinedicarboxylic acid"), was the first to propose for the pyrazine nucleus a six-membered ring structure analogous to pyridine, in which one $-CH=$ group para to the ring nitrogen was replaced by another ring nitrogen atom. However, the position of substituents assigned by Wleügel was in error. Oeconomides (19) reported that Wleügel's product (7) did not form an anhydride, as would be expected for an *o*-dicarboxylic acid, and he claimed its identity by a synthesis from "iminoisonitrosobutyric ester" (6) by heating with fused zinc chloride. Hinsberg (20) had also recently shown that quinoxaline could be synthesized from *o*-phenylenediamine and glyoxal.

The reaction of ammonia on benzoin described by Erdmann was reinvestigated by Japp and Wilson (12) and Japp and Burton (13) and the product, tetraphenylpyrazine, renamed "ditolanazotide" and "tetraphenylazine," respectively.

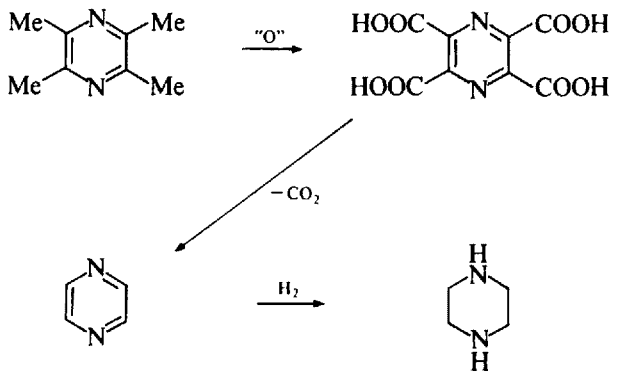


(6)

(7)

In 1887 two workers, Mason (2) and Wolff (3), independently suggested the name "pyrazine" for the nucleus to point out the analogy with pyridine, but the name had been used in the same year by Knorr (21) for pyrrole tetrahydride, and Braun and Meyer (4), in objecting (to pyrazine), proposed the name "aldine" because it would result from self-condensation of the hypothetical aminoacetaldehyde. Widman (5) then clarified the situation with a systematic nomenclature for azines. Compounds containing a six-membered ring consisting of two nitrogen and four carbon atoms were called diazines; these were further classified into *o*-diazines, *m*-diazines, and *p*-diazines according to whether the nitrogen atoms were ortho, meta, or para, respectively. These names were also condensed to oiazine, miazine, and piazine. Although the name "piazine" was promoted by Mason (6), it did not gain acceptance and the term pyrazine has since been employed.

Proof of the structure of the pyrazines was established in 1893 by Wolff (22), who converted tetramethylpyrazine to piperazine (8) by the series of reactions shown. The conversion of α-amino ketones to pyrazines requires the loss of hydrogen as well as the loss of water. Gabriel and Pinkus (23) obtained considerably higher yields when oxidizing agents were added to the reaction mixture after the condensation had been allowed to take place. Snape and Brooke (14) in 1897 established that "amarone" was identical with benzoinimide, ditolanazotide, tetraphenylazine, and tetraphenylpyrazine.



(8)

The bond structure of pyrazines had yet to be established. Kekulé type (**9**) and Dewar type (**10**) formulas were each proposed and supported by various groups (24–28), but the Kekulé structure was finally selected after a study of molecular refractions of a number of pyrazine derivatives by Brühl (29).

(9)

(10)

The parent compound of this series, pyrazine, was first prepared in trace amounts by Wolff (30) by heating aminoacetaldehyde diethyl acetal [$H_2NCH_2CH(OEt)_2$] with anhydrous oxalic acid at 110–190°C, and later in better yield by heating the mercuric or platinic chloride double salts (of the aminoacetaldehyde acetal) with hydrochloric acid (31); it was also obtained from aminoacetaldehyde with mercuric chloride in sodium hydroxide (23). Wolff in 1893 (22) also prepared pyrazine by decarboxylation of the tetracarboxylic acid, obtained by oxidation of tetramethylpyrazine; and Stoehr (32) prepared it by the distillation of piperazine with lime and zinc dust. Brandes and Stoehr (33) in 1896 described the preparation of pyrazine by heating glucose with 25% aqueous ammonia at 100°C.

Significant reviews of pyrazine chemistry have been published by Newbold and Spring (34), Krems and Spoerri (35), Pratt (36), Ramage and Landquist (37), Nováček et al. (38), Cheeseman and Werstiuk (39), and Sasaki (39a).

2. OCCURRENCE

Pyrazines occur in nature in relatively small quantities, and the introduction in the early 1960s of coupled gas-liquid chromatography – mass spectrometry assisted greatly in the isolation and identification of these compounds. Some sources are described below. Fusel oils contain 2,5-dimethyl-, 2,5-diethyl-, trimethyl-, tetramethyl-, and triethylmethylpyrazine (33, 40–44), and it is probable that these compounds are produced from proteins during the fermentation. Ammoniations of inverted molasses have been found to give 2,6-dimethylpyrazine, 2-hydroxymethylpyrazine, 5-hydroxy-2-methylpyrazine, and 2-methyl-5(and 6)-(*arabo*-tetrahydroxybutyl)pyrazines (45–47); and D-glucose with aqueous ammonia gives a complex mixture from which 2-methyl-5[and 6(?)]-(*arabo*-tetrahydroxybutyl)pyrazine have been isolated and identified (48). Galbanum oil has been shown to contain various alkyl- and methoxyalkylpyrazines (49, 50). Cocoa butter and cocoa beans contain 2,3-dimethylpyrazine, 2-ethyl-5-methylpyrazine, trimethylpyrazine, 3-ethyl-2,5-dimethylpyrazine, 2-ethyl-3,5-dimethylpyrazine, and tetramethylpyrazine; the pyrazine content appeared to be greatest in samples from countries where beans were traditionally fermented (51, 52). Tetramethylpyrazine was the only pyrazine detected in unroasted beans, and then only in fermented samples.

A large number of alkyl- and vinylpyrazines have been identified in coffee (53),

17 alklypyrazines have been identified in the products of pyrolysis of water-soluble components of fresh beef (54), and 33 pyrazines have been identified in flavor concentrates isolated from beef cooked superatmospherically at 162.7°C (55). Tetramethylpyrazine has been isolated from "natto," obtained from fermented soy(a) bean (56), and the volatile compounds of Emmentaler and Gouda cheeses have been found to contain alkylpyrazines (57, 58).

Three extremely odorous pyrazines, 3-isopropyl-2-methoxypyrazine, 2-*s*-butyl-3-methoxypyrazine, and 2-isobutyl-3-methoxypyrazine have been shown to be present in green peas, and are likely to be of major significance in the flavor of peas (59). The volatile oil of green bell peppers has been found to contain 2-isobutyl-3-methoxypyrazine as a major component (60, 61). The alkylpyrazines in potato chips (62, 63) and roasted peanuts (63) have been examined. 2-Isopropyl-3-methoxypyrazine has been characterized in the vacuum steam volatile oil of potatoes (64), 2-ethyl-3-methoxypyrazine in cooked potato (65), and 3-ethyl-2,5-dimethylpyrazine and 2-ethyl-3,5-dimethylpyrazine as the components important to the aroma of baked potato (66). A variety of alkylpyrazines have been identified in roasted sesame seeds (67); and 21 pyrazines have been identified in the aroma components isolated from roasted green tea (68).

A review listing the extensive occurrence of pyrazines (mostly alkylpyrazines) in foods and a discussion of the theories of pyrazine formation has been published by Maga and Sizer (69), and a review of the natural occurrence and mass spectra of pyrazines by Brophy and Cavill (69a).

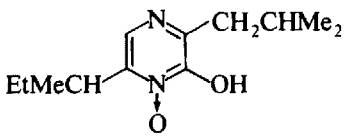
3-Isopentyl-2,5-dimethylpyrazine, 2,5-dimethyl-3-propylpyrazine and the (*Z*) and (*E*) isomers of 2,5-dimethyl-3-styrylpyrazine have been characterized in the heads of Argentine ants (70, 71). Mandibular gland secretions of the ponerine ants *Odontomachus hastatus*, *O. clarus*, and *O. brunneus* have been shown to contain alkylpyrazines; 3-isopentyl-2,5-dimethylpyrazine has been demonstrated in *O. hastatus* and *O. clarus*, and 3,5-dimethyl-2-pentyl-, -butyl-, -propyl-, and -ethylpyrazines in *O. brunneus* (72). 3-Isopentyl-2,5-dimethylpyrazine is also the main constituent in the mandibular gland secretions of workers of *Hypoponera opacior* and *Ponera pennsylvanica* (73). See also reference (74a).

Metasternal gland secretions from the cerambycid beetle have been found to contain 3-isopentyl-2,5-dimethylpyrazine (principally) and the 3-propyl, 3-butyl, 3-pentyl, and 3-(2′-methylbutyl) analogues as major components in one genus, and as minor components in several other genera (74b).

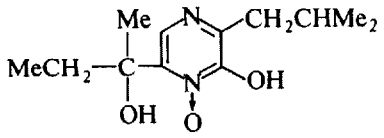
Recent work has shown the presence of pyrazine and 2,6-dimethylpyrazine in leek (75), pyrazine and alkylpyrazines in the volatile constituents of tamarind (76), five alkylpyrazines in soong-neung (extract of cooked and roasted rice) (77) and in shoyu (soy sauce) (78), and alkylpyrazines in white bread (79). Murray and Whitfield (80) have examined vegetable tissue for 2-isopropyl-, 2-*s*-butyl-, and 2-isobutyl-3-methoxypyrazines and observed at least one of these compounds in 23 of the 27 samples studied. 2-Methylpyrazine and 2,5- and 2,6-dimethylpyrazines have been determined in black tobacco and in the smoke of nonfilter cigarettes made from these tobaccos (81).

Pyrazines are produced by certain molds. Thus White (82) and White and Hill

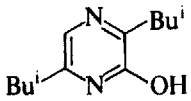
(83) first reported the isolation of the bactericidal antibiotic aspergillic acid from a strain of *Aspergillus flavus*, and after much work (84–93), its structure proved to be 6-*s*-butyl-2-hydroxy-3-isobutylpyrazine 1-oxide (**11**). Hydroxyaspergillic acid was isolated also from cultures of *A. flavus* grown on a medium containing brown sugar (84) and its structure was established later as 2-hydroxy-6-(1′-hydroxy-1′-methylpropyl)-3-isobutylpyrazine 1-oxide (**12**) (94); further work by Dunn et al. (95) led to the discovery of flavacol, 3-hydroxy-2,5-diisobutylpyrazine (**13**), in culture filtrates of *A. flavus*. Macdonald (96) has also studied the production of pyrazines by *A. flavus*. Neohydroxyaspergillic acid (97, 98), 2-hydroxy-6-(1′-hydroxy-2′-methylpropyl)-3-isobutylpyrazine 1-oxide (**14**), and 2-hydroxy-3,6-diisobutylpyrazine 1-oxide (**15**) (98) have been isolated from cultures of *A. sclerotiorum*; and the pigment pulcherrimin, produced by the yeast *Candida pulcherrima* (Linder) Windisch, has been shown to be a polymeric ferric ion complex of pulcherriminic acid (**16**) or the tautomer (**17**) (99–101). Nakamura (102) isolated muta-aspergillic acid (a growth inhibitant against hiochi-bacilli) from culture filtrates of *A. oryzae* and determined its structure as 2-hydroxy-6-(1′-hydroxy-1′-methylethyl)-3-isobutylpyrazine 1-oxide (**18**) (103, 104); and *A. oryzae* A21 grown in media containing 0.05 *M* valine and 0.01 *M* isoleucine gave 3-*s*-butyl-2-hydroxy-6-isopropylpyrazine 1-oxide (104a). Tetramethylpyrazine has been obtained from a strain of *Bacillus subtilis* (105) and from *B. natto* (106), and emimycin, 3-hydroxypyrazine 1-oxide (**19**), has been isolated from the broth of *Streptomyces No 2020-1* (107, 108).



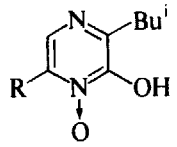
(**11**)



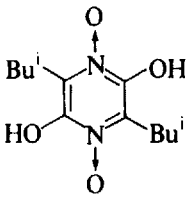
(**12**)



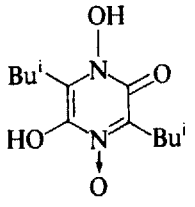
(**13**)



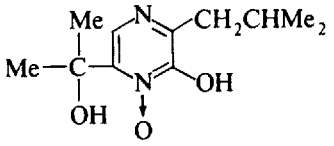
(**14**, R = CH $Pr^{i}OH$)
(**15**, R = Bu^{i})



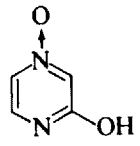
(**16**)



(**17**)

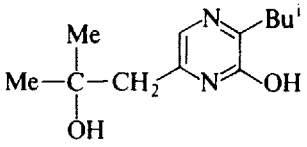


(18)



(19)

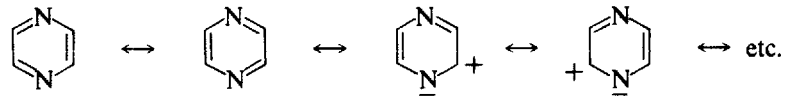
Sasaki and co-workers (109–113) have also made extensive investigations of pyrazines produced by molds. Deoxyneo-β-hydroxyaspergillic acid, 3-hydroxy-5-(2′-hydroxy-2′-methylpropyl)-2-isobutylpyrazine (**20**) is one of the constituents from *Aspergillus ochraceus* WILH. IFM 4443 (113a), which has recently been synthesized (113b), and the production of arglecin, 6-(3′-guanidinopropyl)-3-isobutyl-2-hydroxypyrazine, and related compounds by *Streptomyces toxytricini* (113c, 113d) and *S. filipinensis* (113e) has been reported and discussed.



(20)

3. STRUCTURE

Pyrazine may be represented as a resonance hybrid of the canonical structure illustrated (**21a** ↔ **21d**). The molecule is planar, and Pauling (114) states that it is stabilized by about 40 kcal/mol as in benzene and pyridine, but resonance energies derived by different methods show considerable variation. Some of these resonance energies together with values for benzene and related heterocycles are summarized in Table I.2 (115–117). More recent measurements of heats of hydrogenation are given in Section IV.1B.



(21a) (21b) (21c) (21d)

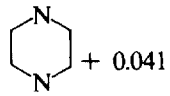
TABLE I.2 RESONANCE ENERGIES (KCAL/MOL) DETERMINED FROM HEATS OF COMBUSTION (115, 116) AND BY CALCULATION (117)

Substance	Tjebbes (115) (1962)	Bedford et al. (116) (1963)	Dewar et al. (117) (1969)
Benzene	40.8		
Pyridine	24.2 (27)	31.9	20.94
Pyrimidine	8.0 (14)		20.20
Pyrazine	8.1 (14)	24.3	14.64

The crystal structure of pyrazine has been determined by three-dimensional Fourier methods and the dimensions of the molecule were found as follows: C–N = 1.334 Å, C–C = 1.378 Å, N–C–C angle 122.4°, C–N–C angle 115.1°, and C–H = 1.05 Å (118). These are similar to those determined for pyridine: N–C = 1.3402 Å, C_2–C_3 = 1.3945 Å, C_3–C_4 = 1.3944 Å and C–N–C angle 116.8° (119). Earlier electron diffraction measurements by Schomaker and Pauling (120) gave the C–N distance as 1.35 Å. Calculation of the bond angles from consideration of interactions by σ-electrons only gave for pyrazine the C–N–C angle 112°, and the N–C–C angle 124° (121). The heat of combustion (ΔH_c°, 25°C) of pyrazine (− 546.25 kcal/mol) is very similar to that of pyrimidine (− 547.88 kcal/mol) (115). The first pK_a value of pyrazine has been determined as 0.65 (122), 0.60 (123), 1.1 (124), and 0.6 (125) and the second as − 5.78 (122) and − 6.25 (126). The first basic pK_a value should be compared with 5.23 for pyridine (123), 1.30 for pyrimidine (123), and 2.33 for pyridazine (123).

Calculations have been made of the π-electron distribution in the pyrazine ring by many methods (127–134); and the effects of protonation on the total electron densities have been calculated using the extended Hückel theory (135). A good correlation was obtained between total carbon electron densities and both proton and carbon-13 chemical shifts. A recent molecular orbital study has been made of protonation in pyrazine (and other diazines) (135a).

The electron distribution varies with the method of calculation but those for pyrazine as determined by Brown and Coller (133) using the VESCF molecular orbital procedure are as shown (**22**). Albert (136) introduced the term π-deficient heterocycle to describe such compounds with a deficiency of electrons on carbon.



(22)

An all-electron SCF–LCAO–MO computation for the ground state wave function of the pyrazine molecule showed that the lone pairs were quite different in character. The lower lone pair was very little delocalized (1.88 electrons on the nitrogen) but the second lone pair was as delocalized as the lone pair in pyridine (1.37 electrons on the nitrogens) (137).

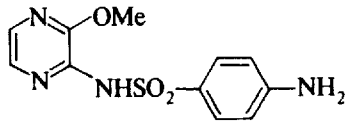
Owing to its symmetrical structure, pyrazine has, for a given substituent, only one monosubstituted derivative (2-position), three disubstituted derivatives (2,3-, 2,5-, and 2,6-positions), and one trisubstituted derivative (2,3,5-positions).

4. BIOLOGICAL ACTIVITY AND USES

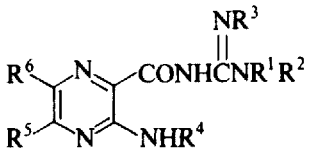
Pyrazines are known to exhibit a range of physiological activities. For example, 2-carbamoylpyrazine ("pyrazinamide") is used in the treatment of tuberculosis (138–141). In animals pyrazinamide was at least twice as active as *p*-aminosalicyclic

acid (139). Substitution with 3-amino or hydroxy, 3- or 6-carbamoyl, 5- or 6-chloro, 5-arylthio, or 6-methyl groups, or conversion to the 1-methyl quaternary salt or 1-oxide removed activity (138). Claims that the *N*-morpholinomethylamide of 2-carboxypyrazine was as active as pyrazinamide but with lower toxicity and a maintained blood level for conversion to pyrazinamide (142) have not been confirmed (143–145). Pyrazinamide is also highly active against *M. lepraemurium* in the mouse (146) and (ethylthio)carbonylpyrazine shows appreciable antituberculosis activity (147).

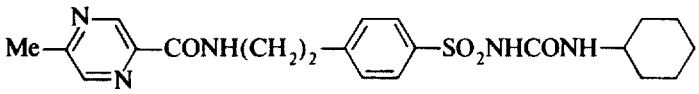
2-*p*-Aminobenzenesulfonamido-3-methoxypyrazine [sulfalene, Kelfizina (**23**)] is a long acting sulfonamide (148) and in combination with 2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine (trimethoprim) has shown dramatic effects in clinical trials against resistant falciparum malaria (149). A group of diuretics has been found among substituted 2-amidinocarbamoyl-3-aminopyrazines (**24**) (150, 151), and 2-amidinocarbamoyl-3,5-diamino-6-chloropyrazine [Amiloride (**24**, $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = NH_2$, $R^6 = Cl$)] is used clinically as a diuretic (152). 2-Methyl-3-piperidin-1′-ylpyrazine and several related compounds are powerful *in vivo* inhibitors of monoamine oxidase (153, 154). 2-Amino-3-chloro-5-*N*-(1′-ethylpyrrolidin-2′-ylmethyl)carbamoyl-6-methoxypyrazine has an anti-emetic effect in dogs (155) and a new pyrazine oral antidiabetic agent [(**25**), K4024, *glipizide*] has been described (156). 2-Mercaptopyrazine is used in anti-dandruff preparations (157), aminocyanopyrazines are claimed as fluorescent brighteners (158), and a variety of alkyl, aryl, and other pyrazines have been patented as food additives (159–161).



(**23**)

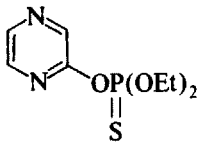


(**24**)



(**25**)

O,O-Diethyl-*O*-2-pyrazinylphosphorothiolate [*thionazin* (**26**)] is a soil insecticide and nematocide (162), 2-{α-hydroxy-α-isopropyl-α[*p*-(1′,1′,2′,2′-tetrafluoroethoxy)-phenyl]methyl}pyrazine showed growth regulating activity on soybean, bluegrass, and chrysanthemums (163); and a series of pyrazinemethanols (**27**) has been claimed to give essentially complete control of powdery mildew on beans (164). Aspergillic acid and pulcherrimin, both antibiotic fungal constituents, have been discussed earlier in this chapter.



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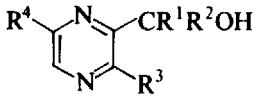
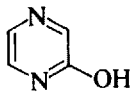


(27)

5. NOMENCLATURE

In this book, the nomenclature of the International Union of Pure and Applied Chemistry (1979)* (the Blue Book) is generally used and all substituents are written in alphabetical order as prefixes to the parent name. Tautomeric hydroxypyrazines (e.g., **28**) are named as such for simplicity, irrespective of any evidence that these compounds may exist as the oxodihydropyrazine (e.g., **29**). Mercaptopyrazines are named similarly. The term "hydro" is attached to the name of the ring system, for example, 2-oxo-1,2-dihydropyrazine and 4-imino-1-methyl-1,4-dihydropteridine, not in alphabetical order. Fully reduced pyrazines are named as piperazines and their oxo derivatives as piperazinones. Reactions of pyrazines bearing relatively complex groups are treated usually under the reactions of the group concerned and classified according to the groups attached directly to the ring or to an alkyl group attached to the ring.



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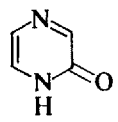


(29)

Journal abbreviations used by The Chemical Society† prior to revision in 1980 are adopted in this publication.

* International Union of Pure and Applied Chemistry, Organic Chemistry Division, Commission on Nomenclature of Organic Chemistry, *Nomenclature of Organic Chemistry Sections A, B, C, D, E, F, and H*, J. Rigaudy and S. P. Klesney, Eds., Pergamon, Oxford, 1979.

† The Chemical Society, *Journal of the Chemical Society*, Notices to Authors No. 4 (1968).

Chemistry of Heterocyclic Compounds, Volume 41
G. B. Badin

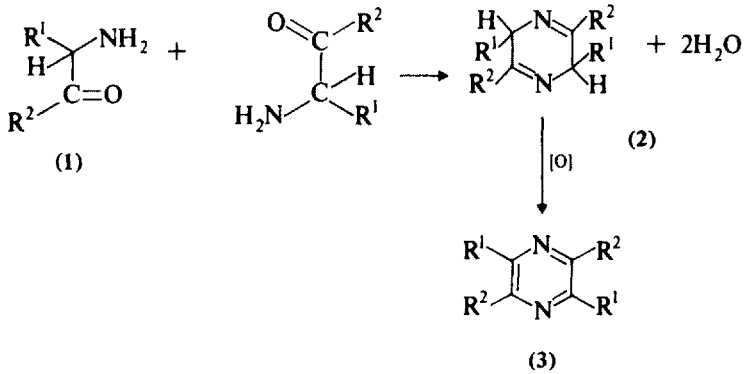
CHAPTER II

Primary Syntheses of Pyrazines

In this chapter the primary syntheses of pyrazines are described. The mechanisms of many of these reactions are unknown; hence their classification has been rationalized according to the starting materials employed.

1. SELF-CONDENSATION OF α-(PRIMARY AMINO) CARBONYL COMPOUNDS

The most general method for the synthesis of 2,5-disubstituted and 2,3,5,6-tetrasubstituted pyrazines (**3**) depends on the self-condensation of α-(primary amino) carbonyl compounds (**1**) to form dihydropyrazines, for example, (**2**), which are subsequently oxidized to the pyrazines as shown in the transformation of (**1**) to (**3**).



(1) (2) (3)

Oxidation of the dihydropyrazines to pyrazines occurs easily with mild oxidizing agents such as air; hydrogen peroxide; cupric, ferric, or mercuric ions; or with bromine water, bromine in acetic acid, or aqueous nitric acid. The α-(primary amino) carbonyl compounds required for the synthesis of pyrazines may be prepared by a large variety of synthetic methods. The products are usually stable as their salts, for example, hydrochlorides, but the free bases show a strong tendency to undergo self-condensation to the pyrazine and for this reason the amino carbonyl compounds are rarely isolated.

In the following survey, the literature preparations of some pyrazines (and also dihydro derivatives) from preformed α-amino carbonyl compounds (irrespective

of their origin) are discussed in Section 1A, and this is followed by a classification of the direct preparation of pyrazines according to the starting materials used for the synthesis of the intermediate α-amino carbonyl compounds (Sections 1B–1P).

A. Preformed α-Amino Carbonyl Compounds

Table II.1 lists literature (89, 165–186) preparations of pyrazines from preformed α-amino carbonyl compounds.

TABLE II.1 PYRAZINES (AND DIHYDROPYRAZINES) PREPARED FROM α-AMINO CARBONYL COMPOUNDS

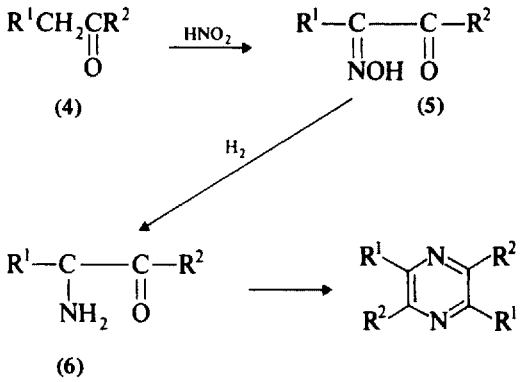
α-Amino Carbonyl Compound	Pyrazine	Refs.
Aminomethyl ethyl ketone	2,5-Diethyl	165
Aminomethyl phenyl ketone	2,5-Diphenyl	166–170
Aminomethyl *s*-butyl ketone	2,5-Di-*s*-butyl	89, 171
Aminomethyl *p*-hydroxyphenyl ketone	2,5-Bis(*p*-hydroxyphenyl)-3,6-dihydro	172
Aminomethyl *m*-hydroxyphenyl ketone	2,5-Bis(*m*-hydroxyphenyl)-3,6-dihydro	172
Aminomethyl phenethyl ketone	2,5-Diphenethyl	173
Aminomethyl isopropyl ketone	2,5-Diisopropyl	174
α-Aminobutyrophenone	2,5-Diethyl-3,6-diphenyl	175
α-Aminopropiophenone	2,5-Dimethyl-3,6-diphenyl	166, 176
α-Amino-α-phenylacetone	2,5-Dimethyl-3,6-diphenyl	166
4-Amino-5-oxohexanoic acid	2,5-Bis(2'-carboxyethyl)-3,6-dimethyl	177
α-Amino-*o*-hydroxyacetophenone	2,5-Di(*o*-hydroxyphenyl)-dihydro	178
α-Aminodeoxybenzoin	2,3,5,6-Tetraphenyl	179
2-Amino-2-deoxy-D-glucose (D-glucosamine)	2,5-Bis(D-*arabo*-tetrahydroxybutyl) (Fructosazine)	180–183
2-Amino-2-deoxy-D-mannose (D-Mannosamine)	2,5-Bis(D-*arabo*-tetrahydroxybutyl)	183
2-Amino-2-deoxy-D-galactose	2,5-Bis(D-*lyxo*-tetrahydroxybutyl) (Tagatosazine)	184
Phenacylamine	2,5-Di-*p*-tolyl	185
Ethyl DL-orthophenylalaninate	2,5-Dibenzyl-3,6-diethoxy-2,5-dihydro	186

In addition to the preparations listed in Table II.1, Gabriel and Colman (187) have obtained, from the reaction of aminoacetone hydrochloride with potassium hydroxide, a liquid base (188, 189) that has now been assigned the structure 2,5-dimethyl-3,6-dihydropyrazine (190).

B. Reduction of α-Hydroxyimino Carbonyl Compounds

This method of preparation (**5** → **6** → **3**), first discovered by Gutknecht (15, 16), is concerned with the reduction of α-hydroxyimino carbonyl compounds (**5**),

earlier known as "isonitroso" ketones, which may be prepared by direct nitrosation of ketones (4). The reduction is most commonly effected with tin, stannous chloride, or zinc in acid solution; and it is usually necessary to treat the reduction mixture with alkali to release the free amino ketone, which then undergoes self-condensation and subsequent oxidation to the pyrazine.



Other reducing conditions have also been widely used. Thus zinc and sodium hydroxide has been utilized for the conversion of 1-hydroxyimino-1-phenylacetone to 2,5-dimethyl-3,6-diphenylpyrazine (191); dithionite for the conversion of α-benzoyl α-hydroxyiminoacetanilide to 2,5-diphenyl-3,6-bis(*N*-phenylcarbamoyl)-pyrazine (192); sodium amalgam for benzil monoxime to tetraphenylpyrazine (193); aluminum amalgam for hydroxyiminoacetoacetic ester to 2,5-bisethoxy-carbonyl-3,6-dimethylpyrazine (194); and sodium and alcohol for benzil dioxime to tetraphenylpyrazine (195).

Table II.2 lists literature preparations of pyrazines by this general method with a wide selection of reducing agents (8, 15, 16, 18, 23, 32, 166, 191–239).

TABLE II.2 PYRAZINES PREPARED BY REDUCTION OF α-HYDROXYIMINO KETONES

α-Hydroxyimino Ketone	Pyrazine	Refs.
Hydroxyiminoacetone	2,5-Dimethyl	23, 32, 196, 197
α-Hydroxyiminoethyl methyl ketone	Tetramethyl	8, 15, 16, 193, 198–201
Dimethylglyoxime	Tetramethyl	202, 203
β-Hydroxyiminolaevulinic acid	Tetramethyl	204
β-Hydroxy-γ-hydroxyiminovaleric acid[a]	Tetramethyl	205
α-Hydroxyimino-α-styryl acetone	2,5-Dimethyl-3,6-di(β-phenethyl)	206
α-Hydroxyiminoethyl phenyl ketone	2,5-Dimethyl-3,6-diphenyl	166, 192 207
α-Hydroxyiminoethyl *p*-tolyl ketone	2,5-Dimethyl-3,6-di-*p*-tolyl	207
α-Hydroxyiminoethyl anisyl ketone	2,5-Dianisyl-3,6-dimethyl	207

TABLE II.2 *Continued*

α-Hydroxyimino Ketone	Pyrazine	Refs.
α-Hydroxyiminobutyl methyl ketone	2,5-Dimethyl-3,6-dipropyl	201, 208
α,β-Bis(hydroxyimino)propyl benzene	2,5-Dimethyl-3,6-diphenyl	209
α-Hydroxyiminoisopentyl methyl ketone	2,6-Diisobutyl-3,5-dimethyl	210
α-Hydroxyiminohexyl methyl ketone	2,5-Dimethyl-3,6-dipentyl	211
α-Benzyl-α-hydroxyiminoacetone	2,5-Dibenzyl-3,6-dimethyl	212
Ethyl α-hydroxyiminoacetoacetate	2,5-Diethoxycarbonyl-3,6-dimethyl	18, 194, 202, 213–217
α-Hydroxyiminopropyl methyl ketone	2,5-Diethyl-3,6-dimethyl	8, 218
Ethyl α-hydroxyiminoethyl ketone	2,5-Diethyl-3,6-dimethyl	219
Benzil monoxime	Tetraphenyl	193, 202
Benzil dioxime	Tetraphenyl	195, 220, 221
α-Hydroxyiminoacetophenone	2,5-Diphenyl	166, 202, 222, 223
Benzyl α-hydroxyimino-β-oxobutyrate	2,5-Bisbenyloxycarbonyl-3,6-dimethyl	224
1-Hydroxyimino-1-phenylacetone	2,5-Dimethyl-3,6-diphenyl	191
1-Hydroxyimino-1-*o*-tolyl acetone	2,5-Dimethyl-3,6-di-*o*-tolyl	191
1-*m*-Chlorophenyl-1-hydroxyiminoacetone	2,5-Di-*m*-chlorophenyl-3,6-dimethyl	191
1-*p*-Chlorophenyl-1-hydroxyiminoacetone	2,5-Di-*p*-chlorophenyl-3,6-dimethyl	191
1-Hydroxyimino-1-pyridin-3′-ylacetone	2,5-Dimethyl-3,6-dipyridin-3′-yl	191
1-*p*-Carboxyphenyl-1-hydroxyiminoacetone	2,5-Di-*p*-carboxyphenyl-3,6-dimethyl	191
Methyl α-hydroxyiminoacetoacetate	2,5-Dimethoxycarbonyl-3,6-dimethyl	215
N-Methyl α-hydroxyiminoacetoacetamide	2,5-Dimethyl-3,6-bis-(*N*-methylcarbamoyl)	215
N,N-Dimethyl-α-hydroxyiminoacetoacetamide	2,5-Bis(*N,N*-dimethylcarbamoyl)-3,6-dimethyl	215
α-Hydroxyiminoacetoacetic acid	2,5-Dicarboxy-3,6-dimethyl	215
1-*p*-Acetamidophenyl-1-hydroxyiminoacetone	2,5-Di-*p*-acetamidophenyl-3,6-dimethyl	191
1-(4′-Acetamido-3′-methoxyphenyl)-1-hydroxyiminoacetone	2,5-Di-(4′-acetamido-3′-methoxyphenyl)-3,6-dimethyl	191
α-Hydroxyiminoisobutyl methyl ketone	2,5-Diisopropyl-3,6-dimethyl	225
Hydroxyiminoacetylacetone	2,5-Diacetyl-3,6-dimethyl	226–230
α-Hydroxyimino-β-(3′,4′-methylenedioxyphenyl)ethyl 3,4-dimethoxyphenyl ketone	2,5-Bis(3′,4′-dimethoxyphenyl)-3,6-di(3′,4′-methylenedioxybenzyl)	231
α-Benzoyl-α-hydroxyiminoacetanilide	2,5-Bis(anilinocarbonyl)-3,6-diphenyl	192
2-Nitrosoindanone-1	Diindeno-[1,2,*b*;1′,2′,*e*]pyrazine	192
β-Benzoyl-β-hydroxyiminopropionic acid	2,5-Bis(carboxymethyl)-3,6-diphenyl (as ethyl ester)	232
t-Butylglyoxal dioxime	2,5-Di-*t*-butyl	233
α-Hydroxyiminoacetoacetanilide	2,5-Bisanilinocarbonyl-3,6-dimethyl-1,4-dihydro	234
Substituted anilide analogues	Substituted anilinocarbonyl analogues	234

[a] Reaction heated at 145°; mechanism unknown.

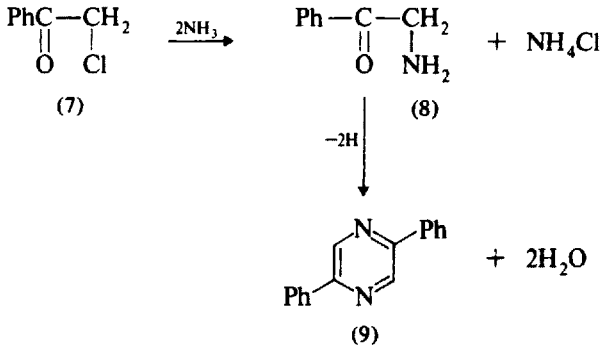
Catalytic reductions employing Raney nickel (213, 221), palladium (206), palladium–charcoal (227), and platinum oxide (228) have been utilized on a number of occasions. Studies of the catalytic reduction of ethyl α-hydroxyiminoacetoacetate to 2,5-bisethoxycarbonyl-3,6-dimethylpyrazine and ethyl α-amino-β-hydroxybutyrate over Raney nickel (213) have shown that the yield of pyrazine was reduced as the pressure of hydrogen was increased. This was taken to mean that at the higher pressure the intermediate imino ketone had less time to undergo self-condensation to the pyrazine before it was reduced to the hydroxy amine. Electrolysis of hydroxyiminoacetone has been shown to give 2,5-dimethylpyrazine (197), and irradiation of α-hydroxyiminoacetophenone in ethanolic ammonia with sunlight for 45 days gave 2,5-diphenylpyrazine (222). A number of examples are recorded in Table II.2 of the reduction of diketone dioximes to pyrazine derivatives. This may arise either by reduction of one oxime group and hydrolysis of the other to give an amino carbonyl compound which self-condenses or by complete reduction of one molecule to an *o*-diamine and complete hydrolysis of another to the diketone, followed by condensation of the two. These two possibilities may lead to different dihydropyrazines, but the mechanism of the reductive condensation has as yet not been determined.

Evans and Mewett (233) prepared 2,5-di-*t*-butylpyrazine by zinc and alkali reduction of *t*-butylglyoxal dioxime but steric hindrance prevented formation of tetra-*t*-butylpyrazine when di-*t*-butylglyoxal monoxime was reduced with zinc and alkali.

Reduction of nitromethyl alkyl ketones over Raney nickel has also been effected to give 2,5-didecyl- and 2,5-dipentylpyrazine (235).

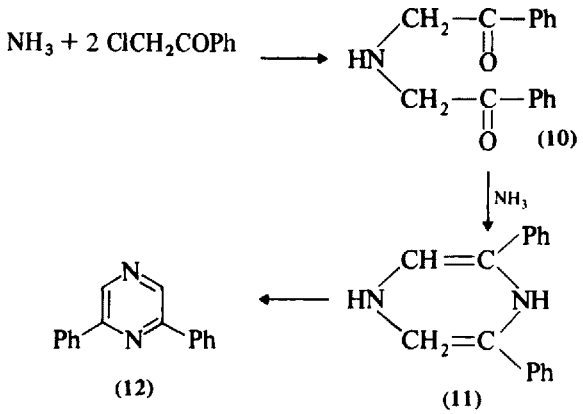
C. Ammonolysis of α-Halogeno Carbonyl Compounds

This method has been widely used for the preparation of pyrazines, and was first employed by Staedel and Rügheimer (10) for the preparation of 2,5-diphenylpyrazine (**9**) from ω-chloroacetophenone (**7**) and aqueous ammonia.

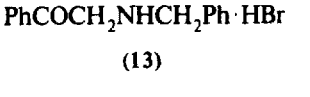


Reactions of such chloro compounds with ammonia also produce some secondary amines. Thus Gabriel (166) examined the reaction of ω-bromoacetophenone

and ammonia and observed some diphenacylamine as well as 2,5-diphenylpyrazine, and Tutin (236) reexamined the reaction of ω-chloroacetophenone with ammonia to find 2,6- as well as 2,5-diphenylpyrazine. The 2,6-diphenylpyrazine (**12**) was produced through the intermediate diphenacylamine (**10**). Cyclization of the primary amino carbonyl compound is usually much more rapid and the 2,5-disubstituted pyrazine is the major product.



A similar reaction involving ω-bromoacetophenone and benzylamine has been studied by Mason and Winder (26). The monophenacylbenzylamine hydrobromide (**13**) (from the reagents) with potassium hydroxide at 100° was claimed incorrectly to form 1,4-dibenzyl-2,5-diphenyl-1,4-dihydropyrazine (**14**) (see p. 344), which gave 2,5-diphenylpyrazine. Bromopyruvic acid with aqueous ammonia and mercuric chloride at 55° gave 2,5-dicarboxypyrazine (236a).



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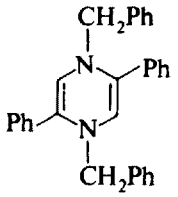


(14)

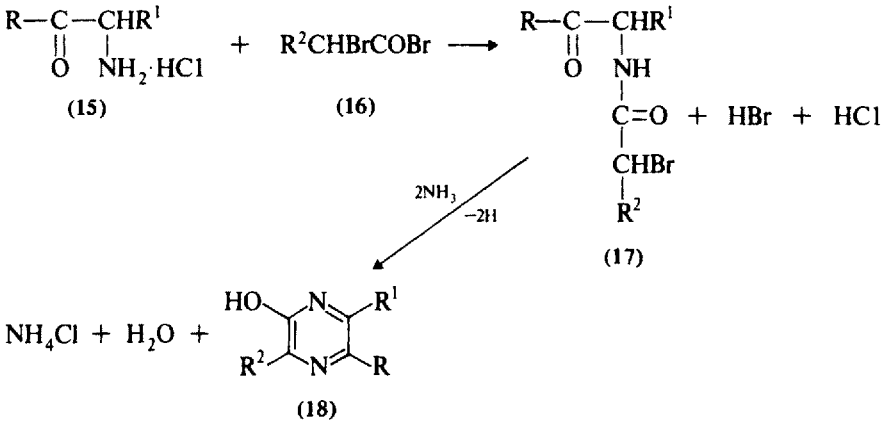
The reaction of α-chloro carbonyl compounds with ammonia is not always successful, for example, ω-chloro-*o*-methoxyacetophenone and ω-chloro-*o*,*p*-dimethoxyacetophenone yield only resinous products (236), but in these cases potassium phthalimide may be used for the ammonation to the α-amino carbonyl compound. This last method was developed by Gabriel (116) and co-workers (187).

Attempted preparations of the parent compound, pyrazine, from halogeneoacetaldehyde and ammonia were not very successful (23, 237). Tschitschibabin and Schtschukina (237) made a careful study of this reaction; their best yield, after oxidation with mercuric salts, was not higher than 17%. Some pyrazines prepared by this method are listed in Table II.3 (3, 10, 23, 31, 166, 193, 209, 236–247).

TABLE II.3 PYRAZINES PREPARED BY AMMONOLYSIS OF α-HALOGENO CARBONYL COMPOUNDS

α-Halogeno Carbonyl Compounds	Pyrazine	Refs.
Bromoacetaldehyde	Parent	23, 237
Chloroacetal	Parent	31
ω-Chloro(or bromo)acetophenone	2,5-Diphenyl and some 2,6-diphenyl	3, 10, 166, 193, 236, 238
α-Chloroethyl methyl ketone	Tetramethyl	239
α-Chloropropyl methyl ketone	2,5-Diethyl-3,6-dimethyl	239
α-Chloroethyl ethyl ketone	2,5-Diethyl-3,6-dimethyl	239
β-Bromolevulinic acid	Tetramethyl	3
α-Bromo-α-phenylacetone	2,5-Dimethyl-3,6-diphenyl	209
α-Bromoethyl phenyl ketone	2,5-Dimethyl-3,6-diphenyl	240–242
α-Bromopropyl phenyl ketone	2,5-Diethyl-3,6-diphenyl	240
ω-Chloro-*p*-methoxyacetophenone	2,5(and some 2,6)-Di-*p*-methoxyphenyl	236
ω-Chloro-*p*-alkylacetophenone	2,5-Di-*p*-alkylphenyl	243
ω-Chloro-*p*-hydroxyacetophenone	2,5(and some 2,6)-Di-*p*-hydroxyphenyl	236
Indacyl bromide	2,5-Diindolyl	244
Bromoacetylskatole	Bis(3'-methylindol-2'-yl)	244
3-Chloroacetyl-2-methylindole	2,5-Bis(2'-methylindol-3'-yl)	245
ω-Chloro-3,4-dimethoxyacetophenone	2,5-Bis(3',4'-dimethoxyphenyl)	236
α,β-Dichlorostyrene	2,5-Diphenyl	246
α,β-Dichloro-*p*-methylstyrene	2,5-Di-*p*-tolyl	246
Chlorosuberone	Bispentamethylene	247
Bromopyruvic acid	2,5-Dicarboxy	236a

A variation of this procedure was introduced by Tota and Elderfield (248), who described a general synthesis for 2,3-disubstituted and 2,3,6-trisubstituted 5-hydroxypyrazines. In this reaction an α-(bromoacetylamino) carbonyl compound (**17**) [prepared from an α-amino carbonyl compound (**15**) with a bromoacetyl bromide (**16**)] was treated with alcoholic ammonia to give the corresponding pyrazine (**18**). The reaction is discussed in more detail in Section 7.



D. Oxidation of α-Amino Alcohols

Pyrazines have been produced by a number of workers from α-amino alcohols by heating at elevated temperatures with catalysts such as copper, copper and zinc oxide, zinc oxide and sodium carbonate, copper chromite, or nickel. The reaction is presumed to proceed by dehydrogenation to the amino aldehyde, cyclization to the dihydropyrazine, and oxidation to the pyrazine. In this way Aston et al. (249) prepared pyrazine in 5.6% yield from ethanolamine at 300°; the reaction has been applied to various alkyl homologues (250–252). α-Amino alcohols with ammonia and cyclohexene over a Raney nickel catalyst at 180° gave a high yield of the corresponding pyrazine (253). Wang and Odell (254) have also shown that heating of certain amino hydroxy compounds such as ethanolamines and glucosamines leads to pyrazines, and they consider that such compounds may be important precursors of pyrazines in foods.

E. Reduction of α-Amino Acids

The hydrochlorides of esters of glycine and alanine have been reduced with sodium amalgam to the amino carbonyl compounds and then oxidized with mercuric chloride in an excess of alkali to yield pyrazine and 2,5-dimethylpyrazine, respectively (255, 256).

F. Reaction of α-Hydroxy Carbonyl Compounds or Polyhydroxy Compounds with Ammonia, Ammonium Salts, or Formamide

Some α-hydroxy carbonyl compounds when heated with ammonia, ammonium acetate or formate, or formamide have been shown to give pyrazines; the reaction presumably proceeds through the α-amino carbonyl compound.

This reaction was first applied by Erdmann (11) to the preparation of tetraphenylpyrazine by heating benzoin (PhCHOHCOPh) with ammonia. The reaction of benzoin with ammonium acetate in glacial acetic acid has been investigated by Davidson et al. (257), and it has been shown that identical results were obtained when the benzoin was replaced by desylamine ($PhCHNH_2COPh$).

Some pyrazines prepared by this method are listed in Table II.4 (3, 11, 12, 205, 257–267).

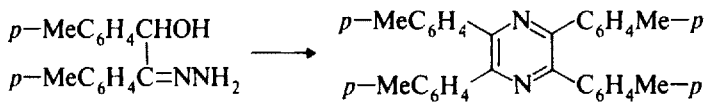
Evans and Mewett (233) were unable to prepare 2,3,5,6-tetra-*t*-butylpyrazine from pivaloin ($Bu^tCHOHCO\ Bu^t$) and ammonium salts and concluded that this may be due to steric hindrance by the *t*-butyl groups.

Hydrazine has been found to give similar reactions. Thus a mixture of *p*-toluoin and hydrazine hydrate, when heated on a steam bath, has been found to give tetra-*p*-tolylpyrazine (**20**) and *p*-toluoin hydrazone (**19**); the latter on heating at 185° gave the former (268). Heating of benzoin hydrazone at 110° also gave tetraphenyl-

TABLE II.4 PYRAZINES PREPARED FROM α-HYDROXY CARBONYL COMPOUNDS AND AMMONIA, AMMONIUM SALTS, OR FORMAMIDE

Reactants	Pyrazine	Refs.
Benzoin	Tetraphenyl	11, 12, 257–263
Anisoin	Tetra-*p*-methoxyphenyl	260, 262
p-Toluoin	Tetra-*p*-tolyl	260
Benzanisoin	2,5-Di-*p*-methoxyphenyl-3,6-diphenyl	260, 262
β-Hydroxylevulinic acid	Tetramethyl	3, 205
1-Acetyl(or benzoyl)anilino-2-oxo-1,2-diphenylethane	Tetraphenyl	264
Benzil, benzylamine	Tetraphenyl	265
Ethyl α-(fur-2′-yl)-α-hydroxymethyl ketone	2,5-Diethyl-3,6-di(fur-2′-yl)	266
1,2-Di(fur-2′-yl)-1-hydroxy-2-oxoethane	Tetra(fur-2′-yl)	266
α-(Fur-2′-yl)-α-hydroxymethyl phenyl ketone	2,5-Di(fur-2′-yl)-3,6-diphenyl	266
1-Hydroxy-2-oxo-1,2-di(thien-2′-yl)-ethane	Tetra(thien-2′-yl)	262
Ethyl α-hydroxybenzyl ketone	2,5-Diethyl-3,6-diphenyl	262
Ethyl α-hydroxy-α-(thien-2′-yl)methyl ketone	2,5-Diethyl-3,6-di(thien-2′-yl)	262
ω-Hydroxyacetophenone	2,5-Diphenyl	262
Substituted benzoins and mixed benzoins	Tetra (substituted phenyl)	262
Benzoin + furoin	2,3-Difuryl-5,6-diphenyl	262
Diethyl α-hydroxy-α′-oxosuccinate	Tetraethoxycarbonyl	267

pyrazine (268, 269). Likewise benzoin and α-methyl-α-phenylhydrazine gave tetraphenylpyrazine (270). Pyrazines have also been prepared by the action of ammonia or its salts on polyhydroxy compounds. For example, when glycerol is mixed with ammonium salts and distilled, low yields of 2,5-dimethylpyrazine (9, 32, 271–274) are obtained; glucose heated with ammonium hydroxide at 100° gave a mixture containing pyrazine, methylpyrazine, and 2,6-dimethylpyrazine (33); D-glucose with aqueous ammonia gave 2-methyl-5- and 2-methyl-6(or 3)-(D-*arabo*-tetrahydroxybutyl)pyrazine (48); and high temperature ammoniation of molasses gave 2,6-dimethylpyrazine (275). Factors affecting the formation of pyrazines from D-glucose and ammonia have been studied in detail by Shibamoto and Bernhard (276). Fructose with methanolic ammonia has been shown to give 2,5-bis(tetrahydroxybutyl)pyrazine (fructosazine) (277).



(19) (20)

The ammonium or sodium salt of dihydroxymaleic acid with strong aqueous ammonia at 50–60° for 0.5 hours has been shown to give 2,5-dicarboxypyrazine (278); and a mixture of 2,3-dihydroxybutane and ammonia over a catalyst of silica gel or alumina at 100–400° gave tetramethylpyrazine (279).

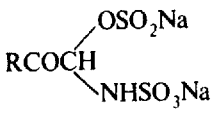
G. Reaction of α,β-Dicarbonyl Compounds with Ammonia

The reaction of phenylglyoxal with ammonia was examined first by Müller and von Pechmann (280) and in more detail by Pinner (281) and shown to give two products that have been identified as 3-hydroxy-2,5-diphenylpyrazine and 2-benzoyl-4(5)-phenylglyoxaline (282). Phenylglyoxal with ammonium formate also gave similar mixtures (282). Pinner proposed that an intermediate diimine was formed, and this condensed with some unchanged dicarbonyl compound. Such a mechanism would not preclude the formation of the isomeric 2-hydroxy-3,5-diphenylpyrazine but neither it nor any diimine has been isolated. The reaction could also proceed through an aldehyde ammonia [$PhCOCH(OH)NH_2$], followed by self-condensation and dehydration.

A series of 3-hydroxy-2,5-bis(*p*-alkylphenyl and *p*-alkoxyphenyl)pyrazines has been prepared, each in small yield, from *p*-substituted phenylglyoxals and ammonia (283); benzil and liquid ammonia (and ammonium chloride or potassium amide) have been shown to give low yields of tetraphenylpyrazine (284); and benzoylformoin, which has been claimed to have an enediol [$PhCOC(OH)=C(OH)COPh$] content of 90%, and ammonia gave 2-hydroxy-3,5-diphenylpyrazine (285).

H. Bisulphite Compounds of α-Hydroxyimino Ketones with Potassium Cyanide

Gastaldi (286) first described this synthesis, in which an α-hydroxyimino ketone was treated with aqueous sodium bisulfite saturated with sulfur dioxide, and the bisulfite compound treated with potassium cyanide followed by hydrolysis with hydrochloric acid. By this procedure, Gastaldi prepared 2,5-dicyano-3,6-dimethylpyrazine from hydroxyiminoacetone, and 2,5-dicyano-3,6-diphenylpyrazine and some 3-cyano-2,5-diphenylpyrazine from hydroxyiminoacetophenone. He proposed a reaction mechanism involving the intermediate compounds **(21)** and **(22)**. Sharp and Spring (287) used the same procedure to prepare 2,5-dicyano-3,6-diethylpyrazine from ethyl hydroxyiminomethyl ketone.



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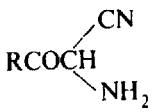
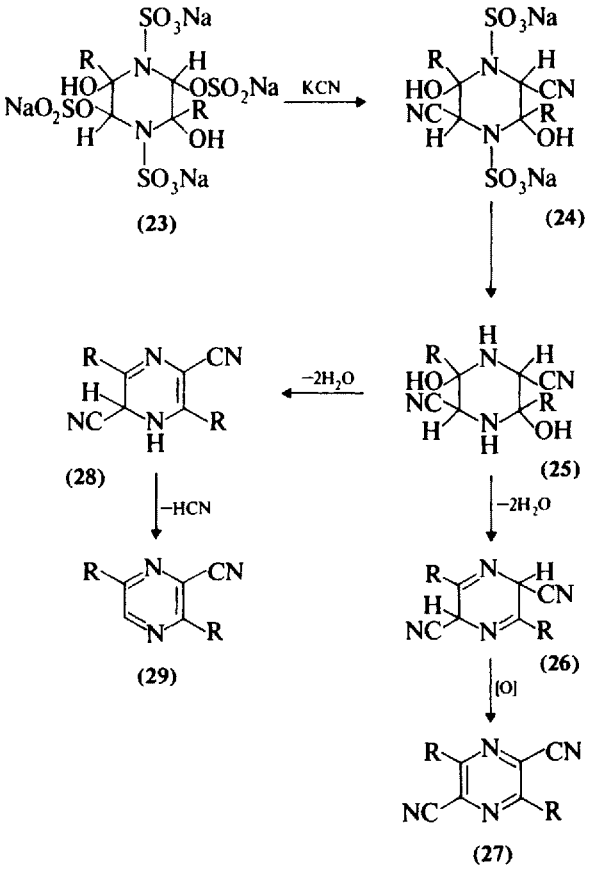


(22)

The Gastaldi reaction has been investigated by Golombok and Spring (288), who pointed out that the self-condensation of α-amino ketones (proposed by Gastaldi)

was improbable in strong acid. They proposed that the reaction proceeded through the dimeric intermediate bisulfite compound (**23**) to the 2,5-dicyano-3,6-diphenylpyrazine (**27**, R = Ph), and the formation of 3-cyano-2,5-diphenylpyrazine (**29**) from hydroxyiminoacetophenone was attributed to an alternative method for the aromatization of the dihydro intermediate (**28**), involving loss of hydrogen cyanide. Golombok and Spring also showed that addition of aminoacetone hydrochloride to the reaction mixture from the hydroxyiminoacetone bisulfite derivative at the commencement of the acid hydrolysis did not lead to the formation of 3-cyano-2,5-dimethylpyrazine, as expected for the mechanism proposed by Gastaldi.



I. Hydrolysis of Acetamidoacetone Derivatives Formed from α-Amino Acids, Acetic Anhydride, and Pyridine

Dakin and West (289–291) and Levine and Steiger (292) have shown that α-primary amino acids (**30**) may be converted into acetamidoacetone derivatives

(31) by the action of acetic anhydride and pyridine with the evolution of carbon dioxide. The *N*-acetyl group may then be hydrolyzed and the α-amino ketone (32) converted to a pyrazine (33). Literature preparations of pyrazines using this method are summarized in Table II.5 (289–293).

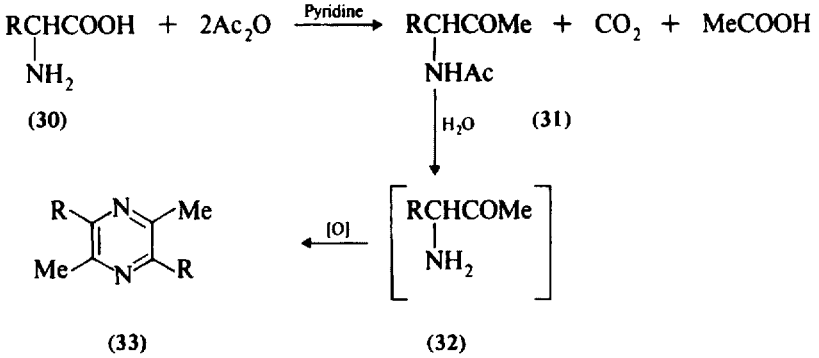


TABLE II.5 PYRAZINES PREPARED FROM AMINO ACIDS BY THE ACTION OF ACETIC ANHYDRIDE AND PYRIDINE FOLLOWED BY HYDROLYSIS

Amino Acid	Pyrazine	Refs.
Alanine	Tetramethyl	289
Glycine	2,5-Dimethyl	289
Hippuric acid	2,5-Dimethyl	289
Glutamic acid	2,5-bis(2'-carboxyethyl)-3,6-dimethyl	290, 293
Phenylalanine	2,5-Dibenzyl-3,6-dimethyl	291, 292
Tyrosine	2,5-Di-(*p*-hydroxybenzyl)-3,6-dimethyl	291, 292
1-Amino-1-phenylacetic acid	2,5-Dimethyl-3,6-diphenyl	292

J. Rearrangement of Some Oximes

It was discussed by Neber and co-workers (294–298) that some oximes (34) can be rearranged to α-amino ketones (36). The oxime was first converted into its *p*-toluenesulfonic ester (35), which rearranged with sodium or potassium ethoxide to produce the amino ketone, which in most cases underwent further condensation to the dihydropyrazine (or pyrazine). The mechanism has been studied carefully in the reaction of 2,4-dinitrobenzyl methyl ketone and the unstable intermediate isolated from the reaction has been assigned (299, 300) the structure (37). The method was not always successful but literature preparations (294–298) are recorded in Table II.6.

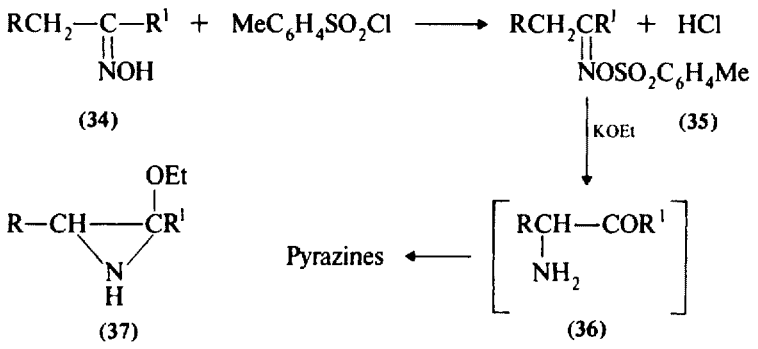


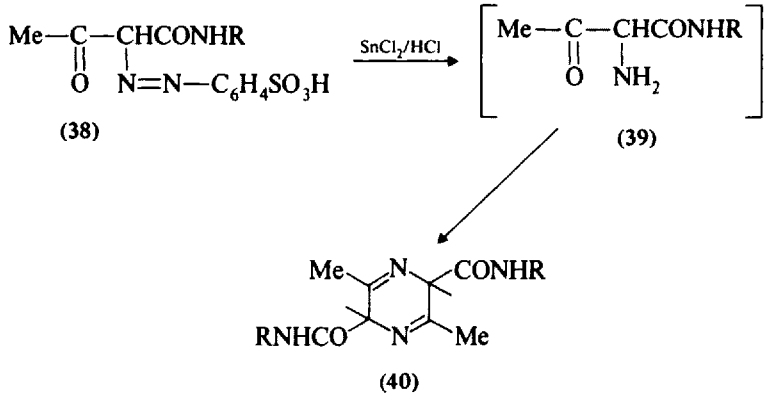
TABLE II.6 REARRANGEMENT OF OXIMES TO PYRAZINES AND DIHYDROPYRAZINES

Oxime	Pyrazine	Refs.
Benzyl methyl ketoxime	2,5-Dimethyl-3,6-diphenyl	294
Methyl *o*-nitrobenzyl ketoxime	2,5-Dimethyl-3,6-di(*o*-nitrophenyl)-3,6-dihydro	294, 297
Methyl phenethyl ketoxime	2,5-Dibenzyl-3,6-dimethyl-2,5-dihydro	295
Dibenzyl ketoxime	2,5-Dibenzyl-3,6-diphenyl-3,6-dihydro	295
Methyl 2,4-dinitrobenzyl ketoxime	2,5-Dimethyl-3,6-di(2',4'-dinitrophenyl)-3,6-dihydro	296
Acetoacetanilide oxime	2,5-Dianilinocarbonyl-3,6-dimethyl-2,5-dihydro	298

K. Reduction of α-Azo, α-Diazo, or α-Azido Ketones

Fierz-David and Ziegler (301) first applied this method to azo compounds. Ethyl acetoacetate and various aromatic amines (aniline, *o*- and *p*-toluidines, *m*-xylidine, *o*-anisidine, and chloroanilines) were convereted to acetoacetanilides and then coupled with diazotized sulfanilic acid. The azo dyes (**38**) were reduced with stannous chloride in hydrochloric acid to the corresponding aminoacetoacetanilides (**39**), which in alkali formed the dihydropyrazines (**40**). Catalytic reduction of *o*-hydroxyphenylglyoxal phenylhydrazone in acetic acid over palladium has been shown also to give 2,5-bis(*o*-hydroxyphenyl)pyrazine (302). Reduction of ω-diazoacetophenone by catalytic and chemical means has been shown to give 2,5-diphenylpyrazine (303, 304) and hydrogenation of benzyl diazomethyl ketone in ethyl acetate over palladium oxide gave 2,5-dibenzylpyrazine (303).

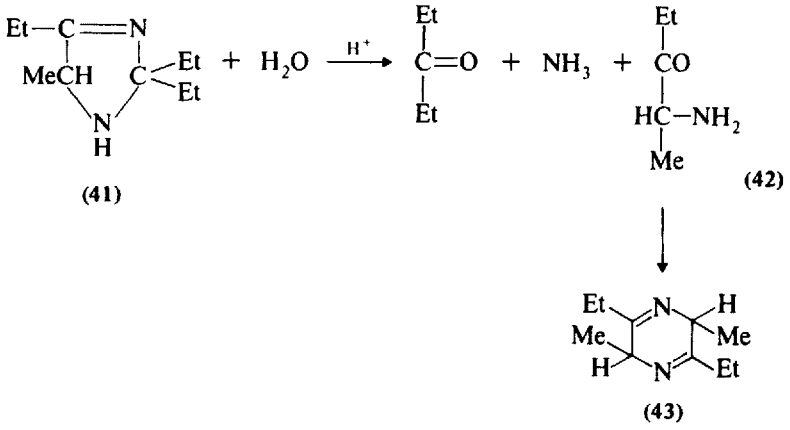
Azidomethyl isopropyl ketone ($Pr^iCOCH_2N_2$) with triphenylphosphine gives 2,5-diisopropylpyrazine, and similar reactions were observed with phenyl and *p*-anisyl analogues (305).



(38) (39) (40)

L. Hydrolysis of 3-Imidazolines (Isoxazoles and Oxazoles)

3-Imidazolines on acid hydrolysis have been shown to give pyrazines (306). Thus 2,2-diethyl-4-methylimidazoline-Δ^3 with dilute hydrochloric acid at 60° gave diethyl ketone (62% of the theoretical) and 2,5-dimethylpyrazine (7%); 2,2-diethyl-4,5-dimethylimidazoline-Δ^3 gave diethyl ketone (70.2%) and tetramethylpyrazine (20.4%); and 2,2,4-triethyl-5-methylimidazoline-Δ^3 (41) gave diethyl ketone (84%) and 2,5-diethyl-3,6-dimethyl-3,6-dihydropyrazine (81%) (43). The pyrazines were formed presumably by self-condensation of the amino ketones (42) produced.

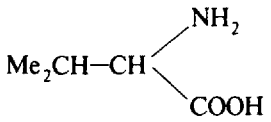


(41) (42) (43)

Tetramethylpyrazine was also formed in low yield from 5-amino-3,4-dimethylisoxazole and semicarbazide in ammonia (307) and 4,5-diethoxycarbonyloxazole in glycol with a little sulfuric acid at 100° gave 2,3,5,6-tetraethoxycarbonylpyrazine (267).

M. 1,2-Dicarbonyl Compounds with α-Amino Acids

Pyrazines have been prepared by heating 1,2-dicarbonyl compounds with α-amino acids. Thus Rizzi (308) observed that under the conditions of the Strecker degradation, equimolar amounts of DL-valine (**44**) and butane-2,3-dione in refluxing bis(2-methoxyethyl) ether, "diglyme," gave isobutyraldehyde, tetramethylpyrazine (9%), and a mixture of *cis*- and *trans*-2-isopropyl-4,5-dimethyl-3-oxazoline (4%). He proposed a reductive amination mechanism in which butane-2,3-dione was converted to 2-aminobutan-3-one which underwent self-condensation to the pyrazine. Tetramethylpyrazine was also prepared when the same reactants were heated in dimethylformamide at 123° for 5 hours (and other pyrazines prepared similarly) (308a).



(44)

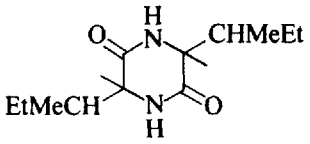
Other workers (309) have extended this reaction and found that mixtures of α-amino acids (glycine, alanine, phenylalanine, tyrosine, tryptophan, leucine, methionine, cysteine) and benzil when heated to 180–220° gave good yields of 2,3,5,6-tetraphenylpyrazine, and a mechanism also involving an α-amino ketone was proposed. Benzoin with glycine, alanine, phenylalanine, or tyrosine at elevated temperatures similarly gave tetraphenylpyrazine.

An equimolar glyoxal–glycine mixture heated under reflux for 4 hours has been shown to give pyrazine and various methylpyrazines (310), but L-leucine and glyoxal sodium bisulfite gave 2-hydroxy-3-isobutylpyrazine (311).

N. α-Amino Acids through Piperazine-2,5-diones

A number of piperazine-2,5-diones (α-amino acid "anhydrides") has been converted to pyrazines by the action of phosphorus halides. Baxter and Spring (312) first described the conversion of isoleucine "anhydride" (**45**) with phosphoryl chloride to 2,5-di-*s*-butyl-3,6-dichloropyrazine (**46**, X = Cl) and 2,5-di-*s*-butyl-3-chloropyrazine (**46**, X = H), and of DL-alanine "anhydride" (**47**) similary to 2,5-dichloro-3,6-dimethylpyrazine (**48**, X = Cl) and 3-chloro-2,5-dimethylpyrazine (**48**, X = H). The formation of the monochloro compound (**48**, X = H) from alanine "anhydride" does not involve an oxidation step, whereas the formation of 2,5-dichloro-3,6-dimethylpyrazine involves the oxidation of an intermediate dihydropyrazine derivative. Treatment of DL-alanine "anhydride" with phosphoryl chloride in the presence of a tertiary base (dimethylaniline) gave only the monochloro derivative: the intermediate dichlorodihydropyrazine presumably loses hydrogen chloride and gives the stable aromatic 3-chloro-2,5-dimethylpyrazine.

3-Chloro-2,5-dimethylpyrazine was not isolated from the reaction of DL-alanine "anhydride" with a mixture of phosphoryl chloride and phosphorus pentachloride, but the reaction gives a poor yield of (**48**, X = Cl) and a small quantity of (**48**, X = OH). Gallagher et al. (282) found that DL-phenylglycine with phosphoryl chloride gave 2,5-dichloro-3,6-diphenylpyrazine and 3-hydroxy-2,5-diphenylpyrazine (presumably formed by loss of the elements of hydrogen chloride from an intermediate 2-chloro-5-hydroxy-3,6-diphenyldihydropyrazine); and Dunn et al. (95) from DL-leucine "anhydride" and phosphoryl chloride prepared flavacol, 3-hydroxy-2,5-diisobutylpyrazine, and a mixture of chloropyrazines, whereas Ohta (101) used phosphoryl chloride and phosphorus pentachloride and obtained flavacol and a little 2-chloro-5-hydroxy-3,6-diisobutylpyrazine.



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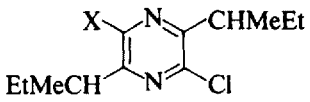

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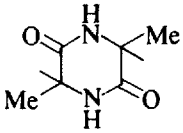

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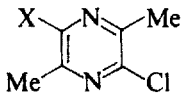


(48)

In a similar manner 2-*s*-butyl-3-hydroxy-5-isobutylpyrazine was prepared from DL-leucyl-DL-isoleucine "anhydride," 3-*s*-butyl-6-isobutylpiperazine-2,5-dione, and phosphoryl chloride (93, 313).

Sammes and co-workers (314, 314a) have recently shown that piperazine-2,5-diones can be converted with excess triethyloxonium fluoroborate to 2,5-diethoxy-3,6-dihydropyrazines and then to 2,5-diethoxypyrazines. This reaction is discussed further in Section 6 below.

O. Aldehyde Cyanohydrins

Early preparations of the product from benzil, hydrogen cyanide, and hydrogen chloride (315) and by the action of hydrogen chloride on mandelonitrile (benzaldehyde cyanohydrin) (316) were formulated by Japp and Knox (317) as 3-hydroxy-2,5-diphenylpyrazine, and a mechanism for the reaction was proposed by Ingham (318). The structure of the product, however, has been refuted by Gallagher et al. (282).

In a procedure similar to that used by Minovici (316), McCombie and Parry

(319) claim the preparation from anisaldehyde cyanohydrin and cinnamaldehyde cyanohydrin with ethereal hydrogen chloride of 3-hydroxy-2,5-di-*p*-methoxyphenylpyrazine and 3-hydroxy-2,5-distyrylpyrazine, respectively, and Ingham (318) has also claimed from *m*(and *p*)-nitrobenzaldehyde cyanohydrins,3-hydroxy-2,5-di-*m*-nitrophenylpyrazine and 3-hydroxy-2,5-di-*p*-nitrophenylpyrazine.

A modification of this procedure was introduced by McKenzie and Kelman (320), who allowed the aldehyde cyanohydrin to react with a Grignard reagent. Thus mandelonitrile with α-naphthylmagnesium bromide gave what appeared to be 2,5-di(α-naphthyl)-3,6-diphenylpyrazine.

P. Miscellaneous

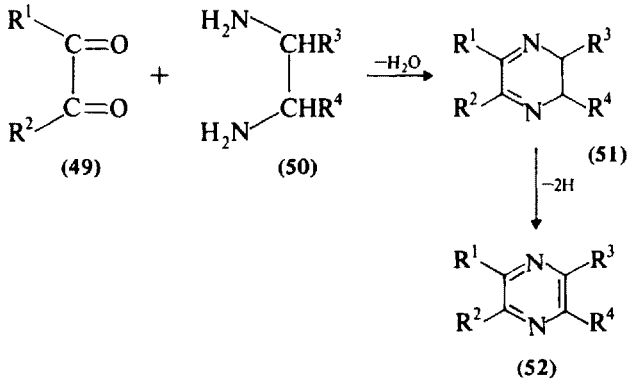
A number of miscellaneous reactions, of which the mechanism is not known but which may involve α-aminocarbonyl compounds, is listed in Table II.7 (14, 242, 321–328) without further comment.

TABLE II.7 MISCELLANEOUS SYNTHESIS OF PYRAZINES POSSIBLY VIA α-AMINO CARBONYL COMPOUNDS

Reactants	Pyrazine	Refs.
Dypnone (PhMeC=CHCOPh) and hydroxylamine for many days at room temperature	2,5-Diphenyl	321
α-(Morpholin-4′-yl)propiophenone and ammonium carbonate at 115° for 2 days	2,5-Dimethyl-3,6-diphenyl and 2,6-dimethyl-3,5-diphenyl (trace)	242
1-Nitro-2-phenylethane and aqueous sodium hydroxide at 120°	2,5-Diphenyl	322
Methyl α-(acetamido)acetoacetate and cinnamoyl chloride in aqueous sodium acetate	2,5-Bismethoxycarbonyl-3,6-dimethyl	323
α-Azidostyrene on thermolysis	2,5-Diphenyl	324
o-Nitromandelonitrile and ethereal hydrogen chloride	3-Hydroxy-2,5-bis(*o*-nitrophenyl)	325
Distillation of α-phenyl-α-(phenylmethyleneamino) acetonitrile (benzoylazotide)	Tetraphenyl	14
anti-3-Aminobutanon-2-oxime heated with triethyl orthoacetate	Tetramethyl	326
Aminoacetone heated with:		327
Formaldehyde	2,3,5-Trimethyl	
Acetaldehyde	3-Ethyl-2,5-dimethyl	
Butyraldehyde	3-Butyl-2,5-dimethyl	
2-Nitro-2,3-diphenyloxirane with ammonia at 100°	Tetraphenyl	328
2-Ethyl-2-nitro-3-phenyloxirane with ammonia at 50°	2,5-Diethyl-3,6-diphenyl	328
2-Methyl-2-nitro-3-phenyloxirane with ammonia at 60°	2,5-Dimethyl-3,6-diphenyl	328
Ethyl α-hydroxyimino-β-iminobutyrate heated with fused zinc chloride	2,5-Diethoxycarbonyl-3,6-dimethyl (?)	19

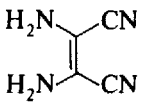
2. CONDENSATION OF α,β-DICARBONYL COMPOUNDS WITH α,β-DIAMINO COMPOUNDS, ETC.

The condensation of α,β-dicarbonyl compounds (**49**) with α,β-diamino compounds (**50**), which proceeds through the dihydropyrazine (**51**), has been much used for the synthesis of alkyl- and arylpyrazines (**52**). These reactions are usually carried out in methanol, ethanol, or ether in the presence of sodium or potassium hydroxide. The dihydropyrazines may be isolated, or oxidized directly to the pyrazine. Dehydrogenating agents that have been employed include oxygen in aqueous alkali (329), air in the presence of potassium hydroxide (330), sodium amylate in amyl alcohol (330a), alcoholic ferric chloride (24), and copper chromite catalyst at 300° (331) (see also Section 1). Pyrazines prepared by this method and modifications described below are listed in Table II.8 (2, 6, 24, 60, 80, 195, 329–382) and some additional data are provided in Sections VI.1A, VIII.1A(1), and IX.4A(1).



(**49**) (**50**) (**51**) (**52**)

The use of α,β-diaminopropionic acid with α,β-dicarbonyl compounds leads to pyrazinecarboxylic acids (351, 352), and diaminomaleonitrile (**53**) gives 2,3-dicyanopyrazines (**52**, $R^3 = R^4 = CN$) (353, 355, 357). The condensation of α,β-diamino compounds with α-keto esters has been shown to give 5-hydroxy-2,3-dihydropyrazines (**51**, $R^2 = OH$) (340).



(**53**)

Jones (361) introduced a very convenient variation of this reaction for the preparation of hydroxypyrazines (**55**) in which α,β-dicarbonyl compounds (**49**) were condensed with α-amino acid amides (**54**). In this way aminomalonamide (**54**, $R^4 = CONH_2$) with glyoxal in aqueous sodium hydroxide gave 3-carbamoyl-2-

TABLE II.8 CONDENSATION OF α,β-DICARBONYL COMPOUNDS WITH α,β-DIAMINO COMPOUNDS, ETC.

α,β-Diamine	α,β-Dicarbonyl Compound	Pyrazine	Refs.
Ethylenediamine	Diacetyl	2,3-Dimethyl	332, 333
		2,3-Dimethyl-5,6-dihydro	331, 333
	Pentane-2,3-dione	2-Ethyl-3-methyl-5,6-dihydro	331
	Hexane-2,3-dione	2-Methyl-3-propyl-5,6-dihydro	331, 334
	4-Methylpentane-2,3-dione	2-Isopropyl-3-methyl-5,6-dihydro	331
	Heptane-2,3-dione	2-Butyl-3-methyl-5,6-dihydro	331
	5-Methylhexane-2,3-dione	2-Isobutyl-3-methyl-5,6-dihydro	331
	Octane-2,3-dione	2-Methyl-3-pentyl-5,6-dihydro	331
	Nonane-2,3-dione	2-Hexyl-3-methyl-5,6-dihydro	331
	Benzil	2,3-Diphenyl and some tetraphenyl	2, 6, 24, 335–337
	Anisil	2,3-Bis(*p*-methoxyphenyl)	335
	p-Tolil	2,3-Bis(*p*-methylphenyl)-5,6-dihydro	336
	Furil	2,3-Di(fur-2′-yl)-5,6-dihydro	338
	1,2-Di(α-cyanobenzyl)-glyoxal	2,3-Di(α-cyanobenzyl)-5,6-dihydro	339
	Ethyl pyruvate	2-Hydroxy-3-methyl-5,6-dihydro	340
	Ethyl phenylglyoxylate	2-Hydroxy-3-phenyl-5,6-dihydro	340
	Phenacylglyoxylic acid	2-Hydroxy-3-phenacyl-5,6-dihydro	341
	1-Chloro-1-(methyl-carbamoyloxyimino)-acetone	2-Methyl-3-(methyl-carbamoyloxyimino)-5,6-dihydro	342
Propylenediamine	Diacetyl	2,3,5-Trimethyl-5,6-dihydro	330, 343, 344
	Pentane-2,3-dione	2-Ethyl-3,5-dimethyl and 3-ethyl-2,5-dimethyl	330
	Isopropylglyoxal	2-Isopropyl-5-methyl and 2-isopropyl-6-methyl	329
	t-Butylglyoxal	2-*t*-butyl-5-methyl and 2-*t*-butyl-6-methyl	329
	Benzil	5-Methyl-2,3-diphenyl	24, 345
	Furil	2,3-Di(fur-2′-yl)-5-methyl-5,6-dihydro	338
	Ethyl phenyl-glyoxylate	2-Hydroxy-6(or 5)-methyl-3-phenyl-5,6-dihydro	340
2,3-Diaminobutane	Diacetyl	2,3,5,6-Tetramethyl-5,6-dihydro	343

TABLE II.8 *Continued*

α,β-Diamine	α,β-Dicarbonyl Compound	Pyrazine	Refs.
2,3-Diaminopentane	Diacetyl	2-Ethyl-3,5,6-trimethyl	330
1,1-Dimethylethylene-diamine	Ethyl phenyl-glyoxylate	2-Hydroxy-5,5(or 6,6)-dimethyl-3-phenyl-5,6-dihydro	340
1,1,2,2-Tetramethyl-ethylenediamine	Ethyl pyruvate	6-Hydroxy-2,2,3,3,5-penta-methyl-2,3-dihydro	340
	Ethyl phenyl-glyoxylate	6-Hydroxy-2,2,3,3-tetra-methyl-5-phenyl-2,3-dihydro	340
	(and many similar reactions)	(and many similar products)	
Phenylethylenediamine	Benzil	2,3,5-Triphenyl	195
Phenylethylenediamine	Benzil	2,5,6-Triphenyl-2,3-dihydro	330a
1-Methyl-2-phenyl-ethylenediamine	Benzil	2-Methyl-3,5,6-triphenyl-2,3-dihydro	330a
1-Ethyl-2-phenyl-ethylenediamine	Benzil	2-Ethyl-3,5,6-triphenyl-2,3-dihydro	330a
1-Isopropyl-2-phenyl-ethylenediamine	Benzil	2-Isopropyl-3,5,6-triphenyl-2,3-dihydro	330a
1-Butyl-2-phenyl-ethylenediamine	Benzil	2-Butyl-3,5,6-triphenyl-2,3-dihydro	330a
1,2-Diphenylethylene-diamine	Benzil	Tetraphenyl	195
1,2-Diamino-1-hydroxy-imino-2-phenylethane	Diacetyl	2-Hydroxyamino-5,6-dimethyl-3-phenyl	346
1,2-Diamino-1-carbamoyl-2-iminoethane	*p*-Fluorophenyl-glyoxal	2-Amino-3-carbamoyl-5(6)-(*p*-fluorophenyl)	347
1,2-Diaminocyclobutane	Benzil	Tetraphenyl	348
1,2-Diamino-3-chloro-propane	Benzil	2-Chloromethyl-5,6-diphenyl-2,3-dihydro	349
α,β-Diaminopropionic acid	Glyoxal	2-Carboxy	350
	Methylglyoxal	2-Carboxy-5(and 6)-methyl	351, 352
	Diacetyl	5-Carboxy-2,3-dimethyl	351, 352
	Phenylglyoxal	2-Carboxy-5-(and 6)-phenyl	351, 352
	Benzil	5-Carboxy-2,3-diphenyl	351, 352
	1,1-Dimethoxy-2-oxobutane	2-Carboxy-5(and 6)-ethyl	352
Diaminomaleonitrile[a]	Glyoxal	2,3-Dicyano	353–355
	Glyoxal	2,3-Dicyano-*x*,*y*-dihydro	356
	Glyoxal (in hot water)	2,3-Dicyano-5-hydroxy-dihydro	357
	Diacetyl	2,3-Dicyano-5,6-dimethyl	353, 355, 357
	Benzil	2,3-Dicyano-5,6,-diphenyl	353, 355, 357
	Phenylglyoxal	2,3-Dicyano-5-phenyl	355
	1-Methyl-2-phenyl-glyoxal	2,3-Dicyano-5-methyl-6-phenyl	355

TABLE II.8 *Continued*

α,β-Diamine	α,β-Dicarbonyl Compound	Pyrazine	Refs.
	α-(Hydroxyimino)-acetophenone	2,3-Dicyano-5-phenyl	355
	α-(Hydroxyimino)-propiophenone	2,3-Dicyano-5-methyl-6-phenyl	355
	Glyoxylic acid	2,3-Dicyano-5-hydroxy	358
	Pyruvic acid	2,3-Dicyano-5-hydroxy-6-methyl	358, 359
	Ethylglyoxylic acid	2,3-Dicyano-5-ethyl-6-hydroxy	358
	Propylglyoxylic acid	2,3-Dicyano-5-hydroxy-6-propyl	358
	Mesoxalic acid	2-Carboxy-5,6-dicyano-3-hydroxy	358
	Phenylglyoxylic acid	2,3-Dicyano-5-hydroxy-6-phenyl	359
	Ethyl ethoxycarbonyl-methylglyoxylate	2,3-Dicyano-5-ethoxy-carbonylmethyl-6-hydroxy	359
	Diethyl mesoxalate	2,3-Dicyano-5-ethoxy-carbonyl-6-hydroxy	359
	1,1-Dihydroxyacetone	2,3-Dicyano-5-methyl	360
α-Aminoacetamide[b]	Glyoxal	2-Hydroxy[c]	361, 362
	Methylglyoxal	2-Hydroxy-5(and -6)-methyl	362
	Diacetyl	5-Hydroxy-2,3-dimethyl	361, 362
	Phenylglyoxal	2-Hydroxy-5-phenyl (and a little 6-isomer)	363–365, 365a
	Benzil	5-Hydroxy-2,3-diphenyl	361, 362
	Diethyl oxalate	2,3,5-Trihydroxy	365b
α-Amino-*N*-methyl-acetamide	Methylglyoxal	1,5-Dimethyl-2-oxo-1,2-dihydro	365c
α-Amino-α-methylthio-ethylacetamide	Glyoxal	2-Hydroxy-3-methylthio-ethyl	361
	Diacetyl	2-Hydroxy-5,6-dimethyl-3-methylthioethyl	361
α-Amino-α-phenyl-acetamide	Glyoxal	2-Hydroxy-3-phenyl	361
	Methylglyoxal	3-Hydroxy-5-methyl-2-phenyl	365d
	Diacetyl	2-Hydroxy-5,6-dimethyl-3-phenyl	361
α-Amino-α-(*p*-hydroxy-benzyl)acetamide	Glyoxal	2-Hydroxy-3-(*p*-hydroxy-benzyl)	361
	Methylglyoxal	2-Hydroxy-3-(*p*-hydroxy-benzyl)-5(6)-methyl	361
	Diacetyl	2-Hydroxy-3-(*p*-hydroxy-benzyl)-5,6-dimethyl	361
α-Aminopropion-amide	Glyoxal	2-Hydroxy-3-methyl	361, 362
	Methylglyoxal	2-Hydroxy-3,5-dimethyl	361, 362
		3-Hydroxy-2,5-dimethyl	362
	Dimethylglyoxal	2-Hydroxy-3,5,6-trimethyl	361, 362

TABLE II.8 *Continued*

α,β-Diamine	α,β-Dicarbonyl Compound	Pyrazine	Refs.
	Phenylglyoxal	2-Hydroxy-3-methyl-5(6)-phenyl	361
	Benzil	2-Hydroxy-3-methyl-5,6-diphenyl	362
α-Amino-β-phenyl-propionamide	Glyoxal	2-Benzyl-3-hydroxy	80, 366
α-Aminobutyramide	Glyoxal	2-Ethyl-3-hydroxy	362, 367
	Methylglyoxal	3-Ethyl-2-hydroxy-5-methyl	362
	Diacetyl	2-Ethyl-3-hydroxy-5,6-dimethyl	362
	Benzil	2-Ethyl-3-hydroxy-5,6-diphenyl	362
α-Aminovaleramide	Glyoxal	2-Hydroxy-3-propyl	362, 367
	Methylglyoxal	2-Hydroxy-5(and 6)-methyl-3-propyl[d]	362
	Diacetyl	2-Hydroxy-5,6-dimethyl-3-propyl	362
	Benzil	2-Hydroxy-5,6-diphenyl 3-propyl	362
α-Amino-β-methyl-butanamide	Glyoxal	2-Hydroxy-3-isopropyl	80, 362, 367
	Methylglyoxal	2-Hydroxy-3-isopropyl-5-methyl	362
	Diacetyl	2-Hydroxy-3-isopropyl-5,6-dimethyl	362
	Benzil	2-Hydroxy-3-isopropyl-5,6-diphenyl	362
α-Amino-β-methyl-pentanamide	Glyoxal	2-*s*-Butyl-3-hydroxy	80
α-Amino-γ-methyl-pentanamide	Glyoxal	2-Hydroxy-3-isobutyl	60, 80, 367
	Methylglyoxal	2-Hydroxy-3-isobutyl-5(and 6)-methyl	368
	Diacetyl	2-Hydroxy-3-isobutyl-5,6-dimethyl	368
α-Aminooctanamide	Glyoxal	2-Hexyl-3-hydroxy	367
Aminomalonamide	Glyoxal	2-Carbamoyl-3-hydroxy	361, 369, 370
	Methylglyoxal	2-Carbamoyl-3-hydroxy-5-methyl	361, 369, 371, 372
	Methylglyoxal	2-Carbamoyl-3-hydroxy-5(and 6)-methyl	373
	Diacetyl	2-Carbamoyl-3-hydroxy-5,6-dimethyl	361, 369, 374
	Phenylglyoxal	3-Carbamoyl-2-hydroxy-5-phenyl and 6-phenyl isomer	361 365a
	Phenylglyoxal	2-Carbamoyl-3-hydroxy-5-phenyl	375

TABLE II.8 *Continued*

α,β-Diamine	α,β-Dicarbonyl Compound	Pyrazine	Refs.
	Benzil	2-Carbamoyl-3-hydroxy-5,6-diphenyl	361
	Ethyl pyruvate	2-Carbamoyl-3,6(5)-dihydroxy-5(6)-methyl	369
α-Aminoacetamidine	Glyoxal	2-Amino	376
	Methylglyoxal	2-Amino-5-methyl	376
	Ethylglyoxal	2-Amino-5-ethyl	376
	Phenylglyoxal	2-Amino-5-phenyl	376, 377
	Diacetyl	5-Amino-2,3-dimethyl	376
	3-Indolylglyoxal	2-Amino-5-(indol-3'-yl)	377
α-Amidino-α-amino-acetamide[e]	Glyoxal	2-Amino-3-carbamoyl	378
	Pyruvaldehyde	2-Amino-3-carbamoyl-5-methyl	378
	Phenylglyoxal	2-Amino-3-carbamoyl-5-phenyl	378
	Cyclohexylglyoxal	2-Amino-3-carbamoyl-5-cyclohexyl	378a
	Diacetyl	2-Amino-3-carbamoyl-5,6-dimethyl	378
α-Amino-α-(benzyl-amidino)acetamide[e]	Glyoxal	2-Benzylamino-3-carbamoyl	379
	Diacetyl	2-Benzylamino-3-carbamoyl-5,6-dimethyl	379
	Benzil	2-Benzylamino-3-carbamoyl-5,6-diphenyl	379
α-Amino-α-(cyclohexyl-amidino)acetamide	Glyoxal	2-Carbamoyl-3-cyclohexyl-amino	379
	Diacetyl	2-Carbamoyl-3-cyclohexyl-amino-5,6-dimethyl	379
	Benzil	2-Carbamoyl-3-cyclohexyl-amino-5,6-diphenyl	379
Glycyl-L-leucine	Glyoxal	1-(1'-Carboxy-3'-methyl-butyl)-2-oxo-1,2-dihydro	380
Other dipeptides	Glyoxal	Corresponding compounds	381
Tripeptides	Glyoxal	3-Alkyl-2-oxo-1-substituted-1,2-dihydro	382
Tetrapeptides	Glyoxal	3-Alkyl-2-oxo-1-substituted-1,2-dihydro	382

[a] H. Bredereck and G. Schmötzer, *Annalen*, 1956, **600**, 95, have described the preparation from the tetramer of hydrocyanic acid with *p,p'*-dibromobenzil and *p,p'*-diphenoxybenzil of 2,3-di(*p*-bromophenyl)-5,6-dicyanopyrazine and 2,3-dicyano-5,6-di(*p*-phenoxyphenyl)pyrazine, which are described in Section IX.4A(1), as well as with phosgene in dioxane of 2,3-dicyano-5,6-dihydroxypyrazine.

[b] M. E. Hultquist, U.S. Pat. 2,805,223 through *Chem. Abs.*, 1958, **52**, 2935, has described similar preparations from α-aminonitriles; e.g., glycine nitrile with glyoxal in 50% sodium hydroxide gave 2-hydroxypyrazine and this is more fully discussed in Section VI.1A.

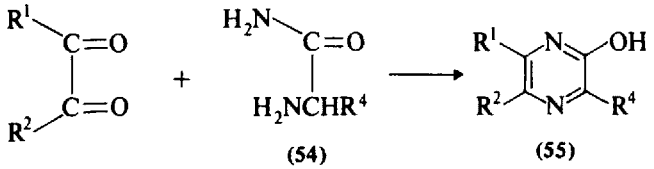
[c] T. Konakahara and Y. Takagi, *Heterocycles*, 1978, **9**, 1733, have examined the effects of reaction temperature and alkali-addition velocity on the yield of 2-hydroxypyrazine from this reaction.

TABLE II.8 *Continued*

[d] J. Maguire, D. Paton, and F. L. Rose, *J. Chem. Soc.* (*C*), 1969, 1593 have succeeded in isolating 2-hydroxy-6-methyl-3-propylpyrazine (3-hydroxy-5-methyl-2-propylpyrazine) from this reaction.

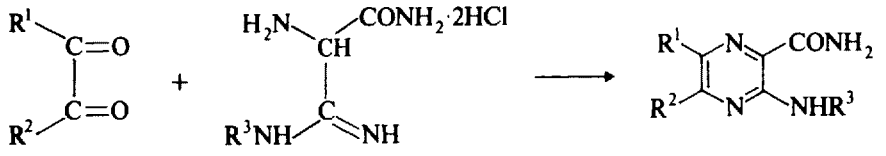
[e] E. J. Cragoe, Belg. Pat. 639,393 through *Chem. Abs.*, 1965, **62**, 7779 and E. J. Cragoe and P. L. Southwick, U.S. Pat. 3,268,406 through *Chem. Abs.*, 1967, **66**, 2585, report the condensation of trifluoromethyl dibromomethyl ketone with α-aminomalondiamidine in aqueous sodium acetate to give 2-amino-3-carbamoyl-5-trifluoromethylpyrazine; J. B. Bicking, C. M. Robb, S. F. Kwong, and E. J. Cragoe, *J. Med. Chem.*, 1967, **10**, 598 also isolated 3-amino-2-carbamoyl-5-trifluoromethylpyrazine rather similarly and condensed α-amidino-α-aminoacetamide with ethylglyoxal, cyclopropylglyoxal, cyclohexylglyoxal, and *p*-chlorophenylglyoxal to give 2-amino-3-carbamoyl-5-ethyl(cyclopropyl, cyclohexyl, and *p*-chlorophenyl)-pyrazines, respectively.

hydroxypyrazine (**55**, $R^1 = R^2 = H$; $R^4 = CONH_2$) and α-aminoacetamide and glyoxal gave 2-hydroxypyrazine. A further extension of this reaction, involving the use of the more convenient α-amino acid amide hydrohalides, was described by Karmas and Spoerri (362).



(54) (55)

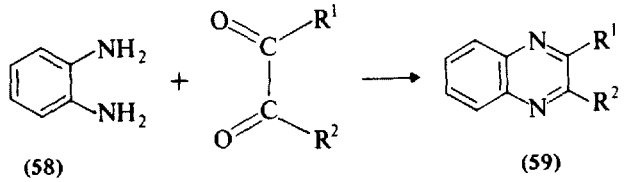
Vogl and Taylor (378) first utilized the reaction of amidines, namely, α-amidino-α-aminoacetamide dihydrochloride (**56**, $R^3 = H$) with α,β-dicarbonyl compounds to give 2-amino-3-carbamoylpyrazines (**57**, $R^3 = H$).



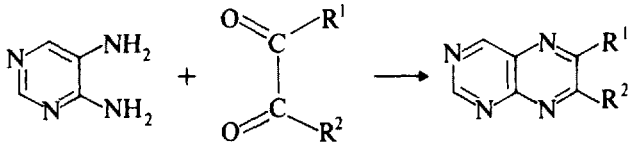
(56) (57)

Methylglyoxal and phenylglyoxal gave exclusively 5-substituted-2-amino-3-carbamoylpyrazines. This reaction was extended to aminoacetamidine by Pitré and Boveri (376), to give a series of 2-aminopyrazines, and to α-(substituted amidino)-α-aminoacetamide monohydrochlorides by Keir et al. (379) to provide 3-(substituted amino)-2-carbamoylpyrazine (**57**).

The condensation of α,β-diamino compounds with α,β-dicarbonyl compounds has been extensively used for the synthesis of quinoxaline (**59**) and pteridines (**61**) from *o*-phenylenediamine (**58**) and 4,5-diaminopyrimidines (**60**), respectively.



(58) (59)



(60) (61)

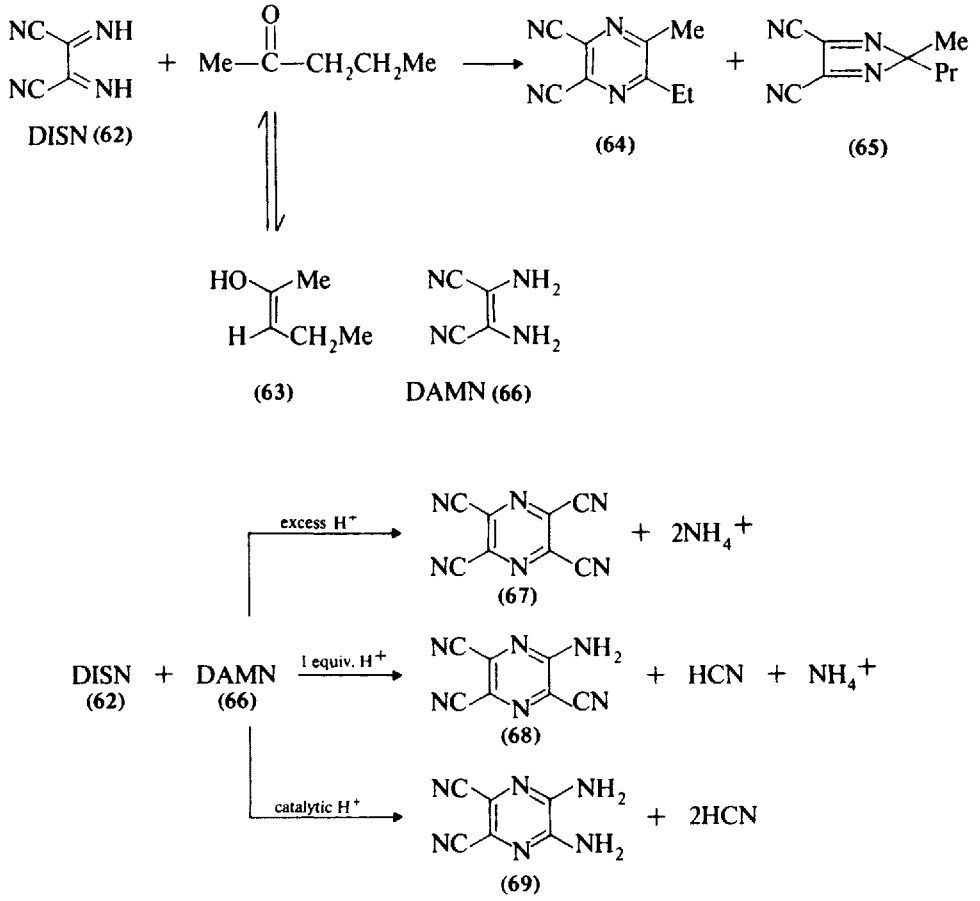
Both these series of bicyclic compounds have been used as important starting materials for the preparation of pyrazines by the oxidative removal of the benzene ring from quinoxaline and by cleavage of the pyrimidine ring in pteridines. Both preparative procedures are discussed in detail in Sections 4 and 5.

The reactions of glyoxal at 100° and pH 5 with dipeptides (380, 381) and tri- and tetrapeptides (382) to give some 2-oxo-1,2-dihydropyrazines are summarized in Table II.8 and discussed in greater detail in Section 7.

3. PYRAZINES FROM α,β-DIAMINO OR α,β-DIIMINO COMPOUNDS AND REAGENTS OTHER THAN α,β-DICARBONYL COMPOUNDS

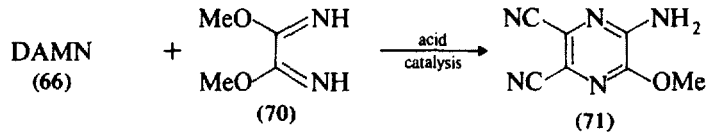
The condensation reactions of diaminomaleonitrile, DAMN (66), and diiminosuccinonitrile, DISN (62) (both derived from HCN), with appropriate reagents other than α,β-dicarbonyl compounds have been studied extensively by Begland et al. (383–386). Thus condensation of DISN (62) with 2-pentanone (63) gave a small amount of 2,3-dicyano-5-ethyl-6-methylpyrazine (64) together with an imidazole (65). The pyrazine is formed presumably by the cycloaddition of the enol tautomer of 2-pentanone (63) with the DISN. Use of 2-butanone gave 2,3-dicyano-5,6-dimethylpyrazine (383). DAMN condenses with DISN to give tetracyanopyrazine (67), aminotricyanopyrazine (68), and 2,3-diamino-5,6-dicyanopyrazine (69) (158, 384). By varying the conditions (summarized schematically below), any one of these tetrafunctional pyrazines can be the major product. The condensation of DISN with DAMN has been shown to be analogous to the condensation of DISN with *o*-phenylenediamine (383); it is strongly acid catalyzed, presumably because of protonation of the DISN; and an acid medium promotes the loss of ammonia from the intermediates. DAMN and DISN form linear 1:1 and 2:1 adducts under other conditions and the 1:1 adduct can be cyclized to the pyrazines. DISN reacts with one molecule of water to form an intermediate, probably iminooxalyl cyanide, which condenses with DAMN to give 2-amino-5,6-

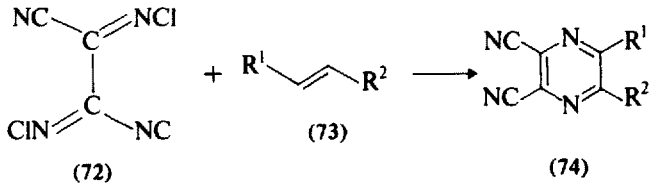
dicyano-3-hydroxypyrazine (384). Two moles of water hydrolyze DISN to oxalyl cyanide, which condenses with DAMN to give tetracyanopyrazine under acidic conditions and 2,3-dicyano-5,6-dihydroxypyrazine under neutral conditions.

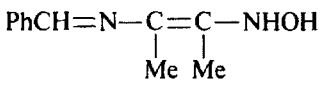


The condensation of DAMN with 1,2-diimino-1,2-dimethoxyethane (**70**) gives 2-amino-5,6-dicyano-3-methoxypyrazine (**71**) (385), but as in the condensation of DAMN with DISN the control of acid concentration is critical. The condensation of DAMN with chloroacetone or pyruvaldehyde has been shown to give 2,3-dicyano-5-methylpyrazine (385) and DAMN with methylsulfinylmethyl phenyl ketone refluxed in ethanol gave 2,3-dicyano-5-phenylpyrazine (386a). *N,N'*-Dichlorodiiminosuccinonitrile (Cl_2DISN) (**72**) reacts with some olefins to give pyrazines. Thus with styrene (**73**, R^1 = Ph, R^2 = H) in benzene it gave 2,3-dicyano-5-phenylpyrazine (**74**, R^1 = Ph, R^2 = H). Similar reactions were observed with β-methylstyrene and 2,3-dihydropyran (387).

2-Benzalamino-3-hydroxyaminobut-2-ene (**75**) when heated with acetic anhydride and potassium carbonate gave tetramethylpyrazine (388).

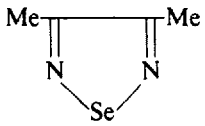






(75)

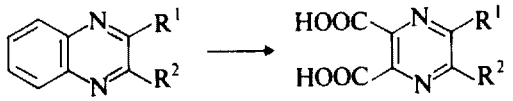
Pyrazines have been prepared from α,β-diamines (such as ethylenediamine or propylenediamine) with ethyleneglycol, propyleneglycol, 1,2-epoxides, or formaldehyde, over catalysts at elevated temperatures (389–394b). Stilbenediamine [$PhCH(NH_2)CH(NH_2)Ph$] and benzaldehyde heated at 180–200° have been shown to give tetraphenylpyrazine (395); and benzylidenediaminomaleonitrile with benzaldehyde and triethylamine in ethanol followed by heating in dimethyl sulfoxide at 80° gave 5-carbamoyl-6-cyano-2,3-diphenyl-1,2-dihydropyrazine (88%) and 6-carbamoyl-5-cyano-2,3-diphenyl-1,2-dihydropyrazine (10%) (395a). Treatment of 3,4-dimethyl-1,2,5-selenadiazole (**76**) (from dimethylglyoxime and selenium dioxide in dimethylformamide) with hydrogen sulfide gave tetramethylpyrazine (396).



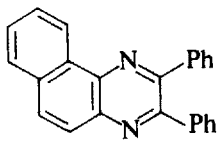
(76)

4. OXIDATION OF QUINOXALINES AND OTHER FUSED PYRAZINES TO PYRAZINECARBOXYLIC ACIDS

The pyrazine ring is relatively stable to oxidation, and many pyrazine-carboxylic acids have been prepared from quinoxalines, phenazines, and other fused pyrazines by oxidation with potassium permanganate. This reaction has been most used for the oxidation of quinoxalines, for example, 77 → 78. The oxidations are usually carried out with potassium permanganate in alkali (397), but may also be effected without added base (398). Crippa and Perroncito (399) have also used chromic oxide in acetic acid–acetic anhydride to oxidize benzo[*f*]quinoxalines (**79**). Pyrazines prepared by this method are summarized in Table II.9 (397–419).



(77) (78)



(79)

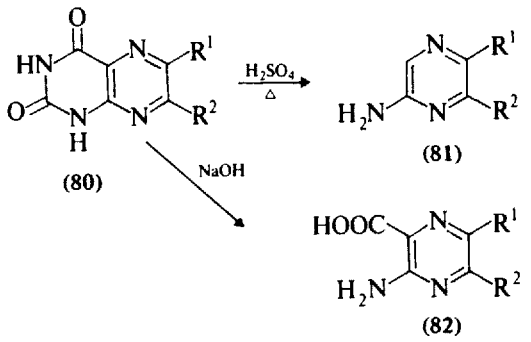
TABLE II.9 PYRAZINECARBOXYLIC ACIDS PREPARED BY THE OXIDATION OF QUINOXALINES, PHENAZINES, AND OTHER FUSED PYRAZINES

Fused Pyrazine	Pyrazinecarboxylic Acid	Refs.
Quinoxaline	2,3-Dicarboxy	397, 398, 400–402
2-Methylquinoxaline	2,3-Dicarboxy-5-methyl	398, 403–405
2,3-Dimethylquinoxaline	2,3-Dicarboxy-5,6-dimethyl	397, 403
3-Phenylbenzo[*f*]quinoxaline-5,6-quinone	3-Carboxy-2(*o*-carboxyphenyl)-5-phenyl	406
2,3-Diphenylbenzo[*f*]quinoxaline (and 5,6-quinone)	2-Carboxy-3(*o*-carboxyphenyl)-5,6-diphenyl	399
2-Carboxymethylbenzo[*f*]quinoxaline	3-Carboxy-5-carboxymethyl-2(*o*-carboxyphenyl)	407
2-Acetamidoquinoxaline	5-Acetamido-2,3-dicarboxy	408
2,3-Dichloroquinoxaline	2,3-Dicarboxy-5,6-dichloro	409
2-Ethoxymethyl quinoxaline	Tricarboxy	410
2-(D-*arabo*-Tetrahydroxybutyl)quinoxaline	Tricarboxy	411, 412
2,3-Dicarboxyquinoxaline	Tetracarboxy	413
Phenazine	Tetracarboxy	414
2-Amino-3-hydroxyphenazine	Tetracarboxy	415
2,3-Diaminophenazine	Tetracarboxy	415
Nitrophenazines	Tetracarboxy	416
1,3-Dibenzoyl-2-oxocyclopenteno[4,5-*b*]-quinoxaline	Tetracarboxy	417
Pyrazino[*d*,*d'*]ditroponemonoiminemonoxime	Tetracarboxy	418
Pyrido[3,4-*b*]pyrazine	2,3-Dicarboxy	419
2,3-Dimethylpyrido[3,4-*b*]pyrazine	2,3-Dicarboxy-5,6-dimethyl	419

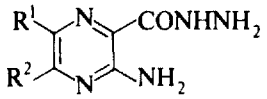
5. CLEAVAGE OF PTERIDINES AND RELATED SYSTEMS TO PYRAZINES

The pyrimidine ring in many pteridines may be cleaved by acid, alkali, and various other nucleophiles to yield pyrazines; the severity of the reaction con-

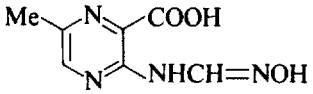
ditions often determines the identity of the products. Weijlard et al. (420) first described the preparation of 2-aminopyrazine as well as its 5- and 6-alkyl(or aryl)-substituted derivatives (**81**) by heating (> 190°) the corresponding lumazines (2,4-dihydroxypteridines; **80**) with sulfuric acid. The concentration of sulfuric acid was important in the cleavage of the lumazines; and for the parent, lumazine, 100% sulfuric acid was found best, whereas for methyl or phenyl derivatives, 80% sulfuric acid gave optimum yields. Lumazines were also found to be cleaved by approximately 12% alkali at 170° for 2 hours and the products were derivatives of 2-amino-3-carboxypyrazine (**82**), which were readily decarboxylated to aminopyrazines. Under more severe reaction conditions lumazine gave 2-carboxy-3-hydroxypyrazine.



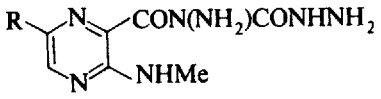
Since these initial studies many workers have examined the ring opening reactions of pteridines generally, and ring cleavage reactions are now much used for the synthesis of pyrazines beginning from 4,5-diaminopyrimidines and proceeding through the relevant pteridine. Albert and co-workers (421–423) examined the reactions of pteridines and 4-hydroxypteridines with dilute acid and alkali. This work has been extended more recently by Clark and co-workers to a detailed study of the ring opening reactions of some 4-hydroxypteridine derivatives with hydrazine to give mixtures of a 4,5-diaminopyrimidine and a 2-amino-3-hydrazinocarbonylpyrazine (**83**) (424) and the reaction of 4-hydroxy-6-methylpteridine with hydroxylamine to give some 3-carboxy-2-hydroxyiminomethylamino-5-methylpyrazine (**84**) (425). Clark et al. also studied the reactions of 4-hydroxypteridines with methoxyamine and methylhydrazines (426, 427) to give pyrimidines and pyrazines and the reactions of some 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridines with hydrazine to give 2-[*N*-amino-*N*-(hydrazinocarbonyl)carbamoyl]-3-methylaminopyrazines (**85**) (428).



(**83**)



(**84**)



(85)

Details of these ring opening reactions of polycyclic compounds to give pyrazines are given in Table II.10 (375, 420–463a) and some additional data are recorded in Sections VI.1A, VII.1C, and VIII.1A(1).

TABLE II.10 CLEAVAGE OF PTERIDINES AND RELATED SYSTEMS TO PYRAZINES

Pteridine or Related System	Reagent	Pyrazine(s)	Refs.
Pteridine	N H_2SO_4	2-Amino3-formyl	423
4-Methylpteridine	0.5 N H_2SO_4	2-Acetyl-3-aminomethylene-amino	423
4-Hydroxypteridine	N H_2SO_4	2-Amino and 2-amino-3-carboxy (trace amide)	422
4-Hydroxypteridine	N H_2SO_4	2-Amino-3-carbamoyl and 2-amino-3-carboxy	421
2,4-Dihydroxypteridine (Lumazine)	H_2SO_4	2-Amino	420
2,4-Dihydroxy-7-methyl-pteridine	H_2SO_4	2-Amino-6-methyl	420
2,4-Dihydroxy-6,7-dimethyl-pteridine	H_2SO_4	5-Amino-2,3-dimethyl	420
2,4-Dihydroxy-6(or 7)-phenylpteridine	H_2SO_4	2-Amino-5(or 6)-phenyl	420
2,4-Dihydroxy-6,7-diphenylpteridine	H_2SO_4	5-Amino-2,3-diphenyl	420
2-Amino-4-hydroxy-6-phenylpteridine	H_2SO_4/EtOH	3-Ethoxycarbonyl-2-hydroxy-5-phenyl	429
7-Chloropteridine	0.1 N HCl	5-Chloro-3-formamido-2-formyl	430
7-Chloropteridine	0.1 N H_2SO_4	3-Amino-5-chloro-2-formyl	430
6,7-Dichloropteridine	0.1 N HCl	2,3-Dichloro-5-formamido-6-formyl	430
6,7-Dichloropteridine	0.1 N H_2SO_4	2-Amino-5,6-dichloro-3-formyl	430
6-Chloropteridine	pH 4	5-Chloro-2-formamido-3-formyl	430
6-Chloropteridine	pH 3.3	2-Amino-5-chloro-3-formyl	430
4-Hydroxypteridine	NaOH	2-Amino-3-carboxy	421, 422, 424
4-Hydroxy-2-methylpteridine	NaOH	2-Amino-3-carboxy	424
4-Hydroxy-6-methylpteridine	NaOH	2-Amino-3-carboxy-5-methyl	421, 424
4-Hydroxy-7-methylpteridine	NaOH	3-Amino-2-carboxy-5-methyl	421, 424
4-Hydroxy-2,6-dimethyl-pteridine	NaOH	2-Amino-3-carboxy-5-methyl	424
4-Hydroxy-2,7-dimethyl-pteridine	NaOH	3-Amino-2-carboxy-5-methyl	424
4-Hydroxy-6,7-dimethyl-pteridine	NaOH	2-Amino-3-carboxy-5,6-dimethyl	424, 431

TABLE II.10 *Continued*

Pteridine or Related System	Reagent	Pyrazine(s)	Refs.
4-Hydroxy-2,6,7-trimethyl-pteridine	NaOH	2-Amino-3-carboxy-5,6-dimethyl	424
4-Hydroxy-6-methylthio-pteridine	NaOH	2-Amino-3-carboxy-5-methylthio	432, 432a
6-Benzylthio-4-hydroxy-pteridine	NaOH	2-Amino-5-benzylthio-3-carboxy	432, 432a
6-Dimethylamino-4-hydroxy-pteridine	NaOH	2-Amino-5-dimethylamino	432
2,4-Dihydroxypteridine[a]	NaOH	2-Amino-3-carboxy	420
2,4-Dihydroxypteridine	NaOH	2-Carboxy-3-hydroxy	420, 433, 433a
2,4-Dihydroxy-7-methyl-pteridine	NaOH/170°	3-Amino-2-carboxy-5-methyl	420, 433
2,4-Dihydroxy-7-methyl-pteridine	NaOH/190°	2-Carboxy-3-hydroxy-5-methyl and 3-amino-2-carboxy-5-methyl	434
2,4-Dihydroxy-6,7-dimethyl-pteridine	NaOH	2-Amino-3-carboxy-5,6-dimethyl	420, 433
2,4-Dihydroxy-6,7-diphenyl-pteridine	NaOH	2-Amino-3-carboxy-5,6-diphenyl	420, 433
1-Methyl-4-oxo-1,4-dihydro pteridine	NaOH	2-Carbamoyl-3-methylamino	423
3-Methyl-4-oxo-3,4-dihydropteridine	NaOH	2-Amino-3-methylcarbamoyl and 2-amino-3-carboxy	423
3,7-Dimethyl-4-oxo-3,4-dihydropteridine	*N* NaOH	3-Amino-5-methyl-2-(*N*-methyl-carbamoyl) and 3-amino-2-carboxy-5-methyl	435
3,7-Dimethyl-4-oxo-3,4-dihydropteridine	Pyridine–water	3-Formamido-5-methyl-2-(*N*-methylcarbamoyl)	435
6-Dimethylamino-3-methyl-4-oxo-3,4-dihydropteridine	NaOH	2-Amino-3-carboxy-5-dimethylamino	432
6-Methoxy-3-methyl-4-oxo-3,4-dihydropteridine	NaOH	2-Amino-3-carboxy-5-methoxy	432
3-Methyl-4-oxo-6-piperidino-3,4-dihydropteridine	NaOH	2-Amino-3-carboxy-5-piperidino	432
3-Methyl-6-isopropylamino-4-oxo-3,4-dihydropteridine	NaOH	2-Amino-3-carboxy-5-isopropylamino	432
6-Benzylamino-3-methyl-4-oxo-3,4-dihydropteridine	NaOH	2-Amino-5-benzylamino-3-carboxy	432
3-(2'-Cyanoethyl)-7-methyl-4-oxo-3,4-dihydro-pteridine	*N* NaOH	3-Amino-2-cyanoethyl carbamoyl-5-methyl and 3-amino-2-carboxy-5-methyl	435
3-Benzyl-4-oxo-5,6-diphenyl-3,4-dihydropteridine	KOH	2-Amino-3-*N*-benzyl-carbamoyl-5,6-diphenyl	436
1,3,6,7-Tetramethyl-4-oxo-3,4-dihydropteridinium salt	NaOH	2,3-Dimethyl-5-methylamino-6-methylcarbamoyl	437
1,3-Dimethyl-4-oxo-6,7-diphenyl-3,4-dihydro-pteridinium salt	NaOH	2-Methylamino-3-methyl-carbamoyl-5,6-diphenyl	437, 438

TABLE II.10 *Continued*

Pteridine or Related System	Reagent	Pyrazine(s)	Refs.
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	*N* NaOH	2-Methylamino-3-methylcarbamoyl	423
1,3-Dimethyl-2,4-dioxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	0.1*N* NaOH	2-Methylamino-3-methylcarbamoyl-5,6-diphenyl	439
3-Methyl-2,4-dioxo-6,7-diphenyl-1,2,3,4-tetrahydropteridine	0.1*N* NaOH	2-Amino-3-methylcarbamoyl-5,6-diphenyl	439
6-Hydroxy-1,3-dimethyl-7-methylcarbamoyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	*N* NaOH	2-Hydroxy-5-methylamino-3,6-bismethylcarbamoyl and 2-carboxy-3-hydroxy-6-methylamino-5-methylcarbamoyl	440
7-Hydroxy-1,3-dimethyl-6-methylcarbamoyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	*N* NaOH	2-Hydroxy-6-methylamino-3,5-bismethylcarbamoyl	440
6-Carboxy-7-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	NaOH	2-Carboxy-3-hydroxy-5-methylamino-6-methylcarbamoyl	441
7-Hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	NaOH	5-Hydroxy-3-methylamino-2-methylcarbamoyl	441
6-Carboxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	NaOH	5-Carboxy-2-methylamino-3-methylcarbamoyl	442
1,3-Bis(2′-cyanoethyl)-6,7-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	NaOH	2-(2′-Cyanoethylamino)-3-cyanoethylcarbamoyl-5,6-dimethyl	443
1,3-Bis(2′-cyanoethyl)-6,7-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	NaOH	2-Carboxy-3-(2′-carboxyethylamino)-5,6-dimethyl	443
1,3,6,7-Tetramethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	NaOH	2,3-Dimethyl-5-methylamino-6-methylcarbamoyl	443
1,3-Dimethyl-7-methylamino-6(*N*-methylcarbamoyl)-2,4-dioxo-1,2,3,4-tetrahydropteridine	*N* NaOH	2,6-Bis(methylamino)-3,5-bis(*N*-methylcarbamoyl)	444
7(2′-Carboxyprop-1′-enyl)-6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	*N* NaOH	2(2′-Carboxyprop-1′-enyl)-3-hydroxy-6-methylamino-5-methylcarbamoyl	445
7-Hydroxy-1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	2*N* NaOH	2-Hydroxy-3-methyl-6-methylamino-5-methylcarbamoyl	445
2-Amino-4-hydroxy-6-methylpteridine	10*N* NaOH	2-Amino-3-carboxy-5-methyl	446
2-Amino-4-hydroxy-7-methylpteridine	NaOH	3-Amino-2-carboxy-5-methyl	446a

TABLE II.10 *Continued*

Pteridine or Related System	Reagent	Pyrazine(s)	Refs.
2-Amino-4-hydroxy-6-phenylpteridine	4 *N* NaOH	3-Carboxy-2-hydroxy-5-phenyl	429
2-Amino-4-hydroxy-7-phenylpteridine	4 *N* NaOH	3-Amino-2-carboxy-5-phenyl and 2-carboxy-3-hydroxy-5-phenyl	429
2,4-Diamino-7-methylpteridine	NaOH	3-Amino-2-carboxy-5-methyl	447
4-Imino-1-methyl-1,4-dihydropteridine hydriodide	2.5 *N* NaOH	2-Amidino-3-methylamino	431
4-Imino-1-methyl-1,4-dihydropteridine	*N* NaOH	2-Carbamoyl-3-methylamino	431
4-Imino-1,6,7-trimethyl-1,4-dihydropteridine hydriodide	2.5 *N* NaOH	2-Amidino-5,6-dimethyl-3-methylamino	431
1-Methyl-4-methylimino-1,4-dihydropteridine	*N* NaOH	2-Carbamoyl-3-methylamino	431
4-Dimethylamino-1-methylpteridinium iodide	pH 10	2-Carbamoyl-3-methylamino	431
1,6,7-Trimethyl-4-methylimino-1,4-dihydropteridine iodide	*N* NaOH	2-Carbamoyl-5,6-dimethyl-3-methylamino	431
7-Imino-1-methyl-1,7-dihydropteridine hydriodide	*N* NaOH	2-Formyl-5-hydroxy-3-methylamino	448
7-Imino-3-methyl-3,7-dihydropteridine hydriodide	*N* NaOH	3-Amino-2-formyl-5-hydroxy	448
7-Imino-3-methyl-3,7-dihydropteridine hydriodide	pH 4.0	3,5-Diamino-2-formyl	448
4(7)-Amino-7(4)-imino-1-methyl-1,7(1,4)-dihydropteridine hydriodide	*N* NaOH	5-Amino-2-carbamoyl-3-methylamino	448
7-Amino-1-methyl-4-oxo-1,4-dihydropteridine	*N* NaOH	5-Amino-2-carbamoyl-3-methylamino	448
4-Amino-1-methyl-7-oxo-1,7-dihydropteridine	*N* NaOH	2-Carbamoyl-5-hydroxy-3-methylamino	449
7-Methoxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine 5-oxide	0.1 *N* KOH	5-Methoxy-3-methylamino-2-methylcarbamoylpyrazine 1-oxide and corresponding 7-hydroxy pteridine 5-oxide	450
1,3-Dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropteridine	0.1 *N* KOH/EtOH	3-Methylamino-2-methylcarbamoyl-5-phenyl	375
1,3-Dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropteridine	NaOH/EtOH 200°	2-Carboxy-3-methylamino-5-phenyl	375
1,3-Dimethyl-2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropteridine	0.1 *N* KOH/EtOH	2-Methylamino-3-methylcarbamoyl-5-phenyl	375
1,3,-Dimethyl-2,4-dioxo-6 phenyl-1,2,3,4-tetrahydropteridine	NaOH/EtOH 140°	3-Carboxy-2-methylamino-5-phenyl	375

TABLE II.10 *Continued*

Pteridine or Related System	Reagent	Pyrazine(s)	Refs.
2-Amino-4-hydroxy-6-phenyl-pteridine	4 *N* NaOH	3-Carboxy-2-hydroxy-5-phenyl	375
2,4-Dihydroxy-6,7-diphenyl-pteridine	NH_4OH	2-Amino-3-carbamoyl-5,6-diphenyl	451
4-Aminopteridine	NH_4OH/170°	2-Amino-3-carboxy	452
1,3-Dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydro-pteridine	NH_3/EtOH/210°	2-Carbamoyl-3-methylamino-5-phenyl	453
Pteridine	2 *N* Na_2CO_3	2-Aminomethyleneamino-3-formyl	423
3-Methyl-7-oxo-3,7-dihydro-pteridine	2 *N* Na_2CO_3	3-Amino-2-formyl-5-hydroxy	449
4-Mercaptopteridine	$ClCH_2COOH$ and K_2CO_3	2-Amino-3-cyano	454
4-Methylthiopteridine	*N* $NaCO_3$	2-Amino-3-cyano and 2-amino-3-carbamoyl	454
4-Mercapto-6,7-diphenyl-pteridine	$ClCH_2COOH$ and K_2CO_3	2-Amino-3-cyano-5,6-diphenyl	454
4-Hydroxypteridine	NH_2NH_2	2-Amino-3-hydrazinocarbonyl	424
4-Hydroxy-2-methylpteridine	NH_2NH_2	2-Amino-3-hydrazinocarbonyl	424
4-Hydroxy-6-methylpteridine	NH_2NH_2	2-Amino-3-hydrazinocarbonyl-5-methyl and isopropylidene derivative	424
4-Hydroxy-7-methylpteridine	NH_2NH_2	3-Amino-2-hydrazinocarbonyl-5-methyl	424
4-Hydroxy-2,6-dimethyl-pteridine	NH_2NH_2	2-Amino-3-hydrazinocarbonyl-5-methyl (as isopropylidene derivative)	424
4-Hydroxy-2,7-dimethyl-pteridine	NH_2NH_2	3-Amino-2-hydrazinocarbonyl-5-methyl	424
4-Hydroxy-6,7-dimethyl-pteridine	NH_2NH_2	2-Amino-3-hydrazinocarbonyl-5,6-dimethyl	424
4-Hydroxy-2,6,7-trimethyl-pteridine	NH_2NH_2	2-Amino-3-hydrazinocarbonyl-5,6-dimethyl	424
2,4-Dihydroxy-6,7-diphenyl-pteridine	NH_2NH_2	2-Amino-3-hydrazinocarbonyl-5,6-diphenyl	451
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	NH_2NH_2	2-[*N*-Amino-*N*-hydrazino-carbonyl(carbamoyl)]-3-methylamino	428
1,3,7-Trimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine	NH_2NH_2/ propan-2-ol	Isopropylidene derivative of 2[*N*-amino-*N*-hydrazino-carbonyl(carbamoyl)]-5-methyl-3-methylamino	428
1,3,6,7-Tetramethyl-2,4-dioxo-1,2,3,4-tetrahydro-pteridine	NH_2NH_2	2-Hydrazinocarbonyl-5,6-dimethyl-3-methylamino	428
1,3-Dimethyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydro-pteridine	NH_2NH_2	2-Hydrazinocarbonyl-3-methylamino-5-phenyl	453
4-Aminopteridine	NH_2NH_2	2-(*N*-Aminoamidino)-3-aminomethyleneamino	452

TABLE II.10 *Continued*

Pteridine or Related System	Reagent	Pyrazine(s)	Refs.
4-Hydroxypteridine	H_2NNHMe	2-Amino-3-(β-methylhydrazino)carbonyl	426
4-Hydroxy-7-methylpteridine	H_2NNHMe	3-Amino-5-methyl-2-(β-methylhydrazino)carbonyl	426
4-Hydroxypteridine	H_2NNMe_2	2-Amino-3-(β,β-dimethylhydrazino)carbonyl and 2-amino-3-carbamoyl	426
4-Hydroxy-2-methylpteridine	H_2NNMe_2	2-Amino-3-(β,β-dimethylhydrazino)carbonyl and 2-amino-3-carbamoyl	426
4-Hydroxy-6-methylpteridine	H_2NNMe_2	2-Amino-3-(β,β-dimethylhydrazino)carbonyl-5-methyl	426
4-Hydroxy-7-methylpteridine	H_2NNMe_2	3-Amino-2-(β,β-dimethylhydrazino)carbonyl-5-methyl and 3-amino-2-carbamoyl-5-methyl	426
4-Hydroxy-2,7-dimethylpteridine	H_2NNMe_2	2-Amino-3-(β,β-dimethylhydrazino)carbonyl-5-methyl	426
4-Hydroxy-6,7-dimethylpteridine	H_2NNMe_2	2-Amino-3-(β,β-dimethylhydrazino)carbonyl-5,6-dimethyl and 2-amino-3-carbamoyl-5,6-dimethyl	426
4-Hydroxy-6-methylpteridine	NH_2OH	3-Carboxy-2-hydroxyimino-methylamino-5-methyl	425
4-Hydroxypteridine	H_2NOMe	2-Methoxycarbamoyl-3-methoxyiminomethylamino	426, 427
4-Hydroxy-6-methylpteridine	H_2NOMe	3-Methoxycarbamoyl-2-methoxyiminomethyl amino-5-methyl	426, 427
4-Hydroxy-7-methylpteridine	H_2NOMe	2-Methoxycarbamoyl-3-methoxyiminomethyl-amino-5-methyl	426, 427
4-Hydroxy-6,7-dimethylpteridine	H_2NOMe	2-Amino-3-methoxy-carbamoyl-5,6-dimethyl	426, 427
4-Hydroxy-6,7-dimethylpteridine	H_2NOMe	2-Methoxycarbamoyl-3-methoxyiminomethylamino-5,6-dimethyl (at pH 7.5)	427
4-Hydroxy-2,7-dimethylpteridine	H_2NOMe	3-Amino-2-methoxy-carbamoyl-5-methyl	426, 427
4-Hydroxypteridine	$PhCH_2NH_2$	2-Amino-3-carbamoyl and 2-amino-3-benzylcarbamoyl	426
4-Hydroxypteridine	Morpholine	2-Amino-3-carbamoyl and 2-amino-3-morpholino-carbonyl	426
2,4-Dihydroxy-6,7-diphenylpteridine	$PhCH_2NH_2$	2-Benzylcarbamoyl-3-(3'-benzylureido)-5,6-diphenyl and 2-amino-3-benzyl-carbamoyl-5,6-diphenyl	451

TABLE II.10 *Continued*

Pteridine or Related System	Reagent	Pyrazine(s)	Refs.
2,4-Dihydroxy-6,7-diphenylpteridine	Morpholine	2-Morpholinocarbonyl-3-morpholinocarbonylamino-5,6-diphenyl and 2-amino-3-morpholinocarbonyl-5,6-diphenyl	451
2,4-Dihydroxy-6,7-diphenylpteridine	Piperidine	2,3-Diphenyl-5-piperidinocarbonyl-6-piperidinocarbonylamino and 2-amino-5,6-diphenyl-3-piperidinocarbonyl	451
2,4-Dihydroxy-6,7-diphenylpteridine	$BuNH_2$	2-Amino-3(butylcarbamoyl)-5,6-diphenyl	455
1-Methyl-2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropteridine	$C_6H_5CH_2NH_2$	2-Benzylcarbamoyl-3-(*N*-benzylcarbamoyl-*N*-methylamino)-5-phenyl	453
2,4-Dihydroxy-6,7-diphenylpteridine	$HOCH_2CH_2NH_2$	2-Amino-3-(β-hydroxyethylcarbamoyl)-5,6-diphenyl	451
4-Aminopteridine	$ClCH_2CHO/H_2O$/pH 6–7/60°	2-Formamido-3-imidazol-2′-yl and 2-amino-3-(1-formylimidazol-2′-yl)	455a
4-Aminopteridine	$ClCH_2CHO/H_2O$/60°	2-Formamido-3-imidazol-2′-yl and 2-(2′-chloroethylideneamino)-3-imidazol-2′-yl	455a
4-Amino-6,7-dimethylpteridine	$ClCH_2CHO/H_2O$/60°	2-Formamido-3-imidazol-2′-yl-5,6-dimethyl	455a
4-Amino-2-methylpteridine	$ClCH_2CHO/H_2O$/60°	2-Acetamido-3-imidazol-2′-yl	455a
4-Amino-2,6,7-trimethylpteridine	$ClCH_2CHO/H_2O$/60°	2-Acetamido-3-imidazol-2′-yl-5,6-dimethyl	455a
5,6-Diphenylfurazano[3,4-*b*]pyrazine	H_2/Pd/C	2,3-Diamino-5,6-diphenyl	455b
5-Methyl-6-phenylfurazano[3,4-*b*]pyrazine	H_2/Pd/C	2,3-Diamino-5-methyl-6-phenyl	455b
5-Phenylfurazano[3,4-*b*]pyrazine	H_2/Pd/C	2,3-Diamino-5-phenyl	455b
6-Benzyl-2,3-dimethyl-5,7-diphenylpyrrolo[3,4-*b*]pyrazine	CrO_3–HOAc	2,3-Dibenzoyl-5,6-dimethyl	456
2-Ethylpyrazino[2,3-*d*]-[1,3]-oxazin-4-one	NH_4OH	2-Carbamoyl-3-propionamido	457
3-Hydroxypyrazolo[3,4-*b*]pyrazine	Raney Ni	2-Amino-3-carbamoyl	458
3-Hydroxy-5,6-dimethylpyrazolo[3,4-*b*]pyrazine	Raney Ni	2-Amino-3-carbamoyl-5,6-dimethyl	458, 459
3-Hydroxy-5,6-diphenylpyrazolo[3,4-*b*]pyrazine	Raney Ni	2-Amino-3-carbamoyl-5,6-diphenyl	458, 459
3-Hydroxy-1-methylpyrazolo[3,4-*b*]pyrazine	Raney Ni	2-Carbamoyl-3-methylamino	458, 459
3-Hydroxy-1-phenylpyrazolo[3,4-*b*]pyrazine	Raney Ni	2-Anilino-3-carbamoyl	458

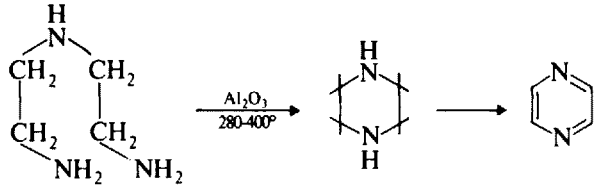
TABLE II.10 *Continued*

Pteridine or Related System	Reagent	Pyrazine(s)	Refs.
3-Hydroxy-2-phenylpyrazolo-[3,4-*b*]pyrazine	Raney Ni	2-Amino-3-(*N*-phenyl-carbamoyl)	458
1-Benzyl-3-hydroxypyrazolo-[3,4-*b*]pyrazine	Raney Ni	2-Benzylamino-3-carbamoyl	458
3-Hydroxy-5-methylpyrazolo-[3,4-*b*]pyrazine	Raney Ni	2-Amino-3-carbamoyl-5-methyl	458
3-Hydroxy-6-methylpyrazolo-[3,4-*b*]pyrazine	Raney Ni	3-Amino-2-carbamoyl-5-methyl	458
2,4,6,8-Tetrahydroxy-pyrimido[5,4-*g*]pteridine	NaOH	2,6-Diamino-3,5-dicarboxy	460
1,3,7,9-Tetramethyl-2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydropyrimido[5,4-*g*]-pteridine	NaOH	2,6-Bismethylamino-3,5-bis(*N*-methylcarbamoyl)	460
2,4,7,9-Tetrahydropyrimido-[4,5-*g*]pteridine	NaOH	2,5-Diamino-3,6-dicarboxy	461
1,3,6,8-Tetramethyl-2,4,7,9-tetraoxo-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]-pteridine	NaOH	2,5-Bismethylamino-3,6-bis(*N*-methylcarbamoyl)	461
1,3,6,8-Tetramethyl-2,4,5,7-tetraoxo-1,2,3,4,5,6,7,8-octahydropyrimido[5,4-*g*]-pteridine 10-oxide	NaOH	3,5-Bismethylamino-2,6-bismethylcarbamoylpyrazine 1-oxide and 2-carboxy-3,5-bismethylamino-6-methyl-carbamoylpyrazine 1-oxide	462
6-Benzamido-5-chloro-2-phenylpyrazino[2,3-*d*]-[1,3]oxazin-4-one	$H_2NSO_2NH_2$	2,6-Diamino-3-aminosulfonyl-carbamoyl-5-chloro	463
2-Methyl-6-R-4*H*-pyrazino-[2,3-*d*][1,3]oxazin-4-ones (where R = MeS, $MeSO_2$, $PhCH_2S$, Me_2N, MeO, Piperidino, Pr^iNH, $PhCH_2NH$)	Guanidine	2-Acetamido-3-amidino-carbamoyl-5-R	432
6-Chloro-2-methyl-4*H*-pyrazino[2,3-*d*]-[1,3]oxazin-4-one	*N*-Phenyl-*N'*-phenylguanidine (and other substituted guanidines)	2-Acetamido-5-chloro-3-(*N*-phenyl-*N'*-phenylamidino-carbamoyl) (and other substituted amidinocarbamoyl analogues)	150, 432a
6-Chloro-2-methyl-4*H*-pyrazino[2,3-*d*]-[1,3]oxazin-4-one	Benzamidine	2-Acetamido-5-chloro-3-(1-phenyl-1-iminomethyl-carbamoyl)	150
2-Methyl-6-R-4*H*-pyrazino-[2,3-*d*][1,3]oxazin-4-ones (where R = Me_2N, $PhCH_2S$, $MeSO_2$)	Aminoguanidine	2-Acetamido-3-guanidino-carbamoyl-5-R	463a

[a] 1-(2',3'-Dimethylphenyl)-4-hydroxy-2-oxo-1,2-dihydropteridine with sodium hydroxide in refluxing ethanol gave 2-carboxy-3-(2',3'-dimethylphenylamino)pyrazine (Laboratories Hermes, Span. Pat. 384,101 through *Chem. Abs.*, 1974, **80**, 37170).

6. DEHYDROGENATION OF PIPERAZINES

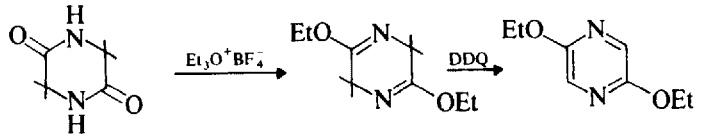
The dehydrogenation of piperazines to pyrazine was first achieved by Stoehr (32), who heated piperazine (87) or its hydrochloride with zinc dust or, better, zinc dust and lime to give a yield of approximately 10% pyrazine (88). Since that time a number of publications and patents has described the conversion of piperazines to pyrazines by heating at elevated temperatures with various catalysts usually containing copper chromite (464) but also with palladium–charcoal (465) and platinum on alkali-washed firebrick (466), and also with other reagents. Some of these preparations are summarized in Table II.11 (464–475).



(86) (87) (88)

Catalytic deamination of diethylenetriamine (86) over kaolin and alumina with some acidic admixtures at 280–400° to give pyrazine, piperazine, and other products has been examined (476). The conversion of α-amino acids, through piperazine-2,5-diones, with phosphoryl chloride to pyrazines has been discussed in Section 1N.

Sammes and co-workers (314) have also shown that some piperazine-2,5-diones (89) react with an excess of triethyloxonium fluoroborate to give a mixture of *cis*- and *trans*-2,5-diethoxy-3,6-dihydropyrazines (90) which can be oxidized with dichlorodicyanobenzoquinone (DDQ) to 2,5-diethoxypyrazines (91) in high yield. Many similar oxidations of dihydropyrazines have recently been described (314a).

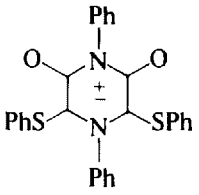


(89) (90) (91)

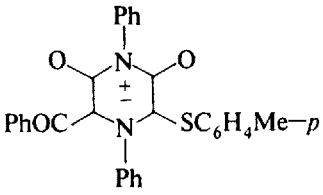
Some unusual zwitterionic pyrazines have been prepared by dehydrogenation of 1,4-disubstituted piperazine-2,6-diones. Honzl et al. (476a) prepared the anhydro-2,6-dihydroxy-1,4-diphenyl-3,5-bis(phenylthio)pyrazinium dihydroxide [*sic*] (92) (which yields adducts by dipolar cycloaddition of maleic anhydride or formaldehyde) by the reaction of 1,4-diphenylpiperazine-2,6-dione with benzenesulfonyl chloride in pyridine. Tanaka et al. (476b), from 1,4-diphenylpiperazine-2,6-dione with benzoyl chloride, and tosyl chloride in pyridine at reflux, obtained the anhydro-3-benzoyl-2,6-dihydroxy-1,4-diphenyl-5-(*p*-tolylthio)pyrazinium dihydroxide [*sic*] (93), together with some of the *S*-*p*-tolyl analogue of (92).

TABLE II.11 SOME DEHYDROGENATIONS OF PIPERAZINES TO PYRAZINES

Starting material	Conditions	Product	Refs.
Piperazine or piperazine · $6H_2O$	Benzene solution over copper chromite catalyst, 215–500° single pass 35–40% yield	Pyrazine	464
Piperazine	Aqueous solution passed (5 h) over CuO–ZnO at 400–420° (86%)	Pyrazine	467
Piperazine (or 2,6-dimethylpiperazine)	Aqueous solution over reduced copper chromite at 300–375°	Pyrazine (79%) (or 2,6-dimethylpyrazine)	468
Piperazine (or alkylpiperazines)	Copper chromite/MnO_2 at 350–370°	Pyrazine (or alkylpyrazines	469
Piperazine	5% Pt/alkali washed firebrick	Pyrazine 18%	466
2-Methylpiperazine	Benzene solution over copper chromite at 390–500°	2-Methylpyrazine	470
2-Methylpiperazine (or homologues)	Prereduced copper chromite at 350°	2-Methylpyrazine (89%) (or homologues)	471
trans-2,3-Dimethyl-piperazine	Copper chromite and $Cd_3(PO_4)_2$–acid clay	2,3-Dimethylpyrazine	472
N-Butyl-2-methyl-piperazine	Benzene solution over copper chromite at 500–530°	2-methylpyrazine	470
2,6-Bis(hydroxy-imino)piperazine	Pd–C reflux dichlorobenzene	2,6-Diaminopyrazine	465
2,3,5,6-Tetrachloro-1,4-diformyl-piperazine	185–200°	2-Chloropyrazine	473
1,4-Bis(chloro-carbonyl)piperazine	Cl_2/u.v./$FeCl_3$/155–160°	2,3-Dichloropyrazine	474
N,N'-Dimethylpiperazine or *N,N'*-bis(hydroxy-ethyl)piperazine	Cl_2/70–230°	Tetrachloropyrazine	475



(92)

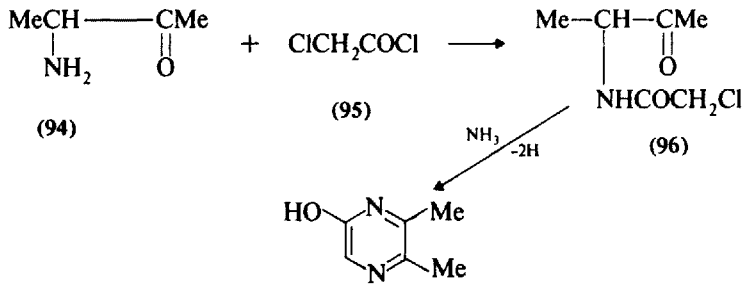


(93)

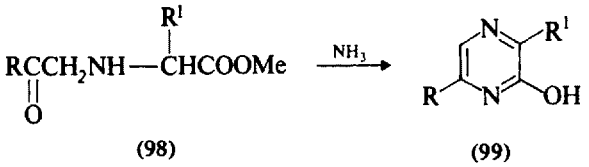
7. RING CLOSURES INVOLVING THE C–C–N–C–C, N–C–C–N–C–C, AND N–C–C–N–C–C–N SYSTEMS

Tota and Elderfield (248) have described a general synthesis for 2,3-disubstituted and 2,3,6-trisubstituted 5-hydroxypyrazines. In this reaction an α-(bromoacetyl-amino) carbonyl compound (prepared from an α-amino carbonyl compound with

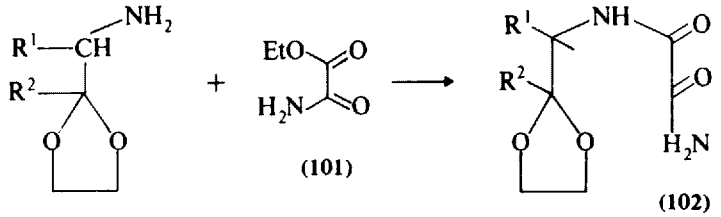
an halogenoacetyl halide) was treated with alcoholic ammonia to give the corresponding pyrazine. Thus 3-amino-2-butanone (**94**) condensed with chloroacetyl chloride (**95**) to give 3-chloroacetamido-2-butanone (**96**), which on treatment with alcoholic ammonia gave 5-hydroxy-2,3-dimethylpyrazine (**97**). In a similar manner 5-hydroxy-3-methyl-2-phenyl-, 2-ethyl-3-hydroxy-5-methyl-6-phenyl-, and 3-(β-ethoxyethyl)-5-hydroxy-2-methylpyrazines were prepared; Baxter et al. (477) have also described the preparation of 3-hydroxy-2,5-dimethylpyrazine from 2-(2′-bromopropionamido)propionaldehyde (as diethylmercaptal) (prepared from 2-aminopropionaldehyde diethylmercaptal and bromopropionyl bromide) with ammonia. In contrast to this behavior, Newbold et al. (478) have shown that α-bromopropionyl derivatives of aminomethyl ketones ($RCOCH_2NH_2$) when treated with ammonia gave 2-propionamidopyrazines (Section 8).



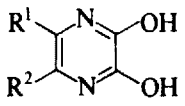
2,5-Disubstituted 3-hydroxypyrazines (**99**) have been prepared by Masaki and Ohta (479) by ring closure of the appropriate ester (**98**) with ammonia. Thus *N*-(2-oxopentyl)leucine methyl ester gave 3-hydroxy-2-isobutyl-5-propylpyrazine, *N*-(2-oxoisohexyl)leucine methyl ester gave 3-hydroxy-2,5-diisobutylpyrazine, and *N*-phenacylleucine methyl ester gave 3-hydroxy-2-isobutyl-5-phenylpyrazine. Likewise *N*-(3-methyl-2-oxopentyl)-L-leucine methyl ester gave deoxyaspergillic acid (5-*s*-butyl-3-hydroxy-2-isobutylpyrazine) (480); and Palamidessi and co-workers (481, 482) have prepared 2,3-dihydroxypyrazine from α-ethoxalylaminoacetaldehyde diethyl acetal [$(EtO)_2CHCH_2NHCOCOOEt$].



Adachi and Sato (483) have prepared six dihydroxypyrazines (**103**, R^1 and R^2 = H, Me, Ph) by condensation of α-aminoketals (**100**) with ethyl oxamate (**101**) to oxamoylamino ketones (**102**), which were subsequently cyclized in acetic acid to give excellent yields of the 2,3-dihydroxypyrazines.



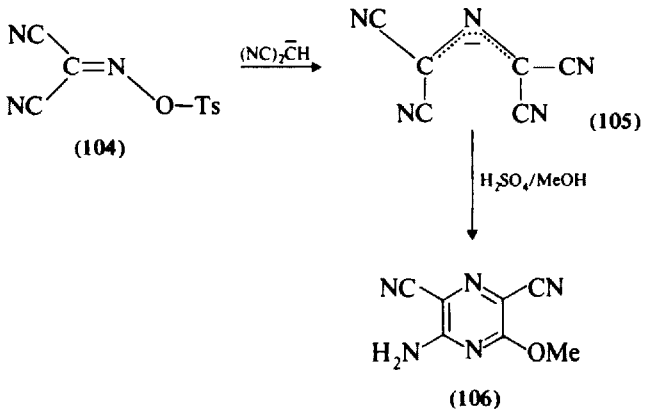
(100) (101) (102)



(103)

Sato (365a) cyclized 2-glycylamino-2-phenylacetaldehyde diethyl acetal in acetic acid and oxidized with manganese dioxide to give 2-hydroxy-6-phenylpyrazine.

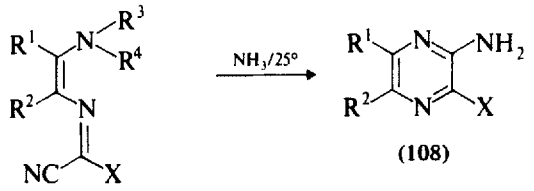
α-(*p*-Toluenesulfonyloxyimino)malononitrile (**104**), when treated with malononitrile in basic conditions, has been shown to give salts of "1,1,3,3-tetracyano-2-azapropenide" (**105**), which with concentrated sulfuric acid in methanol gave 2-amino-3,5-dicyano-6-methoxypyrazine (**106**) (484) and with hydrochloric acid in acetone gave 2-amino-6-chloro-3,5-dicyanopyrazine (485, 486). Catalytic cyclization of 2-(2′-aminobutylamino)butanol with Raney nickel has been found to give a mixture of 2,5-diethylpiperazine (25% yield) and 2,5-diethylpyrazine (8%) (487).



(104) (105) (106)

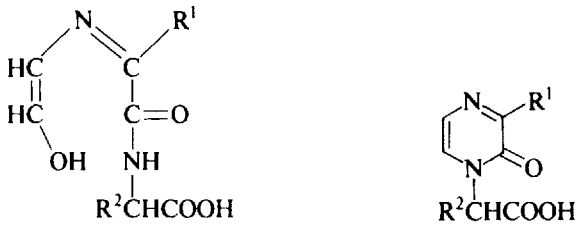
The synthesis of 2-aminopyrazines (**108**) unambiguously substituted at the 5- and 6-positions from substituted 2-azabutadienes (**107**) and ammonia has been described by Lang and Fleury (488). In this way 2-amino-3-cyano(or methoxycarbonyl)-5-methyl(or ethoxycarbonyl)-6-phenyl(or methyl or 5,6-polymethylene)-pyrazines have been obtained. When the Schiff base [$H_2NC(CN)=C(CN)N=C(CN)Ph$;

from diaminomaleonitrile (DAMN) and benzoyl cyanide with phosphorus pentoxide in ethanol] was refluxed in ethanol, it gave 2-amino-5,6-dicyano-3-phenylpyrazine (489, 490).



(107) (108)

The reactions of various dipeptides with glyoxal at 100° and pH 5 have been studied and, besides other products, gave a series of new 1-(1′-carboxyalkyl)-2-oxo-1,2-dihydropyrazines (**110**) (380, 381). The proposed mechanism involved an intermediate of type (**109**) in the formation of the pyrazine. Pyrazines prepared from dipeptides in this manner are listed in Table II.12 (380, 381). The study has been extended to tri- and tetrapeptides (382). Some additional data are recorded in Section VI.9A(1).



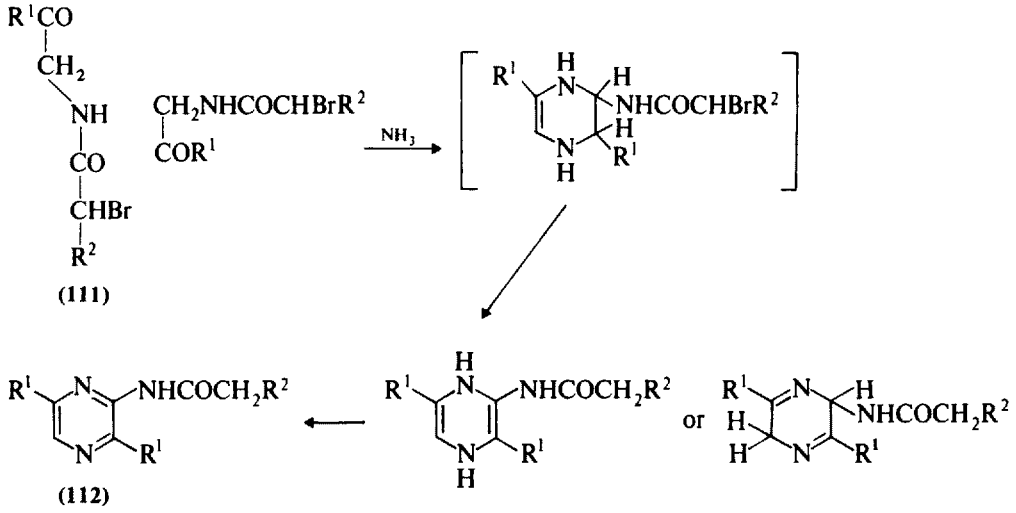
(109) (110)

TABLE II.12 FORMATION OF PYRAZINES FROM DIPEPTIDES AND GLYOXAL

Dipeptide	Pyrazine	Refs.
Glycyl-L-leucine	1-(1′-Carboxy-3′-methylbutyl)-2-oxo-1,2-dihydro	380
Glycylglycine	1-Carboxymethyl-2-oxo-1,2-dihydro	381
Glycyl-DL-alanine	1-(1′-Carboxyethyl)-2-oxo-1,2-dihydro	381
DL-Alanyl-DL-alanine	1-(1′-Carboxyethyl)-3-methyl-2-oxo-1,2-dihydro	381
DL-Alanyl-DL-valine	1-(1′-Carboxyisobutyl)-3-methyl-2-oxo-1,2-dihydro	381
DL-Alanyl-DL-norvaline	1-(1′-Carboxybutyl)-3-methyl-2-oxo-1,2-dihydro	381
DL-Alanyl-DL-norleucine	1-(1′-Carboxypentyl)-3-methyl-2-oxo-1,2-dihydro	381
DL-Alanyl-DL-leucine	1-(1′-Carboxyisopentyl)-3-methyl-2-oxo-1,2-dihydro	381
DL-Leucylglycine	1-Carboxymethyl-3-isobutyl-2-oxo-1,2-dihydro	381
DL-Leucyl-DL-leucine	1-(1′-Carboxyisopentyl)-3-isobutyl-2-oxo-1,2-dihydro	381

8. CONDENSATION OF α-BROMOPROPIONYL (OR α-BROMOPHENYLACETYL) DERIVATIVES OF AMINOMETHYL KETONES WITH AMMONIA TO ACYLAMINOPYRAZINES

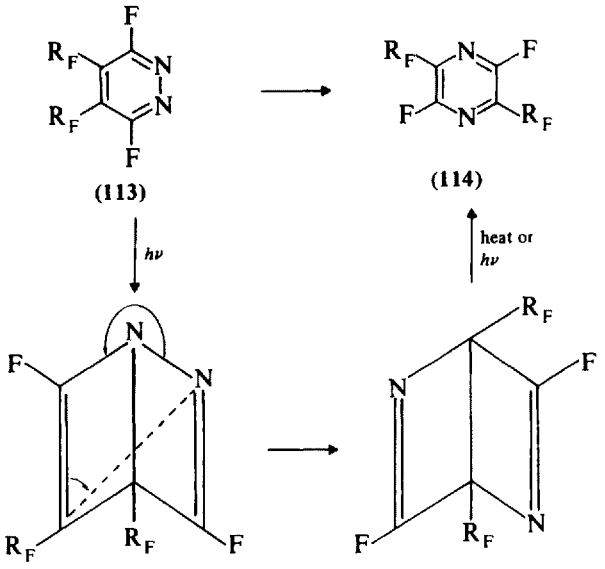
It has been shown by Newbold et al. (478) that whereas α-bromopropionyl derivatives of amino ketones of the type $R^1COCHR^2NH_2$ with ammonia gave trisubstituted hydroxypyrazines (Section II.7), α-bromopropionyl derivatives (**111**, $R^1 = R^2 = Me$) of aminomethyl ketones ($R^1COCH_2NH_2$) with ammonia produced 2-propionamidopyrazine derivatives (**112**, $R^1 = R^2 = Me$). Thus aminoacetone and α-bromopropionyl bromide gave 2,5-dimethyl-3-propionamidopyrazine and the 2,5-diethyl and 2,5-diphenyl analogues were similarly prepared. This work has been extended to the preparation (491) of 2,5-diphenyl-3-phenylacetamidopyrazine and 2,5-dimethyl-3-phenylacetamidopyrazine, and a mechanism has been proposed for the transformation of (**111**) to (**112**). It was suggested that a two stage process was involved in the conversion of the tetrahydropyrazine via the dihydro compound to the pyrazine and that the tetrahydropyrazine was oxidized to the dihydro compound by a simultaneous reductive dehalogenation of the bromoacetyl group. The general reaction depended on the presence of a halogeno substituent in the acyl group (propionamidoacetone was recovered unchanged after treatment with ammonia).



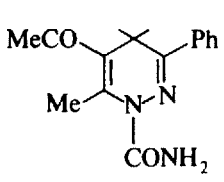
9. RING TRANSFORMATIONS OF PYRIDAZINES AND OTHER HETEROCYCLES TO PYRAZINES

Ultraviolet irradiation of tetrafluoropyridazine (**113**, $R_F = F$) has been shown to give a nearly quantitative yield of tetrafluoropyrazine, and 3,6-difluoro-4,5-

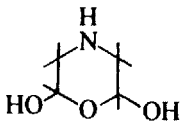
bisheptafluoroisopropylpyridazine isomerizes to 2,5-difluoro-3,6-bisheptafluoroisopropylpyrazine (492); u.v. irradiation of 4,5-dichloro-3,6-difluoropyridazine in Freon 114 at 254 nm also gives 2,5-dichloro-3,6-difluoropyrazine (493). A study of the photolyzed rearrangement of various perfluoroalkylpyridazines (**113**) in the vapor phase has revealed that substituents located 4,5- and 3,5- in the pyridazine occur at the 2,5- and 2,6-positions, respectively, in the resulting pyrazine (**114**) (494), and a mechanism has been proposed for the transformation of (**113**) to (**114**). Flow pyrolysis of perfluoro-4,5-diethylpyridazine gave mainly perfluoro-4,5-diethylpyrimidine and some perfluoro-2,6-diethylpyrazine (495) and pyrolysis of 3,6-difluoro-4,5-bis(heptafluoroisopropyl)pyridazine at 580° gave 4,6-difluoro-2,5-bis(heptafluoroisopropyl)pyrimidine together with 2,5-difluoro-3,6-bis(heptafluoroisopropyl)pyrazine (496).



4-Acetyl-2-carbamoyl-3-methyl-6-phenyl-2,5-dihydropyridazine (**115**) when heated with potassium hydroxide has been shown to give 2,5-diphenylpyrazine (497), and 2,6-dihydroxymorpholine (**116**) has been converted smoothly by hydrazine or hydroxylamine in aqueous hydrochloric acid to pyrazine in good yield (28).

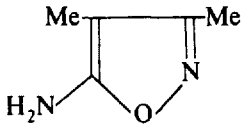


(115)



(116)

Various other heterocycles have also been converted to pyrazines. Thus tetraphenylpyrrole with lead tetraacetate and potassium carbonate in chloroform has been shown to give a 20% yield of tetraphenylpyrazine (498); 5-amino-3,4-dimethylisoxazole (**117**) and 50% hydrazine hydrate, when heated on a water bath and the product treated with hot concentrated hydrochloric acid, gave tetramethylpyrazine (499). Treatment of 3-amino-2-hydroxy-4,4-dimethyltetrahydrofuran (**118**) with strong alkali gave 2,5-bis(hydroxy-*t*-butyl)pyrazine (**119**) (500) and catalytic hydrogenation of furylamines (**120**) over platinum at 220–225° gave alkylpyrazines (**121**) (500a).



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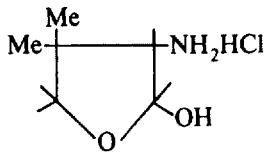
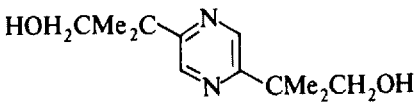


(118)



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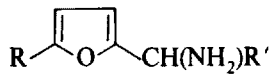

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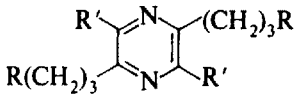
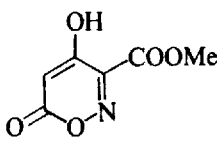


(121)

Hydrogenation of 4-hydroxy-3-methoxycarbonyl-6-oxo-1,2(6*H*)-oxazine (**122**) in methanol over palladium–charcoal has been shown to give 2,5-dimethoxycarbonyl-3,6-dimethylpyrazine (501); and 3-amino-4-hydroxycoumarin (**123**, $R^1 = R^2 = H$), 3-amino-4-hydroxy-6,8-dimethylcoumarin and 3-acetamido-4-hydroxy-6-methylcoumarin, when heated with 2*N* sodium hydroxide, gave 2,5-bis(2′-hydroxyphenyl)-3,6-dihydropyrazine [which was dehydrogenated over palladium to yield 2,5-bis(2′-hydroxyphenyl)pyrazine], 2,5-bis(2′-hydroxy-3′,5′-dimethylphenyl)-3,6-dihydropyrazine, and 2,5-bis(2′-hydroxy-5′-methylphenyl)-3,6-dihydropyrazine, respectively (302).



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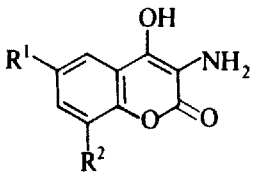
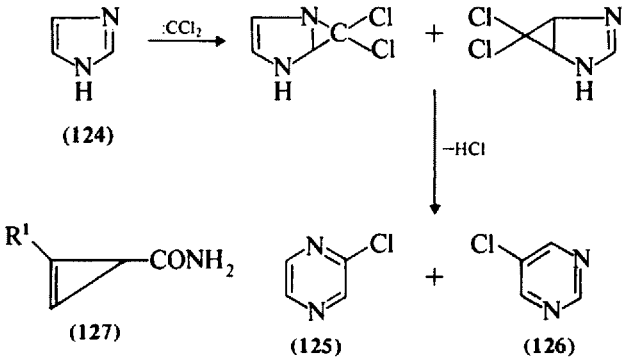


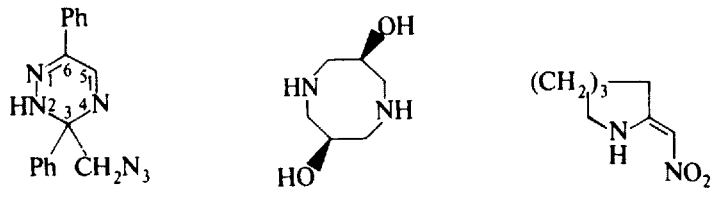
(123)

The reaction of imidazole (**124**) with dichlorocarbene (generated from chloroform) at 550° has been shown to give a 30% yield of 5-chloropyrimidine (**126**) and 3% 2-chloropyrazine (**125**) (502). Reaction of amarine (2,4,5-triphenyl-4,5-dihydroimidazole) with amalgams in ethanol gave tetraphenylpyrazine as a minor product (503, 504). 5-Aminoisoxazoles and 2-carbamoyl-2*H*-azirines (**127**) when heated at 150° gave 2,5-biscarbamoylpyrazines, and 2-carbamoyl-3-phenyl-2*H*-azirine was cleaved by refluxing ethanolic hydrogen chloride to amino(benzoyl)-acetamide hydrochloride [$PhCOCH(N^+H_3)CONH_2 \cdot Cl^-$], which with ethanolic ammonia afforded 2,5-dicarbamoyl-3,6-diphenylpyrazine (505). 2-Arylazirines are converted at room temperature into 2,5-diarylpyrazines by silver perchlorate in benzene (505a) and by group VI metal carbonyls [$M(CO)_6$, M = Cr, Mo, W] in dry tetrahydrofuran (which also gave isomeric dihydropyrazines) (505b).



(**124**) (**127**) (**125**) (**126**)

If the monoazide, 3-azidomethyl-3,6-diphenyl-2,3-dihydro-1,2,4-triazine (**128**), was refluxed in decalin in an atmosphere of nitrogen it was converted into 2,5-diphenylpyrazine (506), and *cis*-3,7-dihydroxyoctahydro-1,5-diazocine (**129**), when vaporized and passed over alumina at 360°, gave a mixture of 2-methyl-, 2,5- and 2,6-dimethyl-, and 2,3,5-trimethylpyrazines (507). Pyrazines have also been prepared by hydrogenation of nitromethylenealkylenimines: for example, hydrogenation of 2-nitromethylenehexahydroazepine (**130**) in methanol containing acetic acid over palladium–charcoal gave 2,5-bis(5′-aminopentyl)pyrazine (507a–c).



(**128**) (**129**) (**130**)

10. MISCELLANEOUS

Some preparations of pyrazines that are not classified elsewhere are included in this miscellaneous section and are tabulated below. In some of these reactions, products other than pyrazines are also formed but these compounds have not been recorded in Table II.13 (28, 190, 305, 508–523).

TABLE II.13 MISCELLANEOUS PREPARATIONS OF PYRAZINES

Reactants and Conditions	Pyrazine	Refs.
2,6-Dihydroxymorpholine and hydrazine or hydroxylamine in hydrochloric acid	Pyrazine	28
Sucrose and aqueous β-aminopropionitrile	2-Methyl- and 2,5-dimethyl pyrazine and other pyrazines	508
Acetone and nitrogen iodide in aqueous ammonia	2,5-Dimethylpyrazine	190
Electrolysis of acetone in aqueous ammoniacal potassium iodide	2,5-Dimethylpyrazine	190
Azidomethyl isopropyl ketone and triphenylphosphine	2,5-Diisopropylpyrazine	305
Hydrogenation of bis(dimethylglyoximato)-cobalt(II)	Tetramethylpyrazine	509
α-Acetimidoylpropionitrile, hydroxylamine and Fe^{2+}	Tetramethylpyrazine	510
Acetylene and ammonia over a catalyst containing zinc oxide and alumina at 400°	2,5-Diethyl-3,6-dimethylpyrazine	511
Diethyl ketone and nitrogen iodide in aqueous ammonia	2,5-Diethyl-3,6-dimethylpyrazine	512
Propiophenone and nitrogen iodide in aqueous ammonia	2,5-Dimethyl-3,6-diphenyl-pyrazine	512
U.v. irradiation of β-(β-methyl)styryl isocyanate	2,3-Dimethyl-5,6-diphenyl-pyrazine	513
Azidomethyl phenyl ketone and triphenylphosphine	2,5-Diphenylpyrazine	305
U.v. irradiation of β-styryl isocyanate	2,5-Diphenylpyrazine	513, 514
"α-Benzildioxime *N,N'*-dimethyl ether," carbon monoxide, and hydrogen at 225°	Tetraphenylpyrazine	515
o-Bromoanisole and lithium dibenzylamide (and similar amides)	2,3,5,6-Tetraphenylpyrazine (and similar pyrazines)	516
Benzaldehyde heated with formamide or acetamide	Tetraphenylpyrazine	517
Benzaldehyde and magnesium nitride	Tetraphenylpyrazine	518
Benzylazide in *p*-xylene at 170–180°	Tetraphenylpyrazine	519
Benzoin–anil–anilide with ammonia at 130°	Tetraphenylpyrazine	520
Sodio derivative of benzylidenebenzylamine with cupric bromide	Tetraphenylpyrazine	521
Azidomethyl *p*-anisyl ketone and triphenylphosphine	2,5-Bis(*p*-methoxyphenyl)pyrazine	305
Phenacylhydrazine warmed in ethanol at 60°	3-Hydroxy-2,5-diphenylpyrazine	522
α,α'-Dibromoacetophenone azine with hydrazine	2,5-Diphenylpyrazine	522a

TABLE II.13 *Continued*

Reactants and Conditions	Pyrazine	Refs.
Thermolysis of α,α'-diazidoacetophenone azine	2,5-diphenylpyrazine	522a
Dianil from formaldehyde (and other aldehydes) and ethylenediamine at 350–520° over Al–Cr catalysts	Pyrazine (and 2,3-alkyl pyrazines)	522b
2-Formylpyridine and aminoacetal with concentrated mineral acid	1,4-Bis(pyrid-2'-ylmethylene)-1,4-dihydropyrazidi-inium salts	523
2-Acetylpyridine and aminoacetal with concentrated mineral acid	1,4-Bis[pyrid-2'-yl(*C*-methyl)-methylene]-1,4-dihydro-pyrazidi-inium salts	523

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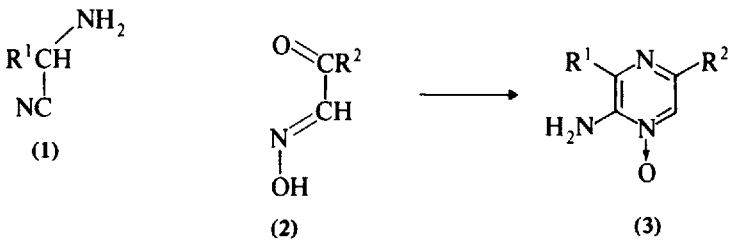
CHAPTER III

Primary Syntheses of Pyrazines *N*-Oxides

The primary syntheses of pyrazine *N*-oxides from aliphatic components only are described in this chapter. The preparations of pyrazine *N*-oxides by oxidation of pyrazines are dealt with under the reactions of the appropriately substituted pyrazines; for example, those of pyrazine and alkylpyrazine *N*-oxides are described in Chapter IV, and of halogenopyrazine *N*-oxides in Chapter V. The cleavage of *N*-oxides of pteridines and related systems to aminopyrazine *N*-oxides is described in Section VIII.3A(2).

1. 2-AMINOPYRAZINE 1-OXIDES FROM α-AMINO NITRILES AND α-HYDROXYIMINO CARBONYL COMPOUNDS

α-Amino nitriles have been shown to condense with α-hydroxyimino carbonyl compounds to give a variety of 2-aminopyrazine 1-oxides. Thus Sharp and Spring (524) found that α-aminopropionitrile (**1**, R^1 = Me) with α-hydroxyiminoacetone (**2**, R^2 = Me), gave 2-amino-3,5-dimethylpyrazine 1-oxide (**3**, $R^1 = R^2$ = Me); and the reaction was applied to three similar preparations using α-aminopropionitrile with ethyl hydroxyiminomethyl ketone, α-aminophenylacetonitrile with hydroxyiminoacetone, and α-aminopropionitrile with α-hydroxyiminoacetophenone. Newbold et al. (92) then extended the reaction to α-hydroxyimino aldehydes, to yield 3,6-disubstituted 2-aminopyrazine 1-oxides; from α-aminopropionitrile and α-hydroxyiminopropionaldehyde (**4**, R^2 = Me) they prepared 2-amino-3,6-dimethylpyrazine 1-oxide (**5**, $R^1 = R^2$ = Me). These reactions were carried out in chloroform solution in which the free α-amino nitriles were first liberated from their hydrochlorides with *N*-methylmorpholine. This reaction was then applied to the



(1) (2) (3)

TABLE III.1 2-AMINOPYRAZINE 1-OXIDES FROM α-AMINO NITRILES AND α-HYDROXYIMINO CARBONYL COMPOUNDS

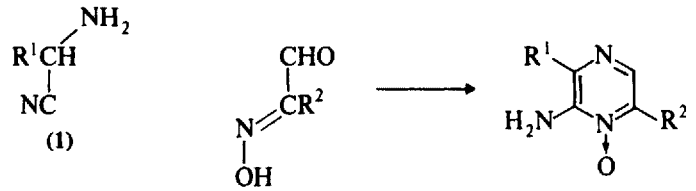
α-Amino Nitrile	α-Hydroxyimino Carbonyl Compound	Pyrazine 1-Oxide	Refs.
Aminoacetonitrile	Hydroxyiminoacetone	2-Amino-5-methyl	535
	Phenylglyoxalaldoxime	2-Amino-5-phenyl	377
α-Aminopropionitrile	Hydroxyiminoacetone	2-Amino-3,5-dimethyl	524
	Ethyl hydroxyiminomethyl ketone	2-Amino-5-ethyl-3-methyl	524
	α-Hydroxyiminoacetophenone	2-Amino-3-methyl-5-phenyl	524, 527
	1-Phenylglyoxal 1-oxime[a]	2-Amino-3-methyl-6-phenyl	527
	α-Hydroxyiminopropionaldehyde	2-Amino-3,6-dimethyl	92
	3-(α-Hydroxyiminoacetyl)indole	2-Amino-5-(indol-3′-yl)-3-methyl	527
α-Aminophenylacetonitrile	Hydroxyiminoacetone	2-Amino-5-methyl-3-phenyl	524
α-Amino-γ-methylvaleronitrile	α-Hydroxyimino-β-methylvaleraldehyde	2-Amino-6-*s*-butyl-3-isobutyl	92, 536
	α-Hydroxyimino-β-methylbutyraldehyde	2-Amino-3-isobutyl-6-isopropyl	103, 525
Isoleucine nitrile	4-Methyl-2-hydroxyiminopentanal	2-Amino-3-*s*-butyl-6-isobutyl	93
Aminocyanoacetamide	Hydroxyiminoacetone	2-Amino-3-carbamoyl-5-methyl	531, 535, 537
	α-Hydroxyiminoacetophenone	2-Amino-3-carbamoyl-5-phenyl	531
Ethyl aminocyanoacetate	Glyoxime	2-Amino-3-ethoxycarbonyl	538
	Hydroxyiminoacetone	2-Amino-3-ethoxycarbonyl-5-methyl	531, 537
	Bis(hydroxyimino)acetone	2-Amino-3-ethoxycarbonyl-5-hydroxyiminomethyl	539
	Hydroxyiminomethyl propyl ketone	2-Amino-3-ethoxycarbonyl-5-propyl	531
	Hydroxyiminomethyl styryl ketone	2-Amino-3-ethoxycarbonyl-5-styryl	531, 537
	α-Hydroxyiminoacetophenone	2-Amino-3-ethoxycarbonyl-5-phenyl	531, 537
	1-Hydroxyimino-4-methylpent-3-en-2-one	2-Amino-3-ethoxycarbonyl-5-(2′-methyl-1′-propenyl)	537
	3-Hydroxyimino-4-methylpent-4-en-2-one	2-Amino-3-ethoxycarbonyl-6-isopropenyl-5-methyl	531
	D-Glucosone aldoxime	2-Amino-5-(D-*arabo*-tetrahydroxybutyl)-3-ethoxycarbonyl	540
	D-Xylosone aldoxime	2-Amino-3-ethoxycarbonyl-5-(D-*threo*-trihydroxypropyl)	540
Benzyl aminocyanoacetate	Pyruvaldehyde 1-oxime	2-Amino-3-benzyloxycarbonyl-5-methyl	540
	D-Xylosone aldoxime	2-Amino-3-benzyloxycarbonyl-5-(D-*threo*-trihydroxypropyl)	540
Benzyl aminocyanoacetate methanesulfonate	5-Deoxy-L-arabinosone aldoxime	2-Amino-3-benzyloxycarbonyl-5-(L-*erythro*-1′,2′-dihydroxypropyl)	540, 541
2-Amino-5-phthalimidovaleronitrile	3-(α-Hydroxyiminoacetyl)indole	2-Amino-5-indol-3′-yl-3-(3′-phthalimidopropyl)	527
Aminomalononitrile	Glyoxime	2-Amino-3-cyano	530, 532
	α-Hydroxyiminoacetone	2-Amino-3-cyano-5-methyl	532, 537
	Bis(hydroxyimino)acetone	2-Amino-3-cyano-5-hydroxyiminomethyl	528, 532
	Chloromethyl hydroxyiminomethyl ketone	2-Amino-5-chloromethyl-3-cyano[b]	529
	1-Hydroxyiminobutan-2-one	2-Amino-3-cyano-5-ethyl	532

TABLE III.1 *Continued*

α-Amino Nitrile	α-Hydroxyimino Carbonyl Compound	Pyrazine 1-Oxide	Refs.
	1-Hydroxyiminopentan-2-one	2-Amino-3-cyano-5-*n*-propyl	532
	1-Hydroxyimino-3-methylbutan-2-one	2-Amino-3-cyano-5-isopropyl	532
	1-Hydroxyimino-4-methylpentan-2-one	2-Amino-3-cyano-5-isobutyl	532
	1-Hydroxyiminoheptan-2-one	2-Amino-3-cyano-5-pentyl	532
	Heptadecyl hydroxyiminomethyl ketone	2-Amino-3-cyano-5-heptadecyl	532
	Styryl hydroxyiminomethyl ketone	2-Amino-3-cyano-5-styryl	532
	α-Hydroxyiminoacetophenone	2-Amino-3-cyano-5-phenyl	532
	o-Methoxybenzoyl formaldoxime	2-Amino-3-cyano-5-(2′-methoxyphenyl)	532
	α-Chloro-α-hydroxyiminoacetone	2-Amino-6-chloro-3-cyano-5-methyl	533
	β-Bromopyruvaldoxime + benzyl mercaptan	2-Amino-5-benzylthiomethyl-3-cyano	542
	β-Chloro-α-hydroxyiminopropionaldehyde	2-Amino-6-chloromethyl-3-cyano	534
	β-Chloro-α-hydroxyiminobutyraldehyde	2-Amino-6-(1′-chloroethyl)-3-cyano	534
	β-Chloro-α-hydroxyiminocapraldehyde	2-Amino-6-(1′-chlorobutyl)-3-cyano	534
	β-Bromopyruvaldoxime + *p*-nitroaniline	2-Amino-3-cyano-5(*p*-nitroanilinomethyl)	542
	β-Bromopyruvaldoxime + *N*-methyl-*p*-nitroaniline	2-Amino-3-cyano-5-(*N*-methyl-4-nitroanilinomethyl)	542
	β-Bromopyruvaldoxime + triphenylphosphine	2-Amino-3-cyano-5-methyl	542
	D-glucosone aldoxime	2-Amino-5-(D-*arabo*-tetrahydroxybutyl)-3-cyano	540

[a] Incorrectly named in the experimental section of this reference.

[b] A. Rosowsky and K. K. N. Chen, *J. Med. Chem.*, 1974, 17, 1308 describe the preparation of 2-amino-5-chloromethyl-3-cyano-6-methylpyrazine 1-oxide from aminomalononitrile tosylate and 1-chloro-3-hydroxyimino-2-butanone using a method similar to that described (529) for an analogue.



(1) (4) (5)

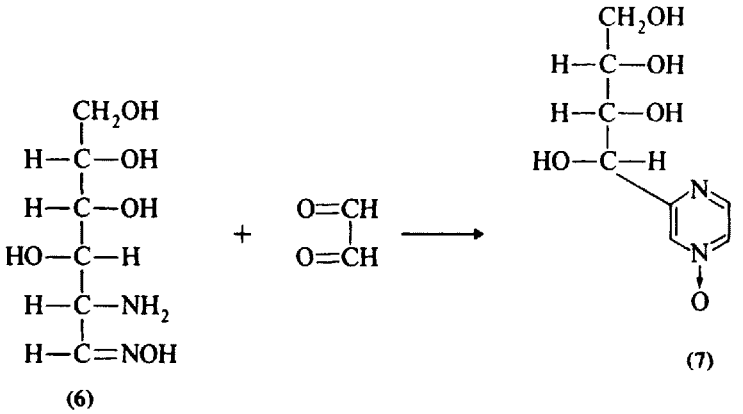
synthesis of 2-amino-3-isobutyl-6-isopropylpyrazine 1-oxide (**5**, $R^1 = Bu^i$, $R^2 = Pr^i$) from α-hydroxyimino-β-methylbutyraldehyde (**4**, $R^2 = Pr^i$) and α-amino-γ-methylvaleronitrile (DL-leucine nitrile) (**1**, $R^1 = Bu^i$) by Nakamura (103, 525).

Addition of titanium tetrachloride to the Sharp and Spring (524) synthesis of 2-aminopyrazine 1-oxides gave greatly increased yields (526); for example, the yield of 2-amino-3-methly-5-phenylpyrazine 1-oxide from α-hydroxyiminoacetophenone and α-aminopropionitrile was increased from 3 to 51%. A change of solvent from chloroform to pyridine in the corresponding preparation of 2-amino-5(indol-3′-yl)-3-methylpyrazine 1-oxide also led to a much improved yield (526, 527).

Taylor and co-workers (528–534) have carried out extensive work on the further development of this reaction; details of this and other work are summarized in Table III.1 (92, 93, 103, 377, 524–542).

2. 3-SUBSTITUTED PYRAZINE 1-OXIDES FROM 2-AMINO-2-DEOXY-D-GLUCOSE (OR MANNOSE) OXIME WITH GLYOXAL

3-(D-*arabo*-Tetrahydroxybutyl)pyrazine 1-oxide (**7**) has been prepared by Fujii and Kobatake (543, 544) by the condensation of 2-amino-2-deoxy-D-glucose oxime (**6**) or 2-amino-2-deoxy-D-mannose oxime with glyoxal in water at room temperature.



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3. 2-HYDROXYPYRAZINE 1-OXIDES FROM α-AMINOHYDROXAMIC ACIDS AND 1,2-DICARBONYL COMPOUNDS OR α,β-UNSATURATED α-BROMOALDEHYDES

Dunn and co-workers (545, 546) first reported the reaction of α-aminohydroxamic acids (**8**) with 1,2-dicarbonyl compounds (**9**) to give 2-hydroxypyrazine 1-oxides (**10**). For example, DL-alanine hydroxamic acid (**8**, R^1 = Me) and diacetyl (**9**, $R^2 = R^3$ = Me) gave 2-hydroxy-3,5,6-trimethylpyrazine 1-oxide (**10**, $R^1 = R^2 = R^3$ = Me); but the α-keto aldehyde methylglyoxal gave exclusively 2-hydroxy-3,5-dimethylpyrazine 1-oxide (**10**, $R^1 = R^2$ = Me, R^3 = H) and none of the isomeric 3,6-disubstituted compound, and DL-phenylglycine hydroxamic acid with phenylglyoxal also gave 2-hydroxy-3,5-diphenylpyrazine 1-oxide only. The results of this work, together with those from further studies by Safir and Williams (547) and Palamidessi and Bernardi (547a), are recorded in Table III.2 (546–547a).

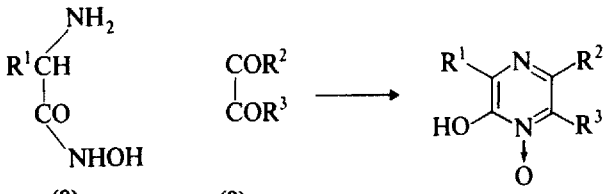

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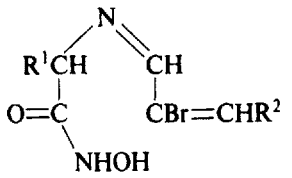
TABLE III.2 2-HYDROXYPYRAZINE 1-OXIDES FROM α-AMINOHYDROXAMIC ACIDS AND 1,2-DICARBONYL COMPOUNDS

α-Aminohydroxamic Acid	1,2-Dicarbonyl Compound	Pyrazine 1-Oxide	Refs.
Glycine hydroxamic acid	Glyoxal	2-Hydroxy	547a
	Phenylglyoxal	2-Hydroxy-5-phenyl	546
DL-Alanine hydroxamic acid	Methylglyoxal	2-Hydroxy-3,5-dimethyl	546
	Diacetyl	2-Hydroxy-3,5,6-trimethyl	546
	Phenylglyoxal	2-Hydroxy-5-phenyl-3-methyl	546
DL-Phenylglycine hydroxamic acid	Diacetyl	2-Hydroxy-5,6-dimethyl-3-phenyl	546
	Phenylglyoxal	2-Hydroxy-3,5-diphenyl	546
L-Leucine hydroxamic acid	Diacetyl	2-Hydroxy-3-isobutyl-5,6-dimethyl	547
	Benzil	2-Hydroxy-3-isobutyl-5,6-diphenyl	547
DL-Isoleucine hydroxamic acid	Diacetyl	3-*s*-Butyl-2-hydroxy-5,6-dimethyl	547
Aminomalonodihydroxamic acid	Glyoxal	2-Hydroxy-3-hydroxycarbamoyl	547
	Diacetyl	2-Hydroxy-3-hydroxycarbamoyl-5,6-dimethyl	547

In an attempt to force the condensation of an α-aminohydroxamic acid and a potential α-keto aldehyde to give 3,6-disubstituted 2-hydroxypyrazine 1-oxides, Dunn and co-workers (545, 546) studied the condensation of α-aminohydroxamic

acids and α,β-unsaturated α-bromoaldehydes. Glycine hydroxamic acid (α-amino-*N*-hydroxyacetamide) condensed readily with 2-bromocinnamaldehyde to yield 2-bromocinnamylideneglycine hydroxamic acid (**11**, $R^1 = H$, $R^2 = Ph$), which on treatment with sodium ethoxide in ethanol gave 6-benzyl-2-hydroxypyrazine 1-oxide (**12**, $R^1 = H$, $R^2 = Ph$). In a similar manner, condensation of α-amino-*n*-butyrohydroxamic acid with 2-bromocinnamaldehyde gave α-(2-bromocinnamylideamino)butyrohydroxamic acid (**11**, $R^1 = Et$, $R^2 = Ph$). This remained uncyclized in sodium ethoxide but with potassium *t*-butoxide in boiling *t*-butyl alcohol, it did give a small yield of 6-benzyl-3-ethyl-2-hydroxypyrazine 1-oxide (**12**, $R^1 = Et$, $R^2 = Ph$). Likewise Ramsay and Spring (548) from α-amino-*n*-butyrohydroxamic acid and α-bromocrotonaldehyde prepared α-(2-bromocrotonylideneamino)-*n*-butyrohydroxamic acid (**11**, $R^1 = Et$, $R^2 = Me$) and thence, 3,6-diethyl-2-hydroxypyrazine 1-oxide (**12**, $R^1 = Et$, $R^2 = Me$).



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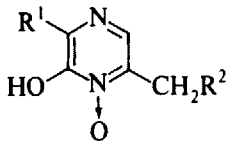

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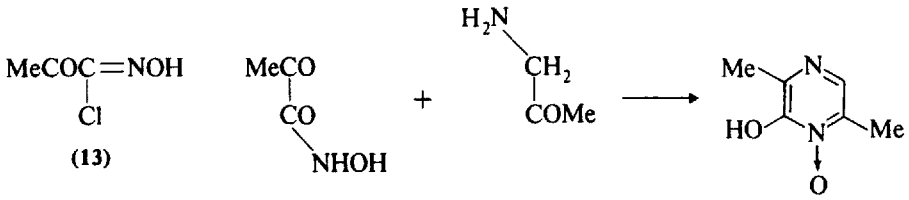
4. 2-HYDROXY-3,6-DIMETHYLPYRAZINE 1-OXIDE FROM THE BISULFITE DERIVATIVE OF PYRUVOHYDROXAMIC ACID AND AMINOACETONE

Ramsay and Spring (548) found that treatment of α-chloro-α-hydroxyiminoacetone (**13**) with sodium hydrogen sulfite gave the bisulfite derivative of pyruvohydroxamic acid, which after purification from sodium hydrogen sulfite condensed with aminoacetone to give 2-hydroxy-3,6-dimethylpyrazine 1-oxide (**14**).



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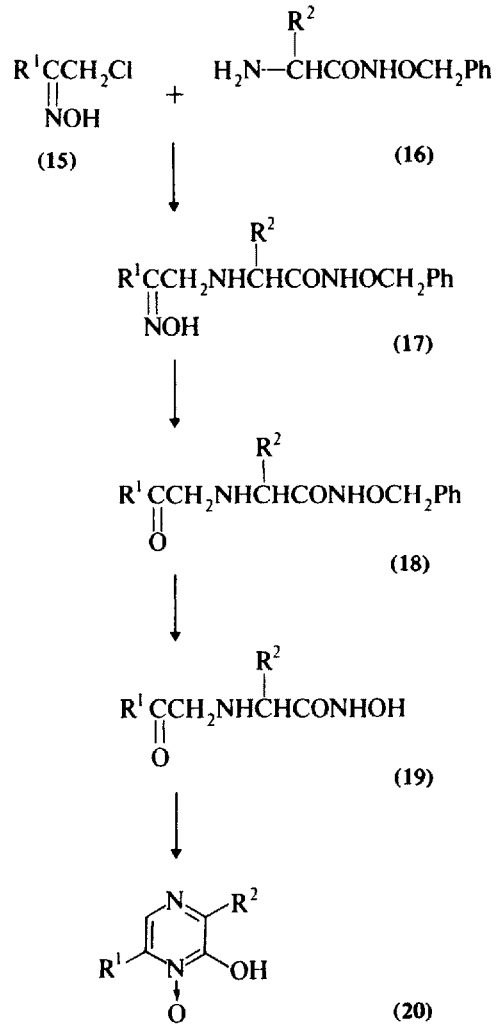
(14)

5. RING CLOSURE OF THE C–C–N–C–C–N–O SYSTEM

The preparation of 3,6-disubstituted 2-hydroxypyrazine 1-oxides from (**11**), which were derived from α-aminohydroxamic acids and α,β-unsaturated α-bromo-

aldehydes, has been discussed in detail in Section 3 from the publications of Ramsay, Spring and co-workers (545, 546, 548).

Masaki and Ohta (549) introduced a new versatile synthesis of a homologue of aspergillic acid in which 1-chloropentan-2-one oxime (**15**, R^1 = Pr) was condensed with *N*-leucyl-*O*-benzylhydroxylamine (**16**, $R^2 = Bu^i$) to give compound (**17**, R^1 = Pr, $R^2 = Bu^i$). Hydrolysis of this oxime gave *N*-[4-methyl-2-(2′-oxopentylamino)valeryl]-*O*-benzylhydroxylamine (**18**, R^1 = Pr, $R^2 = Bu^i$) which was catalytically debenzylated to 4-methyl-2-(2′-oxopentylamino)valerohydroxamic acid (**19**, R^1 = Pr, $R^2 = Bu^i$) and then heated with ammonia to give 2-hydroxy-3-isobutyl-6-propylpyrazine 1-oxide (**20**, R^1 = Pr, $R^2 = Bu^i$). In a similar manner Masaki and co-workers synthesized neoaspergillic acid (2-hydroxy-3,6-diisobutylpyrazine 1-oxide) (550, 551), aspergillic acid (6-*s*-butyl-2-hydroxy-3-isobutylpyrazine 1-oxide)



(551, 552), and mutaaspergillic acid [2-hydroxy-6(1′-hydroxy-1′-methylethyl)-3-isobutylpyrazine 1-oxide] (553).

Details of these preparations are summarized in Table III.3 (546, 548–553).

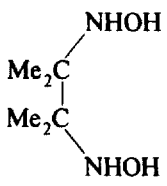
TABLE III.3 SYNTHESIS OF PYRAZINE 1-OXIDES BY RING CLOSURE OF THE C–C–N–C–C–N–O SYSTEM

Reactant	Pyrazine 1-Oxide	Refs.
2(2′-Bromocinnamylideneamino)butyrohydroxamic acid	6-Benzyl-3-ethyl-2-hydroxy	546
2-Bromocinnamylideneglycine hydroxamic acid	6-Benzyl-2-hydroxy	546
2-(2′-Bromocrotonylideneamino)butyrohydroxamic acid	3,6-Diethyl-2-hydroxy	548
4-Methyl-2-(2′-oxopentylamino)valerohydroxamic acid	2-Hydroxy-3-isobutyl-6-propyl	549
4-Methyl-2-(4′-methyl-2′-oxopentylamino)valerohydroxamic acid	2-Hydroxy-3,6-diisobutyl (neoaspergillic acid)	550, 551
4-Methyl-2-(3′-methyl-2′-oxopentylamino)valerohydroxamic acid	6-*s*-Butyl-2-hydroxy-3-isobutyl) (aspergillic acid)	551, 552
2-(3′-Hydroxy-3′-methyl-2′-oxobutylamino)-4-methylvalerohydroxamic acid	2-Hydroxy-3-isobutyl-6(1′-hydroxy-1′-methylethyl)	553

6. MISCELLANEOUS

syn-ω-Aminoacetophenone oxime when heated with triethyl orthoacetate in dioxane gives 2,5-diphenylpyrazine 1-oxide (326), and α-benzil dioxime when treated with potassium ferrocyanide gave a secondary product which after crystallization from acetic acid and heating at 100° formed tetraphenylpyrazine 1,4-dioxide (554).

Dihydropyrazine 1,4-dioxides have been reported by Lamchen and Mittag (555) who reduced 2,3-dimethyl-2,3-dinitrobutane to 2,4-dihydroxyamino-2,3-dimethylbutane (**21**), which on formation of the monosulfate, half neutralized, and treated with one equivalent of butane-2,3-dione gave hexamethyl-2,3-dihydropyrazine 1,4-dioxide (**22**); Karpetsky and White (556), from acid hydrolysis of α,α-dimethoxyacetophenone oxime (**23**), prepared 2,5-dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-dioxide.



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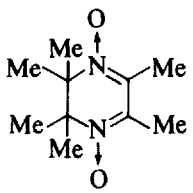

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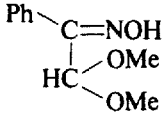

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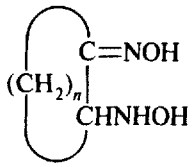
An acid-catalyzed autocondensation of 1,2-hydroxyamino oximes **(24)** (obtained from olefin–dinitrogen trioxide by isomerization, followed by partial reduction of the 1,2-nitroximes with hydrogen over palladium–charcoal) with concentrated sulfuric acid gave 2,3;5,6-bistetra(or hexa)methylenepyrazine 1,4-dioxides **(25)** (556a).



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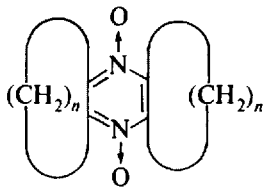

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G. B. Badin

CHAPTER IV

Pyrazine, its *C*-Alkyl, *C*-Aryl, and *N*-Oxide Derivatives

1. PYRAZINE (UNSUBSTITUTED)

A. Preparation of Pyrazine

Methods of preparation of pyrazine include vapor phase dehydration, dehydrogenation, and deamination reactions by suitable catalysts at elevated temperatures. Thus pyrazine results from the dehydrogenation of ethanolamine vapor over a copper catalyst at 300° (249); the passage of diethylenetriamine or *N*-(2′-hydroxyethyl)ethylenediamine vapor over activated alumina at 400° (557); the deamination of diethylenetriamine over kaolin and alumina with some acidic additives at 280–400° (476); the reaction of ethylenediamine and ethylene glycol or ethylene glycol and hydrazine over alumina (389, 392); the vapor phase contact of ethylenediamine and ethylene glycol over Cu–Cr catalyst at 400° (good yield) (390); from ethylenediamine and ethylene oxide at 400° over Cu–Cr–Ba catalyst (391); and from ethylenediamine and formaldehyde over alumina at 410° (393). A number of methods has been described for the dehydrogenation of piperazines to pyrazines. These include the passage of piperazine in an inert diluent over copper chromite and a variety of other catalysts at temperatures between 215 and 500° (464, 467–469, 471, 558–562), and passage of piperazine vapor over palladium–charcoal at 240° (563).

Distillation of a mixture of piperazine or piperazine hydrochloride with lime and zinc dust also gives pyrazine (32). In addition, pyrazine has been prepared from oxidation of aminoacetaldehyde with mercuric chloride and sodium hydroxide (23, 255, 256); from bromoacetaldehyde and ammonia in ether followed by the action of mercuric chloride (237); from 2-aminoacetal by heating with anhydrous oxalic acid at 110–190° or by heating its mercuric chloride or platinic chloride double salt with hydrochloric acid (30, 31); and from diacetylamine (28).

Pyrazine has also been prepared by decarboxylation of 2-carboxypyrazine (564), 2,3-dicarboxypyrazine (397, 564), 2,5-dicarboxypyrazine (22, 272, 564, 565), 2,3,5-tricarboxypyrazine, and tetracarboxypyrazine (564). It is also produced on heating glucose with 25% aqueous ammonia at 100° (33), on heating 2,6-dioxomorpholine with hydrazine or hydroxylamine in hydrochloric acid solution, and on heating "morpholylsemicarbazide" with 20% hydrochloric acid (28).

B. Properties of Pyrazine

Pyrazine is a colorless water-soluble solid of m.p. 54° and b.p. 115.5–115.8° (755 mm Hg) (28) which crystallizes as prisms (from water) and plates (from ether), $D_4^{60.9}$ 1.0311, $n_D^{60.9}$ 1.4953 (566). It forms a mercuric chloride salt [m.p. 273° (dec.); from water] (272); picrate (m.p. 157° from water) (22); methiodide (272, 565), and complex ($C_4H_4N_2 \cdot 2OsO_4$) with osmium tetroxide (566a). The first pK_a value (in water) has been recorded as 0.65 (122), 0.60 (123), 1.1 (124), and 0.6 (125); the second as −5.78 (122) or −6.25 (126). These may be compared with the first basic pK_a values of 5.23 for pyridine (123), 1.30 for pyrimidine (123), and 2.33 for pyridazine (123). The lowest ionization potential of pyrazine has been determined as 9.29 eV (567), which is very similar to that of pyrimidine (9.35) (567), pyridazine (8.71) (567), pyridine (9.27) (568), and benzene (9.25) (569). In pyrazine the ionization is thought to be from the highest occupied π-orbital, and calculations (570) have supported this assignment; open-shell π-electron calculations have also been performed on several singlet excited states of pyridine, pyrazine, pyrimidine, pyridazine, and naphthalene using a recently developed variational technique (571). Other experimentally determined ionization potentials of pyrazine are 9.29 (572) and 9.27 (573). Calculations have been made by Maeda and Nakajima and Pullman (574). Infrared spectra of pyrazine (and derivatives) have been recorded and discussed (575).

The molecular susceptibility ($-\chi_M \times 10^6$/cm^3 mol) of pyrazine has been determined as 37.7 (576) or 38.0 (577); these show large differences from those of pyrimidine (43.1) and pyridazine (40.5). The nature of these differences suggests that they result from delocalization of the "lone-pair" orbitals of the nitrogen atoms in these compounds (577).

Pyrazine forms an azeotrope with water [60% pyrazine–40% water, b.p. 95.5° (uncorr.) (760 mm Hg) n_D^{25} 1.4510] (578). A method of assay for pyrazine and some common impurities has been developed (579). The dipole moment (Debye units) of pyrazine has been determined in dioxane, cyclohexane, and benzene as zero (580, cf. 581) and it has also been calculated as zero (133, 582). The e.s.r. spectrum (583) and the polarized single-crystal absorption spectra of pyrazine (and tetramethylpyrazine) (584) have been recorded. The photoelectron spectra of pyrazine and tetramethylpyrazine have been determined and suggest a different behavior towards electrophilic attack in the two cases (585).

Polarographic studies have been made on pyrazine and methylpyrazines; they indicate that 1,4-dihydropyrazines are produced, and that substitution (by methyl groups) makes the reduction more difficult. The reduction of the parent pyrazine proceeds reversibly (125, 586–588). The experimental half-wave reduction potentials [pyrazine (2.17 eV), methylpyrazine (2.23); 2,6-dimethylpyrazine (2.28), tetramethylpyrazine (2.50), pyridine (2.76), and quinoxaline (1.80)] also revealed that pyrazine was more easily reduced than pyridine but less easily reduced than quanoxaline (589).

Kinetic studies of hydrogen–deuterium exchange in pyrazine (590, 591) and

pyridine show that exchange occurs faster in pyrazine. The rate constant, k_2, in CH_3OD–CH_3ONa at 164.6°C was 3.1×10^{-4}/M sec.

Electron diffraction photography of benzene, pyridine, and pyrazine are closely similar (120).

Pyrazine is exceptional, by comparison with pyridine, pyrimidine, and pyridazine, in forming a relatively stable anion (592); the ion pair association of pyrazine radical anions with alkali metals has been studied using e.s.r. techniques (593–595); and a study has been made of the kinetics of their dimerization (596).

Radical anions of 2,3-dimethylpyrazine and 2,5-di-*t*-butyl-3-isopropylpyrazine have been prepared with metallic potassium in 1,2-dimethoxyethane, and their e.s.r. spectra examined (596a). Heats of hydrogenation of compounds containing isolated and conjugated C=N double bonds have been measured, and the empirical delocalization energy for pyrazine has been determined as 22.3 kcal/mol (93.3 kJ/mol) and corresponds to only 62% of the empirical delocalization energy of benzene (597).

Phase transitions of pyrazine have been studied by calorimetry, X-ray diffraction, and low-frequency vibrational spectroscopy (597a).

Pyrazine and its alkyl derivatives are potentially useful bidentate ligands which form complexes with the following transition metals: Cu^{I}, Co^{II}, Ni^{II}, Fe^{II}, Mo^{VI}, and Ti^{IV}. Some of this literature has been summarized by Cheeseman and Werstiuk (39).

C. Reactions of Pyrazine

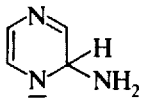
Pyrazines are particularly unsuited to direct substitution by the usual electrophilic reagents owing to the inductive effect of the ring nitrogen atoms, and to resonating structures such as (**1**).

(1)

Pyrazine is halogenated at elevated temperatures to give mono- to polyhalogenopyrazines. Pyrazine hydrochloride (or hydrobromide) with bromine at temperatures up to 215° gave 2-bromopyrazine (598); and several patents describe the chlorination of pyrazine under a variety of conditions to give mono- and di- and tetrachloropyrazine (599–605). These include the reaction of pyrazine with chlorine in the presence of water vapor at 300–600° and the two reactants in nitrogen over activated carbon or cupric chloride on diatomaceous earth at 450–600°. Higher concentrations of halogen gave polyhalogenopyrazines.

Pyrazine is aminated to 2-aminopyrazine with sodium amide in liquid ammonia at room temperature (606), in solvents such as dioxane or pyridine at room temperature or above (yields to 16%), or in the absence of added solvent at 50–55° (yields 36–60%) (607). N.m.r. evidence has been obtained for the anionic σ complex (**2**) in the amination of pyrazine (608). 3-Substituted 1-methylpyrazinium ions

react with ammonia at about $-40°C$ to give covalent amination products; reaction occurred at the 2-position to give 3-substituted 2-amino-1-methyl-1,2-dihydropyrazines when the substituent was chloro or methoxy and at the 6-position when it was a carbamoyl group. 1-Methylpyrazinium ion first forms a 2-adduct at $-50°$ and then a 2,3-diadduct (3) at $-28°$ (609).



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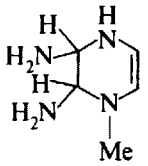


(3)

Pyrazine with hydroxylamine-*O*-sulfonic acid underwent *N*-amination to give *N*-aminopyrazinium derivatives (610).

Homolytic amidation of pyrazine to 2-carbamoylpyrazine can be effected in $>80\%$ yield by using concentrated sulfuric acid with carbamoyl radicals ($\cdot CONH_2$) generated from the action of hydrogen peroxide and ferrous sulfate on formamide (611).

Alkylation of pyrazine has been achieved under a variety of conditions. Treatment of pyrazine in ether at $-20°$ with butyllithium gave a 10% yield of 2-butylpyrazine but with phenyllithium only polymeric material or unchanged starting material was obtained (612). Pyrazine is alkylated at the 2-position by the radical $MeNHCO(CH_2)_4CH_2\cdot$ generated from 2-methyl-3,3-pentamethyleneoxazirane and ferrous sulfate (613). Aldehydes and ketones in the presence of a solution of an alkali or alkaline earth metal in liquid ammonia (or a suspension of these metals in other solvents) can be made to alkylate the pyrazine ring in moderate to good yields. Thus from pyrazine and ethyl methyl ketone, a 60% yield of 2-*s*-butylpyrazine was obtained (614).

The reactions of pyrazine (and methyl and 2,5-dimethylpyrazine) with ethyllithium, butyllithium, and 2-methylbutyllithium in ether or in hexane solution to give ring alkylation at temperatures between $-25°$ and $34°$ have been examined. Low reaction temperatures resulted in poor conversions (about 4%) but higher selectivity in monoalkylation; higher temperatures resulted in higher conversions (up to 18%) but the products included di-, tri-, and tetrasubstituted pyrazines. The main dialkylpyrazine formed in the reaction of pyrazine with an organolithium reagent was the 2,3-isomer (615). The homolytic acylation of pyrazine with aldehydes as the source of acyl radicals in the presence of *t*-butyl hydroperoxide has been shown to give 2,5-disubstituted derivatives (616); and the direct introduction of a 2-dioxanyl group into pyrazine has been achieved by means of *t*-butylhydroperoxide or hydrogen peroxide with ferrous ion and dioxane (617).

The reaction of pyrazine with allylmagnesium chloride gave an addition complex which, on hydrolysis, gave a low yield of 2-allylpyrazine and other products (618).

Monoquaternary salts (272, 565, 619), including the *N*-(2′-sulfoethyl) internal salt (620), and diquaternary salts (621, 622) of pyrazine have been prepared. The

diquaternary salts, which were prepared using oxonium salts, for example, triethyloxonium tetrafluoroborate, as alkylating agents were found to undergo spontaneous radical cation formation upon dissolution in alcohols.

The 1,4-dihydropyrazine system has been prepared by reductive silylation of pyrazine with alkali metals and halogenosilanes. Thus pyrazine with lithium and trimethylchlorosilane gives 1,4-bis(trimethylsilyl)-1,4-dihydropyrazine (623). Reduction of pyrazine with sodium in ethanol gives piperazine (22).

Pyrazine, unlike quinoxaline, does not add bisulfites or hydrogen cyanide; and it is not attacked by iodine in liquid ammonia (624). It is susceptible to alkaline permanganate in the cold (272). Oxidation of pyrazine with hydrogen peroxide in acetic acid gives pyrazine *N*-oxides: the monoxide is formed first and heating at a slightly higher temperature and longer time with an excess of peroxide gives the di-*N*-oxide (625–627). The preparation of the *N*-oxides in the presence of sodium tungstate has also been described (628). Details of preparations of pyrazine *N*-oxides are tabulated in Table IV.1, Section 3A. The reaction of pyrazine with 1-diethylaminopropyne ($Me{-}C{\equiv}C{-}NEt_2$) and boron trifluoride in acetonitrile has been found to give low yields of 3-diethylamino-4-methylpyridine, 2,4- and 2,6-bis(diethylamino)-3,5-dimethylpyridine, and 25% *N*,*N*-diethylpropionamide (629); and pyrazine heated with pyridine 1-oxide and Pt/Pd/C gave 2,2′-bipyrazine (630). Photolysis of solutions of pyrazine at 254 nm and irradiation of pyrazine in the vapor phase at the same wavelength produces a low yield of pyrimidine (631, 632). Vapor phase pyrolysis of pyrazine over silica at 997° C has been shown to give acetylene, hydrogen cyanide (36%), pyrimidine (3%), and pyridine (0.7%), and unreacted pyrazine (45%) (633).

2. *C*-ALKYL- AND *C*-ARYLPYRAZINES

A. Preparation of Alkyl- and Arylpyrazines

C-Alkyl- and *C*-arylpyrazines are most generally prepared by primary syntheses, which have been discussed in Chapter II; they may also be prepared by alkylation (or arylation) of pyrazines at nuclear or side chain carbon atoms, and by decarboxylation of alkyl carboxy pyrazines.

(1) *Primary Syntheses*

Detailed discussion of the preparation of a variety of alkyl- and arylpyrazines by primary syntheses, principally from aliphatic components, appears in Chapter II. These include, for example, the preparation of 2,5-disubstituted and 2,3,5,6-tetrasubstituted alkyl- and arylpyrazines from α-amino carbonyl compounds, which may be produced by many methods such as reduction of α-hydroxyimino carbonyl compounds, aminolysis of α-halogeno carbonyl compounds, oxidation of α-amino

alcohols, and reduction of α-amino acids (Chapter II.1); the condensation of α,β-dicarbonyl compounds with α,β-diamino compounds (Chapter II.2); and the dehydrogenation of piperazines (Chapter II.6) and dihydropyrazines with, for example, metal oxides in basic solvents (633a).

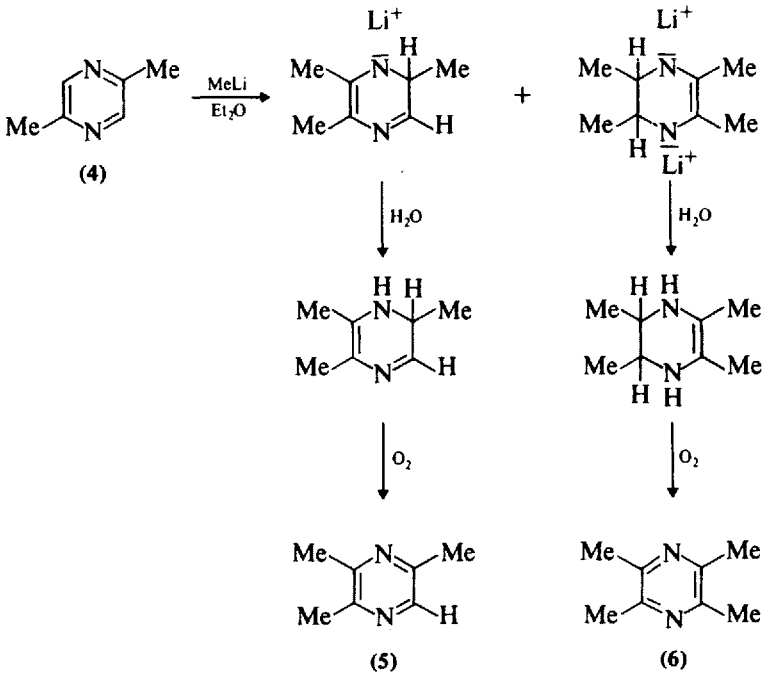
(2) *Alkylation at Nuclear Carbon*

The alkylation of pyrazine at a nuclear carbon atom has been discussed in detail in Section 1C (612–615, 617, 634). For example, 2-butylpyrazine was prepared from pyrazine and butyllithium in ether at $-20°$ (612), 2-*s*-butylpyrazine was prepared from pyrazine, ethyl methyl ketone, and alkali or alkaline earth metals in liquid ammonia (614); the effect of temperature on the products, specificity, and yields from the alkylation of pyrazine by ethyllithium (and other alkyllithiums) in ether or hexane solutions between $-25°$ and $34°$ has been examined (615).

Nuclear *C*-alkylation of alkyl pyrazines has been extensively studied; methylpyrazines react with organolithium reagents to form products resulting from ring alkylation (or arylation) and side chain metalation (635).

The reactions of 2,5-dimethylpyrazine (and pyrazine) with various alkyl(and phenyl)lithium compounds in ether were first examined by Klein and Spoerri (612, 636) and found to give 3-alkyl (or phenyl)-2,5-dimethylpyrazines; and Gelas and Rambaud (637) have examined the reactions of 2,3-, 2,5-, and 2,6-dimethylpyrazine with ethyllithium to give, respectively, 3–5% of 5-ethyl-2,3-dimethyl-, 20–30% of 3-ethyl-2,5-dimethyl-, and 20–30% of 2-ethyl-3,5-dimethylpyrazine. 2,5-Diethyl-3,6-dimethylpyrazine and 2,6-diethyl-3,5-dimethylpyrazine were also obtained as shown by n.m.r. spectroscopy. Schwaiger and Ward (615) examined the reactions of methylpyrazine and 2,5-dimethylpyrazine with ethyllithium, butyllithium, and 2-methylbutyllithium in ether or in hexane solution, at different temperatures between $-25°$ and $34°$. They found that low reaction temperatures resulted in poor conversions (about 4%) but higher selectivity in monoalkylation; higher temperatures resulted in higher conversions (up to 18%) but the products included di-, tri-, and tetrasubstituted pyrazines, and homologues resulting from side chain alkylations. It was confirmed that the main dialkylpyrazine formed in the reaction of a monoalkylpyrazine with an organolithium reagent was the 2,3-isomer; from methylpyrazine and butyllithium the major dialkylated product was 2-butyl-3-methylpyrazine, accompanied by one isomer, the 2,6-disubstituted pyrazine in the ratio 3:2. Although it has been reported (635) that trimethylpyrazine was not alkylated with methyllithium, it reacted readily with butyllithium to give butyltrimethylpyrazine in 12% yield. Rizzi (635) has investigated the reactions of isomeric dimethylpyrazines and trimethylpyrazine with methyllithium in some detail. Evidence was found for hydropyrazine intermediates in the ring methylation of 2,5-dimethylpyrazine as shown in the conversions of (**4**) to (**5**) and (**6**). Metalation of the side chain of 2,5-dimethylpyrazine was observed as well as ring methylation. The presence of the methyl metalated species was established by trapping it with methyl benzoate to form 2-methyl-5-phenacylpyrazine. In other solvents vicinal

dimethylated pyrazines gave products resulting exclusively from side chain metalation. In hexane and benzene as solvents 2,3-dimethylpyrazine underwent partial ring alkylation with ethyllithium and *n*-butyllithium to form trialkylpyrazines. The reaction of 2,3-dialkylpyrazines and methyllithium has been further investigated by Rizzi (638) and indirect evidence presented for ring metalation.

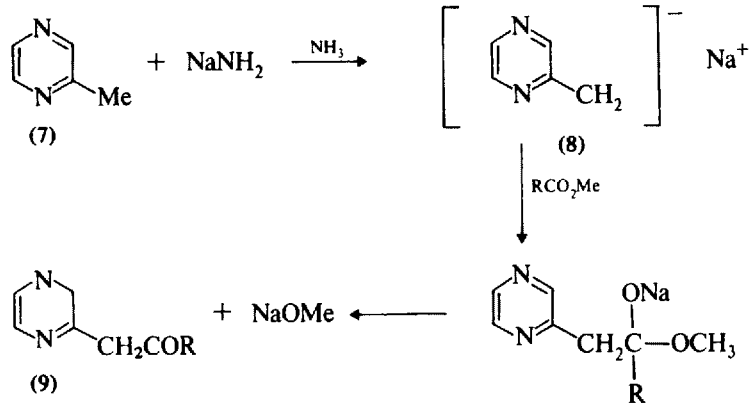


Ring allylation and propenylation of methylpyrazine has been described (634); acetonylpyrazine with phenyllithium gives 2-acetonyl-6-phenylpyrazine (639); and 2,5-dimethylpyrazine with isopentyllithium gave 3-isopentyl-2,5-dimethylpyrazine (70). Aldehydes and ketones in the presence of a solution of an alkali or alkaline earth metal in liquid ammonia, or a suspension of these metals in other solvents, can be used to alkylate the pyrazine ring in moderate to good yields (614, 640, 641). This alkylation has been successfully applied to alkyl- and dialkyl(amino- and methoxy)pyrazines, and a mechanism has been proposed for the reaction (614). For example, the reaction of potassium with methylpyrazine and ethyl methyl ketone, catalyzed by sodamide (0.25 mol) gave 88% of 2-*s*-butyl-6-methylpyrazine.

(3) *Extranuclear C-Alkylation (and Acylation)*

The reactions of pyrazinylmethylsodium (8), prepared from methylpyrazine (7) and sodium amide in liquid ammonia, with a series of aliphatic, aromatic, and heterocyclic esters have been shown to give in most cases 2-(acylmethyl)pyrazines

(9) as the only products in high yields, but acylation of pyrazinylmethylsodium with methyl picolinate gave a mixture of 2-pyridinyl pyrazinylmethyl ketone (42.6%) and 2-pyridinylbis(pyrazinylmethyl)carbinol (22.8%), and its acylation with ethyl formate gave only bis(pyrazinylmethyl)carbinol (48.7%) (642). These authors found that the methyl group of methylpyrazine was not appreciably metalated by phenyllithium. Similar acylation of 2-methylpyrazine with 2-methoxycarbonylpyrazine or 4-ethoxycarbonylpyrimidine and potassium ethoxide in benzene has been described (642).



Methylpyrazine has been alkylated at its methyl group with a series of alkyl halides (including benzyl chloride) and arylated with bromobenzene, using in each case the sodium amide–liquid ammonia method (638, 643); and alkylated with benzyl alcohol using potassium hydroxide as the condensing agent. Pyrazinylmethylsodium (8) with *N*-methyl-*N*-phenylcyanamide gives 2-cyanomethylpyrazine (644).

Sodium amide in liquid ammonia effects the metalation of the side chains of 2,6-dimethylpyrazine [and 2-(3′-dimethylaminopropyl)pyrazine], and the intermediates when condensed with aliphatic, aromatic, and heterocyclic esters gave the corresponding ketones (9) (645). Similar reactions of dimethylpyrazines with ethyl acetate have also been described (634). Benzyl chloride and several alkyl halides condensed with 2-methyl-6-pyrazinylmethylsodium to give the corresponding 2-alkyl(and 2-phenethyl)-6-methylpyrazines (645). 2,6-Bis(acylmethyl)pyrazines have been synthesized by (*a*) the monoacylation of 2-acylmethyl-6-methylpyrazines and (*b*) the direct acylation of 2,6-dimethylpyrazine with the appropriate ester and sodium amide in liquid ammonia as the condensing agent (646); and tetramethylpyrazine can be made similarly (or with phenyllithium in ether) to undergo mono- and diacylation (647).

Tetramethylpyrazine, in the presence of sodium amide and phenyllithium, has been alkylated with several alkyl halides to give mixtures of alkyltrimethylpyrazines and perhaps 2,5-dialkyl-3,6-dimethylpyrazines (648).

Reactions of the isomeric dimethylpyrazines and trimethylpyrazines with methyllithium have been studied in detail (635). Metalation of the side chain of

2,5-dimethylpyrazine was observed, as well as ring methylation. In ether solvent vicinally dimethylated pyrazines gave products exclusively from side chain metalation (635). The chain alkylation of methylpyrazine has been patented (649), and methylpyrazine has been acylated with benzoate (and phthalate) esters using sodium hydride as the condensing agent to afford phenacylpyrazine (650).

2,6-Dimethoxyphenyllithium has been found to be more effective than phenyllithium (642) in the preparation of phenacylpyrazine from methylpyrazine and methyl benzoate (651).

(4) *Decarboxylation of Alkyl Carboxy Pyrazines*

Like pyrazinecarboxylic acids, alkylpyrazinecarboxylic acids are decarboxylated on heating to elevated temperatures. For example, 2,3-dicarboxypyrazine and 2,3-dicarboxy-5,6-dimethylpyrazine are decarboxylated in acetic acid at 180° to pyrazine and 2,3-dimethylpyrazine, respectively, but on distillation under vacuum they give 2-carboxypyrazine and 5-carboxy-2,3-dimethylpyrazine, respectively (397).

Decarboxylation of alkylpyrazine carboxylic acids to alkylpyrazines is discussed fully in Section IX.1C(1).

(5) *Replacement of Halogeno Substituents by Alkyl Groups*

Preparations of alkylpyrazines by such reactions are discussed in Section V.5H.

(6) *Preparations of Particular Methyl-, Dimethyl-, and Vinylpyrazines*

To illustrate further the general methods of preparation described above, literature preparations of methyl-, dimethyl- and vinylpyrazine are summarized below.

2-Methylpyrazine. 2-Methylpyrazine has been prepared by decarboxylation of 2-carboxy-5-methylpyrazine (272), 2,3-dicarboxy-5-methylpyrazine (405, 652), and 2-carboxy-3-methylpyrazine (472); from glucose with 25% aqueous ammonia at 100° (33); by dehydrogenation of 2-methylpiperazine (or *N*-butyl-2-methylpiperazine) over copper chromite at elevated temperatures (470, 471) (Section II.6); and in high yield by dehydrogenation of methylpiperazine over catalysts containing CuO, Cr_2O_3, or MnO_2 at 350–370° (469). Other catalysts have also been used for this dehydrogenation (471, 562).

2,3-Dimethylpyrazine. Ethylenediamine with diacetyl has been shown to give 2,3-dimethyl-5,6-dihydropyrazine which may then be oxidized with a variety of oxidizing agents (Fehling solution, aerial oxidation in alkali, heated with copper chromite and mercuric chloride) to 2,3-dimethylpyrazine (331–333, 472, 633a, 635, 653). Decarboxylation of 2,3-dicarboxy-5,6-dimethylpyrazine in acetic acid at 180° (397, 654) and catalytic dehydrogenation of 2,3-dimethylpiperazine give

2,3-dimethylpyrazine (472, 562). 2,3-Dimethylpyrazine has also been prepared from diamines and diols over Cu–Cr catalyst at about 400° (390).

2,5-Dimethylpyrazine. This has been synthesized from glycerol by distillation with ammonium salts (32, 271–274) (Section II.1F); from α-hydroxyiminoacetone by reduction with a variety of reagents (23, 32, 196, 197, 411) (Section II.1B); from ethyl DL-alaninate by reduction through α-aminopropionaldehyde (255, 256); by decarboxylation of 3-carboxy-2,5-dimethylpyrazine (in acetic acid) (32), from acetamidoacetone by saponification and oxidation (289); from acetone and nitrogen iodide (190, 512); and by dehydrogenation of 2,5-dimethylpiperazine over Cu chromite–SiO_2–Al_2O_3 catalyst (562). 2,5-Dimethylpyrazine is also obtained by heating isopropanolamine and finely ground nickel (251, 252, 655) or copper chromite at 275° (250); sucrose and β-aminopropionitrile gave a mixture containing 2,5-dimethylpyrazine (508); and 1,2-propylenediamine and 1,2-propyleneglycol over an alumina catalyst at 400° gave 2,5-dimethylpyrazine and other alkylpyrazines (394).

2,6-Dimethylpyrazine. This is produced, in addition to other products, by heating glucose and 25% ammonia at 100° (33), by dehydrogenation (91% yield) of 2,6-dimethylpiperazine over copper chromite at 355–360° (468), and (with other products) from 1,2-propylenediamine and 1,2-propyleneglycol over an alumina catalyst at 400° (394).

2-Vinylpyrazine. This has been prepared by dehydration of 2-hydroxyethylpyrazine with molten potassium hydroxide (470) and pyrolysis (low yield) (656). A better preparation is claimed from β-dimethylaminoethylpyrazine through β-(pyrazinylethyl)trimethylammonium chloride by removal of the iodide ion and treatment with alkali (657). Dehydrogenation of 2-ethylpyrazine over a CaO–P_2O_5–CoO catalyst at 600° also gives 2-vinylpyrazine (658).

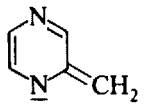
B. Properties of Alkylpyrazines

Alkylpyrazines are liquids or low melting solids, the boiling points of which increase with additional substitution [2-methylpyrazine, b.p. 135°/761 mm Hg (272); 2,3-dimethyl-, b.p. 155.5–156.5°/atm. (654); 2,5-dimethyl-, b.p. 155°/760, m.p. 15° (32); 2,6-dimethyl-, b.p. 155.6°/atm., m.p. 39° (659); 2,3,5-trimethyl-, b.p. 171–172°/735 (660); and tetramethyl-, b.p. 189.5°/760 (660)]. The methylpyrazines are soluble in ethanol and ether but their solubility in water decreased with increasing substitution (tetramethylpyrazine is soluble in hot water) (3). The crystal structure of tetramethylpyrazine has been determined (661). Early workers thought that pyrazines were monoacid bases but Tutin and Caton (662) showed them to form mono- and diacid salts: dihydrochlorides, dihydrobromides, and disulfates of some aryl-substituted pyrazines were prepared in nonaqueous media. The first and second basic ionization constants of pyrazine, and its methyl, 2,5-dimethyl, 2,6-dimethyl, and tetramethyl derivatives have been determined as 0.65, −5.78; 1.45, −5.25; 1.85, −4.60; 1.90, −4.57; and 3.55, −2.70, respectively (122), and show increasing values for increased substitution by methyl groups. First

basic ionization constants have also been determined by Keyworth (124). The polarography of methylpyrazines (125) shows three waves: the first is due to a two-electron irreversible reduction, probably to a dihydropyrazine. Okano and Ohira (588) have also examined the polarographic behavior of 2,5-dimethyl- and tetramethylpyrazine (and pyrazine) involving reduction of the pyrazine nucleus to 1,4-dihydro compounds.

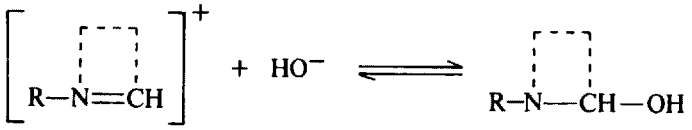
Electric dipole moments of methylpyrazines have been reported: methylpyrazine, 0.74*D* (663); 2,5-dimethylpyrazine, 0.0; and 2,6-dimethylpyrazine, 0.53, 0.6, and 0.66 (659, 663, 664).

2-Methylpyrazine in the presence of excess potassium amide at -40° undergoes deprotonation to give the charge delocalized anion (**10**) (665).

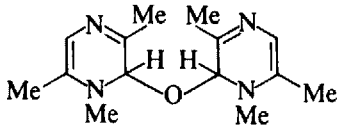


(**10**)

Methylpyrazine is methylated with methyl iodide in dimethyl sulfoxide at room temperature to give 1-methyl-3-methylpyrazinium iodide and 1-methyl-2-methylpyrazinium iodide, in a ratio of 3.9 : 1. The rate of methylation relative to pyrazine was 2.06 (666). The reaction of 2,5-dimethylpyrazine with iodo- or bromoacetic acid to give the 1,2,5-trimethylpyrazinium salt has been investigated (3). A kinetic study of the reaction of sodium hydroxide on quaternary pyrazinium salts (667, 668) has been made using a conductivity method to follow the progress of the reaction (**11** ⇌ **12**). In the case of 1,2,5-trimethylpyrazinium hydroxide, equilibrium lies toward (**11**), which slowly disappears, presumably forming the ether (**13**) (668). When 1,2,5-trimethylpyrazinium bromide was heated in a sealed tube trimethyl- and tetramethylpyrazine were produced (660).



(**11**) (**12**)



(**13**)

Comparison between the photoelectron spectra of pyrazine, 2,6-dimethylpyrazine, and tetramethylpyrazine suggests a different behavior toward electrophilic attack on tetramethylpyrazine compared to the others (585).

Irradiation of 2-methylpyrazine and 2,5- and 2,6-dimethylpyrazine at 254 nm has been shown to give various methyl- and dimethylpyrimidines (632). Pyrolyses and thermal stabilities of 2,5-dialkylpyrazines have been examined (688a).

C. Reactions of Alkylpyrazines

(1) *Oxidation*

The oxidation of pyrazine and alkylpyrazines to pyrazine *N*-oxides is discussed in Section 3A. Here, the oxidation of alkylpyrazines to pyrazinecarboxylic acids is described. Aqueous potassium permanganate has been most generally used for these oxidations. Thus 2-methylpyrazine (272) and 2-ethylpyrazine (669) have been oxidized to 2-carboxypyrazine, and the latter method has been used commercially (670); 2,3-dimethylpyrazine and aqueous potassium permanganate at 20–25° and then 70° gave 2-carboxy-3-methylpyrazine, and further oxidation gave 2,3-dicarboxypyrazine (671); 2,5-dimethylpyrazine with aqueous potassium permanganate on a steam bath gave 2,5-dicarboxy- and 2-carboxy-5-methylpyrazine (3, 32, 272, 672, 673); 2-hydroxymethyl-5-methylpyrazine and aqueous potassium permanganate at 20–24° gave 2-carboxy-5-methylpyrazine (673); 2-(D-*arabo*-tetrahydroxybutyl)-5-methylpyrazine with aqueous potassium permanganate at reflux gave 2,5-dicarboxypyrazine (48); 2,6-dimethylpyrazine with aqueous potassium permanganate at 70–75° gave 2-carboxy-6-methylpyrazine (673); tetramethylpyrazine gave tetracarboxypyrazine (3, 22); 3-ethyl-2,5-dimethylpyrazine with potassium permanganate solution gave tricarboxypyrazine and 3-carboxy-2,5-dimethylpyrazine (27, 32); 2,5-diethyl-3,6-dimethylpyrazine with 8 mol potassium permanganate in aqueous solution on a water bath gave 2,5-dicarboxy-3,6-dimethylpyrazine (19, 674); 2,5-dimethyl-3,6-diphenylpyrazine with 2% aqueous potassium permanganate gave 2,5-dicarboxy-3,6-diphenylpyrazine (209); 2-styrylpyrazine was oxidized to 2-carboxypyrazine (675); and 2,5-bis(4′-methoxystyryl)pyrazine was oxidized to 2,5-dicarboxypyrazine (411).

Other oxidations include that of methylpyrazine with selenious acid in pyridine to give 64% of 2-carboxypyrazine (669) and 2,5-dimethylpyrazine with selenium dioxide to 2,5-dicarboxypyrazine (676); a patent (677) claims oxidation of methylpyrazine with sodium dichromate and aqueous phosphoric acid in an autoclave at 225–350° to give 74% 2-carboxypyrazine. Likewise, 2,5-dimethylpyrazine gives 67% 2,5-dicarboxypyrazine, and 2,6-dimethylpyrazine gives 59% 2,6-dicarboxypyrazine.

Some 2,3-dialkylpyrazines have been oxidized in one step with sodium dichromate in acetic acid, in good yields, to the corresponding 2-acyl-3-alkylpyrazines (678). Thus 2-ethyl-3-methylpyrazine gave 2-acetyl-3-methylpyrazine, 2,3-diethylpyrazine gave 2-acetyl-3-ethylpyrazine, and 2-ethyl-3,5(or 3,6)-dimethylpyrazine gave 2-acetyl-3,5(or 3,6)-dimethylpyrazine (678).

(2) *Halogenation*

The chlorination of methyl- and dialkylpyrazines in carbon tetrachloride solution has been investigated by a number of workers (679–683). Chlorination of 2-methyl-

pyrazine with chlorine in carbon tetrachloride solution (679–681) has been shown to give 2-chloro-3-methyl- (679, 680) and 2-chloro-6-methylpyrazine (681), and not 2-chloro-3-methyl- and 2-chloro-5-methylpyrazine, as claimed by Hirschberg and Spoerri (679). 2,5-Dimethyl- and 2,5-diethylpyrazine similarly gave 3-chloro-2,5-dimethyl- (679, 680) and 3-chloro-2,5-diethylpyrazine (680), respectively, in good yield.

2,3-Dimethylpyrazine dissolved in carbon tetrachloride and treated with (*a*) chlorine in the presence of ultraviolet light or (*b*) *N*-chlorosuccinimide and a catalytic amount of benzoyl peroxide gave 2,3-bis(chloromethyl)pyrazine (654). In allowing 2,6-dimethylpyrazine to react with chlorine, it was found that ultraviolet radiation was essential and the product was the unstable 2,6-bis(α-chloromethyl)pyrazine (679).

Vapor phase chlorination of methylpyrazine in carbon tetrachloride at 545° in 15 times the molar ratio of chlorine gave tetrachloropyrazine (684).

Chlorination of 2-methylpyrazine in acetic acid at 100° gave 2-trichloromethylpyrazine (685, 686), whereas 2-chloro-3-methylpyrazine under similar conditions gave 2-chloro-3-dichloromethylpyrazine (685, 687, 688). Chlorine bubbled into a stirred solution of 3-dimethylamino-2,5-dimethylpyrazine in chloroform gave the 6-chloro derivative (689).

Halogenations with *N*-halogenosuccinimides have also been studied. Treatment of 2-methyl- and 2,5-dimethylpyrazine with one equivalent of *N*-chlorosuccinimide and a small quantity of benzoyl peroxide gave the unstable 2-chloromethyl (679, 690) and 2-chloromethyl-5-methylpyrazine (679). 2-Ethyl-3-methylpyrazine and 2,3-diethylpyrazine with *N*-bromosuccinimide in the presence of benzoyl peroxide gave 2-(1′-bromoethyl)-3-methyl(and 3-ethyl)pyrazine, respectively (691, 692).

A series of monoalkylpyrazines has been chlorinated specifically at the 3-position with sulfuryl chloride in the presence of *N,N*-dimethylformamide; the nucleus of 2,6-dialkylpyrazines is also readily chlorinated (687, 693). The reaction of isobutylpyrazine with phosphoryl chloride and phosphorus pentachloride gave 2-chloro-5-isobutylpyrazine in 25% yield (693). 2-Acetonylpyrazine and 2-phenacylpyrazine with aqueous potassium hypochlorite gave 2-dichloromethylpyrazine (694).

(3) *Reduction*

Pyrazines may be reduced with a variety of reducing agents to the corresponding piperazines; other reductions gave dihydropyrazines. Some simple piperazines prepared in these ways include piperazine (sodium in ethanol) (22); methylpiperazine (sodium in ethanol) (272); 2,5-dimethylpiperazine [sodium in ethanol (32, 695–697), hydrogen over nickel (698)]; 2,3,5-trimethylpiperazine (sodium in ethanol) (695); tetramethylpiperazine [sodium in ethanol (695), hydrogen over platinum (699), aluminum amalgam in neutral solution (699), sodium amalgam in aqueous acetic acid or hydrochloric acid (699), tin and hydrochloric acid (699), hydrogen under pressure and at a high temperature with or without catalyst (700)]; 3-ethyl-2,5-dimethylpiperazine (sodium in ethanol) (32); and 2,3-diphenylpiperazine (sodium

in boiling amyl alcohol) (6). Catalytic reduction of tetramethylpyrazine methiodide with hydrogen over platinum gave the pentamethylpiperazine (701).

Other reducing conditions gave dihydropyrazines. For example, reduction of 2,5-diphenylpyrazine with hydriodic acid and red phosphorus gave 2,5-diphenyl-3,6-dihydropyrazines (286). Some electrochemical reductions of pyrazines to dihydropyrazines have also been effected (125, 702). In alkaline aqueous methanol and aqueous dimethylformamide electrochemical reduction leads to 1,4-dihydropyrazines too easily oxidizable to be isolated (703), and these compounds isomerize into 1,2- or 1,6-dihydropyrazines. It has also been shown that 2,5-diphenyl-3,6-dihydropyrazine and 2,5-diphenyl-1,6-dihydropyrazine are in thermodynamic equilibrium (703).

(4) *Alkylation*

(a) *N*-ALKYLATION

Monomethiodides of pyrazine and methylpyrazines have been readily prepared (3, 32, 272, 565, 660). Rates and position of quaternization of 2-substituted pyrazines with methyl iodide in dimethyl sulfoxide at room temperature have been determined by a kinetic competition method (666); 2-methylpyrazine gave 1,3-dimethylpyrazinium iodide as the major product (704), with some 1,2-dimethylpyrazinium iodide (666).

Diquaternary salts of methylpyrazines have been prepared by treatment with triethyloxonium fluoroborate (621, 622). Steric hindrance has a considerable effect on the reaction as illustrated by the yield as follows: pyrazine (97%), 2,5-dimethylpyrazine (95%), 2,6-dimethylpyrazine (46%), and 2,3,5,6-tetramethylpyrazine (5%).

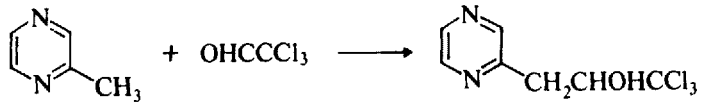
(b) *C*-ALKYLATION

Nuclear and extranuclear *C*-alkylation has been discussed in detail in Sections 2A(2) and 2A(3), respectively.

(5) *Aldol-type Condensation*

The enhanced activity of alkyl groups attached to the pyrazine nucleus is illustrated by methylpyrazine, which undergoes aldol type condensations with aldehydes and ketones. Methylpyrazine (**14**) formed an adduct (**15**) with chloral in pyridine solution (405); with paraformaldehyde at 165°, it gave 2-hydroxyethylpyrazine (470) (which was subsequently dehydrated with molten potassium hydroxide to 2-vinylpyrazine); and with benzophenone and sodamide it gave the corresponding carbinol (705).

In more extensive studies of these condensations, Behun and Levine (706) prepared the corresponding carbinols from methylpyrazine and eight aldehydes and ketones with sodium amide in liquid ammonia generally in high yield;



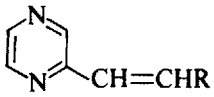
(14) (15)

Kamal and Levine (707) have effected aldol-type condensations with 2-methyl-6-pyrazinylmethylsodium and 12 aldehydes and ketones to give the corresponding secondary and tertiary carbinols; 2-(3′-dimethylaminopropyl)pyrazine with three representative ketones using sodium amide in liquid ammonia gave the corresponding tertiary carbinols; and methylpyrazine anion with styrene oxide gave the secondary carbinol.

A number of carbinols has been prepared by the reaction of tetramethylpyrazine with aldehydes and ketones using phenyllithium as the condensing agent (648).

(a) DEHYDRATION OF CARBINOLS FROM ALDOL-TYPE CONDENSATIONS

Depending on the reaction conditions, carbinols (**15**) produced in aldol-type condensations may be dehydrated to olefinic products (**16**). Thus Franke (708) treated 2,5-dimethylpyrazine with several aromatic aldehydes (and chloral) in a bomb at 160–200° using zinc chloride as catalyst. Under these conditions, mono- and disubstituted olefinic products, which resulted from the dehydration of the initially formed carbinols, were obtained in unreported yields; Mager and Berends (411) found that 2,5-dimethylpyrazine and *p*-methoxybenzaldehyde with zinc chloride at 185° gave a 40% yield of 2,5-bis(*p*-methoxystyryl)pyrazine. 2-Styrylpyrazine has been prepared from 2-methylpyrazine (and 2-methylpiperazine ?) (709), benzaldehyde, and zinc chloride (709, 710), and 2,5-bis(*N*,*N*-dimethylcarbamoyl)-3,6-di(substituted styryl)pyrazines by the condensation of 2,5-bis(*N*,*N*-dimethylcarbamoyl)-3,6-dimethylpyrazine with substituted benzaldehydes (710a), but 2-methylpyrazine with 4-dimethylaminobenzaldehyde under azeotropic conditions (with toluene) in the presence of piperidinium acetate [conditions that gave the styryl compound from 2-methylquinoxaline and 4-dimethylaminobenzaldehyde (711)] gave no styryl base (712). 2-Methylpyrazine with 2-, 3-, and 4-formylpyridine and zinc chloride gave the corresponding triazastilbenes (712a).

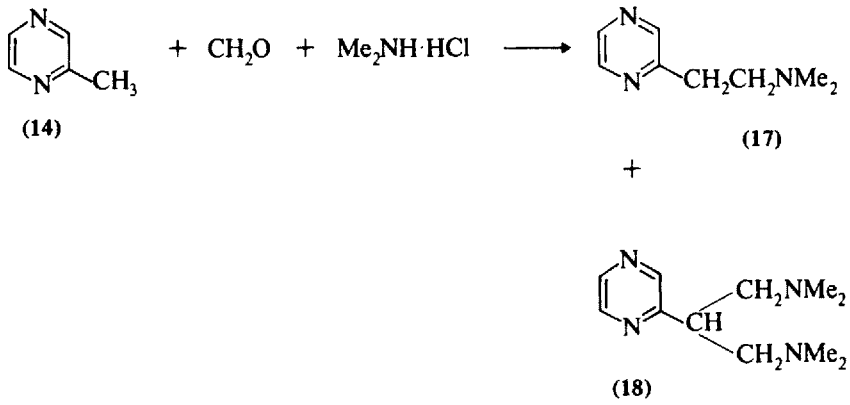


(16)

Tetramethylpyrazine, *p*-dimethylaminobenzaldehyde, and 37% hydrochloric acid have been shown to give 2,3,5,6-tetra(*p*-dimethylaminostyryl)pyrazine (713). Similar condensations have also been applied to quarternary salts of methylpyrazines with a piperidine catalyst (714). Thus 1,2,5-trimethylpyrazinium methylsulfate and benzaldehyde gave 1,5-dimethyl-2-styrylpyrazinium methylsulfate.

(6) *Mannich Reaction*

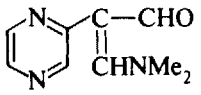
In the pyrazine series, the Mannich reaction was applied first to 2,5-dimethylpyrazine by Linder and Spoerri (715). Of the amines tried, positive reactions were obtained only with dimethylamine, piperidine, and morpholine, and it was found that one, or more usually two, of the hydrogen atoms of each of the methyl groups could be substituted. Thus 2,5-dimethylpyrazine, dimethylamine hydrochloride, and formalin in refluxing isopentyl alcohol gave 2,5-bis[bis(dimethylaminomethyl)-methyl]pyrazine and 2,5-bis(β-dimethylaminoethyl)pyrazine. Reaction of 2-methylpyrazine with formalin and diethylamine hydrochloride gave 2-β-diethylaminoethylpyrazine (716); similarly dimethylamine hydrochloride gave 2-dimethylaminoethylpyrazine (**17**) and some 2-[bis(dimethylaminomethyl)]methylpyrazine (**18**) (657).



(**14**) (**17**) (**18**)

(7) *Vilsmeier Reaction*

Condensation of 2-methylpyrazine with the Vilsmeier reagent, phosphoryl chloride, and dimethylformamide gave 2-(2′-dimethylamino-1′-formylvinyl)pyrazine (**19**) (717).



(**19**)

(8) *Amination at Ring Carbon and Nitrogen*

Amination of 2,5-dimethylpyrazine proceeds very slowly with $NaNH_2$ in xylene. Only on strong heating in solvents is an evolution of hydrogen observed, and a small quantity of 3-amino-2,5-dimethylpyrazine isolated (718); most of the

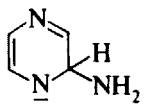
2,5-dimethylpyrazine is recovered unchanged. Joiner and Spoerri (719) found that when dimethylamine was used as solvent at 165° the yield was increased to 35%.

Direct amination of 2,5-di-*s*-butylpyrazine with sodamide gave 3-amino-2,5-di-*s*-butylpyrazine (89, 171, 720).

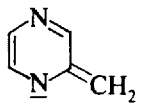
Zoltewicz and Helmick (665) found that, whereas pyrazine reacts with potassium amide to form the anionic σ complex (**20**), methylpyrazine undergoes deprotonation to give the delocalized carbanion (**21**); and the p.m.r. spectrum shows that pyrazine with phenyllithium at $-45°$ is converted completely into a dihydro adduct analogous to (**20**) (720a).

1,2,5-Trimethylpyrazinium iodide in liquid ammonia adds at the 6-position to form the 6-adduct (**22**) (609); nitromethide and ethanethiolate ions at $-60°$ add to the 6-position of 1,2,5-trimethylpyrazinium ion to give adducts (**23**, X = $CHNO_2^-$ and SCH_3), respectively (721).

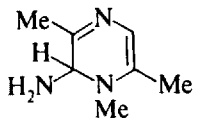
N-Aminopyrazinium derivatives (**24**, $R^1 = R^2 = H$; $R^1 = H$; $R^2 = Me$; $R^1 = R^2 = Me$) have been synthesized by *N*-amination of pyrazine derivatives with hydroxylamine-*O*-sulfonic acid (H_2NOSO_2H) as the potassium salt, and later addition of hydriodic acid (610).



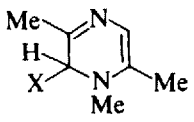
(**20**)



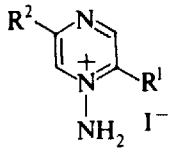
(**21**)



(**22**)



(**23**)



(**24**)

(9) *Ring Transformations*

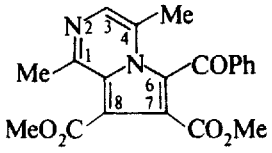
The photoisomerization of pyrazine and its methyl derivatives to pyrimidines has been described (632). Thus photolysis at 254 nm of 2-methylpyrazine gave 4- and 5-methylpyrimidine, 2,6-dimethylpyrazine gave 4,5-dimethylpyrimidine, and 2,5-dimethylpyrazine gave 2,5- and 4,6-dimethylpyrimidine. 2-Methylpyrazine with 1-diethylaminopropyne and boron trifluoride in acetonitrile has been shown to give 5-diethylamino-2,4-dimethylpyridine, 3-diethylamino-2,4-dimethylpyridine, and other compounds (629).

(10) *Photoeliminations*

Irradiation at 313 nm of benzene solutions of 2-butylpyrazine and 2-(2′-hydroxyethyl)pyrazine gave 2-methylpyrazine (722).

(11) *Addition Reactions*

2,5-Dimethyl-1-phenacylpyrazinium bromide (from 2,5-dimethylpyrazine and phenacyl bromide) and dimethyl acetylenedicarboxylate has been shown to give 6-benzoyl-7,8-bis(methoxycarbonyl)-1,4-dimethylpyrrolo[1,2-*a*]pyrazine (**25**) and 7,8-bis(methoxycarbonyl)-1,4-dimethylpyrrolo[1,2-*a*]pyrazine (**26**) (723), and 1,2,5-trimethylpyrazinium iodide and dimethyl acetylenedicarboxylate also gave a 1% yield of (**26**). Addition reactions of 2-methyl- (724), 2,6-dimethyl- (724), 2,5-dimethyl- (725), and 2,3,5,6-tetramethylpyrazine (725), with dimethyl acetylenedicarboxylate have also been investigated.



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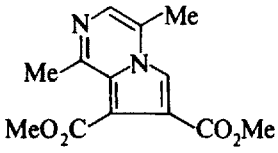
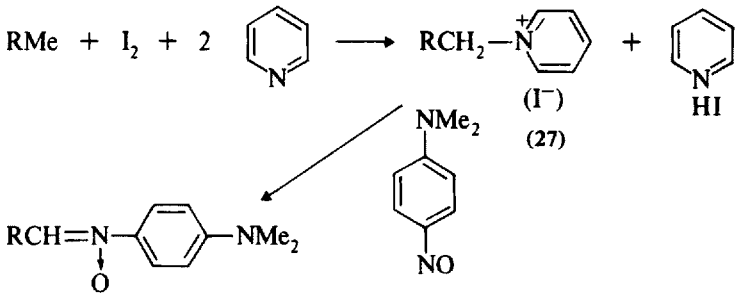


(26)

(12) *Miscellaneous*

A patent (726) has described the preparation of 2-cyanopyrazine from 2-methylpyrazine by reaction with ammonia and air at 350° over a catalyst containing vanadium pentoxide and potassium sulfate; a series of cyanomethylpyrazines has been prepared from the corresponding methylpyrazines by reaction with sodium amide in liquid ammonia followed by *N*-methyl-*N*-phenylcyanamide in dioxane (644). 2-Hydroxyiminomethylpyrazine has been prepared from 2-methylpyrazine, sodium amide, and liquid ammonia with butyl nitrite (727, 728), and 2-hydroxyiminomethyl-3,6-dimethyl-5-pentylpyrazine similarly from 2,3,5-trimethyl-6-pentylpyrazine (648). Nitrones (**28**) have been prepared from 2,3- and 2,5-dimethyl- and tetramethylpyrazine through the substituted methylpyridinium (perchlorates) (**27**) by reaction with *p*-nitroso-*N*,*N*-dimethylaniline (729). Dehydrogenation of ethylpyrazine at 600° over a calcium cobaltous phosphate catalyst gives 2-vinylpyrazine (658).



(28)

(13) *Reactions of Vinylpyrazine*

A series of aminoethylpyrazines ($C_4H_3N_2CH_2CH_2N=$) has been prepared by the reaction of vinylpyrazine with amines in the presence of methanolic acetic acid or metallic sodium as the catalyst (730); and likewise 2-[2′-(1″-oxocyclohexan-2″-yl)ethyl]pyrazine from vinylpyrazine and cyclohexanone (731).

Ozonolysis of vinylpyrazine gives 2-formylpyrazine (732).

3. PYRAZINE *N*-OXIDES, THEIR *C*-ALKYL AND *C*-ARYL DERIVATIVES

A. Preparation of Alkyl- and Arylpyrazine *N*-Oxides by Oxidation

In addition to the primary syntheses of alkyl- and arylpyrazine *N*-oxides described in Chapter III (involving ring closure reactions) these compounds may also be prepared by *N*-oxidation. Such oxidations are usually carried out with hydrogen peroxide in acetic acid solution but sodium tungstate has also been employed as a catalyst (628); and *t*-pentyl hydroperoxide in the presence of $MoCl_5$ or $Mo(CO)_6$ is claimed to give rapid reactions and high yields (733). *N*-Oxides of 2,5-dialkylpyrazine have been prepared by oxidations with peroxymaleic acid (733a), and 2-phenylpyrazine has been oxidized with peroxysulfuric acid in low yield to 3-phenylpyrazine 1-oxide (733b).

The preparations of some simple alkyl- and arylpyrazine *N*-oxides by oxidation are summarized in Table IV.1 (191, 233, 625–628, 648, 713, 733–743).

Pyrazine 1-oxide is also conveniently prepared by vacuum distillation of 3-carboxypyrazine 1-oxide at 250° and pyrazine 1,4-dioxide by treating 2-carboxypyrazine with hydrogen peroxide in acetic acid (744).

B. Properties of Pyrazine *N*-Oxides and their *C*-Alkyl Derivatives

Pyrazine monoxide and substituted pyrazine monoxides are somewhat deliquescent or hygroscopic solids which sublime readily (626).

The strong base-weakening effect of an *N*-oxide substituent upon a para-situated sp^2 nitrogen atom is exemplified by a comparison of the pK_a of pyrazine [0.65 (122)] with that of pyrazine *N*-oxide [0.05 (745)]. The pK_a of 3-methylpyrazine 1-oxide is 0.46 (745). Pyrazine *N*-oxides form salts; thus 2,5-dimethylpyrazine *N*-oxide forms 1:1 addition products with hydrogen chloride, methyl iodide, and benzyl chloride (625). Thermodynamic parameters for the second protonation of tetramethylpyrazine 1,4-dioxide have been determined from measurements at 25, 40, 60, 80, and 90° (746).

Kinetics have been studied for ring D exchange in MeOK–MeOD for pyrazine *N*-oxide (590), and the first-order rate constant at 120° for H–D exchange for pyrazine *N*-oxide in liquid ND_3 has been determined as 1.0×10^{-5} sec^{-1} (747).

TABLE IV.1 OXIDATION OF PYRAZINES TO PYRAZINE *N*–OXIDES

Pyrazine	Reagents and Conditions	Product	Refs.
Unsubstituted	30% H_2O_2/acetic acid/70–80°	Mono- and dioxide	625, 626
	30% H_2O_2/acetic acid/95°	Dioxide	626
	35% H_2O_2/Na_2WO_4/40°	Monoxide	628
	30% H_2O_2/Na_2WO_4/70°	Dioxide	628
2-Methyl	35% H_2O_2/acetic acid/70–80°	4(and 1)-Oxide and dioxide	625, 735–736
	30% H_2O_2/acetic acid/70°	1- and 4-Oxide	626 (see 734)
	30% H_2O_2/acetic acid/95°	Dioxide	626
	35% H_2O_2/acetic acid/100°	Dioxide	737
	30% H_2O_2/acetic acid/70°	1- and 4-Oxide	738
	30% H_2O_2/acetic acid/75°	Dioxide	738
2-Phenyl	30% H_2O_2/acetic acid	4-Oxide	733b
	Potassium persulfate/H_2SO_4	4-Oxide	733b
2,3-Dimethyl	Peroxyacetic acid	Dioxide	739
2,5-Dimethyl	30% H_2O_2/acetic acid/70–80°	Monoxide	625
	30% H_2O_2/acetic acid/70°	Monoxide	626
	30% H_2O_2/acetic acid/95°	Dioxide	626
	30% H_2O_2/acetic acid/56°	Mono- and dioxide	740
2,6-Dimethyl	30% H_2O_2/acetic acid/70°	1- and 4-Oxide	626
	30% H_2O_2/acetic acid/95°	Dioxide	626
2,5-Di-*s*-butyl	30% H_2O_2/acetic acid/56°	Dioxide	740
2,5-Di-*t*-butyl	30% H_2O_2/acetic acid/95°	Mono- and dioxide	233
2-Isobutyl-5-isopropyl	90% H_2O_2/maleic anhydride/chloroform/20°	1- and 4-Oxide and dioxide	740a
2,3-Diphenyl	Peroxyacetic acid/50°	Mono- and dioxide	741
2,5-Diphenyl	30% H_2O_2/acetic acid/70°	Monoxide	742
2,6-Diphenyl	Peroxyacetic acid/50°	4(?)-Oxide	741
3-Butyl-2,5-dimethyl	30% H_2O_2/acetic acid/70°	Dioxide	626
2,5-Dimethyl-3-pentyl	30% H_2O_2/acetic acid/70°	Dioxide	626
2,5-Dimethyl-3-phenyl	30% H_2O_2/acetic acid/70°	Dioxide	626
3-Hexyl-2,5-dimethyl	30% H_2O_2/acetic acid/70°	Dioxide	626
2,5-Dimethyl-3,6-dipentyl	30% H_2O_2/acetic acid/50°	1-Oxide	648
	H_2O_2/acetic acid/40°	Monoxide	743
	30% H_2O_2/acetic acid/60°	Dioxide	191
Tetramethyl	30% H_2O_2/acetic acid/70°	1-Oxide	626
	30% H_2O_2/acetic acid/95°	Dioxide	626
	28% H_2O_2/acetic acid/80°	Dioxide	713
	t-Amyl hydroperoxide/$MoCl_5$	Dioxide	733

Hydrogen–deuterium exchange rates of H_2 and H_6 in some 3-substituted pyrazine 1-oxides in NaOD–D_2O have been correlated with σ constants, and the log of the H_2 exchange rates have been shown to be rectilinearly related to the pK_a values of these compounds (745). A considerable exchange-rate enhancement was caused by replacement of the $=C_4–H$ function in a pyridine *N*-oxide by a $=N_4$ with formation of a pyrazine *N*-oxide (745).

The dipole moment of pyrazine 1-oxide has been determined in benzene at 25° as 1.66*D*, and comparison with those obtained by SMO (simple molecular orbitals) calculations show that agreement is good (748). Other determinations of dipole moment were as follows: pyrazine 1-oxide, 1.60 (carbon tetrachloride, 25°) (749) and 1.62 (benzene, 25°) (663); 2,5- and 3,5-dimethylpyrazine 1-oxides, 1.68 and 2.14, respectively (benzene, 25°) (663); 2-phenylpyrazine 1-oxide, 1.39 (benzene, 25°) (733a); and 3-phenylpyrazine 1-oxide, 2.03 (benzene, 25°) (733a).

The polarographic behavior of the 1-oxides and 1,4-dioxides of pyrazine, 2,5-dimethylpyrazine, and tetramethylpyrazine at various pH values has been investigated. It was assumed that at lower pH values, the *N*-oxide group was reduced in its protonated form. In acid media the 1-oxides exhibited double waves, the first of which is attributable to the reduction of *N*-oxide groups and the second to that of the pyrazine nucleus (production of 1,4-dihydro compounds). Reduction of both *N*-oxide groups of pyrazine-1,4-dioxide proceeded simultaneously (588). Half-wave potentials of the voltammetric oxidation and reduction of pyrazine mono- and di-*N*-oxides have been measured in dimethylformamide, and in acetonitrile by the technique of a rotating platinum electrode (750).

Hydrogen-bonding effects of ethanol, phenol, and water on the e.s.r. spectra of the anion radicals of pyrazine mono- and di-*N*-oxides have been studied quantitatively (751).

Pyrazine *N*-oxide with potassium metal *in vacuo* has been shown to give the pyrazine anion radical accompanied by removal of the oxygen atom (752). The cation radical of pyrazine di-*N*-oxide has been generated electrochemically and its e.s.r. spectrum recorded (753).

Infrared absorption spectra of pyrazine *N*-oxides and alkylpyrazine *N*-oxides have been recorded and discussed (575, 625, 626). The ligand 2,3-bis(pyridin-2′-yl)pyrazine 1,4-dioxide and its complexes with cobalt(II), nickel(II), and copper(II) have been prepared and are polymeric octahedral in structure (754).

Pyrazine 1-oxide and 1,4-dioxide could not be cyanated at the α-position with potassium cyanide and potassium ferricyanide in protic solvents, even at 130° (755). Attempts to nitrate 2,5-dimethylpyrazine 1,4-dioxide (625) and 3-methylpyrazine 1-oxide (626) were unsuccessful.

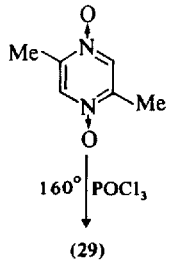
C. Reactions of Alkylpyrazine *N*-Oxides

(1) *Halogenation and Deoxygenation*

2,5-Dialkylpyrazines as their mono- and di-*N*-oxides are smoothly converted by phosphoryl chloride into 2-chloro- and 2,5-dichloro-3,6-dialkylpyrazines, respectively (740). Thus 2,5-dimethylpyrazine 1-oxide with phosphoryl chloride gives 3-chloro-2,5-dimethylpyrazine in 85% yield (612, 740), but 2,5-dimethylpyrazine di-*N*-oxide gave a low yield of 2,5-dichloro-3,6-dimethylpyrazine which was not increased when sulfuryl chloride was used in place of phosphoryl chloride. Similar

conversions were observed for 2,5-di-*s*-butylpyrazine mono- and di-*N*-oxides (740); and 2,3-diphenylpyrazine 1-oxide with phosphoryl chloride gave 5-chloro-2,3-diphenylpyrazine (741).

Matsuura and co-workers (756) have reexamined the reactions of the *N*-oxides of 2,5-dimethylpyrazine and found that 2,5-dimethylpyrazine di-*N*-oxide (**29**) when heated with phosphoryl chloride at 160° gave 2,5-dichloro-3,6-dimethylpyrazine (6%) (**30**), 3-chloro-2,5-dimethylpyrazine 1-oxide (5%) (**31**), and 5-chloromethyl-2-methylpyrazine 1-oxide (9%) (**32**). In addition small amounts of other chlorinated products, 3-chloro-2-chloromethyl-5-methylpyrazine (**33**) and 2,5-bischloromethylpyrazine (**34**), were identified. These authors also examined the action of *p*-tosyl chloride, methane sulfonyl chloride, and mixtures of phosphoryl chloride and concentrated sulfuric acid, but state that these did not give good results. Pyrazine 1-oxide and phosphoryl chloride have been shown to give 2-chloropyrazine; and pyrazine 1,4-dioxide gave 2,6-dichloropyrazine (737, 757), but under milder reaction conditions it gave 2-chloropyrazine 1-oxide (757). Pyrazine 1,4-dioxide and benzenesulfonyl chloride also gave a low yield of 2-chloropyrazine 1-oxide (758).



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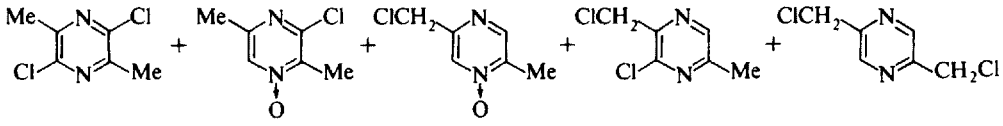


(30) (31) (32) (33) (34)

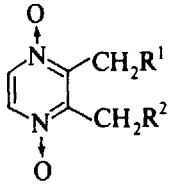
Both 2-methylpyrazine 1- and 4-oxides (625) (obtained by oxidation of 2-methylpyrazine with peroxyacetic acid) on treatment with phosphoryl chloride have been claimed to give 2-chloro-3-methylpyrazine (626) but the "2-methylpyrazine-4-oxide" used is now known to have been a mixture of the 1- and 4-isomers (734). More recently other workers (735, 736) have claimed that the mixed 2-methylpyrazine *N*-oxides with phosphoryl chloride gave a mixture of 2-chloro-3-, -5-, and -6-methylpyrazine; but Nakel and Haynes (686) have shown that 2-methylpyrazine 1-oxide with phosphoryl chloride followed by sodium methoxide gave 2-methoxy-3-methylpyrazine and 6-methoxy-2-methylpyrazine, and 2-methylpyrazine 4-oxide (3-methylpyrazine 1-oxide) similarly treated gave only 2-methoxy-6-methylpyrazine. 3-Trifluoromethylpyrazine 1-oxide with benzenesulfonyl chloride at 100° has been shown to give 2-chloro-6-trifluoromethylpyrazine (44%) (759).

2-Methylpyrazine 1,4-dioxide with phosphoryl chloride gives a mixture of

dichloromethylpyrazine and a monochloromethylpyrazine *N*-oxide (which is isomeric with the *N*-oxide produced by direct oxidation of 2-chloro-3-methylpyrazine or 2-chloro-6-methylpyrazine) (737). When tetraphenylpyrazine 1,4-dioxide was heated at 140–150° with phosphorus pentachloride it gave a chlorotetraphenylpyrazine (554).

(2) *Halogenation*

Bromination of 2,3-dimethylpyrazine 1,4-dioxide has been shown to give 30.5% 2-bromomethyl-3-methylpyrazine 1,4-dioxide (**35**, R^1 = Br, R^2 = H) and 29.8%, 2,3-bis(bromomethyl)pyrazine 1,4-dioxide (**35**, $R^1 = R^2$ = Br) (739).



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(3) *Rearrangement with Acetic Anhydride*

The first studies of the reactions of methylpyrazine *N*-oxides with acetic anhydride were carried out by Koelsch and Gumprecht (625). They found that 2,5-dimethylpyrazine monoxide reacted with acetic anhydride to form 2-acetoxymethyl-5-methylpyrazine; 2,5-dimethylpyrazine dioxide gave 2-acetoxymethyl-5-methylpyrazine and 2,5-bisacetoxymethylpyrazine; and 2-acetoxymethyl-5-methylpyrazine dioxide was partly deoxygenated by acetic anhydride to give 2,5-bisacetoxymethylpyrazine, its monoxide, and 2-acetoxymethyl-5-methylpyrazine monoxide (625). These workers also based their assignment of the structures of the two isomeric monoxides of 2-methylpyrazine (prepared by oxidation with hydrogen peroxide in acetic acid) on reactions with acetic anhydride. 2-Methylpyrazine 1-oxide gave an acetate saponified to 2-hydroxymethylpyrazine (625) and 3-methylpyrazine 1-oxide was claimed to give an acetate saponified to 2-hydroxy-5-methylpyrazine (625), but this has been disputed (760); Asao (738) and Klein et al. (760) claim that 3-methylpyrazine 1-oxide (2-methylpyrazine 4-oxide) does not react with acetic anhydride.

Details of these and other studies are summarized in Table IV.2 (113b, 625, 737–739, 758, 760, 760a).

Klein et al. (760) observed that acetoxymethylpyrazines were formed only when a methyl group was adjacent to the *N*-oxide function, and they proposed, for these reactions, the mechanism shown in the transformation (**36** → **39**).

Although Klein et al. (760) claimed that both pyrazine 1-oxide and 1,4-dioxide did not react with acetic anhydride, Asai (738) found that pyrazine 1-oxide when

TABLE IV.2 REACTION OF PYRAZINE *N*-OXIDES WITH ACETIC ANHYDRIDE

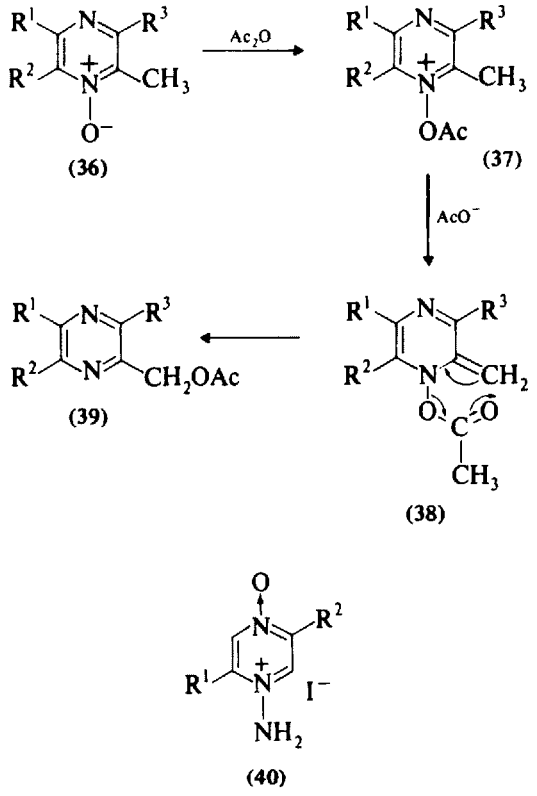
Pyrazine *N*-oxide	Product(s)	Refs.
Pyrazine 1-oxide	No reaction	760
	2-Acetoxypyrazine (3%)	738
Pyrazine 1,4-dioxide	No reaction	760
	Pyrazine 1-oxide	758
2-Methylpyrazine 1-oxide	2-Acetoxymethylpyrazine	625, 738
3(2)-Methylpyrazine 1(4)-oxide	No reaction	738, 760
2-Methylpyrazine 1,4-dioxide	2-Acetoxymethylpyrazine, 3-Acetoxymethylpyrazine 1-oxide, 2-methylpyrazine 1-oxide	738
	3-Acetoxymethylpyrazine 1-oxide	760
2,3-Dimethylpyrazine 1,4-dioxide	2,3-Bis(acetoxymethyl)pyrazine	739
2,5-Dimethylpyrazine 1-oxide	2-Acetoxymethyl-5-methylpyrazine	625, 760
2,5-Dimethylpyrazine 1,4-dioxide	2-Acetoxymethyl-5-methylpyrazine and 2,5-bisacetoxymethylpyrazine	625
	2,5-Dimethylpyrazine 1-oxide, 2-acetoxymethyl-5-methylpyrazine 1-oxide, and 2,5-diacetoxymethylpyrazine (prolonged heating)	760
2,6-Dimethylpyrazine 1-oxide	2-Acetoxymethyl-6-methylpyrazine	760
3,5-Dimethylpyrazine 1-oxide	No reaction	760
2,6-Dimethylpyrazine 1,4-dioxide	2-Acetoxymethyl-6-methylpyrazine and 2,6-dimethylpyrazine 4-oxide	760
2,3,5,6-Tetramethylpyrazine 1-oxide	2-Acetoxymethyl-3,5,6-trimethylpyrazine	760
3-Chloro-2-methylpyrazine 1-oxide	2-Chloro-3-hydroxymethylpyrazine (after hydrolysis)	737
3-Chloro-2,5-diisobutylpyrazine 1-oxide	2-(1'-Acetoxy-2'-methylpropyl)-3-chloro-5-isobutylpyrazine	760a
2-Chloro-3,6-diisobutylpyrazine 1-oxide	5-(1'-Acetoxy-2'-methyl)propyl-3-chloro-2-isobutylpyrazine	113b

refluxed with acetic anhydride for 8 hours gave 2-acetoxypyrazine (3%), and Elina and Musatova (758) observed that pyrazine 1,4-dioxide and acetic anhydride on prolonged boiling gave some pyrazine 1-oxide.

Variations in the products obtained from the reaction of 2,5-dimethylpyrazine 1,4-dioxide with acetic anhydride by two groups of workers (625, 760) may be explained by procedural differences.

(4) *N-Amination*

N-Amination of pyrazine 1-oxide and 2,5-dimethylpyrazine 1-oxide has been effected with hydroxylamine-*O*-sulfonic acid and hydriodic acid to give 4-aminopyrazinium 1-oxide iodide (**40**, $R^1 = R^2 = H$) and 4-amino-2,5-dimethylpyrazinium 1-oxide iodide (610).



(36) (37) (38) (39) (40)

(5) *Methyl- to Styrylpyrazine N-Oxides*

Methylpyrazine 1-oxides react with benzaldehyde to give styrylpyrazine 1-oxides. Thus tetramethylpyrazine 1,4-dioxide, *p*-dimethylaminobenzaldehyde, and 37% hydrochloric acid at 140° for 15 hours gave 2,3,5,6-tetra(*p*-dimethylaminostyryl)-pyrazine 1,4-dioxide (713); 2,5-dimethylpyrazine 1,4-dioxide, benzaldehyde, and sodium hydroxide gave 2,5-distyrylpyrazine 1,4-dioxide, and 2,5-dimethylpyrazine 1-oxide gave 2,5-distyrylpyrazine 1-oxide without any apparent difference in reactivity of one of the methyl groups (625). Elina and Musatova (710) found that 2-methyl- and 2,3-dimethylpyrazine 1,4-dioxide condense with aromatic aldehydes in sodium hydroxide or sodium methoxide to give styryl derivatives.

(6) *Deoxygenation*

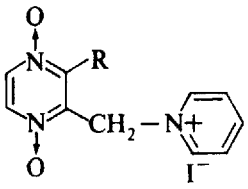
Alkyl- and arylpyrazine *N*-oxides may be deoxygenated by reduction. For example, tetraphenylpyrazine 1,4-dioxide with zinc dust and acetic acid at 100° gives tetraphenylpyrazine and a small quantity of tetraphenylpiperazine (554),

and catalytic reduction (H_2/Pt) of 2-methylpyrazine 1- and 4-oxides in ethanol gives 2-methylpyrazine (738). 2,5-Diphenylpyrazine 1-oxide with phosphorus trichloride in chloroform has been shown to give 2,5-diphenylpyrazine (326) and ultraviolet irradiation of a benzene solution of 2,5-diphenylpyrazine *N*-oxide gives 50% 2,5-diphenylpyrazine together with other products (742).

3-Phenylpyrazine 1-oxide, 2,3-diphenylpyrazine 1-oxide and 2,5-diphenylpyrazine 1-oxide have been deoxygenated in good yield by aqueous chromium(II) chloride in methanol, acetone, and chloroform at room temperature (761), and deoxygenation of 5-(substituted aminomethyl)-2-amino-3-cyano-6-methylpyrazine 1-oxide by triethyl phosphite in hot dimethylformamide has been described (762).

(7) *Miscellaneous*

2-Methyl- and 2,3-dimethylpyrazine 1,4-dioxide when heated with pyridine and iodine undergo King's reaction; from 2-methylpyrazine 1,4-dioxide the quaternary salt, 2-pyridiniomethylpyrazine 1,4-dioxide iodide (**41**, R = H) was obtained, and this with *p*-nitrosodimethylaniline in alkaline medium gave the nitrone (**42**, R = H) (763).



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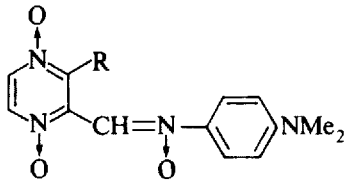
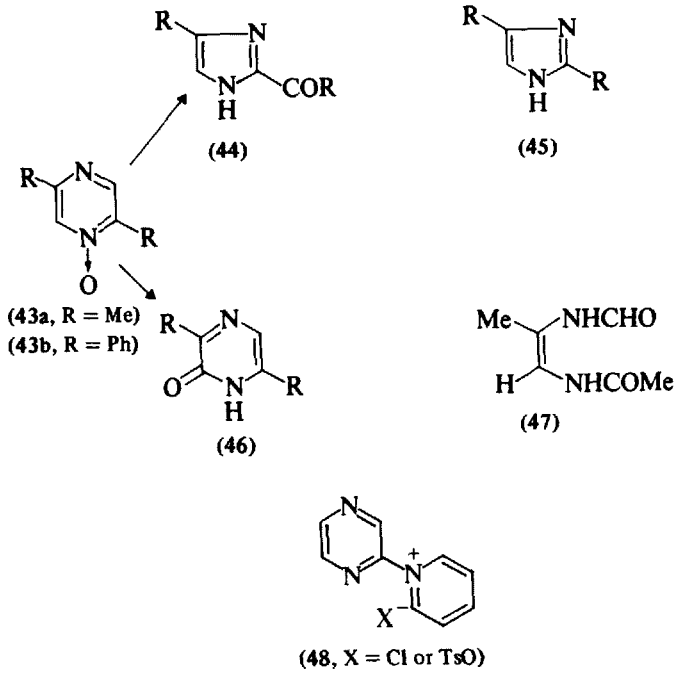


(42)

An interesting series of reactions for 2,5-dimethyl(and 2,5-diphenyl)pyrazine 1-oxide have been reported by Ikekawa and Honma (742). Photolysis of 2,5-dimethylpyrazine 1-oxide (**43a**) in benzene stirred by a stream of nitrogen gave 2-acetyl-4-methylimidazole (**44a**) and 2,4-dimethylimidazole (**45a**), but irradiation of 2,5-dimethylpyrazine 1-oxide in aqueous solution gave 3-hydroxy-2,5-dimethylpyrazine (**46a**) and 1-acetamido-2-formamidoprop-1-ene (**47**), in all low yield. Irradiation of 2,5-diphenylpyrazine 1-oxide in benzene gave a high yield of deoxygenated product and a low yield of 3-hydroxy-2,5-diphenylpyrazine (**46b**) and 2,4-diphenylimidazole (**45b**). 2,5-Dimethylpyrazine mono- and di-*N*-oxides with 1-propanethiol in boiling acetic anhydride gave 2,5-dimethyl-3-propylthio- and 2,5-dimethyl-3,6-dipropylthiopyrazines, respectively (764). Pyrazine 1-oxide with tosyl chloride in the presence of pyridine has been shown to give 2-pyridiniopyrazine salts (**48**) (765).



Quaternization of the four dimethylpyrazine *N*-oxides and 2,3-diphenylpyrazine 1-oxide with methyl iodide in a sealed tube at 80° gave the 4-methylpyrazinium 1-oxide iodides, but 3-phenyl-, 2,5-diphenyl- and 3,5-diphenylpyrazine 1-oxides and dimethylpyrazine 1,4-dioxides could not be quaternized. The quaternary salts were reduced by sodium borohydride to *N*-hydroxypiperazines (766).

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CHAPTER V

Halogenopyrazines and *N*-Oxide Derivatives

1. THE PREPARATION OF NUCLEAR HALOGENOPYRAZINES

A. Direct Chlorination with Chlorine

(1) *Simple Cases*

Many patents describe the chlorination of pyrazine to chloropyrazine and polychloropyrazines under a variety of conditions. Thus chlorination of pyrazine in the presence of water vapor at 500–565° so that the reaction zone contained pyrazine 0.05, water 0.45, and chlorine 0.06 mole fraction gave 64% 2-chloropyrazine (599); chlorination of pyrazine in nitrogen (as an inert diluent) over activated carbon and copper chloride on diatomaceous earth at 340° gave 44% 2-chloropyrazine (600, 602); and chlorination of pyrazine in a diluent consisting of steam, nitrogen, carbon dioxide, and sulfur dioxide gave 37.7% chloropyrazine (and 4.5% dichloropyrazine) (604). Pyrazine with a two molar ratio of chlorine with steam gave 30–35% chloropyrazine and 40–45% dichloropyrazine (2,3-, 2,5-, and 2,6-isomers) (603). Dichloropyrazines were also obtained from chlorinations at 400–500° (767). Chlorination of chloropyrazine at 425–625° gave di-, tri-, and tetrachloropyrazines (768), and in the presence of 2-oxazolidone at 62–75° gave 92% 2,6-dichloropyrazine (769). Chlorinations of 2-chloropyrazine in dimethylformamide to give 2,3- and 2,6-dichloropyrazine have been described (770, 771). 2-Chloropyrazine with chlorine in the liquid phase at 65–150° under autogenous pressure produces 2,6-dichloropyrazine (772), pyrazine in the presence of water with sufficient chlorine gave tetrachloropyrazine (601), and 2-chloropyrazine with chlorine in the presence of a water-soluble polar organic solvent containing at least 0.02 mol% water gave 2,6-dichloropyrazine, whereas less than this amount of water resulted in preferential formation of the 2,3-isomer (693). 2-Chloropyrazine, dimethylformamide, phosphoryl chloride, and chlorine gave 2,6-dichloropyrazine (770). Chlorination of 2,3-dichloropyrazine in the presence of ferric chloride gave trichloropyrazine (365b) but at 200° in the presence of a mercury-vapor lamp for 4 hours gave 50% tetrachloropyrazine (773).

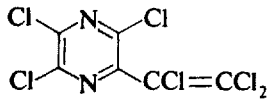
Gas phase chlorination of piperazine in carbon tetrachloride has been shown to give tetrachloropyrazine (605), and treatment of 1,4-bis(chlorocarbonyl)piperazine

with chlorine and ultraviolet light at 150–220° has been shown to give dichloropyrazine (474, 774). Tetrachloropyrazine has also been prepared by chlorination of *N,N'*-dimethyl or *N,N'*-bis(hydroxyethyl)piperazine at elevated temperatures (475). The reactions of alkylpyrazines with chlorine under a variety of conditions have been investigated by many workers. Methylpyrazine with chlorine in carbon tetrachloride gave a mixture of 2-chloro-3-methylpyrazine (679–683) and 2-chloro-6-methylpyrazine (681, 775) rather than 2-chloro-5-methylpyrazine (as claimed by Hirschberg and Spoerri) (679).

2,5-Dimethylpyrazine (and 2,5-diethylpyrazine) with chlorine in carbon tetrachloride has been shown to give 3-chloro-2,5-dimethyl(and diethyl)pyrazine in good yield (679–683). Whereas the chlorination of 2,5-dimethylpyrazine proceeded in the absence of ultraviolet light, ultraviolet radiation was essential for the reaction of 2,6-dimethylpyrazine with chlorine in carbon tetrachloride to give the unstable 2,6-bis(α-chloromethyl)pyrazine (679). Chlorination of 2,3-dimethylpyrazine in carbon tetrachloride under irradiation with ultraviolet light gave 2,3-bis(α-chloromethyl)pyrazine (654).

Vapor phase chlorination of methylpyrazine in carbon tetrachloride (10% w/w) at 545° with 15 times the molar ratio of chlorine for 13 sec has been claimed to give tetrachloropyrazine (776) and chlorine passed into a refluxing solution of 2-chloro-3-methylpyrazine in acetic acid gave 2-chloro-3-dichloromethylpyrazine (688).

2-*s*-Butylpyrazine with chlorine in carbon tetrachloride at 40° has been shown to give 95% 2-*s*-butyl-3-chloropyrazine and its isomers (649), and halogenation of trimethylpyrazine gave 2-halogeno-3,5,6-trimethylpyrazine (330). Vinylpyrazine with chlorine in a reactor has been claimed to give perchlorovinylpyrazine (**1**) (777). Tetraphenylpyrazine was unsubstituted by chlorine (or bromine) in chloroform in the presence of aluminum chloride and sunlight (261).



(1)

(2) *In the Presence of Amino Groups*

Chlorination of 2-amino-3-methoxycarbonylpyrazine in aqueous acetic acid at about 40° has been shown to give 5-chloro-2-chloroamino-3-methoxycarbonylpyrazine and thence 2-amino-5-chloro-3-methoxycarbonylpyrazine (150, 378a, 432a, 778–787), but in the presence of polar aprotic solvents (such as acetonitrile and dichloroethane) at temperatures between room temperature and reflux it gave 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine (788).

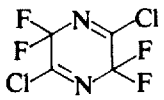
Chlorination of 2-methoxycarbonyl-3-methylaminopyrazine gave 2,3-dichloro-5-methoxycarbonyl-6-methylaminopyrazine (789), 5-chloro-2-(2'-dimethylaminoethylamino)-3-methoxycarbonylpyrazine at room temperature gave 2,3-dichloro-5-

(2′-dimethylaminoethylamino)-6-methoxycarbonylpyrazine (790), 3,5-diamino-2-guanidinocarbonylpyrazine in aqueous acetic acid at 40° gave 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine (and many similar preparations) (791), 2-amino-3-cyanopyrazine in acetic acid gave 2-amino-5-chloro-3-cyanopyrazine (792), and 3-dimethylamino-2,5-dimethylpyrazine in chloroform gave 2-chloro-5-dimethylamino-3,6-dimethylpyrazine (689, 793).

(3) *In Other Cases*

Patents describe the preparation (by chlorination) of 2,3,5-trichloro-6-cyanopyrazine (794, 795); and the chlorination of 2-methoxy-3-methoxycarbonylpyrazine (product not stated) has been described (155).

Chlorination of tetrafluoropyrazine has been shown to give 3,6-dichloro-2,2,5,5-tetrafluoro-2,5-dihydropyrazine (2) (50%) and 5,6-dichloro-2,2,3,3-tetrafluoro-2,3-dihydropyrazine (3) (10%) (796).



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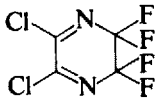


(3)

B. Direct Bromination with Bromine

(1) *Simple Cases*

Pyrazine hydrobromide (0.124 mol) and bromine (0.066 mol) at elevated temperatures, preferably in an inert diluent, gave 2-bromopyrazine (598), and vapor phase bromination of pyrazine in molar ratios of 2:1 with water as a preferred diluent gave conversions of 38–92% and yields as follows: monobromo (7–43%), dibromo (12–38%), and tribromopyrazines (17%) (603).

Vapor phase bromination of bromopyrazine (feed ratios 1:1) at 425–625° with water as a diluent gave dibromopyrazines, and increased feed ratios favored formation of tribromopyrazine (768). The reaction of 2-bromopyrazine (0.10 mol) and bromine (0.11 mol) with a trace of phosphorus tribromide and ferrous bromide at 95° formed 2,3-dibromopyrazine (797). Bromination of 2-bromo-3-chloromethylpyrazine in carbon tetrachloride has been claimed to give 2,5-dibromo-3-chloromethylpyrazine, 2,6-dibromo-3-chloromethylpyrazine, and 2,5,6-tribromo-3-chloromethylpyrazine (688).

(2) *In the Presence of Amino and Carboxy Groups*

Bromination of 2-amino-3-methoxycarbonylpyrazine in acetic acid gave 2-amino-5-bromo-3-methoxycarbonylpyrazine (787, 798) and the 2-methylamino analogue

has been prepared in a similar manner (799–801). Likewise bromination of 3-amino-2-methoxycarbonyl-5-methyl(and phenyl)pyrazine in acetic acid gave 2-amino-5-bromo-3-methoxycarbonyl-6-methyl(and phenyl)pyrazine (780, 802); and 2-amino-3-carbamoylpyrazine gave 2-amino-5-bromo-3-carbamoylpyrazine (803). Bromination of 2-acetamido-6-carboxypyrazine in warm acetic acid gave 3-acetamido-2-bromo-5-carboxypyrazine (434) but bromination of 2-amino-3-carboxypyrazine and subsequent heating gave 2-amino-3,5-dibromopyrazine (804), as did 2-amino-5-bromo-3-carboxypyrazine with bromine and acetic acid–sodium acetate (805). 2-Amino-3,5-dibromopyrazine was also produced from 2-amino-3-bromopyrazine, 2-amino-5-bromo-3-carboxypyrazine, and 2-amino-5-bromo-3-methoxycarbonylpyrazine with bromine in aqueous hydrobromic acid (806, 807).

Bromination of 2-amino-3-cyanopyrazine in acetic acid gave 2-amino-5-bromo-3-cyanopyrazine (792, 808) and bromination of 3,5-diamino-2-methoxycarbonylpyrazine and 3-amino-5-methoxy-2-methoxycarbonylpyrazine in acetic acid gave 2,6-diamino-3-bromo-5-methoxycarbonylpyrazine (780, 781, 809) and 2-amino-5-bromo-6-methoxy-3-methoxycarbonylpyrazine (790), respectively.

(3) *In the Presence of Amino and Other Groups*

2-Aminopyrazine with bromine in acetic acid gave 2-amino-3,5-dibromopyrazine (804, 810, 811), also obtained from bromination of 2-amino-3-bromopyrazine in aqueous hydrobromic acid (806, 807), and 5-amino-2,3-dimethylpyrazine with bromine in acetic acid gave 2-amino-3-bromo-5,6-dimethylpyrazine (812). 2-Amino-5-phenylpyrazine with bromine and pyridine in chloroform at 20° gave 2-amino-3-bromo-5-phenylpyrazine (365a), and 2-amino-3-chloropyrazine with 20% hydrobromic acid and bromine gave 2-amino-5-bromo-3-chloropyrazine (806, 807).

2-Chloro-3-morpholinopyrazine treated with allyl alcohol followed by bromination in the presence of water has been shown to give 5-bromo-2-(3′-bromo-2′-hydroxypropoxy)-3-morpholinopyrazine (813), and bromination of 2-amino[or 2-(*p*-toluenesulfonamido)]-3-methoxypyrazine with a mixture of potassium bromide and bromate in 6*N* sulfuric acid gave 2-amino-[or 2-(*p*-toluenesulfonamido)]-5-bromo-3-methoxypyrazine (814). The bromination (814) of 2-methoxy-3-sulfanilamidopyrazine in methanol was anomalous (815, 816) [see Section 5D(2)].

(4) *In the Presence of Hydroxy Groups*

Bromination of 5-*s*-butyl-3-hydroxy-2-isobutylpyrazine (deoxyaspergillic acid) in aqueous solution or acetic acid gave 2-bromo-3-*s*-butyl-5-hydroxy-6-isobutylpyrazine (bromodeoxyaspergillic acid) (87); bromination of 2-*s*-buty-3-hydroxy-5-isobutylpyrazine in acetic acid gave 2-bromo-6-*s*-butyl-5-hydroxy-3-isobutylpyrazine (93); and 3-hydroxy-2,5-diphenylpyrazine behaved similarly (282). This procedure with bromine in acetic acid was unsatisfactory when applied to simpler hydroxypyrazines (817), and bromination of 3,6(and 5,6)-disubstituted-2-hydroxypyrazines and 2-

hydroxy-3-phenylpyrazine was achieved with bromine in acetic acid with two equivalents of pyridine (817). 2-Alkyl-3-hydroxypyrazines were rapidly destroyed by the combination of bromine, acetic acid, and an excess of pyridine and much milder conditions were required for successful bromination. One equivalent of pyridine–bromine complex in chloroform was added slowly to a very cold (− 25°) solution of the hydroxypyrazine in chloroform to give 3-alkyl-5-bromo-2-hydroxypyrazine (817). 2-Hydroxy-3,5-dimethylpyrazine which had no free position ortho or para to the hydroxyl group gave no bromopyrazine (817). 2-Hydroxy-5-phenylpyrazine with sodium hypobromite gave 3-bromo-2-hydroxy-5-phenylpyrazine (365a).

C. Phosphoryl Chloride with Hydroxypyrazines

(1) *Simple Cases*

The reaction of simple hydroxypyrazines with phosphoryl chloride has been used extensively for the preparation of chloropyrazines. 2-Hydroxypyrazine with phosphoryl chloride alone (818) gave 2-chloropyrazine (819–821), and 2-chloro-[1-^{15}N]pyrazine (822) and 2-chloro[2-^{14}C]pyrazine (823) have been prepared by the method described by Karmas and Spoerri (362).

Karmas and Spoerri have made extensive studies of the preparation of chloropyrazines. They (362) prepared a series of 22 2-chloropyrazines with or without 3-alkyl and 5,6-alkyl or aryl substituents by chlorination of the corresponding hydroxy compound with phosphoryl chloride containing a drop of sulfuric acid (and in three cases with added phosphorus pentachloride). In connection with reactions with phosphoryl chloride alone it was observed that an alkyl group in the 3-position in no case hindered replacement of hydroxyl by chlorine, and the reaction occurred rapidly in refluxing phosphoryl chloride. When ethyl, propyl, and isopropyl groups were at position 3 and a methyl group was at position 5, replacement was much more difficult and required heating in a sealed tube at 140°. Heating at 190–200° was required to obtain good yields of chloro compounds from 2-hydroxy-3-ethyl(and propyl or isopropyl)-5,6-dimethyl(and diphenyl)pyrazines. A series of 2,3- and 2,5-dichloropyrazines with dimethyl, phenyl, and diphenyl substituents has also been prepared by Karmas and Spoerri (817), by reaction of the dihydroxy, bromohydroxy, hydroxynitro, and chlorohydroxy analogues with phosphoryl chloride at 170–180°.

2-Chloro-3-methylpyrazine (101, 535) and 2-chloro-5-phenylpyrazine (363, 365a, 377, 824, 825) have been prepared from the corresponding hydroxy compound and phosphoryl chloride, 2-chloro-6-methylpyrazine from 2-hydroxy-6-methylpyrazine and phosphoryl chloride with one drop of dimethylformamide (681), and 2-benzyl(or *s*-butyl, isobutyl, or isopropyl)-3-chloropyrazines from the hydroxy analogue and phosphoryl chloride with a trace of concentrated sulfuric acid (80). 2-Chloro-6-methyl-3-propyl- (826), 3-chloro-5-phenyl-, 2-chloro-3,5-diphenyl-, and 3-chloro-2,5-diphenylpyrazine (827) were prepared similarly.

Dichloropyrazines have also been prepared from the corresponding hydroxy compounds as follows: 2,3-dihydroxypyrazine with phosphoryl chloride containing pyridine (481, 757) [see Schneller and May (828) re the use of phenylphosphonic dichloride at 150–170°]; 2,3-dihydroxypyrazine and its methyl, dimethyl, phenyl, diphenyl, and 5-methyl-6-phenyl derivatives with phosphoryl chloride (483, 829) [N.B. error in work of Minovici and Bente (830)]; 2-chloro-5-hydroxypyrazine with phosphoryl chloride (831); 2-chloro-6-hydroxypyrazine with phosphoryl chloride at reflux for 6 hours (832); and 2,5-dihydroxy-3-phenylpyrazine and 3,5-dihydroxy-2-phenylpyrazine with phosphoryl chloride at 180–200° (829).

2-Chloro-5-hydroxy-3,6-dimethylpyrazine with phosphoryl chloride gave a low yield of 2,5-dichloro-3,6-dimethylpyrazine (312); 3-chloro-5-hydroxy-2-methylpyrazine gave 3,5-dichloro-2-methylpyrazine (535) and 2-chloro-5-hydroxy-3,6-diisobutylpyrazine with phosphoryl chloride at 150° for 5 hours gave 2,5-dichloro-3,6-diisobutylpyrazine (101).

2-Hydroxy-3-methoxy-5-phenylpyrazine refluxed with phosphoryl chloride formed 2-chloro-3-methoxy-5-phenylpyrazine (365a).

(2) *In the Presence of Amino Groups*

Amino chloropyrazines may be prepared from amino hydroxypyrazines with phosphoryl chloride. 2-Amino-3-hydroxypyrazine with phosphoryl chloride gave 2-amino-3-chloropyrazine (369, 370, 833), which was prepared in highest yield in a sealed tube at 118° (370). The same product was also obtained from 2-acetamido-3-hydroxypyrazine with phosphoryl chloride (834). 2-Amino-3-chloro-5(and 6)-methylpyrazine (373, 835), 2-amino-3-chloro-5,6-dimethylpyrazine (374), and 3-amino-2-chloro-5-phenylpyrazine (365a) have each been obtained from the corresponding aminohydroxy compound and phosphoryl chloride.

3-Amino-2-carbamoyl-5-hydroxypyrazine in dimethylformamide with phosphoryl chloride gave 3-amino-5-chloro-2-cyanopyrazine (538).

(3) *In the Presence of Carboxy Groups*

Many derivatives of carboxy chloropyrazines have been prepared by the action of phosphoryl chloride on the corresponding hydroxypyrazine. In this way were prepared 2-chloro-3-methoxycarbonylpyrazine (371, 423, 836), 2-chloro-3-methoxycarbonyl-5,6-diphenylpyrazine (but the corresponding hydroxy compound did not react with phosphorus tribromide) (837), and 3-chloro-2-methoxycarbonyl-5-methylpyrazine (371) (2-carboxy-3-chloropyrazine could not be prepared by the action of phosphoryl chloride on 2-carboxy-3-hydroxypyrazine) (423). 2-Chloro-5-methoxycarbonylpyrazine was similarly prepared with phosphoryl chloride containing a few drops of concentrated hydrochloric acid (838). 2-Hydroxy-6-methoxycarbonylpyrazine with phosphoryl chloride gave 2-chloro-6-methoxycarbonylpyrazine (744) [cf. Nováček et al. (839)].

2-Carbamoyl-3-hydroxypyrazine and phosphoryl chloride have been shown to give 2-chloro-3-cyanopyrazine (810, 811, 840); likewise 2-carbamoyl-3-hydroxy-5,6-diphenylpyrazine gave 2-chloro-3-cyano-5,6-diphenylpyrazine (837), and 2-cyano-5-hydroxy-3,6-dimethylpyrazine gave 2-chloro-5-cyano-3,6-dimethylpyrazine (288). The sodium salt of hydroxypyrazine, phosphoryl chloride, dimethylformamide, and chlorine gave 2,3-dichloropyrazine (770) and 2-carbamoylpyrazine, phosphoryl chloride, and bromine have been claimed to give 5(?)-chloro-2-cyanopyrazine (839).

(4) *In the Presence of Nitro Groups*

Whereas 2-hydroxy-3-nitro-5,6-diphenylpyrazine with phosphoryl chloride at reflux has been shown to give a mixture of 2-chloro-3-hydroxy- and 2,3-dichloro-5,6-diphenylpyrazine involving replacement of the nitro group (817, 834) [and at 170° gave only the latter compound (817)], 2-hydroxy-3-phenyl-5-nitropyrazine with phosphoryl chloride at reflux gave 2-chloro-3-phenyl-5-nitropyrazine (834) [and at 170° gave 2,5-dichloro-3-phenylpyrazine (834)]. [2-Hydroxy-3-nitro-5,6-diphenylpyrazine with phosphorus trichloride, acetyl chloride, thionyl chloride, dry hydrogen chloride in dioxane, or iodine chloride has been shown to give 2-chloro-3-hydroxy-5,6-diphenylpyrazine (841)].

(5) *From Amino Acid Anhydrides and Piperazinones*

Baxter and Spring (312) first observed that DL-isoleucine anhydride (3,6-di-*s*-butylpiperazine-2,5-dione) and phosphoryl chloride gave a mixture of 3-chloro-2,5-di-*s*-butylpyrazine and 2,5-dichloro-3,6-di-*s*-butylpyrazine (312, 720) and DL-alanine anhydride (3,6-dimethylpiperazine-2,5-dione) similarly gave a mixture of 3-chloro-2,5-dimethylpyrazine and 2,5-dichloro-3,6-dimethylpyrazine (312, 720, 756, 842). The formation of the monochloro compound did not involve an oxidation step, whereas the formation of the dichloro compound involved the oxidation of an intermediate dihydropyrazine. Treatment of DL-alanine anhydride with phosphoryl chloride in the presence of a tertiary base (dimethylaniline) gave only the monochloro derivative, the intermediate dichlorodihydropyrazine presumably losing hydrogen chloride and thereby yielding the stable aromatic 3-chloro-2,5-dimethylpyrazine (312). DL-Phenylglycine anhydride with phosphoryl chloride gave a mixture from which 2,5-dichloro-3,6-diphenylpyrazine and 3-hydroxy-2,5-diphenylpyrazine have been isolated (282), and DL-leucyl-DL-isoleucyl anhydride (3-*s*-butyl-6-isobutylpiperazine-2,5-dione) with phosphoryl chloride gave a mixture from which, after treatment with alkali and acid, was isolated 2-*s*-butyl-3-hydroxy-5-isobutylpyrazine, 2(or 5)-*s*-butyl-3-chloro-6-hydroxy-5(or 2)-isobutylpyrazine and a mixture of chloropyrazines (93, 313). Treatment of DL-leucine anhydride with phosphoryl chloride gave 3-hydroxy-2,5-diisobutylpyrazine and a mixture of chloropyrazines, probably 3-chloro-2,5-diisobutylpyrazine and 2,5-dichloro-

3,6-diisobutylpyrazine (95, 843) [compare with the reaction with mixed phosphoryl chloride–phosphorus pentachloride (101)]. 3-Isopropyl-6-methylpiperazine-2,5-dione (and its 3,6-dimethyl and 3,6-diisopropyl analogues) with phosphoryl chloride gave 2,5-dichloro-3-isopropyl-6-methylpyrazine and 2-chloro-3(and 6)-isopropyl-6(and 3)-methylpyrazine (and analogues) (844). Chlorination of DL-valyl-leucyl anhydride (3-isobutyl-6-isopropylpiperazine-2,5-dione) with phosphoryl chloride gave a mixture of 2,5-dichloro-3-isobutyl-6-isopropylpyrazine, 3-chloro-2-isobutyl-5-isopropylpyrazine, and 3-chloro-5-isobutyl-2-isopropylpyrazine (740a), and piperazine-2,3,5-trione with phosphoryl chloride (or phosphorus pentachloride) gave 2,3,5-trichloropyrazine (365b, 845).

D. Chlorinations with Phosphorus Pentachloride

Many chloropyrazines have been prepared from hydroxypyrazines by reaction with mixed phosphorus pentachloride–phosphoryl chloride as follows: 2-hydroxypyrazine to 2-chloropyrazine (818), 2-hydroxy-3-phenylpyrazine to 2-chloro-3-phenylpyrazine (535), 2-hydroxy-6-methyl- and 5-hydroxy-2,3-dimethylpyrazine to 2-chloro-6-methyl- and 5-chloro-2,3-dimethylpyrazines, respectively (362), 2-hydroxy-6-phenylpyrazine to 2-chloro-6-phenylpyrazine (827), 5-hydroxy-2,3-diphenylpyrazine to 5-chloro-2,3-diphenylpyrazine (846), 3-hydroxy-2,5-diisobutylpyrazine to 3-chloro-2,5-diisobutylpyrazine (843), 2-*s*-butyl-3-hydroxy-5-isobutylpyrazine to 2-*s*-butyl-3-chloro-5-isobutylpyrazine (313), piperazine-2,5-dione to 2,5-dichloro-3,6-dihydropyrazine (847), piperazinetrione (in an autoclave at 150°) to trichloropyrazine (365b, 845), DL-alanine anhydride to a poor yield of 2,5-dichloro-3,6-dimethylpyrazine and a small quantity of 2-chloro-5-hydroxy-3,6-dimethylpyrazine but no 3-chloro-2,5-dimethylpyrazine (312), leucine anhydride to a little 2-chloro-5-hydroxy-3,6-diisobutylpyrazine (and 3-hydroxy-2,5-diisobutylpyrazine) (101), 5-bromo-2-hydroxy-3-methoxypyrazine to 5-bromo-2-chloro-3-methoxypyrazine (535), 2-carbamoyl-5-chloro-3-hydroxy-6-methylpyrazine to 2,6-dichloro-3-cyano-5-methylpyrazine (535), and 2-carbamoyl-3-hydroxy-5,6-diphenylpyrazine to 2-chloro-3-cyano-5,6-diphenylpyrazine (848).

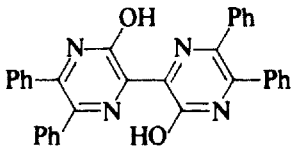
2-Isobutylpyrazine with mixed phosphorus pentachloride–phosphoryl chloride at 95° gave 2-chloro-5-isobutylpyrazine (693).

Other chlorinations have been effected with phosphorus pentachloride alone as follows: piperazine-2,5-dione in carbon tetrachloride to 2,5-dichloro-3,6-dihydropyrazine (847, 849) [but at 250°/24 hours to tetrachloropyrazine (850, 851)]; 2-chloropyrazine at 320–330° (850–852), 2-hydroxypyrazine at 310° (850–852), piperazine (and its dihydrochloride) at 300° (852), and 2,3-dicarboxypyrazine at 300° (851) each to tetrachloropyrazine; and 1,4-dialkylpiperazine-2,5-diones gave 1-alkyl-3,5,6-trichloro-2-oxo-1,2-dihydropyrazines accompanied in some cases by 1,4-dialkyl-3,3,5,5,6,6-hexachloropiperazin-2-one (853).

1,4-Diphenylpiperazine-2,5-dione and phosphorus pentachloride gave, after hydrolysis, 5,6-dichloro-2,3-dioxo-1,4-diphenyl-1,2,3,4-tetrahydropyrazine, and 1-cyclohexyl-4-phenylpiperazine-2,5-dione with phosphorus pentachloride in

1,1,2,2-tetrachloroethane at reflux gave a low yield of 3,5,6-trichloro-2-oxo-1-phenyl-1,2-dihydropyrazine together with substituted piperazines (853).

3,3′-Dihydroxy-5,5′,6,6′-tetraphenyl-2,2′-bipyrazinyl (**4**) on prolonged heating with phosphorus halides did not give any detectable amount of halogenobipyrazinyl (837).



(4)

E. Chlorinations with Sulfuryl Chloride and Thionyl Chloride

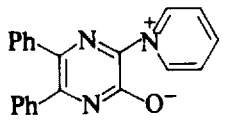
Many chlorinations of pyrazines have been achieved with sulfuryl chloride. A series of monoalkylpyrazines has been chlorinated specifically in the 3-position with sulfuryl chloride in the presence of *N,N*-dimethylformamide; for example, 2-*s*-butylpyrazine in *N,N*-dimethylformamide with sulfuryl chloride at 45° gave 2-*s*-butyl-3-chloropyrazine. The nucleus of 2,6-dialkylpyrazines was also readily chlorinated (687, 693). 2,6-Dimethylpyrazine and sulfuryl chloride in *N,N*-dimethylformamide gave 2-chloro-3,5-dimethylpyrazine (687, 844), and 3-methoxy-2,5-dimethylpyrazine gave 2-chloro-5-methoxy-3,6-dimethylpyrazine (844).

2-Chloropyrazine with sulfuryl chloride at 65–150° gave 2,6-dichloropyrazine (772, 832) but 2-chloropyrazine with sulfuryl chloride in *N,N*-dimethylformamide at 70–75° was claimed to give a 62.5% yield of 2,3-dichloropyrazine (770, 771).

2-Amino-3-methoxycarbonylpyrazine refluxed with sulfuryl chloride in benzene gave 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine (779, 780, 782, 809, 854–859); 2-amino-3-benzyloxycarbonylpyrazine with sulfuryl chloride gave 2-amino-3-benzyloxycarbonyl-5,6-dichloropyrazine (860); 2-methoxycarbonyl-3-methylaminopyrazine gave 2,3-dichloro-5-methoxycarbonyl-6-methylaminopyrazine (861); 2-amino-3-methoxycarbonyl-5-methyl(phenyl or cyclohexyl) pyrazine gave 2-amino-6-chloro-3-methoxycarbonyl-5-methyl(phenyl or cyclohexyl)pyrazine (378a, 780, 782, 783, 802); and 3-amino-2-methoxycarbonyl-5-phenyl(and methyl)pyrazine gave 2-amino-5-chloro-3-methoxycarbonyl-6-phenyl(and methyl)pyrazine (378a, 782). 2-Amino-5-chloro(bromo or iodo)-3-methoxycarbonylpyrazine with sulfuryl chloride all gave 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine (378a, 782, 809).

Some chlorinations have been reported with thionyl chloride. 2,3-Dicyano-5,6-dihydroxypyrazine refluxed with thionyl chloride in pyridine was reported to give 2,3-dichloro-5,6-dicyanopyrazine (862); and 2-hydroxy-3-nitro-5,6-diphenylpyrazine with thionyl chloride gave 2-chloro-3-hydroxy-5,6-diphenylpyrazine (817, 841) but with thionyl chloride and pyridine it gave the betaine of 2-hydroxy-5,6-diphenyl-3-pyridiniopyrazine chloride (**5**) (863), which was hydrolyzed in acid to 2,3-dihydroxy-5,6-diphenylpyrazine (863). No product could be isolated from 2-methylpyrazine when refluxed with thionyl chloride (864). 1,4-Dimethylpiperazine-

2,5-dione did not react with oxalyl chloride at reflux in ether but 1,4-diacetylpiperazine-2,5-dione gave a white precipitate, presumed to be a chlorination product (847).



(5)

F. Brominations with Phosphorus Bromides and Other Reagents

2-Hydroxypyrazine with phosphoryl bromide and phosphorus pentabromide has been found to give a mixture of 2-bromopyrazine and 2,6-dibromopyrazine (818, 865); the former was converted to the latter under similar reaction conditions (865). Phenyl-substituted 2-hydroxypyrazines were found to be transformed in good yield by phosphorus tribromide alone to the corresponding 2-bromopyrazines, but this procedure was not satisfactory when applied to alkylhydroxypyrazines because they formed complexes insoluble in phosphorus tribromide and the yields of bromopyrazines were poor (866). Phosphoryl bromide alone, or with phosphorus tribromide as diluent, was a useful reagent for the synthesis of alkylated 2-bromopyrazines but it complicated the reaction by yielding polybromides as by-products [presumably as a result of free radical bromination of alkyl substituents and of the pyrazine nucleus (866)]. This behavior precluded the use of forcing conditions to increase the yield of monobromopyrazines.

Refluxing phosphorus tribromide converted 2-bromo-3-hydroxy-5,6-diphenylpyrazine and 2-bromo-5-hydroxy-3,6-diphenylpyrazine to the dibromopyrazines; 2,3-dichloro-5,6-dimethylpyrazine and 2,5-dichloro-3-phenylpyrazine to the dibromopyrazines (817); 5-chloro-2,3-diphenylpyrazine (and its 6-ethyl derivative) to 5-bromo-2,3-diphenylpyrazine (and its 6-ethyl derivative) (866); and 2-hydroxy-3-nitro-5,6-diphenylpyrazine also to 2,3-dibromo-5,6-diphenylpyrazine (834, 841). 2,3-Dihydroxy-5-phenyl-, 2,5-dihydroxy-3-phenyl-, and 3,5-dihydroxy-2-phenylpyrazines were each converted with phosphorus tribromide at 180–200° to the corresponding dibromopyrazine (829). 2-Cyano-3-hydroxy-5,6-diphenylpyrazine and 2-carbamoyl-3-hydroxy-5,6-diphenylpyrazine with boiling phosphorus tribromide each gave 2-bromo-3-cyano-5,6-diphenylpyrazine (837).

2-Amino-3-hydroxypyrazine with phosphoryl bromide at 140–150° for 20 minutes gave 2-amino-3-bromopyrazine (807) and 2-hydroxy-6-methoxycarbonylpyrazine with phosphoryl bromide at 125° for 10 minutes gave 2-bromo-6-methoxycarbonylpyrazine (867).

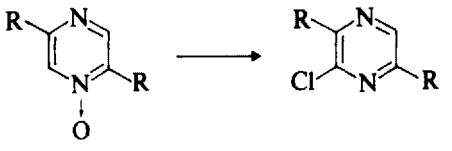
1,4-Diphenylpiperazine-2,5-dione with phosphorus pentabromide in *o*-dichlorobenzene at 140–150° gave 3,6-dibromo-1,4-diphenylpiperazine-2,5-dione (853).

2-Hydroxy-3-nitro-5,6-diphenylpyrazine with acetyl bromide, iodine bromide, or dry hydrogen bromide in dry dioxane gave 2-bromo-3-hydroxy-5,6-diphenyl-

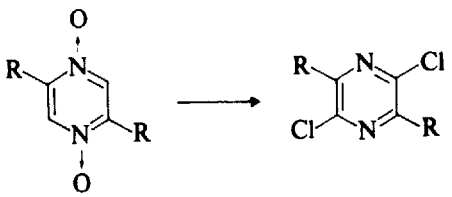
pyrazine (841) but thionyl bromide (or phosphorus tribromide) gave 2,3-dibromo-5,6-diphenylpyrazine (841).

G. Pyrazine *N*-Oxides with Phosphoryl Chloride (and Other Acid Chlorides)

The reaction of alkylpyrazine *N*-oxides (e.g., **6**, **8**) with phosphoryl chloride to give alkyl chloropyrazines (e.g., **7**, **9**) was first observed by Newbold and Spring (740), and has been discussed in Section IV.3C(1). Since the initial work this reaction has been applied to many variously substituted and unsubstituted pyrazine *N*-oxides, which are listed in Table V.1. The references for the table are 101, 313, 330, 365a, 535, 538, 544, 547a, 575, 626, 686, 735–738, 740, 741, 744, 756–759, 760a, 793, 808, 817, 829, 831, 838–840, 842 and 868–881. Usually the *N*-oxide and phosphoryl chloride were refluxed for the periods up to one hour, but the conditions may vary from heating at 40–50° for 5 minutes [for the conversion of 3-morpholinocarbonylpyrazine 1-oxide to 2-chloro-6-morpholinocarbonylpyrazine (868)] to heating at 140° [for the conversion of 2-*s*-butyl-5-isobutylpyrazine 1-oxide to 5-*s*-butyl-3-chloro-2-isobutylpyrazine (313)]. Nuclear chlorination usually occurs, but side chain chlorination of methyl groups may also take place; for example, the reaction of 2,5-dimethylpyrazine di-*N*-oxide with phosphoryl chloride at 160° (756) [Section IV.3C(1)] and the reaction of 3-ethoxy-2,5-dimethylpyrazine 1-oxide with phosphoryl chloride at reflux (10 min) gave 2-chloro-5-ethoxy-3,6-dimethylpyrazine and 2-chloromethyl-3-ethoxy-5-methylpyrazine (872).



(6) (7)



(8) (9)

Earlier results from the reactions of 2-methylpyrazine 1-oxide and 3-methylpyrazine 1-oxide with phosphoryl chloride (626, 735, 736) now appear to have been clarified (686) [see Section IV.3C(1)].

Although halogenation of the nucleus may be expected to occur at a position

TABLE V.1 REACTIONS OF PYRAZINE *N*-OXIDES WITH PHOSPHORYL CHLORIDE (AND OTHER ACID CHLORIDES)[a]

Pyrazine *N*-Oxides	Product(s)	Refs.
Unsubstituted/1-oxide	2-Chloro	575, 737
Unsubstituted/1,4-dioxide	2,6-Dichloro[b]	737, 757
	2-Chloro/1-oxide and 2,6-dichloro[b]	757, 838
	2-Chloro/1-oxide[c]	758
2-Methyl/1-oxide	2-Chloro-3-methyl and 2-chloro-6-methyl	686, cf. 626, 735, 736
3-Methyl/1-oxide	2-Chloro-3-methyl	626, 686
2-Methyl/1,4-dioxide	Dichloromethyl and chloromethyl/*N*-oxide	737
2,3-Diphenyl/1-oxide	5-Chloro-2,3-diphenyl	741
3,5-Dimethyl/1-oxide	2-Chloro-3,5-dimethyl	737
2,5-Dimethyl/1-oxide	3-Chloro-2,5-dimethyl	740
2,5-Dimethyl/1,4-dioxide	2,5-Dichloro-3,6-dimethyl, 3-chloro-2,5-dimethyl/1-oxide, 5-chloromethyl-2-methyl/1-oxide, 3-chloro-2-chloromethyl-5-methyl, and 2,5-bis(chloromethyl)	756, cf. 740
2,5-Di-*s*-butyl/1-oxide	3-Chloro-2,5-di-*s*-butyl	740
2,5-Di-*s*-butyl/1,4-dioxide	2,5-Dichloro-3,6-di-*s*-butyl	740
2-*s*-Butyl-5-isobutyl/1-oxide	5-*s*-Butyl-3-chloro-2-isobutyl	313
Trimethyl/*N*-oxide	2-Chloro-3,5,6-trimethyl	330
2(1′-Acetoxy-2′-methylpropyl)-5-isobutyl/1-oxide	5-(1′-Acetoxy-2′-methylpropyl)-3-chloro-2-isobutyl	760a
3-Acetoxymethyl/1-oxide	2-Acetoxymethyl-*x*-chloro	738
3-(D-*arabo*-tetraacetoxybutyl)/1-oxide	2-Chloro-5-(D-*arabo*-tetraacetoxybutyl)	544
3-Trifluoromethyl/1-oxide[c]	2-Chloro-6-trifluoromethyl	759
3-Carbamoyl/1-oxide	2-Chloro-6-cyano[b]	744, 757, cf. 839
2-Carbamoyl/1- and 4-oxide mixture	2-Carbamoyl-5-chloro and 2-chloro-5(and 6)-cyano	840, cf. 744, 839
3-Carboxy/1-oxide	2-Carboxy-6-chloro[b]	868–871
	2-Carboxy-5(?)-chloro[d]	839, cf. 744
3-Methoxycarbonyl/1-oxide[e]	2-Chloro-6[b, d][or 5(?)]-methoxycarbonyl	839, 868, 870
3-Ethoxycarbonly/1-oxide[f]	2-Bromo-5(?)-ethoxycarbonyl	839

TABLE V.1 *Continued*

Pyrazine *N*-Oxides	Product(s)	Refs.
3-Morpholinocarbonyl/1-oxide	2-Chloro-6-morpholinocarbonyl[b]	868
	2-Chloro-6-morpholinocarbonyl[b] and 2-chloro-3-morpholinocarbonyl (small quantity)[g]	870
3-Chloro/1-oxide	2,3- and 2,6-Dichloro	759, 831, cf. 737
3,5-Dichloro/1-oxide	Trichloro	365a
3-Chloro-2,5-dimethyl/1-oxide	2,5-Dichloro-3,6-dimethyl and 3-chloro-2-chloromethyl-5-methyl	842, cf. 872
2,5-Dichloro-3,6-dimethyl/1,4-dioxide	2,5-Dichloro-3,6-bis(chloromethyl) and 2,5-dichloro-3-chloromethyl-6-methyl/1-oxide[h]	756
2-Methoxy/1-oxide	2-Chloro-3-methoxy[b] and 2-chloro-6-methoxy	838
3-Methoxy/1-oxide	2-Chloro-3-methoxy and 2-chloro-6-methoxy[b]	838
3-Methoxy-2-phenyl/1-oxide	5-Chloro-2-methoxy-3-phenyl	817
3-Ethoxy-2,5-dimethyl/1-oxide	2-Chloro-5-ethoxy-3,6-dimethyl and 2-chloromethyl-3-ethoxy-5-methyl	872
2,5-Dimethoxy(or diethoxy)-3,6-dimethyl/1,4-dioxide	2,5-Bis(chloromethyl)-3,6-dimethoxy(or diethoxy)	756
3-Hydroxy-2,5-diisobutyl/1-oxide	2-Chloro-5-hydroxy-3,6-diisobutyl	101
2-Hydroxy-5-phenyl/1-oxide	3-Chloro-5-hydroxy-2-phenyl	829
2-Hydroxy-3,5-diphenyl/1-oxide	2-Chloro-6-hydroxy-3,5-diphenyl	873
2-Hydroxy-3-methyl-5-phenyl/1-oxide	2-Chloro-6-hydroxy-5-methyl-3-phenyl	873
2-Hydroxy-5-methyl-3-phenyl/1-oxide	2-Chloro-6-hydroxy-3-methyl-5-phenyl	873
3-Amino/1-oxide	2-Amino-3-chloro	547a, 838
2-Amino-5-methyl/1-oxide	5-Amino-3-chloro-2-methyl	535
3-Dimethylamino-2,5-dimethyl/1-oxide	2-Chloro-5-dimethylamino-3,6-dimethyl	793
2-Amino-3-carbamoyl-5-methyl/1-oxide	2-Amino-3-carbamoyl-6-chloro-5-methyl	535
2-Amino-3-cyano/1-oxide	3-Amino-5-chloro-2-cyano	538
2-Amino-3-cyano-5-methyl/1-oxide	2-Amino-6-chloro-3-cyano-5-methyl	538
2-Amino-5-chloromethyl-3-cyano/1-oxide	2-Amino-6-chloro-5-chloromethyl-3-cyano	874
3-Amino-2-cyano/1-oxide	2-Amino-5-chloro-3-cyano	538
2-Amino-5-chloro-3-methoxycarbonyl/1-oxide	2-Amino-5,6-dichloro-3-methoxycarbonyl	875, 876

TABLE V.1 *Continued*

Pyrazine *N*-Oxides	Product(s)	Refs.
2-Amino-5-bromo-3-methoxycarbonyl/1-oxide	2-Amino-5-bromo-6-chloro-3-methoxycarbonyl	808, 875, 877–879
2-Amino-3-methoxycarbonyl/1-oxide[i]	3-Amino-5-chloro-2-methoxycarbonyl	876, 880
3-Carbamoyl-2-methoxy/1-oxide	3-Cyano-5-chloro-2-methoxy[b]	881

[a] Other chlorinating reagents that have also been used are indicated in the table.

[b] The chloro substituent in these compounds is meta to the ring nitrogen which formed part of the *N*-oxide group in the starting material. See Section 1G for a discussion of the results.

[c] This reaction with benzene sulfonyl chloride.

[d] This reaction with thionyl chloride.

[e] Reactions with thionyl chloride and acetyl chloride have been described (838).

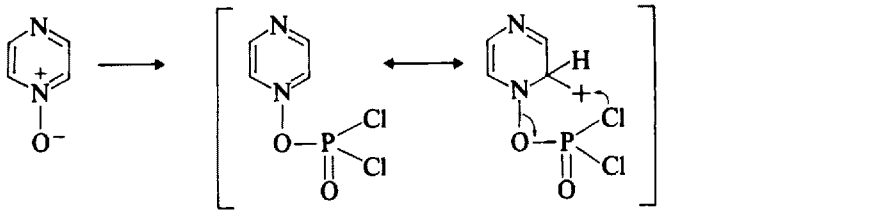
[f] This reaction with phosphoryl bromide.

[g] Reactions with thionyl chloride (870) and sulfuryl chloride (838) have been described.

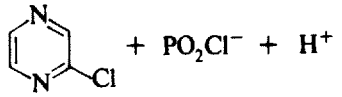
[h] Other products were obtained as the result of deoxygenation.

[i] This reaction with phosphoryl chloride in dimethylformamide.

ortho to the original *N*-oxide group [see acetoxylation, Section IV.3C(3)], as illustrated in the transformation of pyrazine *N*-oxide to 2-chloropyrazine (**10** → **11**), there are many reactions listed in Table V.1 (and marked accordingly) in which halogenation occurs meta to the *N*-oxide group. For example, 3-carboxypyrazine 1-oxide with phosphoryl chloride was claimed to give 2-carboxy-6-chloropyrazine (868–870) [but 3-carboxypyrazine 1-oxide and thionyl chloride was reported to give 2-chloro-5(?)-carboxypyrazine (839); cf. Foks (744)]; 3-chloropyrazine 1-oxide gave 2,3- and 2,6-dichloropyrazine (757, 831); and 2- and 3-methoxypyrazine 1-oxide both gave a mixture of 2-chloro-3(and 6)-methoxypyrazine (838).

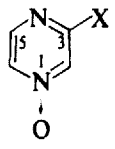


(**10**)

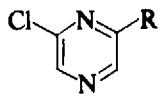


(**11**)

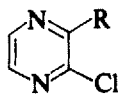
Okada et al. (838), from comprehensive studies of the reactions of 3-substituted pyrazine 1-oxides (**12**) with phosphoryl (thionyl and sulfuryl) chloride, concluded that when the substituent was an electron-withdrawing group (e.g., methoxycarbonyl) the substitution would be at the 5-position to give the 2,6-disubstituted pyrazine (e.g., **13**, R = COOMe), whereas the 2-chloro compound (e.g., **14**, R = NH_2) would be obtained when the substituent was electron-donating (e.g., amino). When a weak electron-donating group (e.g., methoxy) was present both types of pyrazines (e.g., **13** and **14**, R = OMe) would be formed.



(**12**)



(**13**)



(**14**)

In the reactions they examined no 2,5-disubstituted pyrazines could be detected in the products. A mechanism of substitution in the β-position of pyrazine *N*-oxides has been proposed (838).

In addition to the reactions with phosphoryl chloride mentioned above,

phosphoryl bromide (839), thionyl chloride, sulfuryl chloride and acetyl chloride (838, 839, 870), and benzenesulfonyl chloride (758) have been used, and other reactions with methanesulfonyl chloride and a mixture of phosphoryl chloride and concentrated sulfuric acid have been examined (756). 3-Trifluoromethylpyrazine 1-oxide with benzenesulfonyl chloride has been shown to give 2-chloro-6-trifluoromethylpyrazine (759).

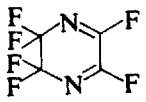
H. The Preparation of Fluoropyrazines

2-Fluoropyrazine has been prepared from 2-chloropyrazine and anhydrous potassium fluoride in refluxing dimethyl sulfoxide (882) or *N*-methyl-2-pyrrolidone at 185° (883). Similarly 3-fluoro-2,5-dimethylpyrazine has been prepared from its chloro analogue and dry potassium fluoride in *N*-methyl-2-pyrrolidone and 2-chloro-6-fluoropyrazine and 2,6-difluoropyrazine from 2,6-dichloropyrazine (883).

Diazotization of aminopyrazine in fluoroboric acid containing copper powder with sodium nitrite gave 2-fluoropyrazine (882, 884).

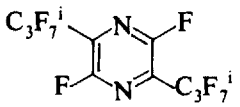
Tetrafluoropyrazine was prepared by heating tetrachloropyrazine with anhydrous potassium fluoride in a sealed vessel in the range 315–345° (684, 850–852), but under milder reaction conditions partly fluorinated products, namely, 2-chloro-3,5,6-trifluoropyrazine, 2,6-dichloro-3,5-difluoropyrazine, and 2,3,5-trichloro-6-fluoropyrazine, were obtained (850–852).

Trifluoropyrazine has been prepared from tetrafluoropyrazine through 2,3,5-trifluoro-6-hydrazinopyrazine by removal of the hydrazino substituent with aqueous copper sulfate (885). Fluorination of tetrafluoropyrazine in nitrogen in the presence of cobalt(III) fluoride and calcium fluoride at 80° gave perfluoro-1,4-diazocyclohexa-1,3-diene (**15**) (886).



(15)

Irradiation of tetrafluoropyridazine, using an unfiltered medium-pressure mercury lamp, gave an almost quantitative yield of tetrafluoropyrazine (492) and 3,6-difluoro-4,5-bisheptafluoroisopropylpyridazine similarly gave 2,5-difluoro-3,6-bisheptafluoroisopropylpyrazine (**16**) (492). Other rearrangements of fluoropyridazines to fluoropyrazines have been discussed in Section II.9 (493–496).



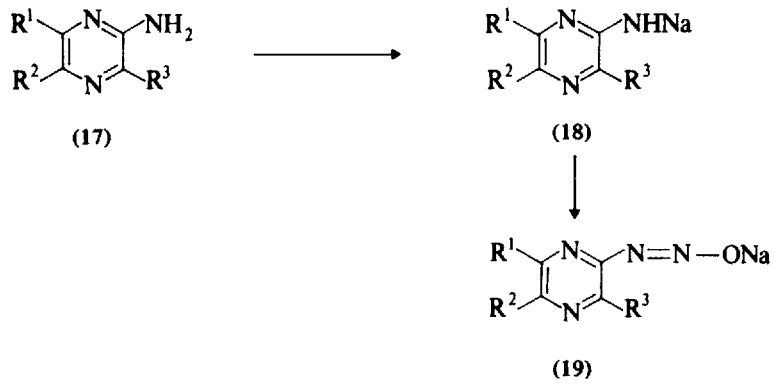
(16)

I. The Preparation of Iodopyrazines

2-Iodopyrazine and six mono- and dialkyl- and phenyl-substituted 2-iodopyrazines have been prepared (30–60% yield) by displacement of the chloro substituent from the corresponding chloro compounds with a solution of sodium iodide and hydriodic acid in ethyl methyl ketone (887). Attempts to prepare iodopyrazine by treating the hydroxypyrazine with phosphorus triiodide were unsuccessful (887).

Iodination of 2-amino-3-methoxycarbonyl- and 3,5-diamino-2-methoxycarbonylpyrazines with iodine, potassium iodide, and mercuric acetate in aqueous dioxane gave 2-amino-5-iodo-3-methoxycarbonylpyrazine (150, 378a, 781, 782, 787) and 2,6-diamino-3-iodo-5-methylcarbonylpyrazine (780, 809), respectively; and similar iodination of the corresponding nitriles gave 2-amino-3-cyano-5-iodopyrazine (792) and 2,6-diamino-3-cyano-5-iodopyrazine (878), respectively.

The isodiazotate salts (**19**) of 2-amino-3-methyl- and 3-amino-2,5-dimethylpyrazines (**17**, $R^1 = R^2 = H$; $R^3 = Me$; $R^1 = R^3 = Me$, $R^2 = H$, respectively) [prepared from the corresponding amine by refluxing with sodium amide in diethyl ether and allowing the resulting sodium salt (**18**) to react with isoamyl nitrite] on treatment with hydriodic acid gave 2-amino-5-iodo-3-methyl- and 2-amino-5-iodo-3,6-dimethylpyrazines, respectively (887), which were also prepared by iodination of the corresponding 2-aminopyrazines with sodium hypoiodite. The isodiazotate salt of 2-aminopyrazine gave 2-iodopyrazine only in poor yield (887). 2-Amino-3-ethylpyrazine did not give appreciable quantities of iodinated product (through the isodiazotate salt) nor did it react with sodium hypoiodite (887).

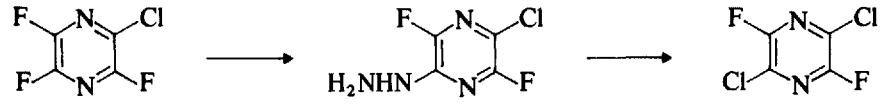


J. Interconversion of Halogeno Substituents

The preparations of fluoro- and iodopyrazines, some of which involved the displacement of chloro substituents, have been discussed in Sections 1H and 1I.

Tetrafluoropyrazine has been converted to 2,3,5-trifluoro-6-hydrazinopyrazine and thence to 2-chloro- and 2-bromo-3,5,6-trifluoropyrazine by reaction with ferric chloride in concentrated hydrochloric acid and cupric bromide in aqueous

hydrobromic acid, respectively (851). Similarly, 2-chloro-3,5,6-trifluoropyrazine (**20**) was converted to 2-chloro-3,6-difluoro-5-hydrazinopyrazine (**21**) and thence with ferric chloride in dilute hydrochloric acid gave 2,5-dichloro-3,6-difluoropyrazine (**22**) (888).



(20) (21) (22)

2-Dimethylamino-3,5,6-trifluoropyrazine with aluminum trichloride at 100° gave 2-chloro-6-dimethylamino-3,5-difluoropyrazine, 2-chloro-5-dimethylamino-3,6-difluoropyrazine similarly gave 2,6-dichloro-3-dimethylamino-5-fluoropyrazine, and 2-chloro-5,6-bis(dimethylamino)-3-fluoropyrazine gave 2,3-dichloro-5,6-bis(dimethylamino)pyrazine (888).

In an analogous manner anhydrous aluminum tribromide and hydrogen bromide with tetrafluoropyrazine heated in a sealed tube at 100° for 48 hours gave tetrabromopyrazine and a dibromodifluoropyrazine (851); 2,3-dichloro-5,6-diphenylpyrazine with phosphorus tribromide gave 2,3-dibromo-5,6-diphenylpyrazine (834), and 5-chloro-2,3-diphenylpyrazine (and its 6-ethyl derivative) gave 5-bromo-2,3-diphenylpyrazine (and its 6-ethyl derivative) (866), but very little displacement occurred when alkylmonochloropyrazines were heated with phosphoryl bromide (866).

Passage of hydrogen bromide into a refluxing solution of tetrachloropyrazine in acetic acid has been shown to give tetrabromopyrazine (889) and 2-bromo-3,5,6-trichloropyrazine, and 2,6-dibromo-3,5-dichloropyrazine in chloroacetic and or β-chloropropionic acid similarly with hydrogen bromide gave tetrabromopyrazine (889). 2-Chloro-3-dichloromethylpyrazine with hydrogen bromide in acetic acid at 45–60° gave 2-bromo-3-dichloromethylpyrazine and 2-bromo-3-chloromethylpyrazine (688). Selective replacement of one chloro substituent from tetrachloropyrazine by conversion to 2,3,5-trichloro-6-hydrazinopyrazine and subsequent treatment with hydrobromic acid containing cupric bromide gave 2-bromo-3,5,6-trichloropyrazine (888) [tetrachloropyrazine with lithium aluminum hydride gave trichloropyrazine (888)].

2-Bromo-3-hydroxy-5,6-dimethylpyrazine and 2-bromo-5-hydroxy-3,6-diphenylpyrazine with phosphoryl chloride afforded 2,3-dichloro-5,6-dimethylpyrazine and 2,5-dichloro-3,6-diphenylpyrazine, respectively (817); and the bromo substituent in 2-amino-3-bromo-5,6-dimethylpyrazine and its *p*-aminobenzenesulfonyl derivative have been replaced by chlorine on treatment with aqueous hydrochloric acid in ethanol (812).

K. Conversion of Amino to Bromo Substituents

Ellingson and Henry (798) first showed that 2-amino-3-methoxycarbonylpyrazine

with hydrobromic acid, bromine, and sodium nitrite in water gave 2-bromo-3-methoxycarbonylpyrazine (798, 890), and that 2-amino-5-bromopyrazine similarly treated gave 2,5-dibromopyrazine (798). Analogous reactions occurred with 2-amino-5-chloro-(and bromo)-3-methoxycarbonylpyrazine and 2-amino-5-chloro-6-dimethylamino(and ethylamino)-3-methoxycarbonylpyrazine to give 2-bromo-5-chloro-3-methoxycarbonylpyrazine, 2,5-dibromo-3-methoxycarbonylpyrazine, and 2-bromo-5-chloro-6-dimethylamino(and ethylamino)-3-methoxycarbonylpyrazine, respectively (799, 800, 891, 892). 2-Amino-3,5-dibromopyrazine in 20% hydrobromic acid with bromine and sodium nitrite has been shown to give 2,3,5-tribromopyrazine, and 2-amino-5-bromo-3-chloropyrazine treated similarly gave 2,5-dibromo-3-chloropyrazine, but 2-amino-3-bromopyrazine gave 2-amino-3,5-dibromopyrazine (807).

L. Primary Syntheses

Preparations of halogenopyrazines utilizing primary syntheses from α-(*p*-toluenesulfonyloxyimino)malononitrile have been discussed in Section II.7. α-Aminophenylacetonitrile with chloral (or bromal) were claimed to give 2,3-dichloro(or dibromo)-5-phenylpyrazine (830, 893), but this has now been shown to be in error (829).

M. Degradation

Halogenopyrazines may be prepared by degradation of fused pyrazine ring systems as follows. Oxidation of 2,3-dichloroquinoxaline with potassium permanganate followed by esterification by methanol gave 2,3-dichloro-5,6-dimethoxycarbonylpyrazine (409) (Section II.4). Ring opening reactions of 6- and 7-chloro- and 6,7-dichloropteridines to give pyrazines have been reported (430) and discussed (Section II.5); for example, 6,7-dichloropteridine with 0.1 *N*-sulfuric acid gave 2,3-dichloro-5-formamido-6-formylpyrazine and 2-amino-5,6-dichloro-3-formylpyrazine (430).

N. Ring Transformations

Ring transformations which give halogeno(fluoro and chloro)pyrazines (492, 496, 502) have been discussed in Section II.9.

O. Miscellaneous

2,3,5,6-Tetrachloro-1,4-diformylpiperazine heated at 185–200° has been found to give monochloropyrazine (hydrochloride) (473, 894, 895), and 2,3,5-trichloro-

6-hydrazinopyrazine with potassium hydroxide in ethylene glycol at 150° gave 2,5-dichloropyrazine (896).

2. THE PREPARATION OF EXTRANUCLEAR HALOGENOPYRAZINES

A. By Direct Halogenation

Chlorination of methylpyrazines with chlorine in acetic acid at 100° occurred at the methyl group to give chloromethyl-, dichloromethyl-, and trichloromethylpyrazines (685, 686) [cf. Section 1A(1)]. Whereas 2-trichloromethylpyrazine was prepared from 2-methylpyrazine (685), 2-chloro-3-dichloromethylpyrazine (with no 2-chloro-3-trichloromethylpyrazine) was prepared under similar conditions from 2-chloro-3-methylpyrazine (685). Chlorination of 2-chloro-3-methylpyrazine in carbon tetrachloride to 2-chloro-3-chloromethylpyrazine (897) and 2-chloro-3-methylpyrazine in acetic acid to 2-chloro-3-dichloromethylpyrazine (687, 688) have been described. Direct chlorination of 2,6-dimethylpyrazine in carbon tetrachloride under ultraviolet irradiation (the reaction was slow in its absence) gave 2,6-bis(chloromethyl)pyrazine (679), and 2,3-dimethylpyrazine gave 2,3-bis(chloromethyl)pyrazine (654), although 2,5-dimethylpyrazine under similar conditions gave 3-chloro-2,5-dimethylpyrazine (679). 2,3,5-Trichloro-6-methoxypyrazine in carbon tetrachloride, when chlorinated for 2.5 hours under sun lamp irradiation, gave 2,3,5-trichloro-6-trichloromethoxypyrazine and a small amount of 2,3,5-trichloro-6-dichloromethoxypyrazine (898).

Methylpyrazines with *N*-halogenosuccinimide and a catalytic amount of benzoyl peroxide gave α-halogenomethylpyrazines. In this way methylpyrazine with one equivalent of *N*-chlorosuccinimide gave a product presumed to be α-chloromethylpyrazine (679, 690) and with greater quantities of reagent it gave α-(dichloromethyl)pyrazine (690). 2,3-Dimethylpyrazine with one and two equivalents of *N*-chlorosuccinimide (and benzoyl peroxide) in carbon tetrachloride gave 2-chloromethyl-3-methyl- and 2,3-bis(chloromethyl)pyrazine (654), 2,5-dimethylpyrazine with one equivalent of *N*-chlorosuccinimide gave 2-chloromethyl-5-methylpyrazine (679), and 2,6-dimethylpyrazine with two equivalents in chloroform gave 2,6-bis(chloromethyl)pyrazine (679). Likewise tetramethylpyrazine with *N*-bromosuccinimide in the presence of light and benzoyl peroxide gave a quantitative yield of 2-bromomethyl-3,5,6-trimethylpyrazine (330).

Behun and Levine (694) have shown that α,α-dichloromethylpyrazine was obtained when acetonyl- and phenacylpyrazines were treated with potassium hypochlorite.

B. By Reaction of *N*-Oxides with Phosphoryl Chloride

The reactions of various methylpyrazine *N*-oxides with phosphoryl chloride to

give, in some cases, chloromethylpyrazines has been described in Section IV.3C(1). The *N*-oxides of 2,5-dimethylpyrazine and their 3,6-disubstituted (chloro or alkoxy) derivatives reacted with phosphoryl chloride to give various compounds substituted by chlorine on the nucleus and/or on the methyl groups. Some examples are as follows: 2,5-dimethylpyrazine 1,4-dioxide with phosphoryl chloride at 160° gave 5-chloromethyl-2-methylpyrazine 1-oxide, 3-chloro-2-chloromethyl-5-methylpyrazine, 2,5-bis(chloromethyl)pyrazine, and other products (756).

2,5-Dichloro-3,6-dimethylpyrazine 1,4-dioxide with phosphoryl chloride at 170° gave 2,5-dichloro-3,6-bis(chloromethyl)pyrazine and 2,5-dichloro-3-chloromethyl-6-methylpyrazine 1-oxide; and 2,5-dichloro-3,6-dimethylpyrazine 1-oxide gave 2,5-dichloro-3-chloromethyl-6-methylpyrazine (756).

p-Tosyl chloride and methanesulfonyl chloride were tried as substitutes for phosphoryl chloride in the above reaction but did not give good results (756).

2,5-Dimethoxy(or diethoxy)-3,6-dimethylpyrazine 1,4-dioxide with phosphoryl chloride have been shown to give 2,5-bis(chloromethyl)-3,6-dimethoxy(or diethoxy)-pyrazine (756), 3-ethoxy-2,5-dimethylpyrazine 1-oxide gave 2-chloro-5-ethoxy-3,6-dimethylpyrazine and 2-chloromethyl-3-ethoxy-5-methylpyrazine (872), and 3-chloro-2,5-dimethylpyrazine 1-oxide gave 2,5-dichloro-3,6-dimethylpyrazine and 3-chloro-2-chloromethyl-5-methylpyrazine (842).

C. By Primary Syntheses

The synthesis of 2-chloromethyl-5,6-diphenyl-2,3-dihydropyrazine from 1,2-diamino-3-chloropropane and benzil has been described (349) in Section II.2 and 2,5-bis(trichloropropenyl)pyrazine from 2,5-dimethylpyrazine and chloral (708) in Section IV.2C(5)(a).

D. Ring Transformations

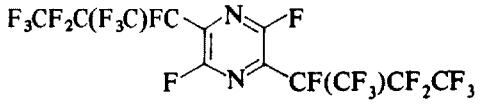
Various rearrangements of perfluoroalkylpyridazines to perfluoroalkylpyrazines have been described in Section II.9.

E. Miscellaneous

Deoxygenation of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide with phosphorus trichloride in tetrahydrofuran has been shown to give 3-amino-2-cyano-5-chloromethylpyrazine (534).

Tetrafluoropyrazine, cesium fluoride, octafluorobut-2-ene and sulpholan heated and rotated at 160° for 4 hours gave perfluoro-2,5-di-*s*-butylpyrazine (23) (494) and 2-carboxypyrazine with sulfur tetrafluoride in hydrogen fluoride at 150° gave 2-trifluoromethylpyrazine (759). 2-(ω-Chloroacetyl)pyrazine has been prepared from 2-diazoacetylpyrazine and dry hydrogen chloride in ether (138) and

2,3,5,6-tetracarboxypyrazine heated with sulfur tetrafluoride (SF_4) at 150° gave 2,3,5,6-tetra(trifluoromethyl)pyrazine (899).



(23)

3. THE PREPARATION OF NUCLEAR AND EXTRANUCLEAR HALOGENOPYRAZINE *N*-OXIDES

A. By *N*-Oxidation of Halogenopyrazines

Halogenopyrazine *N*-oxides are most usually prepared by oxidation of the halogenopyrazine with a variety of peroxyacid oxidizing agents. Examples of some such oxidations are summarized in Table V.2. The references for the table are 101, 113b, 365b, 688, 733b, 737, 740a, 757, 759, 760a, 793, 808, 842, 843, 872, 877–879, 900–907. Trifluoroperoxyacetic acid was the reagent of choice for di-*N*-oxidation (842).

Chlorinated pyrazines are specifically oxidized on the nitrogen adjacent to the halogen-bearing carbon by means of Caro's acid (peroxysulfuric acid) in concentrated sulfuric acid, and this procedure affords the first simple, direct, and high yield synthesis of 2-chloropyrazine 1-oxides. In general the oxidation terminates at the mono-*N*-oxide stage regardless of the amount of oxidizing agent employed. Only in the case of tetrachloropyrazine was the bis-*N*-oxide obtained. This peroxysulfate oxidation method is apparently limited to 1,4-diazines (900).

B. By Direct Synthesis

The synthesis of 2-amino-5-chloromethyl-3-cyanopyrazine 1-oxide (529) from aminomalononitrile and chloromethyl hydroxyiminomethyl ketone, and of 2-amino-6-chloromethyl(and chloroalkyl)-3-cyanopyrazine 1-oxide (534) from aminomalononitrile and β-chloro-α-hydroxyiminopropionaldehyde (prepared from the addition of nitrosyl chloride to acrolein) has been described in Section III.1.

C. By Halogenation

Bromination of 2,3-dimethylpyrazine 1,4-dioxide in dioxane in the presence of benzoyl peroxide gave 2-(bromomethyl)-3-methyl- and 2,3-bis(bromomethyl)-pyrazine 1,4-dioxide (739), and 2-methylpyrazine 1,4-dioxide gave 2-bromo-

TABLE V.2 THE PREPARATION OF HALOGENOPYRAZINE *N*-OXIDES BY OXIDATION OF HALOGENOPYRAZINES

Halogenopyrazine	Reagent(s) and Conditions	Product(s)	Refs.
2-Chloro	$K_2S_2O_8/H_2SO_4$	2-Chloro/1-oxide	733b, 900
	H_2O_2/acetic acid/65–85°	3-Chloro/1-oxide	733b, 737, 757
2,3-Dichloro	$K_2S_2O_8/H_2SO_4$	2,3-Dichloro/1-oxide	900
2,6-Dichloro	$K_2S_2O_8/H_2SO_4$	2,6-Dichloro/1-oxide	900
	H_2O_2/acetic acid/100°	3,5-Dichloro/1-oxide	365b
2,3,5-Trichloro	H_2O_2/trifluoroacetic acid	2,3,5-Trichloro/1-oxide	901
2,3,5-Tribromo	H_2O_2/trifluoroacetic acid	2,3,5-Tribromo/1-oxide	901
2-Trifluoromethyl	H_2O_2/acetic acid/70°	3-Trifluoromethyl/1-oxide	759
Tetrachloro	H_2O_2/trifluoroacetic acid/84°	Tetrachloro/1-oxide	901
	1 equiv. $K_2S_2O_8/H_2SO_4$	Tetrachloro/1-oxide	900
	2 equiv. $K_2S_2O_8/H_2SO_4$	Tetrachloro/1,4-dioxide	900
	H_2O_2/trifluoroacetic acid/H_2SO_4	Tetrachloro/1-oxide and tetrachloro/1,4-dioxide	902
	H_2O_2/H_2SO_4/45–55°/2.5 h H_2O_2/H_2SO_4/22–23°/20 h	Tetrachloro/1,4-dioxide	903, 904
Tetrabromo	H_2O_2/trifluoroacetic acid	Tetrabromo/1-oxide	901
2-Chloro-3-methyl	H_2O_2/acetic acid/65–70°	3-Chloro-2-methyl/1-oxide	737, 793
2-Chloro-6-methyl	H_2O_2/acetic acid/65–70°	3-Chloro-5-methyl/1-oxide	737
2-Chloro-3-phenyl	30% H_2O_2/acetic acid	3-Chloro-2-phenyl/1-oxide	733b
	$K_2S_2O_8/H_2SO_4$	2-Chloro-3-phenyl/1-oxide	733b
2-Chloro-5-phenyl	30% H_2O_2/acetic acid	2-Chloro-5-phenyl/1-oxide and 5-chloro-2-phenyl/1-oxide (1 : 1)	733b
	$K_2S_2O_8/H_2SO_4$	2-Chloro-5-phenyl/1-oxide	733b
2-Chloro-6-phenyl	30% H_2O_2/acetic acid	3-Chloro-5-phenyl/1-oxide	733b
3-Chloro-2,5-dimethyl	$K_2S_2O_8/H_2SO_4$	2-Chloro-3,6-dimethyl/1-oxide	842, 900
	H_2O_2/acetic acid/56–80°	3-Chloro-2,5-dimethyl/1-oxide	842, 872, 900, 905
3-Chloro-2,5-dimethyl/1-oxide	H_2O_2/trifluoroacetic acid/70°	3-Chloro-2,5-dimethyl/1,4-dioxide and 2-chloro-3,6-dimethyl/1-oxide (formed from the di-*N*-oxide)	842

TABLE V.2 *Continued*

Halogenopyrazine	Reagent(s) and Conditions	Product(s)	Refs.
3-Chloro-2,5-diisobutyl	$K_2S_2O_8/H_2SO_4$	2-Chloro-3,6-diisobutyl/1-oxide	113b
	Peroxymaleic acid/reflux	3-Chloro-2,5-diisobutyl/1-oxide and 1,4-dioxide	843
3-Chloro-2-isobutyl-5-isopropyl	Peroxymaleic acid/chloroform/20°	3-Chloro-2-isobutyl-5-isopropyl/1-oxide and 1,4-dioxide	740a
3-Chloro-5-isobutyl-2-isopropyl	Peroxymaleic acid/chloroform/20°	3-Chloro-5-isobutyl-2-isopropyl/1-oxide and 1,4-dioxide	740a
2-(1′-Acetoxy-2′-methylpropyl)-3-chloro-5-isobutyl	Peroxymaleic acid/methylene chloride/120°	2-(1′-Acetoxy-2′-methylpropyl)-3-chloro-5-isobutyl/1-oxide	760a
5-(1′-Acetoxy-2′-methylpropyl)-3-chloro-2-isobutyl	Peroxymaleic acid/methylene chloride/reflux	5-(1′-Acetoxy-2′-methylpropyl)-3-chloro-2-isobutyl/1-oxide and 1,4-dioxide	760a
2,5-Dichloro-3,6-diisobutyl	Peroxymaleic acid/chloroform/reflux	2,5-Dichloro-3,6-diisobutyl/1-oxide and 1,4-dioxide	101
2,5-Dichloro-3,6-dimethyl	H_2O_2/trichloroacetic acid/70°	2,5-Dichloro-3,6-dimethyl/1,4-dioxide	842
2-Chloro-3-trichloromethyl	H_2O_2/hexafluoroacetic anhydride	2-Chloro-3-trichloromethyl/1-oxide	688
3,5-Dichloro-2,6-difluoro	H_2O_2/trifluoroacetic acid	3,5-Dichloro-2,6-difluoro/1-oxide	901
3,5-Dichloro-2-methoxy	H_2O_2/trifluoroacetic acid	3,5-Dichloro-2-methoxy/1-oxide	901
2-Amino-3-chloro	H_2O_2/acetic acid/60–75°	2-Amino-3-chloro/1-oxide	906
2-Amino-3-bromo-5,6-dimethyl	Peroxymaleic acid/sodium acetate/60–65°	2-Amino-3-bromo-5,6-dimethyl/1-oxide	907
2-Amino-5-bromo-3-methoxycarbonyl	*m*-Chloroperoxybenzoic acid/chloroform/reflux	2-Amino-5-bromo-3-methoxycarbonyl/1-oxide	808, 877–879

methylpyrazine 1,4-dioxide (739). Whereas 6-*s*-butyl-2-hydroxy-3-isobutylpyrazine 1-oxide (aspergillic acid) in glacial acetic acid or chloroform was not attacked by bromine; in aqueous solvents such as 5*N* hydrochloric acid, it reacted readily to give 3-bromo-2-*s*-butyl-6-hydroxy-5-isobutylpyrazine 1-oxide (bromoaspergillic acid) (and some bromodeoxyaspergillic acid) (87).

D. By Reaction of Pyrazine 1,4-Dioxide with Phosphoryl Chloride (and Other Acid Chlorides)

The preparation of certain halogenopyrazine *N*-oxides from pyrazine 1,4-dioxide with phosphoryl chloride (and other acid chlorides) has been described in Section 1G.

4. PROPERTIES OF HALOGENOPYRAZINES

The halogenopyrazines are liquids but the polyhalogeno compounds are usually low melting solids (Table V.3 contains representative literature values). 2-Chloropyrazine is a strong smelling liquid and 2-chloromethylpyrazine a lacrimatory oil (679).

TABLE V.3 PHYSICAL PROPERTIES OF SIMPLE HALOGENOPYRAZINES[a]

Halogenopyrazines	B.p. (°C/mm Hg)	M.p. (°C)
2-Bromo	58/9	
2,3-Dibromo		59–61
2,5-Dibromo		6.5–8.0
2,6-Dibromo	97/10	51–52
2,3,5-Tribromo		46
Tetrabromo		152–154
2-Chloro	150–153/atm.	
2,3-Dichloro	125–130/30	23–24
2,5-Dichloro	90–91/44	13–14
2,6-Dichloro	120–122/40	57–58
2,3,5-Trichloro		32
Tetrachloro	100/0.1	99–100.5
2-Fluoro	108–109.5/atm.	
2,6-Difluoro	90–92/atm.	
2,3,5-Trifluoro	89/atm.	0–1
Tetrafluoro		53–54
2-Iodo	109–110/34	

[a] For references see tables of compounds.

Dipole moments (*D*, in benzene, unless otherwise specified) of some chloropyrazines have been determined as follows: 2-chloropyrazine [1.42 (663), 1.38 (773a)]; 2-chloropyrazine 1-oxide (2.07) (733a); 3-chloropyrazine 1-oxide [1.46

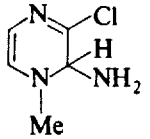
(749), 1.52 (733a)]; 2,3-dichloropyrazine [2.04 (663), 2.07 (767), 2.01 (749)]; 2,5-dichloropyrazine (1.14) (767); 2,6-dichloropyrazine [1.13 (663), 1.52 (767), 1.38 (744)]; 3,5-dichloropyrazine 1-oxide (0.23) (663); 2-chloro-3-methylpyrazine (1.33) (680); 2-amino-3-chloropyrazine [1.86; 2.26, dioxane (749)]; 2-chloro-6-cyanopyrazine [3.18 (744); 3.44, dioxane (749)]; and 2-amino-5-bromo-3-mercapto-pyrazine (2.22, dioxane) (749). The electronic interactions have been claimed to be greater in chloro(and methyl)pyrazines than in analogous benzene and pyridine compounds (663). The pyrolysis and thermal stability of 2-chloropyrazine have been examined (668a).

An investigation has been made of the reactions of *p*-nitrophenoxide ion in methanol with equimolar quantities of chloropyrazine and (other monochlorodiazabenzenes) in the presence of a tenfold excess of *p*-nitrophenol (908). The second-order rate coefficient for 2-chloropyrazine at 80° was determined as 9.57×10^{-5} l/mol · sec and $E^{\ddagger}$ as 23.4 kcal/mol and $\log_{10}B$ as 10.5; and its reactivity (at 50°) compared to that of chlorobenzene was 4.1×10^{14}, whereas the estimated value for 2-chloropyridine (relative to chlorobenzene) was 2.7×10^{8} (908). Kinetics have also been measured for the reaction of 2-chloropyrazine with piperidine in toluene and the energy of activation and entropy of activation determined as 13.2 and 46.2 (909); the corresponding values for 2-chloropyridine are 17.1 and 42.2, respectively.

It has been established by means of ^{15}N- and ^{14}C-labeling studies that in 2-chloropyrazine both positions 3 and 6 are more favored for nucleophilic attack by amide ion than position 2 (822, 823, 910, 911), and the influence of phenyl groups on the course of the reaction has been studied (827).

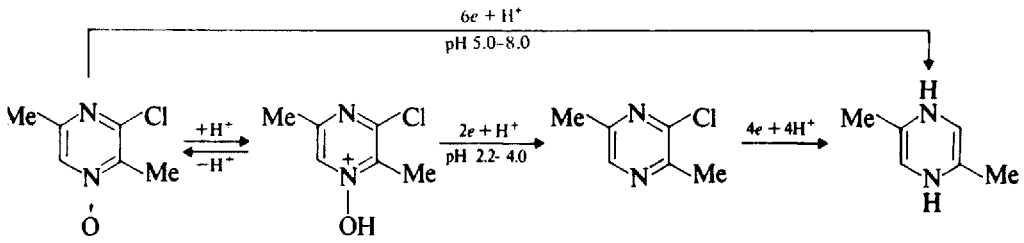
Rates of methylation (from n.m.r. studies) of 2-fluoro- and 2-chloropyrazines with methyl iodide in dimethyl sulfoxide at room temperature relative to pyrazine have been determined as 0.16 and 0.15, respectively (666). Methylation of 2-chloropyrazine with methyl iodide in benzene at reflux gave one methiodide (912). 2-Chloropyrazine also formed a *p*-fluorophenacyl bromide salt (913).

3-Chloro-1-methylpyrazinium ion with liquid ammonia reacted by addition at the 2-position to give 2-amino-3-chloro-1-methyl-1,2-dihydropyrazine (**24**) (609). The hexafluoroantimonate salt of perfluoropyrazine has been prepared and ^{19}F n.m.r. measurements used to determine the relative order of its base strength with other perfluoroheterocycles (914). Hydrogen–deuterium exchange rates of H_2 and H_6 in 3-chloro(and other substituted)pyrazine 1-oxide(s) have been correlated with σ-constants, and the logs of the H_2 exchange rates have been shown to be linearly related to the pK_a values (745). The pK_a value of 3-chloropyrazine 1-oxide is -1.05 (745).



(24)

The polarographic behavior of 3-chloro-2,5-dimethylpyrazine and its 1-oxide (25) (and other pyrazines) at various pH values have been investigated (588). The first wave for the compound (25) was attributed to the reduction of the *N*-oxide group (which is pH dependent), and the second wave to the reduction that involved hydrogenation of the nitrogen atoms of the ring and, at the same time, detachment of the chloro radical from the ring. The detachment of chlorine was confirmed further through controlled-potential electrolysis (588). The proposed sequence of reactions from (25) is shown.



(25)

A three-dimensional X-ray structure determination of 2,5-dichloro-3-methoxypyrazine (915) and 2,3-dichloro-5-ethylamino-6-methoxypyrazine (916) has been completed.

2-Chloro-6-(piperazin-1′-yl)pyrazine inhibits the uptake of ^{3}H-labeled serotonin in cerebral cortical tissue of rats (917); and dipole moments measured.

I.r. and n.m.r. spectra have been used to determine the position of the *N*-oxide group in alkylchloropyrazine *N*-oxides (733b).

5. REACTIONS OF NUCLEAR HALOGENOPYRAZINES

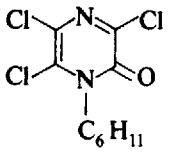
A. Removal by Halogeno Substituents

(1) *By Catalytic Hydrogenation*

Halogenopyrazines may be dehalogenated by catalytic hydrogenation in solution in the presence of base. For example, 2-chloro-3(and 6)-methylpyrazine underwent hydrogenolysis (and deuterolysis) to give 2-methylpyrazine (and the 3- and 6-deutero analogues) in the presence of palladium, on both charcoal (5%) and alumina (5%), although the reactions appeared to be faster with the former catalyst (687). The reactions were carried out in the presence of sodium methoxide (to neutralize hydrogen chloride generated) in dioxane solution. Hydrogenolysis of 2-chloro-3(?)-phenylpyrazine with H_2/Pd/C in ethyl acetate in the presence of triethylamine gave phenylpyrazine (733b). Dechlorinations of chloro-2,5-dialkylpyrazines with H_2/Pd/C in the presence of sodium acetate have been described (733a, 740a). Other catalytic dehalogenations of halogenopyrazines (catalyst, solvent, base) to the corresponding

pyrazines (except where otherwise stated) were as follows: 2,5-dichloro-3,6-difluoropyrazine (palladium–charcoal, ether, diethylamine) to 2,5-difluoropyrazine (493); 2-amino-3-chloro-5(and 6)-methylpyrazine (palladium–charcoal, methanol, potassium hydroxide) (373); 3-amino-2-chloro-5-phenylpyrazine, 2-amino-3-bromo-5-phenylpyrazine, and 2-chloro-3-methoxy-5-phenylpyrazine (palladium–charcoal, ethyl acetate, triethylamine) (365a); 2,3-diamino-5-bromopyrazine (palladium–charcoal, ethanol, potassium hydroxide) (804); 2,6-diamino-3,5-dichloropyrazine (palladium–charcoal, methanol, potassium hydroxide) (773); 2,3-diamino,5,6-dichloropyrazine (733); 3-amino-5-chloro-2-methoxy- and 3-amino-2-chloro-5-methoxypyrazine (palladium–charcoal, ethanol, potassium hydroxide) (365b); 2-amino-5,6-dichloro-3-methoxypyrazine (palladium–charcoal, methanol, potassium hydroxide) (773); 2-amino-5-bromo-3-methoxypyrazine (palladium–charcoal, methanol, potassium hydroxide) (804, 810, 811); 5-chloro-3-methoxy-2-sulfanilamidopyrazine (palladium–charcoal, water, sodium hydroxide) (845); 2,6-diamino-3-chloro-5-methoxycarbonylpyrazine (palladium–charcoal, methanol, magnesium oxide) (780, 855, 859); 2-amino-5-chloro-6-dimethylamino(and other amino-, hydroxy-, and methoxy-substituted)-3-methoxycarbonylpyrazine (palladium–charcoal, methanol, magnesium oxide) (780, 790, 809, 855, 859); 2,6-diamino-3-chloro-5-guanidinocarbamoylpyrazine (palladium–charcoal, methanol, magnesium oxide) (781); 2,6-diamino-3-chloro-5-cyanopyrazine (palladium–charcoal, methanol, magnesium oxide) (878); and 2-chloro-3,5-dimethoxy-6-methoxycarbonylpyrazine (palladium–charcoal, methanol, potassium hydroxide) (881).

Partial dechlorinations have also been achieved as follows: 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine (palladium–charcoal, dimethylformamide, triethylamine) gave 2-amino-5-chloro-3-methoxycarbonylpyrazine (918); and 2-amino-5,6-dichloro-3-guanidinocarbonylpyrazine on reduction in the presence of platinum but absence of triethylamine gave 2-amino-5-chloro-3-guanidinocarbonylpyrazine (918); many similar dechlorinations with palladium–charcoal, platinum, nickel, and cobalt catalysts were also described (918). Hydrogenation of 3,5,6-trichloro-1-cyclohexyl-2-oxo-1,2-dihydropyrazine (**26**) in acetic acid over platinum oxide, and reaction of the product with *p*-toluenesulfonyl chloride gave 1-cyclohexyl-4-tosylpiperazin-2-one (**27**); and 3,5,6-trichloro-1-phenyl-2-oxo-1,2-dihydropyrazine similarly treated gave 1-cyclohexyl-4-tosylpiperazin-2-one and 1,4-ditosylpiperazine (853). 5,6-Dichloro-1,4-diphenyl-2,3-dioxo-1,2,3,4-tetrahydropyrazine on hydrogenation in acetic acid over platinum oxide gave 1,4-dicyclohexylpiperazine-2,5-dione (6%), 1,4-dicyclohexylpiperazin-2-one (23%), and probably dicyclohexylpiperazine (853). (Hydrogenation of 3,6-dibromo-1,4-diphenylpiperazine-2,5-dione over palladium in dioxane gave 1,4-diphenylpiperazine-2,5-dione (853)).



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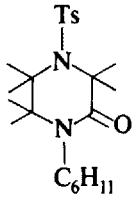


(27)

(2) *By Other Methods*

Lithium aluminum hydride (in excess) with tetrachloropyrazine in ether–tetrahydrofuran gave a low yield of trichloropyrazine (and a considerable quantity of unchanged tetrachloropyrazine) (888).

Attempts to convert 2-chloro-5-hydroxy-3,6-dimethylpyrazine into 3-hydroxy-2,5-dimethylpyrazine by reduction in alkaline solution with Raney nickel alloy were unsuccessful (312), but this transformation was effected by heating with powdered potassium hydroxide at 180–200° (312). Heating of 5,6-dichloro-2,3-dioxo-1,4-diphenyl-1,2,3,4-tetrahydropyrazine with phenol and 35% hydrogen bromide in acetic acid at 70° gave 2,3-dioxo-1,4-diphenyl-1,2,3,4-tetrahydropyrazine (853).

Tetrafluoropyrazine with hydrazine gives 2,3,5-trifluoro-6-hydrazinopyrazine which on warming with aqueous copper sulfate gave trifluoropyrazine and 2,3-difluoro-5-hydrazino-6-methoxypyrazine similarly treated gave 2,3-difluoro-5-methoxypyrazine (885), but 2,3,5-trichloropyrazine could not be prepared from 2,3,5-trichloro-6-hydrazinopyrazine (888). 2,3,5-Trichloropyrazine with hydrazine gave 2,5-dichloro-3-hydrazinopyrazine, which with cupric sulfate in acetic acid gave 2,5-dichloropyrazine. 2,3-Dichloropyrazine (and 2,6-dichloropyrazine) similarly treated gave chloropyrazine (919).

B. Replacement of Halogeno Substituents by Amino Groups

(1) *With One Halogeno Substituent*

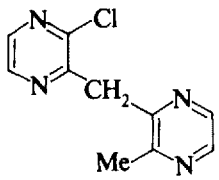
Rutner and Spoerri (882, 884) have examined the reactions of 2-fluoropyrazine with amines to give the corresponding aminopyrazines under the conditions indicated as follows: 2-amino (28% aqueous ammonium hydroxide at 20° for 3 days) (882, 884) (methanolic ammonia at 20° or anhydrous ammonia in boiling benzene did not react with 2-fluoropyrazine) (884); 2-methylamino (aqueous methanol at 20° for 3 days) (882); 2-piperidino (methanol at 20° for 4 days) (882); 2-benzylamino (methanol at 20° for 3 days) (882, 884); and 2-anilino (130–135° for 9 h) (882).

Chloropyrazine undergoes normal nucleophilic substitution with ammonia and amines to give the following aminopyrazines: 2-amino (28% ammonium hydroxide at 200°) (818) (ethanolic ammonia at 175° for 3 h) (920) (140° for 16 h) (921); 2-methylamino (150° for 7 h) (821); 2-ethylamino (668a); 2-dimethylamino (150° for 7 h) (821) (20–30° for 48–60 h) (922); 2-diethylamino (150° for 7 h) (668a); 2-isopropylamino (668a); 2-piperidino (kinetics in toluene at 64.5–93.7°) (909); 2-(piperazin-1′-yl) (140° for 1 h) (759, 923); 2-(2′-dimethylaminoethyl)amino (130–140° for 3 h) (924, 925); 2-butylamino (120° for 8 h, 74.5%) (921) (at reflux it did not give reasonable yields) (921); 2-anilino (160° for 7 h, 33%) (926); 2-benzylamino (reflux at 1 h also gave benzaldehyde and aminopyrazine) (921); and 2-metanilamido (at reflux with potassium carbonate at 160–180° for 5 h) (927, 928).

Normal nucleophilic substitution reactions of alkyl and aryl chloropyrazines have been examined as follows: 2-chloro-3-methyl- and 3-chloro-2,5-dimethyl(and diethyl)pyrazine with ammonia and various amines (535, 679, 680); 2-chloro-3(and 6)-methylpyrazine with methylamine and dimethylamine (681, 844), piperidine and other amines (681, 921); 2-chloro-5(and 6)-methylpyrazine with aqueous ammonia (362); alkyl (and phenyl) chloropyrazines with ammonium hydroxide at 200° (887); 2-chloro-3-methylpyrazine with aniline and substituted anilines (929), and piperazine at 140° (759); 2-chloro-3-methyl(and ethyl)pyrazine with piperidine (aqueous potassium hydroxide at reflux) (930,931) [cf. the formation of the 2,6-isomer(?) (932)]; 2-chloro-3,6-dimethylpyrazine with benzylamine at 184–250° (benzaldehyde and 2-amino-3,6-dimethylpyrazine were also produced) (921); 2-chloro-3,5,6-trimethylpyrazine with aqueous ammonia and copper powder at 140–150° (933) and with dimethylamine at 180° for 3 days (934,935); 2-chloro-6-trifluoromethylpyrazine with piperazine in acetonitrile at reflux (759); 2-chloro-3-phenylpyrazine with aqueous ammonia at 200° (535); 2-chloro-5-phenylpyrazine with liquid ammonia in an autoclave at 170° (377); 2-chloro-5-phenylpyrazine with piperazine in refluxing butanol (759); but the 6-isomer in acetonitrile (759); 5-chloro-2,3-diphenylpyrazine and piperidine at reflux (741); and 5-chloro-2,3-diphenylpyrazine with 2-hydroxyethylamine in a sealed tube at 125° for 40 hours (834).

2-Chloropyrazine with trimethylamine in benzene at 100° did not give the trimethylammonio compound but gave 2-dimethylaminopyrazine with loss of methyl halide (936). 2-Chloro-5-phenylpyrazine heated with hexamethylphosphoric triamide at 200° for 1 hour gave 2-dimethylamino-5-phenylpyrazine, and similar reactions were observed with 3-chloro-2,5-diethyl-, 3-chloro-2,5-diisobutyl-, 2-chloro-3,5-diphenyl-, 3-chloro-2,5-diphenyl-, and 5-chloro-2,3-diphenyl-pyrazines (937).

2-Chloro-3-methylpyrazine with *N*-methylaniline at reflux gave 50% 2-methyl-3-(*N*-methylanilino)pyrazine and 37% 2-anilino-3-methylpyrazine, but 2-chloro-3-methylpyrazine and diphenylamine at reflux failed to react. In an attempt to prepare 2-(*N*,*N*-diphenylamino)-3-methylpyrazine, 2-chloro-3-methylpyrazine was allowed to react with sodium diphenylamine (from sodium hydride and diphenylamine) and gave various products depending on the conditions. At room temperature, these reagents gave only recovered diphenylamine and a self-coupling product of 2-chloro-3-methylpyrazine, namely, 2-chloro-3-(3′-methylpyrazin-2′-ylmethyl)pyrazine (**28**), but if this reaction mixture was refluxed for 24 hours it gave some 2-(*N*,*N*-diphenylamino)-3-methylpyrazine (929).



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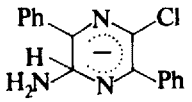
The reaction of 2-chloropyrazine with potassium amide in liquid ammonia to give 2-cyanoimidazole, imidazole, and 2-aminopyridine has been investigated (911). It has been found that 2-chloropyrazine containing an excess of ^{15}N in position 1, on treatment with potassium amide in liquid ammonia at $-65°$ yields 2-aminopyrazine in which the exocyclic nitrogen contains all the excess ^{15}N, and an addition–nucleophilic–ring opening–ring closure (ANRORC) mechanism was proposed (822). The mechanism of the conversions into imidazole (823) and 2-cyanoimidazole (910) has also been investigated using labeled compounds and has been established as involving attack at position 3.

The reactions of various chlorophenylpyrazines with potassium amide in liquid ammonia have been investigated in detail (827). Treatment of 2-chloro-3-phenylpyrazine with potassium amide in liquid ammonia gave only 2-amino-3-phenylpyrazine, but 2-chloro-6-phenylpyrazine gave 4(5)-phenylimidazole and 2-cyano-4(5)-phenylimidazole, and 2-chloro-5-phenylpyrazine gave a mixture of 2-amino-5-phenylpyrazine, 4(5)-phenylimidazole, and 2-cyano-4(5)-phenylimidazole. The 2-chloro-3,5(5,6 and 3,6)-diphenylpyrazines showed divergent behavior: 2-chloro-3,5-diphenylpyrazine gave only the corresponding 2-aminopyrazine; 5-chloro-2,3-diphenylpyrazine gave a mixture of the amino product and two ring contraction products, 4,5-diphenylimidazole and 2-cyano-4,5-diphenylimidazole; and 3-chloro-2,5-diphenylpyrazine was found to be relatively inactive toward potassium amide in liquid ammonia (827). The varied behavior was explained by the high susceptibility of positions 3 and 6 of the 2-chloropyrazine to nucleophilic attack. Further examination revealed that when 3-chloro-2,5-diphenylpyrazine was added to liquid ammonia containing three equivalents of potassium amide a colored solution was obtained and p.m.r. studies clearly indicated that the addition of amide ion occurred at position 5 to yield the complex (**29**), which, via a rearrangement into (**30**), gave 3-amino-2,5-diphenylpyrazine ultimately (938).



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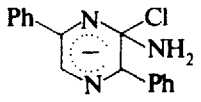


(30)

2-Bromopyrazine and anhydrous ammonia in ethanol gave 2-aminopyrazine (939), and 5-bromo-2,3-diphenylpyrazine with ethanolamine at 125° gave 5-(2′-hydroxyethyl)amino-2,3-diphenylpyrazine (834).

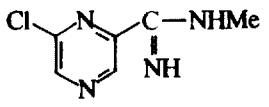
2-Aminopyrazine with some mono- and di-methyl, ethyl, and/or phenyl derivatives were also obtained from the relevant 2-iodopyrazine and ammonium hydroxide at 200° (887).

(2) *With One Halogeno and Other Substituents*

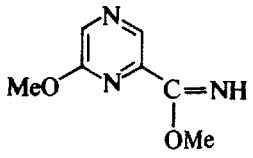
2-Chloro-6-cyanopyrazine with anhydrous methylamine (940), diethylamine, and other amines in refluxing benzene (941, 942), thiomorpholine, and *N*-methyl-

piperazine (943) gave normal substitution products; whereas with aqueous methylamine at 0°, the amidine (2-chloro-6-*N*-methylamidinopyrazine) (**31**) was obtained as the main product, but at reflux it gave a mixture of 2-carbamoyl-6-methylamino- and 2-methylamino-6-methylcarbamoylpyrazine (940). 2-Cyano-6-(2′-methylpiperidino)pyrazine was prepared from 2-chloro-6-cyanopyrazine and 2-methylpiperidine with triethylamine in refluxing benzene (944).

2-Cyano-6-methylaminopyrazine was also prepared from the chloro compound with methylamine hydrochloride and sodium hydroxide in aqueous dioxane (945) and 2-cyano-6-(2′,2′-dimethylhydrazino)pyrazine was prepared similarly (945). 2-Chloro-6-cyanopyrazine with methanol (and similarly with ethanol) and triethylamine gave 2-methoxy-6-(*C*-methoxyformidoyl)pyrazine (**32**) [see Section 5D(2)], and 2-chloro-6-carbamoylpyrazine with concentrated aqueous ammonia at 170–175° gave 2-amino-6-carboxypyrazine (744). 2-Chloro-3-cyano-5,6-diphenylpyrazine with ammonium hydroxide and potassium iodide formed 2-amino-3-carbamoyl-5,6-diphenylpyrazine, but on fusion with ammonium acetate it gave 2-amino-3-cyano-5,6-diphenylpyrazine (848).



(**31**)

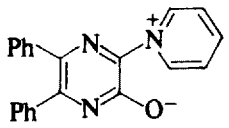


(**32**)

Normal nucleophilic substitution occurred on treatment of 2-carbamoyl-3-chloropyrazine with alcoholic methylamine at 130° (423, 836); 2-chloro-3-(4′-morpholinocarbonyl)pyrazine with morpholine at reflux in benzene (867); 2-chloro-3-methoxycarbonylpyrazine with methylamine (423, 789, 861), *N*-cyclopropyl-*N*-methylamine in dimethyl sulfoxide at 65° (857) and cyclohexylamine in benzene at reflux (946); 3-chloro-2-methoxycarbonyl-5-phenylpyrazine with alcoholic methylamine at 140° (375); 2-carboxy-3-chloropyrazine with anhydrous ammonia at 100° for 5 hours (947); 2-carbamoyl-6-chloropyrazine with aqueous methylamine at reflux (940); 2-chloro-6-(4′-morpholinocarbonyl)pyrazine (and other amides) and 2-chloro-6-methoxycarbonylpyrazine with morpholine (and other amines) (870, 948, 949); and 2-chloro-6-methoxycarbonylpyrazine with liquid ammonia at 80° (870). 2-Chloro-3-methoxycarbonylpyrazine fused with guanidine carbonate gave 2-amino-4-hydroxypteridine; and its 7-methyl-, 7-phenyl, and 6,7-diphenyl analogues were prepared similarly (371, 375).

2-Chloro-3-hydroxy-5(and 6)-methylpyrazine with ammonium hydroxide, copper, and cupric chloride at 125° for 15 hours gave 2-amino-3-hydroxy-5(and 6)-methylpyrazine (373, 835), but 2-chloro-5-hydroxy-3,6-dimethylpyrazine was recovered unchanged after treatment with alcoholic ammonia under drastic conditions (312) and 2-chloro-3-hydroxy-5,6-diphenylpyrazine with pyridine and its hydrochloride at reflux gave the betaine (**33**) from 2-hydroxy-5,6-diphenyl-3-pyridiniopyrazine chloride (863). Replacement of the chloro substituent occurred

in 2-chloro-6-methoxy(methylthio and phenylthio)pyrazine with piperazine in acetonitrile on a steam bath (759).



(33)

The corresponding diamines were obtained from the following reactions: 2-amino-3-chloropyrazine with aqueous ammonia (d. 0.88), with liquid ammonia and copper bronze at 135° for 24 hours (370) and concentrated ammonium hydroxide with copper powder at 135° (369, 804, 833); 2-amino-3-chloropyrazine with dimethylamine under similar conditions (370); 2-amino-3-chloro-5,6-dimethylpyrazine with ammonium hydroxide and copper powder (374); 2-chloro-3,6-dimethyl-5-dimethylaminopyrazine with dimethylamine at 200° for 18 hours (689, 793); 2-chloro-6-dimethylaminopyrazine with piperazine at 140° (759); 3-amino-5-chloro-2-methoxycarbonylpyrazine with ethylamine in dimethyl sulfoxide (880); and 2-amino-6-chloro-3-methoxycarbonyl-5-phenyl(and methyl)-pyrazine with dimethylamine in methanol at 25° (780, 802). 2-Amino-5-chloro-3-methoxycarbonylpyrazine under most vigorous conditions with amines failed to react (432) but with aniline in acetone containing hydrogen chloride at reflux gave 5-anilino-2-isopropylideneamino-3-methoxycarbonylpyrazine (432, 778, 780, 786). 2-Amino-6-chloro-3,5-dicyanopyrazine reacted with pyridine and diethylamine by replacement of the chloro substituent (484), but 2-amino-5-chloro-6-dimethylamino-3-methoxycarbonylpyrazine with β-hydroxyethylamine (and ethylamine) in dimethyl sulfoxide at 100° gave 2-chloro-3-dimethylamino-5-(2′-hydroxyethylamino and ethylamino)-6-methoxycarbonylpyrazine (891). Fusion of 2-chloro-3-cyano-5,6-diphenylpyrazine with guanidine carbonate gave 2,4-diamino-6,7-diphenylpteridine (848). Replacement of the bromo substituent occurred in the following reactions: 2-amino-3-bromo-5,6-dimethylpyrazine with ammonium hydroxide and copper powder at 128° for 24 hours (812), with aqueous methylamine and isopropylalcohol at 170° for 8 hours (907), and with dimethylamine and copper bronze at 130° for 24 hours (370); 2-bromo-5,6-dimethyl-3-sulfanilamidopyrazine with ammonium hydroxide and copper at 105° (812); and 5-bromo-2,3-dimethoxypyrazine with ammonium hydroxide, copper, and cuprous chloride at 115° (535).

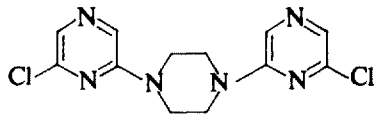
2-Bromo-3-methoxycarbonylpyrazine with 2,3-dimethylaniline in refluxing toluene gave 2-(2′,3′-dimethylphenyl)amino-3-methoxycarbonylpyrazine (950) [hydrolysis of this product with sodium hydroxide in ethanol gave 2-carboxy-3-(2′,3′-dimethylphenyl)aminopyrazine, which was also obtained by treatment of 1-(2′,3′-dimethylphenyl)lumazine with sodium hydroxide in refluxing ethanol (950)]. 3-Bromo-2-hydroxy-5-phenylpyrazine with ammonium hydroxide and copper at 150° gave 3-amino-2-hydroxy-5-phenylpyrazine (365a). Replacement of the iodo substituent from 2-amino-5-iodo-3,6-dimethylpyrazine has been effected with ammonium hydroxide (887).

(3) *With Two Halogeno Substituents*

One nuclear fluoro substituent is replaced from 2,5-difluoro-3,6-bis(heptafluoroisopropyl)pyrazine on stirring (at 25°?) with aqueous ammonia (496).

Monoaminochloropyrazines have been prepared from the dichloropyrazines as follows: 2,3-dichloro (ammonium hydroxide at 130–140° for 14 h) (481, 838); 2,3-dichloro and 2,3-dichloro-5-methyl (ammonium hydroxide, activated copper powder, and potassium bromide at 130–160°) (483); and 2,6-dichloro (ammonium hydroxide at 140° for 14 h) (757).

The corresponding diamines have been prepared from 2,3-dichloro-5-methyl-, 2,3-dichloro-5-phenyl-, and 2,3-dichloro-5-methyl-6-phenylpyrazines and ammonium hydroxide at 200–220° (483); and from 2,3-dichloro(and 2,3-dibromo)-5,6-diphenylpyrazine with alcoholic ammonia and copper at 125° (834). Preparations of other substituted aminochloropyrazines from the corresponding dichloropyrazines have been reported: 2,6-dichloro with piperazine (951); 2,3-, 2,5-, and 2,6-dichloro with *p*-aminobenzenesulfonamide (767, 805, 952); 2,3-dichloro with morpholine (813); 2,6-dichloro with morpholine (813); and 2,3-, 2,5-, 2,6-dichloro with piperazine or *N*-substituted derivatives (759, 953). [2,6-Dichloropyrazine and piperazine in acetonitrile on the steam bath gave 2-chloro-6-(piperazin-1′-yl)pyrazine hydrochloride and *N*,*N*-bis(2′-chloropyrazin-6′-yl)piperazine (**34**); and a series of the former have been evaluated for central serotonin-like activity (759)]; and 2,6-dichloro with dimethylamine in 2-propanol at 35–40° (759).



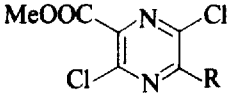
(34)

2,5-Dichloro-3,6-dipropyl(or 3,6-diisopropyl or 3,6-diisobutyl)pyrazine heated with hexamethylphosphoramide at 200° for 2–3 hours gave 81% 2-chloro-5-dimethylamino-3,6-dipropyl(or 3,6-diisopropyl or 3,6-diisobutyl)pyrazine (937), but 2,6-dichloro-3,5-diphenylpyrazine heated with hexamethylphosphoramide at 200° for 3 hours gave 64% 2,6-bisdimethylamino-3,5-diphenylpyrazine (937). 2,6-Dibromopyrazine with ammonium hydroxide at 195–200° for 21 hours gave 2,6-diaminopyrazine (865), and 2,3-dibromo-5,6-diphenylpyrazine with alcoholic ammonia and copper at 125° for 24 hours gave 2,3-diamino-5,6-diphenylpyrazine (834). 2,6-Dibromopyrazine with ammonium acetate gave 2-amino-6-bromopyrazine and with sodium sulfanilamide gave 2-bromo-6-sulfanilamidopyrazine (954).

(4) *With Two Halogeno and Other Substituents*

In reactions with amines the 2-halogeno substituent was replaced from 2,5-dihalogeno-3-methoxycarbonylpyrazines (**35**) and 2,3-dichloro-5-methoxycarbonyl-

pyrazines (**36**) (also cyano, carbamoyl, and other esters) as follows: 2,5-dibromo-3-methoxycarbonylpyrazine with dimethylamine and piperidine (799, 800), and cyclopropylamine (955); 2-bromo-5-chloro-3-methoxycarbonylpyrazine with 2-dimethylaminoethylamine, *p*-chlorobenzylamine, and *p*-methoxybenzylamine (790, 799, 800) and with cyclopropylamine and cyclopropylmethylamine in dimethyl sulfoxide (955, 956); 2-bromo-5-chloro-3-methoxycarbonyl-6-dimethylaminopyrazine with ethylamine or 2-hydroxyethylamine; 2-bromo-5-chloro-6-ethylamino-3-methoxycarbonylpyrazine with allylamine or 2-methoxyethylamine (799, 800); 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine with ammonia in acetone (or dimethyl sulfoxide at 65–70° (781, 783, 809, 854–856, 858, 859), with liquid ammonia at 100° (808, 809), with a wide variety of primary and secondary amines some in refluxing isopropanol (779–781, 809, 855, 859, 891, 957–960), with piperazine in acetonitrile on the steam bath (759), and with prop-2-ynylamine in dimethyl sulfoxide (961, 962); 2-amino-3-benzyloxycarbonyl-5,6-dichloropyrazine with ammonia in dimethylformamide at 60° (860); 2,3-dichloro-5-methoxycarbonyl-6-methylaminopyrazine with ammonia in dimethylformamide (789, 861); 2,3-dichloro-5-(*N*-cyclopropyl-*N*-methylamino)-6-methoxycarbonylpyrazine with ammonia in dimethyl sulfoxide at 65–70° (857); 2-amino-3-carbamoyl-5,6-dichloropyrazine in dimethyl sulfoxide with isopropylamine (808), with dimethylamine (808, 878), and with ethylamine (963); 2-amino-5,6-dichloro-3-guanidinocarbonylpyrazine with aqueous dimethylamine in dimethylformamide on the steam bath (378a, 780, 809, 858); 2,3-dichloro-5,6-dicyanopyrazine with ammonia or allylamine (862) or *t*-butylamine (to give 2-*t*-butylamino-3-chloro-5,6-dicyanopyrazine, which gives some control of late blight in tomatoes) (964); 2-amino-5,6-dichloro-3-cyanopyrazine with ammonia (878) and with methoxyamine, ethylamine, diethylamine, 2-hydroxyethylamine, or furylamine in dimethyl sulfoxide at 65° (808, 877); 2-amino-5-bromo-6-chloro-3-cyanopyrazine with ammonia in dimethyl sulfoxide at 100° (878); and 2,3-dichloro-5-methoxy-6-methoxycarbonylpyrazine with ammonia (155). 2,3-Dichloro-5,6-bis(methoxycarbonyl)pyrazine with ethanolic ammonia at 20° gave 2-amino-5,6-dicarbamoyl-3-chloropyrazine, but at 130° formed 2,3-diamino-5,6-dicarbamoylpyrazine (49%), and with ammonia in dimethylformamide at 70° gave 2-amino-3-chloro-5,6-bis(methoxycarbonyl)pyrazine (93%) but at 100° gave 2-amino-5,6-bis(methoxycarbonyl)-3-dimethylaminopyrazine (82%) and 2,3-diamino-5,6-bis(methoxycarbonyl)pyrazine (2%) (409). 2-Amino-3,5-dibromopyrazine with ammonium hydroxide or dimethylamine at 130°, or aqueous piperidine under reflux, gave 2,3-diamino-5-bromo-, 2-amino-5-bromo-3-dimethylamino(or piperidino)pyrazine, respectively (804). 3,6-Dibromo-1,4-diphenylpiperazine-2,5-dione with aniline gave 3,6-dianilino-1,4-diphenylpiperazine-2,5-dione (853).



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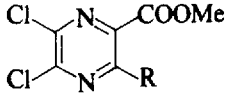
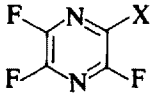


(36)

(5) *With Three Halogeno Substituents*

2,3,5-Trifluoropyrazine undergoes reaction with aqueous dimethylamine or excess aqueous ammonia in tetrahydrofuran at room temperature by replacement of the 3-fluoro substituent (885).

2,3,5-Trichloropyrazine reacts similarly with concentrated ammonium hydroxide at 80° to give exclusively 3-amino-2,5-dichloropyrazine (365b). It has also been claimed (845) that 2,3,5-trichloropyrazine reacts with sodium sulfanilamide in acetamide at 100° or with excess aqueous ammonia at 100° by replacement of the 2-chloro substituent. The orientation of substitution in trifluoropyrazines (**37**, X = H, Cl, Br, OMe, or NMe_2) by dimethylamine (and sodium methoxide) has been investigated (885) using ^{19}F n.m.r. spectroscopy: attack para to the H, Cl, Br and ortho to the OMe substituents occurs; but attack ortho to the Me_2N substituent was observed when steric factors permitted (885). For example, 2-chloro-3,5,6-trifluoropyrazine (**37**, X = Cl) with dimethylamine gave 2-chloro-5-dimethylamino-3,6-difluoropyrazine (**38**); 2,3,5-trifluoro-6-methoxypyrazine (**37**, X = OMe) was less reactive but gave essentially one isomer, 2-dimethylamino-5,6-difluoro-3-methoxypyrazine (**39**); and 2-dimethylamino-3,5,6-trifluoropyrazine (**37**, X = NMe_2) with sodium methoxide gave mostly 2-dimethylamino-5,6-difluoro-3-methoxypyrazine (**40**) [together with 2-dimethylamino-3,6-difluoro-5-methoxypyrazine (10%)]; but 2-dimethylamino-3,5,6-trifluoropyrazine (**37**, X = NMe_2) with dimethylamine in methanol gave a mixture of the three isomeric bis(dimethylamino)difluoropyrazines. These reactions have been explained in terms of the stability of the transition states (885). Some other reactions of fluoropyrazines were also studied: 2,3,5-trifluoro-6-methoxypyrazine with aqueous ammonia in dioxane gave 2-amino-5,6-difluoro-3-methoxypyrazine (885); 2-chloro-6-dimethylamino-3,5-difluoropyrazine with dimethylamine gave 2-chloro-5,6-bis(dimethylamino)-3-fluoropyrazine (888), and 2,6-dichloro-3-dimethylamino-5-fluoropyrazine with dimethylamine gave 2,6-dichloro-3,5-bis(dimethylamino)pyrazine (888). The reactions of some 6-substituted 2,3,5-trichloropyrazines with amines have been investigated. 2,3,5-Trichloro-6-dimethylaminopyrazine with dimethylamine at 100° gave 2,6-dichloro-3,5-bis(dimethylamino)pyrazine, 2,3-dichloro-5,6-bis(dimethylamino)pyrazine, and 2,5-dichloro-3,6-bis(dimethylamino)pyrazine in the ratio of 80:20:1 (888); 2,3,5-trichloro-6-methoxypyrazine under the same conditions gave 2,3-dichloro-5-dimethylamino-6-methoxypyrazine (888); 3,5,6-trichloro-1-cyclohexyl(or ethyl)-2-oxo-1,2-dihydropyrazine with ethylamine in ethanol formed 5,6-dichloro-1-cyclohexyl(or ethyl)-3-ethylamino-2-oxo-1,2-dihydropyrazine (853); and 3,5,6-trichloro-1-phenyl-2-oxo-1,2-dihydropyrazine with ethylamine in ethanol–tetrahydrofuran gave 5,6-dichloro-3-ethylamine-1-phenyl-2-oxo-1,2-dihydropyrazine (853).



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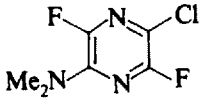

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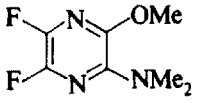

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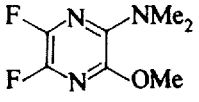
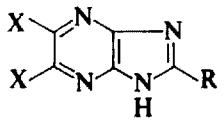


(40)

(6) *With Four Halogeno Substituents*

Tetrafluoropyrazine with aqueous ammonium hydroxide at 20° for 8 hours gave 2-amino-3,5,6-trifluoropyrazine (850, 851, 965) and after 4 days 2,3-diamino-5,6-difluoropyrazine (684) [which with trifluoroacetic anhydride gave the corresponding imidazo[4,5-*b*]pyrazine (**41**, X = F, R = CF_3)]; but with reaction conditions of 25° and 14 days, the product (similar melting points) was claimed to be 2,6-diamino-3,5-difluoropyrazine (966). Tetrafluoropyrazine with dimethylamine gave 2-dimethylamino-3,5,6-trifluoropyrazine which reacted further with dimethylamine in methanol at room temperature to give the three possible bis(dimethylamino)difluoropyrazines (885).

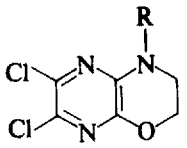


(41)

Tetrachloropyrazine is less reactive than its fluoro analogue and with ammonium hydroxide at 115° for 2.5 hours gave 2-amino-3,5,6-trichloropyrazine (773), but at 120° for 14 hours gave 2,3-diamino-5,6-dichloropyrazine [from which with acetic anhydride was formed 5,6-dichloro-2-methylimidazo[4,5-*b*]pyrazine (**41**, R = Me, X = Cl)] and 2,6-diamino-3,5-dichloropyrazine (773). Aqueous dimethylamine or methylamine in methanol at room temperature with tetrachloropyrazine for 0.5 hour each gave the monoaminopyrazine, but with dimethylamine under more vigorous conditions gave 2,6-dichloro-3,5-bis(dimethylamino)pyrazine as the major product together with the other two possible dichlorobis(dimethylamino)pyrazines (888).

Tetrachloropyrazine with 2-hydroxyethylamines gave 2,3,5-trichloro-6-(2′-hydroxyethylamino)pyrazine, which cyclized with sodium ethoxide to 6,7-dichloro-3,4-dihydro-2*H*-pyrazino[2,3-*b*][1,4]oxazines (**42**) (967).

Tetrachloropyrazine with *o*-phenylenediamine in dimethylformamide at reflux for 1 hour formed 2,3-dichloro-5,10-dihydropyrazino[2,3-*b*]quinoxaline (**43**) (968), and with pyridine at room temperature gave 2,5-dichloro-3,6-dipyridiniopyrazine dichloride (**44**) (969).



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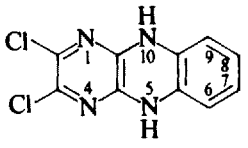

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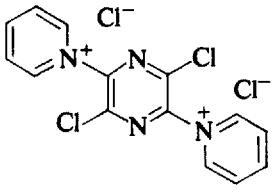


(44)

Tetrabromopyrazine with concentrated ammonium hydroxide at 120° afforded 2,3-diamino-5,6-dibromopyrazine and 2,6-diamino-3,5-dibromopyrazine (684, 970). 2,5-Dichloro-3,6-difluoropyrazine and dimethylamine gave 2,5-dichloro-3-dimethylamino-6-fluoropyrazine, and under more severe conditions 2,5-dichloro-3,6-bis(dimethylamino)pyrazine (888). 2-Bromo-3,5,6-trifluoropyrazine with dimethylamine gave 2-bromo-5-dimethylamino-3,6-difluoropyrazine (885).

C. Replacement of Halogeno Substituents by Hydrazino, Azido, and Amido Groups

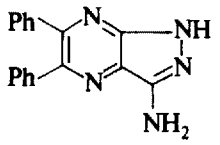
2-Chloropyrazine and its 5,6-dimethyl and 5,6-diphenyl derivatives reacted with 98% hydrazine in absolute ethanol (846) and aqueous hydrazine (971) to give the corresponding hydrazinopyrazine. The use of hydrazine hydrate resulted in diminished yields (846), and the reaction in water, which also gave other products (971), has been investigated in some detail. 2-Chloropyrazine with hydrazine in ethanol gave 2-hydrazinopyrazine and glyoxal bishydrazone, and the latter was also produced when hydrazine hydrochloride was allowed to react with hydrazinopyrazine (972). The interconversion of glyoxal bishydrazone with hydrazinopyrazine has been studied (972).

Preparations of the corresponding hydrazino compounds from 2-chloro-3(or 6)-methylpyrazine and 2-chloro-3,6-dimethylpyrazine with 98% hydrazine in absolute ethanol at reflux (775) and from 2-chloro-3,5-dimethyl-, 2-chloro-3,5,6-trimethyl-, 2-chloro-5- and 6-methyl-3-propyl-, or 2-chloro-5,6-dimethyl-3-propylpyrazines with excess hydrazine hydrate in a sealed tube at 110–130° for 24 hours or for a similar period under reflux in butanol (826) have been described.

2,3-Dichloropyrazine with hydrazine in ethanol gave 2-chloro-3-hydrazinopyrazine (828, 919) and 2,6-dichloropyrazine with hydrazine hydrate in ethanol gave 2-chloro-6-hydrazinopyrazine (919, 973). 2,3,5-Trichloropyrazine with hydrazine gave 2,5-dichloro-3-hydrazinopyrazine (919).

Tetrafluoropyrazine with ethanolic or methanolic hydrazine hydrate at 20° gave 2,3,5-trifluoro-6-hydrazinopyrazine (851, 885); and in reactions with hydrazine, tetrachloropyrazine gave 2,3,5-trichloro-6-hydrazinopyrazine (888, 896), 2-chloro-3,5,6-trifluoropyrazine gave 2-chloro-3,6-difluoro-5-hydrazinopyrazine (888), 2,3,5-trifluoro-6-methoxypyrazine gave 2,3-difluoro-5-hydrazino-6-methoxypyrazine (885), 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine gave 2-amino-5-chloro-6-hydrazino-3-methoxycarbonylpyrazine (891), and 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine with methylhydrazine formed 2-amino-5-chloro-3-methoxycarbonyl-6-(1′-methylhydrazino)pyrazine (809). Reaction of 2-chloro-3-cyano-5,6-diphenylpyrazine with hydrazine hydrate in the presence of potassium iodide led to 3-amino-5,6-diphenylpyrazolo[3,4-*b*]pyrazine (**45**) (848). 2-Fluoropyrazine reacted with sodium azide in ethanol gave tetrazolo[1,5-*a*]pyrazine (**46**) (882), probably resulting from cyclization of the intermediate azidopyrazine (**47**); 2-chloropyrazine with metanilamide and K_2CO_3 at 160–180° gave 2-metanilamidopyrazine (928) and fusion of 2-chloro-3-cyano-5,6-diphenylpyrazine

with thiourea or urea formed 4-amino-2-mercapto-6,7-diphenylpteridine and 4-amino-2-hydroxy-6,7-diphenylpteridine, respectively (848).



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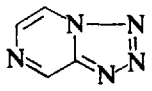

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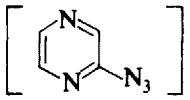


(47)

D. Replacement of Halogeno Substituents by Alkoxy Groups

(1) *With One Halogeno Substituent*

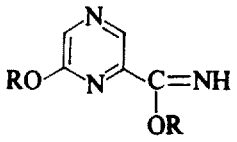
Kinetics have been measured for the reactions of *p*-nitrophenoxide ion in methanol with equimolar quantities (0.01–0.02 *M*) of 2-chloropyrazine, 3- and 4-chloropyridazines, and 2-, 4-, and 5-chloropyrimidines in the presence of a tenfold excess (0.1–0.2 *M*) of *p*-nitriphenol (908). There was evidence for mild acid catalysis by the *p*-nitrophenol added to prevent concurrent methanolysis. The reactivity order observed was 2-chloropyrimidine > 4-chloropyrimidine > 4-chloropyridazine ≃ 3-chloropyridazine ≃ 2-chloropyrazine > 5-chloropyrimidine, and corresponded with the theoretical order as modified by mild acid catalysis, more effective in the order ortho > meta > para to the point of substitution, and including the inverted order, 2- > 4-chloropyrimidine, whereas the usual reactivity order with anionic reagents was 4- > 2-chloropyrimidine (908).

Replacement reactions of chloropyrazines with a large number of alkoxides have been observed. Some examples are 2-chloropyrazine with methoxide (974), perdeuteromethoxide (975), ethoxide and isopropoxide ions (668a), and as follows. *Methoxide ion*: 2-chloro-3-methyl (49, 686, 687, 735, 736, 976); 2-chloro-5-deutero-3-methyl (687); 2-chloro-5-methyl (686, 735, 736); 2-chloro-6-methyl (686, 735, 736); 2-chloro-3,5-dimethyl (687, 844); 3-chloro-2,5-dimethyl (844, 977–979); 2-chloro-3-*s*-butyl (80, 649, 693); 2-chloro-3-isobutyl (80, 693); 2-chloro-5-isobutyl (693); 2-chloro-5(and 6)-*s*-butyl (649); 2-chloro-3-isopropyl (80); 3-chloro-2-isopropyl-5-methyl (844); 3-chloro-2-isobutyl-5-isopropyl (740a); 3-chloro-5-isobutyl-2-isopropyl (740a); 2-chloro-3-phenyl (817); 2-chloro-6-phenyl (365a); 2-chloro-3-benzyl (80, 366); 2-chloro-3-nonyl (649); 3-bromo-2,5-diphenyl (866); and 3-chloro-2,5-diisobutyl (980). *Ethoxide ion*: 2-chloro (668a, 818); 2-chloro-3-methyl (679, 978); 2-chloro-6-methyl (981); 2-chloro-3-ethyl (368); 3-chloro-2,5-dimethyl (312, 679, 978); 5-*s*-butyl-3-chloro-2-isobutyl (130°) (313); 3-chloro-2,5-diisobutyl (95, 720); and 3-chloro-5(1′-hydroxy-2′-methylpropyl)-2-isobutyl (113b). *Isopropoxide ion*: 2-chloro (668a). *Phenoxide*: 2-chloro-3-methyl (929). *Benzyloxide*: 3-chloro-2,5-di-*s*-butyl (982). *Allyloxide*: 2-chloro-3-methyl (680). *Decyloxide*: 2-chloro-3-methyl (649). *Butoxide*: 2-chloro-3-methyl (680, 977). *Myristyloxide*: 2-chloro-3-methyl (680). 2-Chloro-3-phenylpyrazine with

(*S*)-2-phenyl-3-*t*-butyl-5-hydroxymethyloxazolidine followed by acid hydrolysis gave the β-sympatholytic (*S*)-(-)-2-(3-*t*-butylamino-2-hydroxypropoxy)-3-phenylpyrazine (983), and 2-chloro-3-dichloromethylpyrazine with three equivalents of sodium methoxide gave 3,5-dimethoxy-2-methoxymethylpyrazine (Section 6A) (685).

(2) *With One Halogeno and Other Substituents*

Replacement of the chloro substituent by methoxide has been observed in the following pyrazines: 2-chloro-3-methoxycarbonyl (at $< 5°$) (867); 2-chloro-6-methoxycarbonyl (870); 2-chloro-3-methoxycarbonyl-5,6-diphenyl (371, 837); 2-carboxy-6-chloro (869, 871); 2-carbamoyl-5(?)-chloro (839); 2-carbamoyl-6-chloro (805, 839); 2-chloro-6-(4′-morpholinocarbonyl) (870); 2-chloro-3-cyano (810, 811); 5-chloro-3-cyano-2-methoxy (reflux 14 h) (881); 2-chloro-5-methoxy-3,6-dimethyl (844); 2-chloro-5-isopropyl-6-methoxy-3-methyl (50, 844); 2-chloro-5-methoxy-3,6-diphenyl (1.1 equivalents of 20% methanolic sodium methoxide at 135° for 20 h) (797); 2-benzyloxy-6-chloro(at reflux) (832, cf. 883); 2-chloro-3-pyridinio(pyrazine)chloride (or tosylate) (to give 2,3-dimethoxypyrazine) (765); 2-amino-3-chloro (804, 810, 811) [and also with ethoxide ion (984)]; 2-amino-6-chloro (at 140°) (805); 5-amino-3-chloro-2-methyl (at 120°) (535); 2-amino-3-chloro-5(or 6)-methyl and 2-amino-3-chloro-5,6-dimethyl (at 130–135°) (373, 835); 2-chloro-3,6-dimethyl-5-dimethylamino (at 125° for 18 h) (689, 793); 2-(*p*-aminobenzenesulfonamido)-3-chloro (at 110°) (810), and 2-[bis(*p*-acetamidobenzenesulfonamido)]-3-chloro (at 120°) (810); 2-amino-6-chloro-3,5-dicyano (484); and 2-(*p*-aminobenzenesulfonamido)-6-chloro (805). 2-Chloro-6-cyanopyrazine with one equivalent of sodium alkoxide (methoxide, ethoxide, propoxide, or isopropoxide) in the corresponding alcohol at reflux for 15 min gave the 2-alkoxy-6-(*C*-alkoxyformidoyl)pyrazine (**48**) [also formed with methanol or ethanol and triethylamine (985)]; but 2-chloro-6-cyanopyrazine with 3 mol of sodium methoxide (or ethoxide) at reflux for 2 hours gave 2-carboxy-6-methoxy(or ethoxy)pyrazine (986).



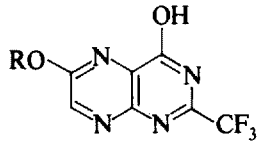
(48)

Other alkoxy dechlorinations were: 2-chloro-5-ethoxy-3,6-dimethylpyrazine (872) and 2-amino-6-chloro-3,5-dicyanopyrazine (484) with ethoxide ion; 5-chloro-2-methoxy-3-phenylpyrazine with butoxide ion (at reflux for 22 h) (797); 2-amino-3-chloropyrazine with ethoxide ion (984); and 2-chloro-3-morpholinopyrazine with allyloxide ion (813).

2-Benzyloxy-6-chloropyrazine with 3.5 *N* sodium hydroxide in aqueous ethanol at reflux gave a mixture from which 2-benzyloxy-6-ethoxypyrazine and other

products were isolated (883), but 2-chloro-6-hydroxy-3,5-diphenylpyrazine with sodium methoxide at high temperatures did not give the anticipated 2,6-dihydroxy-3,5-diphenylpyrazine (but 2-hydroxy-3,5-diphenylpyrazine) (873), and 2-amino-5-chloro-3-methoxycarbonylpyrazine with sodium alkoxides failed to react even under the most vigorous conditions (432).

2-Amino-5-bromo-3-carbamoylpyrazine heated with trifluoroacetamide and sodium ethoxide (or butoxide) gave 6-ethoxy(or butoxy)-4-hydroxy-2-trifluoromethylpteridine (**49**) (987) and 2-chloro-3-pyridiniopyrazine chloride with methoxide ion gave 2,3-dimethoxypyrazine (765). 2-Amino-3-bromo-5-phenylpyrazine with sodium methoxide in methanol at 134° for 8 hours formed 2-amino-3-methoxy-5-phenylpyrazine (365a) and 3-bromo-2-hydroxy-5-phenylpyrazine similarly treated gave 2-hydroxy-3-methoxy-5-phenylpyrazine (365a).



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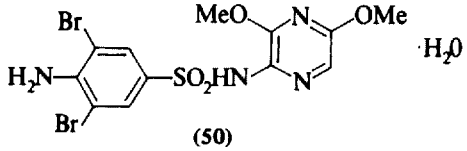
Bromination of 2-methoxy-3-sulfanilamidopyrazine in methanol did not give 2-(4′-amino-3′,5′-dibromobenzene)sulfonamido-3,5-dimethoxypyrazine hydrate (**50**) as reported (814) but the 5-(4′-amino-3′,5′-dibromobenzene)sulfonimido-6-hydroxy-2,3-dimethoxy-2,3,4,5-tetrahydropyrazine (**51**) (815, 816): the structure was determined by spectroscopic and chemical means, and bromination in deuteromethanol, CD_3OD, showed that both methoxy groups originate from the solvent.



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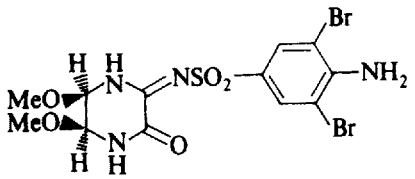


(51)

(3) *With Two Halogeno Substituents*

2,3-Dibromopyrazine when refluxed with an excess of sodium methoxide in methanol (797) and 2,6-dibromopyrazine when refluxed with an excess of sodium methoxide, ethoxide, or isopropoxide in the corresponding alcohol (865)

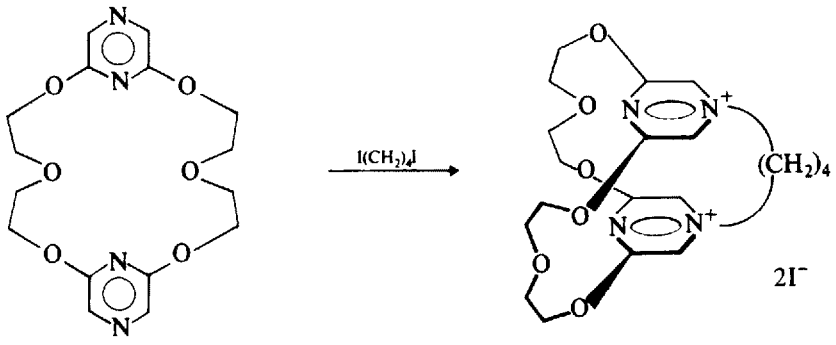
each gave the corresponding dialkoxypyrazine, but 2,3-dibromo-5,6-dimethyl(and diphenyl)pyrazine with one equivalent of methanolic sodium methoxide at reflux gave the 2-bromo-3-methoxypyrazines (797) and 2,5-dibromo-3,6-diphenylpyrazine with an excess of sodium methoxide or ethoxide at reflux in the alcohol gave 2-bromo-5-methoxy(or ethoxy)-3,6-diphenylpyrazine (797).

The reactivity of dichloropyrazines with alkoxide ions has been summarized by Cheeseman and Godwin (883). 2,6-Dichloropyrazine with methanolic sodium methoxide is unexceptional in that, depending on the amount of reagent used, either a mono- or a dimethoxypyrazine (832) can be prepared (838, 883). In a similar way 2,5-dichloro-3,6-dimethylpyrazine can be converted into 2-chloro-5-methoxy-3,6-dimethylpyrazine (883). The preparation of the 2,5-dimethoxy derivative has been reported (797) to require the use of 25% methanolic sodium methoxide at 120°. The pronounced deactivation of the chlorine atom in the chloromonomethoxy compound is probably mainly electronic in origin, since a similar deactivation is apparent in the reactions of 2-amino-3,5-dibromopyrazine (804), in which the electron-releasing amino group selectively deactivates the para-substituted bromo substituent so that reaction with nucleophiles results in displacement of the 3-bromo substituent.

Cheeseman and Godwin (883) repeated the literature preparation of 2,5-dimethoxy-3,6-dimethylpyrazine (797) and obtained the dimethoxy compound in the expected yield together with 2-chloro-5-hydroxy-3,6-dimethylpyrazine (25%). Although no rigorous precautions were taken to exclude moisture, the formation of the last compound was attributed to the attack by methoxide ion at the extra-nuclear methoxycarbon atom (883).

The following alkoxypyrazines have been prepared from the corresponding dichloropyrazines and alkoxide ions: 2,3-dimethoxy-5,6-dimethyl(and diphenyl) (797); 2,3-dibenzyloxy [sodium benzyl oxide in benzyl alcohol at reflux for 24 hours (883)] [but 2,3-dichloropyrazine with sodium hydride and benzyl alcohol in xylene gave 1,4-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydropyrazine) (988)]; 2-chloro-5-methoxy (838); 2,5-diethoxy-3,6-dimethyl (872); 2-chloro-5-ethoxy-3,6-dimethyl (872); 2,5-dibenzyloxy-3,6-dimethyl (756); 2-chloro-5-methoxy-3-phenyl (817) and 5-chloro-2-methoxy-3-phenyl (817) (2,5-dichloro-3-phenylpyrazine with 4% methanolic sodium methoxide refluxed for 2 h); 2,5-dimethoxy-3-phenyl (817); 2-chloro-5-methoxy(and ethoxy)-3,6-diphenyl (817); 2,5-dimethoxy-3,6-dimethyl (and diisopropyl) (844); 2,5-dimethoxy-3-isopropyl-6-methyl (methanolic potassium methoxide at reflux for 6 days) (844); 2(5)-*s*-butyl-3-chloro-6-ethoxy-5(2)-isobutyl (93); 2-chloro-6-methoxy (838, 883); 2,6-dimethoxy (reflux for 8 h) (832); 2,6-diethoxy (reflux for 14 h) (883); 2-benzyloxy-6-chloro (1 equiv. of sodium hydride and benzyl alcohol in benzene at reflux) (832); 2,6-dibenzyloxy (5 equiv. of sodium benzyloxide in benzene at reflux gave 70%) (832); and 3,5-dimethoxy-2-methyl (535).

The reactions of 2,6-dichloropyrazine with numerous glycol dianions at reflux in xylene to give in most cases heteromacrocyclic ethers (e.g., **52**) have been studied. The compound (**52**) when refluxed with 1,4-diiodobutane in ethanol was diquaternized to give the salt (**53**) (989).



(52) (53)

(4) *With Two Halogeno and Other Substituents*

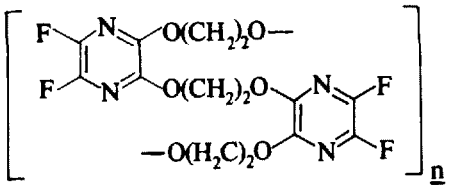
The following alkoxypyrazines have been prepared from the corresponding dihalogeno compounds with alkoxide ions (unless specified otherwise): 2-amino-5-bromo-3-methoxy (804, 810, 811); 5-chloro-3-methoxy-2-sulfanilamido (845) (cf. ref. 365b concerning the orientation of the analogous amino compounds); 3-amino-5-chloro-2-methoxy and 3-amino-2-chloro-5-methoxy (365b, cf. 845); 2-cyano-3,5-dimethoxy-6-methyl (535); 2-amino-5-chloro-6-methoxy-3-methoxycarbonyl (780, 790, 808, 809, 855, 858, 859) [and 6-ethoxy, 6-phenoxy, and 6-dimethylamino-ethoxy analogues (809)]; 2-amino-3-carbamoyl-5-chloro-6-methoxy (808); and 5-bromo-2,3-dimethoxy (from 5-bromo-2-chloro-3-methoxypyrazine) (535).

3,6-Dibromo-1,4-diphenylpiperazine-2,5-dione boiled with ethanol gave 3,6-diethoxy-1,4-diphenylpiperazine-2,5-dione (853); 2,3-dichloro-5,6-dimethoxycarbonylpyrazine with methanolic hydrogen chloride gave a mixture of 36% 2-chloro-3-methoxy- and 14% 2,3-dihydroxy-5,6-dimethoxycarbonylpyrazine (409); and 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine on refluxing with guanidine in ethanol gave 2-amino-5-chloro-6-ethoxy-3-methoxycarbonylpyrazine (780).

(5) *With Three or Four Halogeno Substituents*

Pyrazines with three and four halogeno substituents may react readily with alkoxide ions to give mono- and dialkoxypyrazines depending on the reaction conditions. The following pyrazines have been prepared accordingly: 2,5-difluoro-3-methoxy and 5-fluoro-2,3-dimethoxy (an excess of sodium methoxide) (885); 2,5-difluoro-3-methoxy-6-methyl (at $-40°$) (851) and 2-fluoro-5,6-dimethoxy-3-methyl (at $+20°$) (851); 2,3,5-trifluoro-6-methoxy (at $-10°$) (851) and 2,3-difluoro-5,6-dimethoxy (at 20°) (851) (compare orientation with that given in reference 852); 2-ethoxy-3,5,6-trifluoro (at $-10°$) (851); 2-*t*-butoxy-3,5,6-trifluoro (at $-20°$) (851); 2,3,5-trifluoro-6-(2′-hydroxyethoxy) (851) and 2,3-difluoro-5,6-

bis(2′-hydroxyethoxy) (at −15°) (851); 2,3,5-trichloro-6-methoxy (1.1 equiv. of sodium methoxide) (888, 898); 2,3-dichloro-5,6-dimethoxy (888) and 2,5-dichloro-3,6-dimethoxy (excess sodium methoxide) (888); 2,3,5-trichloro-6-ethoxy (isopropoxy, phenoxy, or 2′-hydroxyethoxy) (898); 2-chloro-3,6-difluoro-5-methoxy (from 2-chloro-3,5,6-trifluoropyrazine at −15°) (851); 2-dimethylamino-5,6-difluoro-3-methoxy (together with ca. 10% 2-dimethylamino-3,6-difluoro-5-methoxypyrazine) (885); 2-ethoxy-5,6-difluoro-3-methoxy (from 2,3,5-trifluoro-6-methoxypyrazine) (851); poly-2,3-bisethylenedioxy-5,6-difluoro (**54**) [from 2,3,5-trifluoro-6-(2′-hydroxyethoxy)pyrazine] (851); 2,5-dichloro-3,6-dimethoxy (from 2,5-dichloro-3,6-difluoropyrazine) (888); 2,6-dichloro-3-dimethylamino-5-methoxy and a small amount of 2,3-dichloro-5-dimethylamino-6-methoxy (from 2,6-dichloro-3-dimethylamino-5-fluoropyrazine slightly contaminated with 2,3,5-trichloro-6-dimethylaminopyrazine, and also from the latter alone) (888); 2-amino-5,6-dichloro-3-methoxy (773); 5,6-dichloro-1-cyclohexyl-3-methoxy(or ethoxy)-2-oxo-1,2-dihydro and 5,6-dichloro-3-ethoxy-2-oxo-1-phenyl-1,2-dihydro (853); and 2,5-dichloro-3-methoxy (915).



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Treatment of tetrafluoropyrazine in concentrated sulfuric acid with methanol at 20° has been shown to give 2,3,5-trifluoro-6-methoxypyrazine, and similar treatment of the latter gave 2,3-difluoro-5,6-dimethoxypyrazine (851).

E. Replacement of Halogeno Substituents by Hydroxyl Groups

The reactivity of 2-fluoropyrazine with aqueous sodium hydroxide to give 2-hydroxypyrazine has been investigated (882, 884). In 1.07*N* sodium hydroxide at 26° the reaction followed pseudo-first-order kinetics with a half-life of 43 minutes, whereas under the same conditions 2-chloropyrazine had a half-life of 18 days, and 2-iodopyrazine and 2-fluoropyridine remained unchanged (882, 884). Thus, under the above conditions, 2-fluoropyrazine was 640 times more reactive than 2-chloropyrazine (882). Hydrolysis of 2-fluoropyrazine in 6*N* hydrochloric acid proceeded at a much slower rate with a half-life of 4 days at room temperature (884). Some literature preparations of hydroxypyrazines by hydrolysis of halogenopyrazines (chloropyrazines with aqueous sodium or potassium hydroxide unless otherwise specified) are as follows: 2-hydroxy (150°) (818); 2-hydroxy-3-methyl (reflux) (680); 2-hydroxy-3,5-dimethyl (reflux) (978); 3-hydroxy-2,5-dimethyl (reflux) (98, 312, 680, 740) [at 120° (978)]; 3-hydroxy-2,5-di-*s*-butyl (powdered potassium

hydroxide at 180°) (740); 2-fluoro-6-hydroxy (from 2,6-difluoropyrazine and sodium hydroxide in aqueous tetrahydrofuran) (883); 2-chloro-6-hydroxy [from 2,6-dichloropyrazine with sodium hydroxide in aqueous tetrahydrofuran at reflux (832) and also from 2-chloro-6-fluoropyrazine (883)]; 2-bromo-6-hydroxy (865); 2-chloro-5-hydroxy-3,6-dimethyl (potassium hydroxide in aqueous dioxane at reflux) (312); 2,5-di-*s*-butyl-3-chloro-6-hydroxy (powdered potassium hydroxide at 160–180°) (312); 2,3,5-trifluoro-6-hydroxy (from tetrafluoropyrazine with potassium hydroxide in *t*-butanol at reflux) (851); 5,6-dichloro-1-cyclohexyl-3-hydroxy-2-oxo-1,2-dihydropyrazine (from 3,5,6-trichloro-1-cyclohexyl-2-oxo-1,2-dihydropyrazine with *N* sodium hydroxide in dioxane at 70–80°) (853); 2-amino-5-bromo-3-hydroxy (from 2-amino-3,5-dibromopyrazine by hydrolysis with 2*N* sodium hydroxide (804) and 3.5*N* sulfuric acid) (807); 2-amino-3-carbamoyl-5-cyano-6-hydroxy (from 2-amino-6-chloro-3,5-dicyanopyrazine) (484); 2-amino-3-hydroxy-5,6-bis(methoxycarbonyl) (aqueous sodium hydroxide at 20° or concentrated sulfuric acid at 40°) (409); and 2-amino-3-carboxy-5-chloro-6-hydroxy (from 2-amino-5,6-dichloro-3-methoxycarbonylpyrazine) (809, 858). 2-Benzyloxy-6-chloropyrazine with 3.5*N* sodium hydroxide in aqueous ethanol at reflux gave 2-chloro-6-hydroxypyrazine (32%), 2-benzyloxy-6-hydroxypyrazine (2%), 2-benzyloxy-6-ethoxypyrazine, and minor amounts of 2-chloro-6-ethoxypyrazine and 2,6-diethoxypyrazine (883); and 2-benzylthio-6-chloropyrazine with 3.5*N* sodium hydroxide at reflux gave, after oxidation with potassium permanganate in acetic acid, 2,6-di(benzylsulfonyl)pyrazine (883). 2-Bromo-3-hydroxy-5,6-dimethyl(and diphenyl)pyrazine refluxed with 48% hydrobromic acid gave 2,3-dihydroxy-5,6-dimethyl(and diphenyl)pyrazine (817) and 2-amino-5-bromo-3-chloropyrazine refluxed with 3.5*N* sulfuric acid gave 2-amino-5-bromo-3-hydroxypyrazine (807). Slow addition of water to a solution of tetrafluoropyrazine in sulfuric acid left it unchanged whereas addition of methanol gave 2,3,5-trifluoro-6-methoxypyrazine (851).

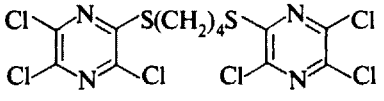
Bromodesoxyaspergillic acid (2-bromo-3-*s*-butyl-5-hydroxy-6-isobutylpyrazine) with zinc dust in glacial acetic acid gave a product thought to be 3-*s*-butyl-6-isobutylpiperazine-2,5-dione (87).

2-Chloropyrazine reacted with benzyl *N*-hydroxy-*N*-phenylcarbamate [PhN(OH)-$COOCH_2Ph$] in ethanolic potassium hydroxide to give 5-(4′-benzyloxycarbonyl-aminophenyl)-2-hydroxypyrazine which with hydrogen bromide in acetic acid gave 5-(4′-aminophenyl)-2-hydroxypyrazine (990).

F. Replacement of Halogeno Substituents by Alkylthio Groups

Halogenopyrazines react with alkylthiolate ions to give alkylthiopyrazines, by replacement of one or, in some cases, two halogeno substituents; the reaction is usually carried out at reflux or at elevated temperatures in sealed tubes. The following pyrazines have been prepared by these methods from the chloropyrazines unless otherwise specified: 2-ethylthio and 2-isopropylthio (668a); 2-methyl-3-methylthio (735, 844, 977); 2-methyl-5(and 6)-methylthio (735); 2,5-dimethyl-3-methyl(ethyl,

furfuryl, or acetyl)thio (991); 2-methyl-3-phenyl(and alkylphenyl)thio (929); 2-chloro-6-methylthio (reaction in dimethylformamide at 100°) (759); 2-chloro-6-phenylthio (759); 2-chloro-6-benzylthio (from 2,6-dichloropyrazine and sodium benzylthiolate at reflux in benzene) (883); 2,6-bisbenzylthio (from 2,6-dichloropyrazine and an excess of sodium benzylthiolate in boiling methanol) (883); 2,5-difluoro-3,6-bisphenylthio (tetrafluoropyrazine with sodium thiophenoxide in *N*-methylpyrrolidin-2-one) (852); 2,3,5-trichloro-6-methylthio (and other alkylthio and arylthio analogues) (methanethiolate ion in propan-2-ol at 20°) (898); 2,3,5-tribromo-6-methylthio (898); 2,3,5-triiodo-6-methylthio (898); 2-cyano(and 2-carbamoyl)-5-phenylthio (840); 2-ethylthio-(propylthio, benzylthio, or phenylthio)-6-cyano (992); 2-cyano(and 2-carbamoyl)-5-phenyl (and substituted phenyl)thio (840, 993); 5-bromo-3-methoxycarbonyl-2-methylthio (799, 890, 892); 2-carbamoyl-6-phenylthio (992); 2-amino-6-methylthio (or 6-ethylthio) (994); variously substituted 2-amino-3-alkoxycarbonylmethylthio (995); 2-amino-5-chloro-3-methoxycarbonyl-6-methylthio (780, 790, 809, 855, 858, 859); and 2-benzylthio-3-ethylamino-6-(ethylpyrrolidinylmethylcarbamoyl)-5-methoxy (in dimethylformamide at room temperature) (996). 2-Amino-5-chloro-3-methoxycarbonylpyrazine and sodium mercaptides, even under most vigorous conditions, failed to react (432). Reactions of 2,6-dichloropyrazine with the dianions of ethanedithiol, bis(2-mercaptoethyl)sulfide, and bis(2-mercaptoethyl)ether to give various sulfides have been studied (989). Tetrachloropyrazine with 1,4-bismercaptobutane in methanolic sodium hydroxide gave 2,3,5-trichloro-6-[4′-(3″,5″,6″-trichloropyrazin-2″-ylthio)butylthio]pyrazine (**55**) (997, 998). 2,3,7,8-Tetracyano-bis[1,4]dithiino-[2,3-*b*:2′,3′-*e*]pyrazine (**56**) has been prepared from tetrachloropyrazine and the sodium salt of dimercaptomaleonitrile (999, 1000), and 2,3-dichloropyrazine gave



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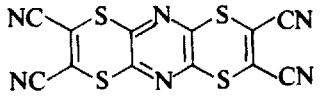

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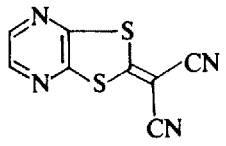

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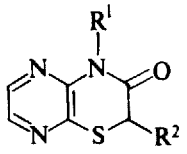
an analogous product (1000, 1001). 2,3-Dichloropyrazine with the potassium salt of bismercaptomethylenemalononitrile in dimethylformamide at 85° gave 2-dicyanomethylen[1,3]dithiolo[4,5-*b*]pyrazine (**57**) (1002). 2,3-Dichloro-5,6-dicyanopyrazine with disodium dimercaptomethylenemalononitrile in dimethylformamide at 40° gave 5,6-dicyano-2-[dicyanomethylene]-1,3-dithiolo[4,5-*b*]pyrazine, which was claimed to be useful as a fungicide and bactericide (1003). 2-Chloro-3-methylaminopyrazine with ethyl thioglycolate and sodium ethoxide in dioxane at reflux formed 4-methylpyrazino[2,3-*b*][1,4]thiazin-3(4*H*)-one (**58**, R^1 = Me, R^2 = H);



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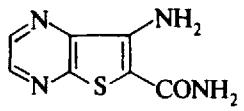

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analogous products (**58**, R^1 = Et, Pr, Me_2CH, $PhCH_2$, R^2 = H; R^1 = Me, Et, $PhCH_2$, R^2 = Me) were also prepared (1004). 2-Chloro-3-cyanopyrazine with mercaptoacetamide in the presence of potassium hydroxide gave 6-amino-5-carbamoylthieno[2,3-*b*]pyrazine (**59**) (1005).

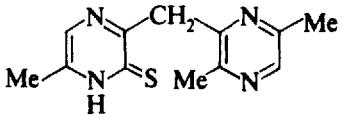
G. Replacement of Halogeno Substituents by Mercapto Groups

Halogenopyrazines may react with sodium (or potassium) hydrogen sulfide or polysulfide to give the mercaptopyrazine and in some cases the corresponding sulfide.

2-Chloropyrazine with potassium hydrogen sulfide in ethanol at 110° for 6 hours gave 2-(pyrazin-2′-yl)thiopyrazine as the major product together with a small amount of 2-mercaptopyrazine (1006), whereas with potassium hydrogen sulfide in water at 100° for 6 hours the same two products were obtained but the mercapto compound predominated (43%) (821), and with sodium hydrogen sulfide in dimethylformamide at 100° for 3 hours the only product reported was 2-mercaptopyrazine (89%) (821) (2-chloropyrazine failed to react with thiourea) (821). Other mercaptopyrazines have been prepared from the corresponding chloro compounds (unless otherwise specified) and sodium (or potassium) hydrogen sulfide under similar conditions or with sodium polysulfide as follows: 3-mercapto-2,5-dimethyl (1007); 2-mercapto-3,5,6-trimethyl (sodium hydrogen sulfide in ethanol at 120–130° for 8 hours) (933); 2-mercapto-3-phenyl (potassium hydrogen sulfide in dimethylformamide) (1008); 2-mercapto-3-methoxycarbonyl (from 2-bromo-3-methoxycarbonylpyrazine with sodium polysulfide in ethanol (799, 890, 892); 2-amino-3-mercapto (potassium hydrogen sulfide in dimethylformamide) (1009); 2-amino-3-mercapto-5,6-dimethyl(and diphenyl) (1010); 5-chloro-2-mercapto-3-methoxycarbonyl (from 2-bromo-5-chloro-3-methoxycarbonylpyrazine with sodium polysulfide in ethanol) (799, 890, 892); 2-chloro-3-ethylamino-5-mercapto-6-methoxycarbonyl (892); 2-amino-5-bromo-3-mercapto (from 2-amino-3,5-dibromopyrazine with potassium hydrogen sulfide in methanol) (805, 1011); 2-amino-5-chloro-6-mercapto-3-methoxycarbonyl (sodium polysulfide in ethanol) (780, 790, 809, 858); and 2-amino-5,6-dichloro-3-mercaptopyrazine (sodium sulfide) (1012).

Castle and co-workers (1013) showed that 2-chloro-3-methylpyrazine with phosphorus pentasulfide in boiling pyridine afforded 2-mercapto-3-methylpyrazine, and 3-chloro-2,5-dimethylpyrazine similarly treated gave 3-mercapto-2,5-dimethylpyrazine.

By using thiourea in 2*N* sulfuric acid, Cullen and Harrison (905) were able to convert 2-chloro-3-methylpyrazine at reflux for 30 minutes to 2-mercapto-3-methylpyrazine (55%), and 3-chloro-2,5-dimethylpyrazine similarly treated gave 3-mercapto-2,5-dimethylpyrazine together with another higher molecular weight compound, postulated as either (**60**) or (**61**). 2-Amino-3-chloropyrazine refluxed with thiourea in alcohol, and the thiouronium salt refluxed with aqueous sodium hydroxide, produced 2-amino-3-mercaptopyrazine (535). 2-Chloropyrazine failed to react with thiourea (821) under the mild conditions that converted 2-chloroquinoxaline to 2-mercaptoquinoxaline (1014).



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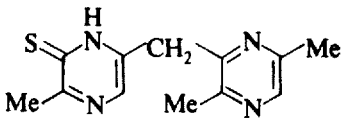

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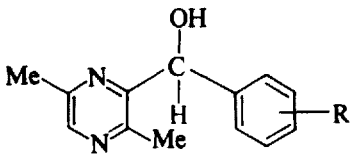
H. Replacement of Halogeno Substituents with the Formation of a Carbon–Carbon Bond (except C–CN)

The first lithiopyrazine derivative was prepared by Hirschberg et al. (1015) from 3-iodo-2,5-dimethylpyrazine and butyllithium in ether; subsequent reaction with (*a*) carbon dioxide gave 3-carboxy-2,5-dimethylpyrazine, and (*b*) several aromatic aldehydes gave the carbinols (**62**, R = H, *p*-methoxy, *m*-nitro) (1015). Similar reactions were observed when 2-formylpyridine and 2-acetylpyridine (1016) were used as the carbonyl compounds, but with acetaldehyde attempted reactions were unsuccessful (1015). A patent also describes the preparation of many carbinols from 2,5-disubstituted 3-iodopyrazines (164). The lithio reagent derived from 3-iodo-2,5-dimethylpyrazine (with butyllithium in hexane) with 2-nitrobenzaldehyde gave 2,5-dimethyl-3[1′-hydroxy-1′(2″-nitrophenyl)methyl]pyrazine (1017).



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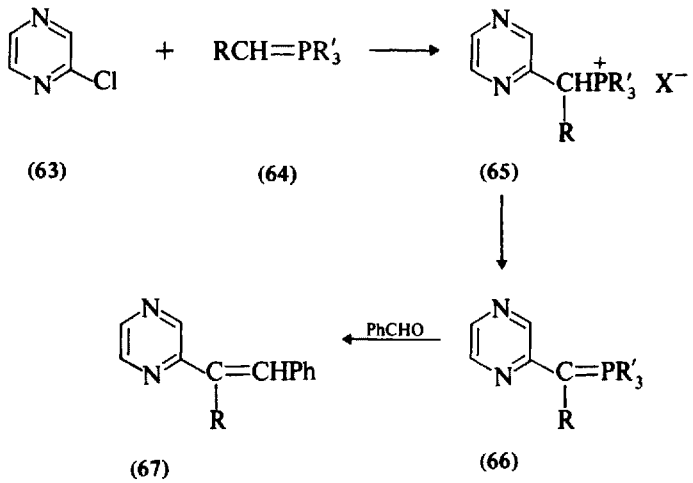
2-Iodopyrazine with butyllithium in ether at −35° likewise gave 2-lithiopyrazine, which was carbonated to 2-carboxypyrazine (1016), and with ketones gave carbinols (1017a).

Alkylations of halogenopyrazines have been effected as follows: tetrafluoropyrazine with ethereal methyllithium at −70° gave 2,3,5-trifluoro-6-methylpyrazine (851, 965), and with butyllithium in ether–hexane gave 2-butyl-3,5,6-trifluoro-, 2,5-dibutyl-3,6-difluoro-, and 2,3,5-tributyl-6-fluoropyrazines (851); tetrachloro-

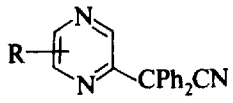
pyrazine with methyllithium (and phenyllithium) in diethyl ether at − 70°, then at − 25 to − 30°, gave 2,3,5-trichloro-6-methyl(and -phenyl)pyrazine, but butyllithium did not yield identifiable products (1018); and 2,3,5-trifluoro-6-methoxypyrazine with ethereal methyllithium gave 2,3-difluoro-5-methoxy-6-methylpyrazine (851).

Taylor and Martin (1019, 1020) have described a new procedure for the direct introduction of alkenyl substituents into the pyrazine nucleus: 2-chloropyrazine (**63**) with methylenetriphenylphosphorane (a Wittig reagent) (**64**, R = H) (from methyltriphenylphosphonium bromide and butyllithium) in 1,2-dimethoxyethane and subsequent treatment with benzaldehyde gave 2-styrylpyrazine (**67**, R = H). A similar reaction with propionaldehyde gave 2-(but-1′-enyl)pyrazine (1020).



(63) (64) (65) (67) (66)

2-Chloropyrazine and derivatives have been shown to react with alkali metal derivatives of a phenylacetonitrile or of a phenylacetamide: for example, 2-chloropyrazine treated with diphenylacetonitrile in toluene with sodium amide gave 2-(1′-cyano-1′,1′-diphenylmethyl)pyrazine (**68**, R = H) (1021, 1022). 2-Chloro-5-phenylpyrazine(s) with diethyl methylmalonate and sodium hydride gave 2-[1′,1′-di(ethoxycarbonyl)ethyl]-5-phenylpyrazine(s) (363–365, 824, 825), and a similar reaction occurred with 2-chloropyrazine (364, 365, 1023).



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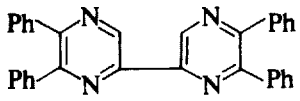
2,6-Dichloropyrazine in anhydrous ether with methyl magnesium iodide at 10° gave 2-chloro-6-methylpyrazine and 2,6-dimethylpyrazine; and 2,3-dimethylpyrazine was likewise obtained from 2-chloro-3-methylpyrazine (687). A Grignard derivative has been prepared from 2-chloro-3,5,6-trimethylpyrazine and magnesium turnings in tetrahydrofuran and on treatment with diethyl sulfate produced 2-ethyl-3,5,6-trimethylpyrazine (330).

The Ullmann reaction has been applied to some halogenopyrazines (837). 5-Bromo-2,3-diphenylpyrazine with activated copper in dimethylformamide gave 5,5′,6,6′-tetraphenyl-2,2′-bipyrazinyl (**69**); 2-bromo-3-methoxy-5,6-diphenylpyrazine gave 3,3′-dimethoxy-5,5′,6,6′-tetraphenyl-2,2′-bipyrazinyl; and 2-bromo-3-cyano-, 2-carbamoyl-3-chloro-, and 2-chloro-3-methoxycarbonyl-5,6-diphenylpyrazines gave only low yields of the expected products (837). In an attempt to generate diphenylpyrazyne and synthesize 2,3,6,7-tetraphenyl-1,4,5,8-tetraazabiphenylene (**70**), 2,3-dibromo-5,6-diphenylpyrazine was subjected to the Ullmann reaction but gave much intractable material together with a small amount of 5,5′,6,6′-tetraphenyl-2,2′-bipyrazinyl (837). 2-Bromo-3,5,6-trifluoropyrazine heated with excess copper bronze at 190° for 24 hours gave hexafluorobipyrazinyl (885). Tetrafluoropyrazine with hexafluoropropene and cesium fluoride in tetrahydrothiophen dioxide at 110° gave 2,5-difluoro-3,6-bisheptafluoroisopropylpyrazine (492, 496), and with octafluorobut-2-ene in sulpholan at 160° gave perfluoro-2,5-di-*s*-butylpyrazine (494).



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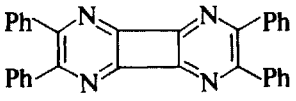

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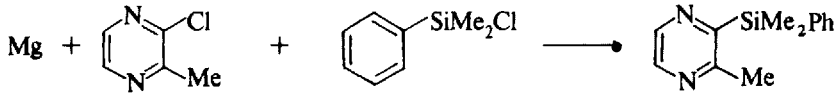
I. Replacement of Halogeno Substituents by Cyano, Sulfo, and Silyl Groups

Displacement of the chloro substituent from pyrazines by the cyano group has not been satisfactorily accomplished (866), but many cyanopyrazines have been prepared from the bromo analogues. Karmas and Spoerri (866) prepared 11 cyanopyrazines with mono-, di-, or trialkyl or phenyl substituents from the corresponding bromo compounds and cuprous cyanide in refluxing dry 4-picoline, but the procedure was not suitable for the preparation of 2-cyanopyrazine (866). It was prepared in 29% yield when the reaction was performed in pyridine (866). Another preparation of 2-cyano-3-phenylpyrazine from the bromo analogue has also been reported (1024).

The facile displacement of halogen by cyanide observed for monobromopyrazines did not pertain for *o*- or *p*-dibromopyrazines; complex tarry mixtures were always formed when the dibromides were heated with cuprous cyanide in 4-picoline and the dinitriles were obviously very easily polymerized by cuprous salts (797). 2,6-Dibromopyrazine heated with cuprous cyanide and cupric sulfate gave 2,6-dicyanopyrazine (9%) and 2-bromo-6-cyanopyrazine (13.5%) (865); 2,5-dibromopyrazine heated with cuprous cyanide and potassium cyanide in aqueous alcohol at 125° gave a low yield of 2,5-dimethyoxycarbonylpyrazine (after esterification) (798); and 2,5-dibromo-3,6-diphenylpyrazine, cuprous cyanide, and 4-picoline at reflux, and then treated with 4*N* hydrochloric acid, gave 2-carboxy-5-hydroxy-3,6-diphenylpyrazine (797), which is a known reaction of the authentic dinitrile (286),

but 2,3-dibromo-5,6-diphenylpyrazine did not react with one molecular equivalent of potassium cyanide in dimethylformamide even after prolonged heating, and treatment with cuprous cyanide in 4-picoline gave only tars (837). 2-Amino-5-bromopyrazine with cuprous cyanide and potassium cyanide at 170° gave a product which hydrolyzed to 2-amino-5-carboxypyrazine (798), 2-bromo-3-methoxycarbonylpyrazine similarly treated at 125° gave 2,3-dimethoxycarbonylpyrazine (after esterification) (798); and 2-bromo-3-methoxy-5,6-diphenylpyrazine refluxed with cuprous cyanide in 4-picoline gave, after treatment with cold 3*N* hydrochloric acid, 2-cyano-3-hydroxy-5,6-diphenylpyrazine (797). 3-Iodo-2,5-dimethylpyrazine with cuprous cyanide in anhydrous 3-picoline gave 3-cyano-2,5-dimethylpyrazine in high yield (1015).

2-Fluoropyrazine refluxed with aqueous sodium sulfite for 2 hours gave the sodium salt of 2-sulfopyrazine (ca. 70%) (882, 884), whereas 2-chloropyrazine with aqueous sodium sulfite at 150° for 12 hours gave only 44% of the desired product (819, 884). 2-Chloro-3-methylpyrazine (**71**) with magnesium (and a little methyl iodide) in tetrahydrofuran with phenyldimethylchlorosilane (**72**) gave 2-methyl-3-dimethylphenylsilylpyrazine (**73**) (929).



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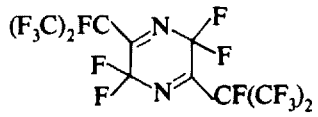
J. Other Reactions

2,5-Difluoro-3,6-bisheptafluoroisopropylpyrazine (perfluoro-2,5-diisopropylpyrazine) subjected to fluorination over a mixture of cobalt trifluoride with calcium fluoride at 156° gave perfluoro-2,5-diisopropyl-3,6-dihydropyrazine (**74**) (1025).



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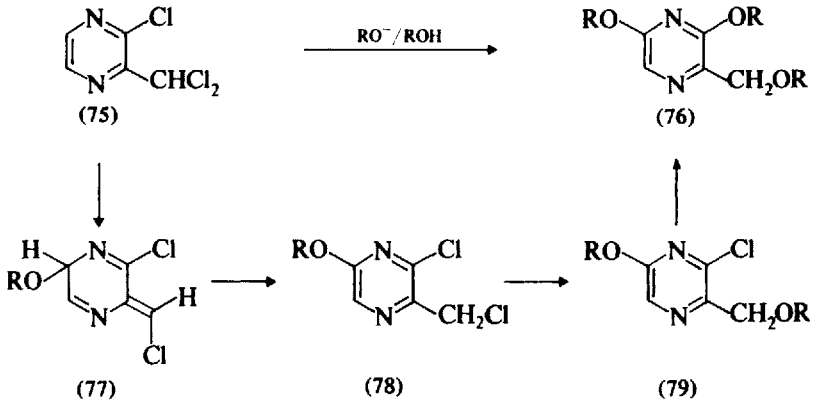
6. REACTIONS OF EXTRANUCLEAR HALOGENOPYRAZINES

A. Replacement of Halogeno Substituents by Alkoxy, Hydroxy, and Alkylthio Groups

α-Monochloromethylpyrazines react with alkoxide ions by normal replacement of the chloro substituent: 2-chloromethylpyrazine with ethoxide ions gave 2-

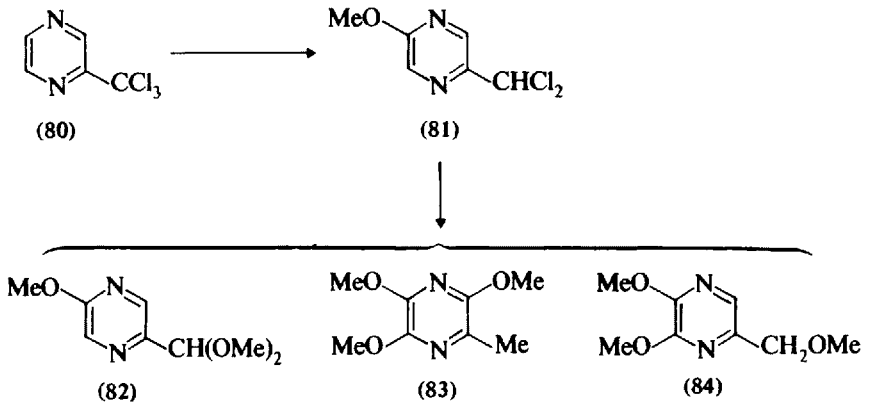
ethoxymethylpyrazine, 2,6-bis(chloromethyl)pyrazine gave 2,6-bis(ethoxymethyl)-pyrazine (679), and similar reactions were observed with 2-chloromethyl-5-methylpyrazine (679), 2,3-bis(chloromethyl)pyrazine (654), and 2-chloromethyl-3-ethoxy-5-methylpyrazine (872). 2,5-Dialkoxy-3,6-bis(chloromethyl)pyrazines with sodium alkoxides at room temperatures or under slight warming gave low yields of 2,5-dialkoxy-3,6-bis(alkoxymethyl)pyrazines (756).

The reactions of certain α,α-dichloromethyl- and α,α,α-trichloromethylpyrazines with alkoxide ions were found to be abnormal. 2-Chloro-3-dichloromethylpyrazine (**75**) with three equivalents of sodium methoxide in refluxing methanol was found to give a quantitative yield of 3,5-dimethoxy-2-methoxymethylpyrazine (**76**, R = Me) and the mechanism (**75** → **77** → **78** → **79** → **76**) was proposed (685). The following additional observations appeared to support this proposed mechanism: (*a*) (**75**) reacted with one equivalent of ethoxide ions in ethanol at 0° to give (**78**, R = Et) as the principal product; (*b*) (**75**) reacted with two equivalents of ethoxide ion in ethanol at 25° to give (**79**, R = Et) as the principal product; and (*c*) (**75**) with three equivalents of ethoxide ion in refluxing ethanol gave a quantitative yield of (**76**, R = Et). The initial abnormal nucleophilic displacement of chloride ion from (**75**) is the result of the susceptibility of the pyrazine ring to nucleophilic substitution (1026), the electron-withdrawing nature of the substituents present in (**75**), and the steric bulk of these substituents, which retards initial S_N2 displacement (685). Reactions of 2-chloro-3-dichloromethylpyrazine with sodium methoxide have been examined further (687, 688).



2-(Trichloromethyl)pyrazine (**80**) with three equivalents of methoxide ion in refluxing methanol also underwent an abnormal reaction and gave a quantitative yield of the three isomeric pyrazines: 2-dimethoxymethyl-5-methoxypyrazine (75%) (**82**), 2,3,5-trimethoxy-6-methylpyrazine (15%) (**83**), and 2,3-dimethoxy-5-methoxymethylpyrazine (10%) (**84**) (685). Subsequent treatment of (**80**) with one equivalent of methoxide ion in methanol at 5° gave 2-dichloromethyl-5-methoxypyrazine (**81**).

Although Behun and Levine (694) claimed to have prepared 2-(α,α-dimethoxymethyl)pyrazine by heating 2-(dichloromethyl)pyrazine with sodium methoxide,



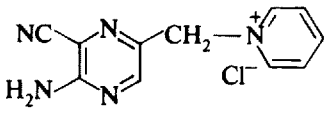
Abushanab (1027) repeated the experiment and claims the product is not the acetal but rather 2-methoxy-3-methoxymethylpyrazine or 2-methoxy-5-methoxymethylpyrazine.

Hydrolysis of 2-chloromethyl-3-ethoxy-5-methylpyrazine with aqueous potassium hydroxide gave 3-ethoxy-2-hydroxymethyl-5-methylpyrazine (872), but attempted acid hydrolysis of 2-chloromethyl-3-ethoxy-5-methylpyrazine (and 3-ethoxy-2-ethoxymethyl-5-methylpyrazine) was unsuccessful (872). Attempts to convert 2-chloromethylpyrazine to 2-hydroxymethylpyrazine were also unsuccessful (679).

2-Chloro-3-dichloromethylpyrazine with sodium methanethiolate has been claimed to give a mixture of products analogous to those obtained from its reaction with sodium methoxide (688). 2-Amino-5-chloromethyl-3-cyanopyrazine with 4-chlorothiophenol and sodium ethoxide has been shown to give 2-amino-3-cyano-5-(*p*-chlorophenylthiomethyl)pyrazine (542), and with *p*-ethoxycarbonylphenylthiolate anion gave 2-amino-3-cyano-5-[(*S*-*p*-ethoxycarbonylphenyl)thiomethyl]-pyrazine (1028).

B. Replacement of Halogeno Substituents by Amines

α-Chloromethylpyrazine with potassium phthalimide in dimethylformamide at reflux gave 2-phthalimidomethylpyrazine, which can be hydrolyzed to 2-aminomethylpyrazine (1029). The corresponding substituted aminomethylpyrazines have been prepared from 2-chloromethylpyrazine with butylamine (679), ethanolamine, and bis(2-hydroxyethyl)amine (1029), and from 2-amino-5-chloromethyl-3-cyanopyrazine with 3,4-dichloroaniline, 2,4- and 3,4-dichlorobenzylamines, sulfanilamide, diethylamine, and ethyl *p*-aminobenzoate (542). 2-Chloromethyl-3-methylpyrazine with piperidine in xylene at reflux for 24 hours has been claimed to give 2-methyl-6-piperidinomethylpyrazine (62.6%) and 2-methyl-3-piperidinomethylpyrazine (3.3%) (932); 2-amino-5-chloromethyl-3-cyanopyrazine with pyridine at room temperature gave 2-amino-3-cyano-5-pyridiniomethylpyrazine chloride (85) (1030); and 2-amino-5-bromomethyl-3-cyanopyrazine with potassium phthalimide gave 2-amino-3-cyano-5-phthalimidomethylpyrazine (1031).



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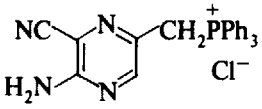
C. Replacement of Halogeno Substituents by Other Groups

Deuterolysis of 3-chloro-2-chloromethyl-5-methoxypyrazine over 5% palladium on alumina in the presence of sodium isopropoxide in 2-propanol afforded 3-deutero-2-monodeuteromethyl-5-methoxypyrazine (687); and methylation of the bromomagnesium derivative from 2-bromomethyl-3,5,6-trimethylpyrazine with methyl sulfate or methyl iodide gave 2-ethyl-3,5,6-trimethylpyrazine (330).

2-Amino-5-bromomethyl-3-cyanopyrazine with the sodium salt of diethyl malonate in tetrahydrofuran at room temperature gave 2-amino-3-cyano-5-(2′,2′-diethoxycarbonylethyl)pyrazine together with a little dialkylated product (1031). Similar reactions were observed with the sodium salts of ethyl acetoacetate and ethyl γ-ethoxyacetoacetate, but methyl cyanoacetate gave only dialkylated product (1031). 2-Amino-5-chloromethyl-3-cyanopyrazine and 1-pyrrolidino-1-cyclohexene in tetrahydrofuran have been shown to give 2-amino-3-cyano-5-(2′-oxocyclohexylmethyl)pyrazine (542).

2-Amino-5-chloromethyl-3-cyanopyrazine on treatment with potassium acetate in propan-2-ol at 80–90° gave 5-acetoxymethyl-2-amino-3-cyanopyrazine (542), and 2-amino-6-chloro-5-chloromethyl-3-cyanopyrazine with anhydrous sodium acetate in dimethylformamide gave 2-acetoxymethyl-5-amino-3-chloro-6-cyanopyrazine (874).

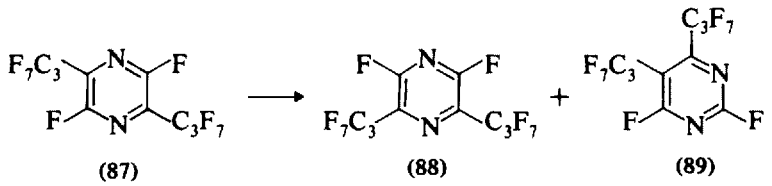
The chloro substituent from some α-chloromethylpyrazines has been replaced using triphenylphosphine: 2-amino-5-chloromethyl-3-cyanopyrazine with triphenylphosphine in dimethylformamide at 80–90° gave 2-amino-3-cyano-5-triphenylphosphinomethylpyrazine chloride (**86**), which with acetaldehyde and triethylamine in chloroform gave 2-amino-3-cyano-5-(prop-1′-enyl)pyrazine (529) [the 5-(non-1′-enyl), 5-(3′,4′-methylenedioxystyryl), and 5-(3′,4′-dichlorostyryl) analogues were prepared similarly (529)]. 3-Amino-5-chloromethyl-2-cyanopyrazine likewise reacted with triphenylphosphine to give the corresponding triphenylphosphinomethylpyrazine chloride (534).



(86)

2-Chloromethylpyrazine with sodium azide in refluxing aqueous acetonitrile gave 2-azidomethylpyrazine (690), and 2-amino-5-bromomethyl-3-cyanopyrazine with sodium cyanide in dimethyl sulfoxide at 40° gave 2-amino-3-cyano-5-cyanomethylpyrazine (1031).

Irradiation of the liquid phase of perfluoro-2,5-diisopropylpyrazine (87) caused slow rearrangement to the 2,6-isomer (88) plus some perfluoro-4,5-diisopropylpyrimidine (89), and prolonged irradiation of (88) gave a small amount of (87) (494).



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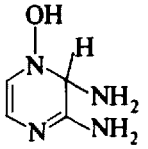
7. REACTIONS OF HALOGENOPYRAZINE *N*-OXIDES

A. Reactions of Nuclear Halogenopyrazine *N*-Oxides

(1) *Replacement of Halogeno Substituents by Amino Groups*

Marked activation of the chloro substituent by the *N*-oxide function to nucleophilic replacement by ammonia and amines has been demonstrated by comparison of the reactivities of chloropyrazine and 3-chloropyrazine 1-oxide. The preparation of 2-aminopyrazine in 87% yield from 2-chloropyrazine and aqueous ammonia required at least 16 hours at 140°, but when 3-chloropyrazine 1-oxide was heated with an excess of aqueous ammonia at 115–120° for 2.5 hours (547a), 3-aminopyrazine 1-oxide was formed in good yield (921). [3-Chloropyrazine 1-oxide and aqueous ammonia, heated under the more usual amination conditions at 140° for 16 h, gave a mixture of 2-aminopyrazine and 2,3-diaminopyrazine; the latter product was the only one isolated when 3-aminopyrazine 1-oxide was heated with aqueous ammonia at 140–145° for 16 h. This formation of 2,3-diaminopyrazine may involve an intermediate of the type (**90**) (921)]. 2-Butylaminopyrazine could not be prepared in reasonable yield by heating 2-chloropyrazine with butylamine under reflux for periods up to 16 hours, but it was prepared in 75% yield by heating the reactants in a sealed vessel at 120° for 8 hours, whereas 3-butylaminopyrazine 1-oxide was readily formed in 60% yield when 3-chloropyrazine 1-oxide was refluxed with an excess of butylamine for 30 minutes (921).



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Comparative *N*-oxide activation was likewise observed when other amines such as hexylamine, aniline, benzylamine, piperidine, and dimethylamine were used. It was also noted, in every example studied, that amination of the chloropyrazine *N*-oxide or alkylchloropyrazine *N*-oxide at elevated temperatures in a sealed vessel gave mixtures containing greater or lesser amounts of deoxygenated halogenopyrazine or aminopyrazine (921). Similar enhanced activation by the *N*-oxide group was observed when 3-chloro-2,5-dimethylpyrazine and its 1-oxide in reaction with various amines were compared, although dialkyl substitution further retarded overall aminolysis (793, 921).

2-Chloropyrazine 1-oxide and 3-chloropyrazine 1-oxide both react with sulfanilamide to give the corresponding sulfanilamidopyrazine *N*-oxides (1032, 1033); 3-chloro-2-methylpyrazine 1-oxide with piperidine at reflux gave 2-methyl-3-piperidinopyrazine 1-oxide, and with dimethylamine gave 3-dimethylamino-2-methylpyrazine 1-oxide (793); 2-amino-3-chloropyrazine 1-oxide with aqueous ammonia and copper powder at 140–150° for 18 hours gave 2,3-diaminopyrazine 1-oxide (906); 3,5-dichloropyrazine 1-oxide with 20% aqueous dimethylamine at reflux for 20 hours gave 3,5-bis(dimethylamino)pyrazine 1-oxide (663); and 2-amino-3-bromo-5,6-dimethylpyrazine 1-oxide with aqueous methylamine and isopropyl alcohol at 100–120° for 12 hours gave 2-amino-3-methylamino-5,6-dimethylpyrazine 1-oxide (907). The preparation of 2-chloro-6-piperazinylpyrazine 1- and 4-oxides from 2,6-dichloropyrazine 1- and 4-oxides and piperazine has been reported (951).

2-*s*-Butyl-3-hydrazino-5-isobutylpyrazine 1-oxide was prepared from the chloro analogue and hydrazine hydrate at 130° (313) and 2-(1′-acetoxy-2′-methylpropyl)-3-chloro-5-isobutylpyrazine 1-oxide with 80% hydrazine hydrate at 130° was claimed to give 3-hydrazino-2-(1′-hydroxy-2′-methylpropyl)-5-isobutylpyrazine 1-oxide (760a). 3-Hydrazino-2-isobutyl-5-isopropylpyrazine 1-oxide and 3-hydrazino-5-isobutyl-2-isopropylpyrazine 1-oxide were prepared similarly (740a).

(2) *Replacement of Halogeno Substituents by Hydroxy Groups*

Enhanced reactivity of halogenopyrazine *N*-oxides relative to the corresponding halogenopyrazine has also been shown in their reactions toward hydroxide ions (978): 2-chloropyrazine 1-oxide refluxed with aqueous alkali for 2 hours gave a 60% yield of 2-hydroxypyrazine 1-oxide (547a), whereas heating of 2-chloropyrazine with aqueous alkali at 150° for 7 hours was required to produce a comparable yield of 2-hydroxypyrazine (818); 3-chloro-2-methylpyrazine 1-oxide refluxed with aqueous alkali for 15 minutes showed the maximum absorption due to 3-hydroxy-2-methylpyrazine 1-oxide (978), whereas 2-chloro-3-methylpyrazine required boiling with concentrated aqueous alkali for 9 hours to replace the chloro group (680); and 3-hydroxy-2,5-dimethylpyrazine 1-oxide was formed in 60% yield by heating 3-chloro-2,5-dimethylpyrazine 1-oxide with aqueous alkali for 1 hour whereas 3-chloro-2,5-dimethylpyrazine required boiling with aqueous alkali for 59 hours to give the corresponding hydroxy compound (978).

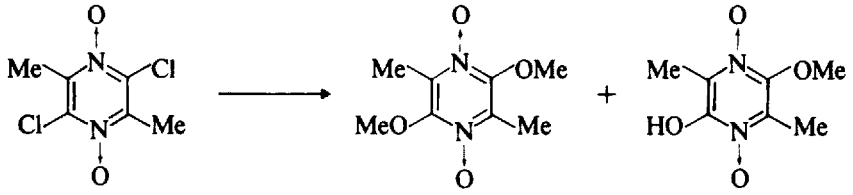
Klein et al. (978) first attempted the alkaline hydrolysis of 3-chloropyrazine 1-oxide to 3-hydroxypyrazine 1-oxide, and although spectroscopic evidence indicated the formation of the hydroxy compound, good quality homogeneous material could not be isolated. Later work by Berkowitz and Bardos (1034) has shown that 3-chloropyrazine 1-oxide was hydrolyzed by refluxing with two equivalents of aqueous sodium hydroxide, and treatment of the product with trimethylsilyl chloride and triethylamine gave 3-(trimethylsilyl)oxypyrazine 1-oxide. 3,6-Di-*s*-butyl-2-hydroxypyrazine 1-oxide has been prepared from the chloro analogue (no details given) (982). Hydrolysis of 2-amino-6-chloro-3-cyano-5-methylpyrazine 1-oxide with aqueous 0.5 *N* sodium hydroxide at room temperature gave 2-amino-3-cyano-6-hydroxy-5-methylpyrazine 1-oxide (and some 2-amino-3-carbamoyl-6-chloro-5-methylpyrazine 1-oxide), whereas 95% acetic acid at 100° for 3 hours gave 82% of the cyano compound only (533).

2,5-Dichloro-3,6-dimethylpyrazine 1,4-dioxide with 0.5 *N* sodium hydroxide at 20° for 5 hours gave 2-chloro-5-hydroxy-3,6-dimethylpyrazine 1,4-dioxide which resisted further alkaline hydrolysis (842) (possibly due to anion formation, whereas sodium ethoxide and sodium benzyloxide rapidly displaced both chloro substituents). Similarly bromoaspergillic acid (3-bromo-2-*s*-butyl-6-hydroxy-5-isobutylpyrazine 1-oxide) was unchanged by treatment with 0.5 *N* methanolic potassium hydroxide at room temperature or by 1.25 *N* sodium hydroxide at 100° for several hours (87). 3-Hydroxy-2,5-diisobutylpyrazine 1,4-dioxide (843) and 5-*s*-butyl-3-hydroxy-2-isobutylpyrazine 1,4-dioxide (313) were both prepared from the corresponding chloropyrazine with alcoholic potassium hydroxide. 5-(1′-Acetoxy-2′-methylpropyl)-3-chloro-2-isobutylpyrazine 1,4-dioxide refluxed with ethanolic potassium hydroxide gave 3-hydroxy-5-(1′-hydroxy-2′-methylpropyl)-2-isobutylpyrazine 1,4-dioxide (760a) and 3-chloro-2-isobutyl-5-isopropylpyrazine 1,4-dioxide refluxed with aqueous ethanolic potassium hydroxide afforded 3-hydroxy-2-isobutyl-5-isopropylpyrazine 1,4-dioxide; 3-hydroxy-5-isobutyl-2-isopropylpyrazine 1,4-dioxide was prepared similarly (740a).

(3) *Replacement of Halogeno Substituents by Other Groups*

The following alkoxypyrazine *N*-oxides have been prepared from the corresponding chloropyrazine *N*-oxides and sodium alkoxide in the appropriate alcohol (unless otherwise specified): 3-methoxypyrazine 1-oxide (838); 2-methoxypyrazine 1-oxide (no details (838); 3-ethoxypyrazine 1-oxide (978); 3-ethoxy-2-methylpyrazine 1-oxide (potassium hydroxide in ethanol) (978); 3-ethoxy-2,5-dimethylpyrazine 1-oxide (sodium ethoxide or potassium hydroxide in ethanol) (872, 978); and 3-methoxy-2,5-dimethylpyrazine 1-oxide (588).

2,5-Dichloro-3,6-dimethylpyrazine 1,4-dioxide (**91**) with sodium methoxide at room temperature gave 2,5-dimethoxy-3,6-dimethylpyrazine 1,4-dioxide (**92**) and a trace of 2-hydroxy-5-methoxy-3,6-dimethylpyrazine 1,4-dioxide (**93**) (756). Similarly 2,5-dichloro-3,6-dimethylpyrazine 1,4-dioxide (*a*) with sodium ethoxide gave 2,5-diethoxy-3,6-dimethylpyrazine 1,4-dioxide (756, 842) and 2-hydroxy-5-

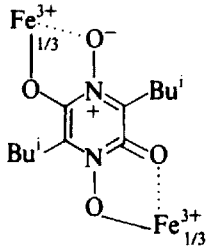


(91) (92) (93)

ethoxy-3,6-dimethylpyrazine 1,4-dioxide (756); and (*b*) with sodium benzyloxide gave 2,5-dibenzyloxy-3,6-dimethylpyrazine 1,4-dioxide and 2-benzyloxy-5-hydroxy-3,6-dimethylpyrazine 1,4-dioxide (756, 842).

2,5-Dichloro-3,6-diisobutylpyrazine 1,4-dioxide when refluxed with an excess of powdered sodium methoxide in dioxane did not give a methoxy compound but gave an acidic substance which on treatment with ferric chloride solution (and hydrochloric acid) afforded an iron complex (101) corresponding to pulcherrimin (**94**) (39). 3-Chloropyrazine 1-oxide with sodium hydrogen sulfide in ethanol at room temperature gave 3-mercaptopyrazine 1-oxide (1035). 3-Chloro-2-methylpyrazine 1-oxide with thiourea in 2*N* sulfuric acid (which was found to be beneficial) at reflux for 30 minutes gave 3-mercapto-2-methylpyrazine 1-oxide, and 3-chloro-2,5-dimethylpyrazine 1-oxide similarly gave 3-mercapto-2,5-dimethylpyrazine 1-oxide (905). 2-Chloropyrazine 1-oxide and 3-chloropyrazine 1-oxide with aqueous sodium sulfite gave 2-sulfopyrazine 1-oxide and 3-sulfopyrazine 1-oxide, respectively (838). 2,3-Dichloropyrazine 1-oxide with the sodium salt of bismercaptomethylenemalononitrile $[(NaS)_2C{=}C(CN)_2]$ in dimethylformamide formed 1,3-dithiolo[4,5-*b*]pyrazin-2-ylidenepropanedinitrile 4-oxide (**95**), which is useful as a fungicide and algicide, for the preservation of wood, and for marine antifouling paints (1036, 1037).

3-Chloropyrazine 1-oxide with cuprous cyanide in *N*-methylpyrrolidine or dimethylformamide did not give 3-cyanopyrazine 1-oxide (838).



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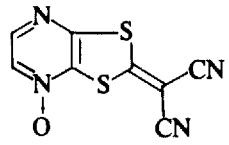


(95)

(4) *Reactions Involving Removal of Halogeno Substituents and/or the N-Oxide Function*

The chloro substituent can be removed from 2-*s*-butyl-3-chloro-5-isobutylpyrazine 1-oxide by heating with hydrazine hydrate at 130° and then treating the

hydrazino compound with copper sulfate in acetic acid to give 2-*s*-butyl-5-isobutylpyrazine 1-oxide (313); 2-(1′-acetoxy-2′-methylpropyl)-3-chloro-5-isobutylpyrazine 1-oxide similarly treated gave 2-(1′-hydroxy-2′-methylpropyl)-5-isobutylpyrazine 1-oxide (760a). The chloro substituent has also been removed from 3-chloro-2-isobutyl-5-isopropylpyrazine 1-oxide and 3-chloro-5-isobutyl-2-isopropylpyrazine 1-oxide by heating with hydrazine hydrate at 120° and treating the hydrazino compound with copper sulfate in aqueous acetic acid (740a).

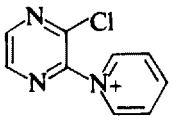
Treatment of bromoaspergillic acid (3-bromo-2-*s*-butyl-6-hydroxy-5-isobutylpyrazine 1-oxide with zinc dust in acetic acid gave a product thought to be 3-*s*-butyl-6-isobutylpiperazine-2,5-dione (87).

2-Chloro-5-phenylpyrazine 1(and 4)-oxides have been deoxygenated in good yield with aqueous chromium(II) chloride in methanol and acetone at room temperature (761).

Deoxygenations of halogenopyrazine *N*-oxides by phosphoryl chloride accompanied by nuclear (and side chain) halogenations have been included in previous discussions (Section 1G and Table V.1) and have been applied to the following compounds: 3-chloropyrazine 1-oxide (757, 831, cf. 737); 3,5-dichloropyrazine 1-oxide (365b); 3-chloro-2,5-dimethylpyrazine 1-oxide (842); 2,5-dichloro-3,6-dimethylpyrazine 1,4-dioxide (756); and 2-amino-5-bromo-3-methoxycarbonylpyrazine 1-oxide (808, 875, 877–879).

The reaction of 3-chloro-2-methylpyrazine 1-oxide with glacial acetic acid and acetic anhydride to give (after treatment with aqueous sodium hydroxide) 2-chloro-3-hydroxymethylpyrazine (737) has been covered previously [Section IV.3C(3)].

3-Chloropyrazine 1-oxide with tosyl chloride in the presence of pyridine gave 2-chloro-3-pyridiniopyrazine salts (**96**) (765), and 2-chloro-3,6-diisobutylpyrazine 1-oxide heated with acetic anhydride at 190° gave 5-(1′-acetoxy-2′-methyl)propyl-3-chloro-2-isobutylpyrazine (113b). Catalytic hydrogenation of 3-chloro-2-phenylpyrazine 1-oxide over palladium–charcoal in the presence of triethylamine gave 2-phenylpyrazine 1-oxide (44%) together with 2-phenylpyrazine (24%) and 2-chloro-3-phenylpyrazine (2%) (733b).



$X^-(=Cl^- \text{ or } TsO^-)$

(96)

(5) *Other Reactions*

2-Chloropyrazine 1-oxide with phenylmagnesium bromide in tetrahydrofuran at reflux gave 2-chloro-6-phenylpyrazine 1-oxide (733b).

B. Reactions of Extranuclear Halogenopyrazine *N*-Oxides

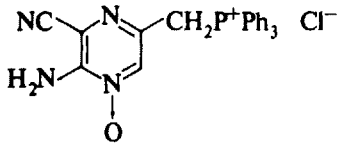
(1) *Deoxygenation*

Certain α-chloromethylpyrazine *N*-oxides have been deoxygenated with phosphorus trichloride. Treatment of 2-amino-5-chloromethyl-3-cyanopyrazine 1-oxide (and 2-amino-3-cyano-5-methoxymethylpyrazine 1-oxide) with phosphorus trichloride at room temperature in tetrahydrofuran resulted in smooth deoxygenation to 2-amino-5-chloromethyl-3-cyanopyrazine (and 2-amino-3-cyano-5-methoxymethylpyrazine) (529), whereas 2-amino-6-chloromethyl-3-cyanopyrazine 1-oxide was best deoxygenated to 3-amino-5-chloromethyl-2-cyanopyrazine by phosphorus trichloride in refluxing tetrahydrofuran (534). The more vigorous conditions necessary for the last reaction may be a reflection of increased steric hindrance at the *N*-oxide grouping (529). Use of solvents like chloroform or dioxane led to slow reactions which were accompanied by the formation of numerous unidentified by-products (534).

2-Amino-5-chloromethyl-3-cyanopyrazine 1-oxide was also deoxygenated by sodium hydrosulfite (dithionite) in boiling water to give a poor yield of 2-amino-5-chloromethyl-3-cyanopyrazine, but 2-amino-6-chloromethyl-3-cyanopyrazine 1-oxide under the same conditions underwent both deoxygenation and reductive dehalogenation to 2-amino-3-cyano-6-methylpyrazine (529, 534).

(2) *Replacement of Halogeno Substituents by Triphenylphosphine*

2-Amino-5-chloromethyl-3-cyanopyrazine 1-oxide with triphenylphosphine in dimethylformamide at 80–90° gave 2-amino-3-cyano-5-(triphenylphosphonio)-methylpyrazine 1-oxide chloride (**97**) (520) and the 5-bromomethyl analogue reacted similarly with triphenylphosphine in propan-2-ol (542). Compound (**97**) on hydrolysis with 30% aqueous ethanol containing a small amount of triethylamine gave 2-amino-3-cyano-5-methylpyrazine 1-oxide and thus enabled removal of the chloro substituent from the chloromethylpyrazine (529); compound (**97**) with triethylamine and acetaldehyde (and other aldehydes) in chloroform at room temperature gave 2-amino-3-cyano-5-(prop-1′-enyl)pyrazine 1-oxide (and other alkenyl analogues) (529).



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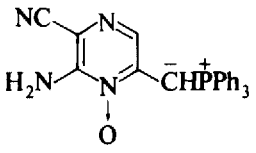
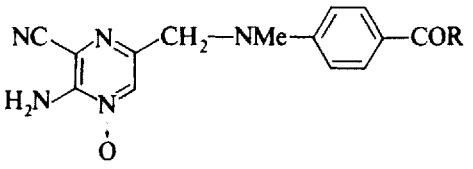
An analogous series of reactions was observed from 2-amino-6-chloromethyl-3-cyanopyrazine 1-oxide and the 2-amino-3-cyano-6-(triphenylphosphonio)-methylpyrazine 1-oxide chloride with aqueous sodium bicarbonate gave the betaine **(98)** (534).



(98)

(3) *Replacement of Halogeno Substituents by Other Groups*

2-Amino-5-chloromethyl-3-cyanopyrazine 1-oxide at reflux in methanol gave 2-amino-3-cyano-5-methoxymethylpyrazine 1-oxide (529), and with various *p*-(methylamino)benzamides gave the 2-amino-3-cyano-5-(*N*-methyl-*N*-substituted phenyl)aminomethylpyrazine 1-oxides **(99)** (1038, 1039). 2-Amino-5-chloromethyl-3-cyano-6-methylpyrazine 1-oxide and diethyl *p*-(methylamino)benzoylglutamate **(100)** in tetrahydrofuran and potassium carbonate formed 2-amino-3-cyano-5-[*N*-(diethylglutamylcarbonylphenyl)-*N*-methyl]aminomethyl-6-methylpyrazine 1-oxide **(101)** (762).



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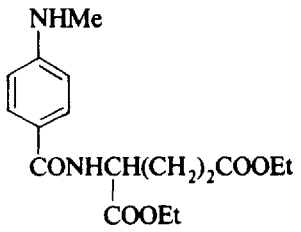

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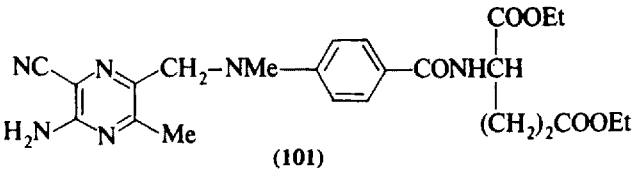

(101)

Condensation of 2-amino-5-bromomethyl-3-cyanopyrazine 1-oxides with the appropriate substituted amine afforded a series of 2-amino-5-{[(aryl and aralkyl)-amino]methyl}-3-cyanopyrazine 1-oxides (1040), and with *p*-chlorophenol and arylthiols gave 2-amino-5-[(*p*-chlorophenoxy)methyl]-3-cyanopyrazine 1-oxide and 2-amino-5[(arylthio)methyl]-3-cyanopyrazine 1-oxides (1041).

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G. B. Badin

CHAPTER VI

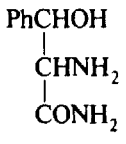
Hydroxypyrazines And Their Derivatives

1. PREPARATION OF HYDROXYPYRAZINES

A. By Primary Synthesis

The preparations of hydroxypyrazines by primary syntheses have been described in Chapter II, and are summarized briefly, together with further data, as follows: Section II.1G, from the reaction of α,β-dicarbonyl compounds with ammonia [282 (cf. 281, 280), 283, 285] with additional information (1042, 1043); Section II.1M, from 1,2-dicarbonyl compounds with α-amino acids (311); Section II.1N, from α-amino acids through piperazine-2,5-diones (93, 95, 101, 282, 312, 313) with additional data (843); Section II.1O, from aldehyde cyanohydrins (?) [317–319 (cf. 282)] and Section II.1P, from *o*-nitromandelonitrile and ethereal hydrogen cyanide (325). The preparations from α,β-dicarbonyl compounds with α,β-diamino compounds are described in Section II.2 (60, 80, 358, 359, 361–365b, 365d, 366–375); additional data have also been reported (824, 825, 827, 845, 846, 971, 1044, 1045); and some reaction products have been isolated as the dihydropyrazines (340, 341, 357).

The condensation of pyruvaldehyde and glycine amide (362, 1046) to give 2-hydroxy-5(and 6)-methylpyrazine was further investigated by Lutz et al. (681), who could isolate only 2-hydroxy-6-methylpyrazine. The reaction of glycine amide with phenylglyoxal to give 2-hydroxy-5-phenylpyrazine has been reported by Sugiura et al. (377), and 2-hydroxy-3,5-diphenylpyrazine has been prepared from DL-phenylglycine amide and phenylglyoxal (546). *threo*-β-Phenylserine (**1**) reacted



(1)

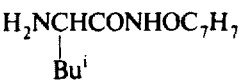
with glyoxal, pyruvaldehyde, diacetyl, or benzil to give 2-hydroxy-3-(α-hydroxybenzyl)pyrazine, and its 5-methyl, 5,6-dimethyl, and 5,6-diphenyl analogues (1045).

Hultquist (1047) has described the preparation of a number of hydroxypyrazines from α-amino acid nitriles with dicarbonyl compounds. Thus glyoxal and glycine nitrile sulfate in 50% sodium hydroxide gave 2-hydroxypyrazine; glycine nitrile hydrochloride and diacetyl or benzil gave 5-hydroxy-2,3-dimethylpyrazine or 5-hydroxy-2,3-diphenylpyrazine; and α-alanine nitrile with glyoxal, diacetyl, or benzil gave 2-hydroxy-3-methyl-, 2-hydroxy-3,5,6-trimethyl-, and 2-hydroxy-3-methyl-5,6-diphenylpyrazine, respectively. The effect of the reaction temperature and velocity of addition of alkali on the yield of hydroxypyrazine from the condensation of glycine amide hydrochloride with glyoxal has been studied (1048), and it was found that the lower the reaction temperature, the higher was the yield of hydroxypyrazine unless the reaction mixture solidified.

Bredereck and Schmötzer (1044), from diaminomaleonitrile (DAMN; hydrogen cyanide tetramer) and oxalyl chloride, prepared 2,3-dicyano-5,6-dihydroxypyrazine; but Stetten and Fox (1049) could not prepare 2,3-diamino-5-hydroxypyrazine from glycine amide and oxamide. Section II.3 lists preparations from α,β-diamino or α,β-diimino compounds and reagents other than α,β-dicarbonyl compounds (384) with additional data (1050); and oxidation of 2,3-dichloroquinoxaline with hot aqueous potassium permanganate gave 2,3-dicarboxy-5,6-dihydroxypyrazine (1051).

Section II.5 includes the cleavage of pteridines and related ring systems to yield hydroxypyrazines (375, 420, 429, 433–434, 440, 441, 445, 448, 449). Additional data are given in references 372, 907, 1052 and 1053. 2-Amino-6-(*p*-fluorophenyl)-4-hydroxypteridine with 4*N* sodium hydroxide at 170° gave 3-carboxy-5-(*p*-fluorophenyl)-2-hydroxypyrazine, and a similar preparation of the isomeric 6-(*p*-fluorophenyl)pyrazine was also described (347).

Section II.7 describes some ring closures of the C–C–N–C–C, N–C–C–N–C–C, and N–C–C–N–C–C–N systems to give hydroxypyrazines (248, 365a, 477, 479, 480–483); more information can be found in reference 1054. Newbold and Spring (89) described the reaction of 2-bromo-*N*-(1′-methyl-2′-oxopropyl)propionamide with ethanolic ammonia to give 2-hydroxy-3,5,6-trimethylpyrazine; and Masaki et al. (551) have described the reaction of *N*-leucyl-*O*-benzylhydroxylamine (**2**) with phenacyl bromide in methanol saturated with ammonia to give 3-hydroxy-2-isobutyl-5-phenylpyrazine and 2,5-diphenylpyrazine.



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B. By Hydrolysis of Halogenopyrazines

The reactions of halogenopyrazines with hydroxide ion to produce the hydroxy compounds have been described in Section V.5E.

In addition to the above preparations, the following hydrolyses have been

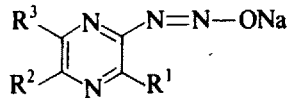
recorded. 2,3-Dichloro-5,6-dimethoxycarbonylpyrazine on treatment with aqueous sodium hydroxide, followed by methanolic hydrogen chloride, gave 2-chloro-3-methoxy-5,6-dimethoxycarbonylpyrazine (35.5%) and 2,3-dihydroxy-5,6-dimethoxycarbonylpyrazine (14%) (409). 5-*s*-Butyl-3-chloro-2-isobutylpyrazine with excess sodium ethoxide in ethanol at 130° afforded a mixture which, on treatment with ethanolic hydrochloric acid at 150–160°, gave 5-*s*-butyl-3-hydroxy-2-isobutylpyrazine (DL-deoxyaspergillic acid) (313); 2,5-dibromo-3,6-diphenylpyrazine with cuprous cyanide in γ-picoline at reflux for 7 hours and treatment with 4*N* hydrochloric acid gave 2-carboxy-5-hydroxy-3,6-diphenylpyrazine (presumably by hydrolysis of the dinitrile); and 2-bromo-3-methoxy-5,6-diphenylpyrazine with cuprous cyanide in γ-picoline formed 2-cyano-3-hydroxy-5,6-diphenylpyrazine (possibly by cleavage of the methoxy group with hydrochloric acid during workup) (797). 2-Amino-6-chloro-3-cyano-5-methylpyrazine hydrolyzed with aqueous trifluoroacetic acid produced 2-amino-3-carbamoyl-6-hydroxy-5-methylpyrazine (538).

C. From Aminopyrazines

Diazotization of 2-aminopyrazine with nitrous acid in dilute or concentrated sulfuric acid gave 2-hydroxypyrazine (to 67% yield) (86, 477, 720, 818). Many such conversions have been described, mostly using nitrosylsulfuric acid in concentrated sulfuric acid solution. Preparations of hydroxypyrazines from the aminopyrazines are summarized as follows: 2-hydroxy-3-methylpyrazine (sodium nitrite in concentrated sulfuric acid–acetic acid) (681), 2-hydroxy-3,5-dimethylpyrazine (aqueous nitrous acid, then at 60°) (524), 3-hydroxy-2,5-dimethylpyrazine (477), 2,5-diethyl-3-hydroxypyrazine (aqueous nitrous acid) (478), 2-hydroxy-6-phenylpyrazine (365a), 2-hydroxy-3,5-diphenylpyrazine (nitrous acid in *N* hydrochloric acid) (524), 3-hydroxy-2,5-diphenylpyrazine (282), 2-*s*-butyl-3-hydroxy-5-isobutylpyrazine (93), 5-*s*-butyl-3-hydroxy-2-isobutylpyrazine (92, 536), 2,5-di-*s*-butyl-3-hydroxypyrazine (89, 720), 3-hydroxy-2-isobutyl-5-isopropylpyrazine (103, 525), 2,3-dihydroxypyrazine (from 2-amino-3-hydroxypyrazine) (757, 1055) and its 1-methyl derivative (poor yield) (832), 2,5-dihydroxy-3,6-dimethylpyrazine [prepared from the diamine and nitrosylsulfuric acid in concentrated sulfuric acid (887); but earlier attempts to prepare this compound from 2-amino-5-hydroxy-3,6-dimethylpyrazine with nitrous acid were unsuccessful (872)], 2-hydroxy-3-methoxy-5-phenylpyrazine (365a), 2-chloro-5-hydroxypyrazine (831), 3-chloro-2-hydroxy-5-methylpyrazine (nitrosylsulfuric acid in concentrated sulfuric acid) (373, 835), 2-chloro-3-hydroxy-5-methylpyrazine (373), 3-chloro-5-hydroxy-2-methylpyrazine (535), 2-carboxy-3-hydroxypyrazine (423, 818, 836, 1056), 2-carboxy-5-hydroxypyrazine (aqueous nitrous acid in 2*N* sulfuric acid at 80°) (408), 2-carboxy-3-hydroxy-5-methylpyrazine (361), 3-carboxy-2-hydroxy-5-phenylpyrazine (nitrosylsulfuric acid) (378), 2-hydroxy-5-methoxycarbonylpyrazine (aqueous nitrous acid and heated at 80°) (1057), 2-alkoxycarbonyl-3-hydroxypyrazines (890), 5-bromo-2-hydroxy-3-methoxycarbonylpyrazine (sodium nitrite and concentrated sulfuric

acid at 0°) (799, 892), 5-chloro-2-hydroxy-3-methoxycarbonylpyrazine (1058), 2-carbamoyl-5-chloro-3-hydroxy-6-methylpyrazine (sodium nitrite in concentrated sulfuric acid) (535), 2-chloro-5-hydroxy-3-methoxy-6-methoxycarbonylpyrazine (881), 5-bromo-2-hydroxy-3-methoxypyrazine (535), and 2-chloro-3-ethylamino-(and diethylamino)-5-hydroxy-6-methoxycarbonylpyrazine (892).

2-Hydroxy-, 2-hydroxy-3-methyl-, 2-hydroxy-3,6-dimethyl-(3-hydroxy-2,5-dimethyl-), and 2-hydroxy-3-ethylpyrazines have been prepared by hydrolysis of the corresponding isodiazotate salts (**3**) in cold 40% aqueous sulfuric acid in 42–72%



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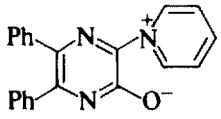
yield (887). 2-Amino-5-chloro-3-guanidinocarbonylpyrazine with sodium nitrite in aqueous methanesulfonic acid gave 5-chloro-3-guanidinocarbonyl-2-hydroxypyrazine (799, 892) and 5-chloro-3-guanidinocarbamoyl-2-hydroxypyrazine was prepared similarly (1058). 2-Amino-3,5-dibromopyrazine with aqueous hydrobromic acid, bromine, and sodium nitrite afforded 3,5-dibromo-2-hydroxypyrazine (52%) and 2,3,5-tribromopyrazine (29%), and 2-amino-5-bromo-3-chloropyrazine with aqueous hydrobromic acid and sodium nitrite gave 5-bromo-3-chloro-2-hydroxypyrazine (50%) and 2,5-dibromo-3-chloropyrazine (32%) (807).

Hydrolyses of amino compounds with acid or base also gave hydroxypyrazines. Thus 2-amino-3-carboxypyrazine heated with 20% sodium hydroxide at 170° for 20 hours afforded 2-carboxy-3-hydroxypyrazine (81%) (420, 1059), and 2,3-di-*N*(4)-acetylsulfanilamidopyrazine boiled with 4*N* hydrochloric acid gave 2,3-dihydroxypyrazine (833). 2-Amino-3-carboxy-5-(*p*-fluorophenyl)pyrazine with sulfuric acid is claimed to give 3-carboxy-5-(*p*-fluorophenyl)-2-hydroxypyrazine (347), and the zwitterion of 2-hydroxy-5,6-diphenyl-3-pyridiniopyrazine (**4**) refluxed with 20% sulfuric acid gave 2,3-dihydroxy-5,6-diphenylpyrazine (863). 2-Substituted 3-amino-5,6-dicyanopyrazines with water are claimed to give 2-substituted 3-hydroxy-5,6-dicyanopyrazines (**5**) (489), and mild hydrolysis of



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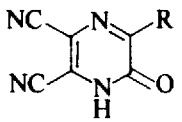

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stizolamine (3-guanidino-6-hydroxymethyl-1-methyl-2-oxo-1,2-dihydropyrazine) with water at 90–95° for 48 hours gave 6-hydroxymethyl-1-methyl-2-oxo-3-ureido-1,2-dihydropyrazine and 3-hydroxy-6-hydroxymethyl-1-methyl-2-oxo-1,2-dihydropyrazine (1060).

D. From Alkoxypyrazines

Pyrazines ethers are cleaved by acidic (and alkaline) hydrolysis to give the corresponding hydroxypyrazines. Some acidic hydrolyses are summarized as follows: 3-ethoxy-2,5-dimethylpyrazine (5 *N* hydrochloric acid at reflux for 18 h) (312); 2-chloro-5-ethoxy-3,6-dimethylpyrazine (6 *N* sulfuric acid for 16 hours gave 2-chloro-5-hydroxy-3,6-dimethylpyrazine) (872); 3-ethoxy-2,5-diisobutylpyrazine (6 *N* hydrochloric acid at reflux) (95); 2(or 5)-*s*-butyl-6-chloro-3-ethoxy-5(or 2)-isobutylpyrazine (ethanolic hydrogen chloride) (93); 2-isobutyl-5-isopropyl-3-methoxypyrazine and 5-isobutyl-2-isopropyl-3-methoxypyrazine (ethanolic hydrogen iodide) (740a); 2-dimethylamino-5-methoxy-3,6-dimethylpyrazine (concentrated hydrochloric acid at reflux) (689, 793); 2,3-dimethoxypyrazine (42% hydrobromic acid at reflux for 15 min) (797); 2,5-dimethoxy-3,6-diphenylpyrazine (42% hydrobromic acid in acetic acid at reflux) (797); 3-methoxy-2,5-diphenylpyrazine (48% hydrobromic acid at reflux) (866); 2-methoxy-6-phenylpyrazine (47% hydrobromic acid and acetic acid at reflux) (365a); 5-chloro-2-methoxy-3-phenylpyrazine and 2-chloro-5-methoxy-3-phenylpyrazine [acetic acid–hydrochloric acid (1:1) at reflux produced the chlorohydroxypyrazine] (817). 2-Cyano-5-ethoxy-3,6-dimethylpyrazine refluxed with 4 *N* hydrochloric acid for 2 hours gave 2-cyano-5-hydroxy-3,6-dimethylpyrazine (288) but with 50% sulfuric acid at reflux for 10 hours produced 3-hydroxy-2,5-dimethylpyrazine (288), and with aqueous 5 *N* potassium hydroxide at reflux for 10 hours formed 2-carboxy-5-hydroxy-3,6-dimethylpyrazine (288).

Demethylation of 5-(2′-hydroxy-2′-methylpropyl)-2-isobutyl-3-methoxypyrazine occurred on refluxing with 10% hydrochloric acid to give 3-hydroxy-5-(2′-hydroxy-2′-methylpropyl)-2-isobutylpyrazine but 2-isobutyl-3-methoxy-5-(2′-methylprop-1′-enyl)pyrazine and 3-hydroxy-2-isobutyl-5-(2′-methylprop-1′-enyl)pyrazine were also produced (113b).

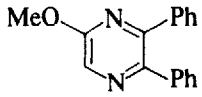
Other hydrolyses with sodium hydroxide have been described as follows. 2-Benzyloxy-6-chloropyrazine in ethanol with 3.5 *N* sodium hydroxide at reflux for 4.5 hours gave 2-chloro-6-hydroxypyrazine (832), 2-chloro-6-methoxypyrazine with aqueous ethanolic sodium hydroxide gave 2-chloro-6-hydroxypyrazine (43%) possibly containing a small amount of 2-hydroxy-6-methoxypyrazine) (883), and 2,6-dimethoxypyrazine with aqueous ethanolic sodium hydroxide at reflux for 24 hours formed 2-hydroxy-6-methoxypyrazine (832).

Cleavage of pyrazine diethers by sodium methoxide has been developed as a method of preparing *o*- and *p*-dihydroxypyrazines and hydroxypyrazine ethers (797). Such a procedure offers no advantage over mineral acid cleavage for the simple monoethers but with diethers stepwise reaction can be achieved by this method (797).

As described in Section V.5D(3), 2,5-dihalogenpyrazines require heating with excess sodium methoxide at 120–130° to give *p*-diethers, but higher temperatures yield mixtures of phenolic products which contain halogen, and it seems that under these conditions the halide ion may also effect nucleophilic displacement. Starting from *p*-diethers and a five- to tenfold excess of methoxide ion at tempera-

tures to 150°, cleavage can be confined to one ether group; both ether groups in *o*-dimethoxypyrazines were cleaved by a large excess of sodium methoxide at 150–180°, but when the proportion of base was reduced to 1.2 molar equivalents, the *o*-hydroxypyrazyl ethers were obtained in 70% yield (797). Examples are as follows: 2,3-dimethoxy-5,6-dimethyl(or diphenyl)pyrazine with one equivalent of sodium methoxide at 150–155° for 40 hours gave 2-hydroxy-3-methoxy-5,6-dimethyl(or diphenyl)pyrazine, 2,5-dimethoxy-3,6-dimethyl(and diphenyl)pyrazine and 20% sodium hydroxide (4–10 mol) at 150° for 24 hours gave 2-hydroxy-5-methoxy-3,6-dimethyl(and diphenyl)pyrazine, 5-butoxy-2-methoxy-3-phenylpyrazine similarly treated gave a mixture of 5-hydroxy-2-methoxy-3-phenylpyrazine and 5-butoxy-2-hydroxy-3-phenylpyrazine, and 2,5-dimethoxy-3-phenylpyrazine produced 2-hydroxy-5-methoxy-3-phenylpyrazine and 5-hydroxy-2-methoxy-3-phenylpyrazine (797). 2,5-Dimethoxy-3,6-dimethylpyrazine with excess methanolic sodium methoxide at 175° for 40 hours afforded 2,5-dihydroxy-3,6-dimethylpyrazine; and the diphenyl analogue was obtained similarly (797). 6-Chloro-1-methyl-2-oxo-3,5-diphenyl-1,2-dihydropyrazine with methanolic sodium methoxide refluxed for 1 hour and acidified with dilute hydrochloric acid gave 6-hydroxy-1-methyl-2-oxo-3,5-diphenyl-1,2-dihydropyrazine (873).

Demethylations with methylmagnesium halides have been described. 5-Methoxy-2,3-diphenylpyrazine (6) heated with methylmagnesium bromide at 150° gave 5-hydroxy-2,3-diphenylpyrazine, and 2,5-diisobutyl-3-methoxypyrazine similarly treated gave 3-hydroxy-2,5-diisobutylpyrazine (980). 5-(2′-Hydroxy-2′-methylpropyl)-2-isobutyl-3-methoxypyrazine heated with methylmagnesium iodide gave 3-hydroxy-5(2′-hydroxy-2′-methylpropyl)-2-isobutylpyrazine (deoxyneo-β-hydroxyaspergillic acid) (113b), which had previously been isolated from *Aspergillus ochraceus WILH* (1061).



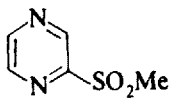
(6)

Benzyl groups may be removed by catalytic hydrogenation. Thus 2,6-dibenzyloxypyrazine with 0.67 molar proportions of hydrogen over palladium–charcoal gave 2-benzyloxy-6-hydroxypyrazine (but 2.0 molar proportions of hydrogen gave piperazine-2,6-dione) (832) and debenzylation of 2-benzyloxy-6-methoxypyrazine with 1.0 molar proportion of hydrogen in the presence of palladium–charcoal catalyst resulted in a good yield of 2-hydroxy-6-methoxypyrazine (832).

E. From Methylsulfonyl- and Methylsulfinylpyrazines

The reactive methylsulfonyl and methylsulfinyl substituents may be displaced by alkali to give hydroxypyrazines. For example, 2-methylsulfonylpyrazine (7) with *N* sodium hydroxide at 90° for 2 hours produced 2-hydroxypyrazine (1062) and 2-

methylsulfinylpyrazine (8) under similar conditions gave 2-hydroxypyrazine (90%) and 2-methylthiopyrazine (10%) (1063). 2-Amino-5-chloro-3-methoxycarbonyl-6-methylsulfinylpyrazine in aqueous acetic acid at 95° for 3 hours formed 2-amino-5-chloro-6-hydroxy-3-methoxycarbonylpyrazine (780, 809, 855, 859).



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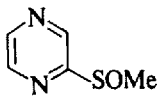
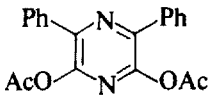


(8)

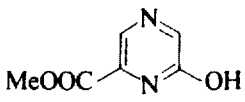
F. By Hydrolysis of Acetoxypyrazines

Hydrolysis of 2,6-diacetoxy-3,5-diphenylpyrazine (9) (from 2-hydroxy-3,5-diphenylpyrazine 1-oxide by refluxing with acetic acid–acetic anhydride) with potassium hydrogen carbonate in methanol gave 2,6-dihydroxy-3,5-diphenylpyrazine (873), and 2-acetoxy-6-methoxycarbonylpyrazine (from 3-methoxycarbonylpyrazine 1-oxide with acetic anhydride) with methanolic hydrogen chloride gave 2-hydroxy-6-methoxycarbonylpyrazine (838).



(9)

3-Amino-2-carbamoyl-5-hydroxypyrazine has been prepared from 2-amino-3-cyanopyrazine 1-oxide by reflux with acetic acid–acetic anhydride followed by ready deacetylation by refluxing in methanol (538), and in a similar manner 3-amino-2-ethoxycarbonyl-5-hydroxypyrazine has been prepared from 2-amino-3-ethoxycarbonylpyrazine 1-oxide through 3-acetamido-2-ethoxycarbonyl-5-hydroxypyrazine (538), and 2-amino-3-carbamoyl-6-hydroxy-5-methylpyrazine from 2-amino-3-cyano-5-methylpyrazine 1-oxide (538). The preparation of 2-hydroxy-6-methoxycarbonylpyrazine (**10**) has been claimed from 3-methoxycarbonylpyrazine 1-oxide with acetic anhydride followed by hydrolysis (1057) [cf. Nováček et al. (839), who claim it to be the 5-isomer, and Foks (744)].



(10)

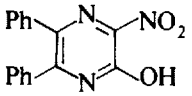
G. By Hydrolysis of Other Substituted Pyrazines

Alkaline hydrolysis of 2,5-dicyano-3,6-diphenylpyrazine gave 2-carboxy-5-hydroxy-3,6-diphenylpyrazine, and analogous reactions were observed with the

dimethyl analogue (286) but 2,5-dicyano-3,6-dimethyl(and diethyl)pyrazine shaken at room temperature with 5% aqueous sodium hydroxide produced 2-cyano-5-hydroxy-3,6-dimethyl(and diethyl)pyrazine which was hydrolyzed with 15% aqueous potassium hydroxide to the carboxylic acid (287–288).

Irradiation of pyrazine derivatives with an α-carbonyl substituent under an atmosphere of nitrogen has given hydroxypyrazines. Thus 2,5-dimethoxycarbonyl-3,6-dimethylpyrazine in diethyl ether irradiated with an USHIO UM-425 450-W high-pressure mercury lamp for 6 hours resulted in a 23–54% yield of 2-hydroxy-5-methoxycarbonyl-3,6-dimethylpyrazine and 1,4-dihydropyrazines. 2,5-Diacetyl-3,6-dimethylpyrazine similarly treated gave 2-acetyl-5-hydroxy-3,6-dimethylpyrazine, and other hydroxypyrazines were prepared likewise (1064).

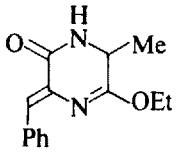
Hydrolysis of 2-hydroxy-3-nitro-5,6-diphenylpyrazine (**11**) in aqueous sulfuric acid or aqueous hydrochloric acid–acetic acid afforded 2,3-dihydroxy-5,6-diphenylpyrazine (817, 1065), and similar results were obtained with dry hydrogen chloride in glacial acetic acid (841).



(11)

H. By Other Reactions

cis- or *trans*-2-Benzylidene-6-ethoxy-3-hydroxy-5-methyl-2,5-dihydropyrazine (**12**) stirred with methanolic potassium hydroxide at room temperature produced 2-benzyl-6-ethoxy-3-hydroxy-5-methylpyrazine (**13**) (1066) and *trans*-3-benzylidene-6-methylpiperazine-2,5-dione (**14**) heated with *N* sodium hydroxide at 100°, cooled, and acidified with 2*N* hydrochloric acid gave 2-benzyl-3,6-dihydroxy-5-methylpyrazine (1066). A similar reaction was observed with the *p*-methoxy derivative (1066) and with similar analogues (1067). (*cis–trans*)-1,4-



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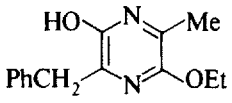

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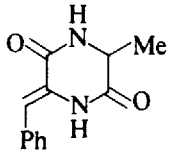
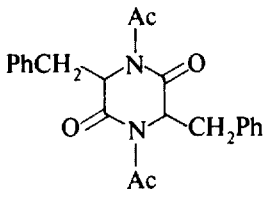


(14)

Diacetyl-3,6-dibenzylpiperazine-2,5-dione (**15**) reacted with sulfur in dimethylformamide and triethylamine to form, after hydrolytic removal of the acetyl groups, 3-benzyl-6-benzylidenepiperazine-2,5-dione (**16**) (1068). 2-Chloro-5-hydroxy-3,6-dimethylpyrazine heated with solid potassium hydroxide gave 3-hydroxy-2,5-dimethylpyrazine (312), and 2-chloro-6-hydroxy-3,5-diphenylpyrazine with an excess of methanolic sodium methoxide at 150° formed 2-hydroxy-3,5-diphenylpyrazine (873). Decarboxylation of 2-carboxy-3-hydroxypyrazine gave 2-hydroxypyrazine (420) and in this way 2-hydroxy[2-^{14}C]pyrazine (823) and 2-hydroxy[1-^{15}N]pyrazine (822) have been prepared.



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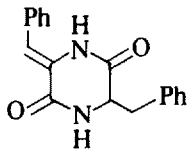


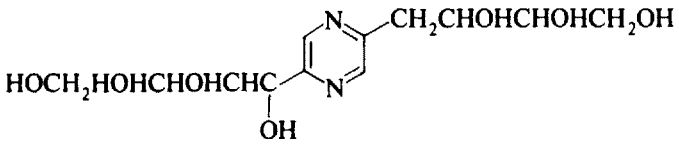
(16)

3-Ethoxypyrazine 1-oxide refluxed with 40% alcoholic hydrogen chloride yielded 2-ethoxy-5-hydroxypyrazine (1069). Ultraviolet irradiation of 2,5-dimethylpyrazine 1-oxide in water afforded 3-hydroxy-2,5-dimethylpyrazine (10%) and 2,5-diphenylpyrazine 1-oxide in benzene gave 3-hydroxy-2,5-diphenylpyrazine (3%) (742). A small yield of 2-ethyl-5-hydroxy-3,6-dimethylpyrazine has been isolated as by-product from the reaction of 2,5-dimethylpyrazine with ethyllithium in ether (615).

2. PREPARATION OF EXTRANUCLEAR HYDROXYPYRAZINES

A. By Primary Synthesis

Extranuclear hydroxypyrazines have been prepared by primary synthesis as follows: 2,5-bis(D-*arabo*-tetrahydroxybutyl)pyrazine (fructosazine) [from 2-amino-2-deoxy-D-glucose (or mannose) hydrochloride with sodium methoxide] (180, 183, 1070); 2-methyl-6-D-*arabo*-tetrahydroxybutyl-, 2-methyl-5-D-*arabo*-tetrahydroxybutyl-3-D-*erythro*-trihydroxypropyl-, and 2,5-bis(D-*arabo*-tetrahydroxybutyl)-pyrazine (from 2-amino-2-deoxy-D-glucose hydrochloride with aqueous ammonia at room temperature) (182); 2-methyl-5-(and 2)-methyl-6(or 3)-(D-*arabo*-tetrahydroxybutyl)pyrazine (from D-glucose with aqueous ammonia) (48); 2,5-bis(D-*lyxo*-tetrahydroxybutyl)pyrazine (tagatosazine) (from 2-amino-2-deoxy-D-galactose hydrochloride with methanolic sodium methoxide) (184); fructosazine (from fructose with methanolic ammonia) (277, 1071); and "deoxyfructosazine" (**17**) (from 2-amino-2-deoxy-D-glucose in hot acetic acid) (1072).



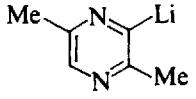
(17)

The reaction of an aqueous solution of sucrose with glycinamide at 140° has been reported to give a mixture which contains 2,5-bis(D-*arabo*-tetrahydroxybutyl)-pyrazine and 2-(D-*arabo*-tetrahydroxybutyl)-5-hydroxypyrazine (1073); and molasses inverted with 30% sulfuric acid and treated with ammonia under pressure produced a mixture containing 2-hydroxymethylpyrazine, 5-hydroxy-2-methyl-pyrazine, and 2-*arabo*-tetrahydroxybutyl-6-methylpyrazine (47).

B. From Halogenopyrazines

2-Amino-6-chloro-5-chloromethyl-3-cyanopyrazine with sodium acetate in dimethylformamide afforded 2-acetoxymethyl-5-amino-3-chloro-6-cyanopyrazine (874), and 2-amino-5-chloromethyl-3-cyanopyrazine with potassium acetate in 2-propanol gave 5-acetoxymethyl-2-amino-3-cyanopyrazine (542).

2-Iodopyrazines with ketones and butyllithium have been reported to produce 2-(1′-hydroxyalkyl)pyrazines (164), and 3-lithio-2,5-dimethylpyrazine (**18**) condensed with 2-formylpyridine to form 3-(*C*-hydroxy-*C*-pyridin-2′-ylmethyl)-2,5-dimethylpyrazine (**19**) (1016). 3-Iodo-2,5-dimethylpyrazine with butyllithium followed by 2-nitrobenzaldehyde gave 2,5-dimethyl-3-[*C*-hydroxy-*C*-(*o*-nitrophenyl)-methyl]pyrazine (1017).



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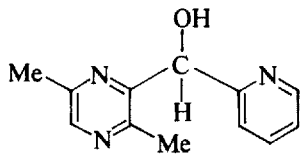
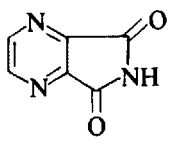


(19)

C. From Carboxylic Acid Derivatives

Hydroxymethylpyrazines may be prepared by reduction of carboxylic acid derivatives. Thus reduction of 2-amino-3-methoxycarbonylpyrazine with lithium aluminum hydride in tetrahydrofuran gave 2-amino-3-hydroxymethylpyrazine (1074, 1075); the imide from 2,3-dicarboxypyrazine (**20**) with sodium borohydride in tetrahydrofuran gave 2-carbamoyl-3-hydroxymethylpyrazine (**21**), and the methylcarbamoyl analogue was prepared similarly (1076).



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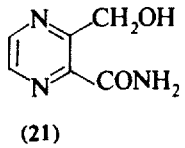


(21)

2-Methoxy-3-methoxycarbonyl-5-methylpyrazine with methylmagnesium iodide in ether gave 3-(α-hydroxyisopropyl)-2-methoxy-5-methylpyrazine (844).

D. From Alkylpyrazine *N*-Oxides with Acetic Anhydride Followed by Hydrolysis

The reactions of methylpyrazine *N*-oxides with acetic anhydride have been discussed in Section IV.3C(3) (113b, 625, 737–739, 760, 760a) with additional data (867). For example, 2-methylpyrazine 1-oxide rearranged when boiled with acetic anhydride to give 2-acetoxymethylpyrazine which was hydrolyzed by 10% aqueous sodium hydroxide to 2-hydroxymethylpyrazine (625, 738). Many of the acetoxymethylpyrazines so obtained were hydrolyzed to the hydroxymethyl analogues (113b, 760, 760a).

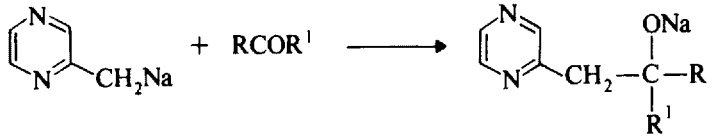
In addition to the above reactions the following have been reported. 3-Ethoxy-2-methylpyrazine 1-oxide with acetic acid and acetic anhydride at reflux gave 2-acetoxymethyl-3-ethoxypyrazine which was hydrolyzed by 10% sodium hydroxide at room temperature to 2-ethoxy-3-hydroxymethylpyrazine (978); 3-chloro-2-methylpyrazine 1-oxide similarly gave 2-chloro-3-hydroxymethylpyrazine (737). 2-Hydroxy-5-methyl-3-phenylpyrazine 1-oxide and 2-hydroxy-3-methyl-5-phenylpyrazine 1-oxide with acetic anhydride afforded 5-acetoxymethyl-2-hydroxy-3-phenyl- and 3-acetoxymethyl-2-hydroxy-5-phenylpyrazines, respectively (873), and 3-dimethylamino-2,5-dimethylpyrazines 1-oxide at reflux with acetic anhydride followed by hydrolysis with potassium hydroxide produced 3-dimethylamino-2-hydroxymethyl-5-methylpyrazine (793). 5-(1′-Acetoxy-2′-methylpropyl)-3-chloro-2-isobutylpyrazine (from 2-chloro-3,6-diisobutylpyrazine 1-oxide with acetic anhydride) refluxed with aqueous potassium carbonate in methanol gave 3-chloro-5-(1′-hydroxy-2′-methylpropyl)-2-isobutylpyrazine (113b).

E. From Alkylpyrazines with Aldehydes and Ketones

2-Methylpyrazine heated with paraformaldehyde at 165° for 4.5 hours formed 2-(2′-hydroxyethyl)pyrazine (38%) (470, 722), and with benzophenone and sodium amide gave 2-(2′-hydroxy-2′,2′-diphenylethyl)pyrazine (705). A series of substituted 2-(2′-hydroxyethyl)pyrazines (e.g., **23**) have been prepared from sodio-2-methylpyrazine (**22**) (from methylpyrazine and sodium in liquid ammonia) and aldehydes or ketones (706). Similarly 2-methyl-6-pyrazinylmethylsodium with aldehydes and ketones undergoes aldol-type condensations to give the corresponding secon-

dary and tertiary carbinols containing the pyrazine nucleus. 2-(3′-Dimethylaminopropyl)pyrazine condensed with three representative ketones using sodium amide in liquid ammonia to produce the corresponding tertiary carbinols, and methylpyrazine anion condensed with styrene oxide to give the corresponding secondary carbinol (which was oxidized to the ketone) (707).

Sodio-2-methylpyrazine with methyl picolinate afforded a mixture containing 2-(pyridin-2′-ylcarbonylmethyl)pyrazine (42.6%) (**24**) and 2-pyridinylbis(pyrazinylmethyl)carbinol (22.8%), and with ethyl formate gave only bis(pyrazinylmethyl)carbinol (642).



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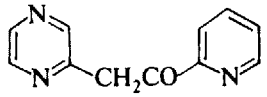
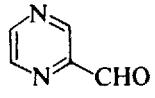


(24)

F. By Other Reactions

2-Formylpyrazine (**25**) undergoes the Cannizzaro reaction with 40% sodium hydroxide to yield 2-hydroxymethylpyrazine (**26**) and 2-carboxypyrazine (1077) and with sulfur dioxide in chloroform gave 2-(1′-hydroxy-1′-sulfomethyl)pyrazine (1077). The preparation of 2,5-di-(hydroxy-*t*-butyl)pyrazine from 3-amino-2-hydroxy-4,4-dimethyltetrahydrofuran has been described in Section II.9 (500).



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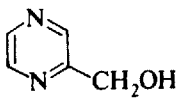
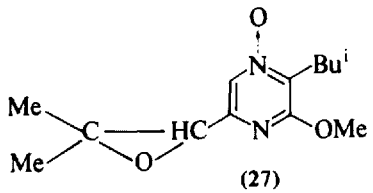


(26)

Deoxygenation of 3-(D-*arabo*-tetraacetoxybutyl)pyrazine 1-oxide with phosphoryl chloride gave 2-(D-*arabo*-tetraacetoxybutyl)-5-chloropyrazine (544) which with methanolic ammonia gave 2-(D-*arabo*-tetrahydroxybutyl)-5-chloropyrazine (544); and catalytic deoxygenation of 3-(D-*arabo*-tetrahydroxybutyl)pyrazine 1-oxide or 2-(D-*arabo*-tetrahydroxybutyl)pyrazine 1-oxide in methanol over Pd/C produced 2-(D-*arabo*-tetrahydroxylbutyl)pyrazine (544). 5-(1′,2′-Epoxy-2′-methylpropyl)-2-isobutyl-3-methoxypyrazine 1-oxide (**27**) was catalytically reduced over Raney nickel at 50° under high pressure to 5-(2′-hydroxy-2′-methylpropyl)-2-

isobutyl-3-methoxypyrazine (28) (113b) [but at room temperature also gave some 5-(1′,2′-epoxy-2′-methylpropyl)-2-isobutyl-3-methoxypyrazine (29) and 5-(2′-hydroxy-2′-methylpropyl)-2-isobutyl-3-methoxypyrazine 1-oxide (30) (113b)].



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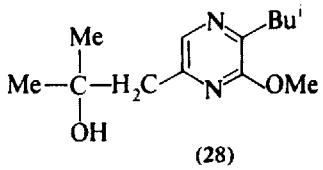

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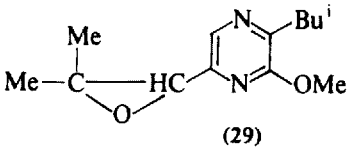

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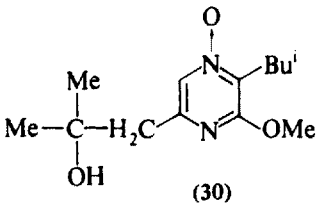

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3. PREPARATION OF ALKOXY- AND ARYLOXYPYRAZINES

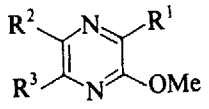
A. From Halogenopyrazines

The preparation of alkoxy- and aryloxypyrazines has been described in Sections V.5D and V.6A.

B. By Alkylation of Hydroxypyrazines

The preparation of alkoxypyrazines by alkylation of hydroxypyrazines with several reagents is discussed in detail in Section 6D. Many such alkylations give rise to both *N*- and *O*-alkyl derivatives.

Methoxypyrazines (31) have been prepared by diazomethane methylation of 2-hydroxy-3-isobutylpyrazine (60, 311, 367), 2-hydroxy-3-isopropylpyrazine (59, 367), 2-hydroxy-3-propyl(ethyl or hexyl)pyrazine (367), 3-hydroxy-2-isobutyl-5(and 6)methylpyrazine and 2-hydroxy-3-isobutyl-5,6-dimethylpyrazine (368), 2,3-dihydroxypyrazine (832), 2-hydroxy-5-methoxy- and 2,5-dihydroxy-3,6-diphenylpyrazine (832), 2-hydroxy-6-methoxy(and benzyloxy)pyrazine (832), 2,6-dihydroxy-3,5-diphenylpyrazine (873), 2,3,5-trifluoro-6-hydroxypyrazine (851), 2-chloro-6-hydroxy-3,5-diphenylpyrazine (873), 2-chloro-6-hydroxy-5-methyl-3-phenylpyrazine (873), 2-chloro-6-hydroxy-3-methyl-5-phenylpyrazine (873), 5,6-dichloro-1-cyclohexyl-3-hydroxy-2-oxo-1,2-dihydropyrazine (853), 2-chloro-5-hydroxy-3-methoxy-6-methoxycarbonylpyrazine (881), 2-(4′-amino-3′,5′-dibromophenylsulfonamido)-3-hydroxy-6-methoxypyrazine (881), 2-amino-3-hydroxy-



(31)

pyrazine (832), and pulcherriminic acid (2,5-dihydroxy-3,6-diisobutylpyrazine 1,4-dioxide) (99).

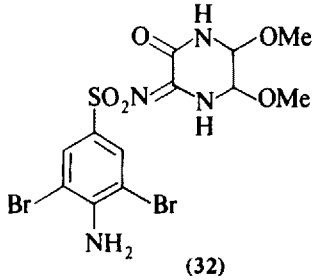
A series of methoxy compounds have been prepared from 2-hydroxy-3-(α-hydroxybenzyl)pyrazines and dimethyl sulfate (1045), and 2-benzyl-3,6-dihydroxypyrazine with diethyl sulfate and sodium ethoxide gave the 3,6-diethoxy derivative (1066).

C. From Aminopyrazines

Diazotization of 2-amino-3-alkoxycarbonylpyrazine followed by treatment with alcohols gave 2-alkoxy-3-alkoxycarbonylpyrazines (890); and 2-amino-5-chloro-3-methoxycarbonylpyrazine diazotized, and the product refluxed with methanol formed 5-chloro-2-methoxy-3-methoxycarbonylpyrazine (799, 892).

D. By Dehydrogenation

A number of alkoxypyrazines have been prepared from hydropyrazines. 5-(4′-Amino-3′,5′-dibromobenzenesulfonylimino)-6-hydroxy-2,3-dimethoxy-2,3,4,5-tetrahydropyrazine (32) refluxed with 2*N* sodium hydroxide gave 2-(4′-amino-3′,5′-dibromobenzenesulfonamido)-3-hydroxy-6-methoxypyrazine (881). Piperazine-2,5-dione (33) with an excess of triethyloxonium fluoroborate in dichloromethane gave 2,5-diethoxy-3,6-dihydropyrazine which was oxidized with dichlorodicyanobenzoquinone (DDQ) to 2,5-diethoxypyrazine; 2,5-diethoxy-3,6-dimethylpyrazine was prepared in a similar manner (314). Pyrolysis of *trans*-2,5-dibenzyl-3,6-diethoxy-2,5-dihydropyrazine at 250–270° gave 3-benzyl-2,5-diethoxypyrazine (90%) together with traces of 2,5-dibenzyl-3,6-diethoxypyrazine; pyrolysis of racemic 3,6-diethoxy-2,5-dimethyl-2,5-dihydropyrazine gave a low yield of 2,5-diethoxy-3-methylpyrazine (314).



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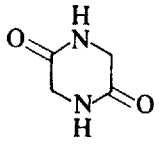
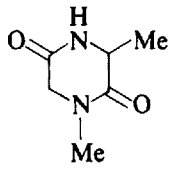
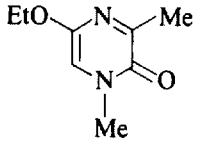


(33)

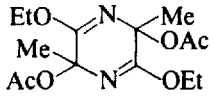
1,3-Dimethylpiperazine-2,5-dione (**34**) on treatment with triethyloxonium fluoroborate in dichloromethane gave 5-ethoxy-1,3-dimethyl-2-oxo-1,2,3,6-tetrahydropyrazine which was oxidized by DDQ in dry benzene to 5-ethoxy-1,3-dimethyl-2-oxo-1,2-dihydropyrazine (**35**) (1067). 1,3,6-Trimethylpiperazine-2,5-dione similarly treated gave three products, one of which was assigned the structure 5-methoxy-1,3,6-trimethyl-2-oxo-1,2-dihydropyrazine; 3-benzyl-5-methoxy-1,6-dimethyl-2-oxo-1,2-dihydropyrazine was also prepared similarly (1078). When 3,6-diethoxy-2,5-dimethyl-2,5-dihydropyrazine was refluxed with lead tetraacetate in dry benzene it gave a mixture of 2,5-diacetoxy-3,6-diethoxy-2,5-dimethyl-2,5-dihydropyrazine (**36**) (4 parts) and 2,5-diethoxy-3,6-dimethylpyrazine (1 part) (1068).



(**34**)



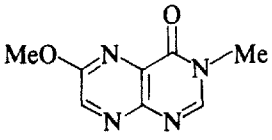
(**35**)



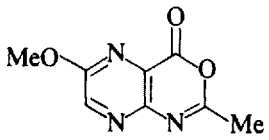
(**36**)

E. From Other Ring Systems

The cleavage of 6-methoxy-3-methyl-4-oxo-3,4-dihydropteridine (**37**) to 2-amino-3-carboxy-5-methoxypyrazine (432) [with further data (783)] and of 6-methoxy-2-methyl-4*H*-pyrazino[2,3-*d*][1,3]oxazin-4-one (**38**) to 2-acetamido-3-amidinocarbamoyl-5-methoxypyrazine (432) has been discussed in Section II.5.



(**37**)

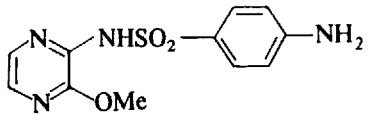


(**38**)

F. By Other Reactions

The methylsulfonyl substituent was readily displaced from pyrazine. Thus 2-methylsulfonylpyrazine (7) with methoxide ion at 87° for 3 hours gave 2-methoxypyrazine (1079), and 2-methylsulfinylpyrazine displayed similar reactivity, but 2-methylthiopyrazine was less reactive (1080).

2,5-Dicyano-3,6-dimethylpyrazine shaken with sodium ethoxide at room temperature for 10 hours produced 2-cyano-5-ethoxy-3,6-dimethylpyrazine (288). Bromination of 2-methoxy-3-sulfanilamidopyrazine (**39**) in methanol led to 5-(4′-amino-3′,5′-dibromobenzenesulfonimido)-6-hydroxy-2,3-dimethoxy-2,3,4,5-tetrahydropyrazine (**32**) which with 2 *N* sodium hydroxide gave 3-(4′-amino-3′,5′-dibromobenzenesulfonamido)-2-hydroxy-5-methoxypyrazine (**40**) (816). The preparation of 2-amino-3,5-dicyano-6-methoxy(and ethoxy)pyrazine from α-(*p*-toluenesulfonyloxyiminomalononitrile and malononitrile has been described in Section II.7 (484). 2-Methoxycarbonyl(and cyano)-5-pyridiniopyrazine chloride (**41**) is reported (conditions not stated) to give 2-carboxy(and carbamoyl)-5-methoxypyrazine (765).



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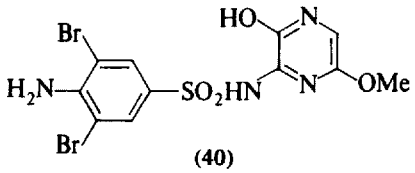

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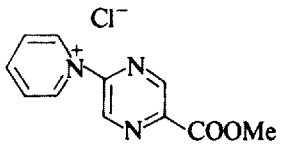
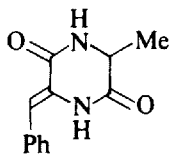


(41)

trans-2-Benzylidene-6-ethoxy-3-hydroxy-5-methyl-2,5-dihydropyrazine with 0.25 *N* methanolic potassium hydroxide at room temperature has been shown to give 2-benzyl-6-ethoxy-3-hydroxy-5-methylpyrazine (1066), *trans*-3-benzylidene-6-methylpiperazine-2,5-dione (**42**) with excess triethyloxonium fluoroborate gave 2-benzyl-3,6-diethoxy-5-methylpyrazine (1066), and *trans*-2-benzylidene-3-ethoxy-6-hydroxy-5-methyl-2,5-dihydropyrazine (**43**) with *N* sodium hydroxide at 100° formed 2-benzyl-3-ethoxy-6-hydroxy-5-methylpyrazine (1066).



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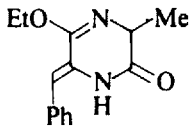
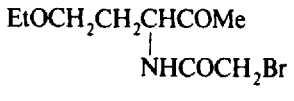


(43)

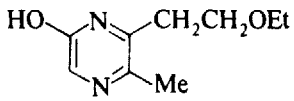
2,5-Diisobutyl-3-methoxypyrazine 1,4-dioxide with phosphorus trichloride in ethyl acetate at 40° gave 2,5-diisobutyl-3-methoxypyrazine (and 2,5-diisobutyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide similarly treated gave 3,6-diisobutyl-1-methoxy-2-oxo-1,2-dihydropyrazine) (see Section 15) (980).

4. PREPARATION OF EXTRANUCLEAR ALKOXYPYRAZINES

The preparation of extranuclear alkoxypyrazines from extranuclear halogeneopyrazines has been described in Section V.6A (654, 672, 679, 685, 687, 688, 694, 756, 872, 1027). 2-Amino-3-cyano-5-methoxymethylpyrazine 1-oxide with phosphorus trichloride in tetrahydrofuran afforded 2-amino-3-cyano-5-methoxymethylpyrazine (529); and 3-(bromoacetamido)-1-ethoxy-4-oxopentane (**44**) with alcoholic ammonia gave 5-hydroxy-3-(2′-ethoxyethyl)-2-methylpyrazine (**45**) (248).



(**44**)



(**45**)

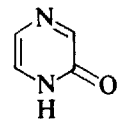
5. PROPERTIES AND STRUCTURE OF HYDROXY- AND ALKOXYPYRAZINES

Examination of the basic ionization constants (820) and ultraviolet spectra (821, 1081) of 2-hydroxypyrazine and its *N*- and *O*-methyl derivatives (Table VI.1) (820, 821, 1082) has revealed that the neutral species of 2-hydroxypyrazine exists in aqueous solution as the amide form (**46**) but, in the absence of a common cation, tautomeric ratios could not be determined (821, 1083). The infrared spectra of 2-hydroxypyrazine in the solid state and in chloroform solution led to a similar conclusion (1084, 1085). Infrared spectra (680) for 2-hydroxy-3-methylpyrazine and p.m.r. spectra (979, 1086) of 2-hydroxy- and 2-methoxypyrazines also indicate that the hydroxy compounds exist in the amide form, and are further supported by MO-calculated and experimental electronic spectra (1083).

TABLE VI.1 IONIZATION CONSTANTS AND ULTRAVIOLET SPECTRA OF 2-HYDROXYPYRAZINE AND ITS *N*- AND *O*-METHYL DERIVATIVES

Compound	Basic pK_a	U.v. Spectra[c] of Neutral Species (in H_2O)		
		λ_{max} (nm)	log ϵ	pH
2-Hydroxypyrazine	-0.1[a,b]	221, 316	3.96, 3.74	5.1
2-Methoxypyrazine	0.75[a]	< 210, 292	—, 3.71	5.1
1-Methyl-2-oxo-1,2-dihydropyrazine	-0.04[a]	223,319	3.94, 3.75	5.2

[a] Ref. 820.
[b] Ref. 1082 gives 8.23 for the acidic pK_a.
[c] Ref. 821.



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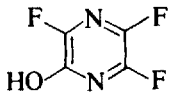
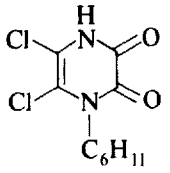


(47)

However, in 2,3,5-trifluoro-6-hydroxypyrazine (**47**), the infrared spectrum of the solid was reported to show no absorption attributable to the carbonyl group, and its ultraviolet spectrum (in ethanol) was similar to that of 2,3,5-trifluoro-6-methoxypyrazine, thus indicating that it was a true hydroxy compound (851). A similar phenomenon has been observed in the pyridine (1087–1089) and pyrimidine (1090) series, but differs from observations in the pyridazine series (1091).

In 2,3-dihydroxypyrazine and derivatives Honzl (853), from measurements of infrared spectra in chloroform and ultraviolet spectra in aqueous alcohol, has proposed that 5,6-dichloro-l-cyclohexyl-3-hydroxy-2-oxo-1,2-dihydropyrazine (pK_a in water 4.66, 5.66) exists in the form (**48**). The p.m.r. spectra of some 5- and 6-methyl- and 5- and 6-phenyl-2,3-dihydroxypyrazines have been reported (483). In the 2,5-dihydroxypyrazine series, the infrared spectrum (Nujol) of 2-benzyl-3,6-dihydroxy-5-methylpyrazine has been interpreted as indicating that the major tautomeric form present in the solid state was the dihydroxy form (**49**), but the ultraviolet spectrum in ethanol was considered consistent with the coexistence of the dihydroxy (**49**) and oxo–hydroxy form, for example, (**50**). Although the structure (**51**) has been proposed for 3-butyl-2,5-dihydroxypyrazine (1092), the evidence in favor of this structure is inconclusive.



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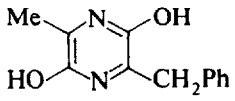

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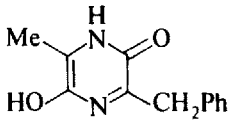

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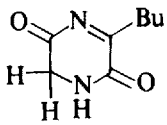
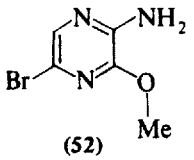


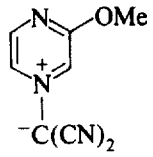
(51)

Crystal structures of 3,5,6-tri-*t*-butyl-2-hydroxypyrazine (1093); 2,5-dichloro-3-methoxypyrazine (915); and 2,3-dichloro-5-ethylamino-6-methoxypyrazine (916) have been determined. The dipole moment of 2-amino-5-bromo-3-methoxypyrazine (2.94*D*; in benzene) is consistent with the *S-cis* configuration (**52**) (749); and the polarographic behavior of 3-hydroxy(and methoxy)-2,5-dimethylpyrazine (and their *N*-oxides) at various pH values has been investigated (588).



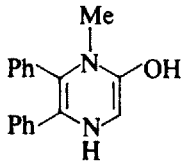
(52)

Methylation (666, 912) of 2-methoxypyrazine with methyl iodide in dimethyl sulfoxide at room temperature gave 3-methoxy-1-methylpyrazinium iodide with a rate of methylation relative to pyrazine of 1.05 (666). 2-Methoxypyrazine with tetracyanoethylene oxide gave a small yield of 3-methoxypyrazinium dicyanomethylide (**53**) (1094). Alkylation of 2-methoxypyrazine with ethyl methyl ketone in the presence of sodium in liquid ammonia to give 2-*s*-butyl-6-methoxypyrazine (17%) has been described (614). The reactions of 3-hydroxy-2,5-dimethylpyrazine and alkylhalides have been examined (1095).



(53)

Pyrolyses and thermal stabilities of 2-hydroxy-, 2-ethoxy-, and 2-isopropoxypyrazines have been studied. 2-Hydroxypyrazine was very stable, but the alkoxypyrazines underwent thermal elimination of olefin to yield 2-hydroxypyrazine (668a). Electrochemical reductions of 1-methyl-2-oxo-5,6-diphenyl-1,2-dihydropyrazine and 5-hydroxy(and 5-methoxy)-2,3-diphenylpyrazine are reported to involve the intermediate enamine, for example, 6-hydroxy-1-methyl-2,3-diphenyl-1,4-dihydropyrazine (**54**) (1096, cf. 1097). When tested on mice 2-carbamoyl-5-methoxypyrazine had less antitubercular activity than did pyrazinamide (1098).



(54)

A large number of 2-alkyl-3-methoxypyrazines has been isolated from raw vegetables (59, 60, 64, 65, 69, 80, 1099), bell peppers (60, 61) and gambanum oil (49). 2-Isobutyl-3-methoxypyrazine is already finding commercial use as a flavoring material (368) and 2-ethoxy-3-methylpyrazine may be used for pineapple flavor (981). The odor characteristics (367, 368, 976, 977) and structure (977) of some alkoxy alkylpyrazines have been examined. 3-Guanidino-6-hydroxymethyl-1-methyl-2-oxo-1,2-dihydropyrazine has been isolated from seeds of *Stizolobium hassjoo* and on mild alkaline hydrolysis gave 3-hydroxy-6-hydroxymethyl-1-methyl-2-oxo-1,2-dihydropyrazine (1060).

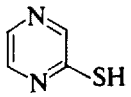
6. REACTIONS OF HYDROXYPYRAZINES

A. Conversion to Halogenopyrazines

Conversions of hydroxypyrazines to halogenopyrazines by phosphoryl chloride, phenylphosphonic dichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride, phosphorus bromides, and other reagents have been discussed in Sections V.1C–V.1F.

B. Conversion to Mercaptopyrazines

2-Hydroxypyrazine with phosphorus pentasulfide in refluxing pyridine for 45 minutes was readily converted to 2-mercaptopyrazine (46%) (**55**) (its 1-methyl analogue was prepared similarly) (821, 1100) and 5-mercapto-2,3-diphenylpyrazine was prepared likewise (834, 1008). 2-Amino-3-mercaptopyrazine was prepared from 2-amino-3-hydroxypyrazine and phosphorus pentasulfide in refluxing β-picoline (1101).



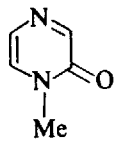
(55)

C. Bromination of Hydroxypyrazines

Brominations of hydroxypyrazines have been described in Section V.1B(4).

D. Alkylation of Hydroxypyrazines

Alkylation of hydroxypyrazines may lead to *O* or *N*-alkylation or, more frequently, a mixture containing both. Diazomethane methylation of 2-hydroxypyrazine has been reported to give 1-methyl-2-oxo-1,2-dihydropyrazine (**56**) (86), also obtained by methylation with dimethyl sulfate and potassium carbonate in acetone (821) and with dimethyl sulfate and methanolic sodium methoxide (1102). Diazomethane methylation of 2-hydroxy-3-isobutylpyrazine, however, has been reported to give 2-methoxy-3-isobutylpyrazine (**57**) (31%) and 3-isobutyl-1-methyl-2-oxo-1,2-dihydropyrazine (58%), and similar methylation of the propyl, isopropyl, ethyl, or hexyl analogues gave the corresponding products in approximately the same ratios as found for the isobutyl homologue (367). Analogous diazomethane methylations of 3-hydroxy-2-isobutyl-5(and 6)-methylpyrazine and 2-hydroxy-3-isobutyl-5,6-dimethylpyrazine to give *N*- and *O*-methyl derivatives have been described (368).



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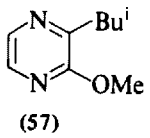
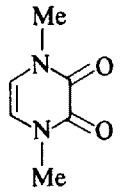


(57)

2,3-Dihydroxypyrazine (which was converted into its *N,N*-dimethyl derivative by treatment with dimethyl sulfate and alkali) gave, on reaction with an excess of ethereal diazomethane a mixture of its *N,N*-, *O,N*-, and *O,O*-dimethyl derivatives **(58–60)** (832). 2-Hydroxy-5-methoxy- and 2,5-dihydroxy-3,6-diphenylpyrazine with ethereal diazomethane gave predominantly 2,5-dimethoxy-3,6-diphenylpyrazine and only minor amounts of *N*-methylated products (832). Methylation of 2-hydroxy-6-methoxypyrazine with ethereal diazomethane produced a mixture of *O*- and *N*-methyl derivatives in which the *O*-methyl derivative predominated but the corresponding reaction of 2-benzyloxy-6-hydroxypyrazine gave almost exclusively the *O*-methyl derivative (832) [the results of these methylations were correlated with the carbonyl stretching frequency (1103) in the parent lactam (832)].



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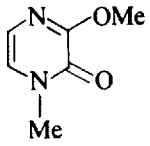

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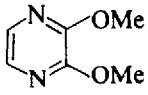
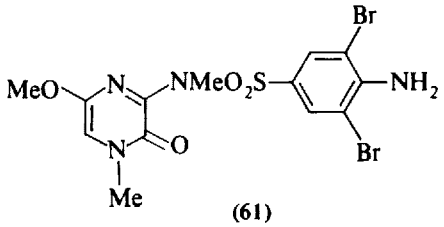


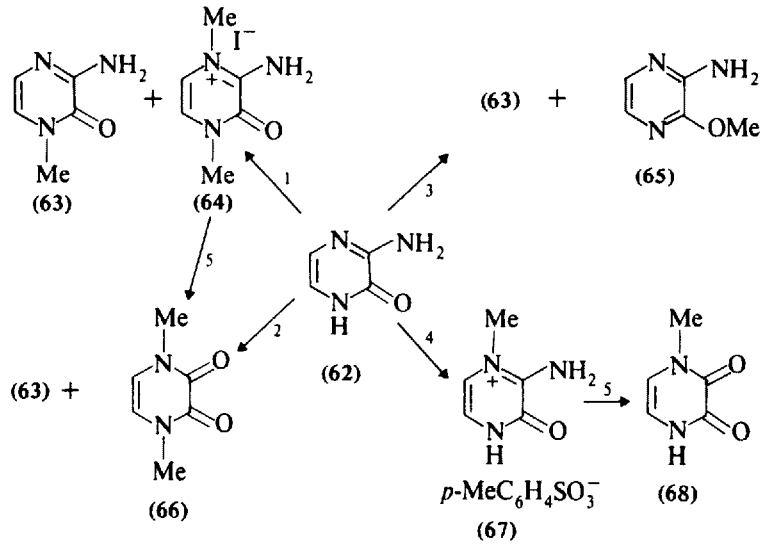
(60)

Other methylations with diazomethane are as follows: 2,6-dihydroxy-3,5-diphenylpyrazine formed a mixture of products from which only 2,6-dimethoxy-3,5-diphenylpyrazine was isolated (873); 2,3,5-trifluoro-6-hydroxypyrazine gave 2,3,5-trifluoro-6-methoxypyrazine (60%) (851); 2-chloro-6-hydroxy-3,5-diphenylpyrazine, 2-chloro-6-hydroxy-5-methyl-3-phenylpyrazine, and 2-chloro-6-hydroxy-3-methyl-5-phenylpyrazine gave both *O*- and *N*-1-methyl pyrazines (873); 5,6-dichloro-1-cyclohexyl-3-hydroxy-2-oxo-1,2-dihydropyrazine gave 5,6-dichloro-1-cyclohexyl-3-methoxy-2-oxo-1,2-dihydropyrazine (853); 2-chloro-5-hydroxy-3-methoxy-6-methoxycarbonylpyrazine gave 2-chloro-3,5-dimethoxy-6-methoxycarbonylpyrazine (881); 2-(4′-amino-3′,5′-dibromophenylsulfonamido)-3-hydroxy-6-methoxypyrazine with diazomethane in dichloromethane gave a mixture containing 2-(4′-amino-3′,5′-dibromobenzenesulfonamido)-3,6-dimethoxypyrazine (and its extranuclear *N*-methyl derivative) and 3-[*N*-(4′-amino-3′,5′-dibromobenzenesulfonyl)-*N*-methylamino]-5-methoxy-1-methyl-2-oxo-1,2-dihydropyrazine **(61)** (881) and 2-hydroxy-6-methylamino-3,5-bis-*N*-methylcarbamoylpyrazine in methanol with ethereal diazomethane gave 2-methoxy-6-methylamino-3,5-bis-*N*-methylcarbamoylpyrazine (440).



(61)

Methylation of 2-amino-3-hydroxypyrazine (**62**) with methyl iodide and sodium methoxide afforded 3-amino-1-methyl-2-oxo-1,2-dihydropyrazine (**63**), and when an excess of methyl iodide was used, a mixture of compound (**63**) and its methiodide (**64**) was isolated. Reaction with dimethyl sulfate and alkali gave compound (**63**) and 1,4-dimethyl-2,3-dioxo-1,2,3,4-tetrahydropyrazine (**66**); the latter was presumed to be formed by hydrolysis of an intermediate quaternary salt since it was also obtained by treatment of the methiodide (**64**) with aqueous sodium hydroxide. Reaction of 2-amino-3-hydroxypyrazine with ethereal diazomethane produced a mixture of *N*- and *O*-methyl derivatives, (**63**) and 2-amino-3-methoxypyrazine (**65**). With methyl toluene-*p*-sulfonate the quaternary salt 2-amino-3-hydroxy-1-methylpyrazinium toluenesulfonate (**67**) was obtained; on alkaline hydrolysis it gave 3-hydroxy-1-methyl-2-oxo-1,2-dihydropyrazine (**68**) (832). Pulcherriminic acid with diazomethane gave a dimethyl derivative (99).



Reagents: 1, MeI–MeONa; 2, Me_2SO_4–NaOH; 3, CH_2N_2; 4, *p*-$MeC_6H_4SO_3Me$; 5, NaOH.

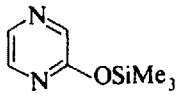
3-Hydroxy-2,5-diphenylpyrazine, methyl iodide, and methanol and some potassium hydroxide heated in a sealed tube at 100° for 10 hours formed the methiodide of 1-methyl-3,6-diphenyl-2-oxo-1,2-dihydropyrazine (1104) [3-hydroxy-

2,5-dimethylpyrazine reacted similarly (1104), and this in aqueous solution reacted with potassium hydroxide to give a product claimed to be 1,4,5-trimethyl-2-methylene-3-oxo-1,2,3,4-tetrahydropyrazine (1105)].

Methylation of 2-hydroxy-3-*N*-phenylcarbamoylpyrazine with dimethyl sulfate and potassium carbonate in boiling acetone gave 1-methyl-2-oxo-3-*N*-phenylcarbamoyl-1,2-dihydropyrazine; and the 3-(*N*-methyl-*N*-phenylcarbamoyl) analogue was prepared likewise (1055). Similar methylation of 2-hydroxy-3-(*o*-methylaminophenyl)pyrazine produced 1-methyl-3-(*o*-methylaminophenyl)-2-oxo-1,2-dihydropyrazine (1055). A series of 2-hydroxy-3-(α-hydroxybenzyl)pyrazines has been methylated with dimethyl sulfate in aqueous sodium hydroxide to the 2-methoxy analogues (1045); and 2-benzyl-3,6-dihydroxy-5-methylpyrazine with diethyl sulfate and sodium ethoxide formed 2-benzyl-3,6-diethoxy-6-methylpyrazine (1066).

The direct glucosidation (with tetra-*O*-acetyl-α-D-glucopyranosyl bromide) of 2-hydroxypyrazine by the silver or mercury salt method gave mostly 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyrazine (1008, 1106, 1107) and attempts to rearrange the *O*-glucoside to the *N*-glucoside were unsuccessful. Other glycosidations of unsubstituted 2-hydroxy- and 2-mercaptopyrazines and with substituents at position 6 involving reaction at *O*, *N*, and *S* have been described (1008, 1108, 1109).

Ribosidation of the trimethylsilyl derivative of 2-hydroxypyrazine (**69**) (prepared with trimethylsilyl chloride and bistrimethylsilylamine) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and titanium tetrachloride in 1,2-dichloroethane, followed by deacetylation with sodium methoxide, gave 2-oxo-1-(β-D-ribofuranosyl)-1,2-dihydropyrazine; and its 4-oxide was prepared similarly (1035). A similar reaction occurred with the trimethylsilyl derivative of 3-hydroxypyrazine 1-oxide and 1,2,3-tri-*O*-acetyl-D-erythrose (1110).



(**69**)

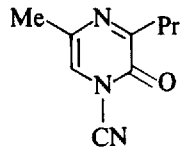
2,3-Dihydroxypyrazine with hexamethyldisilazane in the presence of ammonium sulfate produced 2,3-bis(trimethylsilyloxy)pyrazine (1111), and 2-amino-3-hydroxypyrazine behaved similarly (1111). 2,3-Bis(trimethylsilyloxy)pyrazine with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide and silver perchlorate in benzene gave 1,4-bis(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3-dioxo-1,2,3,4-tetrahydropyrazine, and other similar reactions have also been described (1111).

The sodium salt of 2-hydroxypyrazine with thiophosphoryl chloride at room temperature gave 2-(dichlorophosphinothioyloxy)pyrazine (1112, 1113) and in *N*-methyl-2-pyrrolidone with *O*,*O*-diethyl phosphorochloridothioate [$(EtO)_2P(=S)Cl$] it gave 2-(diethoxyphosphinothioyloxy)pyrazine (1114, 1115), also prepared in the absence of *N*-methyl-2-pyrrolidone (1116). The potassium salt of 2-hydroxypyrazine in *t*-butanol–dioxane with *O*,*O*-diphenyl phosphorochloridothioate

afforded 2-(diphenoxyphosphinothioyloxy)pyrazine and none of the *N*-substituted isomer (1117) and 5-(dimethoxyphosphinothioyloxy)-2,3-dimethylpyrazine was prepared similarly (1118). The sodium salt of 2-hydroxypyrazine also with *O,O*-diethyl phosphorochloridothioate in the presence of benzyltriethylammonium chloride and triethylamine (and other reagents) gave 2-[diethoxyphosphinothioyloxy]pyrazine (1119), and a number of analogous compounds have been prepared in a similar manner (1120, 1121).

Karmas and Spoerri (817) found that whereas 2-hydroxypyrazines couple with diazonium compounds at the 5(para)-position in neutral or mildly alkaline solution (1122), addition of phenyldiazonium chloride to hydroxypyrazines in molar aqueous sodium hydroxide resulted in a Gomberg type of phenylation of the nucleus with evolution of nitrogen. In this reaction substitution occurred preferentially at a free 3-position but may also occur at positions 5 and 6 if these also originally bore hydrogen (817). For example, 2-hydroxypyrazine in 5% aqueous sodium hydroxide with benzenediazonium chloride produced 2-hydroxy-3-phenylpyrazine (47%) and 3-hydroxy-2,5-diphenylpyrazine (4%) (817).

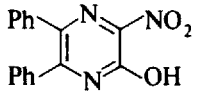
2-Hydroxy-5-methyl-3-propylpyrazine with cyanogen halides in aqueous dimethylformamide with sodium hydroxide gave 1-cyano-5-methyl-2-oxo-3-propyl-1,2-dihydropyrazine (**70**) (1123).



(70)

E. Nitration and Coupling With Diazonium Salts

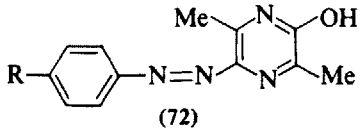
A notable characteristic of the pyrazine nucleus is its resistance to electrophilic substitution but some hydroxypyrazines may be nitrated. Nitration of 5-hydroxy-2,3-diphenylpyrazine with fuming nitric acid in acetic acid gave the readily purified 2-hydroxy-3-nitro-5,6-diphenylpyrazine (**71**) (1065) [which reacts readily with hydrazine to give 2-hydrazino-3-hydroxy-5,6-diphenylpyrazine (1124)]. 3-Hydroxy-2,5-diphenylpyrazine undergoes random nitration under a variety of strongly acidic conditions (1065) but brief boiling of an acetic acid solution of equivalent amounts of 3-hydroxy-2,5-diphenylpyrazine and nitric acid produced 2-hydroxy-5-nitro-3,6-diphenylpyrazine (75%) (817).



(71)

2-Hydroxy-3-phenylpyrazine nitrate (prepared from 2-hydroxy-3-phenylpyrazine and one equivalent of nitric acid in acetic acid) boiled in acetic acid gave 2-hydroxy-5-nitro-3-phenylpyrazine. It was postulated that, in hot acetic acid, dissociation of the nitrate was a relatively slow and temperature-dependent process which was followed by very rapid nitration of the nucleus (817).

Hydroxypyrazines (like phenals) couple with diazonium salts in neutral or weakly alkaline solution but in *N*-sodium hydroxide arylation of the nucleus occurs (Section 6D). 3-Hydroxy-2,5-dimethylpyrazine with benzenediazonium or *o*- or *p*-tolyldiazonium salts gave the corresponding azo compounds (72) (1105, 1125), and this has been attributed to a tendency to assume the lactim form (1122, 1125), but 1,3,6-trimethyl-2-oxo-1,2-dihydropyrazine did not couple with diazonium salts (1122). Carboxyhydroxypyrazines which contained a carboxy group in the position para to the hydroxyl group coupled with elimination of the carboxy group: for example, 2-carboxy-5-hydroxy-3,6-dimethylpyrazine coupled readily with diazonium salts and the resulting azo compound was identical with that from 3-hydroxy-2,5-dimethylpyrazine (1122). Other coupling reactions of hydroxypyrazines, which have been studied, include the reaction of 5-hydroxy-2,3-dimethylpyrazine with benzenediazonium chloride to give 2-hydroxy-5,6-dimethyl-3-phenylazopyrazine (817), 5-hydroxy-2,3-diphenylpyrazine to give a small amount of 2-hydroxy-3-phenylazo-5,6-diphenylpyrazine (1065), deoxyaspergillic acid (5-*s*-butyl-3-hydroxy-2-isobutylpyrazine) and 2,5-di-*s*-butyl-3-hydroxypyrazine to give phenylazodeoxyaspergillic acid and 2,5-di-*s*-butyl-3-hydroxy-6-phenylazopyrazine, respectively (90), and 2-*s*-butyl-3-hydroxy-5-isobutylpyrazine to give the 6-phenylazo derivative (93); 3-ethyl(propyl or isopropyl)-2-hydroxy-5-methylpyrazines coupled with *o*-tolyldiazonium chloride (362); and a series of azo coupled pyrazine dyes was prepared from 2-hydroxy-6-methylpyrazine with diazotized aromatic amines (434) and their reduction with stannous chloride gave 2-amino-5-hydroxy-3-methylpyrazine (434).



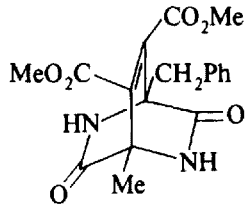
(72)

F. Other Reactions of Hydroxypyrazines

2,3-Dihydroxy-5,6-diphenylpyrazine refluxed with aqueous hydrazine hydrate gave 2-hydrazino-3-hydroxy-5,6-diphenylpyrazine, which was also obtained by heating 2-hydroxy-3-nitro-5,6-diphenylpyrazine with aqueous hydrazine (1124). Distillation of the compound claimed by Japp and Knox (317) to be 3-hydroxy-2,5-diphenylpyrazine (317, cf. 282) with zinc dust produced 2,5-diphenylpyrazine (317); reduction of the former with hydriodic acid and red phosphorus at 200° for 6 hours gave what was regarded as 2,5-diphenyl-3,4-dihydropyrazine (317).

5-Hydroxy-2,3-diphenylpyrazine (and its *N*-4-methyl derivative) are electrochemically reduced to the 5,6-dihydro derivatives which isomerize to the 3,6-

dihydro derivatives, and these on electrochemical reduction gave 1,2,3,6-tetrahydro derivatives (1097, cf. 1096). Reaction of 2-hydroxypyrazine with pyridine 1-oxide and platinized palladium–charcoal catalyst at 145–155° formed a minute amount of 2-hydroxy-3-(pyridin-2′-yl)pyrazine (630). 2,5-Dihydroxypyrazines and related systems undergo Diels–Alder reactions with dienophiles (1067, 1126). For example, 2-benzyl-3,6-dihydroxy-5-methylpyrazine with dimethyl acetylenedicarboxylate in dimethylformamide at room temperature gave the bicyclic adduct (**73**). 2,5-Dibenzyl-3,6-dihydroxypyrazine when irradiated with visible light in an oxygenated solution of dichloromethane with fluorescein on a polymer support as sensitizer gave the corresponding peroxide (**74**) (1127, 1128). 2,5-Dibenzyl-3,6-dihydroxypyrazine was also oxidized with sulfur in dimethylformamide containing triethylamine to 2,5-dibenzylidenepiperazine-3,6-dione (**75**) (1068).



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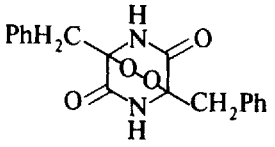

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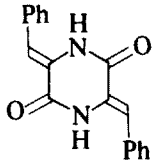


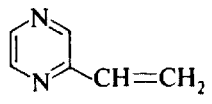
(75)

Oxidations of hydroxypyrazines to their *N*-oxides are described in Section 10B.

2-Benzoyloxypyrazine and 2-benzoyloxy-6-bromopyrazine were each prepared from the hydroxypyrazine with benzoyl chloride in anhydrous pyridine (865) but it has been reported that 3-hydroxy-2,5-diphenylpyrazine could not be acetylated (317), and 2-hydroxy-6-methylpyrazine could not be acetylated or benzoylated in pyridine solution (434).

7. REACTIONS OF EXTRANUCLEAR HYDROXYPYRAZINES

2-(2′-Hydroxyethyl)pyrazine on pyrolysis gave 2-vinylpyrazine (**76**) (656), which was also prepared over molten potassium hydroxide (470). Iodine-effected dehydrations of substituted 2-(2′-hydroxyethyl)pyrazines by distillation with benzene or toluene have been described (657). Heating of 2-(2′-hydroxypropyl) pyrazine with potassium hydrogen sulfate gave 2-allylpyrazine (618) and 5-(1′-hydroxy-2′-methylpropyl)-2-isobutyl-3-methoxypyrazine similarly treated gave 2-isobutyl-3-methoxy-5-(2′-methylprop-1′-enyl)pyrazine (113b). 2,5-Diethoxy-3-(1′-hydroxy-1′-methylethyl)pyrazine could be dehydrated using toluene-*p*-sulfonic acid and molecular sieves in benzene to give 2,5-diethoxy-3-isopropenylpyrazine (**77**) (314a).



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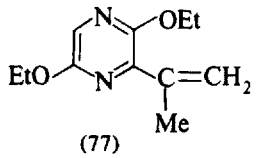

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2-(2′-Hydroxy-2′,2′-diphenylethyl)pyrazine was reductively cleaved with ethanolic potassium hydroxide to give 2-methylpyrazine and benzhydrol (Ph_2CHOH), whereas its reaction with potassium hydroxide in *t*-butyl alcohol gave methylpyrazine and benzophenone (706); and 2-(2′-hydroxy-2′-methyl-2′-phenylethyl)pyrazine, on reaction with ethanolic potassium hydroxide, was converted to a mixture of methylpyrazine, acetophenone, methylphenylcarbinol, and 1,5-diphenyl-3-methylpentane-1,5-dione (706). Polarographic reduction of 5-(D-*arabo*-tetrahydroxybutyl)-2-methylpyrazine and 2,5-bis(D-*arabo*-tetrahydroxybutyl)pyrazine has been examined (125).

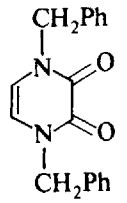
Extranuclear acetoxyalkylpyrazines have been prepared from hydroxyalkylpyrazines by acetylation with acetic anhydride and dry pyridine as follows: 2-methyl-6-(D-*arabo*-tetraacetoxybutyl)pyrazine (182), 2,5-bis(D-*arabo*-tetraacetoxybutyl)-pyrazine (182), and 2-acetoxymethyl-3-aminopyrazine (1075); and 2-methyl-5-(D-*arabo*-tetrabenzoyloxybutyl)-3-(D-*erythro*-tribenzoyloxypropyl)pyrazine from 2-methyl-5-(D-*arabo*-tetrahydroxybutyl)-3-(D-*erythro*-trihydroxypropyl)pyrazine with benzoyl chloride and dry pyridine (182).

Hydroxyalkylpyrazines may be oxidized with potassium permanganate in acid, water, or alkali, or with hydrogen peroxide in alkaline solution, to the carboxypyrazine. Some examples are as follows: 2,5-bis(D-*arabo*-tetrahydroxybutyl)pyrazine (fructosazine) with potassium permanganate in 5 *N* sulfuric acid (182) or aqueous potassium hydroxide (183), and 2-methyl-5-(D-*arabo*-tetrahydroxybutyl)pyrazine with aqueous potassium permanganate at reflux (48) (a similar reaction was observed with the 2,6-isomer) (48) and each gave 2,5-dicarboxypyrazine; 2-(D-*arabo*-tetrahydroxybutyl)pyrazine with aqueous potassium permanganate at 90° produced 2-carboxypyrazine (544); 2-hydroxymethyl-5-methylpyrazine with aqueous potassium permanganate at room temperature gave 2-carboxy-5-methylpyrazine (673); and 2,5-bis(D-*arabo*-tetrahydroxybutyl)pyrazine (fructosazine) (1071) and deoxyfructosazine (1072) with hydrogen peroxide in sodium hydroxide were converted to 2,5-dicarboxypyrazine.

8. REACTIONS OF ALKOXYPYRAZINES

The cleavage of pyrazine ethers with acid, alkali, methylmagnesium halides, and catalytic hydrogenation has been described in Section 1D; and chloro and bromo substituents have been introduced into various alkoxypyrazines as described in Sections V.1A(3) (155), V.1B(3) (814), V.1E (844), and V.2A (898).

Whereas 2,3-dichloropyrazine reacted with an excess of sodium benzyl oxide in boiling benzene to give the expected 2,3-dibenzyloxypyrazine, the reaction in boiling xylene gave 1,4-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydropyrazine (78), presumably as a result of thermal rearrangement of the first-formed di-*O*-benzyl ether (883). The cleavage of 5-methoxy-2,3-diphenylpyrazine with methylmagnesium bromide at 150° to 5-hydroxy-2,3-diphenylpyrazine and similar reactions has been described in Section 1D. Apparent rearrangement of 2,5-dimethoxy-3,6-



(78)

diphenylpyrazine has been observed on heating with methyl iodide at 150° for many hours to give the isomeric *O,N*-dimethylpyrazine (832).

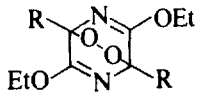
Electrochemical reduction of 5-methoxy-2,3-diphenylpyrazine produced a 1,6-dihydro derivative which isomerized to the electrochemically reducible 3,6-dihydro derivative (1097).

5-Ethoxy-1,3-dimethyl-2-oxo-1,2-dihydropyrazine has been shown to undergo ready cycloaddition reactions even with nonactivated double bonds (1067), and also rapidly reacts with oxygen on exposure to air.

Irradiation with visible light, of an oxygenated solution of 2,5-dibenzyl-3,6-diethoxypyrazine in dichloromethane with methylene blue as sensitizer, afforded a quantitative yield of the stable peroxide (**79**, R = Bz). A slow oxidation of the pyrazine also occurred in the absence of the methylene blue, producing low yields of the peroxide (1127, 1128). 2,5-Diethoxy-3,6-dimethylpyrazine reacted similarly to give (**79**, R = Me). 2,5-Diethoxy-3-(1′-hydroxy-1′-methylpropyl)-6-(2′-methyl-prop-2′-enyl)pyrazine reacted similarly without affecting the isolated double bond (314a). Reduction with triphenylphosphine resulted in abstraction of one oxygen atom to produce an oxide formulated as (**80**). Treatment of (**79**, R = Me) with sodium borohydride produced the diol (**81**) (1127, 1128), and (**79**, R = Me) on hydrolysis with strong acid gave 2,5-diethoxy-3,6-dimethylpyrazine (1128).

3-Methoxy-1-methylpyrazinium ions reacted with liquid ammonia at low temperature to give 2-amino-3-methoxy-1-methyl-1,2-dihydropyrazine (**82**) (609).

3-(2′-Ethoxyethyl)-5-hydroxy-2-methylpyrazine heated in acetic acid saturated with hydrogen bromide formed a crystalline bromine-containing compound which with 5% sodium carbonate gave 5-hydroxy-2-methyl-3-vinylpyrazine (248). Heteromacrocyclic ethers have been quaternized (989).



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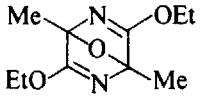

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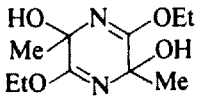

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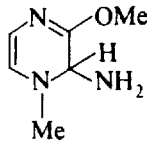

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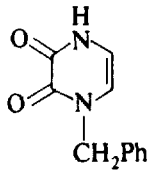
9. *N*-ALKYLATED OXODIHYDROPYRAZINES

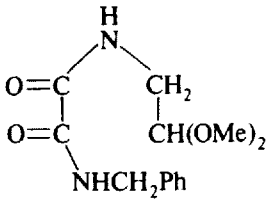
A. Preparation

(1) *By Primary Synthesis*

Preparations of some *N*-substituted 2-oxo-1,2-dihydropyrazines have been discussed in Section II.2 from the reactions of di-, tri-, and tetrapeptides with glyoxal (380–382); and Cheeseman and co-workers (1111) have described the preparation of 1-benzyl-3-hydroxy-2-oxo-1,2-dihydropyrazine (**83**) (and similarly its 1-methyl analogue) from ethyl *N*-(2′,2′-dimethoxyethyl)oxamate and benzylamine through *N*-benzyl-*N*′-(2′,2′-dimethoxyethyl)oxamide (**84**) by the application of a standard procedure (482).



(**83**)



(**84**)

(2) *By Alkylation of Hydroxypyrazines*

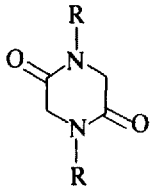
Alkylation of hydroxypyrazines to give *N*- or *O*-alkyl derivatives (and mixtures of both formed particularly from methylations with diazomethane) have been described in Section 6D.

(3) *By Rearrangement of Alkoxypyrazines*

Rearrangements of alkoxypyrazines to 1-alkyl-2-oxo-1,2-dihydropyrazines have been described in Section 8 (832, 883).

(4) *By Oxidation of* N-*Alkyl(or Aryl)piperazinones With Phosphorus Pentachloride*

Honzl (853) has described the preparation of alkyl(or aryl)-2-oxo-1,2-dihydropyrazines by reaction of *N,N*′-dialkyl(or aryl)piperazine-2,5-diones with phosphorus pentachloride. For example, 1,4-dicyclohexyl(or diethyl)piperazine-2,5-dione (**85**, R = cyclohexyl, Et) with phosphorus pentachloride in 1,2-dichloroethane gave



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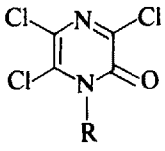


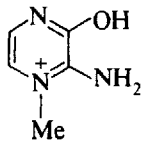
(86)

3,5,6-trichloro-1-cyclohexyl(or ethyl)-2-oxo-1,2-dihydropyrazine (**86**, R = cyclohexyl, Et); (1-cyclohexyl-4-phenylpiperazine-2,5-dione formed 3,5,6-trichloro-1-phenyl-2-oxo-1,2-dihydropyrazine) which with aqueous sodium hydroxide in dioxane (or sodium methoxide at reflux) gave 5,6-dichloro-1-cyclohexyl-3-hydroxy-(or methoxy)-2-oxo-1,2-dihydropyrazine (853). Other analogous reactions were also described (853).

(5) *By Other Means*

Hydrolysis of 2-amino-3-hydroxy-1-methylpyrazinium toluenesulfonate (**87**) with aqueous sodium hydroxide at 95° afforded 3-hydroxy-1-methyl-2-oxo-1,2-dihydropyrazine which was also prepared in poor yield from the action of nitrous acid on 3-amino-1-methyl-2-oxo-1,2-dihydropyrazine (832); and hydrolysis of 6-chloro-1-methyl-2-oxo-3,5-diphenyl-1,2-dihydropyrazine with boiling methanolic sodium methoxide (followed by acidification) gave 6-hydroxy-1-methyl-2-oxo-3,5-diphenyl-1,2-dihydropyrazine (873). 1,3,6-Trimethyl-2-oxo-1,2-dihydropyrazine methiodide has been converted through 1,4,6-trimethyl-3-methylene-2-oxo-1,2,3,4-tetrahydropyrazine and 3-benzoylmethylene-1,4,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrazine (in water) to 1,4,6-trimethyl-2,3-dioxo-1,2,3,4-tetrahydropyrazine (1129).

The preparation of 4-alkyl-3-oxo-3,4-dihydropyrazine 1-oxides is described in Section 12.



p-$MeC_6H_4SO_3^-$

(87)

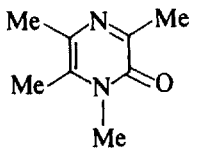
B. Properties and Reactions

1-Methyl-2-oxo-1,2-dihydropyrazine is lower melting and has a higher solubility than 2-hydroxypyrazine. Its pK_a value (− 0.04) approximates that of 2-hydroxy-

pyrazine (basic pK_a −0.01) (820). Thiation with phosphorus pentasulfide in refluxing pyridine gave 1-methyl-2-thio-1,2-dihydropyrazine (821, 1100).

"Methylfluorosulfonate" and 1-methyl-2-oxo-1,2-dihydropyrazine gave a quantitative yield of 1,4-dimethyl-2-oxo-1,2-dihydropyrazinium fluorosulfonate, which reacted instantaneously and exothermically at room temperature and in high yields with hydroxide ion, hydrosulfide ion, and ammonia to give interesting new cage systems (1130).

Irradiation of 1,3,5,6-tetramethyl-2-oxo-1,2-dihydropyrazine (88) in tetrahydrofuran produced an unstable photoisomer which can be trapped by hydrogenation to 1,2,4.6-tetramethyl-3-oxo-2,5-diazobicyclo[2,2,0]hexane (89) (1131).



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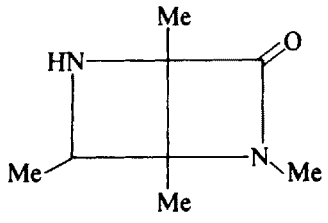


(89)

Electrochemical reduction of 1-methyl-2-oxo-5,6-diphenyl-1,2-dihydropyrazine has been discussed in Section 6F (1096, 1097). Direct amination of the oxo group appears to be unexplored, and little is known of the action of phosphorus halides except that a number of 1-alkyl-3,5,6-trichloro-2-oxo-1,2-dihydropyrazines has been prepared from 1,4-dialkylpiperazine-2,5-diones and phosphorus pentachloride (853) Section 9A(4)].

The reactions in the decomposition of 1,3,6-trimethyl-2-oxo-1,2-dihydropyrazine methiodide with alkali metal hydroxide to give 1,4,6-trimethyl-3-methylene-2-oxo-1,2,3,4-tetrahydropyrazine (1105) and its reaction with benzenediazonium chloride or phenylhydrazine to give 1,4,6-trimethyl-2-oxo-3-phenylazomethylene-1,2,3,4-tetrahydropyrazine (1105, 1132) have been described.

10. PREPARATION OF HYDROXYPYRAZINE *N*-OXIDES AND EXTRANUCLEAR HYDROXYPYRAZINE *N*-OXIDES

A. By Primary Synthesis

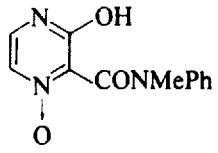
Preparations of hydroxypyrazine *N*-oxides by primary syntheses have been included in Chapter III and are summarized briefly as follows: Section III.3, 2-hydroxypyrazine 1-oxides from α-aminohydroxamic acids and 1,2-dicarbonyl compounds or α,β-unsaturated α-bromo aldehydes (545–548); Section III.4, 2-hydroxy-3,6-dimethylpyrazine 1-oxide from the bisulfite derivatives of pyruvohydroxamic acid and aminoacetone (548); and Section III.5, ring closure of the C–C–N–C–C–N–O system (545, 546, 548–553). In addition to these preparations

phenylglyoxal and DL-phenylalanylhydroxylamine gave 3-benzyl-2-hydroxy-5-phenylpyrazine 1-oxide (1133).

Preparations of pyrazine *N*-oxides containing extranuclear hydroxyl groups are also described in Chapter III as follows: Section III.1, 2-aminopyrazine 1-oxides from α-amino nitriles and α-hydroxyimino carbonyl compounds (540, 541); Section III.2, 3-substituted pyrazine 1-oxides from 2-amino-2-deoxy-D-glucose(or mannose) oxime with glyoxal (543, 544); and Section III.5, ring closure of the C–C–N–C–C–N–O system (553).

B. By *N*-Oxidation

Oxidation of nuclear and extranuclear hydroxypyrazines (and derivatives) to their *N*-oxides has been achieved with hydrogen peroxide in acetic acid, and with *m*-chloroperoxybenzoic acid in 1,2-dichloroethane. 3-Hydroxy-2,5-diisobutylpyrazine was oxidized with 30% hydrogen peroxide in acetic acid at 70° to 3-hydroxy-2,5-diisobutylpyrazine 1-oxide (101), 3-hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine 1-oxide (**90**) was also prepared from the corresponding pyrazine [its *N*-4-methyl derivative was prepared similarly and also by methylation of (**90**) (1055)], and 3-hydroxy-2-(*N*-methyl-*N*-*p*-tolylcarbamoyl)pyrazine 1-oxide (1055) was synthesized analogously.



(**90**)

2-Benzoyloxypyrazine was oxidized with *m*-chloroperoxybenzoic acid in 1,2-dichloroethane to 3-benzoyloxypyrazine 1-oxide (1035), which with methanolic sodium methoxide gave 3-hydroxypyrazine 1-oxide (1035); the 5- and 6-methyl- and 5-methoxycarbonyl analogues were prepared similarly (1035).

Peroxyacetic acid oxidation of 2-acetoxymethyl-5-methylpyrazine gave the 1,4-dioxide which hydrolyzed in 0.1% sulfuric acid to 2-hydroxymethyl-5-methylpyrazine 1,4-dioxide (625); and 2,3-di(acetoxymethyl)pyrazine 1,4-dioxide was subjected to transesterification with lower alcohols in the presence of a catalytic amount of alkali to give 2,3-di(hydroxymethyl)pyrazine 1,4-dioxide (739).

C. By Hydrolysis of Halogenopyrazine *N*-Oxides

Alkaline hydrolysis of halogenopyrazine *N*-oxides to hydroxypyrazine *N*-oxides has been described in Section V.7A(2).

D. From Aminopyrazine *N*-Oxides

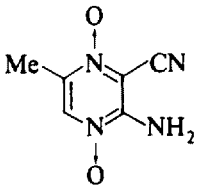
3-Aminopyrazine 1-oxide with nitrous acid in sulfuric acid on warming and dilution with water (108, 547a), and also by treatment with potassium cuprous cyanide (838), has been shown to give 3-hydroxypyrazine 1-oxide. 2-Amino-3,5-dimethylpyrazine 1-oxide with about 40% sodium hydroxide at reflux in a bath at 140° produced 2-hydroxy-3,5-dimethylpyrazine 1-oxide (524).

E. From Alkoxypyrazine *N*-Oxides

Alkoxypyrazine *N*-oxides may be hydrolyzed with acid to hydroxypyrazine *N*-oxides. Some examples are the hydrolysis of 3-ethoxy-2,5-dimethylpyrazine 1-oxide at reflux with 3 *N* hydrochloric acid to give 3-hydroxy-2,5-dimethylpyrazine 1-oxide (872); 2,5-diethoxy-3,6-dimethylpyrazine 1,4-dioxide with 2 *N* hydrochloric acid at 70° gave 2-ethoxy-5-hydroxy-3,6-dimethylpyrazine 1,4-dioxide; and 2,5-dibenzyloxy-3,6-dimethylpyrazine 1,4-dioxide similarly treated but at room temperature gave the 2-benzyloxy analogue (842), but with 10 *N* hydrochloric acid at room temperature it gave 2,5-dihydroxy-3,6-dimethylpyrazine 1,4-dioxide (842).

F. By Other Means

2-Amino-3-cyano-5-methylpyrazine 1,4-dioxide (**91**) refluxed for several minutes with acetic anhydride formed 3-acetamido-2-cyano-5-hydroxy-6-methylpyrazine 1-oxide (**92**) (24%) (532) and 2-acetoxymethyl-5-methylpyrazine 1,4-dioxide refluxed with acetic anhydride afforded a mixture of 2,5-di(acetoxymethyl)pyrazine 1-oxide, with some 2,5-diacetoxymethylpyrazine and a monoxide of 2-acetoxymethyl-5-methylpyrazine (625). 2-Formylpyrazine hydrate 1,4-dioxide with aqueous sodium hydroxide or bicarbonate at $< 37°$ in an unusual reaction gave 3-carboxypyrazine 1-oxide mixed with 5-carboxy-2-hydroxypyrazine 1-oxide (739).



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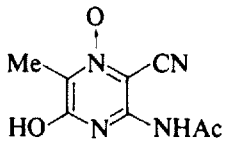
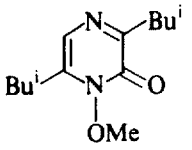


(92)

Cleavage of the Me–O bond in 3,6-diisobutyl-1-methoxy-2-oxo-1,2-dihydropyrazine (**93**) with methylmagnesium iodide at 150° gave 2-hydroxy-3,6-diisobutylpyrazine 1-oxide (**94**) and the 1,4-dioxide was prepared similarly from 2,5-diisobutyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide and also from 2,5-diisobutyl-3-methoxypyrazine 1,4-dioxide (980).



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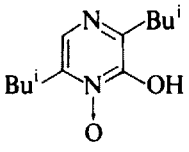


(94)

Boron tribromide in dry chloroform was used to convert 3-isobutyl-6-isopropyl-1-methoxy-2-oxo-1,2-dihydropyrazine to 2-hydroxy-3-isobutyl-6-isopropylpyrazine 1-oxide, and 6-isobutyl-3-isopropyl-1-methoxy-2-oxo-1,2-dihydropyrazine behaved similarly (740a). Ohta (843) reports the preparation of 2-hydroxy-3,6-diisobutylpyrazine 1-oxide from 3,6-diisobutyl-1-methoxy-2-oxo-1,2-dihydropyrazine (as intermediate) and hydrogen iodide.

11. PREPARATION OF *C*- AND *N*-ALKOXYPYRAZINE *N*-OXIDES

A. From Halogenopyrazine *N*-Oxides

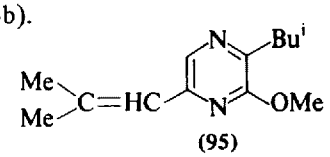
The preparations of nuclear and extranuclear alkoxypyrazine *N*-oxides from chloropyrazine *N*-oxides and extranuclear chloropyrazine *N*-oxides have been described in Section V.7A(3) (588, 756, 838, 842, 872, 978) and Section V.7B(3) (529), respectively.

3-Chloropyrazine 1-oxide hydrolyzed with aqueous sodium hydroxide and the product treated with triethylamine and trimethylsilyl chloride gave 3-(trimethylsilyl)oxypyrazine 1-oxide (1034).

B. By Oxidation

Alkoxypyrazine *N*-oxides may also be prepared by oxidation of the alkoxypyrazine with peroxyacetic acid. In this way the following have been prepared: 3-ethoxypyrazine 1-oxide (100°/20 h) (978); 3-(trideuteromethoxy)pyrazine 1-oxide (75°/19 h) (975); 3-ethoxy-2-methylpyrazine 1-oxide (65–75°/24 h) (978); 3-methoxy-2-phenylpyrazine 1-oxide (55°/20 h) (817); 3-ethoxy-2,5-dimethylpyrazine 1-oxide (56°/16 h) (872); 3-carbamoyl-2-methoxypyrazine 1-oxide (80°/20 h) (881); and 2-cyano-5-ethoxy-3,6-dimethylpyrazine *N*-oxide (55°/20 h) (288).

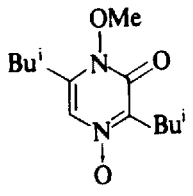
Oxidation of 2-isobutyl-3-methoxy-5-(2′-methylprop-1′-enyl)pyrazine (**95**) with peroxymaleic acid gave 5-(1′,2′-epoxy-2′-methyl)propyl-2-isobutyl-3-methoxypyrazine 1-oxide (**27**) (113b).



(95)

C. By Alkylation

Diazomethane methylation of 3-hydroxy-2,5-diisobutylpyrazine 1,4-dioxide has been shown to give the 4-methoxypyrazine 1-oxide, 2,5-diisobutyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide (**96**) (843, 980) [and some 3-methoxy-2,5-diisobutylpyrazine 1,4-dioxide (4 : 1) (980)]; 5-*s*-butyl-3-hydroxy-2-isobutylpyrazine 1,4-dioxide gave 5-*s*-butyl-2-isobutyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide (313); 3-hydroxy-2-isobutyl-5-isopropylpyrazine 1,4-dioxide gave 2-isobutyl-5-isopropyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide (740a); 3-hydroxy-5-isobutyl-2-isopropylpyrazine 1,4-dioxide gave 5-isobutyl-2-isopropyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide (740a); and 2,5-dihydroxy-3,6-dimethylpyrazine 1,4-dioxide gave 4,6-dimethoxy-2,5-dimethyl-3-oxo-3,4-dihydropyrazine 1-oxide (**97**) (842). 3-Hydroxypyrazine 1-oxide in methanol reacted with diazomethane in ether to give a methyl ether which on spectroscopic evidence was assigned the structure 3-methoxypyrazine 1-oxide (108).



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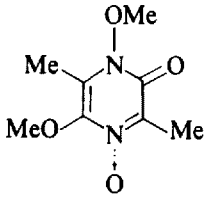
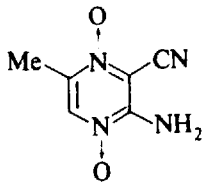


(97)

D. By Other Means

2-Amino-3-cyano-5-methylpyrazine 1,4-dioxide (**98**) when refluxed with sodium methoxide overnight has been shown to give 3-amino-2-cyano-5-methoxy-6-methylpyrazine 1-oxide (532).



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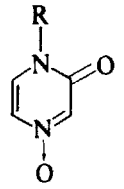
12. PREPARATION OF 4-ALKYL-3-OXO-3,4-DIHYDROPYRAZINE 1-OXIDES

1-Methyl-2-oxo-1,2-dihydropyrazine was oxidized by *m*-chloroperoxybenzoic acid in boiling 1,2-dichloroethane to give a low yield of 4-methyl-3-oxo-3,4-dihydropyrazine 1-oxide (**99**, R = Me) (1035). The preparations of 4-alkyl deri-



(99)

vatives from 3-hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine 1-oxide (1055) and 3-hydroxypyrazine 1-oxide (1034, 1035) are described in Section 14D.

13. PROPERTIES AND STRUCTURE OF HYDROXY- AND ALKOXYPYRAZINE *N*-OXIDES

The antibiotic emimycin was first isolated (107) from *Streptomyces* No. 2021-1 and subsequent work (108) showed it to be 3-hydroxypyrazine 1-oxide which from infrared evidence (Nujol) was assigned the pyrazine structure (**99**, R = H) [alkyl derivatives have been assigned similar structures (978)]. It had an acidic pK_a 6.2 (108) and was a stronger acid than 2-hydroxypyrazine [acidic pK_a 8.23 (1082)]. Emimycin did not form acetyl derivatives under a variety of conditions: acetic anhydride and pyridine, acetyl chloride and pyridine, or acetic anhydride and sulfuric acid (108).

The isolation of some hydroxypyrazine *N*-oxides including the antibiotic aspergillic acids and analogues from various cultures has been described in Section I.2. *Aspergillus flavus* PRL 932, grown on 2% yeast extract containing 1% methionine, produced various 2-hydroxypyrazine 1-oxides containing the methylthioethyl substituent (1134). Nakamura and Shiro (1135) have reported growth inhibition by hydroxyaspergillic acid against Hiochi bacteria.

The following pK_a values have been measured: 3-methoxypyrazine 1-oxide, −0.45 (745); aspergillic acid, 5.5 (94); and hydroxyaspergillic acid, 4.9 (94). P.m.r. measurements have shown that 2-methoxypyrazine 1,4-dioxide protonates at N-4 (1136).

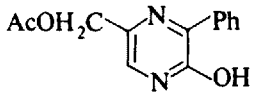
14. REACTIONS OF HYDROXYPYRAZINE *N*-OXIDES

A. Chlorination and *N*-Deoxygenation With Phosphoryl Chloride

The reactions of phosphoryl chloride and some hydroxypyrazine *N*-oxides with an unsubstituted position adjacent to the *N*-oxide function to give chlorohydroxypyrazines have been described in Section V.1G. In this way 3-hydroxy-2,5-diisobutylpyrazine 1-oxide was converted to 2-chloro-5-hydroxy-3,6-diisobutylpyrazine (101) and 2-hydroxy-3,5-diphenylpyrazine 1-oxide gave 2-chloro-6-hydroxy-3,5-diphenylpyrazine (873).

B. Acetoxylation in Conjunction with *N*-Deoxygenation

When 2-hydroxy-3,5-diphenylpyrazine 1-oxide was heated under reflux with an excess of acetic anhydride, a crystalline triacetoxy compound was obtained which was thought to have an open chain structure [AcO–CH=CPh–N=CPh–C(OAc)=N–OAc], but when the 2-hydroxypyrazine-1-oxide was boiled with a mixture of acetic anhydride and acetic acid, 2,6-diacetoxy-3,5-diphenylpyrazine was obtained (873) which was hydrolyzed by potassium hydrogen carbonate in methanol to 2,6-dihydroxy-3,5-diphenylpyrazine (873). 2-Hydroxy-5-methyl-3-phenylpyrazine 1-oxide behaved differently and when refluxed with acetic anhydride gave 5-acetoxymethyl-2-hydroxy-3-phenylpyrazine (**100**); and 2-hydroxy-3-methyl-5-phenylpyrazine 1-oxide similarly gave 3-acetoxymethyl-2-hydroxy-5-phenylpyrazine (873). When 2-(1′-hydroxy-2′-methylpropyl)-5-isobutylpyrazine 1-oxide was heated with a mixture of acetic anhydride and sodium acetate on a water bath 2-(1′-acetoxy-2′-methylpropyl)-5-isobutylpyrazine 1-oxide was obtained (760a).



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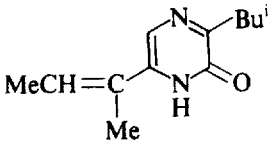
C. *N*-Deoxygenation

Many hydroxypyrazine *N*-oxides have been *N*-deoxygenated to pyrazines with a variety of reducing agents which include heating with hydrazine hydrate in alcohols; hydriodic acid and red phosphorus in acetic or phosphoric acid; iodine and red phosphorus in refluxing acetic acid; phosphorus tribromide in ethyl acetate; sodium dithionite; catalytic reduction with hydrogen over Raney nickel; dry distillation with copper–chromite catalyst; and titanium trichloride in tetrahydrofuran at room temperature.

Deoxygenations with hydrazine hydrate in alcohols were as follows: 2-hydroxy-3,5,6-trimethylpyrazine 1-oxide ($NH_2NH_2 \cdot H_2O$/MeOH/180°/4 h) (546); 2-hydroxy-3,5-dimethylpyrazine 1-oxide (546); 2-hydroxy-3-methyl-5-phenylpyrazine 1-oxide (546); 2-hydroxy-3,6-dimethylpyrazine 1-oxide ($NH_2NH_2 \cdot H_2O$/MeOH/180°/4 h) (548); 2-hydroxy-5,6-dimethyl-3-phenylpyrazine 1-oxide ($NH_2NH_2 \cdot H_2O$/EtOH/160°/1.5 h) (546); 2-hydroxy-3,5-diphenylpyrazine 1-oxide (546); 6-*s*-butyl-2-hydroxy-3-isobutylpyrazine 1-oxide (aspergillic acid) ($NH_2NH_2 \cdot H_2O$/EtOH/100°/12 h) (86), (170°/9 h) (90); and 2-hydroxy-6-(1′-hydroxy-1′-methylpropyl)-3-isobutylpyrazine 1-oxide (hydroxyaspergillic acid) ($NH_2NH_2 \cdot H_2O$/EtOH/180°/5 h) (94).

Deoxyaspergillic acid was also produced from aspergillic acid by refluxing in acetic acid with red phosphorus and hydriodic acid, and by dry distillation with copper–chromite catalyst (86). Reduction of 2,5-dihydroxy-3,6-diisobutylpyrazine 1,4-dioxide (pulcherriminic acid) with red phosphorus and iodine in refluxing acetic

acid gave 2,5-dihydroxy-3,6-diisobutylpyrazine (99), and 2-hydroxy-3,6-diisobutylpyrazine 1-oxide similarly treated gave 3-hydroxy-2,5-diisobutylpyrazine (98). Hydroxyaspergillic with iodine and red phosphorus in acetic acid at reflux has been shown to give 3-hydroxy-2-isobutyl-5-(1′-methylprop-1′-enyl)pyrazine (dehydrodeoxyaspergillic acid) (**101**) (94), but with hydriodic acid and red phosphorus in syrupy phosphoric acid at 150–160° it formed deoxyaspergillic acid (94), and a similar reaction with 2-hydroxy-6-(1′-hydroxy-1′-methylethyl)-3-isobutylpyrazine 1-oxide (mutaaspergillic acid) (**102**) gave 3-hydroxy-2-isobutyl-5-isopropylpyrazine (deoxymutaaspergillic acid) (103).



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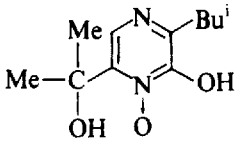


(102)

2-Isobutyl-5-isopropyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide with phosphorus tribromide in ethyl acetate gave 3-isobutyl-6-isopropyl-1-methoxy-2-oxo-1,2-dihydropyrazine (740a).

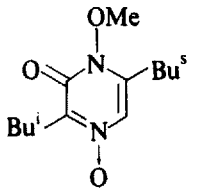
3-Hydroxypyrazine 1-oxide was reduced with hydrogen at atmospheric pressure over Raney nickel to 2-hydroxypyrazine (108) [but failed to react with phosphorus trichloride in chloroform (108)], and 3-hydroxy-2-isobutyl-5-isopropylpyrazine 1,4-dioxide was reduced with hydrogen over nickel to 3-hydroxy-2-isobutyl-5-isopropylpyrazine (740a). 2-(*N*-Anilino-*N*-methylcarbamoyl)-4-methyl-3-oxo-3,4-dihydropyrazine 1-oxide with sodium dithionite produced 3-(*N*-anilino-*N*-methylcarbamoyl)-1-methyl-2-oxo-1,2-dihydropyrazine (1137).

3-Hydroxy-5-(1′-hydroxy-2′-methylpropyl)-2-isobutylpyrazine 1,4-dioxide was deoxygenated by titanium trichloride in dry tetrahydrofuran under nitrogen at room temperature to give 2-hydroxy-6-(1′-hydroxy-2′-methylpropyl)-3-isobutylpyrazine 1-oxide (DL-neohydroxyaspergillic acid) (760a).

D. Alkylation

The alkylation of hydroxypyrazine *N*-oxides to *C*- and *N*-alkoxypyrazine *N*-oxides has been described in Section 11C.

5-*s*-Butyl-3-hydroxy-2-isobutylpyrazine 1,4-dioxide with diazomethane gave a methyl derivative, thought to be 5-*s*-butyl-2-isobutyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide (**103**) [which on treatment with phosphorus trichloride and then hydriodic acid gave 6-*s*-butyl-2-hydroxy-3-isobutylpyrazine 1-oxide (aspergillic acid)] (313), and 3-hydroxy-2,5-diisobutylpyrazine 1,4-dioxide behaved similarly (843). 3-Hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine 1-oxide was methylated with dimethyl sulfate and potassium carbonate in boiling acetone to form 4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxo-3,4-dihydropyrazine 1-oxide (1055).



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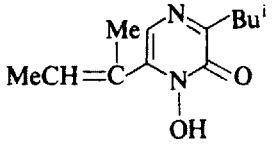


(104)

3-Hydroxypyrazine 1-oxide with trimethylsilyl chloride and bistrimethylsilylamine heated at 90–95° for 1 hour and the 3-(trimethylsilyl)oxypyrazine 1-oxide in 1,2-dichloro ethane treated with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and titanium tetrachloride at reflux for 4 hours followed by deacetylation produced 3-oxo-4-(β-D-ribofuranosyl)-3,4-dihydropyrazine 1-oxide (1035). Treatment of 3-(trimethylsilyl)oxypyrazine 1-oxide with 2-deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)-α-D-*erythro*-pentofuranosyl chloride in benzene in the presence of 4A molecular sieves gave an anomeric mixture ($\alpha/\beta = 1.2:1.0$) of 4-[2′-deoxy-3′,5′-di-*O*-(*p*-chlorobenzoyl)-α(and β)-D-*erythro*-pentofuranosyl]-3-oxo-3,4-dihydropyrazine 1-oxides, which on treatment with methanolic ammonia at 5° afforded the 4-(2′-deoxy-α(and β)-D-*erythro*-pentofuranosyl]-3-oxo-3,4-dihydropyrazine 1-oxides, the β-anomer of which was more active than the α-anomer in inhibiting the growth of *S. faecium* and *E. coli* (1034).

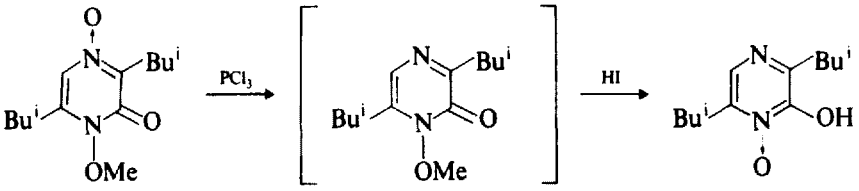
E. Other Reactions

Bromination of aspergillic acid in aqueous solution gave bromoaspergillic acid (87). 2-Hydroxy-6-(1′-hydroxy-1′-methylpropyl)-3-isobutylpyrazine 1-oxide (hydroxyaspergillic acid) heated with syrupy phosphoric acid at 150° produced a mixture of 3-hydroxy-2-isobutyl-5-(1′-methylprop-1′-enyl)pyrazine (dehydrodeoxyaspergillic acid) (**102**) and 2-hydroxy-3-isobutyl-6-(1′-methylprop-1′-enyl)pyrazine 1-oxide (dehydroaspergillic acid) (**104**) (94). 2-Acetoxymethylpyrazine 1,4-dioxide on treatment with phenylhydrazine and *N* sodium hydroxide gave 3-phenylhydrazonomethylpyrazine 1-oxide (1138) and oxidation of 3-(D-*arabo*-tetrahydroxybutyl)pyrazine 1-oxide with potassium permanganate in aqueous potassium hydroxide gave 3-carboxypyrazine 1-oxide (543).

15. REACTIONS OF *C*- AND *N*-ALKOXYPYRAZINE *N*-OXIDES

Reactions of *C*-alkoxypyrazine *N*-oxides with phosphoryl chloride have been described in Section V.1G (756, 817, 838, 872, 881). For example, 3-ethoxy-2,5-dimethylpyrazine 1-oxide refluxed with phosphoryl chloride for 10 minutes gave 2-chloro-5-ethoxy-3,6-dimethylpyrazine and 2-chloromethyl-3-ethoxy-5-methylpyrazine (872).

3-Ethoxypyrazine 1-oxide boiled with 40% alcoholic hydrogen chloride formed 2-ethoxy-5-hydroxypyrazine (1069). 2,5-Diisobutyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide (**105**) treated with phosphorus trichloride in ethyl acetate was deoxygenated to 3,6-diisobutyl-1-methoxy-2-oxo-1,2-dihydropyrazine (**93**) (843, 980), which on treatment with 57% hydriodic acid in ethanol (1:1) at 115° produced 2-hydroxy-3,6-diisobutylpyrazine 1-oxide (neoaspergillic acid) (**106**) (843); and 5-*s*-butyl-2-isobutyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide reacted in an analogous manner (313). Similar deoxygenations of 2-isobutyl-5-isopropyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide occurred with phosphorus tribromide in ethyl acetate at room temperature to 3-isobutyl-6-isopropyl-1-methoxy-2-oxo-1,2-dihydropyrazine (740a) and 5-isobutyl-2-isopropyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide reacted in the same way (740a).



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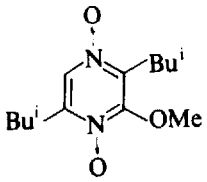
2,5-Diisobutyl-3-methoxypyrazine 1,4-dioxide (**107**) with phosphorus trichloride in ethyl acetate at 40° gave 2,5-diisobutyl-3-methoxypyrazine (980). 2-Amino-5-[(*p*-chlorophenoxy)methyl]-3-cyanopyrazine 1-oxide was deoxygenated with triethyl phosphite in dimethylformamide at 120° (1041).



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Cleavage of the ether linkage occurred when 3,6-diisobutyl-1-methoxy-2-oxo-1,2-dihydropyrazine (**93**) was heated with methylmagnesium iodide at 150° and gave 2-hydroxy-3,6-diisobutylpyrazine 1-oxide (980). 2,5-Diisobutyl-4-methoxy-3-oxo-3,4-dihydropyrazine 1-oxide and 2,5-diisobutyl-3-methyoxypyrazine 1,4-dioxide similarly treated are both reported to have given 3-hydroxy-2,5-diisobutylpyrazine 1,4-dioxide (980).

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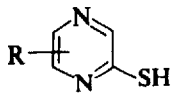
CHAPTER VII

Mercaptopyrazines And Their Derivatives

1. PREPARATION OF MERCAPTOPYRAZINES

A. From Halogenopyrazines

The preparation of mercaptopyrazines (**1**) by the reaction of halogenopyrazines with sodium (or potassium) hydrogen sulfide or sodium polysulfide in various solvents (780, 790, 799, 805, 809, 821, 858, 890, 892, 993, 1006–1011), by reaction with phosphorus pentasulfide in pyridine (1013), and by reaction with thiourea in acid (905) and in alcohol followed by alkali (535) has been described in Section V.5G.



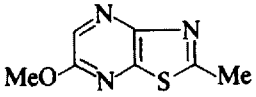
(1)

B. From Hydroxypyrazines

Preparations of mercaptopyrazines from hydroxypyrazines by reaction with phosphorus pentasulfide in boiling pyridine or β-picoline have been reported in Chapter VI.6B.

C. By Degradation

6-Methoxy-2-methylthiazolo[4,5-*b*]pyrazine (**2**), when refluxed with aqueous methanolic sodium hydroxide, has been shown to give 2-amino-3-mercapto-5-methoxypyrazine (805, 1011).



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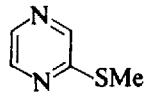
2. PREPARATION OF ALKYLTHIO- AND ARYLTHIOPYRAZINES

A. By Alkylation of Mercaptopyrazines

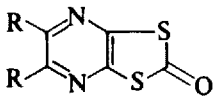
Alkylation of mercaptopyrazines usually takes place at sulfur to give the alkylthiopyrazines in good yield. Thus 2-mercaptopyrazine (**1**, R = H) in aqueous sodium hydroxide with methyl iodide gave 2-methylthiopyrazine (**3**) (68%) (821, 1100). 2-Mercapto-3,5,6-trimethylpyrazine with *p*-chloronitrobenzene and sodium ethoxide in ethanol gave 2,3,5-trimethyl-6-(*p*-nitrophenylthio)pyrazine (933); and 3-mercapto-2,5-dimethylpyrazine in aqueous sodium hydroxide with cyanogen bromide gave 2,5-dimethyl-3-thiocyanatopyrazine (1139) and with chloroacetone gave 3-acetonylthio-2,5-dimethylpyrazine (1140).



(3)

2-Amino-3-mercaptopyrazine in aqueous sodium hydroxide with methyl iodide or ethyl iodide and 2-amino-3-mercapto-5-methoxypyrazine treated similarly with methyl iodide each gave the corresponding alkylthiopyrazine (535). 2-Amino-3-mercaptopyrazine and phenacyl bromide gave 2-amino-3-phenacylthiopyrazine, and analogous reactions were observed with other halogeno compounds such as chloroacetone (1009, 1141, 1142). 2-Amino-3-mercapto-5,6-dimethylpyrazine with chloroacetic acid produced 2-amino-3-carboxymethylthio-5,6-dimethylpyrazine, and analogous compounds were also prepared (1010). 2-Amino-3-mercapto-5,6-diphenylpyrazine similarly gave 2-amino-3-phenacylthio-5,6-diphenylpyrazine (1142). 2-Amino-5-chloro-3-hydrazinocarbonyl-6-mercaptopyrazine in ethanolic sodium hydroxide was alkylated with a series of reagents to form, for example, 2-amino-5-chloro-6-(ethoxycarbonylmethylthio)-3-hydrazinocarbonylpyrazine (790, 963).

2,3-Dimercaptopyrazine (and its 5,6-dimethyl derivative) with phosgene or thiophosgene in alkali produced 2-oxo(or thio)-1,3-dithiolo[4,5-*b*]pyrazine (**4**, R = H) (1143, 1144) and 2,3-dimercapto-5,6-dimethylpyrazine disodium salt with methyl chloroformate gave 2,3-bis(methoxycarbonylthio)-5,6-dimethylpyrazine (1143–1145). 5-Mercapto-2,3-diphenylpyrazine with tetra-*O*-acetyl-α-D-glucopyranosyl bromide and sodium hydroxide in acetone–water mixtures afforded *S*-glucosidation which did not rearrange to the *N*-glucoside on boiling with mercuric bromide in toluene (1108); but 2-mercaptopyrazine with tetra-*O*-acetyl-α-D-glucopyranosyl bromide and sodium hydroxide in aqueous acetone was reported to give a small yield of *N*- (2.5%) as well as *S*-glucosidation (1008).



(4)

B. From Halogenopyrazines

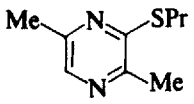
Alkylthiopyrazines may be prepared from halogenopyrazines by reaction with the appropriate sodium (or potassium) alkylthiolate, usually at elevated temperatures. In this way 2-ethylthio- and 2-isopropylthiopyrazine were prepared from 2-chloropyrazine by refluxing with ethylmercaptan or isopropylmercaptan and sodium hydroxide in ethanol for 30 minutes (668a). Alkyl(and aryl)thiopyrazines prepared thus have been described in Section V.5F. The reactions of 2-amino-5-chloromethyl-3-cyanopyrazine with sodium 4-chlorothiophenate [to give 2-amino-5-(4′-chlorophenylthiomethyl)-3-cyanopyrazine] (542) and with sodium *p*-ethoxycarbonylphenylmercaptide (1028) and the reaction of 2-chloro-3-dichloromethylpyrazine with sodium methanethiolate (688) have been described in Section V.6A.

C. By Cleavage of Pteridines and Other Ring Systems

The preparation of 2-amino-3-carboxy-5-methylthio(and 5-benzylthio)pyrazines by saponification of 4-hydroxy-6-methylthio(and 6-benzylthio)pteridine with 5% sodium hydroxide has been described in Chapter II.5 (432, 432a). Some additional references also describe these preparations (778, 780, 783, 786, 858). 2-Acetamido-3-amidinocarbamoyl-5-methylthio(and benzylthio)pyrazine has been prepared from 2-methyl-6-methylthio(and benzylthio)-4*H*-pyrazino[2,3-*d*][1,3]oxazin-4-one with guanidine and sodium methoxide (432); similar reactions were observed with aminoguanidine (463a).

D. By Other Reactions

Bauer and Hirsch (764) found that 2,5-dimethylpyrazine 1-oxide refluxed for 2 hours with propane-1-thiol in acetic anhydride gave 2,5-dimethyl-3-propylthiopyrazine (**5**), and 2,5-dimethylpyrazine 1,4-dioxide similarly treated gave 2,5-dimethyl-3,6-dipropylthiopyrazine, but attempted reactions with benzenesulfonyl chloride instead of acetic anhydride (as in the pyridine series) were unsuccessful.



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3. STRUCTURE AND PROPERTIES OF MERCAPTO- AND ALKYLTHIOPYRAZINES

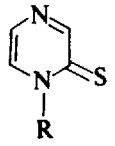
The structure of 2-mercaptopyrazine (**1**, R = H) in aqueous solution has been examined by comparison of its ionization constants and ultraviolet spectra with

TABLE VII.1 IONIZATION CONSTANTS AND ULTRAVIOLET SPECTRA[a] OF 2-MERCAPTOPYRAZINE AND ITS *N*- AND *S*-METHYL DERIVATIVES

Compound	Basic pK_a	U.v. Spectra of Neutral Species (H_2O)		
		λ_{max} (nm)	Log ϵ	pH
2-Mercaptopyrazine	−0.73[b]	227, 279, 382	3.53, 4.09, 3.82	3.48
2-Methylthiopyrazine	0.48	251, *300*, 322	3.89, *3.51*, 373	7.0
1-Methyl-2-thio-1,2-dihydropyrazine	−0.45	222, 279, 375	3.56, 4.07, 3.81	7.0

[a] Data from reference 1100.
[b] Reference 1100 gives 6.32 for the acidic pK_a.

those of its *N*- (6, R = H) and *S*-methyl (3) derivatives (821, 1100) (see Table VII.1) and was shown to exist predominantly as the thione (6, R = H). The tautomeric ratio could not be calculated because a common cation was not formed by the mercapto compound and its *N*- and *S*-methyl derivatives. Infrared spectra determined in aqueous solution also supported the structure (6, R = H) (1146). Calculated (MO) and experimental ultraviolet spectra agreed on the thione formulation (1083). 2-Mercaptopyrazine has some antithyroid activity (1147). Although 2-mercaptopyrazine was purified satisfactorily by vacuum sublimation, at atmospheric pressure it melted with decomposition and evolution of hydrogen sulfide and formation of dipyrazinyl sulfide (7) (821). The dipole moment of 2-amino-5-bromo-3-mercaptopyrazine (2.22 *D* in dioxane) showed that it exists in the thione form (8) (749).



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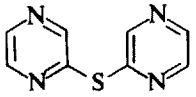

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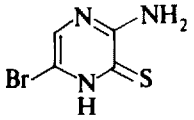


(8)

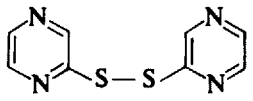
Kinetics have been determined for the displacement of the methylthio group from 2-methylthiopyrazine by methoxide ion. At 129.9° the rate coefficient was 2.83×10^{-3} l/mol · sec, energy of activation 24.6 kcal/mol, and log *A* 10.76 (1080). The reaction was bimolecular but the methoxide ion concentration remained constant throughout the reaction owing to its regeneration from the oxidation of the methanethiol produced (1080).

2-Methylthiopyrazine gives a methiodide with methyl iodide in benzene at reflux (912). Thermal stabilities of 2-isopropylthio- and 2-ethylthiopyrazines have been examined; elimination of olefin occurred to yield 2-mercaptopyrazine which gives dipyrazinyl sulfide (7) (668a). Hydrolyses of the *S*-β-D-glucoside of 2-mercaptopyrazine has been studied with almond emulsion, 0.1 *N* hydrochloric acid, and 0.1 *N* potassium hydroxide. The rate constant for a 0.0125 *M* solution of the glycoside with 0.1 *N* hydrochloric acid at 80° was 0.749 $hour^{-1}$ and 0.025 *M* solution of the glycoside with 0.1 *N* potassium hydroxide at 80° was 6.17 $hour^{-1}$ (1148, 1149).

4. REACTIONS OF MERCAPTOPYRAZINES

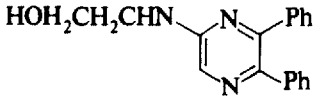
2-Mercaptopyrazine on heating to 220° decomposed to hydrogen sulfide and dipyrazinyl sulfide (**7**) (821) and was oxidized by iodine in aqueous potassium iodide to dipyrazinyl disulfide (**9**) (821).

Alkylation of mercaptopyrazines has been described in Section 2A.



(9)

Displacement of the mercapto group from 5-mercapto-2,3-diphenylpyrazine occurred on heating for 40 hours with ethanolamine to give 5-(2′-hydroxyethylamino)-2,3-diphenylpyrazine (**10**) (834). The mercapto group has been removed from 2-mercaptopyrazine with Raney nickel in refluxing aqueous ammonia with formation of pyrazine (1150), and from 2-amino-3-mercapto-5-methoxypyrazine by refluxing with Raney nickel in dioxane with formation of 2-amino-5-methoxypyrazine (805, 1011). 2-(2′-Mercaptoethyl)pyrazine reacts with diisopropyl azodicarboxylate ($Pr^iOOCN{=}NCOOPr^i$) in chloroform in the presence of sulfuric acid at reflux to give 2-{2′-[*N*,*N*′-bis(isopropoxycarbonyl)hydrazinothio]ethyl}-pyrazine (1151).

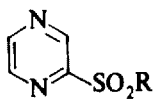


(10)

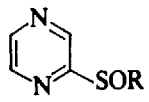
5. REACTIONS OF ALKYLTHIOPYRAZINES

A. Oxidation of Alkylthiopyrazines

2-Methylthiopyrazine has been oxidized by excess potassium permanganate in 8*N* acetic acid at 25° to 2-methylsulfonylpyrazine (**11**) (1079), but with one equivalent of *m*-chloroperoxybenzoic acid in chloroform at 20° it gave 2-methylsulfinylpyrazine (**12**) (1080). Other oxidations that have been described include the oxidation of 2-benzylthio-6-chloropyrazine and 2,6-dibenzylthiopyrazine with potassium permanganate in aqueous acetic acid to the methylsulfonyl compounds (883); the preparation of 2-amino-3-carboxy-5-methylsulfonylpyrazine from the methylthio analogue with potassium permanganate in aqueous sodium hydroxide



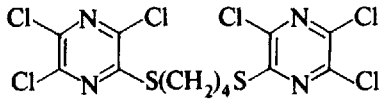
(11)



(12)

(432, 778, 780, 783, 786); and the 5-benzylsulfonyl analogue was prepared similarly (786).

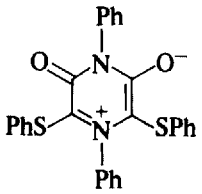
Oxidations with hydrogen peroxide in acetic acid to give both sulfoxides and sulfones have also been described. 2-Cyano-5-phenylthiopyrazine with 30% hydrogen peroxide in acetic acid at 50° for 3 hours gave 2-cyano(and some 2-carbamoyl)-5-phenylsulfonylpyrazine; 2-carbamoyl-5-phenylthiopyrazine with a similar reagent at 45–50° for 1 hour gave 2-carbamoyl-5-phenylsulfinylpyrazine but at 55–60° for 3–4 hours it gave 2-carbamoyl-5-phenylsulfonylpyrazine (840, 993). 2-Amino-5-chloro-3-methoxycarbonyl-6-methylthiopyrazine with 30% hydrogen peroxide in acetic acid at room temperature for 18 hours gave the 6-methylsulfinyl analogue (780, 809, 855, 858, 859) which was further oxidized with more of the same reagent to the methylsulfonyl compound (809); oxidations of 2-chloro-3-dichloromethyl-5-(naphth-2′-ylthio)pyrazine with (30%) hydrogen peroxide in mixed acetic acid–acetic anhydride to the sulfinyl and sulfonyl compounds have been described (688). Sulfones have been prepared by oxidations with hydrogen peroxide in acetic acid on 2-amino-3-(*N*-carbamoylcarbamoyl)-5-chloro-6-methylthiopyrazine at room temperature (1152), 2,3,5-trimethyl-6-*p*-nitrophenylthiopyrazine at 60–70° (933), and 2,3,5-trichloro-6(2′,3′,5′-trichloropyrazin-6′-ylthiobutylthio)pyrazine (**13**) (997, 998). 2-Cyano-6-ethylthiopyrazine in acetic acid with hydrogen peroxide at 40–50° gave 2-cyano-6-ethylsulfinylpyrazine (992), whereas with an excess of the same reagent at 50–60° the ethylsulfonyl compound was obtained (992). 2-Carbamoyl-6-phenylthiopyrazine similarly oxidized gave 2-carbamoyl-6-phenylsulfinyl(and phenylsulfonyl)pyrazine (992).



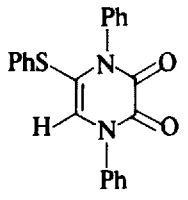
(**13**)

B. Displacement of Alkylthio Substituents

2-Methylthiopyrazine reacts with methoxide ion at elevated temperatures to give 2-methoxypyrazine, and the kinetics have been determined (Section 3) (1080). Anhydro-2,6-dihydroxy-1,4-diphenyl-3,5-bis(phenylthio)pyrazinium dihydroxide, for example, (**14**), with a saturated solution of hydrogen chloride in acetic acid at room temperature gave 2,3-dioxo-1,4-diphenyl-5-phenylthio-1,2,3,4-tetrahydropyrazine (6.4%) (**15**) and 1,4-diphenyl-6-phenylthiopiperazine-2,3,5-trione (60%) (476a).



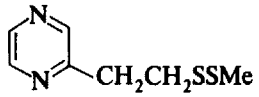
(**14**)



(**15**)

6. DIPYRAZINYL DISULFIDES AND SULFIDES; PYRAZINESULFONIC ACIDS

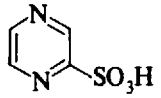
Oxidation of 2-mercaptopyrazine in aqueous sodium hydroxide with a solution of iodine in potassium iodide afforded dipyrazinyl disulfide (**9**) (821). Dipyrazinyl sulfide (**7**) has been prepared from heating 2-mercaptopyrazine at 220° until evolution of hydrogen sulfide ceased, and it is produced together with 2-mercaptopyrazine from the reaction of approximately equimolar quantities of 2-chloropyrazine and potassium hydrogen sulfide in water at 100° (821). A mixture of 2-chloropyrazine, isothiourea, and ethanol autoclaved at 120° for 20 hours gave dipyrazinyl sulfide (147), also prepared from sodiomercaptopyrazine and 2-chloropyrazine at 150° for 20 hours (147). 2-{2′-[*N*,*N*′-Bis(isopropoxycarbonyl)hydrazinothio]ethyl}pyrazine reacted with excess methanethiol in isopropanol at 0° in the presence of *N*-ethyl-*N*,*N*-diisopropylamine to give the disulfide, 2-[2′-(methyldithio)ethyl]pyrazine (**16**) (1151).



(**16**)

2-Mercaptopyrazine in aqueous hydrochloric or acetic acids was chlorinated to give the sulfonyl chloride which with excess liquid ammonia gave 2-sulfamoylpyrazine (1006, 1153). Direct sulfonation of the pyrazine ring has never been reported (819) but 2-sulfopyrazine (**17**) has been prepared from 2-chloropyrazine and aqueous sodium sulfite at 150° (819), and from 2-fluoropyrazine and aqueous sodium sulfite at reflux for 2 hours (882, 884). 2-Amino-3-mercaptopyrazine in aqueous sodium hydroxide with concentrated ammonia and sodium hypochlorite has been shown to give 2-amino-3-sulfamoylpyrazine (1101).

Oxidation of dipyrazinyl sulfide with hydrogen peroxide in acetic acid gave dipyrazin-2-yl sulfone (821).



(**17**)

7. ALKYLSULFONYL- AND ALKYLSULFINYLPYRAZINES

A. Preparation

The oxidation of alkylthiopyrazines to alkylsulfonyl- and alkylsulfinylpyrazines (e.g., **11** and **12**, respectively) has been described in Section 5A, and cleavage of 2-methyl-6-methylsulfonyl-4*H*-pyrazino[2,3-*d*][1,3]oxazin-4-one by guanidine (432)

and aminoguanidine (463a) to give methylsulfonylpyrazines in Section II.5. 4-Hydroxy-6-methylsulfonylpteridine was also cleaved by 5% aqueous sodium hydroxide on a steam bath for 13 hours to give 2-amino-3-carboxy-5-methylsulfonylpyrazine (432a).

In addition to these methods of preparation, 2,6-dichloropyrazine with sodium methylsulfinate in dimethylformamide at 100° produced 2,6-bis(methylsulfonyl)-pyrazine (759).

B. Properties

The ionization constant of 2-methylsulfonylpyrazine has been determined as −2.47 compared to 0.65 for pyrazine (1079). Kinetics of the reactions of 2-methylsulfonyl- and 2-methylsulfinylpyrazines with methoxide ions to give 2-methoxypyrazine have been measured (1079). The reaction of 2-methylsulfonylpyrazine with methoxide ion obeyed normal second-order kinetics: at 29.9° the second-order rate coefficient (k_2) was 3.89×10^{-3} l/mol · sec, and the energy of activation 18.3 kcal/mol and log A 10.8 (1079). 2-Methylsulfinylpyrazine and methoxide ion also underwent a bimolecular reaction but only 0.5 ion equivalents of methoxide ion was consumed for each mole of sulfoxide owing to partial regeneration of methoxide ion as a by-product of subsequent reactions with methanol of the unstable sodium methanesulfenate (MeSONa) initially formed. At 30.0°, the second-order rate coefficient for the reaction of 2-methylsulfinylpyrazine with methoxide ion (calculated from a modified form of the normal second-order rate equation) was 4.32×10^{-3} l/mol · sec and the energy of activation 18.5 kcal/mol and log A 10.98 (1080). The ratio of the reactivity of 2-methylsulfonyl- to 2-methylthiopyrazine towards methoxide ion at 30° was 3.41×10^4 (1080).

C. Reactions

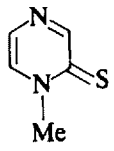
The high reactivity of methylsulfonyl- and methylsulfinylpyrazines toward nucleophilic displacement is useful for synthesis. 2-Methoxypyrazine has been prepared from sodium methoxide and 2-methylsulfonylpyrazine at 87° for 3 hours (1079) and from 2-methylsulfinylpyrazine at 50° for 24 hours (1080). 2-Methylsulfonylpyrazine with N sodium hydroxide at 90° for 2 hours gave 2-hydroxypyrazine (50%) (1062), and with propylamine at 150° for 18 hours gave 2-propylaminopyrazine (63%) (1062). 2-Methylsulfinylpyrazine with aqueous sodium hydroxide at 90° for 2 hours, however, gave 2-hydroxypyrazine (90%) together with 2-methylthiopyrazine (10%) (presumably formed by reduction of the sulfoxide in the oxidation of methanesulfenate anion produced in the reaction), and with butylamine at 145° for 20 hours gave 2-butylaminopyrazine (73%) (1063).

2-Amino-5-chloro-3-methoxycarbonyl-6-methylsulfinylpyrazine with dilute acetic acid on the steam bath for 3 hours produced 2-amino-5-chloro-6-hydroxy-3-methoxycarbonylpyrazine (78, 855) and 2-amino-3-(*N*-carbamoylcarbamoyl)-

5-chloro-6-methylsulfonylpyrazine with ammonia in isopropanol at reflux gave 2,6-diamino-3-(*N*-carbamoylcarbamoyl)-5-chloropyrazine (1152).

8. OTHER DERIVATIVES OF MERCAPTOPYRAZINES

1-Methyl-2-oxo-1,2-dihydropyrazine with phosphorus pentasulfide in pyridine at reflux was converted into 1-methyl-2-thio-1,2-dihydropyrazine (**18**) (821, 1100), and 3-chloropyrazine 1-oxide with sodium hydrogen sulfide in ethanol at room temperature gave 3-mercaptopyrazine 1-oxide (**19**) (1035). Whereas 3-chloro-2,5-dimethylpyrazine 1-oxide reacted slowly with thiourea in ethanol, and the use of water in place of ethanol caused some increase in reaction rate, the reaction in 2*N* sulfuric acid at reflux for 30 minutes gave 3-mercapto-2,5-dimethylpyrazine 1-oxide (85%), and 3-mercapto-2-methylpyrazine 1-oxide was prepared similarly (905).



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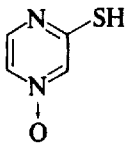

(19)

2-Amino-3-cyano-5-(benzylthiomethyl)pyrazine 1-oxide has been prepared from β-bromopyruvaldoxime, benzylmercaptan, and aminomalononitrile tosylate in propan-2-ol (542).

2-Amino-5[(*p*-chlorophenylthio)methyl]-3-cyanopyrazine 1-oxide (prepared from the 5-bromomethylpyrazine 1-oxide) was deoxygenated with triethyl phosphite in dimethylformamide at 120° (1041).

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CHAPTER VIII

Aminopyrazines, Their *N*-Oxides, and Related Nitrogenous Derivatives

Most methods of preparation of aminopyrazines and their *N*-oxides have been described in detail in earlier chapters under pyrazine and pyrazine *N*-oxide ring syntheses, and their reactions. These are discussed only briefly below; reference made to the relevant chapter and literature references.

Few nitro- and phenylazopyrazines are known, and these too are discussed in this chapter.

1. AMINOPYRAZINES

A. Preparation of Aminopyrazines

(1) *By Primary Synthesis*

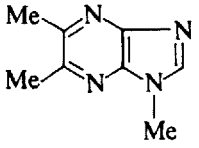
Some primary syntheses of aminopyrazines have already been described under syntheses of pyrazines in Chapter II and are summarized briefly as follows: the condensation of various α,β-dicarbonyl compounds with α,β-diamino compounds to give monoaminopyrazines has been discussed in Section II.2 (342, 346, 347, 376–379) and further information (782, 786, 802) relates to the preparation of 2-amino-3-carbamoyl-5-cyclohexylpyrazine. Additional preparations of 2-amino-3-carbamoylpyrazines not listed in Table II.8 (Section II.2) include the condensations of α-amidino-α-aminoacetamide with ethylglyoxal (778, 780, 786, 802) with cyclopropylglyoxal (778, 786, 802), and with *p*-chlorophenylglyoxal (780, 802) to give 2-amino-3-carbamoyl-5-ethyl(cyclopropyl, and *p*-chlorophenyl)pyrazines, respectively; and the condensation of dibromomethyl trifluoromethyl ketone with α-aminomalondiamidine or α-aminomalonamidamidine in sodium acetate to give 2-amino-3-carbamoyl-5-trifluoromethylpyrazine (781, 787, 802) and 3-amino-2-carbamoyl-5-trifluoromethylpyrazine (802). 3-[^{15}N]Carbamoyl-2-hydroxy-[1-^{15}N]pyrazine (822) and 3-carbamoyl-2-hydroxy[2-^{14}C]pyrazine/3-[^{14}C]carbamoyl-2-hydroxypyrazine (ratio 1 : 1) (823) have been prepared using procedures (361, 369) published for the unlabeled compounds.

Section II.3 (384–386) contains some preparations from α,β-diamino or α,β-diimino compounds and reagents other than α,β-dicarbonyl compounds, and further information has been published (1050, 1154); Section II.4 records the oxidation of 2-acetamidoquinoxaline (408) to 5-acetamido-2,3-dicarboxypyrazine.

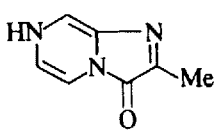
The cleavage of many pteridines and related ring systems, which gave mostly aminopyrazines, has been described in Section II.5 and other sources are relevant (347, 463a, 778, 780, 781, 783–786, 802, 836, 858, 859, 1058, 1155–1163). Other studies of ring opening reactions to give aminopyrazines have been recorded. The reaction of 1-methyl-4-methylimino-1,4-dihydropteridine hydrochloride with *N* sodium hydroxide at 100° for 2.5 hours gave 2-carboxy-3-methylaminopyrazine (1164); 1-phenyllumazine and 1-(2′,3′-dimethylphenyl)lumazine with sodium hydroxide in refluxing ethanol afforded 2-anilino-3-carboxypyrazine and 2-carboxy-3-(2′,3′-dimethylphenyl)aminopyrazine (950); 3-benzyl-4-oxo-2,6,7-triphenyl-3,4-dihydropteridine with sodium ethoxide in ethanol gave 2-amino-3-*N*-benzylcarbamoyl-5,6-diphenylpyrazine (1165); 7-acetonylxanthopterin diacetate with methyl sulfur chloride (MeSCl) in tetrahydrofuran was thought to give a carboxy hydroxyaminopyrazine (1052); and 6,7-dimethylpteridine with hydroxylamine yielded 2-hydroxyiminomethyl-3-hydroxyiminomethylamino-5,6-dimethylpyrazine and 2,6,7-trimethylpteridine with methoxyamine afforded 2-(1′-methoxyiminoethyl)amino-3-methoxyiminomethyl-5,6-dimethylpyrazine (1166).

Equilibria in aqueous solutions of pteridine have been investigated. When pteridine was added to acid, the cation of 4-hydroxy-3,4-dihydropteridine was rapidly formed and this slowly underwent ring fission to the cation of 2-aminomethyleneamino-3-formylpyrazine. Both 2- and 7-methylpteridine behaved similarly; 4-methylpteridine gave 3-acetyl-2-aminomethyleneaminopyrazine, but production of 4-hydroxy-4-methyl-3,4-dihydropteridine could not be demonstrated (1167).

Imidazo[4,5-*b*]pyrazine derivatives have been subjected to hydrolytic cleavage to give pyrazines: 1,5,6-trimethylimidazo[4,5-*b*]pyrazine (**1**) refluxed with 2.5 *N* sodium hydroxide gave 2-amino-3-methylamino-5,6-dimethylpyrazine, but with 3 *N* hydrochloric acid at reflux it gave 2-hydroxy-3-methylamino-5,6-dimethylpyrazine; 1-benzyl-5,6-dimethylimidazo[4,5-*b*]pyrazine under similar conditions gave 2-amino-3-benzylamino-5,6-dimethylpyrazine and 2-benzylamino-3-hydroxy-5,6-dimethylpyrazine, respectively; and 5,6-dimethylimidazo[4,5-*b*]pyrazine (cleaved only in acid) refluxed with 3 *N* HCl gave 2,3-diamino-5,6-dimethylpyrazine and 2-amino-3-hydroxy-5,6-dimethylpyrazine (907). 3-Hydroxy-2-methylimidazo-[1,2-*a*]pyrazine (**2**) with potassium *t*-butoxide in tetrahydrofuran at room temperature gave a chemiluminescent reaction and formed 2-acetamidopyrazine (1168).

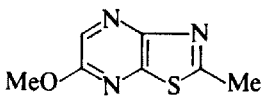


(1)



(2)

6-Methoxy-2-methylthiazolo[4,5-*b*]pyrazine (**3**) refluxed with 2*N* sodium hydroxide in methanol gave 2-amino-3-mercapto-5-methoxypyrazine (**4**) (805, 1011), and 3,2';5,6-bis[(1,3-diethyl-2,4-dioxo-1,2,3,4-tetrahydro)-1,4-pyrimidino]-pyrazine refluxed in ethanol with *N* sodium hydroxide for 2.5 hours gave 2,6-bis(ethylamino)-3,5-bis-*N*-ethylcarbamoylpyrazine (1169).



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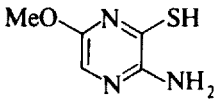


(4)

Dehydrogenation of 2,6-bishydroxyiminopiperazine to 2,6-diaminopyrazine has been recorded in Section II.6 (465), ring closures involving the C–C–N–C–C, N–C–C–N–C–C, and N–C–C–N–C–C–N system to give aminopyrazines in Section II.7 (478, 484–486, 488–490) with some further data (1170), and some condensation reactions in Section II.8 (491).

(2) *By Direct Amination*

The direct amination of pyrazine and alkylpyrazine has been discussed in Sections IV.1C and IV.2C (**8**), respectively.

(3) *From Halogenopyrazines*

The preparation of aminopyrazines and hydrazinopyrazines from halogenopyrazines has been described in Sections V.5B and V.5C, respectively.

(4) *From Mercapto-, Alkylthio-, Alkylsulfonyl-, and Alkylsulfinylpyrazines*

Aminopyrazines have been prepared as previously described from mercaptopyrazines (Section VII.4), and alkylsulfonyl- and alkylsulfinylpyrazines (Section VII.7C).

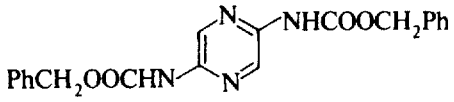
(5) *From Carbamoylpyrazines*

Aminopyrazines may be prepared from carbamoylpyrazines by the Hofmann degradation. Gabriel and Sonn (397) first prepared 2-aminopyrazine from 2,3-dicarbamoylpyrazine with potassium hypobromite through 2-amino-3-carboxypyrazine, which was decarboxylated when heated above its melting point (or in refluxing nitrobenzene) (397, 477). 2,3-Dicarbamoylpyrazine with 2 mol of

potassium hypobromite gave lumazine (397), possibly through a carbamate. Later Hall and Spoerri (1171) found that 2-carbamoylpyrazine with sodium hypochlorite gave the intermediate sodium pyrazine carbamate, which on acidification gave 2-aminopyrazine and carbon dioxide (804, 1171). Spoerri and Erickson (1172) claimed that 2,5-dicarbamoylpyrazine was stable to both hypochlorous and hypobromous acid. Aminopyrazines have been prepared from the corresponding carbamoylpyrazines by Hofmann degradation as follows: 2-carbamoyl-5-methylpyrazine (420, 673, 1173); 2-carbamoyl-6-methylpyrazine (673); 2-carbamoyl-5(and 6)-ethylpyrazine (376); 2-carbamoyl-3-methoxypyrazine (810, 811); 2-carbamoyl-6-methoxy(?)pyrazine (805); 2-carbamoyl-3,5-dimethoxy-6-methylpyrazine (535); 2-carbamoyl-6-chloropyrazine (757); 3-carbamoyl-5-chloro-2-methoxypyrazine (881); 2-carbamoyl-3-hydroxypyrazine (369, 833); 2-carbamoyl-3-hydroxy-5-methylpyrazine (369); 3-carbamoyl-2-hydroxy-5-methylpyrazine (373); 3-carbamoyl-2-hydroxy-5-phenylpyrazine (365a); 2-carbamoyl-3-hydroxy-5,6-dimethylpyrazine (374); 2-carbamoyl-3-hydroxy-5,6-diphenylpyrazine (1065); and 5-carbamoyl-2,3-bis(fur-2′-yl)pyrazine (4%) (1163). In addition to the above, the sodium salt of 2-*N*-benzoyloxycarbamoyl-3-carboxypyrazine methanolate, when refluxed in toluene (or xylene) for 3 hours gave 2-amino-3-methoxycarbonylpyrazine (40%) and 2-amino-3-carboxypyrazine (24%) (1174). Ellingson et al. (1175) were unsuccessful in an attempt to prepare 2,3-diaminopyrazine by the Hofmann degradation of 2-amino-3-carbamoylpyrazine, and Ellingson and Henry (798) could not prepare 2-amino-5-carboxypyrazine by partial Hofmann degradation of 2,5-dicarbamoylpyrazine.

(6) *From Acid Azides and Hydrazides and Urethanes (Alkoxycarbonylaminopyrazines)*

2,5-Bis(azidocarbonyl)pyrazine heated with anhydrous benzyl alcohol at 180° for 30 minutes, and then at 220° for 15 minutes gave 2,5-bis(benzyloxycarbonylamino)pyrazine (**5**), which with concentrated sulfuric acid followed by pouring onto ice afforded 2,5-diaminopyrazine (1176); but 2,5-bis(azidocarbonyl)pyrazine refluxed with ethanol gave 2,5-bis(ethoxycarbonylamino)pyrazine, which could not be converted into the amine with (fuming) hydrochloric acid to 210°, with concentrated sulfuric acid, or with potassium hydroxide (1172).

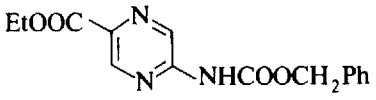


(5)

2-Hydrazinocarbonyl-5-phenylpyrazine treated with aqueous nitrous acid gave 2-azidocarbonyl-5-phenylpyrazine, converted by heating in benzyl alcohol at 150° to 2-benzyloxycarbonylamino-5-phenylpyrazine, and with 30% hydrobromic acid in glacial acetic acid gave 2-amino-5-phenylpyrazine (376). 2-Hydrazinocarbonyl-6-

phenylpyrazine on similar treatment afforded 2-amino-6-phenylpyrazine (352). From 5-azidocarbonyl-2,3-bis(fur-2′-yl)pyrazine, 5-amino-2,3-bis(fur-2′-yl)pyrazine was obtained (1163).

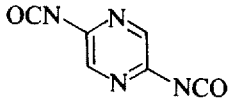
Schut et al. (1177) have investigated several methods for converting urethanes into amines; the following were found to be the most satisfactory. Refluxing 2-(benzyloxycarbonylamino)-5-ethoxycarbonylpyrazine (6) with 4 N hydrochloric acid for 3 hours gave 2-amino-5-carboxypyrazine (76%); and catalytic hydrogenation of 2-(benzyloxycarbonylamino)-5-carboxy(or ethoxycarbonyl or carbamoyl)-pyrazine at atmospheric temperature and pressure over 10% palladium–charcoal gave the corresponding 2-aminopyrazines in practically quantitative yields [2-(benzyloxycarbonylamino)-5-carboxypyrazine was reduced in aqueous alkaline solution, and the ethyl ester and amide in 96% ethanol]. The procedure employed by Sharefkin and Spoerri (1176), for converting 2,5-bis(benzyloxycarbonylamino)pyrazine with concentrated sulfuric acid to 2,5-diaminopyrazine was less attractive, alkaline hydrolysis of 2-(benzyloxycarbonylamino)-5-carboxy(or 5-alkoxycarbonyl)pyrazine led to the evolution of ammonia, and application of the Ing and Manske procedure (1178, 1179) to 2-(benzyloxycarbonylamino)-5-ethoxycarbonylpyrazine gave some 2-amino-5-carboxypyrazine (?) although the procedure was not thoroughly examined (1177).



(6)

Hydrogenation of 3-(benzyloxycarbonylamino)-2,5-dimethoxypyrazine in ethanol over palladium–charcoal gave 3-amino-2,5-dimethoxypyrazine and 2-amino-3,5-dimethoxypyrazine was prepared similarly (881).

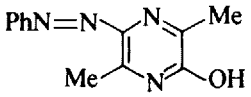
2,5-Diisocyanatopyrazine (7) was stable toward (fuming) hydrochloric acid or potassium hydroxide (1172).



(7)

(7) *By Reduction of Nitro- and Phenylazopyrazines*

Reduction of 2-hydroxy-3,6-dimethyl-5-phenylazopyrazine (8) with sodium hydrosulfite (dithionite) gave 2-amino-5-hydroxy-3,6-dimethylpyrazine (872), and vigorous reduction of the disodium salt of 2-(*p*-sulfophenylazo)-3-methyl-5-hydroxypyrazine with stannous chloride and hydrochloric acid gave 2-amino-5-hydroxy-3-methylpyrazine (434). 2-Hydroxy-5,6-diphenyl-3-phenylazopyrazine in methanol was reduced with hydrogen over Raney nickel to 2-amino-3-hydroxy-5,6-



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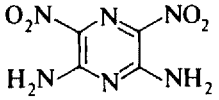
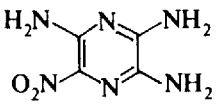


(9)

diphenylpyrazine (1065). 2,6-Diamino-3,5-dinitropyrazine (**9**) in water was reduced with hydrogen over palladium–charcoal to tetraaminopyrazine, but reduction of 2,6-diamino-3,5-dinitropyrazine in *N,N*-dimethylacetamide with hydrogen over platinum oxide or in aqueous solution with sodium sulfide and ammonium chloride at room temperature gave 2,3,5-triamino-6-nitropyrazine (**10**) (1180). 2-Amino-6-chloro-3-(*N'*,*N'*-dimethylureido)-5-ethylaminopyrazine (**11**) has been prepared from 2-chloro-5-(*N'*,*N'*-dimethylureido)-3-ethylamino-6-nitropyrazine in dimethylformamide in the presence of triethylamine with hydrogen at 50 p.s.i. over palladium–charcoal at 25° (1181).



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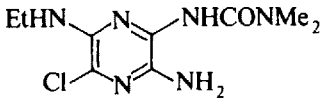
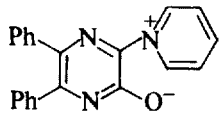


(11)

(8) *By Other Methods*

A solution of 2-hydroxy-3-nitro-5,6-diphenylpyrazine in dry pyridine treated dropwise with thionyl chloride gave a slightly exothermic reaction and after standing for 18 hours gave the zwitterion of 2-hydroxy-5,6-diphenyl-3-pyridiniopyrazine (**12**) (863); and 2,3-dihydroxy-5,6-diphenylpyrazine with boiling 50% aqueous hydrazine gave 2-hydrazino-3-hydroxy-5,6-diphenylpyrazine (**13**) (which was also prepared from 2-hydroxy-3-nitro-5,6-diphenylpyrazine) (1124).



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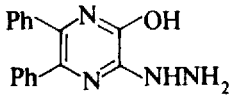
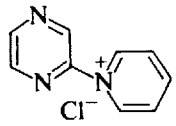


(13)

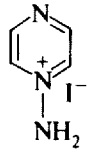
Tetracyanopyrazine has been reported to react with liquid ammonia in tetrahydrofuran to give 2,6-diamino-3,5-dicyanopyrazine (1180, 1182), and with dimethylamine in tetrahydrofuran at 0° to give 2,3,5-tricyano-6-dimethylaminopyrazine (97.7%) (158), and this on treatment with ammonia in tetrahydrofuran gave 2-amino-3,5-dicyano-6-dimethylaminopyrazine (89%) (158).

Pyrazine 1-oxide and 3-amino- and 3-chloropyrazine 1-oxide with tosyl chloride in the presence of pyridine gave 2-pyridiniopyrazine chloride (**14**) and 2-amino- or 2-chloro-3-pyridiniopyrazine chloride, respectively; and 3-methoxycarbonyl(or morpholinocarbonyl or cyano)pyrazine 1-oxide treated similarly gave 2-methoxy-



(14)

carbonyl(morpholinocarbonyl or cyano)-5-pyridiniopyrazine chloride (765). *N*-Amination of pyrazines has been effected with hydroxylamine-*o*-sulfuric acid. In this way 1-aminopyrazinium iodide (**15**) (33.7%), 1-amino-3-methylpyrazinium iodide (21.7%), and 1-amino-2,5-dimethylpyrazinium iodide (55.2%) have been prepared (610). The preparation from these compounds of pyrazolo[1,5-*a*]pyrazines (**16**) has been described (610).



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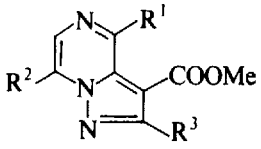


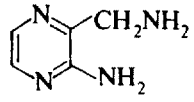
(16)

2-(2′-Chloroethylideneamino)-3-(imidazol-2′-yl)pyrazine was hydrolyzed by warming with 1*N* sodium hydroxide at 70° for 20 hours to 2-amino-3-(imidazol-2′-yl)pyrazine (455a).

B. Preparation of Extranuclear Aminopyrazines

(1) *By Reduction of a Nitrile, Imine, or Hydroxyamino Compound*

2-Amino-3-cyanopyrazine in ethanolic ammonia has been reduced with hydrogen over nickel to 2-amino-3-aminomethylpyrazine (**17**) and its 5-methyl derivative was prepared similarly (1183, 1184); reduction of 2-(*p*-ethoxycarbonylphenyliminomethyl)-3-methylpyrazine with sodium borohydride in methanol gave 2-(*p*-ethoxycarbonylphenylaminomethyl)-3-methylpyrazine (1185); and catalytic reduction (Ni/H_2, 70°, 1000 p.s.i.) of 2-(4′-diethylamino-1′-hydroxyaminobutyl)-pyrazine gave 2-(1′-amino-4′-diethylaminobutyl)pyrazine (1186); but 2-(2′-carboxy-2′-hydroxyiminoethyl)pyrazine on reduction in aqueous ammonia (10% $Pd–C/H_2$, 60 p.s.i.) gave only 10% of 2-(2′-amino-2′-carboxyethyl)pyrazine, possibly due to some reduction of the pyrazine ring (1187).



(17)

(2) *By the Mannich Reaction*

The preparation of extranuclear aminopyrazines by the Mannich reaction has been described in Section IV.2C(6) (657, 715, 716).

(3) *From Halogenopyrazines*

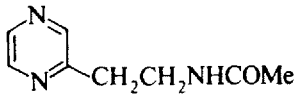
Some preparations of extranuclear aminopyrazines from extranuclear halogenopyrazines and amines have been described in Section V.6B (542, 679, 932, 1029–1031). 2-Chloromethylpyrazine also reacted with sodium azide and gave 2-azidomethylpyrazine, which was hydrogenated in 95% ethanol over Adams catalyst to 2-aminomethylpyrazine (690).

(4) *From Amides by the Hofmann Reaction*

One only "known" extranuclear aminopyrazine has been prepared by the Hofmann reaction: 2-(2′-carbamoylethyl)pyrazine with sodium hypochlorite gave 2-(2′-aminoethyl)pyrazine (405).

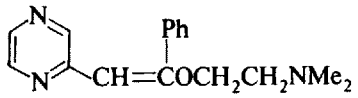
(5) *By Other Reactions*

A series of aminoethylpyrazines has been prepared in high yields by the reaction of 2-vinylpyrazine with ammonia or amines using methanolic acetic acid or metallic sodium as catalyst (730); 2-vinylpyrazine with acetamide and sodium at 120–130° gave 2-(2′-acetamidoethyl)pyrazine (**18**) (731).



(**18**)

Alkylation of 2-methylpyrazine with 2-dimethylaminoethyl chloride using sodium amide as condensing agent gave 2-(3′-dimethylaminopropyl)pyrazine (643) but similar alkylation of the anion of 2-phenacylpyrazine (from 2-phenacylpyrazine with one equivalent of sodium amide in liquid ammonia) gave 2-[2′-(2″-dimethylaminoethoxy)styryl]pyrazine (**19**) (645). 2-Methylpyrazine refluxed with sodium and 5-methyl-3-azahex-3-ene for 2 hours gave 8% of isopentylpyrazine plus 62% of a mixture of 2-(1′-ethylamino-2′-methylpropyl)-6-methylpyrazine and its 2,3-isomer in the ratio 55 : 45 (614). 2-(*p*-Ethoxycarbonylphenylaminomethyl)-3-methylpyrazine with 5-bromomethyluracil, sodium carbonate, and a trace of sodium iodide in tetrahydrofuran at reflux gave 2-[*N*-(*p*-ethoxycarbonylphenyl)-*N*-thyminylamino]-3-methylpyrazine (1185).

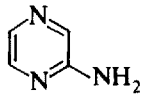


(19)

The Vilsmeier reaction on 2-methylpyrazine has been described in Section IV.2C(7) (717), and King's reaction on 2-methyl(and 2,3-dimethyl)pyrazine 1,4-dioxide has been described in Section IV.3C(7) (763). Pyrazine with *N,N*-dimethylacetamide, ammonium peroxydisulfate, and ferrous sulfate gave 2-(*N*-acetyl-*N*-methylaminomethyl)pyrazine (1188).

C. Properties of Aminopyrazines

2-Aminopyrazine is a yellowish crystalline solid with m.p. 118–120° (420). It is a weak base with reported pK_a values of 3.14 (123) and 2.96 (821) (others are recorded in Chapter X). The similarity in the ultraviolet spectra (in water) of the neutral molecules of 2-amino-, 2-methylamino-, and 2-dimethylaminopyrazines, and of their monocations, and their similar basic strengths (2.96, 3.42, 3.27) (821) supports the conclusion that in aqueous solution 2-aminopyrazine exists mainly in the amino form (**20**) (821). The ultraviolet spectrum of 2-aminopyrazine cation differs from that of the neutral molecule of pyrazine, thus indicating that protonation does not take place at the extranuclear nitrogen atom (821); 2-aminopyrazine in fact protonates at N_1 (see below).



(20)

The ultraviolet spectra in aqueous solution (821) of the methiodides isolated from the methylation of 2-amino- and 2-dimethylaminopyrazines with methyl iodide in methanol (821) differed from those obtained by protonation of 2-amino- and 2-dimethylaminopyrazine, respectively. This methiodide of 2-aminopyrazine was rapidly decomposed by aqueous alkali but did not form 1-methyl-2-oxo(or imino)-1,2-dihydropyrazine or 2-methylaminopyrazine (821). These and other observations were consistent with protonation of 2-amino(2-methylamino or 2-dimethylamino)pyrazine at N_1 and with the methiodides isolated involving quaternization at N_4 (821). It has been claimed from studies of ultraviolet and infrared spectra and from reactions with cyanoguanidine that in 2-aminopyrazine *p*-toluenesulfonate, the amino group is protonated (1189).

Spin couplings between an aromatic ^{14}N nucleus and ring protons in the p.m.r. spectrum of 3-amino-1-methylpyrazinium iodide have been examined (704).

Proton magnetic resonance measurements in dimethyl sulfoxide indicate that 2-aminopyrazine and its 3-methyl derivative exist predominantly in the amino form (979, 1086), in agreement with theoretical and experimental electronic spectra (1083). Proton magnetic resonance analysis of the methylation of 2-aminopyrazine with methyl iodide in dimethyl sulfoxide at room temperature showed it to be methylated 8.8 times as fast as pyrazine to give both 3-amino-1-methyl- and 2-amino-1-methylpyrazinium iodides in the ratio 2.9 : 1 (666). Proton magnetic resonance spectra of ionized 2-aminopyrazine in liquid ammonia have also been reported (665).

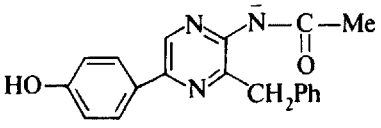
Polarographic reduction of 2-aminopyrazine and 2-amino-3-carboxypyrazine to 1,4-dihydro derivatives that give 1,2-dihydro derivatives by acid catalysis has been studied (1190).

Pyrolysis and thermal stabilities of aminopyrazines have been studied mass spectrometrically. 2-Aminopyrazine was thermally stable at 280°. Its alkyl derivatives were less stable; monoalkylation on the amino group destabilized the molecule more strikingly than dialkylation (668a). Attempts to resolve 3-amino-2,5-di-*s*-butylpyrazine were unsuccessful (89).

Dipole moments (*D*) of some aminopyrazines have been determined as follows: 2-amino-6-methoxy (3.08, benzene; 3.42, dioxane); 2-amino-5-bromo-3-methoxy (2.94, benzene); 2-amino-3-chloro (1.86, benzene; 2.26, dioxane); 2-amino-5-bromo-3-mercapto (2.22, dioxane); and 3-amino/1-oxide (3.43, dioxane) (749).

Methylation of 2-amino-3-hydroxypyrazine with various reagents (832) have been described in Section VI.6D. The crystal structure of 2,3-dichloro-5-ethylamino-6-methoxypyrazine has been determined (916).

Renilla (sea pansy) luciferin (and certain of its synthetic analogues) produces a brilliant blue chemiluminescence when dissolved in organic solvents such as dimethylformamide and involves the anion of 2-acetamido-3-benzyl-5-(*p*-hydroxyphenyl)pyrazine (21) (1191). 5-Hydrazino-2-hydrazinocarbonylpyrazine is effective against *mycobacterium tuberculosis* and *m. kansasii in vitro* (1098). Aminonitropyrazines have been claimed as useful yellow dyes for wool (1180); and tetraaminopyrazine (1180) and *N*-substituted amides of 2-carboxy-3,5-bismethylamino-6-(*N*-methylcarbamoyl)pyrazines (1192) as fluorescent brighteners (or optical bleaching agents) for textiles.



(21)

The free energy of the rotational barriers, ΔG^*, about the =CH–NMe_2 bond in 2-(*N*,*N*-dimethylaminomethyleneamino)pyrazine has been determined as 17.5 kcal/mol, and in its 3,5-dibromo and 5-chloro derivatives as 19.9 and 18.6, respectively (1193). 2-Chloro-6-(piperazin-1′-yl)pyrazine is claimed to show central serotonin-like activity (1194).

D. Reactions of Aminopyrazines

(1) *Replacement of Amino by Hydroxy and Alkoxy Groups*

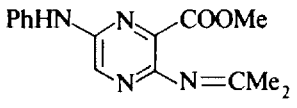
The conversions of amino to hydroxy groups have been described in Sections VI.1C and VI.9A(5), and to alkoxy groups in Section VI.3C.

(2) *Replacement of Amino (and Hydrazino) by Halogeno Substituents*

The replacement of amino groups by fluoro, bromo, and iodo substituents has been described in Section V.1H (882, 884), Section V.1K (798–800, 807, 890–892) and Section V.1I (887), respectively; and of hydrazino groups by chloro and bromo substituents in Section V.1J (851, 888).

(3) *Formation of Anils (Schiff Bases)*

When 2-amino-5-chloro-3-methoxycarbonylpyrazine was refluxed with aniline and concentrated hydrochloric acid in acetone for 16 hours, the anil, 5-anilino-2-isopropylideneamino-3-methoxycarbonylpyrazine (**22**) was formed (432, 778, 780), and 2-amino-5-chloro-3-methoxycarbonyl-6-(1′-methylhydrazino)pyrazine with benzaldehyde in ethanol gave 2-amino-6-(2′-benzylidene-1′-methylhydrazino)-5-chloro-3-methylcarbonylpyrazine (**23**) (809). A series of hydrazones has been prepared by refluxing equimolar quantities of 2-hydrazinopyrazine and carbonyl compounds in the presence of catalytic quantities of *p*-toluenesulfonic acid in benzene (1195). Other preparations of similar hydrazones have been described (1196).



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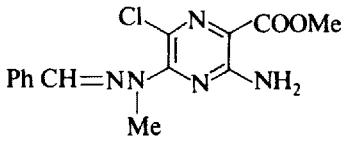


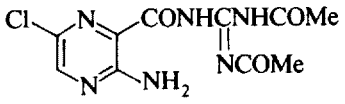
(23)

(4) *Acyl Derivatives of Aminopyrazines*

(a) ACETYLATION

Aminopyrazines may be acetylated under a variety of conditions that mostly use acetic anhydride alone or in admixture with acetic acid, pyridine, or perchloric acid to give the following acetamidopyrazines (with reaction conditions): 2-acetamido-3-carbamoylpyrazine (acetic anhydride–acetic acid at 100°/10 h) (1175);

2-acetamido-3-hydroxypyrazine (acetic anhydride–acetic acid, 100°/9 h) (834) (or acetic anhydride at reflux 3 h) (1111); 2-acetamido-5-bromo-3-carbamoylpyrazine (acetic anhydride–acetic acid, reflux 3 h) (987); 2,5-diacetamidopyrazine (acetic anhydride) (1176); 2-acetamido-3-acetoxymethylpyrazine (2-amino-3-hydroxymethylpyrazine with acetic anhydride at reflux) (1075); 2-diacetylamino-5,6-dimethoxycarbonyl-3-dimethylaminopyrazine (acetic anhydride at 160°) (409); 2-(*N*-acetyl-*N*-*p*-nitrobenzenesulfonamido)-3-methoxypyrazine (acetic anhydride–pyridine at 95°/1 h) (810, 984), and its 5,6-dimethyl derivative under similar conditions (835); 2-acetamido-5-(indol-3′-yl)pyrazine (acetic anhydride–pyridine at room temperature for 17 h) (1168); 2-acetamido-3-methoxycarbonylpyrazine (acetic anhydride–acetic acid–70% perchloric acid at 85–90°), and also its 2-butyramido analogue (433a); 2-acetamido-5(and 6)-methylpyrazine (acetic anhydride–acetic acid–perchloric acid) (376, 673); and 2,3-diphenyl-5-(triacetylhydrazino)pyrazine (acetic anhydride–acetic acid at reflux) (846). 2-Amino-5-chloro-3-amidinocarbamoylpyrazine with acetyl chloride in pyridine at 100° gave 2-amino-5-chloro-3-[*N*-(*N*′,*N*″-diacetylamidino)carbamoyl]pyrazine (**24**) (150), 2-amino-3-dimethoxymethylpyrazine with the same reagents in chloroform gave 2-acetamido-3-dimethoxymethylpyrazine (1075); and 5-hydrazino-2,3-diphenylpyrazine in pyridine with acetyl chloride at room temperature gave 5-(1′,2′-diacetylhydrazino)-2,3-diphenylpyrazine (846). 2-Amino-3-benzoylpyrazine with bromoacetyl bromide in methylene chloride and 10% aqueous sodium carbonate formed 2-benzoyl-3-bromoacetamidopyrazine (1197), and 2-amino-3-dimethoxymethylpyrazine with trifluoroacetic anhydride at 0° gave 2-dimethoxymethyl-3-trifluoroacetamidopyrazine (1075).



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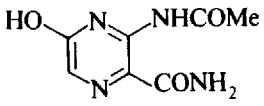
Aminopyrazine *N*-oxides may rearrange and acetylate in the presence of acetic anhydride. Thus 2-amino-3-cyanopyrazine 1-oxide with acetic anhydride and acetic acid at reflux for 2 hours gave 3-acetamido-2-carbamoyl-5-hydroxypyrazine (**25**), 2-amino-3-ethoxycarbonylpyrazine 1-oxide similarly treated gave 3-acetamido-2-ethoxycarbonyl-5-hydroxypyrazine (538), and 2-amino-3-cyano-5-methylpyrazine 1-oxide with trifluoroacetic acid–trifluoroacetic anhydride gave 2-carbamoyl-5-hydroxy-6-methyl-3-trifluoroacetamidopyrazine (538).

2-Aminopyrazine with acetonitrile in the presence of aluminum chloride formed 2-acetimidoylaminopyrazine (**26**) (1198, 1199).



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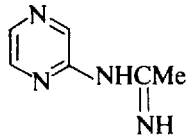
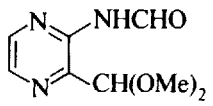


(26)

(b) FORMYLATION

Formylaminopyrazines have been prepared as follows. 2-Amino-3-dimethoxymethylpyrazine stirred at 0° with acetic formic anhydride gave 2-dimethoxymethyl-3-formamidopyrazine (27) (1075), and 2-amino-3-methylpyrazine similarly treated gave 2-formamido-3-methylpyrazine (1200).



(27)

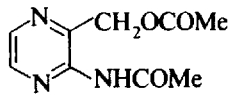
Addition of phosphoryl chloride to a solution of 2-amino-3-formylpyrazine in dimethylformamide gave 2-formamido-3-formylpyrazine (1166); and 2-cyano-3-ethoxymethyleneaminopyrazine in aqueous ethanol at 20–25° gave 2-cyano-3-formamidopyrazine (803).

(c) BENZOYLATION AND OTHER ACYLATIONS

Benzamidopyrazines may be prepared from aminopyrazines by reaction with the benzoyl chloride in the presence of base. In this way the following compounds (base) have been prepared: 2-benzamidopyrazine (pyridine) (1201); 2-benzamidomethylpyrazine (triethylamine) (1202); 2-benzamido-3-methoxycarbonyl(or carbamoyl)pyrazine (pyridine in chloroform, or triethylamine in dioxane) (433a, 1203); and 2-amino-5-chloro-3-[(*N*′,*N*″-dibenzoylamidino)carbamoyl]pyrazine (pyridine at 100°) (150). Some other acylaminopyrazines have also been prepared as follows: 2-butyramido-3-methoxycarbonylpyrazine (butyric anhydride and 70% perchloric acid) (433a); 2,5-dimethyl(diethyl or diphenyl)-3-propionamidopyrazine (propionic anhydride at 90° for 15 minutes) (478); 3-(*N*,*N*-diacetylamino)-2,5-diphenylpyrazine (acetic anhydride at reflux for 15 minutes) (478); 2,5-dimethyl-3-phenylacetamidopyrazine (phenylacetyl chloride in dry benzene) (491); 2,5-di-*s*-butyl-3-succinimidopyrazine (succinic anhydride at 120–125° for 45 minutes) (89); and 2,5-di-*s*-butyl-3-phthalimidopyrazine (phthalic anhydride at 170–180°) (89).

(d) DEACYLATION OF ACYLAMINOPYRAZINES

Acylaminopyrazines have been deacylated by hydrolysis in acid, or alkali, by methanolysis, or by hydrazinolysis (in propan-2-ol) under a variety of conditions to give the corresponding amino compound unless otherwise specified in the following examples: 2-acetamido-3-acetoxymethylpyrazine (28) (dilute acetic acid at reflux for 6 h) (1075); 2-acetamido-5-chloro-3-amidinocarbamoylpyrazine (5% hydrochloric acid–acetic acid at 100°) (150); 2-acetamido-3-*N*-(benzimidoyl)-carbamoyl-5-chloropyrazine (5% hydrochloric acid at room temperature) (150); 2-acetamido-5-dimethylamino(or 5-methylthio, 5-methylsulfonyl, or 5-benzylthio)-3-guanidinocarbonylpyrazine (10% hydrochloric acid at 100° for 15 minutes) (432, 1158); 2-acetamido-5-chloro-3-(2′,3′-diphenylguanidinocarbonyl)pyrazine (5% aqueous hydrochloric acid in isopropanol) (783); 2-(butylthio)carbonyl-3,5-



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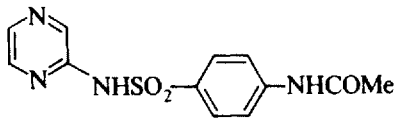
dibutyramido-6-chloropyrazine (5% hydrogen chloride and propan-2-ol) (1161); 2-acetamido-3-carbamoylpyrazine (heated with aqueous dilute acid) (1160); 5-acetamido-2,3-dicarboxypyrazine (refluxed with 0.12 *N* hydrochloric acid for 30 minutes) (408); 2,5-dimethyl-3-propionamidopyrazine (reflux with 10% potassium hydroxide for 4 h) (478), and similarly for the diethyl and diphenyl analogues (478); 2,5-diphenyl(and 2,5-dimethyl)-3-phenylacetamidopyrazine (0.1*N* sodium hydroxide at reflux for 3 days) (491); 3-acetamido-2-carbamoyl(and 2-ethoxycarbonyl)-5-hydroxypyrazine (reflux in methanol for 4.5 days) (538); 2-carbamoyl-5-hydroxy-6-methyl-3-trifluoroacetamidopyrazine (reflux in methanol for 2 h) (538); 2-acetamido-3-(imidazol-2′-yl)pyrazine (reflux with 0.1*N* hydrochloric acid) (455a); and 2-acetamido-3-(imidazol-2′-yl)-5,6-dimethylpyrazine (heated with 1*N* hydrochloric acid at 80°) (455a). 2,3-Diphenyl-5-(1′,2′,2′-triacetylhydrazino)-pyrazine warmed in methanol was found to give 5-(1′,2′-diacetylhydrazino)-2,3-diphenylpyrazine (846). 2-(Dibenzoylamino)-3-methoxycarbonylpyrazine in boiling dioxane diluted with propan-2-ol and treated with one equivalent of 96% hydrazine hydrate was monodebenzoylated to give 2-benzamido-3-methoxycarbonylpyrazine (95%) (433a).

2-(2′-Cyanoethyl)carbamoyl-3-formylamino-5-methylpyrazine boiled with *N* sodium hydroxide for 30 seconds gave 3-amino-2-cyanoethylcarbamoyl-5-methylpyrazine (435); 2,3-dichloro-5-formamido-6-formylpyrazine was readily deformylated under acid or alkaline conditions (e.g., 2*N* sodium carbonate at 20°) (430); and 2-formamido-3-(imidazol-2′-yl)pyrazine was deformylated by refluxing with 0.1*N* hydrochloric acid for 4 hours and its 5,6-dimethyl derivative reacted similarly (455a).

(e) ARYLSULFONAMIDOPYRAZINES

Many arylsulfonamidopyrazines have been prepared, most usually by the reaction of the (*p*-acetamido)arylsulfonyl chloride, and aminopyrazine in pyridine (the *N*-acetyl group may be removed by acid or alkaline hydrolysis). In this way the following have been synthesized: 2-(N^4-acetylsulfanilamido)pyrazine (**29**) (400, 1175, 1204, 1205) [hydrolyzed by acid (400, 1204) and alkali (1205) to 2-sulfanilamidopyrazine], and various *C*-alkyl (and *C*-phenyl) derivatives (420, 535); 2-(*p*-



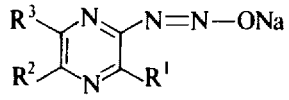
(29)

hydroxybenzenesulfonamido)pyrazine (1206); 3-(N^4-acetylsulfanilamido)-2,5-dimethylpyrazine (719) (hydrolyzed by 6 *N* hydrochloric acid to 2,5-dimethyl-3-sulfanilamidopyrazine) (719); 3-(N^4-acetylsulfanilamido)-2,5-di-*s*-butylpyrazine (1207); 2-methoxy-3-*p*-toluenesulfonamidopyrazine (814); 2-methoxy-3-(*p*-nitrobenzenesulfonamido)pyrazine (810, 984); 2-methoxy-5,6-dimethyl-3-(*p*-nitrobenzenesulfonamido)pyrazine (835); 2-methoxy-3-sulfanilamidopyrazine (810, 814, 984); 2-ethoxy-3-sulfanilamidopyrazine (984); 2-(N^4-acetylsulfanilamido)-3-methoxy-5-methylpyrazine (835); 3-(N^4-acetylsulfanilamido)-2-methoxy-5-methylpyrazine (835); 2-(N^4-acetylsulfanilamido)-3-methoxy-5-(or 6)-methylpyrazine (373); 2-(N^4-acetylsulfanilamido)-3-methoxy-5,6-dimethylpyrazine (373); 2-(N^4-acetylsulfanilamido)-5-methoxypyrazine (805, 1011); (hydrolyzed in aqueous sodium hydroxide to 2-methoxy-5-sulfanilamidopyrazine) (805, 1011); 2-(N^4-acetylsulfanilamido)-3,5-dimethoxypyrazine (881); 3-(N^4-acetylsulfanilamido)-2,5-dimethoxypyrazine (881); 2-(N^4-acetylsulfanilamido)-3,5-dimethoxy-6-methylpyrazine (535); 2-(N^4-acetylsulfanilamido)-3-methoxy-5,6-dimethylpyrazine (prepared at 50°) (835); 2-(N^4-acetylsulfanilamido)-6-methoxypyrazine (hydrolyzed in 2 *N* sodium hydroxide to 2-methoxy-6-sulfanilamidopyrazine) (805); 5-(N^4-acetylsulfanilamido)-2,3-dimethoxypyrazine (535); 2-chloro-3-disulfanilylaminopyrazine (833); 5-(N^4-acetylsulfanilamido)-3-chloro-2-methylpyrazine (535); 2-(N^4-acetylsulfanilamido)-3-chloro-5,6-dimethylpyrazine and some 2-di-(N^4-acetylsulfanilyl)amino-3-chloro-5,6-dimethylpyrazine (812); 2-(N^4-acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (hydrolyzed with hydrobromic acid in ethanol to 2-bromo-5,6-dimethyl-3-sulfanilamidopyrazine) (812); 2-(N^4-acetylsulfanilamido)-5-chloro-3-methoxypyrazine (845); 2-(N^4-acetylsulfanilamido)-5-bromo-3-methoxypyrazine (810, 984) (hydrolyzed in refluxing 2 *N* sodium hydroxide to 5-bromo-3-methoxy-2-sulfanilamidopyrazine) (810, 984); 5-bromo-3-methoxy-2-(*p*-toluenesulfonamido)pyrazines (814); 2-(N^4-acetylsulfanilamido)-3-methylthio(and ethylthio)pyrazine (535); 2-(N^4-acetylsulfanilamido)-6-methylthio(and 6-ethylthio)-pyrazine (prepared at 50–60°/1.5 h) (1208); 2-(N^4-acetylsulfanilamido)-5-methoxy-3-methylthiopyrazine (535); 2-(N^4-acetylsulfanilamido)-3-methoxycarbonylpyrazine (prepared at 70°/3.5 h) (1175) (deacetylated with methanolic hydrogen chloride to 2-methoxycarbonyl-3-sulfanilamidopyrazine) (1175); 2-(N^4-acetylsulfanilamido)-3-carbamoylpyrazine (70°/3.5 h) (1175); 2,3-di-(N^4-acetylsulfanilamido)pyrazine (833) (but attempted deacetylation with refluxing 4 *N* hydrochloric acid gave 2,3-dihydroxypyrazine) (833); (2,3-diaminopyrazine with 2 mol of *p*-nitrobenzenesulfonyl chloride in pyridine gave mono-, di-, and trisubstituted products) (833); 2,3-di-(N^4-acetylsulfanilamido)-5,6-dimethylpyrazine (812) (deacetylated with alcoholic hydrogen chloride to 2,3-dimethyl-5,6-disulfanilamidopyrazine) (812); 2,6-di-(N^4-acetylsulfanilamido)pyrazine (865); 2-(2′-phthalimidoethylsulfonamido) pyrazine (1209); and 2-(2′-aminoethanesulfonamido)pyrazine (1209).

2-Amino-3-hydroxypyrazine and acetylsulfanilyl chloride heated in pyridine failed to condense, but the same two reagents with one equivalent of sodium hydroxide in aqueous acetone gave a mixture of 2-(N^4-acetylsulfanilamido)-3-hydroxypyrazine and the sulfonate, 2-(N^4-acetylsulfanilyl)-3-aminopyrazine (833). Pyrolysis of sulfapyrazine gave 2-aminopyrazine (1210).

(5) *Diazotization*

The diazotization of aminopyrazines has been described in earlier sections. Section V.1H records the preparation of 2-fluoropyrazine from 2-aminopyrazine in fluoroboric acid containing copper powder with sodium nitrite (882, 884) and Section V.1I the preparation of iodopyrazines from some aminopyrazines via isodiazotate salts (**30**) (887). These salts were assigned the isodiazotate structure, on the basis of their inability to couple with β-naphthol in alkaline solution (887) and they were characterized by hydrolysis in cold 40% aqueous sulfuric acid to the hydroxypyrazine (887). Section V.1K describes the conversion of aminopyrazines to bromopyrazines (798, 800, 807, 890–892); for example, 2-amino-3-methoxycarbonylpyrazine with hydrobromic acid, bromine, and sodium nitrite in water gave 2-bromo-3-methoxycarbonylpyrazine (798, 890). The diazotization of aminopyrazines to hydroxypyrazines has been described in Section VI.1C, to alkoxypyrazines in Section VI.3C, and to oxopyrazines in Section VI.9A(5). 2-Aminopyrazine with isopentyl nitrite in benzene gave 2-phenylpyrazine (45%) and some 2-isopentoxypyrazine and "2,2′-dipyrazinyl amino isomers" (1211).



(30)

(6) *Bicyclic Heterocycles from Aminopyrazines*

Various bicyclic heterocyclic compounds have been prepared by cyclization reactions from various aminopyrazines, and some of these preparations are listed in Table VIII.1.

(7) *C-Substitution of Aminopyrazines*

(a) HALOGENATION

The halogenation of aminopyrazines has been described in Chapter V.

(b) NUCLEAR AND EXTRANUCLEAR *C*-ALKYLATION

2-Aminopyrazine was alkylated with ethyl methyl ketone and sodium in liquid ammonia (in the absence of a catalyst) to 2-amino-6-butylpyrazine, and a similar reaction occurred with isobutyraldehyde (614); and 2-cyano-3-(*N*,*N*-dimethylaminomethyleneamino)-5-methylpyrazine was deprotonated with lithium diisopropylamide (from butyllithium and diisopropylamine) and alkylated with ethyl iodide followed by removal of the protecting group by acid hydrolysis to give 3-amino-2-cyano-5-propylpyrazine (1031).

TABLE VIII.1 BICYCLIC COMPOUNDS FROM AMINOPYRAZINES

Structure	Compound	Refs.
A	Pteridines	379, 421, 423, 427, 432, 432a, 433a, 435, 440, 451, 453, 455, 455a, 457, 484, 529, 532, 534, 538, 542, 762, 778, 780, 783, 786, 803, 858, 874, 879, 987, 1028, 1030, 1031, 1038–1041, 1075, 1165, 1183, 1184, 1212–1221
B	4*H*-Pyrazino[2,3-*d*][1,3]oxazin-4-ones	150, 432, 432a, 457, 778, 780, 781, 783–786, 858, 1159, 1222
C	Pyrazino[2,3-*b*]pyrazines	370, 812, 1223
D	Imidazo[4,5-*b*]pyrazines	369, 374, 409, 684, 773, 834, 880, 891, 907, 957, 963, 1181, 1224–1227
E	1,2,5-Thiadiazolo[3,4-*b*]pyrazines	970, 1228
F	2*H*-Pyrazino[2,3-*e*][1,2,4]thiadiazine 1,1-dioxide	1101
G	5*H*-Pyrazino[2,3-*b*][1,4]thiazines	1004, 1009, 1010, 1142, 1229
H	Thiazolo[4,5-*b*]pyrazines	805, 1012
I	Imidazo[1,2-*a*]pyrazines	973, 1230–1232
J	3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyrazines	1233
K	Pyrrolo[2,3-*b*]pyrazines	1195, 1200
L	*S*-Triazolo[1,5-*a*]pyrazines	1198, 1199, 1234, 1235
M	Imidazolino[1,2-*a*]pyrazines	834
N	Pyrido[2,3-*b*]pyrazines	1236, 1237
O	7*H*-Pyrazino[2,3-*f*][1,4]diazepines	1197
P	Imidazo[1,5-*a*]pyrazines	690, 1202
Q	*s*-Triazolo[4,3-*a*]pyrazines	775, 826, 828, 846, 971, 973, 1123, 1238
R	4*H*-Pyrazino[2,1-*c*]-*as*-triazines	1239

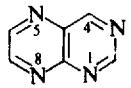
Pyrazine	Reagent (and Conditions)	Product	Refs.
			
	(A) Pteridine		
$2\text{-}NH_2\text{-}3\text{-}CONH_2$	$Ac_2O/HC(OEt)_3$, or HCOOH at 115°	4-OH	1212

TABLE VIII.1 *Continued*

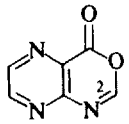
Pyrazine	Reagent (and Conditions)	Product	Refs.
2-NH_2-3-$CONH_2$	$Ac_2O/MeC(OEt)_3$	4-OH-2-Me	987, 1213
2-NH_2-3-$CONH_2$	$HCONH_2$/NaOBu	4-OH	987
2-NH_2-3-$CONH_2$	$MeCONH_2$/NaOBu	4-OH-2-Me	987
2-NH_2-3-$CONH_2$	F_3CCONH_2/NaOEt	4-OH-2-CF_3	987
2-NH_2-3-$CONH_2$	$PhCONH_2$/NaOBu	4-OH-2-Ph	987
2-NHCOMe-3-$CONH_2$	*N* KOH	4-OH-2-Me	987
2-NH_2-3-$CSNH_2$	$Ac_2O/HC(OEt)_3$	4-SH	1212
2-NH_2-3-$CSNH_2$	F_3CCONH_2/NaOEt	4-SH-2-CF_3	987
2-NHMe-3-$CONH_2$	Ac_2O/HCOOH	1-Me-4=O	423
2-NH_2-3-CONHMe	Ac_2O/HCOOH	3-Me-4=O	421
2-NH_2-3-CONHMe	$Ac_2O/HC(OEt)_3$	3-Me-4=O	1213
2-NH_2-3-CONHEt	$Ac_2O/HC(OEt)_3$	3-Et-4=O	1213
2-NH_2-3-$CONHC_6H_{11}$	$Ac_2O/EtC(OEt)_3$	3-C_6H_{11}-2-Et-4=O	1213
2-NH_2-5-CN-6-OMe-3-C(NH)OMe	$Ac_2O/HC(OEt)_3$	6-CN-4,7$(OMe)_2$	484
3-NH_2-2-$CONH_2$-5-Me	$Ac_2O/HC(OEt)_3$	4-OH-7-Me	435
2-NH_2-3-$CSNH_2$-5,6-Ph_2	$Ac_2O/HC(OEt)_3$	4-SH-6,7-Ph_2	455
2-NH_2-3-$CONHCH_2Ph$-5,6-Ph_2	$Ac_2O/HC(OEt)_3$	3-CH_2Ph-4=O-6,7-Ph_2	455
2-NH_2-3-CONHBu-5,6-Ph_2	Ac_2O/HCOOH	3-Bu-4=O-6,7-Ph_2	455
2-NH_2-3-$CONHCH_2Ph$-5,6-Ph_2	Ac_2O/HCOOH/NaAc	3-CH_2Ph-4=O-6,7-Ph_2	451
2-NH_2-3-$CONH_2$-5-Cl	$Ac_2O/HC(OEt)_3$	6-Cl-4-OH	432, 432a, 778, 780, 783, 786, 858
2-NH_2-3-CONHMe-5-Cl	$Ac_2O/HC(OEt)_3$	6-Cl-3-Me-4=O	778, 783
2-NH_2-3-CONHPh-5-Br	$Ac_2O/MeC(OEt)_3$	6-Br-2-Me-4=O-3-Ph	1213
2-NH_2-3-$CONH_2$-5,6-Ph_2	PhCOCl	4=O-2,6,7-Ph_3	1165
2-NH_2-3-$CONHCH_2Ph$-5,6-Ph_2	PhCOCl	3-CH_2Ph-4=O-2,6,7-Ph_3	1165
2-NH_2-3-$CONH_2$-5,6-Ph_2	PhNCS/pyridine	2-SH-4=O-3,6,7-Ph_3	1165
2-NH_2-3-CONHBu-5,6-Ph_2	PhNCS/pyridine	2-NHPh-4=O-3,6,7-Ph_3	1165
2-NH_2-5,6-Ph_2-3-$CSNH_2$	PhCOCl	2,6,7-Ph_3-4=S	1165

TABLE VIII.1 *Continued*

Pyrazine	Reagent (and Conditions)	Product	Refs.
2-NH_2-5,6-Ph_2-3-$CSNH_2$	PhNCS/pyridine	2-NHPh-6,7-Ph_2-4=S	1165
2-NH_2-3-$CONHCH_2$Ph-5,6-Ph_2	$HCONH_2$/190°	4-OH-6,7-Ph_2	455
2-NH_2-3-CONHBu-5,6-Ph_2	$HCONH_2$/190°	4-OH-6,7-Ph_2	455
2-NH_2-3-$CONH_2$	$F_3CCOOH/(F_3CCO)_2O$	4-OH-2-CF_3	987
2-NH_2-3-$CONH_2$	F_3CCONH_2/NaOEt	4-OH-2-CF_3	987
2-NH_2-3-$CSNH_2$	F_3CCONH_2/NaOEt	4-SH-2-CF_3	987
2-$CONH_2$-5,6-Ph_2-3-NHCONHPh	Polyphosphoric acid	2-OH-4=O-3,6,7-Ph_3	1165
2-$CONH_2$-3-NHCSNHPr^i-5,6-Ph_2	NaOEt	3-Pr^i-2-SH-4=O-6,7-Ph_2 and 4-OH-2-NHPr^i-6,7-Ph_2	1165
2-$CONHCH_2$Ph-3-NHCSNHPr^i-5,6-Ph_2	NaOEt	3-CH_2Ph-2-NHPr^i-4=O-6,7-Ph_2	1165
2-$CONHCH_2$Ph-3-NHCOOEt-5,6-Ph_2	NaOEt	3-CH_2Ph-2-OH-4=O-6,7-Ph_2	455
2-CONHBu-3-NHCOOEt-5,6-Ph_2	NaOEt	3-Bu-2-OH-4=O-6,7-Ph_2	455
2-NH_2-3-CSNHBu-5,6-Ph_2	$HCOOH/Ac_2O$	3-Bu-6,7-Ph_2-4=S	455
2-NH_2-3-CSNHBu-5,6-Ph_2	$Ac_2O/HC(OEt)_3$	3-Bu-6,7-Ph_2-4=S	455
2-NH_2-3-CSNHBu-5,6-Ph_2	ClCOOEt	3-Bu-2-OH-4-SH-6,7-Ph_2	455
2-OH-6-NHMe-3,5-$(CONHMe)_2$	ClCOOEt	7-OH-1,3-Me_2-6-CONHMe-2,4(=O)$_2$	440
2-NH_2-3-$CONHN=CMe_2$	$Ac_2O/HC(OEt)_3$	3-N=CMe_2-4=O	1214
2-NH_2-3-CONHN=CHPh	$Ac_2O/HC(OEt)_3$	4=O-3-N=CHPh	1214
2-NH_2-3-CONHOH	$Ac_2O/HC(OEt)_3$	4-OH/1-oxide	1215
2-NHCOMe-3-COOH	$PhNH_2/PCl_3$/toluene	2-Me-4=O-3-Ph	1216
2-NHAc-3-$CONHNH_2$	Pr^{i}OH reflux	3-NH_2-2-Me-4=O	433a
2-NHCOPr-3-$CONHNH_2$	Pr^{i}OH reflux	3-NH_2-4=O-2-Pr	433a
2-NHCOPh-3-$CONHNH_2$	$BuOH/Et_3N$/reflux	3-NH_2-4=O-2-Ph	433a
2-NH_2-3-CN-5-Me(R)	$H_2NC(NH)NH_2$	2,4-$(NH_2)_2$-6-Me(R)	532
2-NH_2-3-CN-5-halogeno-6-subst	$H_2NC(NH)NH_2$	2,3-$(NH_2)_2$-6-halogeno-7-subst	879, 1217, 1218
2-NH_2-3-CN-5(and 6)-subst	$H_2NC(NH)NH_2$	2,4-$(NH_2)_2$-6(and 7)-subst	529, 534, 538, 542, 762, 874, 1028, 1030, 1031, 1038–1041, 1218

TABLE VIII.1 *Continued*

Pyrazine	Reagent (and Conditions)	Product	Refs.
2-NH_2-3-CN	$HN{=}CHNH_2 \cdot MeCOOH$/pentanol	4-NH_2	803
2-NH_2-3-$CONH_2$	$HN{=}CHNH_2 \cdot MeCOOH$/BuOH	4-OH	987
2-NH_2-3-CN	EtOOCCOCl	2-COOEt-3,4-H_2	1184
2-CN-3-N(Me)COOEt-5-Ph	NaOMe	1-Me-2,4-(=O)$_2$-7-Ph	453
2-NH_2-3-CH_2NH_2	$MeC(OEt)_3$	2-Me-3,4-H_2	1183, 1184
2-NH_2-3-CH_2NH_2	$HC(OEt)_3$	3,4-H_2	1183, 1184
2-NH_2-3-CH_2NH_2-5-Me	$HC(OEt)_3$	6-Me-3,4-H_2	1183, 1184
2-NH_2-3-CONHOMe	$HCOOH/Ac_2O$	3-OMe-4=O	427
2-NH_2-3-CONHOMe	Ac_2O/AcOH	3-OMe-2-Me-4=O	427
2-NH_2-3-CH_2NHCOOEt	NaOEt	2-OH-3,4-H_2	1183, 1219
2-$NHCH_2$Ph-3-$CONH_2$-5,6-Me_2	Ac_2O/HCOOH	1-CH_2Ph-6,7-Me_2-4=O	379
2-$NHCH_2$Ph-3-$CONH_2$	$(EtO)_2CHNMe_2$	1-CH_2Ph-4=O	379
2-$NHCH_2$Ph-3-$CONH_2$	ClCOOEt	1-CH_2Ph-2,4-(=O)$_2$	379
2-NHCOMe-3-$CONH_2$	*N* KOH	4-OH-2-Me	987
3-$CONH_2$-2-NHCOEt	NH_3	2-Et-4-OH	457
2-CN-3-N=$CHNMe_2$	NH_4OAc	4-NH_2	803
2-CN-3-N=$CHNMe_2$	NaHS	4-SH	803
2-NHCOMe-3-CHO	NH_3/EtOH	2-Me	1075
2-NHCOOEt-3-CHO	NH_3/EtOH	2-OH	1075
2-NH_2-3-CPh=NH	$COCl_2$/pyridine/toluene/— 20°	2-OH-4-Ph	1220, 1221
2-NH_2-3-(imidazol-2′-yl)	$HC(OEt)_3$	Imidazo[1,2-*c*]-(pteridine)	455a
2-NH_2-3-(imidazol-2′yl)	$MeC(OEt)_3$	6-Methylimidazo[1,2-*c*](pteridine)	455a
2-NH_2-3-(imidazol-2′yl)	$F_3CCOOH/Et(OEt)_3$	6-Ethylimidazo[1,2-*c*](pteridine)	455a



(B) 4*H*-Pyrazino[2,3-*d*][1,3]oxazin-4-one

TABLE VIII.1 *Continued*

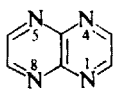
Pyrazine	Reagent (and Conditions)	Product	Refs.
2-NH_2-3-COOH	$(EtCO)_2O$	2-Et	457
2-NH_2-3-COOH-5-Me	Ac_2O/95°	2,6-Me_2	783
2-NH_2-5-SCH_2Ph-3-COOH	Ac_2O/100°	6-SCH_2Ph-2-Me	432, 778, 780, 783, 786, 858
2-NH_2-3-COOH-5-SO_2Me	Ac_2O	2-Me-6-SO_2Me	432, 778, 783
2-NH_2-3-COOH-5-Cl	Ac_2O/100°	6-Cl-2-Me	150, 432a, 781, 783–785 1159, 1222
2-NH_2-3-COOH-5-SMe	Ac_2O/95°	2-Me-6-SMe	783, 858
2-NH_2-3-COOH-5-NMe_2	Ac_2O/95°	6-NMe_2-2-Me	783, 1222
2,6-$(NH_2)_2$-3-COOH-5-Cl	Ac_2O	7-NHAc-6-Cl-2-Me	783
2,6-$(NH_2)_2$-3-COOH-5-Cl	$(PrCO)_2O$	6-Cl-7-NHCOPr-3-Pr	783
	 (C) Pyrazino[2,3-*b*]-pyrazine		
2,3-$(NH_2)_2$	OCHCHO	Unsubstituted	370
2,3-$(NH_2)_2$	OCMeCHO	2-Me	370
2,3-$(NH_2)_2$	OCMeCMeO	2,3-Me_2	370, 812, 1223 (?)
2,3-$(NH_2)_2$-5,6-Me_2	OCMeCHO	2,3,6-Me_3	370
2,3-$(NH_2)_2$-5,6-Me_2	OCMeCMeO	2,3,6,7-Me_4	370, 812
2,3-$(NH_2)_2$	EtOOCCOOEt	2,3-$(OH)_2$	370
2,3-$(NH_2)_2$	EtOOCCH(OH)OEt	2-OH	370

TABLE VIII.1 *Continued*

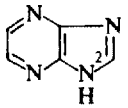
Pyrazine	Reagent (and Conditions)	Product	Refs.
			
	(D) Imidazo[4,5-*b*]pyrazines		
$2,3\text{-}(NH_2)_2$	$HC(OEt)_3$/140–150°	Unsubstituted	369
$2,3\text{-}(NH_2)_2$	Ac_2O/140°	2-Me	369
$2,3\text{-}(NH_2)_2$	H_2NCONH_2/160°/2 h	2-OH	369
$2\text{-}NH_2\text{-}3\text{-}CONHOH$	$C_6H_5SO_2Cl$/NaOH	2-OH	1224
$2,3\text{-}(NH_2)_2$	$HOCH_2COOH$	$2\text{-}CH_2OH$	369
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Me_2$	$HC(OEt)_3$/140–200°	$5,6\text{-}Me_2$	374
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Me_2$	MeCOCl	$2,5,6\text{-}Me_3$	374
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Me_2$	H_2NCONH_2/200°	$2\text{-}OH\text{-}5,6\text{-}Me_2$	374
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Ph_2$	$HC(OEt)_3$/140–145°	$5,6\text{-}Ph_2$	834
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Ph_2$	Ac_2O	$2\text{-}Me\text{-}5,6\text{-}Ph_2$	834
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Ph_2$	H_2NCONH_2/160–170°	$2\text{-}OH\text{-}5,6\text{-}Ph_2$	834
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Cl_2$	Ac_2O	$5,6\text{-}Cl_2\text{-}2\text{-}Me$	773
$2\text{-}NH_2\text{-}3\text{-}NHCH_2CH_2CH_2NMe_2$	Ac_2O	$1\text{-}CH_2CH_2CH_2NMe_2\text{-}2\text{-}Me$	1225
$2\text{-}NH_2\text{-}5\text{-}Cl\text{-}6\text{-}NMe_2\text{-}3\text{-}CONHNH_2$	HNO_2/Δ	$5\text{-}Cl\text{-}6\text{-}NMe_2\text{-}2\text{-}OH$	891, 963
$2\text{-}NH_2\text{-}5\text{-}Cl\text{-}6\text{-}NHEt\text{-}3\text{-}CONHOH$	185°	5-Cl-6-NHEt-2-OH	957
$2\text{-}NH_2\text{-}6\text{-}Cl\text{-}3\text{-}NHCONMe_2\text{-}5\text{-}NHEt$	Δ	5-Cl-6-NHEt-2-OH	1181
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}(COOMe)_2$	Ac_2O	$1\text{-}Ac\text{-}5,6\text{-}(COOMe)_2\text{-}2\text{-}Me$	409
$2\text{-}NH_2\text{-}3\text{-}CON_3\text{-}5\text{-}Cl$	Δ	5-Cl-2-OH	1226
$2\text{-}NH_2\text{-}3\text{-}CONHNH_2\text{-}5\text{-}NHEt$	$C_5H_{11}{}^iNO_2/MeOCH_2CH_2OH$	5-NHEt	880
$2\text{-}NH_2\text{-}3\text{-}NHMe\text{-}5,6\text{-}Me_2$	$HC(OEt)_3$/75–80°	$1,5,6\text{-}Me_3$	907
$2\text{-}NH_2\text{-}3\text{-}NHMe\text{-}5,6\text{-}Me_2$	H_2NCONH_2/160–165°	$2\text{-}OH\text{-}1,5,6\text{-}Me_3$	907
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Cl_2$	$(F_3CCO)_2O$/xylene	$5,6\text{-}Cl_2\text{-}2\text{-}CF_3$	684, 1227

TABLE VIII.1 *Continued*

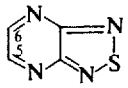
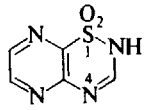
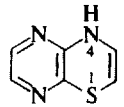
Pyrazine	Reagent (and Conditions)	Product	Refs.
			
	(E) 1,2,5-Thiadiazolo[3,4-*b*]pyrazine		
$2,3\text{-}(NH_2)_2$	$SOCl_2$/pyridine	Unsubstituted	970, 1228
$2,3\text{-}(NH_2)_2\text{-}5,6\text{-}Cl_2$	$SOCl_2$/pyridine	$5,6\text{-}Cl_2$	970, 1228
			
	(F) 2*H*-Pyrazino[2,3-*e*][1,2,4]thiadiazine 1,1-dioxide		
$2\text{-}NH_2\text{-}3\text{-}SO_2NH_2$	$HC(OEt)_3$	Unsubstituted	1101
			
	(G) 2(and 4)*H*-Pyrazino[2,3-*b*][1,4]thiazine		
$2\text{-}NH_2\text{-}3\text{-}SCH_2CN\text{-}5,6\text{-}Ph_2$	KOH/MeOH	[2*H*] $3\text{-}NH_2\text{-}5,6\text{-}Ph_2$	1229
$2\text{-}NH_2\text{-}3\text{-}SCHMeCOOH\text{-}5,6\text{-}Ph_2$	–	[2*H*] $3\text{-}OH\text{-}5,6\text{-}Ph_2$	1010
$2\text{-}NHMe\text{-}3\text{-}SCH_2COOEt$	Heat	[2*H*] 3=0-4-Me-3,4-H_2	1004
$2\text{-}NH_2\text{-}3\text{-}SH$	$p\text{-}O_2NC_6H_4COCH_2Br$	[4*H*] $3\text{-}C_6H_4NO_2\text{-}p$	1009
$2\text{-}NH_2\text{-}3\text{-}SH\text{-}5,6\text{-}Ph_2$	$p\text{-}O_2NC_6H_4COCH_2Br$	[4*H*] $3\text{-}C_6H_4NO_2\text{-}p\text{-}5,6\text{-}Ph_2$	1142

TABLE VIII.1 *Continued*

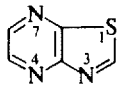
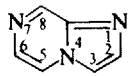
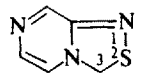
Pyrazine	Reagent (and Conditions)	Product	Refs.
			
	(H) Thiazolo[4,5-*b*]pyrazine		
2-NH_2-5-Br-3-SH	$HC(OEt)_3$	6-Br	805
2-NH_2-5-Br-3-SH	Ac_2O	6-Br-2-Me	805
2-NH_2-5,6-Cl_2-3-SH	$(ClCH_2CO)_2O$	5,6-Cl_2-2-CH_2Cl	1012
			
	(I) Imidazo[1,2-*a*]pyrazine		
2-NH_2	MeCOCHO	3-OH-2-Me	1230
2-NH_2-5-Ph	MeCOCOOH	3-OH-2-Me-6-Ph	1231
2-NH_2-5-(indol-3′-yl)	CH_3COCHO	3-OH-6-(indol-3′-yl)-2-Me	1231
2-NH_2-3-$(CH_2)_3NHC(NH)NH_2$-5-(indol-3′-yl)	Bu^sCOCHO	2-Bu^s-3-OH-6-(indol-3′-yl)-8-$(CH_2)_3$NHC-(NH)NH_2	1231
2-NH_2-3,5-Br_2	$BrCH_2CH(OMe)_2$/HBr	6,8-Br_2	973
2-NH_2	$BrCH_2CHO$	Unsubstituted	1232
			
	(J) 3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyrazine		
2-NH_2	CCl_3SH/Et_3N	3-(Pyrazin-2′-ylimino)	1233

TABLE VIII.1 *Continued*

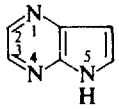
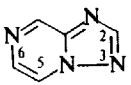
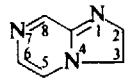
Pyrazine	Reagent (and Conditions)	Product	Refs.
			
	(K) Pyrrolo[2,3-*b*]pyrazine		
2-NH_2-3-Me	$HCOOH/Ac_2O$; NaOEt/325°	Unsubstituted	1200
2-Me-3-N=CHNMePh	$NaNH_2$/PhNHMe/Δ	Unsubstituted	1195
2-NHN : $CHCH_2R$	$HOCH_2CH_2OH$/Δ	7-Me	1195
			
	(L) *s*-Triazolo[1,5-*a*]pyrazine		
2-NHCH=NOH	Polyphosphoric acid	Unsubstituted	1234
2-NHC(NH)Me	$Pb(OAc)_4$/AcOH	2-Me	1198, 1199
2-$\overset{+}{N}$-$\overset{+}{S}Me_2$	ONCCOOEt	2-COOEt/3-oxide	1235
			
	(M) Imidazolino[1,2-*a*]pyrazine		
5-$NHCH_2CH_2OH$-2,3-Ph_2	$SOCl_2$	5,6-Ph_2	834

TABLE VIII.1 *Continued*

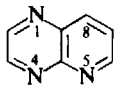
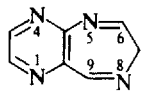
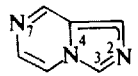
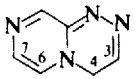
Pyrazine	Reagent (and Conditions)	Product	Refs.
			
	(N) Pyrido[2,3-*b*]pyrazine		
2-Cl-6-NHCH=C(COOEt)$_2$	Ph_2O/260–270°	3-Cl-7-COOEt-8-OH	1236, 1237
			
	(O) 7*H*-Pyrazino[2,3-*f*][1,4]-diazepine		
2-COPh-3-NHCOCH$_2$Br	NH_3	6-OH-9-Ph	1197
			
	(P) Imidazo[1,5-*a*]pyrazine		
2-CH$_2$NHCHO	$POCl_3$	Unsubstituted	690
2-CH$_2$NHCOPh	Polyphosphoric acid	3-Ph	1202
			
	(Q) *s*-Triazolo[4,3-*a*]pyrazine		

TABLE VIII.1 *Continued*

Pyrazine	Reagent (and Conditions)	Product	Refs.
2-$NHNH_2$	$HC(OR)_3$	Unsubstituted	846
2-Cl-6-$NHNH_2$	$MeCOOCH(OEt)_2$	5-Cl	973
2-$NHNH_2$-3-Me	$HC(OR)_3$	8-Me	775, 826
2-$NHNH_2$-3,5-Me_2	CNCl	3-NH_2-6,8-Me_2	1238
2-$NHNH_2$-5-Me-3-Pr	CNCl	3-NH_2-6-Me-8-Pr	826
2-$NHNH_2$-3-Pr	$COCl_2$	3-OH-8-Pr	826
2-$NHNH_2$-5-Me-3-Pr	CS_2	3-SH-6-Me-8-Pr	826
2-Cl-3-$NHNH_2$	$HC(OEt)_3$	8-Cl	828
	$MeC(OEt)_3$	8-Cl-3-Me	828
5-$NHNH_2$-2,3-$Ph_2(Me_2)$	CNCl	3-NH_2-5,6-$Ph_2(Me_2)$	971
2-$NHNH_2$	CNCl	3-NH_2	971
5-$NHNH_2$-2,3-$Ph_2(Me_2)$	$COCl_2$	3-OH-5,6-$Ph_2(Me_2)$	971
5-$NHNH_2$-2,3-Ph_2	$HC(OEt)_3$, HCOOH, $HCONMe_2$, or PhNCS	5,6-Ph_2	846
1-CN-2=O-3-Pr-5-R-1,2-H_2	NH_2NH_2/H_2O/0–10°	3-NH_2	1123
	 (R) 4*H*-Pyrazino[2,1-*c*]-*as*-triazine		
5-$NHNH_2$-2,3-Ph_2	$PhCOCH_2Br$	3,6,7-Ph_3	1239

The reactions of 2-(3′-dimethylaminopropyl)pyrazine with sodium amide in liquid ammonia and aliphatic, aromatic, and heterocyclic esters to give ketones have been described in Section IV.2A(3) (645), and with ketones to give carbinols in Section IV.2C(5) (707).

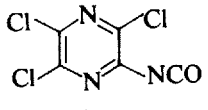
(8) *Replacement of Hydrazino Substituents by Hydrogen*

Hydrazino substituents may be replaced by hydrogen: 2,3,5-trifluoro-6-hydrazinopyrazine warmed with aqueous copper sulfate gave 2,3,5-trifluoropyrazine (885); 2,3-difluoro-5-hydrazino-6-methoxypyrazine similarly treated gave 2,3-difluoro-5-methoxypyrazine (885); and 2,3,5-trichloro-6-hydrazinopyrazine with potassium hydroxide in ethylene glycol at 150° gave 2,5-dichloropyrazine (?) (896).

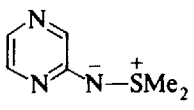
(9) *Other Reactions*

2-Aminopyrazine undergoes the carbylamine test (397, 1171).

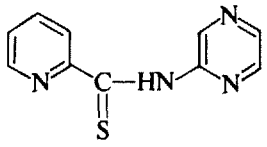
2-Amino-3,5,6-trichloropyrazine refluxed with oxalyl chloride in benzene gave 2,3,5-trichloro-6-isocyanatopyrazine (**31**) (1240–1242). 2-Aminopyrazine and dimethyl sulfide in tetrahydrofuran at −20° with *N*-chlorosuccinimide formed *S,S*-dimethyl-*N*-pyrazinylsulfimide (**32**) (1235), and 2-aminopyrazine refluxed with sulfur and 2-methylpyridine produced 2-(pyridin-2′-yl)thiocarbonylaminopyrazine (**33**) (1243).



(**31**)

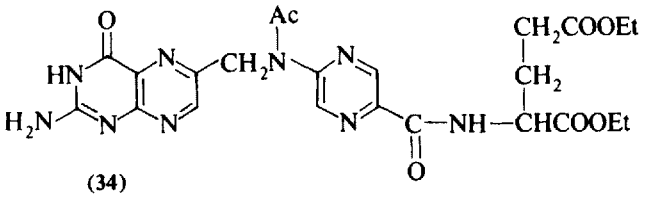


(**32**)

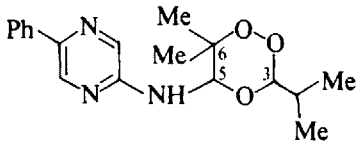


(**33**)

A 2-amino-5-substituted-pyrazine refluxed with *p*-toluenethiol, 2-methoxyethanol, and 2-amino-6-formyl-4-hydroxypteridine followed by heating with acetic anhydride gave the 2-amino-4-hydroxy-6-[*N*-(5′-substituted-pyrazin-2′-yl)-acetamidomethyl]pteridine (**34**) (1244). 2-Amino-5-phenylpyrazine with isobutyraldehyde in ether at room temperature gave 2-(3′-isopropyl-6′,6′-dimethyl-5′,6′-dihydro-1′,2′,4′-trioxin-5′-yl)amino-5-phenylpyrazine (**35**) (1245).



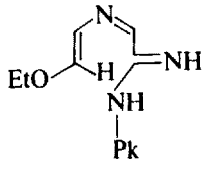
(34)



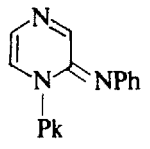
(35)

Equimolar quantities of 2-aminopyrazine and picryl chloride at 25° for 1 hour were found to give 1-ethoxy-5-imino-5-picrylamino-3-aza-1,3-pentadiene (**36**), but treatment of 2-aminopyrazine with two molar equivalents of picryl fluoride in dimethylformamide gave 1-picryl-2-picrylimino-1,2-dihydropyrazine (**37**) (1246). 2-Aminopyrazine with acetonitrile and aluminum chloride and then heated at 190° gave 2-(1′-iminoethylamino)pyrazine (**38**) (1199). 2-Aminomethylpyrazine with ethylene oxide gave 2-(2′-hydroxyethyl)aminomethylpyrazine and 2-di(2′-hydroxyethyl)aminomethylpyrazine (1029). 2-Amino-3-chloropyrazine heated with 10-methoxy-1,6-dimethylergoline-8β-methanol tosylate in dimethylformamide containing sodium hydride at 50° gave compound (**39**) (similar reactions also occurred with mercaptopyrazines) (1247).

Photolysis of *N*-ethoxycarbonyliminopyrazinium ylides (**40**) gave the pyrazoles (**41**) (1248).

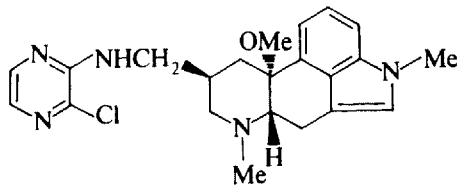


(36)

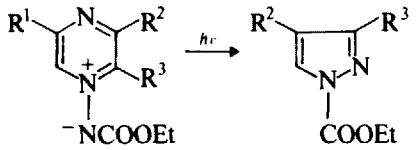


(37)

(38)



(39)



(40) (41)

E. Urethanes (Alkoxycarbonylaminopyrazines)

Urethanes may be prepared from azidocarbonyl compounds by heating with anhydrous alcohols [see Section 1A(6)]. In this way 2,5-bisazidocarbonylpyrazine (with benzyl alcohol at 180–220°) gave 2,5-bis-*N*-benzyloxycarbonylaminopyrazine (5) (1176); 2-azidocarbonyl-5-carbamoylpyrazine (at 150°) gave 2-*N*-benzyloxycarbonylamino-5-carbamoylpyrazine (676, 1249); 2-azidocarbonyl-5-ethoxycarbonylpyrazine (at 100°) gave 2-*N*-benzyloxycarbonylamino-5-ethoxycarbonylpyrazine (676, 1249); 2-azidocarbonyl-5-phenylpyrazine (at 150°) gave 2-benzyloxycarbonylamino-5-phenylpyrazine (376); 2-azidocarbonyl-6-phenylpyrazine (at 150°) gave 2-benzyloxycarbonylamino-6-phenylpyrazine (352); 3-azidocarbonyl-2,5-dimethoxypyrazine (at 180°) gave 3-benzyloxycarbonylamino-2,5-dimethoxypyrazine (881); and 2-azidocarbonyl-3,5-dimethoxypyrazine (at 100°) gave 2-benzyloxycarbonylamino-3,5-dimethoxypyrazine and 3-azidocarbonyl-2,5-dimethoxypyrazine (at 180°) gave 3-benzyloxycarbonyl-3,5-dimethoxypyrazine (881).

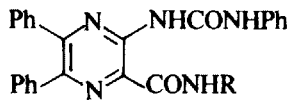
2,5-Bis(azidocarbonyl)pyrazine at reflux with ethanol gave 2,5-bis(ethoxycarbonylamino)pyrazine (1172); 2-carbamoylpyrazine when subjected to the Hofmann degradation gave the sodium salt of 2-carboxyaminopyrazine (which on acidification gave 2-aminopyrazine) (1171).

2-Amino-3-aminomethylpyrazine and ethyl chloroformate ($Et_3N/CHCl_3$) gave 2-amino-3-ethoxycarbonylaminomethylpyrazine (1184); 2-amino-3-*N*-benzyl(and butyl)carbamoyl-5,6-diphenylpyrazine refluxed with ethyl chloroformate gave 2-*N*-benzyl(and butyl)carbamoyl-3-ethoxycarbonylamino-5,6-diphenylpyrazine (455); and 2-amino-3-*N*-methylcarbamoyl-5,6-diphenylpyrazine refluxed with ethyl chloroformate for 20 hours gave 2-ethoxycarbonylamino-3-*N*-methylcarbamoyl-5,6-diphenylpyrazine (1250).

The conversion of urethanes to amines by acid hydrolysis and by catalytic hydrogenation has been described in Section 1A(6).

F. Ureidopyrazines

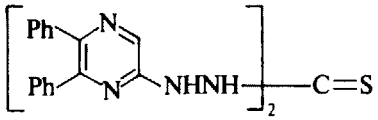
Some ureido- and thioureidopyrazines have been prepared from aminopyrazines with phenyl isocyanate in pyridine, potassium thiocyanate in acid solution, and with phenyl or isopropyl isothiocyanate in pyridine. Thus 2-amino-3-carbamoyl(and *N*-benzylcarbamoyl)-5,6-diphenylpyrazines refluxed with phenyl isocyanate in



(42)

pyridine gave 2-carbamoyl(and *N*-benzylcarbamoyl)-5,6-diphenyl-3-(3′-phenylureido)pyrazines (**42**, R = H, CH_2Ph) (1165); 2-amino-3-carbamoyl-5,6-diphenylpyrazine refluxed in pyridine with phenyl and isopropyl isothiocyanate gave 2-carbamoyl-5,6-diphenyl-3-[3′-phenyl(and 3′-isopropyl)thioureido]pyrazines (1165); 2-aminopyrazine with potassium thiocyanate and one equivalent of hydrochloric acid gave 2-thioureidopyrazine (138); and 2-amino-5-chloropyrazine with 2,6-dichlorobenzoylisocyanate gave 3-(5′-chloropyrazin-2′-yl)-1-(2′,6′-dichlorobenzoyl)-urea (1251). 5-(2′-Dimethylaminoethyl)amino-2,3-dimethylpyrazine with dimethylaminoformyl chloride gave 5-[*N*-(2′-dimethylaminoethyl)-*N*-(dimethylaminoformyl)-amino]-2,3-dimethylpyrazine (925).

5-Hydrazino-2,3-diphenylpyrazine refluxed with carbon disulfide in pyridine gave a poor yield of 1,3-bis(2′,3′-diphenylpyrazin-5′-ylamino)thiourea (**43**) (846).

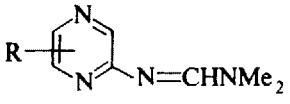


(43)

G. Other Substituted Aminopyrazines

(1) *Dimethylaminomethyleneamines, Hydroxyiminomethylamines, and Alkoxymethyleneamines*

Treatment of some aminopyrazines with dimethylformamide dimethyl acetal or with dimethylformamide and a little phosphoryl chloride has been shown to give dimethylaminomethyleneaminopyrazines (**44**), some of which have been converted with hydroxylamine to the hydroxyiminomethylamino (or hydroxyaminomethyleneamino) analogue. 2-Aminopyrazine (and its 5- and 6-chloro derivatives) (1234) and 2-amino-3,5-dibromopyrazine (1252) each reacted in this way with dimethylformamide dimethyl acetal and the products were converted to the corresponding hydroxyiminomethylaminopyrazine; 3-cyano-2-dimethylaminomethyleneamino-5(and 6)-methylpyrazines were prepared similarly (1031); and 2-dimethylamino-

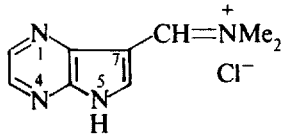


(44)

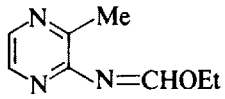
methylenehydrazinopyrazine and its 6-chloro derivative were prepared by an analogous procedure from the corresponding hydrazinopyrazine (973).

In reactions with dimethylformamide and phosphoryl chloride, 2-amino-3-carbamoylpyrazine or 2-amino-3-cyanopyrazine gave 2-cyano-3-dimethylaminomethyleneaminopyrazine (803); 2-amino-3,5-dicyano-6-ethoxypyrazine gave 2,6-dicyano-3-dimethylaminomethyleneamino-5-ethoxypyrazine (484); and 6-substituted 2-amino-3-carbamoyl-5-halogenopyrazines (also with dimethylformamide–thionyl chloride) gave 5-substituted 2-cyano-3-dimethylaminomethyleneamino-6-halogenopyrazines (1253), which were hydrolyzed to 6-substituted 2-amino-3-cyano-5-halogenopyrazines (808, 877, 1218, 1253). 2-Amino-3-methylpyrazine with a limited amount of phosphoryl chloride and dimethylformamide gave 2-dimethylaminomethyleneamino-3-methylpyrazine but with preformed phosphoryl chloride–dimethylformamide complex gave 7-dimethylimmoniomethyl-5*H*-pyrrolo[2,3-*b*]pyrazine chloride (**45**), which after hydrolysis produced 7-formyl-5*H*-pyrrolo[2,3-*b*]pyrazine (1254).

2-Amino-3-methylpyrazine heated with triethyl orthoformate and ethanolic hydrogen chloride to 145° gave 2-ethoxymethyleneamino-3-methylpyrazine (**46**) 1195).



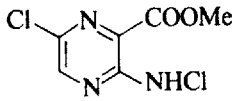
(**45**)



(**46**)

(2) *Chloroamines*

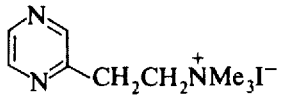
Chlorination of 2-amino-3-methoxycarbonylpyrazine in aqueous acetic acid gave 5-chloro-2-chloroamino-3-methoxycarbonylpyrazine (**47**), which reacts with sodium hydrogen sulfite to give 2-amino-5-chloro-3-methoxycarbonylpyrazine (150, 378a, 778, 779, 781–787).



(**47**)

(3) *Extranuclear Quaternized Pyrazines*

2-(2′-Dimethylaminoethyl)pyrazine was quaternized by methyl iodide to give 2-(2′-trimethylammonioethyl)pyrazine iodide (**48**) (which with aqueous sodium hydroxide gave 2-vinylpyrazine) (657); and 2-hydroxy-3-nitro-5,6-diphenylpyrazine

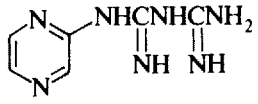


(48)

treated with thionyl chloride in the presence of dry pyridine gave the zwitterion of 2-hydroxy-5,6-diphenyl-3-pyridiniopyrazine (**12**) (hydrolyzed by acid to 2,3-dihydroxy-5,6-diphenylpyrazine) (863).

(4) *Guanidinopyrazines*

2-Aminopyrazine *p*-toluenesulfonate fused with cyanoguanidine at 150–155° gave 2-amidinoguanidinopyrazine (**49**), but 2-aminopyrazine hydrochloride did not react (1189).



(49)

2. NITRO- AND PHENYLAZOPYRAZINES

A. Preparation of Nitropyrazines

Nitropyrazines have been prepared commencing from carboxypyrazines by replacement of the carboxy group(s) and from hydroxypyrazines. The nitration of hydroxypyrazines, for example, 5-hydroxy-2,3-diphenylpyrazine with fuming nitric acid in acetic acid to give 2-hydroxy-3-nitro-5,6-diphenylpyrazine, has been described in Section VI.6E (817, 1065). Among the carboxypyrazines, 2-amino-3-carboxy-5-chloro-6-ethylaminopyrazine in sulfuric acid and treated for 30 minutes at 10–15° with nitric acid in sulfuric acid gave 58% 2-amino-5-chloro-6-ethylamino-3-nitropyrazine (1181) and controlled nitration of 2,6-diamino-3,5-dicarboxypyrazine in concentrated sulfuric acid by gradual addition of concentrated nitric acid at 10–15° in no more than a slight excess over the stoichiometric amount afforded 2,6-diamino-3,5-dinitropyrazine (84%) (1180).

Nitration of 2,5-dimethyl-3,6-diphenylpyrazine with nitric–sulfuric acid occurs in the benzene rings to give 2,5-dimethyl-3,6-di-*m*-nitrophenylpyrazine (191).

B. Reactions of Nitropyrazines

The action of either thionyl chloride or phosphoryl chloride upon 2-hydroxy-3-nitro-5,6-diphenylpyrazine was abnormal and resulted in loss of the nitro group and

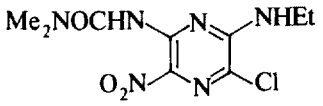
formation of only 2-chloro-3-hydroxy-5,6-diphenylpyrazine in the case of thionyl chloride, and this product together with 2,3-dichloro-5,6-diphenylpyrazine were formed in the case of phosphoryl chloride (817, 834). In an attempt to obtain the unknown 2-chloro-3-nitro-5,6-diphenylpyrazine by normal replacement of the hydroxyl group without loss of the nitro function, 2-hydroxy-3-nitro-5,6-diphenylpyrazine was treated with thionyl chloride in the presence of dry pyridine but gave the zwitterion of 2-hydroxy-5,6-diphenyl-3-pyridiniopyrazine (12), also obtained from 2-hydroxy-3-nitro-5,6-diphenylpyrazine with pyridine at 100° for 2 hours and from 2-chloro-3-hydroxy-5,6-diphenylpyrazine at reflux with pyridine in the presence of pyridine hydrochloride. Thus the nitro group was a better leaving group in this system than the chloro group (863). Acetyl chloride has been found to be the most effective agent for converting 2-hydroxy-3-nitro-5,6-diphenylpyrazine to 2-chloro-3-hydroxy-5,6-diphenylpyrazine (841) and acetyl bromide for preparing the bromo analogues (841).

2-Hydroxy-3-nitro-5,6-diphenylpyrazine heated with aqueous hydrazine gave 2-hydrazino-3-hydroxy-5,6-diphenylpyrazine (1124); whereas when refluxed with hydrazine and Raney nickel in methanol it gave 2-amino-3-hydroxy-5,6-diphenylpyrazine (1065).

2-Hydroxy-3-nitro-5,6-diphenylpyrazine was converted with 72% sulfuric acid at 82° to benzil (24%), 2,3-dihydroxy-5,6-diphenylpyrazine (41%), and an unidentified solid (20%) (1065). The formation of benzil under these conditions was proof that neither of the phenyl groups in the starting material was nitrated (1065). 2-Hydroxy-3-nitro-5,6-diphenylpyrazine refluxed with acetic–6*N* hydrochloric acid (1 : 1) for 1 hours also gave 2,3-dihydroxy-5,6-diphenylpyrazine (94%) (817).

2-Hydroxy-5-nitro-3-phenylpyrazine with phosphoryl chloride at reflux gave 2-chloro-5-nitro-3-phenylpyrazine but at 170° gave 2,5-dichloro-3-phenylpyrazine (817). Phenylhydroxynitropyrazines are claimed not to react with dimethyl sulfate in alkaline solution or with sodium ethoxide and ethyl iodide in hot ethanol (817).

Reduction of 2,6-diamino-3,5-dinitropyrazine in dimethylacetamide with hydrogen over platinum oxide (or with sodium sulfide and ammonium chloride in water at room temperature) gave 2,3,5-triamino-6-nitropyrazine (1180), but reduction with hydrogen and 10% palladium on charcoal at 50 p.s.i. gave tetraaminopyrazine (1180). 2-Amino-5-chloro-6-ethylamino-3-nitropyrazine with 1,1-dimethylurea and hydrochloric acid at reflux gave 2-chloro-5-(3′,3′-dimethylureido)-



(50)

3-ethylamino-6-nitropyrazine (**50**) (1181), which in dimethylformamide with triethylamine was reduced by hydrogen over palladium–charcoal to 2-amino-6-chloro-3-(3′,3′-dimethylureido)-5-ethylaminopyrazine (1181).

C. Preparation of Arylazopyrazines

The preparation of arylazo derivatives from hydroxypyrazines has been described in Section VI.6E; and from 1,4,6-trimethyl-3-methylene-2-oxo-1,2,3,4-tetrahydropyrazine to give 1,4,6-trimethyl-2-oxo-3-phenylazomethylene-1,2,3,4-tetrahydropyrazine in Section VI.9B. In addition to these reactions Princivalle (1122) reports that 2-carboxy-5-hydroxy-3,6-dimethylpyrazine reacted with benzenediazonium chloride and *p*-toluenediazonium chloride by elimination of the carboxy group para to the hydroxy group and coupling to form 2-hydroxy-3,6-dimethyl-5-phenylazo(and *p*-tolueneazo)pyrazines, respectively (1122), identical to those prepared from 3-hydroxy-2,5-dimethylpyrazine.

D. Reactions of Arylazopyrazines

2-Hydroxy-3,6-dimethyl-5-phenylazopyrazine is more acidic than 3-hydroxy-2,5-dimethylpyrazine (1125). The reduction of phenylazopyrazines to aminopyrazines has been described in Section 1A(7).

3. AMINOPYRAZINE *N*-OXIDES

A. Preparation of Aminopyrazine *N*-Oxides

(1) *By Primary Synthesis*

The preparation of 2-aminopyrazine 1-oxides from α-amino nitriles and α-hydroxyiminocarbonyl compounds has been described in Section III.1 (92, 93, 103, 377, 524–542). Armarego and Schou (1255) utilized known chemical procedures (531, 532) and prepared 2-amino-6-deuterio-3-ethoxycarbonyl-5-(partial)-trideuteriomethylpyrazine 1-oxide and 2-amino-3-cyano-6-deuterio-5-trideuteriomethylpyrazine 1-oxide.

(2) *Cleavage of N-Oxides of Pteridines and Related Systems*

Several *N*-oxides of pteridines and related ring systems have been cleaved to yield aminopyrazine *N*-oxides and these are listed in Table VIII.2 (450, 462, 907, 1222, 1256, 1257).

(3) *From Halogenopyrazine N-Oxides*

Preparations of aminopyrazine *N*-oxides from halogenopyrazine *N*-oxides have been described in Sections V.7A(1) and V.7B(3).

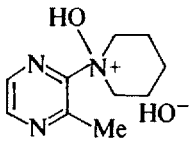
TABLE VIII.2 AMINOPYRAZINE *N*-OXIDES FROM CLEAVAGE OF *N*-OXIDES OF PTERIDINES AND RELATED RING SYSTEMS

N-Oxides of Pteridines and Related Ring Systems	Reagent (and Conditions)	Aminopyrazine *N*-oxide	Refs.
6-Dimethylamino-3-methyl-4-oxo-3,4-dihydropteridine 8-oxide	10% NaOH/100°	2-Amino-3-carboxy-5-dimethylamino/1-oxide	1222
7-Methoxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine 5-oxide	0.1 *N* KOH	5-Methoxy-3-methylamino-2-methylcarbamoyl/1-oxide (and 7-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine 5-oxide)	450
1,3,6,7-Tetramethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine 5-oxide	0.1 *N* NaOH/100°	3-Methylamino-2-methylcarbamoyl-5,6-dimethyl/1-oxide	1256
4-Hydroxy-1,6,7-trimethyl-2-oxo-1,2-dihydropteridine 5-oxide	*N* NaOH/100°	2-Carboxy-5,6-dimethyl-3-methylamino/1-oxide	1256
1,3,6,8-Tetramethyl-2,4,5,7-tetraoxo-1,2,3,4,5,6,7,8-octahydropyrimido[5,4-*g*]pteridine 10-oxide	4 *N* NaOH/60–70°	3,5-Bismethylamino-2,6-bismethylcarbamoyl/1-oxide, 2-carboxy-3,5-bismethylamino-6-methylcarbamoyl/1-oxide, and other products	462
2-Hydroxy-1,5,6-trimethylimidazo[4,5-*b*]pyrazine 4-oxide	60% H_2SO_4/reflux	2-Amino-3-methylamino-5,6-dimethyl/1-oxide	907
1,5,6-Trimethylimidazo[4,5-*b*]pyrazine 4-oxide	30% H_2SO_4/reflux or 2.5 *N* NaOH/reflux	2-Amino-3-methylamino-5,6-dimethyl/1-oxide	907
5,6-Dimethylimidazo[4,5-*b*]pyrazine 4,7-dioxide	60% H_2SO_4/reflux	2,3-Diamino-5,6-dimethyl/1,4-dioxide	907
6-Chloro-2-methyl-4*H*-pyrazino[2,3-*d*][1,3]oxazin-4-one 8-oxide	Guanidine/NaOMe	2-Acetamido-5-chloro-3-guanidinocarbonyl/1-oxide	1222, 1257
6-Dimethylamino-2-methyl-4*H*-pyrazino[2,3-*d*]-[1,3]oxazin-4-one 8-oxide	Guanidine/NaOEt	2-Acetamido-5-dimethylamino-3-guanidinocarbonyl/1-oxide	1222

(4) *By Oxidation of Aminopyrazines*

2-Aminopyrazine was oxidized by hydrogen peroxide in acetic acid at 20° to 3-aminopyrazine 1-oxide and at 50° for 15 hours to 2-aminopyrazine 1,4-dioxide (51%) (also obtained by similar oxidation of 3-aminopyrazine 1-oxide) (1189). *m*-Chloroperoxybenzoic acid was also used for the oxidation of 2-aminopyrazine to its 1-oxide (1258). The following aminopyrazine *N*-oxides have been prepared by oxidation (reagent and conditions): 2-amino-3-methoxycarbonylpyrazine 1-oxide (*m*-chloroperoxybenzoic acid in chloroform at reflux) (880, 1222); 2-amino-5-chloro-3-methoxycarbonyl(and methylcarbamoyl)pyrazine 1-oxide (*m*-chloroperoxybenzoic acid in chloroform at reflux) (1222); 2-amino-5-bromo-3-methoxycarbonylpyrazine 1-oxide (*m*-chloroperoxybenzoic acid in chloroform at reflux) (878, 879, 1222); 2-amino-3-chloropyrazine 1-oxide (peroxyacetic acid) (906); 2-amino-3-bromo-5,6-dimethylpyrazine 1-oxide (peroxyacetic acid) (907); and 2,3-bis(pyridin-2′-yl)pyrazine 1,4-dioxide (hydrogen peroxide in sulfuric acid at room temperature) (754).

Further preparations were the oxidation of 2-methyl-3-piperidinopyrazine with hydrogen peroxide in acetic or formic acid to 3-methyl-2-piperidinopyrazine 1-oxide and 2-(*N*′-hydroxy-*N*′-piperidinio)-3-methylpyrazine hydroxide (**51**) [which was dehydrated by sublimation to 2-methyl-3-(*N*′-piperidino-*N*′-oxide)pyrazine (**52**)] (793); the oxidation of 2-acetamidopyrazine with 30% hydrogen peroxide in acetic acid–acetic anhydride to a mixture of the 1-oxide (24%), 4-oxide (3-acetamidopyrazine 1-oxide) (21.5%), and 1,4-dioxide (8.1%) (1259); and the oxidation of 2-amino-3-cyanopyrazine 1-oxide (538) with hydrogen peroxide in trifluoroacetic acid and 2-amino-3-cyano-5-methylpyrazine 1-oxide (532) with hydrogen peroxide in trifluoroacetic anhydride at room temperature for 40 hours to the corresponding dioxides.



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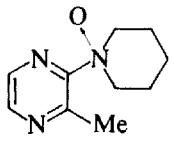
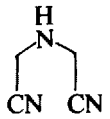


(52)

(5) *By Other Methods*

3-Aminopyrazine 1-oxide has been prepared from 3-carbamoylpyrazine 1-oxide with sodium hypobromite (108, 547a), and the interaction of "iminodiacetonitrile" (**53**) with a mixture of hydroxylamine and its hydrochloride gave 2-amino-6-hydroxyaminopyrazine 1-oxide (20.5%) (which was catalytically reduced in acetic acid with Adams catalyst to 2,6-diaminopyrazine 1-oxide (465). *N*-Amination of pyrazine 1-oxide and 2,5-dimethylpyrazine 1-oxide has been effected with hydroxylamine-*o*-sulfuric acid to give the 1-amino-4-oxidopyrazinium salt (iodide) (**54**) (610).



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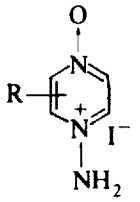


(54)

B. Properties of Aminopyrazine *N*-oxides

Ultraviolet spectral studies have revealed that 2- and 3-aminopyrazine 1-oxides with sulfuric acid protonate first at the ring nitrogen atom, and then diprotonation occurs at the oxygen of the *N*-oxide group (1260); and further ultraviolet and infrared data are said to show that 3-aminopyrazine 1-oxide is protonated by hydrochloric acid at N_4 and 2-aminopyrazine 1,4-dioxide at oxygen on N_1, whereas both compounds are monoprotonated by *p*-toluenesulfonic acid at the amino group (1189). Proton magnetic resonance measurements also show that 2-aminopyrazine 1,4-dioxide protonates at N_1 (1136). A comparison of the ultraviolet 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 existed predominantly in the amino form. This was also true of the 2,5-dimethyl homologue (921).

Dipole moments of 3-aminopyrazine 1-oxide (3.43 *D*, dioxane) (749) and 3,5-bisdimethylaminopyrazine 1-oxide (4.87, benzene) (663) have been measured. Second-order rate constants for hydrogen–deuterium exchange of H_2 and H_6 in sodium deuteroxide–deuterium oxide solutions of 3-amino- and 3-dimethylaminopyrazine 1-oxides have been determined as 2.3×10^{-1}, 1.1×10^{-3}, and 3.3×10^{-2} and 4.5×10^{-4} l/mol·min, respectively. These results (and those of other 3-substituted pyrazine 1-oxides) have been correlated with σ constants, and the log of the H2 exchange rates has been shown to be linearly related to the pK_a values of these compounds (745).

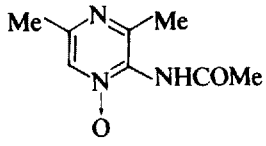
C. Reactions of Aminopyrazine *N*-Oxides

(1) *Replacement of Amino by Hydroxy Groups*

The conversion of aminopyrazine *N*-oxides to hydroxypyrazine *N*-oxides has been described in Section VI.10D.

(2) *Acetylation and Deacetylation*

Acetamidopyrazine *N*-oxides have been prepared readily from acetic anhydride and aminopyrazine *N*-oxides as follows: 2-acetamido-3,5-dimethylpyrazine 1-oxide



(55)

(55) (warmed on steam bath for 30 minutes) (524), 2,6-diacetamidopyrazine 1-oxide (room temperature for 38 hours) (465), and 2-acetamido-3-cyano-5-methylpyrazine 1,4-dioxide (532).

Deacetylations of the following compounds have been effected with 2.5 *N* hydrochloric acid: 2-acetamidopyrazine 1-oxide, 3-acetamidopyrazine 1-oxide, and 2-acetamidopyrazine 1,4-dioxide (1259); and 2-acetamido-5-chloro-3-guanidinocarbonylpyrazine 1-oxide (10 min on a steam bath) (1222) and its 5-dimethylamino, 5-methoxy, 5-benzylthio, and 5-benzylsulfonyl analogues (1222, 1257).

(3) *Bicyclic Compounds from Aminopyrazine N-Oxides*

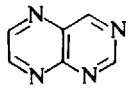
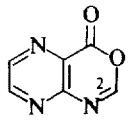
Some bicyclic heterocyclic *N*-oxides have been prepared from aminopyrazine *N*-oxides and some of these are listed together with the reagents in Table VIII.3 (528–531, 533, 534, 537, 539–541, 1039–1041, 1222).

(4) *Deoxygenation*

Aminopyrazine *N*-oxides may be readily deoxygenated. The most used reagent has been sodium dithionite in water or aqueous ethanol and the following compounds have been deoxygenated in this way: 2-amino-3,5-dimethylpyrazine 1-oxide (524); 2-amino-3,6-dimethylpyrazine 1-oxide (92); 2-amino-6-*s*-butyl-3-isobutylpyrazine 1-oxide (92); 2-amino-3-*s*-butyl-6-isobutylpyrazine 1-oxide (93); 2-amino-3-isobutyl-6-isopropylpyrazine 1-oxide (525); 2-amino-5-phenylpyrazine 1-oxide (377); 2,6-diacetamidopyrazine 1-oxide (465); 2-amino-3-cyano-6-methylpyrazine 1-oxide (534); 2-amino-3-cyano-5-methylpyrazine 1,4-dioxide (532); 2-amino-3-carbamoyl-5-methylpyrazine 1-oxide (531, 537); 2-carboxy-3,5-bis(methylamino)-6-*N*-methylcarbamoylpyrazine 1-oxide (462); 3,5-bis(methylamino)-2-*N*-methylcarbamoylpyrazine 1-oxide (462); and 2-amino-5-chloromethyl-3-cyanopyrazine 1-oxide (poor yield) (529) (but the isomeric 6-chloromethyl-compound underwent both deoxygenation and reductive dehalogenation) (529). Reduction of 2-amino-3-cyano-5-phenylpyrazine 1-oxide with sodium dithionite in boiling water gave 2-amino-3-cyano-5-phenylpyrazine and some 2-amino-5-phenylpyrazine (possibly formed by loss of hydrogen cyanide from an intermediate dihydropyrazine) (532).

Phosphorus trichloride alone (793), or more recently in tetrahydrofuran or dimethyl formamide, has been used in the deoxygenation of 2-methyl-3-piperidinopyrazine 1-oxide (793), 2-amino-3-cyanopyrazine 1-oxide (532), 2-amino-3-cyano-

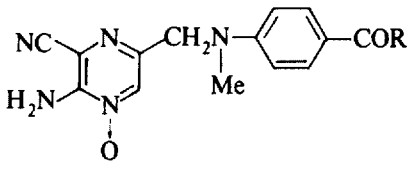
TABLE VIII.3 BICYCLIC HETEROCYCLIC *N*-OXIDES FROM PYRAZINE *N*-OXIDES

Pyrazine	Reagent (and Conditions)	Product	Refs.
	 Pteridine		
2-NH_2-3-CN/1-oxide	Guanidine/NaOMe/MeOH	2,4-$(NH_2)_2$/8-oxide	530
2-NH_2-3-CN-5-Me/1-oxide	Guanidine	2,4-$(NH_2)_2$-6-Me/8-oxide	537
2-NH_2-3-CN-6-Me/1-oxide	Guanidine/NaOMe/MeOH	2,4-$(NH_2)_2$-7-Me/8-oxide	534
2-NH_2-3-CN-5-CH_2OMe/1-oxide	Guanidine/NaOMe/MeOH	2,4-$(NH_2)_2$-6-CH_2OMe/8-oxide	529
2-NH_2-3-CN-5-CH=NOH/1-oxide	Guanidine	2,4-$(NH_2)_2$-6-CH=NOH/8-oxide	528
2-NH_2-3-CN-5-substituted/1-oxide	Guanidine	2,4-$(NH_2)_2$-6-substituted/8-oxide	1039–1041
2-NH_2-3-CN-6-CH=CHPh/1-oxide	Guanidine/NaOMe/MeOH	2,4-$(NH_2)_2$-7-CH=CHPh/8-oxide	534
2-NH_2-3-CN-6-OH-5-Me/1-oxide	Guanidine/NaOMe/MeOH	2,4-$(NH_2)_2$-7-OH-6-Me/8-oxide	533
2-NH_2-3-COOEt-5-CH=NOH/1-oxide	Guanidine/MeOH	2-NH_2-4-OH-6-CH=NOH/8-oxide	539
2-NH_2-3-$COOCH_2$Ph-5-[L-*erythro*-(CHOH · CHOHMe)]/1-oxide	Guanidine/NaOMe/DMF	2-NH_2-4-OH-6[L-*erythro*-(CHOH · CHOHMe)]/1-oxide	540, 541
2-NH_2-3-COOEt-5-[D-*arabo*-$(CHOH)_3CH_2OH$]/1-oxide and 5-[D-*threo*-$(CHOH)_2CH_2OH$] analogue	Guanidine/NaOMe/DMF	2-NH_2-4-OH-6-[D-*arabo*-$(CHOH)_3CH_2OH$]/8-oxide and 6-[D-*threo*-$(CHOH)_2CH_2OH$] analogue	540
2-NHCOOEt-3-$CONH_2$-5-Me/1-oxide	NaOMe	2,4-$(OH)_2$-6-Me/8-oxide	531
2-NH_2-5-Cl-3-CONHMe/1-oxide	$HC(OEt)_3/Ac_2O$	6-Cl-4-OH-3-Me/8-oxide	1222
2-NH_2-3-CONH-C(=NH)NH_2-5-Me/1-oxide and other 5-substituted analogues	Hot DMF	2-NH_2-4-OH-6-Me/8-oxide and other 6-substituted analogues	537
	 4*H*-Pyrazino[2,3-*d*][1,3]oxazin-4-one		
2-NH_2-3-COOH-5-Cl/1-oxide	Ac_2O/100°	6-Cl-2-Me/8-oxide	1222
2-NH_2-3-COOH-5-NMe_2/1-oxide	Ac_2O/100°	6-NMe_2-2-Me/8-oxide	1222

5-heptadecyl (5-methyl, 5-propyl, 5-styryl or 5-phenyl)pyrazine 1-oxide (532), 2-amino-3-cyano-6-deutero-5-(partial)trideuteriomethylpyrazine 1-oxide (dimethylformamide) (1255), 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (529), 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide (534), 2-amino-3-cyano-5-methoxymethylpyrazine 1-oxide (529), and 2-amino-5-benzylthiomethyl-3-cyanopyrazine 1-oxide (542).

2-Amino-3-cyanopyrazine 1,4-dioxide was selectively monodeoxygenated with phosphorus trichloride in tetrahydrofuran at 25° to 3-amino-2-cyanopyrazine 1-oxide (538).

3,5-Bis(methylamino)-2,6-bis(*N*-methylcarbamoyl)pyrazine 1-oxide was deoxygenated by refluxing with triethyl phosphite (462) and 2-amino-3-cyano-5-[*N*-(*p*-carboxyphenyl)-*N*-methyl]aminomethylpyrazine 1-oxide (**56**, R = OH) (and some derivatives) and similar compounds were deoxygenated with triethyl phosphite alone or with dimethylformamide at 120° (762, 1038–1040). Catalytic reduction has been employed with 2-amino-5-methylpyrazine 1-oxide (Pd/C) (535) and 2,3-diamino-5,6-dimethylpyrazine 1,4-dioxide (Raney Ni) in ethanol (907).



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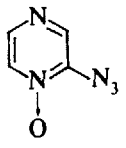
(5) *Deoxygenation with formation of Chloro-, Acetoxy-, and Methoxypyrazines*

The deoxygenation and chlorination of some aminopyrazine *N*-oxides by phosphoryl chloride has been described in Section V.1G (Table V.1).

3-Dimethylamino-2,5-dimethylpyrazine 1-oxide in boiling acetic anhydride gave 2-acetoxymethyl-3-dimethylamino-5-methylpyrazine (793) which was not isolated but saponified directly to 3-dimethylamino-2-hydroxymethyl-5-methylpyrazine (793). 2-Amino-3-cyano-5-methylpyrazine 1,4-dioxide refluxed with (*a*) acetic anhydride gave 3-acetamido-2-cyano-5-hydroxy-6-methylpyrazine 1-oxide (532) and (*b*) sodium methoxide gave 3-amino-2-cyano-5-methoxy-6-methylpyrazine 1-oxide (532).

(6) *Other Reactions*

2-Aminopyrazine 1-oxide with aqueous nitrous acid followed by sodium azide gave 2-azidopyrazine 1-oxide (**57**), which on heating with dry benzene at 85° gave 2-cyano-1-hydroxyimidazole (**58**) (1261, 1262). 3-Aminopyrazine 1-oxide *p*-toluenesulfonate fused with cyanoguanidine at 150–155° gave 3-(amidino-



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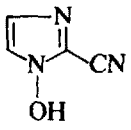

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guanidino)pyrazine 1-oxide (**59**), but 2-aminopyrazine 1,4-dioxide as *p*-toluenesulfonate or hydrochloride and 3-aminopyrazine 1-oxide hydrochloric did not react with cyanoguanidine under these conditions (1189). 3-Aminopyrazine 1-oxide hydrochloride at reflux with 40% alcoholic hydrogen chloride has been claimed to give 2-aminopyrazine (1069).

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CHAPTER IX

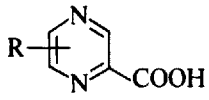
The Pyrazinecarboxylic Acids and Related Derivatives

1. THE CARBOXYPYRAZINES

A. Preparation of Carboxypyrazines

(1) *By Primary Synthesis*

Preparations of carboxypyrazines (1) by primary synthesis have been described in Sections II.1A–C, II.1F, II.1I, II.2, II.4, II.5, and II.7. Additional data on the hydrolysis of some pteridines to hydroxylated carboxypyrazines and amino carboxypyrazines are given in Sections VI.1A and VIII.1A(1), respectively.



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(2) *By Hydrolysis of Esters, Amides, and Nitriles*

The following esters, amides (thioamides), and nitriles have been hydrolyzed (under the conditions indicated) to the corresponding carboxypyrazines (unless otherwise stated) as listed below.

(a) PYRAZINE ESTERS

The following esters have been used: 2-methoxycarbonyl (aq. NaOH/MeOH) (1263); 2-methoxycarbonyl-5-phenyl (85% KOH) (352); 2,5-diethoxycarbonyl-3,6-dimethyl (KOH) (18, 674); 2-chloro-3-methoxycarbonyl (K_2CO_3 or NaOH/reflux) (838); 2-chloro-3-methoxycarbonyl-5,6-diphenyl (NaOMe/MeOH/reflux) (837); 5-ethoxycarbonyl-2,3-bis(5′-nitrofur-2′-yl) and its 6-methyl derivative (50% $AcOH/H_2SO_4$/reflux) (338); 2-amino-5-bromo-3-methoxycarbonyl (NaOH/reflux) (798); 2-amino-5,6-dichloro-3-methoxycarbonyl (NaOH/reflux) (378a, 782, 809); 2-cyclohexylamino-3-methoxycarbonyl (NaOH/EtOH/reflux 1 h) (946); 2-(2′,3′-dimethylphenylamino)-3-methoxycarbonyl (NaOH/EtOH/reflux) (950); 2-amino-

5-chloro-6-ethylamino-3-methoxycarbonyl (957); 2-amino-5-chloro-3-methoxycarbonyl (NaOH) (150, 432a, 781, 783–785, 831); 2-(benzyloxycarbonylamino)-5-ethoxycarbonyl [*N* potassium hydroxide in acetone at room temperature gave 2-(benzyloxycarbonylamino)-5-carboxypyrazine (676, 1249); and 4 *N* hydrochloric acid at reflux for 3 h gave 2-amino-5-carboxypyrazine (1177)]; 3-amino-5-dimethylamino-2-methoxycarbonyl (5% NaOH/100°) (432); 2-amino-5-chloro-6-methoxy-3-methoxycarbonyl (KOH/boil/10 min) (963); 2-hydroxy-6-methoxycarbonyl (NaOEt) (1057); 2-mercapto-3-methoxycarbonyl (aq. NaOH/MeOH/20°/4 h/N_2) (1264); 2,6-diamino-3-chloro-5-methoxycarbonyl [10% NaOH (783, 961, 962); NaOH/Pr^{i}OH/reflux (1058, 1265)]; 2-amino-5-chloro-3-methoxycarbonyl-6-substituted amino (961); 2-(3′-ethoxycarbonyl-3′-phenylpropyl) (20% NaOH) (731); 2-(1′-ethoxycarbonylethyl)-5-phenyl (824); and 2-[1′,1′-di(ethoxycarbonyl)ethyl] and 5-phenyl derivative (50% NaOH) (364, 365).

2-Chloro-3-methoxycarbonyl-5,6-diphenylpyrazine refluxed with sodium methoxide gave 2-carboxy-3-methoxy-5,6-diphenylpyrazine (371) and the attempted Schmidt reaction of 2,5-dimethoxycarbonylpyrazine, in concentrated sulfuric acid with trichloroacetic acid at 60° with subsequent addition of sodium azide, gave 2,5-dicarboxypyrazine (1176). 2-Methoxy-3-methoxycarbonyl-5,6-diphenylpyrazine, when refluxed with cuprous chloride in dry dimethylformamide, gave 2-carboxy-3-methoxy-5,6-diphenylpyrazine (10%); 2-hydroxy-3-methoxycarbonyl-5,6-diphenylpyrazine similarly treated gave 5-hydroxy-2,3-diphenylpyrazine (30%) (837).

Attempted Hofmann degradation of 2-carbamoyl-5-ethoxycarbonylpyrazine gave both 2,5-dicarboxypyrazine and 2-carbamoyl-5-carboxypyrazine (676).

(b) PYRAZINE AMIDES

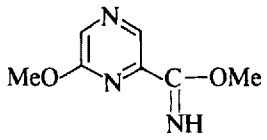
Carboxypyrazines have been prepared from the following amides: 2-carbamoyl [NaOH/reflux (1266); Na_2O_2/100°/2 h (1267)]; 5-carbamoyl-2,3-diphenyl (25) and 5-carbamoyl-2,3-di(*p*-methoxyphenyl) (KOH/EtOH/100°/1 h) (25); 5-carbamoyl-2,3-difur-2′-yl and its 6-methyl derivative (aq. NaOH/EtOH) (338); 2-dimethylamino(thiocarbonyl) (4 *N* NaOH/100°) (1268); 2,3-dicarbamoyl [*N* NaOH at 95–98° (1269, 1270) or aq. Na_2CO_3 at 80–90° (1271) gave 2-carbamoyl-3-carboxypyrazine]; 2,5-dicarbamoyl-3,6-dimethyl (Bouveault's method) (1104); tetracarbamoyl (5 *N* H_2SO_4/reflux/2 days) (384); 2,5-bisanilinocarbonyl-3,6-diphenyl (KOH/ethylene glycol/reflux) (192); 2-carbamoyl-3-hydroxy (Na_2O_2/100°/2 h) (1267); 2-carbamoyl-3-hydroxy-5-methyl and its 5-phenyl analogue (5 *N* NaOH/100°/2 h) (361, 365a, 369, 371); 2-carbamoyl-3-hydroxy-5,6-dimethyl (3 *N* NaOH/100°) (361); 2-carbamoyl-3-hydroxy-5,6-diphenyl [NaOH/EtOH/170°/6 h (371); NaOH/EtOH/reflux/8 h (837)]; 2-carbamoyl-3-hydroxy-5-phenyl (NaOH/EtOH/150°/16 h) (375); 2-carbamoyl-3-hydroxy [3 *N* NaOH/100° (361); NaOH/EtOH/170°/6 h (371)]; 3-[^{15}N]carbamoyl-2-hydroxy[1-^{15}N] (822); 3-carbamoyl-2-hydroxy[2-^{14}C] and 2-[^{14}C]carbamoyl-3-hydroxy (ratio 1:1) (823); 2-amino-3-carbamoyl (and its 5-methyl, 5-ethyl, 5-phenyl, and 5,6-dimethyl derivatives) (3 *N* NaOH/reflux) (378, 378a, 778, 780, 782, 783, 786, 802); 2-amino-3-carbamoyl-5-cyclohexyl (10% NaOH/100°) (778, 782, 786, 802, 854); 3-amino-2-carbamoyl-5-methyl (458) and 2-benzylamino-3-carbamoyl (10% NaOH/reflux) (458); 3-amino-

2-carbamoyl-5-trifluoromethyl (5% NaOH/100°/10 min) (781, 787, 802) (but 2-amino-3-carbamoyl-5-trifluoromethylpyrazine did not survive heating with aqueous sodium hydroxide) (802); 2-amino-3-carbamoyl-5-*p*-fluorophenyl (*N* NaOH/reflux/8 h) (347); 2-carbamoyl-6-methylamino (15% KOH/reflux) (940); 2-*N*-methylcarbamoyl-6-methylamino (940); 2-carbamoyl-3-sulfanilamido (*N* NaOH/100°/3.5 h) (1175); 2-carbamoyl-5-[4′-(4″-acetamidophenylsulfonylamino)phenylthio] (20% Na_2CO_3/reflux/20 h) (840); 2-carbamoyl-3-cyano [Na_2CO_3/85–90°/10 min (1272); aq. Na_2CO_3/EtOH/75–80° (1273)]; and 2-(2′,2′-dimethylhydrazino)-6-thiocarbamoyl (KOH/EtOH/reflux) (945); 2,3-Dicarbamoylpyrazine with potassium hypobromite gave 2-amino-3-carboxypyrazine (477), and attempted Hofmann degradation of 2-carbamoyl-5-ethoxycarbonylpyrazine has been described in Section 1A2(a).

(c) PYRAZINE NITRILES

The following nitriles have been used to prepare carboxypyrazines: 2-cyano-3-phenyl [NaOH/ethylene glycol/reflux (1274); or heated with H_2SO_4/$NaNO_2$ (1024)]; 3-cyano-2,5-dimethyl (NaOH/EtOH/reflux) (1015); 3-cyano-2,5-diphenyl (NaOH) (286); 2,3-dicyano [NaOH/EtOH (354); aq. KOH/EtOH (353); Na_2O_2 (357)]; 2,6-dicyano (5% NaOH/100°/2 h) (865); 2,3-dicyano-5,6-dimethyl (Na_2O_2) (357); 2-cyano-6-ethylthio(propylthio or phenylthio) (NaOH/EtOH/reflux) (992); 2-cyano-5-hydroxy-3,6-dimethyl (and diethyl) (288); and 2-cyano-3-hydroxy-5,6-diphenyl (15% KOH/reflux) (797); 2-cyano-6-dimethylamino (924, 944); 2-cyano-6-thiomorpholino (943); and 2,6-diamino-3,5-dicyano (5% NaOH/reflux/6 days) (1180). 2-(3′-Cyano-3′-phenylpropyl)pyrazine was hydrolyzed by 10% hydrochloric acid to 2-(3′-carboxy-3′-phenylpropyl)pyrazine (731).

When heated with aqueous potassium hydroxide, 2,5-dicyano-3,6-dimethyl(and diphenyl)pyrazine gave 2-carboxy-5-hydroxy-3,6-dimethyl(and diphenyl)pyrazine (286–288) and the diethyl analogue was prepared similarly (287). 2-Chloro-6-cyanopyrazine refluxed with three equivalents of sodium methoxide for 2 hours gave 2-carboxy-6-methoxypyrazine, also obtained from 2-chloro-6-cyanopyrazine with one equivalent of sodium methoxide through 2-(*C*-imino-*C*-methoxymethyl)-6-methoxypyrazine (**2**), which, refluxed with 15% sodium hydroxide, gave 2-carboxy-6-methoxypyrazine (986).



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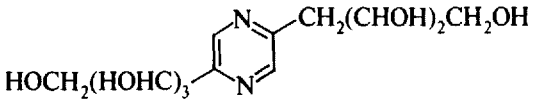
2-Cyano-5-ethoxy-3,6-dimethylpyrazine refluxed with 50% sulfuric acid gave 3-hydroxy-2,5-dimethylpyrazine (288) but when refluxed with 5*N* potassium hydroxide for 10 hours gave 2-carboxy-5-hydroxy-3,6-dimethylpyrazine (288).

(3) *By Oxidation of Alkyl-, Styryl-, Hydroxyalkyl-, and Fused Pyrazine Systems*

The oxidation of alkyl-, styryl-, and hydroxyalkylpyrazines to carboxypyrazines mostly with potassium permanganate in aqueous solution but also with selenious acid in pyridine (669), selenium dioxide (676), and sodium dichromate in aqueous phosphoric acid (677) or acetic acid (678) have been described in Section IV.2C(1), and additional data are given below.

In connection with the oxidation of 2,5-dimethylpyrazine with potassium permanganate in aqueous potassium hydroxide in poor yield to 2,5-dicarboxypyrazine (672), it was found to be an advantage to first convert the starting material into a condensation product with an appropriate aldehyde: 2,5-di(*p*-methoxystyryl)pyrazine was oxidized to 2,5-dicarboxypyrazine (about 61% as determined by conversion to the dimethyl ester) (411). Oxidation of 2,5-distyrylpyrazine with aqueous potassium permanganate gave 2,5-dicarboxypyrazine (1275), and oxidation of 2,3-bis(*p*-methoxybenzyl)pyrazine with potassium permanganate at 100° gave 2,3-dicarboxypyrazine (1276).

The copper salt of 2-carboxy-5-hydroxymethylpyrazine has been oxidized by hydrogen peroxide to 2,5-dicarboxypyrazine (1277); which was also obtained from fructosazine by oxidation with hydrogen peroxide and sodium hydroxide (1071). 2,5-Dicarboxypyrazine was also obtained by permanganate oxidation of 2-carboxy-5-ethylpyrazine (352), fructosazine (182, 183), 2,5-bis(D-*lyxo*-tetraacetoxybutyl)-pyrazine (184), 2,5-diphenethyl-1,4-dihydropyrazine (173), a product from the ammoniation of molasses (46), and by oxidation of "deoxyfructosazine" (3) with hydrogen peroxide and sodium hydroxide at 80° (?) (1072). The oxidation of 2-D-*arabo*-tetrahydroxybutyl)pyrazine with aqueous potassium permanganate at 90° gave 2-carboxypyrazine (544) and 2-carboxy-6-ethylpyrazine at 60° gave 2,6-dicarboxypyrazine (352). Potassium permanganate oxidation of 2,5-dimethyl-3-(2′,5′-dimethylpyrazin-3′-yl)pyrazine gave some 3-carboxy-2,5-dimethylpyrazine, and similar oxidation of 2,5-dimethyl-3-(2′-methylpyrazin-5′-yl)pyrazine gave some 2,5-dicarboxypyrazine and 3-carboxycarbonyl-2,5-dimethylpyrazine (718).



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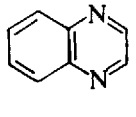
Alkylpyrazines with other substituents have been oxidized to carboxylic acids as follows: 2-acetamido-6-methylpyrazine was oxidized in aqueous magnesium sulfate with potassium permanganate to 2-acetamido-6-carboxypyrazine (434), and 2-chloro-3-methylpyrazine (admixed with the 6-isomer) was oxidized by aqueous potassium permanganate at room temperature to 2-carboxy-3-chloropyrazine, which was also obtained by oxidation of 2-chloro-3-methylpyrazine with selenium dioxide in boiling aqueous pyridine (947). Oxidations of 2-methoxy-3-methyl-

pyrazine with selenium dioxide in pyridine to 2-carboxy-3-methoxypyrazine and similarly of 2-methoxy-3,5-dimethylpyrazine to 3-carboxy-2-methoxy-5-methylpyrazine, 2,5-dimethoxy-3,6-dimethylpyrazine to 2-carboxy-3,6-dimethoxy-5-methylpyrazine, and 3-methoxy-2,5-dimethylpyrazine to 2-carboxy-3-methoxy-5-methylpyrazine have been described (844).

Many fused pyrazine systems that have been oxidized to pyrazine carboxylic acids are summarized below (substrate and conditions of oxidation): 2,3-dicarboxy [from quinoxaline (**4**) with alkaline potassium permanganate (397, 398, 400, 401, 1278–1280); from quinoxaline by electrolytic oxidation in a solution containing potassium permanganate and sodium hydroxide with a copper anode (402, 1281, 1282); from quinoxaline with sodium hypochlorite and potassium permanganate at 60° (1283); from "pyrazinotropone oxime" with potassium permanganate in alkaline solution at 70° (1284); and from 6-hydroxyquinoxaline-7-carboxylic acid with alkaline permanganate (1285)]; 2-carboxy (from quinoxaline with alkaline permanganate at 80–96°, acidified and distilled) (1286); 2,5-dicarboxy [from compound (**5**) with potassium permanganate in acid solution] (1287); 2,3,5-tricarboxy [from 2-ethoxymethylquinoxaline with potassium permanganate in aqueous potassium hydroxide (410); from 2-methylquinoxaline by similar oxidation (865); from the quinoxaline derivative of oxidized reductone (mesoxalaldehyde) with potassium permanganate (1288, 1289); and from 2-D-*arabo*-tetrahydroxybutylquinoxaline with potassium permanganate in alkaline solution (411)]; tetracarboxy [from phenazine or phenazine oxide with permanganate (414, 417, 1290, 1291); from 2,3-dicarboxyquinoxaline with alkaline permanganate (413); from 1,3-dibenzoyl-2-oxo-cyclopenteno[4,5-*b*]quinoxaline (**6**) with alkaline permanganate (417); from pyrazino[*d*,*d'*]ditroponemonoimine monoxime hydrochloride (**7**) with alkaline permanganate (418); from the condensation product of 3,5-dinitrotropolone with *o*-phenylenediamine which was oxidized with alkaline permanganate (1292); and from 2,3-diamino- or 2-amino-3-hydroxyphenazines (both from *o*-diaminobenzene by oxidation with ferric chloride) with alkaline permanganate to give 75% yields of tetracarboxypyrazine (415)]; 2,3-dicarboxy-5-methyl (from 2-methylquinoxaline with alkaline permanganate) (403–405); 2,3-dicarboxy-5,6-dimethyl (from 2,3-dimethylquinoxaline with alkaline permanganate)



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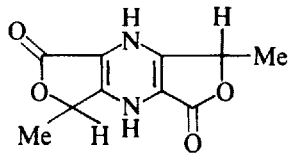

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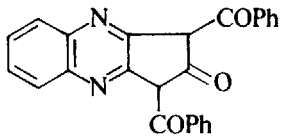

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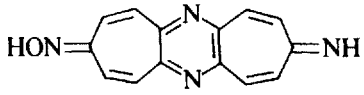

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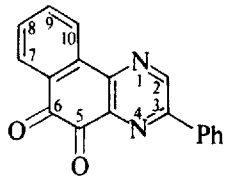
(397, 403, 654); 2,3-dicarboxy-5-phenyl (from 2-phenylquinoxaline with permanganate) (733b); 2,3-dicarboxy-5,6-dihydroxy [from 2,3-dichloroquinoxaline with potassium permanganate at 100° (1051); but 2,3-dialkoxyquinoxaline was very resistant to permanganate oxidation (1293)]; 5-acetamido-2,3-dicarboxy (from 2-acetamidoquinoxaline with potassium permanganate) (408); 3-carboxy-2-(*o*-carboxyphenyl)-5-phenyl [from 5,6-dioxo-3-phenyl-5,6-dihydrobenzo[*f*]quinoxaline (8) with alkaline potassium permanganate] (406); 2-carboxy-3-(*o*-carboxyphenyl)-5,6-diphenyl (from 2,3-diphenylbenzo[*f*]quinoxaline with chromic oxide in acetic acid–acetic anhydride and from 5,6-dioxo-2,3-diphenyl-5,6-dihydrobenzo[*f*]-quinoxaline with potassium permanganate) (399); and 3-carboxy-5-carboxymethyl-2-(*o*-carboxyphenyl) (?) (from 3-carboxymethylbenzo[*f*]quinoxaline with alkaline potassium permanganate) (407).



(8)

(4) *By Other Methods*

Unsubstituted 2-pyrazinyllithium (prepared from 2-iodopyrazine with butyllithium in ether at −35°) has been carbonated with carbon dioxide to give 2-carboxypyrazine (1016), and pyrazine has been carbonated with potassium carbonate, cadmium difluoride, and carbon dioxide at 260° and 50 atm to give 2,5-dicarboxypyrazine (1294). See also Section 5.5H.

The thermal rearrangement of the potassium salt of 2,3-dicarboxypyrazine to 2,5-dicarboxypyrazine in the presence of catalysts at elevated temperatures has been described (1295–1297). Some examples of the conditions of the reaction include heating with cadmium difluoride and carbon dioxide at 275–500° (1295), and heating with catalysts of the type $R_2(CdX_2Y_2)$ and $R(CdX_3)$, where R is an alkali metal cation, X is fluoride, and Y any halogen ion or "half" carbonate at 390–420° (1296, 1297) in an atmosphere of carbon dioxide.

B. Properties of Carboxypyrazines

The crystal structures of 2-carboxypyrazine (1298) and 2,3-dicarboxypyrazine dihydrate (1299) have been determined; and phase diagrams and data have been measured for the binary systems of 2-carboxypyrazine with benzoic acid (1300); nicotinic, isonicotinic, and picolinic acids (1301). The polarography of 2-carboxypyrazine has been examined (1302). Polarography of 2-amino-3-carboxypyrazine has been carried out in aqueous and nonaqueous solutions; the reduction proceeds

in one two-electron wave to give 1,4-dihydro derivatives, which give 1,2-dihydro derivatives by acid catalysis (1190). The stability of the cupric chelate with 2-carboxypyrazine has been examined (1303) and the recovery of 2,3-dicarboxypyrazine from aqueous solutions by preparing the salt of a group II metal and treating its slurry with an acid that forms a soluble salt with the metal has been described (1304).

2-Carboxypyrazine catalyzes the chromic acid oxidation of primary and secondary alcohols (1305). The first-order, specific rates of reduction of Co(III) by Fe(II) in complexes of the type $[(NH_3)_{(4\text{ or }5)}CoLFe(CN)_5]$ with L as chelating 2-carboxylatopyrazine, pyrazine, and 2-methylpyrazine are 1.3×10^{-2}, 5.5×10^{-2}, and 30×10^{-2}/sec, respectively, at 25°, pH 6–7, and $\mu = 0.15M$ (1306). Complexes from 2-carboxypyrazine and lanthanide basic carbonates (1307) and from 2,3-dicarboxypyrazine and transition metals (1308) and its pentaamminechromium(III) complexes have been prepared (1309).

2-Carboxypyrazine and 2,3-dicarboxypyrazine, and their methyl esters and amides, and 2,3-dihydrazinocarbonylpyrazine showed no promise as mold preventatives (1310).

C. Reactions of Carboxypyrazines

(1) *Decarboxylation*

Pyrazinecarboxylic acids may be decarboxylated by heating alone or more usually in a high boiling solvent. The degree of the decarboxylation of polycarboxypyrazines can vary with the conditions of the reaction; 2,3-dicarboxypyrazine heated for 2 hours in acetic acid at 130–145° gave 2-carboxypyrazine (1311) but at 180° gave pyrazine (397). Decarboxylation products may also vary with the method of decarboxylation (411), for example: 2,3,5-tricarboxypyrazine heated at 210–220°/3 mm gave 2,6-dicarboxypyrazine, but when refluxed in dimethylformamide for 3 hours gave 2,5-dicarboxypyrazine, and when a $0.08M$ aqueous solution was refluxed for 72 hours it gave 2,5-dicarboxypyrazine (11.9%), 2,6-dicarboxypyrazine (73%), and unchanged 2,3,5-tricarboxypyrazine (8.8%). Bernardi and Larini (236a) reported that 2,5-dicarboxypyrazine was less easily decarboxylated in nitrobenzene (evolution of carbon dioxide commenced at 210°) than was its 2,3-isomer (decarboxylated at 80–155°). 3-Amino-2-bromo-5-carboxypyrazine could not be decarboxylated by refluxing in tetralin at 205° (434).

Some decarboxylations recorded in the literature are summarized in Table IX.1, the pertinent references are 22, 25, 27, 32, 236a, 272, 286, 287, 353, 357, 365, 365a, 370, 372, 397, 399, 404–406, 408, 411, 420, 429, 433, 434, 446, 447, 461, 477, 564, 565, 652, 654, 671, 673, 733b, 797, 798, 821, 822, 831, 837, 1059, 1156, 1164, 1171, 1175, 1270, 1278, 1286, and 1311–1313, and further reactions which involve decarboxylations are as follows.

2-(1′,1′-Diethoxycarbonylethyl)pyrazine (**9**) refluxed with 50% sodium hydroxide

TABLE IX.1 DECARBOXYLATION OF PYRAZINECARBOXYLIC ACIDS

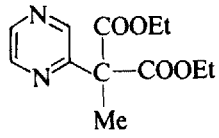
Pyrazinecarboxylic Acid	Product (Pyrazine)	Conditions of Reaction	Refs.
2-COOH	Unsubstituted	Dibutyl phthalate (190–215°)	564
2,3-$(COOH)_2$	Unsubstituted	Acetic acid at 180°/2 h	357, 397
		Dibutyl phthalate (190–215°)	564
2,3-$(COOH)_2$	2-COOH	Acetic acid at 130–145°/2 h	1311
2,3-$(COOH)_2$	2-COOH	Vacuum sublimation	353, 397, 1171
		Boil in toluene, xylene, or chlorobenzene	1286
		Nitrobenzene at 155°	236a
2,5-$(COOH)_2$	Unsubstituted	Slow distillation	22
		Acetic acid at 200°	272, 565
2,5-$(COOH)_2$	2-COOH	Distillation (quick)	22
		Nitrobenzene at 210°	236a
2,3,5-$(COOH)_3$	Unsubstituted	Dibutyl phthalate (190–240°)	564
2,3,5-$(COOH)_3$	2,5- and 2,6-$(COOH)_2$	Boiled with water or acetic acid for 2–3 days	27
2,3,5-$(COOH)_3$	2,6-$(COOH)_2$	210–220°/3 mm	411
2,3,5-$(COOH)_3$	2,5-$(COOH)_2$	Reflux in DMF/3 h	411
2,3,5-$(COOH)_3$	2,5-$(COOH)_2$ (11.9%) + 2,6-$(COOH)_2$ (73%) + 2,3,5-$(COOH)_3$ (8.8%)	0.08 *M* Aqueous solution refluxed for 72 h	411
2,3,5,6-$(COOH)_4$	Unsubstituted	Dibutyl phthalate at 200–240°	564
	2,5-$(COOH)_2$ (+ unsubstituted)	Dipotassium salt in water at 200°	22
2-COOH-3-Me	2-Me	180–200°	671
2-COOH-5-Me	2-Me	Acetic acid at 180–190°	32, 272
		Acetic acid at 195–205°/2 h	405
		Furnace at 250°	652
3-COOH-2,5-Me_2	2,5-Me_2	Acetic acid at 180–200°	32
3-COOH-2,5-Ph_2	2,5-Ph_2	Fuse	286
5-COOH-2,3-Ph_2	2,3-Ph_2	Fuse	25
2,3-$(COOH)_2$-5-Me	2-COOH-5-Me + some 2-COOH-6-Me	Vacuum sublimation at 175–185°	673, cf. 404
2,3-$(COOH)_2$-5-Ph	2-Ph	Heat with powdered CuO at 200–236°	733b

TABLE IX.1 *Continued*

Pyrazinecarboxylic Acid	Product (Pyrazine)	Conditions of Reaction	Refs.
2,3-$(COOH)_2$-5,6-Me_2	2,3-Me_2	Acetic acid at 180° or distil under reduced pressure	397
		Reflux in quinoline	654
3-COOH-2-C_6H_4-*o*-COOH-5-Ph	2,5-Ph_2	Distill over calcium oxide	406
2-COOH-3-C_6H_4-*o*-COOH-5,6-Ph_2	2,3,5-Ph_3 (?)	Distill over calcium oxide	399
5-CH(Me)COOH-2,3-Ph_2	5-Et-2,3-Ph_2	130° for 15 min	365
2-COOH-3-COOMe	2-COOMe	120–140°/vacuo	1278, 1312
2-COOH-3-$CONH_2$	2-$CONH_2$	160–170°	1312
		220°	1270
2-COOH-3-OH	2-OH	Carbitol acetate reflux/10 min	420, 433, 1059, 1313
		Reflux in diethylene glycol monoethyl ether	821
3-COOH-2-OH[1-^{15}N]	2-OH[1-^{15}N]	Carbitol acetate reflux/10 min	822
2-COOH-3-OH-5-Me	2-OH-6-Me	Heat in nitrobenzene	372
2-COOH-3-OH-5-Ph	2-OH-6-Ph	Carbitol acetate at 200°/30 min	365a
2-COOH-5-OH-3,6-Me_2	3-OH-2,5-Me_2	Heat parent or sodium salt	286, 1164
		Heat with powdered glass at 300°/5 min	287
2-COOH-5-OH-3,6-Et_2	3-OH-2,5-Et_2	Heat with powdered glass at 300°/5 min	287
2-COOH-3-OH-5,6-Ph_2	5-OH-2,3-Ph_2	Fuse	797, 837
2-COOH-5-OH-3,6-Ph_2	3-OH-2,5-Ph_2	Heat parent or sodium salt	286
2-COOH-3-OMe-5,6-Ph_2	5-OMe-2,3-Ph_2	200°/0.4 mm	837
2-NH_2-3-COOH	2-NH_2	Fuse	397
		Reflux in carbitol acetate for 15 min or dibutyl phthalate	420, 433, 1059, 1313
		Reflux in nitrobenzene/10 min	477
2-NH_2-3-COOH-5-Me	2-NH_2-5-Me	Reflux in butyl cellosolve for 45 min	446
3-NH_2-2-COOH-5-Me	2-NH_2-6-Me	80% Sulfuric acid at 180°/10 min	420, 433, 434, 447, 1059, 1156
		Tetralin at 205°/30 min	434
3-NH_2-2-COOH-5-Ph	2-NH_2-6-Ph	80% Sulfuric acid at 200°/15 min	429

TABLE IX.1 *Continued*

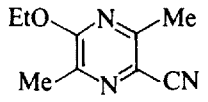
Pyrazinecarboxylic Acid	Product (Pyrazine)	Conditions of Reaction	Refs.
2-NH_2-3-COOH-5,6-Me_2	5-NH_2-2,3-Me_2	80% Sulfuric acid at reflux/10 min	420, 433, 1059
		Diphenyl ether at 210–217°/15 min	370
2-NH_2-3-COOH-5,6-Ph_2	5-NH_2-2,3-Ph_2	80% Sulfuric acid at reflux/30 min	420, 433, 1059
5-NH_2-2,3-$(COOH)_2$	2-NH_2-5-COOH	Heat in water at 170–175°/12 min	408
2,5-$(NH_2)_2$-3,6-$(COOH)_2$	2,5-$(NH_2)_2$	Sublimation	461
2-NH_2-5-Br-3-COOH	2-NH_2-5-Br	Reflux tetralin/30 min	798
2-NH_2-3-COOH-5-Cl	2-NH_2-5-Cl	Reflux in tetralin/1 h	831
2-COOH-3-$NHSO_2C_6H_4$-NH_2-*p*	2-$NHSO_2C_6H_4NH_2$-*p*	Boil in carbitol acetate	1175



(9)

for 1.25 hours gave 2-(1′-carboxyethyl)pyrazine, and the 5-phenyl analogue was prepared similarly (364, 365, 824). 2-(1′,1′-Diethoxycarbonylethyl)pyrazine heated with sodium cyanide in dimethyl sulfoxide at 125–160° for 1 hour gave 2-(1′-ethoxycarbonylethyl)pyrazine, and the 5-phenyl analogue was prepared similarly (365). 2-Amino-3-cyano-5-(2′,2′-diethoxycarbonylethyl)pyrazine heated with sodium chloride in aqueous dimethyl sulfoxide at 155–170° for 6 hours gave 2-amino-3-cyano-5-(2′-ethoxycarbonylethyl)pyrazine, 5-(2′-acetyl-2′-ethoxycarbonylethyl)-2-amino-3-cyanopyrazine similarly treated gave 5-(2′-acetylethyl)-2-amino-3-cyanopyrazine, and 2-amino-3-cyano-5-[(2′-ethoxycarbonyl-2′-ethoxymethylcarbonyl)ethyl]pyrazine gave 2-amino-3-cyano-5-(2′-ethoxymethylcarbonyl)-ethylpyrazine (1031).

Spontaneous decarboxylation of 2,3-dicarboxytetrahydropyrazine has been observed. Hydrolysis of 2,3-dimethoxycarbonyltetrahydropyrazine (from hydrogenation of 2,3-dimethoxycarbonylpyrazine over palladium–charcoal) with the calculated quantity of sodium hydroxide at room temperature followed by removal of sodium ions over a strong acid ion exchange resin (Amberlite 1R-20; 200–300 mesh) resulted immediately in a vigorous evolution of carbon dioxide (1280). Spontaneous decarboxylation has also been demonstrated when 2,3,5-tricarboxypyrazine was hydrogenated catalytically over palladium–charcoal at room temperature and atmospheric pressure in ethanol solution (1280). 2,5-Diethoxycarbonyl-3,6-diethoxycarbonylmethyl-2,5-dihydropyrazine (?) refluxed with 20% hydrochloric acid gave 2,5-dimethylpyrazine (1314, 1315) and 2-cyano-5-ethoxy-3,6-dimethylpyrazine (**10**) refluxed with 50% sulfuric acid for 10 hours gave 3-hydroxy-2,5-dimethylpyrazine (288). Other reactions involving removal of cyano groups are described in Section 4C. 6-Dimethylamino-4-hydroxypteridine heated with 5% sodium hydroxide at 140° for 18 hours gave 2-amino-5-dimethylaminopyrazine (432).



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The brominations of 2-amino-3-carboxypyrazine (804), 2-amino-5-bromo-3-carboxypyrazine (805, 806), and 2-amino-5-bromo-3-methoxycarbonylpyrazine (807) to 2-amino-3,5-dibromopyrazine have been described in Section V.1B (2); nitrations of 2-amino-3-carboxy-5-chloro-6-ethylaminopyrazine to 2-amino-5-chloro-6-ethylamino-3-nitropyrazine (1181) and 2,6-diamino-3,5-dicarboxypyrazine

to 2,6-diamino-3,5-dinitropyrazine (1180) have been reported in Section VIII.2A and the coupling of 2-carboxy-5-hydroxy-3,6-dimethylpyrazine with diazonium salts to give 2-hydroxy-3,6-dimethyl-5-phenylazo(and *p*-tolylazo) pyrazine (1122) in Chapter VI.6E.

Quaternizations of 2,5-dimethylpyrazine with α-halogeno acids have been examined and it has been found that the betaine salts decompose extremely rapidly with loss of carbon dioxide to give 1-alkyl-2,5-dimethylpyrazinium salts (1316).

(2) *Esterification*

Carboxypyrazines have been esterified with a variety of reagents, which are listed below with the pyrazine esters prepared in this way. Some discussion of the various reagents is given in Mager and Berends (411).

Silver salt of the acid with alkyl iodide: 5-methoxy-(and ethoxy)carbonyl-2,3-diphenyl (25); 2,6-dimethoxycarbonyl (poor yield) (411); 2,5-dimethoxycarbonyl-3,6-dimethyl (403); 2,5-diethoxycarbonyl-3,6-dimethyl (sealed tube at 100°) (674); 2,5-diethoxycarbonyl-3,6-diphenyl (209); and 2,3,5-trimethoxycarbonyl (poor yield) (411).

Diazomethane: 2-methoxycarbonyl (1016); 2,6-dimethoxycarbonyl (from the anhydrous acid) (411); 2,3,5-trimethoxycarbonyl (411); tetramethoxycarbonyl (418); 2-methoxycarbonyl-6-methylamino (940); and 2-methoxycarbonyl-6-(4′-methylpiperazin-1′-yl) (943).

Dimethyl sulfate with the sodium salt of the acid: 2-amino-3-methoxycarbonyl-5-methyl (378a, 780, 782, 786, 802).

Phenacyl bromide with the sodium salt of the acid: 2,3-diphenacyloxycarbonylpyrazine (1280).

Chloroacetamide and triethylamine: 2-cyanomethoxycarbonyl (1317).

An alcohol and sulfuric acid: 2-methoxycarbonyl (1318, 1319); 2-methoxycarbonyl-5-methyl (420); 2,3-dimethoxycarbonyl (1280); 2,3-diethoxycarbonyl (419); 2,3-diethoxycarbonyl-5,6-dimethyl (419); 2,5-dimethoxycarbonyl (676, 1072); 2,5-diethoxycarbonyl (676); tetraethoxycarbonyl (1320), tetraalkoxycarbonyl (1321); 5-ethoxycarbonyl-2,3-di(fur-2′-yl) (338); 5-ethoxycarbonyl-2,3-di(fur-2′-yl)-6-methyl (338); 2-amino-3-methoxycarbonyl (1175, 1212, 1322); 2-alkylamino-6-methoxycarbonyl (and ethoxycarbonyl) (942); 2-acetamido-6-methoxycarbonyl (434); 2-amino-3-methoxycarbonyl-5,6-diphenyl (451); 2-chloro-6-methoxycarbonyl (together with 2-methoxy-6-methoxycarbonyl) (870); 2-hydroxy-3-methoxycarbonyl (833); and 2-ethoxycarbonyl-3-hydroxy-5-phenyl (429).

Alcoholic hydrogen chloride: 2-methoxycarbonyl (1171, 1323, 1324); 2-methoxycarbonyl-6-phenyl (352); 2,3-dimethoxycarbonyl (397, 1325); 2,5-dimethoxycarbonyl (183, 184, 411, 1172); 2,5-dimethoxycarbonyl-3,6-dimethyl (403); 2,3,5-trimethoxycarbonyl (411); 2,3,5-triethoxycarbonyl (412); tetramethoxycarbonyl (629, 1326); tetraethoxycarbonyl (412, 413, 415); 2-amino-

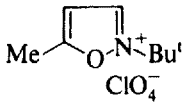
3-methoxycarbonyl (433a); 2-amino-5-methoxycarbonyl (408); 2-amino-5-ethoxycarbonyl (408); 2-methoxycarbonyl-3-methylamino (799–801); 2-amino-3-methoxycarbonyl-5-methyl (778, 786); 2-amino-5-ethyl-3-methoxycarbonyl (778, 780); 2-amino-3-methoxycarbonyl-5-phenyl (378a, 782); 2-amino-3-methoxycarbonyl-5(or 6)-trifluoromethyl (781, 787); 2-amino-5-cyclohexyl-3-methoxycarbonyl (378a, 778, 782, 786); 2-amino-5-cyclopropyl(phenyl or substituted phenyl)-3-methoxycarbonyl (778, 786, 802); 3-amino-2-methoxycarbonyl-5-methyl (378a, 435, 780, 782, 802, 855, 859); 3-amino-2-methoxycarbonyl-5-phenyl (378a, 782, 855, 859); 2-amino-5-cyclohexyl-3-methoxycarbonyl (802, 859) and other 5-substituted analogues (802, 855); 2-methoxycarbonyl-3-methylamino-5-phenyl (453); 2-hydroxy-3-methoxycarbonyl (423, 836); 3-hydroxy-2-methoxycarbonyl-5-methyl (371); 3-hydroxy-2-methoxycarbonyl-5-phenyl (375); 2-ethoxycarbonyl-3-hydroxy-5-phenyl (375); 2-hydroxy-3-methoxycarbonyl-5,6-diphenyl (371); 2-methoxy-6-methoxycarbonyl (869, 871, 1324); 2-methoxy-3-methoxycarbonyl-5,6-diphenyl (371); 2-chloro-6-methoxycarbonyl (together with some 2-methoxy-6-methoxycarbonylpyrazine after reflux for 5 minutes) (870); 2,3-dichloro-5,6-dimethoxycarbonyl (409); and 5-amino-2,3-diethoxycarbonyl (412).

An alcohol and a little thionyl chloride: 2-methoxycarbonyl (1266); 2-ethoxycarbonyl (1266); 2-amino-5-methoxycarbonyl (1057); 2-amino-6-ethoxycarbonyl (744); 2-methoxycarbonyl-6-propylthio (992); 2-methoxycarbonyl-6-phenylthio (992); 2-benzylthio-6-methoxycarbonyl (992); 2-hydroxy-5-methoxycarbonyl (838); 2-methoxycarbonyl-6-(2′-methylpiperidino) (944); and 2-methoxycarbonyl-6-thiomorpholino (943).

Methanol and p-toluenesulfonic acid: 2-methoxycarbonyl-5(and 6)-methyl (1327).

2-Amino-3-carboxypyrazine with boron trifluoride etherate and methanol at reflux gave 2-amino-3-methoxycarbonylpyrazine (this is claimed to be a mild esterifying agent and does not affect other functional groups) (1328).

N-t-Butyl-5-methylisoxazolium perchlorate (**11**) (Woodward's Reagent L), and triethylamine in dimethylformamide has been used to prepare a number of active esters (which are useful as intermediates) from carboxypyrazines. For example, 2,6-diamino-3-carboxy-5-chloropyrazine with *N-t*-butyl-5-methylisoxazolium perchlorate (**11**) in dimethylformamide in the presence of triethylamine gave the active ester 2,6-diamino-3-(1′-*t*-butylcarbamoylmethyleneethoxy)carbonyl-5-chloropyrazine (**12**) (463, 961, 1058, 1265, 1329, 1330), and many similar compounds have been prepared likewise (961). The usefulness of the active ester (**12**) has been demonstrated, for example, with ethylamine in tetrahydrofuran to give 2,6-diamino-3-chloro-5-*N*-ethylcarbamoylpyrazine (1331), and similar reactions with the 6-ethylamino analogue of (**12**) with hydroxylamine in tetrahydrofuran to give 2-amino-5-chloro-6-ethylamino-3-hydroxycarbamoylpyrazine (957), and the 6-methoxy analogue with hydrazine in tetrahydrofuran to give 2-amino-5-chloro-3-hydrazinocarbonyl-6-methoxypyrazine (963). Compound (**12**) with sodium methoxide in methanol gave 2,6-diamino-3-chloro-5-methoxycarbonylpyrazine



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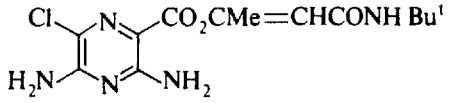


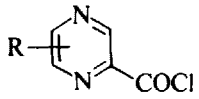
(12)

(1330, 1331) and with benzylmercaptan gave 2,6-diamino-3-benzylthio(carbonyl)-5-chloropyrazine (1331).

(3) *Formation of Acid Chlorides*

Acid chlorides (e.g., **13**) have been prepared from the corresponding carboxypyrazines as follows (reagents and conditions as indicated): 2-carboxy [$SOCl_2$/reflux or $SOCl_2$/benzene/reflux (1278, 1332–1335); $POCl_3/PCl_5$/20°/93 h; or PCl_5/benzene/sealed tube/80–85°/20 min (1336)]; 2-carboxy-3-phenyl ($SOCl_2$/reflux) (1024); 2-carboxy-5-methyl ($SOCl_2$) (1337); 2-carboxy-3-hydroxy ($SOCl_2$/benzene/reflux gave 2-chlorocarbonyl-3-hydroxypyrazine) (1055); 2-carboxy-3-chloro ($SOCl_2$/benzene/reflux) (870); 2-carboxy-3-methoxy ($SOCl_2$) (844); 2-carboxy-3-methoxy-5-methyl (844), 3-carboxy-2-methoxy-5-methyl (844), and 2-carboxy-3,6-dimethoxy-5-methyl ($SOCl_2$) (844); 2,5-dicarboxy (PCl_5/110–115°/1 h) (1172); 2-carboxy-3-methoxycarbonyl ($SOCl_2$/benzene/reflux) (1278); 2,5-dicarboxy-3,6-diphenyl ($SOCl_2$/xylene) (192); and 2-(1′-carboxyethyl) ($SOCl_2$/60°) (364).

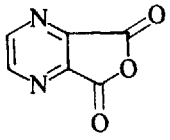
Attempted preparations of the acid chloride from 2,6-diamino-3-carboxy-5-chloropyrazine under a variety of conditions were unsuccessful (1331) and in that respect it resembled anthranilic acid.



(13)

(4) *Formation of Anhydrides and Their Reactions*

2,3-Dicarboxypyrazine refluxed in thionyl chloride (397), or preferably dissolved by warming in acetic anhydride, gave the anhydride (**14**) (397, 1278, 1312, 1338), which was reconverted to the acid in warm water (397, 1278). The anhydride, refluxed in anhydrous methanol, gave 2-carboxy-3-methoxycarbonylpyrazine (1278, 1312); with saturated aqueous ammonia at room temperature it gave 2-carbamoyl-3-carboxypyrazine (1312); and with a solution of hydroxyamine in methanol in the presence of 1 mol of sodium methoxide it gave the disodium salt of 2-carboxy-3-(*N*-hydroxycarbamoyl)pyrazine (which was benzoylated with benzoyl chloride in sodium hydroxide to 2-benzoyloxycarbamoyl-3-carboxypyrazine) (1174). 2,3-Dicarboxypyrazine anhydride, heated with acetic anhydride and acetamide at 120° for 2 hours, gave the imide (**15**), and with acetic anhydride and methylamine hydrochloride it gave the methylimide (1338).



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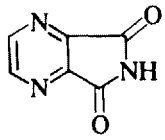
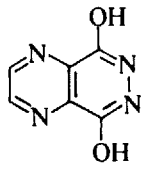


(15)

The anhydride of 2,3-dicarboxypyrazine heated with hydrazine hydrate under various conditions gave some 5,8-dihydroxypyrazino[2,3-*d*]pyridazine (**16**) (1338–1340). Pyrolysis of the anhydride of 2,3-dicarboxypyrazine (**14**) at 830° at 0.05 mm through a silica tube gave an 80% yield of an approximately 1:1 mixture of maleonitrile and fumaronitrile; and the mass spectrum of the anhydride (**14**) was consistent with the formation of the dehydropyrazine (**17**) (1341).



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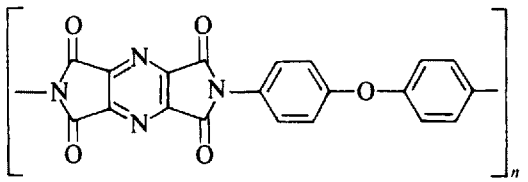
(17)

2,3-Dicarboxy-5,6-dimethylpyrazine, heated with acetic anhydride, also gave the anhydride which with methanol gave 2-carboxy-3-methoxycarbonyl-5,6-dimethylpyrazine (654). 2,3-Dicarboxy-5-methylpyrazine anhydride was prepared similarly and on methanolysis and decarboxylation it gave 2-methyl-5(and 6)-methoxycarbonylpyrazines (1327).

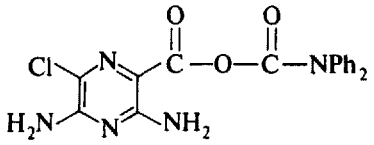
Tetracarboxypyrazine treated with acetic anhydride gave tetracarboxypyrazine dianhydride (1291, 1342). This condensed with *p,p'*-diaminodiphenyl ether to give polyimides (**18**) which could be thermally processed at 40–280° *in vacuo* to give films having high thermal stability (1291, 1343). The preparation of polymers (resistant to thermal degradation) from tetracarboxypyrazine dianhydride and tetraaminopyrazine in polyphosphoric acid at elevated temperatures has been described (1180).



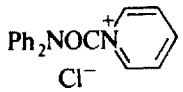
(18)

2,6-Diamino-3-carboxy-5-chloropyrazine *N,N*-diphenylcarbamic anhydride (**19**), an "active ester," has been prepared by addition of diphenylcarbamoyl chloride to 2,6-diamino-3-carboxy-5-chloropyrazine and triethylamine in dimethylformamide, (and other similar compounds were also prepared) (1330, 1344, 1345). This compound was better prepared from 2,6-diamino-3-carboxy-5-chloropyrazine and

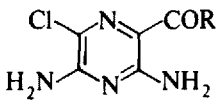
triethylamine with *N,N*-diphenylcarbamoylpyridinium chloride (**20**) in water or ethanol (1345, 1346), and it was more reactive than cyanomethyl esters or the so-called Woodward's esters, acyloxyacrylamides (1345). When it was treated briefly with sodium methoxide in methanol it gave 2,6-diamino-3-chloro-5-methoxycarbonylpyrazine (1345). Compound (**19**) also reacted with weak nucleophiles such as 3-amino-1,2,4-triazole or 2-aminobenzimidazole in refluxing tetrahydrofuran to give amides [**21**, R=$C_2H_3N_4$ or $C_7H_6N_3$ (1330)] and with guanidine hydrochloride in refluxing sodium isopropoxide–isopropanol to give 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine (1344).



(**19**)



(**20**)



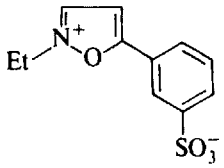
(**21**)

(5) *Other Reactions*

Many salts of carboxypyrazines have been isolated. Some of these are as follows: 2-carboxy (Ag, Cu, Ba, Ca) (272); 2,3-dicarboxy [Ag, Cu, Ba (397); V (1347)]; 2,5-dicarboxy [K, Na, Ca, Sr, Ag (27); Ba (32, 1348)]; 2,6-dicarboxy (Ag) (27); 2,3,5-tricarboxy (Ag, Ca, Sr, Ba, Cd) (27); tetracarboxy [Na, Ag, Ca, Ba (22); K (413)]; 3-carboxy-2,5-dimethyl (Cu) (32); 5-carboxy-2,3-dimethyl (Ag) (397); 5-carboxy-2,3-diphenyl (K, Ag) (25); 2,3-dicarboxy-5,6-dimethyl (Ag) (397); 2,5-dicarboxy-3,6-dimethyl (Ag, Ba) (18); and 2,5-dicarboxy-3,6-diphenyl (Ag) (209). Carboxypyrazines give colored solutions with aqueous ferrous sulfate (22, 27, 272, 278, 397) and some iron complexes have been described (1348). The rearrangement of 2,3-dicarboxypyrazine to 2,5-dicarboxypyrazine has been described in Section 1A(4) (1295–1297). 2,3-Dicarboxypyrazine refluxed with hydrazine hydrate (80%) in methanol gave the monohydrazine salt, which suspended in glycerol and heated at 200–220° for 15 minutes gave 2-carboxy-3-hydrazinocarbonylpyrazine (1349).

Various amides have been prepared directly from the carboxypyrazines. 2,6-Diamino-3-carboxy-5-chloropyrazine in dimethyl sulfoxide (*a*) with *N,N'*-dicyclohexylcarbodiimide gave 2,6-diamino-3-chloro-5-(2',5'-dioxopyrrolidin-1'-ylcarbonyl)pyrazine (?) (962), (*b*) with dicyclohexylcarbodiimide (and 2-hydrazinopyrimidine) gave 2,6-diamino-3-chloro-5-(*N*-cyclohexyl-*N*-cyclohexylcarbamoyl)-carbamoylpyrazine (1331), and (*c*) as its triethylamine salt with *N*-ethyl-5-phenyl-

isoxazolium-3′-sulfonate (22) and various amines gave 2,6-diamino-3-chloro-5-ethylcarbamoylpyrazine (1331). 2,6-Diamino-3-carboxy-5-chloropyrazine mixed with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (23) and aniline in DMSO gave 2,6-diamino-3-anilinocarbonyl-5-chloropyrazine (84%) (1345). 2,6-Diamino-3-carboxy-5-chloropyrazine (and 6-substituted amino analogues) refluxed with guanidines in butanol for 8 hours gave a series of 2,6-diamino-5-chloro-3-guanidinocarbonyl(and guanidinocarbamoyl)pyrazines (1350).



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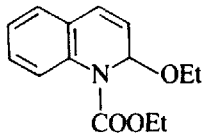
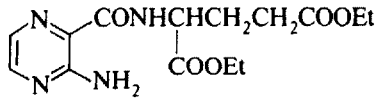


(23)

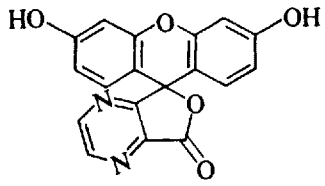
2-Amino-5-carboxypyrazine in anhydrous dimethylformamide with triethylamine and ethyl chloroformate and then diethyl glutamate and stirred at room temperature gave 2-amino-5-(1′,3′-diethoxycarbonylpropyl)carbamoylpyrazine (24) (1244). Similarly a mixture of 2-carboxypyrazine and triethylamine in methylene dichloride with ethyl chloroformate and morpholine gave 2-(*N*-morpholinocarbonyl)-pyrazine (1351). 2-Carboxy-3-hydroxypyrazine refluxed with phosphorus tris(*N*-methylanilide) in toluene gave 2-hydroxy-3-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine (1055), and 2-hydroxy-3-(*N*-methyl-*N*-*p*-tolylcarbamoyl)pyrazine was prepared similarly (1055). Tetracarboxypyrazine heated with sulfur tetrafluoride (SF_4) at 150° gave tetra(trifluoromethyl)pyrazine (899).



(24)

Reduction of 2-carboxypyrazine in aqueous potassium hydroxide over palladium–charcoal at 50° and atmospheric pressure gave 2-carboxypiperazine; and 2,3-dicarboxy-, 2,5-dicarboxy-, 2,6-dicarboxy-, and 2-carbamoyl-3-carboxy-piperazines were prepared in an analogous manner (1269). Similar results were obtained on reduction of the calcium salts (1352). Reduction of 2-chlorocarbonylpyrazine with lithium tri-*t*-butoxyaluminohydride in tetrahydrofuran gave 2-(pyrazin-2′-ylmethoxycarbonyl)pyrazine (1077).

Phthalein type dyes have been prepared from 2,3-dicarboxypyrazine by heating with phenols or aromatic amines and zinc chloride. For example, compound (25) was obtained with resorcinol (1353). Efforts to prepare 2,6-diaminopyrazine through a Curtius–Schmidt reaction on 2-acetamido-6-carboxypyrazine (with sodium azide, sulfuric acid, and trichloroacetic acid) proved unsuccessful (434). The preparation of bicyclic heterocyles from 2-amino-3-carboxypyrazines has been described in Section VIII.1D(6).



(25)

2. ALKOXYCARBONYLPYRAZINES (PYRAZINE ESTERS)

A. Preparation of Esters

(1) *By Primary Synthesis*

Preparation of pyrazine esters by primary synthesis have been described in Sections II.1B (18, 194, 202, 213–217, 224, 232), II.1F (267), II.1P (323), II.5 (429), II.7 (488), and II.9 (501).

In addition to the primary syntheses described in Section II.1, catalytic hydrogenation of ethyl 4-bromo-2-diazo-3-oxostearate over palladium–charcoal in hexane gave DL-2,5-diethoxycarbonyl-3,6-dipentadecyldihydropyrazine, which was also obtained from ethyl DL-2-amino-3-oxostearate hydrobromide in aqueous sodium acetate with acetic anhydride (1354).

Mertes and Lin (1185) condensed ethylenediamine with ethyl 2,3-dioxobutyrate and the unstable intermediate was aromatized by heating with palladium–charcoal to 2-ethoxycarbonyl-3-methylpyrazine (cf. Section II.2).

Additional data, relevant to the preparation of pyrazine esters described in Section II.5, are given in Reference 1161.

(2) *By Esterification of Carboxypyrazines*

Esterifications of carboxypyrazine have been described in Section 1C(2).

(3) *From Acid Chlorides and Anhydrides*

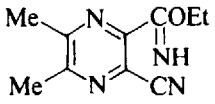
Esters (and thioesters) have been prepared from 2-chlorocarbonylpyrazine and β-dimethylaminoethanol in benzene (1278), lead methylmercaptide (and other mercaptans or mercaptides) (in ether at room temperature) (147, 1355) and thiophenol (in pyridine) (1356); from 2-chlorocarbonyl-3-methoxycarbonylpyrazine with methanol (1278); and from 2-dimethylaminoethanol (1278).

Reduction of 2-chlorocarbonylpyrazine with lithium tri-*t*-butoxyaluminohydride in tetrahydrofuran gave 2-(pyrazin-2′-ylmethoxycarbonyl)pyrazine (1077).

The preparation of some esters from the reactions of anhydrides has been described in Section 1C(4) and 2,3-dicarboxypyrazine anhydride with 2-dibutylaminoethanol in refluxing benzene gave 2-carboxy-3-(2′-dibutylaminoethoxy)carbonylpyrazine (1278).

(4) *By Hydrolysis of Iminoethers (and Iminothioethers)*

Iminoethers have been hydrolyzed to esters and iminothioethers to thioesters. Some examples follow: 2-cyano-3-(*C*-ethoxy-*C*-iminomethyl)-5,6-dimethylpyrazine [2-cyano-3-(*C*-ethoxyformidoyl)-5,6-dimethylpyrazine] (**26**) in boiling water gave 2-cyano-3-ethoxycarbonyl-5,6-dimethylpyrazine (1044); 2-amino-3-(*C*-ethoxy-*C*-iminomethyl)-5-trifluoromethylpyrazine [from 2-amino-3-carbamoyl-5-trifluoromethylpyrazine with Meerwein's reagent (1357), triethyloxonium fluoroborate (Et_3OBF_4)] in dilute acid gave 2-amino-3-ethoxycarbonyl-5-trifluoromethylpyrazine (802); 2-amino-5-cyano-3-(*C*-imino-*C*-methoxymethyl)-6-methoxypyrazine (prepared from salts of 1,1,3,3-tetracyano-2-azapropenide with sodium methoxide in methanol) with 2*N* hydrochloric acid in acetonitrile at 60° gave 2-amino-5-cyano-6-methoxy-3-methoxycarbonylpyrazine (but with dry hydrogen chloride in methanol it gave 2-amino-3-carbamoyl-5-cyano-6-methoxypyrazine) (484); 2-amino-3-(*C*-imino-*C*-methylthiomethyl)pyrazine refluxed in *N* hydrochloric acid gave 2-amino-3-(methylthio)carbonylpyrazine (1075); and 2-methoxy-6-(*C*-imino-*C*-methoxymethyl)pyrazine (from 2-chloro-6-cyanopyrazine with one equivalent of sodium methoxide) acidified with hydrochloric acid gave 2-methoxy-6-methoxycarbonylpyrazine (986).



(26)

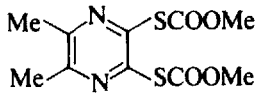
(5) *From Halogenopyrazines*

The preparation of extranuclear alkoxycarbonylpyrazines from chloropyrazines and bromomethylpyrazines has been described in Sections V.5H (363–365, 824, 825, 1023) and V.6C (1031), respectively.

(6) *By Other Methods*

Direct homolytic carboxylation of pyrazine cation has been described. A solution of ethyl pyruvate and hydrogen peroxide prepared at − 10° with a solution of aqueous ferrous sulfate and pyrazine in aqueous sulfuric acid gave 2-ethoxycarbonylpyrazine and diethoxycarbonylpyrazine (1358).

2,3-Dimethylpyrazine and ethereal methyllithium, treated with diethyl carbonate, gave 2-ethoxycarbonylmethyl-3-methylpyrazine (635); and 2,3-dimercapto-5,6-dimethylpyrazine refluxed with methyl chloroformate in benzene gave 2,3-bis(methoxycarbonyl)thio-5,6-dimethylpyrazine (27) (1145).



(27)

B. Properties of Esters

Second-order rate constants have been determined for the alkaline hydrolysis of 2-methoxycarbonylpyrazine in methanol–water (80% w/w) at 10° as 5.2×10^{-2} l/mol · sec (1263) and for 2-ethoxycarbonylpyrazine at 30° in 50 and 60% dimethyl sulfoxide–water and 60, 70, and 80% ethanol–water as 95.9, 199, 12.4, 10.2, and 8.86×10^{-1} l/mol · sec (1359). The failure of 2,5-dimethoxycarbonylpyrazine to undergo the Schmidt reaction has been accounted for in terms of its normal ionization, and "I" values in 100% sulfuric acid gave an average of 2.55 (1176).

Some tetraalkoxycarbonylpyrazines have good heat stability and are claimed to be useful as lubricants and plasticizers (1321).

C. Reactions of Esters

(1) *Hydrolysis*

The hydrolysis of esters to carboxylic acids has been described in Section 1A(2)(a). The second-order rate constant for the alkaline hydrolysis of 2-methoxycarbonylpyrazine in methanol–water (85% w/w) has been determined (1263).

(2) *Formation of Amides and Related Compounds*

Many carbamoylpyrazines and related compounds such as *N*-hydroxyamides (hydroxamic acids), hydrazides, cyanamides, guanidinocarbonyl-, guanidinocarbamoyl-, and ureidocarbonylpyrazines have been prepared from pyrazinecarboxylic esters. The amides were usually prepared with ammonia in methanol (or other alcohols) but also under other conditions.

(a) AMIDES

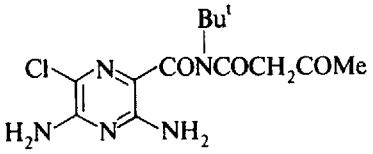
Amides have been prepared from the following esters: 2-methoxycarbonyl (NH_3/MeOH) (1171, 1278, 1312) [Dalmer and Walter (1333, 1360) report the

preparation of 2-carbamoylpyrazine and many other amides and hydrazides from the ester and acid chloride but these are not listed here]; 2-methoxycarbonyl-5-methyl [NH_3/EtOH/2° (420); 25% NH_4OH (1327) and also 6-methyl isomer (1327); and alcoholic ammonia with an ester (138)]; 5-methoxycarbonyl-2,3-diphenyl (NH_3/EtOH/100°) (25); 2,3-dimethoxycarbonyl [NH_3/MeOH (397, 1172); methanolic ammonia with an ester (138)]; 2,3-dialkoxycarbonyl-5-methyl (NH_3/EtOH) (138); 2,3-dimethoxycarbonyl-5,6-dimethyl (NH_3/MeOH) (403); 2,5-dimethoxycarbonyl [NH_3/MeOH (676, 1172); ammonium hydroxide in ethanol at room temperature gave a mixture of 2-carbamoyl-5-ethoxycarbonylpyrazine, 2,5-dicarbamoylpyrazine, and small amounts of 2,5-dicarboxypyrazine and 2,5-diethoxycarbonylpyrazine (676)]; 2,5-diethoxycarbonyl-3,6-dimethyl (NH_3/EtOH/20°/3 days) (287); 2,6-dialkoxycarbonyl (NH_3/MeOH) (138); 2,3,5-triethoxycarbonyl (412) and tetraethoxycarbonyl (NH_3/MeOH/20°) (412); 2-chloro-3-methoxycarbonyl (NH_4OH/20°) (423, 836); 2-chloro-5-methoxycarbonyl (NH_3/EtOH) (839); 2-bromo-5-ethoxycarbonyl (NH_4OH/EtOH/20°/3 h) (839); 2-chloro-6-methoxycarbonyl (NH_4OH/20°) (744, 870); 3-chloro-2-methoxycarbonyl-5-phenyl ($MeNH_2$/EtOH/140°/6 h) (375); 2-chloro-3-methoxycarbonyl-5,6-diphenyl (NH_3/EtOH/2 days) (837); 2,3-dichloro-5,6-dimethoxycarbonyl [NH_3/EtOH/18–20°/4 days gave 2-amino-5,6-dicarbamoyl-3-chloropyrazine (409); NH_3/EtOH/130° gave 2,3-diamino-5,6-dicarbamoylpyrazine (409); NH_3/DMF/70° gave 2-amino-3-chloro-5,6-dimethoxycarbonylpyrazine, but 2-amino-3-dimethylamino-5,6-dimethoxycarbonylpyrazine and some 2,3-diamino-5,6-dimethoxycarbonylpyrazine at 100°) (409)]; 2-hydroxy-3-methoxycarbonyl [NH_4OH (833); methanolic ammonia with an ester (138)]; 2-hydroxy-5-methoxycarbonyl (1057) and 2-hydroxy-6-methoxycarbonyl (NH_4OH/boil/30 min) (1057); 2-methoxy-6-methoxycarbonyl (NH_4OH) (986); 2-amino-3-methoxycarbonyl [NH_3/MeOH (1203); NH_4OH (1175, 1212); methanolic ammonia with an ester (138)]; 2-amino-5-methoxycarbonyl (NH_4OH/100°/3 h) (408); 2-amino-3-methoxycarbonyl-5-methyl (NH_4OH) (1218); 3-amino-2-methoxycarbonyl-5-methyl (NH_4OH) (435); 2-methoxycarbonyl-3-methylamino-5-phenyl (NH_3/EtOH/125°/5 h) (453); 2-amino-5-cyclopropyl-3-methoxycarbonyl (NH_4OH) (1218); 2-amino-3-methoxycarbonyl-5,6-diphenyl (NH_3/MeOH/120°) (455); 2-methoxycarbonyl-6-(2′-methylpiperidino) (NH_4OH/MeOH) (944); 2-amino-3-dimethylamino-5,6-dimethoxycarbonyl (NH_3/EtOH/20°/20 days) (409); 2-(*N*-benzyloxycarbonylamino)-5-ethoxycarbonyl (NH_3/EtOH) (1177); 2-acetamido-6-methoxycarbonyl (NH_4OH/MeOH/boil) (434); 2-methoxycarbonyl-3-methylamino-5-phenyl (benzylamine/reflux/30 min) (453); 2-amino-5-bromo-3-methoxycarbonyl [NH_4OH (1218); methanolic ammonia with an ester (138)]; 2-amino-5-chloro-3-methoxycarbonyl [NH_4OH (432, 432a, 778, 783, 786, 808, 877, 1218, 1253); NH_4OH/100° (808, 879)]; 2,6-diamino-3-chloro-5-methoxycarbonyl [(NH_4OH/20°) (877), (liq. NH_3/100°/3 h) (1361)]; 2-amino-5-chloro-6-isopropylamino-3-methoxycarbonyl (NH_4OH) (877); 2-amino-5-chloro-6-dimethylamino-3-methoxycarbonyl (NH_4OH) (877); 2-amino-5-chloro-6-methoxy-3-methoxycarbonyl (NH_4OH) (877); 2-amino-3-chloro-5,6-bismethoxycarbonyl (NH_3/EtOH/18–20°/4 days) (409); 2-amino-5,6-dichloro-3-methoxycarbonyl [liquid ammonia in an autoclave at room

temperature gave a mixture of equal parts of 2-amino-3-carbamoyl-5,6-dichloropyrazine (878) and 2,6-diamino-3-carbamoyl-5-chloropyrazine (809); $NH_4OH/20°$ (808, 877, 879, 1218)]; 2-[1′-(ethoxycarbonyl)-ethyl] ($NH_4OH/20°$/2 h) (364, 365, 1023); 2-[1′-(ethoxycarbonyl)ethyl]-5-phenyl ($NH_4OH/20°$/3 days) (364, 365, 824); 5-[1′-ethoxycarbonyl)ethyl]-2,3-diphenyl (NH_4OH/EtOH/20–50°) (364); 2-methoxycarbonyl [$MeNH_2$ (and other amines)/EtAc (1268, cf. 1333, 1360); morpholine/reflux/30 min (1324)] [heating with ethylenediamine in methanol gave 2-[(pyrazin-2′-oylaminoethyl)carbamoyl]pyrazine (1319)]; 2-cyanomethoxycarbonyl (2-cyanoethylamine/AcOEt–C_6H_{14}) (1362); 2-amino-3-methoxycarbonyl [$MeNH_2/20°$ (421, 836); piperidine/reflux/17 h (1075)]; 3-amino-2-methoxycarbonyl-5-methyl [aq. $MeNH_2$ (435); 2-cyanoethylamine (435)]; 2-amino-3-methoxycarbonyl-5,6-diphenyl [benzylamine/reflux (451); $MeNH_2$/EtOH/160°/ 16 h (1250, 1363)]; 2-chloro-3-methoxycarbonyl ($MeNH_2$/EtOH/130°/ 6 h: 2-methylamino-3-*N*-methylcarbamoylpyrazine) (423, 836); 2-amino-5-chloro-3-methoxycarbonyl (40% aq. $MeNH_2/20°$) (432, 778, 783, 1222); 2-amino-5-bromo-3-methoxycarbonyl (heat with 2-morpholinoethylamine/15 min) (1160); 2-amino-3-chloro-6-methoxy-5-methoxycarbonyl (2-aminomethyl-1-ethyl-pyrrolidine) (155, 1364); 2-chloro-6-methoxycarbonyl (morpholine/reflux: 2-morpholino-6-morpholinocarbonylpyrazine) (868, 870); 2-methoxy-6-methoxycarbonyl (morpholine/reflux) (869–871, 1324); and 2-[1′-(ethoxycarbonyl)ethyl]-5-phenyl (benzylamine at 100°) (364). 2,5-Dimethoxycarbonylpyrazine (and other esters) with bis(2-aminoethyl)ether (and other similar amino ethers) at reflux in methanol and then heated gave polymers (1365).

Although 2,6-diamino-3-chloro-5-methoxycarbonylpyrazine was sufficiently reactive to condense with many guanidines, some aliphatic amines, and hydrazine, it failed to condense with weak nitrogen bases such as 2-hydrazinopyrazine. Owing to interest in analogues of the effective potassium-sparing diuretic 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine, effort has been directed to the preparation of "active esters" (1331).

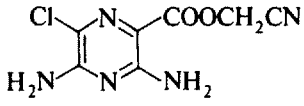
2,6-Diamino-3-(1′-*t*-butylcarbamoylmethyleneethoxy)carbonyl-5-chloropyrazine (**12**), an "active ester," reacted with aliphatic amines (hydrazines, guanidine, or aminoguanidine) to give the corresponding amides (hydrazides, guanidinocarbonyl, or guanidinocarbamoyl compounds) (961, 1330, 1331), but with strong bases, for example, sodium alkoxides or sodium urea in dimethylformamide or dimethyl sulfoxide, rearrangement occurred to give 2-(*N*-acetonylcarbonyl-*N*-*t*-butyl)-carbamoyl-3,5-diamino-6-chloropyrazine (**28**) (1330, 1331). 2,6-Diamino-3-(1′-*t*-butylcarbamoylmethyleneethoxy)carbonyl-5-chloropyrazine (**12**) with sulfurylamide ($H_2NSO_2NH_2$) in acetonitrile with triethylamine gave 2,6-diamino-3-



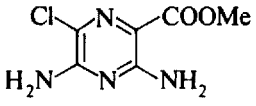
(28)

aminosulfonylcarbamoyl-5-chloropyrazine (463, 961). Compound (**12**) failed to acylate very weak nucleophiles such as 3-amino-1,2,4-triazole or 2-aminobenzimidazole under any conditions but 2,6-diamino-3-carboxy-5-chloropyrazine *N,N*-diphenylcarbamic anhydride (**19**) with the amines in refluxing tetrahydrofuran gave the amides (1330).

A comparison has been made of the reactivity of "active esters" (**12, 19, 29, 30**) of 2,6-diamino-3-carboxy-5-chloropyrazine in reactions with various amines to give amides (1345). Compound (**19**) was the most reactive followed by (**12**) and both more reactive than the others (1345). Compound (**12**) with sulfurylamide in acetonitrile with triethylamine gave 2,6-diamino-3-aminosulfonylcarbamoyl-5-chloropyrazine (463).



(**29**)



(**30**)

(b) HYDRAZIDES

Hydrazides have been prepared from the following esters: 2-methoxycarbonyl [$NH_2NH_2 \cdot H_2O$/MeOH/reflux (1323); $NH_2NH_2 \cdot H_2O$/reflux (1266, cf. 1333, 1360); benzylhydrazine/heat gave 2-(2′-benzylhydrazinocarbonylpyrazine) (1366)]; 2-methoxycarbonyl-5-phenyl ($NH_2NH_2 \cdot H_2O$/EtOH/warm) (376); 2-methoxycarbonyl-6-phenyl ($NH_2NH_2 \cdot H_2O$/EtOH/boil) (352); 2,5-dimethoxycarbonyl ($NH_2NH_2 \cdot H_2O$/MeOH or EtOH/heat) (1172, 1367); 2,5-diethoxycarbonyl [hydrazine hydrate in ethanol at $-5°$ gave 2-ethoxycarbonyl-5-hydrazinocarbonylpyrazine and a little 2,5-bis(hydrazinocarbonyl)pyrazine] (676); 2-carbamoyl-5-ethoxycarbonyl ($NH_2NH_2 \cdot H_2O$/EtOH/reflux/5 min: 2-carbamoyl-5-hydrazinocarbonylpyrazine) (676, 1368); tetraethoxycarbonyl (NH_2NH_2/MeOH/reflux) (412); 2-amino-3-methoxycarbonyl [$NH_2NH_2 \cdot H_2O$/120°/4 h (1203, 1212); $NH_2NH_2 \cdot H_2O$/MeOH (779, 1203)]; 2-acetamido-3-methoxycarbonyl [1 equiv. 96% $NH_2NH_2 \cdot H_2O$/Pr^iOH/20°) (433a); the 2-butyramido- and 2-benzamido analogues were prepared similarly (433a)]; 2-methoxycarbonyl-3-methylamino-5-phenyl (85% $NH_2NH_2 \cdot H_2O$/reflux) (453); 2-methoxy-6-methoxycarbonyl ($NH_2NH_2 \cdot H_2O$/EtOH/reflux/2 h) (986); 2-ethoxycarbonyl-6-ethylthio ($NH_2NH_2 \cdot H_2O$/EtOH) (992); 2-amino-3-methoxycarbonyl-5-methyl ($NH_2NH_2 \cdot H_2O$/MeOH/$< 30°$) (424); 2-methoxycarbonyl-6-methylamino [$NH_2NH_2 \cdot H_2O$/reflux (940)]; 2-alkoxycarbonyl-6-alkylamino ($NH_2NH_2 \cdot H_2O$/EtOH/reflux) (942); 2-methoxycarbonyl-6-thiomorpholino (NH_2NH_2/EtOH) (943); 2-methoxycarbonyl-6-(2′-methylpiperidino) ($NH_2NH_2 \cdot H_2O$/EtOH/reflux) (944); 3-amino-5-ethylamino-2-methoxycarbonyl (NH_2NH_2) (880); 2-amino-5-chloro-3-methoxycarbonyl ($NH_2NH_2H_2O$/EtOH/reflux) (781, 1058); 2-amino-5,6-dichloro-3-methoxycarbonyl (NH_2NH_2/2-methoxyethanol/100°: 2-amino-5-chloro-6-hydrazino-3-hydrazinocarbonylpyrazine) (891); 2,6-diamino-3-chloro-5-methoxycarbonyl [NH_2NH_2/EtOH/reflux (779, 1058, 1329); $MeNHNH_2$/2-methoxyethanol/100°/24 h (1369)];

2-amino-5-chloro-6-dimethylamino-3-methoxycarbonyl ($NH_2NH_2 \cdot H_2O$/EtOH/heat) (779, 958, 1370); 2-amino-5-chloro-6-diethylamino-3-methoxycarbonyl (NH_2NH_2/EtOH/reflux) (1371); and 2-amino-6-chloro-5-mercapto-3-methoxycarbonyl (aq. NH_2NH_2/20°) (790).

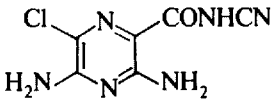
2,3-Dimethoxycarbonylpyrazine heated with hydrazine hydrate in ethanol gave some 5,8-dihydroxypyrazino[2,3-*d*]pyridazine (**16**) (1340). The reactions of 2,6-diamino-3-(1′-*t*-butylcarbamoylmethyleneethoxy)carbonyl-5-chloropyrazine (**12**) with hydrazines (and amines) has been described in Section 2C(2)(a) (961,1330, 1331). An analogous "active ester" was prepared from 2-amino-3-carboxy-5-chloro-6-methoxypyrazine and with hydrazine in tetrahydrofuran gave 2-amino-5-chloro-3-hydrazinocarbonyl-6-methoxypyrazine (963).

(c) *N*-HYDROXYAMIDES (HYDROXAMIC ACIDS)

N-Hydroxyamides have been prepared from the following esters: 2-methoxycarbonyl [aq. NH_2OH/20° (138), (and other amines) (1362); NH_2OH/MeOH (1266)]; 2-amino-3-methoxycarbonyl (NH_2OH/dil NaOH/35–50°) (1215); 3-amino-2-methoxycarbonyl-5-methyl (aq. NH_2OH/40–50°/2 h) (425); 2-methoxycarbonyl-6-methylamino (NH_2OH/MeOH/20°) (940) and 2-alkoxycarbonyl-6-alkylamino (NH_2OH/20°) (942); 2-methoxycarbonyl-6-thiomorpholino (NH_2OH/MeOH) (943); 2-methoxycarbonyl-6-(2′-methylpiperidino) (NH_2OH/MeOH/reflux) (944); and 2-ethoxycarbonyl-6-ethylthio (NH_2OH/MeOH/reflux) (992).

(d) *N*-CYANAMIDES

2,6-Diamino-3-chloro-5-(*N*-cyanocarbamoyl)pyrazine (**31**) has been prepared from 2,6-diamino-3-chloro-5-methoxycarbonylpyrazine by refluxing with sodium cyanamide in methanol (1372–1375). This compound with ammonium hydroxide containing ammonium chloride (and amines) gave 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine (and substituted guanidines) (1372); with hydrogen sulfide and triethylamine in pyridine it gave 2,6-diamino-3-chloro-5-thioureidocarbonylpyrazine (1373); and with acid it gave 2,6-diamino-3-chloro-5-ureidocarbonylpyrazine (and similar compounds were prepared likewise) (1374, 1375).



(**31**)

(e) GUANIDINOCARBONYLPYRAZINES

A series of 2-amino-3-guanidinocarbonylpyrazines has been prepared from the corresponding 2-amino-3-alkoxycarbonylpyrazine when refluxed with guanidine or with a guanidine salt and sodium alkoxide in the alcohol. Some pyrazine esters that have been converted with guanidine to guanidinocarbonyl compounds by the above method are as follows: 2-amino-3-methoxycarbonyl (787, 802); 2-amino-3-methoxycarbonyl-5-methyl(ethyl, cyclopropyl, cyclohexyl, phenyl, and

p-chlorophenyl) (778, 802); 3-amino-2-methoxycarbonyl-5-methyl (855, 859); 3-amino-5-cyclohexyl(phenyl, isopropyl, cyclopropylmethylamino, anilino, trifluoromethylamino, 4-piperidinylmethyl(?), pyrrolidinyl)-2-methoxycarbonyl (855, 859); 3-amino-5-benzyl-2-methoxycarbonyl (859); 2-amino-5-chloro-3-methoxycarbonyl (150, 787, 1376); 2-amino-5-iodo-3-methoxycarbonyl (150, 787, 1376); 2-amino-5-bromo-3-methoxycarbonyl (150, 787, 1376); 5-bromo-3-methoxycarbonyl-2-methylamino (800, 801); 2-amino-3-methoxycarbonyl-5-trifluoromethyl (787, 802, 1376); 5-chloro-2-cyclopropylamino-3-methoxycarbonyl (955, 956, 1377); 5-bromo-2-cyclopropylamino-3-methoxycarbonyl (1377); 5-bromo-2-cyclopropylmethylamino-3-methoxycarbonyl (955); 5-chloro-2-cyclopropylmethylamino-3-methoxycarbonyl (1377); 5-chloro-2-dimethylaminoethyl-3-methoxycarbonyl (801); 5-bromo-3-methoxycarbonyl-2-piperidino (801); 5-bromo-2-dimethylamino-3-methoxycarbonyl (801); 3,5-diamino-2-methoxycarbonyl (791, 809, 855, 859); 3-amino-5-dimethylamino-2-methoxycarbonyl (791, 809, 855, 859); 3-amino-5-benzylamino-2-methoxycarbonyl (791, 809, 855, 859); 5-anilino-2-isopropylideneamino-3-methoxycarbonyl (432, 780, 786); 3-amino-5-cyclopropylmethylamino(isopropylamino, anilino, and other substituted amino)-2-methoxycarbonyl (859); 2,6-diamino-5-chloro-3-methoxycarbonyl (809); 2,6-diamino-3-benzyloxycarbonyl-5-chloro (860); 2-amino-5-chloro-6-dimethylamino-3-methoxycarbonyl (780, 809, 858); 2-amino-3-chloro-5-methoxycarbonyl-6-methlyamino (789, 809); 2-amino-3-chloro-6-(*N*-cyclopropyl-*N*-methyl)amino-5-methoxycarbonyl (809, 857); 2,6-diamino-5-bromo(and iodo)-3-methoxycarbonyl (780, 809); 2-amino-5-chloro-3-methoxycarbonyl-6-(other mono and disubstituted)amino (809); 2,6-diamino-3-butylthiocarbonyl-5-chloro (1161); 2-amino-5,6-dichloro-3-methoxycarbonyl (378a, 782, 809, 858); 2-amino-5-chloro-6-hydroxy(methoxy or ethoxy)-3-methoxycarbonyl (809, 859); 2-amino-5-chloro-6-mercapto(and methylthio)-3-methoxycarbonyl (809); 5-bromo-2-hydroxy-3-methoxycarbonyl (892); 5-chloro-2-methoxy-3-methoxycarbonyl (892); 5-chloro-2-mercapto-3-methoxycarbonyl (892); 5-bromo-3-methoxycarbonyl-2-methylthio (892); 2-chloro-3-dimethylamino-5-hydroxy-6-methoxycarbonyl (892); 3-amino-2-methoxycarbonyl-5-methyl (cyclohexyl or phenyl) (809); 3-amino-5-hydroxy-2-methoxycarbonyl (809, 855, 859); 3-amino-5-methoxy-2-methoxycarbonyl (809, 855); 3-amino-2-methoxycarbonyl-5-trifluoromethyl (802); 2-amino-3-methoxycarbonyl-5,6-diphenyl(and dimethyl) (802); 2-amino-3-methoxycarbonyl-5-methyl-6-phenyl (802); 2-amino-3-methoxycarbonyl-6-methyl-5-phenyl (802); 2-amino-5-bromo-3-methoxycarbonyl-6-methyl-(and phenyl) (802); 2-amino-6-chloro-3-methoxycarbonyl-5-phenyl (802); and 2-amino-6-dimethylamino-3-methoxycarbonyl-5-methyl(and phenyl) (802).

The fusion of some 2-chloro-3-methoxycarbonylpyrazines with guanidine to give 2-amino-4-hydroxypteridines has been described in Section V.5B(2) (371, 375). 2-Amino-5-bromo-3-methoxycarbonylpyrazine heated alone with guanidine gave 2-amino-5-bromo-3-guanidinocarbonylpyrazine (787). The reactions of the "active ester" 2,6-diamino-3-(1′-*t*-butylcarbamoylmethyleneethoxy)carbonyl-5-chloropyrazine with guanidine and aminoguanidines have been discussed in Section 2C(2)(a) (961, 1330, 1331) and further data (1058). 2,6-Diamino-3-chloro-5-(2′,5′-dioxopyrrolidin-1′-yl)carbonylpyrazine (?) and guanidine heated at 145–190° gave

2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine (962) and the 2,3-diphenylguanidino analogue was prepared similarly (962). 2-Amino-5-chloro-3-ureidocarbonylpyrazine with guanidine in DMF at 70° for 8 hours gave 2-amino-5-chloro-3-guanidinocarbonylpyrazine (1374).

Some alkyl-, aryl-, and acylguanidines have also been prepared from the esters, as indicated below.

Alkyl and Aryl Guanidines: 3,5-diamino-2-methoxycarbonyl (791, 859); 5-chloro-2-amino-3-methoxycarbonyl (150, 801); 3-methoxycarbonyl-2-methylamino-5-trifluoromethyl (801); 2-amino-5-bromo-3-methoxycarbonyl (150, 801); 2-amino-5-iodo-3-methoxycarbonyl (150); 2,6-diamino-5-chloro-3-methoxycarbonyl (780, 809, 855); and 2-amino-5-chloro-3-methoxycarbonyl-6-(mono- and disubstituted amino) (809).

Acylguanidines: 2-amino-5-chloro-3-methoxycarbonyl (801); and 2-amino-3-methoxycarbonyl-5-trifluoromethyl (801).

(f) GUANIDINOCARBAMOYL AND AMIDINOCARBONYLGUANIDINOCARBONYLPYRAZINES

A series of 2-amino-3-methoxycarbonylpyrazines with aminoguanidine salts in the presence of sodium ethoxide in ethanol gave 2-amino-3-guanidinocarbamoylpyrazines (780, 781, 1058), and 5-chloro-2-hydroxy-3-methoxycarbonylpyrazine with aminoguanidine hydrochloride and sodium ethoxide gave 5-chloro-3-guanidinocarbamoyl-2-hydroxypyrazine (1378). For the reactions of "active esters" with aminoguanidine see Section 2C(2)(a) (961, 1330, 1331). 2-Amino-3-methoxycarbonylpyrazines with a biguanide derivative in the presence of sodium isopropoxide in isopropanol at reflux gave 2-amino-3-amidinocarbonylguanidinocarbonylpyrazines (1379).

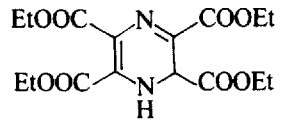
(g) UREIDOCARBONYLPYRAZINES

2-Amino-3-methoxycarbonylpyrazine with urea in the presence of sodium hydride in dimethylformamide at $-15°$ gave 2-amino-3-ureidocarbonylpyrazine (1152, 1322). The reaction was also applied to the following pyrazines: 2-amino-5-chloro-3-methoxycarbonyl (1152); 2,6-diamino-3-chloro-5-methoxycarbonyl (1380); 2-amino-5-chloro-3-methoxycarbonyl-6-methylamino (1380); 2-amino-5-chloro-6-dimethylamino(and other dialkylamino)-3-methoxycarbonyl (1152); and 2-amino-5-chloro-3-methoxycarbonyl-6-methylthio (1152). The preparation of ureidocarbonylpyrazines from *N*-cyanamides has been described in Section 2C(2)(d).

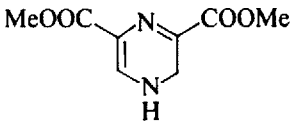
(3) *Reduction*

The catalytic reduction of alkoxycarbonylpyrazines was initially investigated by Mager and Berends (415, 1280, 1320), and also reduction with alkaline sodium dithionite (1320, 1381) was thought to give 1,4-dihydropyrazines, but recent work by Williams et al. (1326) has shown this to be in error. Their results may be summarized as follows. Catalytic reduction (palladium–charcoal) of di-, tri-,

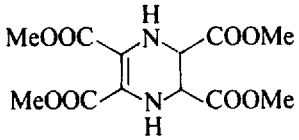
and tetraalkoxycarbonylpyrazines afforded 1,2-, not 1,4-dihydropyrazines, as major products. 2,3,5,6-Tetraethoxycarbonylpyrazine and 3,5-dimethoxycarbonylpyrazine yield only the dihydropyrazines (**32**) and (**33**), respectively; 2,3,5,6-tetramethoxycarbonylpyrazine gave tetramethoxycarbonyl-1,2-dihydropyrazine together with the tetra- and hexahydro products (**34**) and (**35**), respectively; 2,3,5-trimethyloxycarbonylpyrazine afforded the 1,2-dihydropyrazine (**36**) and the 1,2,3,4-tetrahydropyrazine; and 3,5-dimethoxycarbonylpyrazine gave the 1,2-dihydropyrazine (**33**), whereas 2,5-dimethoxycarbonylpyrazine gave the 1,2,3,4-tetrahydropyrazine. Alkaline sodium dithionite reduction of tetramethoxycarbonyl-(and tetraethoxycarbonyl)pyrazine and 2,3,5-trimethoxycarbonylpyrazine gave their 1,2-dihydropyrazines as the only product (1326).



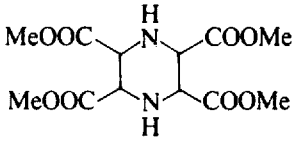
(**32**)



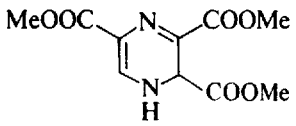
(**33**)



(**34**)



(**35**)



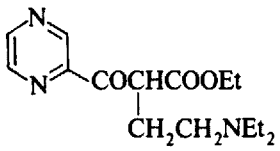
(**36**)

Mager and Berends (1280) found that 2-methoxycarbonylpyrazine on hydrogenation in ethanol over palladium–charcoal takes up two-thirds of the amount of hydrogen necessary for complete hydrogenation to a piperazine nucleus. Hydrogenation of the diphenacyl ester of 2,3-dicarboxypyrazine was also examined (1280). Reduction of 2,3-dimethoxy(and 2,3-diethoxy)carbonylpyrazine in ethanol over palladium–charcoal at atmospheric temperature and pressure gave 2,3-dimethoxy(and 2,3-diethoxy)carbonylpiperazine (1269). 2-Methoxy(and ethoxy)-carbonylpyrazine similarly treated gave no isolable reduction products (1269).

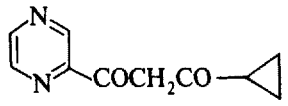
Reduction of 2-ethoxycarbonyl-3-methylpyrazine with lithium aluminum hydride in tetrahydrofuran at -70° gave 2-formyl-3-methoxypyrazine (1185), and reduction of 2-amino-3-methoxycarbonylpyrazine with lithium aluminum hydride in tetrahydrofuran at room temperature (1074) and reflux gave 2-amino-3-hydroxymethylpyrazine (1075).

(4) *Formation of Ketones*

2-Ethoxycarbonylpyrazine condensed with ethyl γ-diethylaminobutyrate in the presence of sodium in dioxane to give the β-keto ester (**37**), which hydrolyzed in 10% sulfuric acid to 2-(γ-diethylaminopropylcarbonyl)pyrazine (1186); 2-methoxycarbonylpyrazine with ethyl acetate and sodium ethoxide (alcohol-free) at reflux (or with sodium in refluxing toluene) gave 2-(ethoxycarbonylmethylcarbonyl)-pyrazine (1382, 1383); pyrazine carboxylate esters condensed with cyclopropyl methyl ketone to yield diketones (**38**) (1384), and with methyl propyl ketone and sodium amide in ether to 2-propylcarbonylmethylcarbonylpyrazine (1383). Ester condensation of 2-ethoxycarbonylpyrazine gave 2-acetylpyrazine (575). 2-Methoxycarbonylpyrazine with the lithio reagent from 2-bromo-4-chloronitrobenzene and phenyllithium gave 2-(5′-chloro-2′-nitrobenzoyl)pyrazine (1017).



(37)

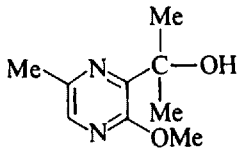


(38)

(5) *Other Reactions*

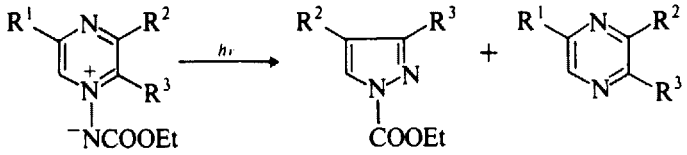
3,5-Dimethoxy-2-methoxycarbonylpyrazine boiled with phosphoryl chloride and phosphorus pentachloride gave the acid chloride, which, treated with aqueous hydrazine, gave 2-hydrazinocarbonyl-3,5-dimethoxypyrazine (881). 2-Methoxy-3-methoxycarbonyl-5-methylpyrazine with methylmagnesium iodide in ether gave 3-(1′-hydroxy-1′-methylethyl)-2-methoxy-5-methylpyrazine (**39**) (844). The bromination of 2-amino-5-bromo-3-methoxycarbonylpyrazine in 30% hydrobromic acid to 2-amino-3,5-dibromopyrazine has been described in Section V.1B (2) (807).

2-[1′,1′-(Diethoxycarbonyl)ethyl]pyrazine heated with sodium cyanide in dimethyl sulfoxide at 125–160° for 1 hour gave 2-[1′-(ethoxycarbonyl)ethyl]-pyrazine (364, 365) and the latter with sodium amide/liquid ammonia and methyl iodide gave 2-(2′-ethoxycarbonylprop-2′-yl)pyrazine (364). 5-(2′-Acetyl-2′-ethoxycarbonylethyl)-2-amino-3-cyanopyrazine with sodium chloride in aqueous dimethyl sulfoxide at 155–170° for 6 hours gave 5-(2′-acetylethyl)-2-amino-3-cyanopyrazine (1031).



(39)

The reactions of mono-, di-, tri-, and tetramethoxycarbonylpyrazines with 1-diethylaminopropyne ($Et_2NC{\equiv}CMe$) leads to pyridine derivatives (629); and irradiation of the *N*-ethoxycarbonyliminopyrazinium ylide (**40**) with a 100-W high-pressure Hg lamp (Pyrex) gave the *N*-ethoxycarbonylpyrazole (**41**) and the parent pyrazine (**42**) (1248).



(**40**) (**41**) (**42**)

3. CARBAMOYLPYRAZINES (AMIDES) AND RELATED COMPOUNDS (HYDRAZIDES, AZIDES, ETC.)

A. Preparation of Amides

(1) *From Esters, Acid Chlorides, and Acids*

Preparations of amides and related compounds from esters have been described in Section 2C(2).

Many amides have been prepared from pyrazinecarboxylic acid chlorides; some are listed below with the relevant amines and references: 2-chlorocarbonyl [$MeNH_2$/EtOAc (138); Me_2NH/EtOAc (138); Bu_2NH etc/EtOAc (138); aniline/EtOAc (138, 1335); other aromatic and heterocyclic amines/EtOAc (138); sulfanilamide/pyridine (1336); *p*-(2′-aminoethyl)benzenesulfonamide (1385); *p*-anisidine/benzene (1334); 4-hydroxypiperidine/benzene–chloroform (1386); morpholine/DMF/20° (1387); 2-aminopyrimidine/benzene (1388); glycine/NaOH/ether (1201, cf. 1333, 1360)]; 2-chlorocarbonyl-5-methyl [$MeNH_2$/benzene (1337); Me_2NH/benzene (1337); 4-phenylpiperazine or diethanolamine/benzene–chloroform (1386)]; 2-chlorocarbonyl-3-phenyl (6-aminopenicillanic acid) (1024); 2-chloro-3-chlorocarbonyl (morpholine/benzene) (838); 2-chloro-5-chlorocarbonyl (NH_4OH) (839); 2-chloro-6-chlorocarbonyl (Et_2NH/benzene) (870, 1389); 2-chlorocarbonyl-5-hydroxy (aniline/benzene) (1055); 2-chlorocarbonyl-3-methoxy (morpholine/benzene) (867); 2-chlorocarbonyl-5-methoxy (morpholine/benzene–chloroform) (1386); and 2-(1′-chlorocarbonylethyl) (morpholine/benzene) (364).

Amides have also been prepared from carboxylic acids as follows: a mixture of 2-carboxypyrazine and triethylamine in methylene chloride treated with ethyl chloroformate and then morpholine gave 2-(*N*-morpholinocarbonyl)pyrazine (1351); 2-carboxy-5(and 6)-methylpyrazine in dioxane with tributylamine and ethyl chloroformate and then treated with ammonia gave 2-carbamoyl-5(and 6)-methylpyrazine (673), and 2-carbamoyl-5(and 6)-ethylpyrazine were prepared

similarly (376); 2-amino-3-carboxypyrazine in dioxane with tributylamine, ethyl chloroformate, and methylamine (and various other amines) gave 2-amino-3-methyl(and various other substituted)carbamoylpyrazines (1213); and 2-amino-5-carboxypyrazine in anhydrous dimethylformamide with triethylamine and ethyl chloroformate, followed by stirring with diethyl glutamate at room temperature, gave 2-amino-5-[*N*-(1′,3′-diethoxycarbonylpropyl)carbamoyl]pyrazine (1244). 2-Carboxy-3-hydroxypyrazine refluxed with phosphorus tri(*N*-methylanilide) in toluene gave 2-hydroxy-3-(*N*-methyl-*N*-phenyl)carbamoylpyrazine, and 2-hydroxy-3-(*N*-methyl-*N*-*p*-tolyl)carbamoylpyrazine was prepared similarly (1055). 2,3-Dicarboxypyrazine heated with urea at $> 210°$ gave 2-carbamoylpyrazine (1390).

The formation of amides from acid anhydrides has been described in Section 1C(4).

(2) *By Primary Synthesis*

Preparations of carbamoylpyrazines and related compounds by primary syntheses have been described in Chapters II.1B (192, 215, 234), II.1J (298), II.1K (301), II.2 (347, 361, 365a, 369–375, 378–379, 382), II.5 and II.9 (505), and further data were given in Section VIII.1A(1). Dehydrogenation of 2-carbamoylpiperazine in a current of nitrogen over palladium–charcoal at 290–305° gave 2-carbamoylpyrazine (1391).

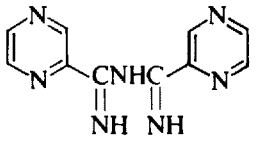
(3) *By Partial Hydrolysis of Nitriles*

Carbamoylpyrazines have been prepared by partial hydrolysis of the corresponding cyanopyrazines using a variety of procedures, which are described below. 2-Cyano-3-methylpyrazine and its 3-ethyl, 3-propyl, 3-phenyl, and 3,5,6-triethyl analogues with concentrated sulfuric acid at 120–125° for 3 hours and then poured onto ice gave the corresponding carbamoylpyrazine (866); and the following pyrazines were prepared similarly: 2,6-dicarbamoyl (115–117°) (865); 2,5-dicarbamoyl-3,6-dimethyl (70°/2 h, then 115°/1 h) (1104); 2-carbamoyl-6-chloro (1 h) (744); 2-carbamoyl-6-imidazolyl (100°) (944); 2-carbamoyl-6-thiomorpholino (80°) (943); and tetracarbamoyl (20°) (384). 2-Amino-3-cyanopyrazine boiled with 50% sulfuric acid for 5 minutes gave 2-amino-3-carbamoylpyrazine (1175) and saponification of 2-chloro-5(?)-cyanopyrazine with 37% hydrochloric acid gave 2-carbamoyl-5(?)-chloropyrazine (839, 840).

Hydrogen peroxide mostly in alkaline solution (Radziszewski reaction) but sometimes in acetic acid has been used to convert nitriles to amides, and the following carbamoylpyrazines have been prepared in this way: 2,3-dicarbamoyl (from 2-carbamoyl-3-cyanopyrazine with 30% aq. H_2O_2 and 28% NH_4OH at $-5°$ to 0°) (1392); 2-carbamoyl-5(?)-chloro (aq. H_2O_2/pH 9/55°/150 min) (839); 2-carbamoyl-6-chloro (aq. H_2O_2/2*N* NaOH/55°) (757); 2-carbamoyl-3-methoxy [H_2O_2/2*N* NaOH/50–55°/4 h (810); aq. H_2O_2/pH 9/50–60° (811)]; 2-carbamoyl-3,5-dimethoxy-6-methyl (aq. H_2O_2/pH 10/50–60°) (535); 3-carbamoyl-2,5-dimethoxy

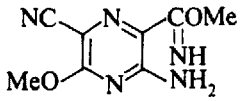
(aq. H_2O_2/NaOH/85°) (881); 3-carbamoyl-5-chloro-2-methoxy (H_2O_2/pH 9/55°) (881); 2-amino-3-carbamoyl-5,6-diphenyl (H_2O_2/aq. alcoholic NaOH/reflux/3 h) (454); 2-carbamoyl-6-dialkylamino (H_2O_2/ethanol/aq. NaOH/40–50°) (942); 2-carbamoyl-6-ethyl(propyl-, phenyl-, or benzyl)thio (H_2O_2/aq. alcoholic NaOH/40–50°/15 min) (992); 2-carbamoyl-6-ethyl-(propyl or benzyl)sulfonyl [from 2-cyano-6-ethyl(propyl or benzyl)thiopyrazine with 30% H_2O_2/AcOH/50–60°/4 h (992); from 2-cyano-6-ethylsulfonyl(ethylsulfinyl, propylsulfinyl, phenylsulfonyl, or benzylsulfonyl)pyrazine in acetic acid with 30% H_2O_2/10% aq. KOH/40–50°/15 min (992)]; and 2-carbamoyl-5-phenylsulfonyl (from 2-cyano-5-phenylthiopyrazine with H_2O_2/AcOH/50°/3 h) (840).

2,3-Dicyanopyrazine in ethanol with sodium molybdate and hydrogen peroxide at room temperature gave 2-carbamoyl-3-cyanopyrazine (1393), 2-chloro-3-cyano-5,6-diphenylpyrazine with ammonium hydroxide and potassium iodide was converted to 2-amino-3-carbamoyl-5,6-diphenylpyrazine (848), 2-cyano-6-(*N'*,*N'*-dimethylhydrazino)pyrazine boiled with concentrated ammonia for 2 hours gave 2-carbamoyl-6-(*N'*,*N'*-dimethylhydrazino)pyrazine (945), and 2-cyano-6-(4'-methylpiperazin-1'-yl)pyrazine refluxed with ethanolic ammonia for 2 hours gave the corresponding amide (943). 2-Cyanopyrazine with concentrated aqueous ammonia was converted through 2-[pyrazin-2'-yl-*C*-(imino)methylamino-*C*-(imino)methyl]pyrazine (**43**) to 2-carbamoylpyrazine, and the 6-chloro derivative was prepared analogously (985). 2-Chloro-6-cyanopyrazine with 40% aqueous methylamine at reflux for 30 minutes gave a mixture of 2-carbamoyl-6-methylaminopyrazine and 2-methylamino-6-methylcarbamoylpyrazine (940); but 2-chloro-6-cyanopyrazine with 40% aqueous methylamine at 0° gave 2-chloro-6-(*N*-methylamidino)pyrazine (and some 2-cyano-6-methylaminopyrazine) which refluxed in water gave 2-carbamoyl-6-chloropyrazine but boiled with 40% aqueous methylamine gave 2-carbamoyl-6-methylaminopyrazine (940).



(**43**)

2-Chloro-6-cyanopyrazine refluxed with one equivalent of sodium methoxide in methanol for 15 minutes gave 2-(*C*-imino-*C*-methoxymethyl)-6-methoxypyrazine, which when boiled with water gave 2-carbamoyl-6-methoxypyrazine (985), and 2-amino-3,5-dicyano-6-methoxypyrazine with sodium methoxide gave 2-amino-5-cyano-3-(*C*-imino-*C*-methoxymethyl)-6-methoxypyrazine (**44**), which with hydrogen chloride in methanol afforded 2-amino-3-carbamoyl-5-cyano-6-methoxypyrazine (484). The reaction of 2-amino-3-cyano-5-methylpyrazine 1-oxide with trifluoroacetic acid and trifluoroacetic anhydride at reflux followed by addition of water gave 2-carbamoyl-5-hydroxy-6-methyl-3-trifluoroacetamidopyrazine, which refluxed in methanol gave 2-amino-3-carbamoyl-6-hydroxy-5-methylpyrazine; the same preparation was achieved using acetic acid–acetic anhydride (538). 2-Amino-



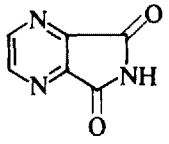
(44)

3-cyanopyrazine 1-oxide refluxed with acetic acid–acetic anhydride and the resulting 3-acetamido-2-carbamoyl-5-hydroxypyrazine refluxed with methanol afforded 3-amino-2-carbamoyl-5-hydroxypyrazine (538).

(4) *By Other Means*

Direct amidations of pyrazine have been described. Pyrazine with formamide, *t*-butylhydroperoxide, and ferrous sulfate gave 2-carbamoylpyrazine, and with dimethylformamide, *t*-butylhydroperoxide, and ferrous sulfate gave 2-*N*,*N*-dimethylcarbamoylpyrazine [but with *N*,*N*-dimethylacetamide and ammonium peroxydisulfate and ferrous sulfate it gave 2-(*N*-acetyl-*N*-methylaminomethyl)-pyrazine (1188). Pyrazine with concentrated sulfuric acid, formamide, hydrogen peroxide, and powdered ferrous sulfate at 10–15° gave 2-carbamoylpyrazine (611). 2,3-Diphenyl-5,6-dihydropyrazine heated with potassium cyanide in dilute alcoholic solution gave 5-carbamoyl-2,3-diphenylpyrazine (25), and its 2,3-(di-*p*-methoxyphenyl) (25), 2,3-di(fur-2′-yl), and 2,3-di(fur-2′-yl)-6-methyl analogues (338) were prepared similarly.

The imide of 2,3-dicarboxypyrazine (**45**) with sodium borohydride in tetrahydrofuran gave 2-carbamoyl-3-hydroxymethylpyrazine, and the 2-methylcarbamoyl analogue was prepared similarly (1076). The imide (**45**) with isopropylamine gave 2-carbamoyl-3-isopropylcarbamoylpyrazine (1394). 2,5-Dihydrazinocarbonylpyrazine with nitrous acid gave 2,5-diazidocarbonylpyrazine (1172).



(45)

B. Properties of Carbamoylpyrazines

The crystal structure of 2-carbamoylpyrazine has been determined: the pyrazine ring is completely planar, with mean C–N = 1.348 and C–C = 1.383 Å, and made an angle about 5° to the amide group (C–O = 1.24_4 and C–N = 1.31_2 Å) (1395). Investigations for 2-carbamoylpyrazine have been made of the heat of sublimation (1396), heat of fusion (1397), and solubilities in various solvents (1398) and the results correlated. The pK_a of 2-carbamoylpyrazine has been determined as −0.5 (140).

The antitubercular activity of 2-carbamoylpyrazine and biological activity of pyrazines generally has been mentioned in Section I.4. Certain pyrimidinyl derivatives of 2-carbamoylpyrazine have been shown to have lower toxicity and rather greater *in vitro* activity against *Mycobacterium tuberculosis* than 2-carbamoylpyrazine (1388), and the antitubercular activity of some extranuclear *N*-substituted carbamoylpyrazines also showed a higher activity than 2-carbamoylpyrazine (1201). When tested on mice *in vivo*, 2-carbamoyl-5-methoxypyrazine and 2-hydrazinocarbonylpyrazine had less antitubercular activity than did 2-carbamoylpyrazine (1098); the antitubercular activities in a series of hydrazinocarbonyl-, carbamoyl-, and thiocarbamoylpyrazines have been examined and compared (1399).

2-Carbamoylpyrazine in dogs and humans is hydrolyzed to 2-carboxypyrazine and then converted to 2-carboxy-5-hydroxypyrazine (1400) and a combined gas chromatographic–mass spectroscopic technique has been described for the simultaneous determination of 2-carbamoylpyrazine, 2-carboxypyrazine, and 2-carboxy-5-hydroxypyrazine (1401). Molecular addition complexes have been prepared with 2-carbamoylpyrazine (and pyrazine) and tetracycline sulfate (1402).

Pyrazinamide is one of the most powerful drugs available for the inhibition of urate excretion in man, consistently providing a 80–90% reduction in the renal clearance of uric acid (1401, 1403). 2-Morpholinocarbonylpyrazine and its 6-methoxy derivative are claimed to have antidiabetic activity (948, 949, 1351, 1387, 1404), and some 2-(*p*-ureidosulfonylphenethylcarbamoyl)pyrazines have been shown to have hypoglycemic activity in mice (1405). The effect of 2-amino-3-hydroxycarbamoylpyrazine on DNA synthesis by Erlich ascites tumor cells *in vitro* has been investigated (1406) as well as the inhibition by 2-amino-3-hydroxycarbamoylpyrazine on L-histidine carboxylyase (1407); many 2-hydroxyimidazo[4,5-*b*]pyrazines (prepared from 2-amino-3-hydrazinocarbonylpyrazines with nitrous acid) are potent hypotensive agents in animals (880, 891, 963, 1181).

Many guanidinocarbonyl- and guanidinocarbamoylpyrazines have been prepared and tested for diuretic activity (150, 432, 799, 802, 809, 1058, 1218, 1408). Compounds of these types promote sodium ion excretion but potassium ion excretion is unaffected or repressed. Amiloride (2-amidinocarbamoyl-3,5-diamino-6-chloropyrazine) is used clinically as a diuretic. A series of ureidocarbonylpyrazines have also been prepared and tested in diuretics (1152). *N*-Substituted amides of 2-carboxy-3,5-bismethylamino-6-*N*-methylcarbamoylpyrazine fluoresce violet-blue or blue to green-blue in ultraviolet light and are claimed to be useful optical bleaching agents for textiles, cosmetic preparations, and polymers (1192).

C. Reactions of Amides

(1) *Dehydration of Amides to Nitriles*

Carbamoylpyrazines with various dehydrating agents afford cyanopyrazines. Ellingson et al. (1175) first dehydrated 2-amino-3-carbamoylpyrazine with phosphorus pentoxide in refluxing pyridine to 2-amino-3-cyanopyrazine; this

dehydrating agent has also been used in nitrobenzene and toluene. Phosphoryl chloride, alone or with phosphorus pentachloride, and phosphorus tribromide have also been employed, but the more commonly used reagent for 2-amino-3-carbamoylpyrazines is phosphoryl chloride with dimethylformamide [the intermediate formamidines ($-N{=}CHNMe_2$) required hydrolysis] (1218). Some dehydration of carbamoylpyrazines to the corresponding nitriles are listed below, together with the reagent and conditions: 2-carbamoyl [$POCl_3$/reflux (575, 1334, 1409, 1410); P_2O_5 gave a lower yield (1410); $POCl_3/Br_2$/90–95°, then 130° was reported to give 2-chloro-5(?)cyanopyrazine (839)]; 2-carbamoyl-5(and 6)-methyl ($POCl_3$/105°/6 h) (1327); 2,3-dicarbamoyl ($SOCl_2$/DMF/reflux/1 h) (1411); 2,5-dicarbamoyl ($P_2O_5/PhNO_2$/reflux) (672); 2,5-dicarbamoyl-3,6-dimethyl (P_2O_5/toluene/boil/16 h) (287); 2-carbamoyl-3-hydroxy ($POCl_3$/reflux: 2-chloro-3-cyanopyrazine) (810, 811, 840); 2-carbamoyl-3-hydroxy-5,6-diphenyl ($POCl_3$/reflux/45 min gave 2-cyano-3-hydroxy-5,6-diphenylpyrazine (837), but $POCl_3$/170°/5 h (837), PCl_3/sealed tube/heat (848), or $POCl_3/PCl_5$ (848) gave 2-chloro-3-cyano-5,6-diphenylpyrazine; PBr_3/reflux gave 2-bromo-3-cyano-5,6-diphenylpyrazine) (837); 2-carbamoyl-5-chloro (840) and 2-carbamoyl-6-chloro ($POCl_3$/reflux/1 h) (840); 2-carbamoyl-5-chloro-3-hydroxy-6-methyl ($POCl_3/PCl_5$/reflux: 2,6-dichloro-3-cyano-5-methylpyrazine) (535); 2-amino-3-carbamoyl [P_2O_5/pyridine/reflux (1175); $POCl_3$/DMF/50°, followed by boiling with water (1075, 1183, 1184)]; 2-amino-3-carbamoyl-5-methyl (and cyclopropyl) ($POCl_3$/DMF, followed by hydrolysis with dilute hydrogen chloride) (1218); 2-carbamoyl-3-methylamino-5-phenyl [ethyl chloroformate/reflux: 2-cyano-3-(*N*-ethoxycarbonyl-*N*-methylamino)-5-phenylpyrazine] (453); 2-amino-3-carbamoyl-5-chloro ($POCl_3$/DMF gave 5-chloro-3-cyano-2-dimethylaminomethyleneaminopyrazine, which was hydrolyzed in 5% aqueous hydrochloric acid at 100° to 2-amino-5-chloro-3-cyanopyrazine) (808, 879, 1218, 1253); 2-amino-5-bromo-3-carbamoyl ($POCl_3$/DMF) (879, 1218); 2-amino-3-carbamoyl-5,6-dichloro ($POCl_3$/DMF) (808, 878, 879, 1218); 2-amino-5-bromo-3-carbamoyl-6-chloro ($POCl_3$/DMF) (878); 2,6-diamino-3-carbamoyl-5-chloro ($POCl_3$/DMF/80°) (808, 1361); 2-amino-3-carbamoyl-5-chloro-6-dimethylamino ($POCl_3$/DMF) (808, 878); and 2-amino-3-carbamoyl-5-chloro-6-isopropylamino ($POCl_3$/DMF) (808, 877, 1253). Some further data on dehydration of carbamoylpyrazines by thionyl or phosphoryl chloride in dimethylformamide have been recorded (792, 878, 1219).

(2) *Transamination of Amides*

2-Carbamoyl-3-hydroxypyrazine refluxed with aniline gave 2-hydroxy-3-*N*-phenylcarbamoylpyrazine (1055) and 2-amino-3-carbamoyl-5,6-diphenylpyrazine refluxed with benzylamine gave 2-amino-3-*N*-benzylcarbamoyl-5,6-diphenylpyrazine but a similar reaction with piperidine was unsuccessful (451). 3-Methylamino-2-*N*-methylcarbamoyl-5-phenylpyrazine was unchanged when heated with liquid ammonia in dry ethanol at 210° for 2 hours (453). 2,6-Diamino-3-carbamoyl-5-chloropyrazine in isopropanol with 1 mol of potassium hydroxide and 1-amidino-

3,5-dimethylpyrazole nitrate at 0° gave 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine (and *N*-substituted analogues were prepared similarly) (1412).

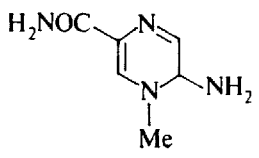
2,6-Diamino-3-chloro-5-(*N*,*N*-dimethylamidino)pyrazine refluxed with guanidine (and aminoguanidine) in ethanol gave 2,6-diamino-3-chloro-5-guanidinocarbonyl- (and 5-guanidinocarbamoyl)pyrazine (1361); 2,6-diamino-3-chloro-5-(2′,5′-dioxopyrrolidin-1′-yl)carbonylpyrazine (?) and 1,3-diphenylguanidine heated at 145–190° for 15 minutes gave 2,6-diamino-3-chloro-5-(*N*′,*N*″-diphenylguanidinocarbonyl)pyrazine (?); and the guanidino analogue was prepared similarly (962).

(3) *Other Reactions*

Carbamoylpyrazines have been hydroxymethylated with formaldehyde and potassium carbonate, and aminomethylated with formaldehyde and amine. In this way the following have been prepared: 2-*N*-hydroxymethylcarbamoylpyrazine (138); 2-*N*-(diethylaminomethyl)carbamoylpyrazine (1413–1416); 2-*N*-(morpholinomethyl)carbamoylpyrazine (1414, 1416); and 2-*N*-[piperidino(pyrrolidino or other amino)methyl]carbamoylpyrazines (1414, 1416). 2-*N*-(Diethylaminomethyl)-carbamoylpyrazine refluxed with morpholine afforded 2-*N*-(morpholinomethyl)-carbamoylpyrazine (1415), and 2-carbamoylpyrazine with *N*-(morpholinomethyl)-benzenesulfonamide gave 2-*N*-(morpholinomethyl)carbamoylpyrazine (1417).

2-Carbamoylpyrazine refluxed with acetic anhydride gave 2-*N*-acetylcarbamoylpyrazine (138, 1418) and 2,5-bis-*N*-acetylcarbamoylpyrazine was prepared similarly (672). 2,3-Dicarbamoylpyrazine heated in a vacuum gave the imide of 2,3-dicarboxypyrazine (397).

2-Carbamoylpyrazine was methylated to 3-carbamoyl-1-methylpyrazinium iodide by methyl iodide in methanol at reflux (138) and by methyl iodide in dimethyl sulfoxide at room temperature (666); under the latter conditions the rate of methylation relative to pyrazine was 0.53 (666). 3-Carbamoyl-1-methylpyrazinium iodide reacted with liquid ammonia at −40° to give 2-amino-5-carbamoyl-1-methyl-1,2-dihydropyrazine (**46**) (609). With nitromethide ions in liquid ammonia, none of the carbon addition reaction was found (721), but with ethanethiolate ion in liquid ammonia it gave 5-carbamoyl-2-ethylthio-1-methyl-1,2-dihydropyrazine (721). 2-(4′-Morpholino)carbonylpyrazine with methyl iodide gave 3-(4′-morpholino)-carbonyl-1-methylpyrazinium iodide (870).



(46)

The conversion of amides to amines has been described in Section VIII.1A(5), hydrolysis of amides to acids in Section 1A(2)(b), the conversion of amides through

iminoethers to esters in Section 2A(4), and the preparation of bicyclic heterocycles from 2-amino-3-carbamoylpyrazines in Section VIII.1D(6). Additionally a series of 3-substituted lumazines has been prepared from *N*-monosubstituted 2,3-dicarbamoylpyrazines with sodium hypochlorite (1394).

Reduction of 2-carbamoylpyrazine in ethanol over palladium–charcoal at atmospheric pressure gave 2-carbamoylpiperazine (870, 1269, 1352), and the 2-carbamoyl-3-carboxy (1269) and 2,3-dicarbamoyl (1269, 1352) analogues were prepared similarly, but 2,3-dicarboxypyrazine imide gave 50% 2,3-dicarboxy-1,4,5,6-tetrahydropyrazine imide (1269). 2-Hydroxy-3-*N*-phenylcarbamoylpyrazine oxidized with hydrogen peroxide in acetic acid at 50° for 96 hours did not give an *N*-oxide but only a tar and 2,3-dihydroxypyrazine (1055).

D. Preparation and Reactions of Thioamides

Thioamides have been prepared from cyanopyrazines with hydrogen sulfide in the presence of base. In this way the following thiocarbamoylpyrazines have been prepared (conditions of reactions): 2-thiocarbamoyl [Et_3N/EtOH/H_2S (1409); Et_3N–pyridine/H_2S/100° (1419); NH_3/EtOH/H_2S (138)]; 2-thiocarbamoylmethyl and its 1′-ethyl or 1′-phenyl derivatives (Et_3N–pyridine/20° or 100°/H_2S) (1420, 1421); 2-amino-3-thiocarbamoyl (triethanolamine/50–55°/12 h/H_2S) (1212); 2-amino-5,6-diphenyl-3-thiocarbamoyl (triethanolamine/ethanol/H_2S/100°/3 h) (454); 2-methylamino-6-thiocarbamoyl (triethylamine/EtOH/H_2S, fusion with thioacetamide/160°, or P_2S_5/pyridine/reflux) (945); 2-ethylamino-6-thiocarbamoyl [NH_4HS/EtOH (945); Et_3N/H_2S (992)]; 2-diethylamino-6-thiocarbamoyl (Et_3N or NH_3/EtOH/H_2S) (941); 2-(2′-methylpiperidino)-6-thiocarbamoyl (Et_3N/EtOH/H_2S) (944); 2-thiocarbamoyl-6-thiomorpholino (Et_3N/EtOH/H_2S) (943); 2-chloro-6-thiocarbamoyl (Et_3N or NH_3/EtOH/H_2S) (941); and 2-ethyl(propyl or phenyl)thio-6-thiocarbamoyl (Et_3N/H_2S) (992).

2-[*N*-Alkyl(thiocarbamoyl)]pyrazines have also been obtained by heating the 2-(*N*-alkylcarbamoyl)pyrazine with phosphorus pentasulfide and potassium sulfide in xylene at 100° (1268) and 2-amino-3-carbamoyl-5,6-diphenylpyrazine refluxed with phosphorus pentasulfide in pyridine gave 2-amino-5,6-diphenyl-3-thiocarbamoylpyrazine and the 3-*N*-butyl(thiocarbamoyl) analogue was prepared similarly (455). 2-Amino-5-chloro-3-(*C*-imino-*C*-methylthiomethyl)pyrazine with hydrogen sulfide in pyridine gave 2-amino-5-chloro-3-thiocarbamoylpyrazine (1218).

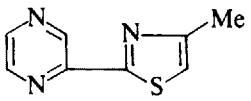
2-Methylpyrazine heated with dimethylformamide and sulfur in *o*-dichlorobenzene at about 150–180° (with and without iodine as catalyst) gave 2-*N*-methyl(thiocarbamoyl)pyrazine and 2-*N*,*N*-dimethyl(thiocarbamoyl)pyrazine (1268, 1422), 2-methylpyrazine with methylformamide, sulfur, and iodine at 170–180° gave 2-*N*-methyl(thiocarbamoyl)pyrazine (1268), and 2,5-bis-methyl(thiocarbamoyl)pyrazine was prepared similarly (1423).

Hydrolysis of 2-*N*,*N*-dimethyl(thiocarbamoyl) [or 2-*N*-methyl(thiocarbamoyl)-pyrazine] with 4*N* sodium hydroxide at 100° gave 2-carboxypyrazine (1268),

and 2-*N*,*N*-dimethyl(thiocarbamoyl)pyrazine heated with sulfur at 240° gave 2-*N*-methyl(thiocarbamoyl)pyrazine (1268). A series of 2-substituted amino-6-thiocarbamoylpyrazines refluxed with hydroxylamine in methanol gave 2-(*C*-amino-*C*-hydroxyiminomethyl)-6-substituted aminopyrazines (1424) and 2-ethylthio-6-thiocarbamoylpyrazine boiled with hydroxylamine in aqueous methanol gave 2-(*C*-amino-*C*-hydroxyiminomethyl)-6-ethylthiopyrazine (992).

2-(*N*′,*N*′-Dimethylhydrazino)-6-thiocarbamoylpyrazine refluxed with aqueous methanolic formaldehyde gave 2-[*N*-hydroxymethyl(thiocarbamoyl)]-6-(*N*′,*N*′-dimethylhydrazino)pyrazine (945) and 2-chloro-6-thiocarbamoylpyrazine was also *N*-hydroxymethylated and *N*-aminomethylated (941).

2-Thiocarbamoylpyrazine refluxed with methyl chloroacetate in methanol gave 2-(4′methylthiazol-2′-yl)pyrazine (47) (1409); 2-imidazol-1′-yl-6-thiocarbamoylpyrazine refluxed with formaldehyde gave 2-imidazol-1′-yl-6-*N*-hydroxymethyl(thiocarbamoyl)pyrazine (944).



(47)

E. Hydrazides and Azides

(1) *Preparation*

(a) FROM ESTERS

The preparation of hydrazides from esters has been described in Section 2C(2)(b) and from ring opening reactions of pteridines in Section II.5.

(b) FROM AMIDES

Hydrazides may also be prepared from amides by heating with hydrazine(s), and these reactions have been effected with the following pyrazine amides (reagent and conditions): 2-carbamoyl (100% $NH_2NH_2 \cdot H_2O$) (1425); 2-carbamoyl-5-methyl (98% NH_2NH_2/100°/1 h) (1426); 2-amino-3-carbamoyl ($NH_2NH_2 \cdot H_2O$/EtOH/reflux) (1214); 3-amino-2-carbamoyl-5(and 6)methyl ($NH_2NH_2 \cdot H_2O$/100°/2.5 h) (424); 2-amino-3-carbamoyl-5,6-dimethyl (Me_2NNH_2/160–165°/45 h) (426); and 3-carbamoyl-2,5-dimethoxy ($NH_2NH_2 \cdot H_2O$/EtOH/reflux/3 h) (881).

(c) FROM ACIDS

2-Carboxypyrazine with isopropylhydrazine and *N*,*N*′-dicyclohexylcarbodiimide in dichloromethane gave 2-(2′-isopropylhydrazinocarbonyl)pyrazine and other products (1366), and 2,3-dicarboxypyrazine refluxed with 80% hydrazine hydrate in methanol gave the monohydrazine salt which, suspended in glycerol and heated at 200–220° for 15 minutes, gave 2-carboxy-3-hydrazinocarbonylpyrazine

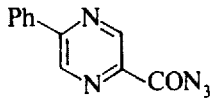
(1349). 2,5-Di(chlorocarbonyl)pyrazine with isophthalic dihydrazide in *N*-methylpyrrolidinone gave the polyhydrazide (1427).

(d) FROM NITRILES

Reaction of 2-chloro-3-cyano-5,6-diphenylpyrazine with hydrazine hydrate is reported to give 2-chloro-3-hydrazinocarbonyl-5,6-diphenylpyrazine (848).

(2) *Reactions of Hydrazides and Azides*

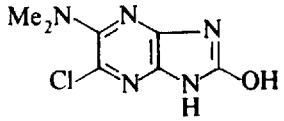
When treated with nitrous acid, hydrazides form azides. In this way 2-hydrazinocarbonyl-5-phenylpyrazine gave 2-azidocarbonyl-5-phenylpyrazine (**48**) (376); 2-hydrazinocarbonyl-6-phenylpyrazine gave 2-azidocarbonyl-6-phenylpyrazine (352); 2,5-bis(hydrazinocarbonyl)pyrazine gave 2,5-diazidocarbonylpyrazine (which could not be prepared by reacting the diacid chloride with sodium azide) (1172); 2-carbamoyl-5-hydrazinocarbonylpyrazine gave 2-azidocarbonyl-5-carbamoylpyrazine (676, 1368); 2-hydrazinocarbonyl-3,5-dimethoxypyrazine gave 2-azidocarbonyl-3,5-dimethoxypyrazine (881); and 2-ethoxycarbonyl-5-hydrazinocarbonylpyrazine gave 2-azidocarbonyl-5-ethoxycarbonylpyrazine (676).



(**48**)

The conversion of hydrazides and azides to amines has been described in Section VIII.1A(6).

2-Amino-5-chloro-3-hydrazinocarbonyl-6-dimethylaminopyrazine with nitrous acid gave 2-amino-3-azidocarbonyl-5-chloro-6-dimethylaminopyrazine which refluxed in ethanol gave 5-chloro-6-dimethylamino-2-hydroxyimidazo[4,5-*b*]pyrazine (**49**) (891), but 2-amino-5-chloro-6-ethylamino-3-hydrazinocarbonylpyrazine with nitrous acid gave 2-amino-3-azidocarbonyl-5-chloro-6-ethylaminopyrazine which, heated in 2-methoxyethanol, gave the 6-ethylamino analogue of (**49**) together with 2-amino-3-carbamoyl-5-chloro-6-ethylaminopyrazine (963). 2-Chloro-3-dimethylamino-5-ethylamino-6-hydrazinocarbonylpyrazine similarly treated gave the azide and 5-chloro-6-dimethylamino-1-ethyl-2-oxo-1,2-dihydroimidazo[4,5-*b*]pyrazine (by heating in methoxyethanol) (891); 2-amino-5-chloro-6-hydrazino-3-hydrazinocarbonylpyrazine gave the azide and 5-azido-6-chloro-2-hydroxyimidazo[4,5-*b*]-pyrazine (by heating in ethoxyethanol) (891).

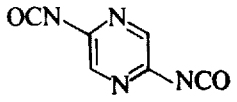


(**49**)

The formation of urethanes by heating azidocarbonyl compounds with anhydrous alcohols has been described in Section VIII.1E.

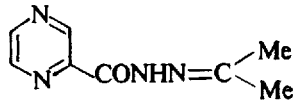
2,6-Diamino-3-chloro-5-hydrazinocarbonylpyrazine with nitrous acid at 50–55° formed 2,6-diamino-3-azidocarbonyl-5-chloropyrazine, which, refluxed with a solution of guanidine hydrochloride and sodium isopropoxide in propan-2-ol, gave 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine and many similar preparations were reported (1371). 2-Amino-5-chloro-3-hydrazinocarbonylpyrazine treated with nitrous acid gave 2-amino-3-azidocarbonyl-5-chloropyrazine, which was pyrolyzed to 5-chloro-2-hydroxyimidazo[4,5-*b*]pyrazine (1226).

2,5-Diazidocarbonylpyrazine refluxed in benzene gave 2,5-diisocyanatopyrazine (**50**) (which was stable to hydrolytic agents) (1172). 5-Azidocarbonyl-2,3-bis(fur-2′-yl)pyrazine reacted with amines to afford the corresponding urea derivatives (1163).



(**50**)

The amino group of hydrazides react with aldehydes and ketones. For example, 2-hydrazinocarbonylpyrazine refluxed with acetone–ethanol gave 2-isopropylidenehydrazinocarbonylpyrazine (**51**) [which was reduced in methanol over palladium–charcoal to 2-(2′-isopropylhydrazinocarbonyl)pyrazine] (1366, 1428, 1429). Other references to similar reactions include the following reactions: 2-hydrazinocarbonylpyrazine with *p*-acetamidobenzaldehyde (138); 4-hydroxy-, 4-hydroxy-3-methoxy- and 2-carboxy-3,4-dimethoxybenzaldehydes (1319); furfural (1201) and pyruvic acid (1201); 2-amino-3-hydrazinocarbonylpyrazine with acetone and benzaldehyde (1214); and 2-hydrazinocarbonyl-5,6-dimethyl-3-methylaminopyrazine with acetone (428).



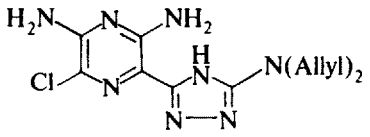
(**51**)

2-Hydrazinocarbonylpyrazine in aqueous hydrochloric acid reacted with potassium cyanate to give 2-semicarbazidocarbonylpyrazine (1201), and 2-amino-5-chloro-3-hydrazinocarbonylpyrazine behaved similarly (1058); 2-hydrazinocarbonylpyrazine with hydrochloric acid and potassium thiocyanate heated at 100° gave 2-thiosemicarbazidocarbonylpyrazine (1201); and 2,6-diamino-3-chloro-5-hydrazinocarbonylpyrazine with potassium thiocyanate in acetic acid gave 2,6-diamino-3-chloro-5-thiosemicarbazidocarbonylpyrazine (which was methylated at sulfur with methyl iodide) (1329). 2-Hydrazinocarbonyl-5-methylpyrazine with ethyl isothiocyanate gave 2-ethylamino(thiocarbonyl)hydrazinocarbonyl-5-methylpyrazine (1426), and 2-amino-5-chloro-6-dimethylamino-3-hydrazinocarbonylpyrazine with

allyl isocyanate in pyridine or acetonitrile gave the semicarbazide (2-allylaminocarbonylhydrazinocarbonyl-3-amino-6-chloro-5-dimethylaminopyrazine (958). 2-Hydrazinocarbonyl-5-methylpyrazine with carbon disulfide and potassium hydroxide in ethanol at 35° formed the potassium salt of 2-(2′-dithiocarboxyhydrazino)-carbonyl-5-methylpyrazine (1426).

Hydrazides react with cyanamide and substituted cyanamides to give guanidinocarbamoylpyrazines. For example, 2-amino-3-hydrazinocarbonylpyrazine with cyanamide in ethanolic hydrogen chloride gave 2-amino-3-guanidinocarbamoylpyrazine and similar reactions were observed with *N*-methyl- and *N,N*-dimethylcyanamide (779).

Some other like reactions were observed with 2-amino-5-chloro-3-hydrazinocarbonylpyrazine and cyanamide in ethanolic hydrogen chloride (781, 1058) or dimethylcyanamide with ethanolic hydrogen chloride (1058); 2,6-diamino-3-chloro-5-hydrazinocarbonylpyrazine with cyanamide in ethanolic hydrogen chloride (779) or dimethylcyanamide and pyridine hydrochloride at 125° for 1 hour (1058, 1370) and 2-amino-5-chloro-6-dimethylamino-3-hydrazinocarbonylpyrazine with cyanamide in ethanolic hydrogen chloride (779); but 2,6-diamino-3-chloro-5-hydrazinocarbonylpyrazine, *t*-butylcyanamide, and pyridine hydrochloride, heated at 125–130° for 2 hours, gave 2,6-diamino-3-(4′-*t*-butylsemicarbazidocarbonyl)-5-chloropyrazine (1369); and with diallylcyanamide a 2-(5′-amino-4′*H*-1′,2′,4′-triazol-3′-yl)pyrazine (**52**) was prepared (1369).



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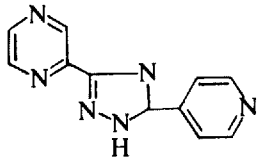
2-Hydrazinocarbonylpyrazine with benzenesulfonyl chloride in pyridine gave 2-benzenesulfonylhydrazinocarbonylpyrazine (138, 1323) [2-(2′-benzoylhydrazinocarbonyl)pyrazine and 2-(pyrazin-2′-ylcarbonylhydrazinocarbonyl)pyrazine were prepared similarly (1201)] which, heated with sodium carbonate under reduced pressure, gave 2-formylpyrazine (138, 1201), but 2-amino-3-*p*-toluenesulfonylhydrazinocarbonylpyrazine heated with sodium carbonate in glycol did not give the expected 2-amino-3-formylpyrazine (1212), and 2-amino-3-hydrazinocarbonylpyrazine with aqueous ammoniacal potassium ferricyanide gave 2-amino-3-carbamoylpyrazine (1212).

2-Amino-5-chloro-3-hydrazinocarbonylpyrazine with *S*-methylthiourea hydriodide and sodium methoxide in dimethyl sulfoxide at 100° gave 2-amino-5-chloro-3-guanidinocarbamoylpyrazine (781, 1058), and 2,6-diamino-3-chloro-5-hydrazinocarbonylpyrazine in propan-2-ol with 1 mol of potassium hydroxide and 1-amidino-3,5-dimethylpyrazole nitrate at room temperature formed 2,6-diamino-3-chloro-5-guanidinocarbamoylpyrazine (1412). 2-Amino-3-hydrazinocarbonylpyrazine refluxed with 98–100% formic acid gave 2-amino-3-(2′-formylhydrazino)carbonylpyrazine (1214).

2-Hydrazinocarbonylpyrazine condensed with 4-cyanopyridine to give 2-[5′-(pyridin-4″-yl)-1*H*-1′,2′,4′-triazol-3′-yl]pyrazine (**53**) (1430), cyanoethylation of 2-hydrazinocarbonylpyrazine with cyanoethylene gave 2-{2′-[2″-(cyanoethyl)-hydrazino]carbonyl}pyrazine (1317), and 2-[1′-(isopropylidenehydrazinocarbonyl)-hydrazinocarbonyl]-5-methyl-3-methylaminopyrazine (**54**) heated with Raney nickel in ethanol gave 2-carbamoyl-5-methyl-3-methylaminopyrazine (428).



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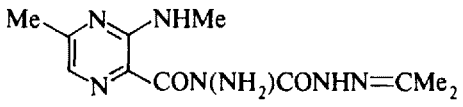
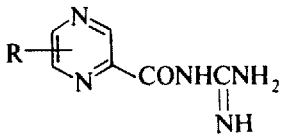


(54)

F. Preparation of Guanidinocarbonyl-, Guanidinocarbamoyl-, and Ureidocarbonylpyrazines

Guanidinocarbonylpyrazines (**55**) have been prepared from 6-substituted 2-methyl-4*H*-pyrazino[2,3-*d*]oxazin-4-ones by ring opening reactions with guanidines as described in Section II.5 and references 778, 781, 783, 784, 786, 1058, 1158, 1159 and 1162 and guanidinocarbamoylpyrazines as described in Section II.5 and references 783 and 858.



(55)

Preparations of guanidinocarbonylpyrazines, guanidinocarbamoylpyrazines, and ureidocarbonylpyrazines from esters have been described in Section 2C(2), from carboxylic acids in Section 1C(5), from amides in Section 3C(2), and from nitriles in Section 4C(2).

2-Amino-5-chloro-3-cyano-6-dimethylaminopyrazine refluxed with guanidine hydrochloride with sodium isopropoxide in propan-2-ol gave 2-amino-5-chloro-6-dimethylamino-3-(1′-guanidino-1′-iminomethyl)pyrazine (792, 878, 1218), and 2,6-diamino-3-cyano-5-iodopyrazine reacted similarly with *N*,*N*′-diethylguanidine (878). 2,6-Diamino-3-chloro-5-cyanopyrazine treated similarly gave 2,6-diamino-3-chloro-5-(*C*-guanidino-*C*-iminomethyl)pyrazine which with 2*N* hydrochloric acid at room temperature formed 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine (1431). 2,6-Diamino-5-bromo-3-cyanopyrazine reacted similarly with benzylguanidine (878). The orthoester, 2,6-diamino-3-chloro-5-triethoxymethylpyrazine [prepared from 2,6-diamino-3-chloro-5-(1′-ethoxy-1′-iminomethyl)pyrazine hydro-

chloride by heating with ethanol], heated with guanidine and acetic anhydride at 140° gave 2-(1′-amidinoimino-1′-ethoxymethyl)-3,5-diamino-6-chloropyrazine, which heated with 2 *N* hydrochloric acid for 5 hours gave 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine, and other similar preparations were also reported (1432). 2-Amino-3-(*C*-ethoxy-*C*-iminomethyl)pyrazine and 2-amino-3-(*C*-ethylthio-*C*-iminomethyl)pyrazine (both prepared from the cyanopyrazine with ethanol and anhydrous hydrogen chloride or ethanethiol in the presence of sodium hydroxide, respectively) with guanidine gave 2-amino-3-(*C*-guanidino-*C*-iminomethyl)pyrazine (792, 878, 1218), 2-amino-3-(*C*-methylthio-*C*-iminomethyl)pyrazine reacted similarly (878), and 2,6-diamino-3-chloro-5-(*N*,*N*-dimethylamidino)pyrazine refluxed with guanidine in ethanol gave 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine (1361) and with aminoguanidine gave 2,6-diamino-3-chloro-5-guanidinocarbamoylpyrazine (1361). 2,6-Diamino-3-chloro-5-hydrazinocarbonylpyrazine with chloral in dimethoxyethane and guanidine at 80° gave 2,6-diamino-3-chloro-5-guanidinocarbonylpyrazine, and other similar compounds were also prepared (1433). 2,6-Diamino-3-chloro-5-cyanocarbamoylpyrazine stirred with 6 *N* hydrochloric acid at room temperature formed 2,6-diamino-3-chloro-5-ureidocarbonylpyrazine, and similar preparations of other pyrazines were also reported (1375). 2,6-Diamino-3-chloro-5-cyanocarbamoylpyrazine in pyridine with triethylamine and hydrogen sulfide gave 2,6-diamino-3-chloro-5-thioureidocarbonylpyrazine (1373), and dicyclohexylcarbodiimide in dimethyl sulfoxide with 2,6-diamino-3-carboxy-5-chloropyrazine and 2-hydrazinopyrimidine gave 2,6-diamino-3-chloro-5-(*N*-cyclohexyl-*N*-cyclohexylcarbamoyl)carbamoylpyrazine (1331).

4. PYRAZINE NITRILES

A. Preparation of Cyanopyrazines

(1) *By Primary Synthesis*

The preparation of cyanopyrazines by primary synthesis has been described in Section II.1H (286–288) and Section II.2 (353–360). Further data have been recorded on the condensation of diaminomaleonitrile with glyoxal (1434, 1435), with a variety of 1,2-dicarbonyl compounds (1435, 1436), and Bredereck and Schmötzer (1044) have described the preparation from the tetramer of hydrocyanic acid with *p*,*p*′-dibromobenzil and *p*,*p*′-diphenoxybenzil of 2,3-bis(*p*-bromophenyl)-5,6-dicyanopyrazine and 2,3-dicyano-5,6-bis(*p*-phenoxyphenyl)pyrazine, and with phosgene in dioxane of 2,3-dicyano-5,6-dihydropyrazine. Other preparations are described in Section II.3 (158, 383–387), with further data given in references 1050, 1154 and 1180, Section II.5 (454) and Section II.7 (484–486, 488–490).

(2) *By Dehydration of Amides*

Dehydration of carbamoylpyrazines to cyanopyrazines has been described in Section 3C(1).

(3) *From Halogenopyrazines*

Preparations of cyanopyrazines from halogenopyrazines have been described in Section V.5I.

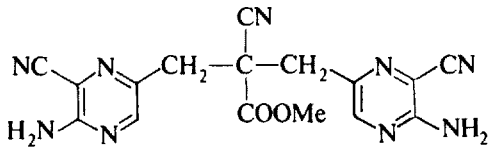
(4) *By Other Methods*

2-Methylpyrazine with ammonia and air over an alumina catalyst containing vanadium pentoxide and potassium sulfate at 350° for 10 hours gave 2-cyanopyrazine (726), also obtained similarly under other conditions (1437).

Deoxygenations of cyanopyrazine *N*-oxides are described in Section 11B.

2-Methylpyrazine with sodium amide in liquid ammonia and *N*-methyl-*N*-phenylcyanamide in dioxane gave 2-cyanomethylpyrazine; and α-propyl, α-ethyl, and other 2-substituted derivatives were similarly prepared (644).

Treatment of diphenylacetonitrile in toluene with sodium amide and 2-chloropyrazine gave 2-(*C*-cyano-*C*,*C*-diphenylmethyl)pyrazine (1021), and 2-vinylpyrazine with phenylacetonitrile and sodium heated at 120–130° for 10 minutes gave 2-(3′-cyano-3′-phenylpropyl)pyrazine (731). 2-Amino-5-bromomethyl-3-cyanopyrazine with sodium hydride and methyl cyanoacetate in tetrahydrofuran formed the dialkylated product (**56**) (1031). 2-Amino-3-mercapto-5,6-dimethylpyrazine in methanol with potassium hydroxide and chloroacetonitrile gave 2-amino-3-cyanomethylthio-5,6-dimethylpyrazine (1229), and 2-carboxypyrazine refluxed with chloroacetonitrile and triethylamine in ethyl acetate for 45 minutes gave the cyanomethyl ester (1317). 2-Hydroxy-5-methyl-3-propylpyrazine with cyanogen halides in aqueous sodium hydroxide–dimethylformamide at 0–5° gave 1-cyano-5-methyl-2-oxo-3-propyl-1,2-dihydropyrazine (1123).



(**56**)

B. Properties of Nitriles

The dipole moment of 2-chloro-3-cyanopyrazine has been determined as 3.44*D* in dioxane (749). Polymers have been prepared from 2,3-diamino-5,6-dicyano-

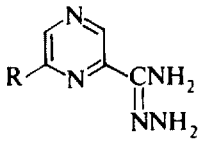
pyrazine and polyphosphoric acid (1438). 2-Amino-3-chloro-5,6-dicyanopyrazine and 2-allylamino-3-chloro-5,6-dicyanopyrazine are reported as useful as fluorescent whiteners (862) and other cyanopyrazines as plant growth inhibitors and (or) fluorescent brighteners (1154). 2-(α-Cyanoalkyl)pyrazines have been tested for plant growth inhibition (1017a).

C. Reactions of Cyanopyrazines

Reactions of cyanopyrazines which lead to the formation of carboxypyrazines have been described in Section 1A(2)(c), carbamoylpyrazines in Section 3A(3), thiocarbamoylpyrazines in Section 3D, 2-aminomethylpyrazines in Section VIII.1B(1), and bicyclic heterocycles in Sections V.5B(2), V.5F, and VIII.1D(6).

(1) *With Hydrazine*

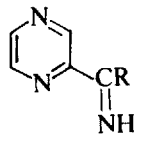
2-Cyanopyrazine (and its 6-chloro derivative) reacted with hydrazine to give the corresponding amidrazone, 2-(*C*-amino-*C*-hydrazonomethyl)pyrazine (and its 6-chloro derivative) (**57**, R = H, Cl) (which have been tested for tuberculostatic activity) (1439). 2-Amino-3-cyanopyrazine stirred with hydrazine hydrate in ethanol at 20–25° gave 2-amino-3-(*C*-hydrazino-*C*-iminomethyl)pyrazine (803), and 2-cyano-3-ethoxymethyleneaminopyrazine similarly treated gave 2-(*C*-hydrazino-*C*-iminomethyl)-3-hydrazinomethyleneaminopyrazine (803). 2-Amino-5-chloro-3-cyanopyrazine refluxed with hydrazine in ethanol gave 2-amino-5-chloro-3-(*C*-hydrazino-*C*-iminomethyl)pyrazine (1218).



(57)

(2) *With Alcohols (and Thioalcohols) and Hydrogen Chloride*

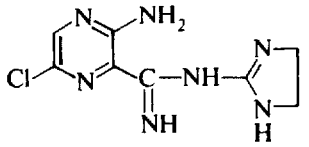
2-Cyanopyrazine with methanol and dry hydrogen chloride in ether gave the iminoether, 2-(*C*-imino-*C*-methoxymethyl)pyrazine (**58**, R = OMe) (138), which reacted with ethanolic ammonia to give 2-amidinopyrazine (**58**, R = NH_2) (138), and 2-cyanopyrazine with ethanolic hydrogen chloride in ether at −15° gave 2-(*C*-ethoxy-*C*-iminomethyl)pyrazine hydrochloride which with ethanolic ammonia at −15° gave the free base but above −15° gave (**58**, R = NH_2) (1334, 1440). 2-Cyano-3,5,6-trimethylpyrazine in anhydrous ethanol with hydrogen chloride in dioxane likewise gave the corresponding iminoether and amidinopyrazine, but



(58)

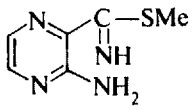
5-cyano-2,3-diphenylpyrazine similarly treated gave 5-carbamoyl-2,3-diphenylpyrazine because the intermediate iminoether hydrochloride spontaneously lost ethyl chloride (866). 2,3-Dicyano-5,6-dimethylpyrazine in dioxane with ethanolic hydrogen chloride gave 2-cyano-3-(*C*-ethoxy-*C*-iminomethyl)-5,6-dimethylpyrazine hydrochloride (1044), which hydrolyzed in boiling water to 2-cyano-3-ethoxycarbonyl-5,6-dimethylpyrazine (1044).

Iminoethers were also prepared from 2-amino-3-cyanopyrazine with ethanolic hydrogen chloride (792, 1218) [the product with guanidine and sodium methoxide in methanol formed 2-amino-3-(*C*-guanidino-*C*-iminomethyl)pyrazine (878, 1218)]; from 2,6-diamino-3-chloro-5-cyanopyrazine with ethanolic hydrogen chloride at 0° (the product heated with ethanol gave 2,6-diamino-3-chloro-5-triethoxymethylpyrazine) (1432); from 2-amino-5-chloro-3-cyanopyrazine {the product with 2-amino-2-imidazoline hydrochloride and sodium methoxide gave 2-amino-5-chloro-3-[*N*-(2′-imidazolin-2′-yl)amidino]pyrazine (**59**) (877)}; and from 2,6-diamino-3-chloro-5-cyanopyrazine [the product heated with dimethylamine in ethanol at 40° gave 2,6-diamino-3-chloro-5-(*N*,*N*-dimethylamidino)pyrazine] (1361). 2-Chloro-6-cyanopyrazine with methanol and triethylamine gave 2-methoxy-6-(*C*-imino-*C*-methoxymethyl)pyrazine, and a similar reaction was observed in ethanol (985); 2-amino-3,5-dicyano-6-methoxypyrazine with sodium methoxide gave 2-amino-5-cyano-3-(*C*-imino-*C*-methoxymethyl)-6-methoxypyrazine (484).



(59)

Iminothioethers have similarly been prepared from nitriles. 2-Amino-3-cyanopyrazine with sodium methanethiolate (other alkanethiolates reached similarly) in ethanol gave 2-amino-3-(*C*-imino-*C*-methylthiomethyl)pyrazine (**60**) (792, 878, 1075) [which with guanidine hydrochloride and sodium methoxide in methanol gave 2-amino-3-(*C*-guanidino-*C*-iminomethyl)pyrazine (878)]; 2-amino-5-chloro-3-cyanopyrazine with methanethiol and sodium hydroxide in methanol gave 2-amino-5-chloro-3-(*C*-imino-*C*-methylthiomethyl)pyrazine (877, 1218) [which with hydrogen sulfide in pyridine gave 2-amino-5-chloro-3-thiocarbamoylpyrazine (1218); or refluxed with 2-amino-2-imidazoline in methanol gave 2-amino-5-chloro-3-[*N*-(2′-imidazolin-2′-yl)amidino]pyrazine (877, 1218)]; but 2-chloro-6-cyanopyrazine refluxed with sodium ethanethiolate in ethanol for 15 minutes gave



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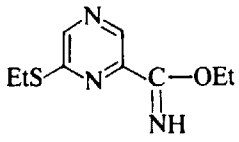
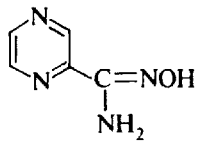


(61)

2-(*C*-ethoxy-*C*-iminomethyl)-6-ethylthiopyrazine (**61**) (which treated with 10% hydrogen chloride for 0.5 hours gave 2-ethoxycarbonyl-6-ethylthiopyrazine) (992).

(3) *With Amines*

2-Cyanopyrazine with concentrated aqueous ammonia was converted through 2-[*N*-(*C*-imino-*C*-pyrazin-2′-ylmethyl)amidino]pyrazine (**43**) to 2-carbamoylpyrazine (985), and 2-chloro-6-cyanopyrazine reacted similarly (985). 2-Ethoxy-6-(*C*-ethoxy-*C*-iminomethyl)pyrazine was found to be a by-product of the reaction of 2-chloro-6-cyanopyrazine with concentrated ethanolic ammonia; and 2-ethoxy(or methoxy)-6-[*C*-ethoxy(or methoxy)-*C*-iminomethyl]pyrazine was obtained from 2-chloro-6-cyanopyrazine by the action of ethanol (or methanol) in the presence of triethylamine (985). 2-Cyanopyrazine treated in water with hydroxylamine hydrochloride and sodium carbonate at 70–75° gave 2-(*C*-amino-*C*-hydroxyiminomethyl)-pyrazine (**62**), and 2-cyanopyrazine fused with aniline and an equimolar amount of aluminum chloride at 140–220° gave 2-(*C*-anilino-*C*-iminomethyl)pyrazine (and similar preparations were carried out with other aromatic amines) (1334, 1410).



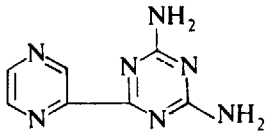
(62)

2-Chloro-6-cyanopyrazine with aqueous methylamine at 0° gave 2-chloro-6-(*N*-methylamidino)pyrazine (940), and 2-cyano-6-dimethylaminopyrazine with dimethylamine in the presence of anhydrous aluminum chloride gave 2-dimethylamino-6-(*C*-dimethylamino-*C*-iminomethyl)pyrazine and similar reactions were observed with other secondary amines (1424).

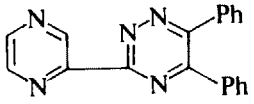
A series of 2-cyano-6-substituted aminopyrazines (and imidoesters) refluxed with hydroxylamine in methanol gave 2-(*C*-amino-*C*-hydroxyiminomethyl)-6-(substituted amino)pyrazines (943, 1424), and 2-cyano(or thiocarbamoyl)-6-ethylthiopyrazine refluxed with hydroxylamine in aqueous methanol gave 2-(*C*-amino-*C*-hydroxyiminomethyl)-6-ethylthiopyrazine (992).

Tetracyanopyrazine with liquid ammonia in tetrahydrofuran formed 2,6-diamino-3,5-dicyanopyrazine (1180, 1182), and tetracyanopyrazine with piperazine similarly gave 2,6-dicyano-3,5-dipiperazin-1′-ylpyrazine (1182).

2-Cyanopyrazine with dicyanodiamide [$(NH_2CN)_2$] gave the 2-(4′,6′-diaminotriazin-2′-yl)pyrazine (**63**), with *o*-phenylenediamine in the presence of polyphosphoric acid at 250° gave 2-(benzimidazol-2′-yl)pyrazine, and with hydrazine gave 2-(*C*-hydrazino-*C*-iminomethyl)pyrazine, which condensed with benzil to 2-(5′,6′-diphenyl-*as*-triazin-3′-yl)pyrazine (**64**) (1441).

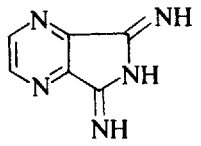


(**63**)



(**64**)

2,3-Dicyanopyrazine with sodium methoxide in methanol with ammonia at reflux gave 5,7-diimino-6*H*-pyrrolo[3,4-*b*]pyrazine (**65**) (1442) and 2,3-dicyano-5,6-dimethyl(and 5,6-diphenyl)pyrazine with hydrazine by the procedure of Patel and Castle (1339) gave 2,3-dimethyl(and 2,3-diphenyl)-5,8-diaminopyrazino[2,3-*d*]-pyridazine(s) (**66**) (1435). Fusion of 2-chloro-3-cyano-5,6-diphenylpyrazine with urea and thiourea was reported to give 4-amino-2-hydroxy(and mercapto)-6,7-diphenylpteridine (848).



(**65**)

(**66**)

(4) *With Grignard Reagents*

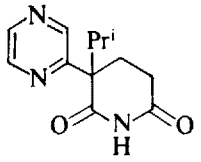
2-Cyanopyrazine treated with a Grignard solution of methylmagnesium bromide in ether followed by treatment with dilute hydrochloric acid formed 2-acetylpyrazine (138). In a similar manner, 2-acetyl-5(and 6)-methylpyrazine (1327), 5-acetyl-2,3-diphenylpyrazine (866), and 2-acetyl-3,5,6-trimethylpyrazine (866) were prepared. 2-Cyanopyrazine with phenylmagnesium bromide has been reported to give 2-(*C*-imino-*C*-phenylmethyl)pyrazine (1220).

(5) *With Alkoxide Ions*

2,5-Dicyano-3,6-dimethylpyrazine shaken with sodium ethoxide at room temperature gave 2-cyano-5-ethoxy-3,6-dimethylpyrazine and 2-cyano-5-hydroxy-3,6-dimethylpyrazine (288). Reactions of 2-chloro-6-cyanopyrazine with sodium methoxide have been described in Sections 1A(2)(c).

(6) *Other Reactions*

5-Cyano-2,3-diphenylpyrazine heated with dry ammonium thiocyanate at 180° gave 5-amidino-2,3-diphenylpyrazine (866). 2-Cyano-5-phenylthiopyrazine heated in acetic acid with hydrogen peroxide for 3 hours gave 2-cyano-5-phenylsulfonylpyrazine and some 2-carbamoyl-5-phenylsulfonylpyrazine (840) and 2-cyanopyrazine with hydrogen peroxide in aqueous alkali at 70° gave 2-carbamoylpyrazine 1-oxide and 2-carbamoylpyrazine (839). 2,5-Dicyano-3,6-diphenylpyrazine was reduced by hydriodic acid and red phosphorus to 2,5-diphenyl-3,6-dihydropyrazine (286), and Linstead et al. (353) report that 2,3-dicyanopyrazine heated with cuprous chloride gave copper tetrapyrazinoporphyrazine tetrahydrate, and heated with etched magnesium at 200° gave tetrapyrazinoporphyrazine tetrahydrate. 2-Cyanopyrazine with sodium azide, acetic acid, and isopropyl alcohol at 150° for 5 days formed 2-(tetrazol-5′-yl)pyrazine (138). 2-(1′-Cyano-2′-methylpropyl)-pyrazine with acrylonitrile, and Triton B in dioxane at 85–90° gave 2-(1′,3′-dicyano-1′-isopropylpropyl)pyrazine, which with a mixture of 78% sulfuric acid and acetic acid at 125° gave the compound (67) (1443). 2-α-Cyanobenzylpyrazine with sodium amide in dioxane with acetonitrile gave 2-(1′,2′-dicyano-1′-phenylethyl)-pyrazine (1443), and 2-cyano-3-dimethylaminomethyleneamino-5-methylpyrazine in a solution of lithium diisopropylamide in tetrahydrofuran with ethyl iodide gave 3-amino-2-cyano-5-propylpyrazine (but a similar reaction was not observed with 3-cyano-2-dimethylaminomethyleneamino-5-methylpyrazine) (1031).



(67)

5. PYRAZINE ALDEHYDES AND THEIR ACETALS

A. Preparation of Formylpyrazines

(1) *By Primary Synthesis*

Formylpyrazines have been prepared by ring opening reactions which have been described in Section II.5 (423, 430, 448, 449). In addition to the above data, pteridine with *N* hydrochloric acid at 20° for 16 hours gave 2-aminomethyleneamino-3-formylpyrazine (1167), 6,7-dimethylpteridine and hydroxylamine gave 2-hydroxyiminomethyl-3-hydroxyiminomethylamino-5,6-dimethylpyrazine (1166), and 2,6,7-trimethylpteridine with methoxyamine afforded 2-(1′-methoxyiminoethylamino)-3-methoxyiminomethyl-5,6-dimethylpyrazine (1166).

(2) *By C-Formylation*

2-Methylpyrazine with dimethylformamide and phosphoryl chloride gave 2-(2′-dimethylamino-1′-formylvinyl)pyrazine (717), which was hydrolyzed by alkali to 2-(*C,C*-diformylmethyl)pyrazine (717).

(3) *By Oxidative Processes*

Ozonolysis of 2-vinylpyrazine in methanol formed 2-formylpyrazine (732); and oxidation of 2-amino-3-hydroxymethylpyrazine with manganese dioxide in chloroform at room temperature gave 2-amino-3-formylpyrazine (1075).

The optimum conditions of the oxidation of 2-methylpyrazine to 2-formylpyrazine in the presence of V_2O_5–MoO_3 (V:Mo = 1:1) catalyst was 400° with a contact time of 0.1 seconds (1444), and with water vapor and an inert gas (1445).

(4) *By Reductive Processes*

Reduction of 2-methoxycarbonylpyrazine in tetrahydrofuran with lithium aluminum hydride at about −70° gave 2-formylpyrazine (46%), but reduction of 2-chlorocarbonylpyrazine with lithium tri-*t*-butoxyaluminohydride in tetrahydrofuran gave 2-(pyrazin-2′-ylmethoxycarbonyl)pyrazine (55%) and 2-formylpyrazine (20%) (1077), and 2-ethoxycarbonyl-3-methylpyrazine was reduced with lithium aluminum hydride in tetrahydrofuran at −70° to 2-formyl-3-methylpyrazine (1185).

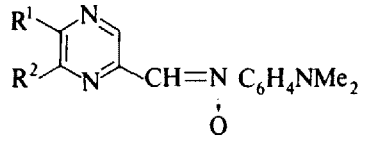
(5) *From Hydrazides*

2-Formylpyrazine has been prepared by the McFadyen–Stevens method. 2-(2′-Benzenesulfonylhydrazino)carbonylpyrazine heated with sodium carbonate at 150–170° gave formylpyrazine (isolated as its thiosemicarbazone) (138), also obtained as distillate when the reactants were heated at 120°/3 mm (1201), but Fand and Spoerri (1323), from the attempted reaction with sodium carbonate in ethylene glycol at 160°, were unable to isolate 2-formylpyrazine; instead 2-(2′-pyrazinoylhydrazinocarbonyl)pyrazine, 2-carboxypyrazine, and other products were obtained.

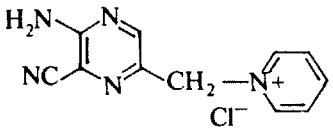
(6) *By Other Methods*

2-Dichloromethylpyrazine has been claimed to react with methanolic sodium methoxide to give 2-(dimethoxymethyl)pyrazine (694); however, this has been disputed (1027) and the product reported as 2-methoxy-3(or 5)-methoxymethylpyrazine (1027).

Nitrones of the type (**68**, $R^1 = R^2 = H$) (prepared from the methylpyrazine through the pyridiniomethylpyrazine cation) with 6*N* hydrochloric acid under ether have been utilized to prepare 2,5-diformylpyrazine (as phenylhydrazone) and 2,5-diformyl-3,6-dimethylpyrazine (as 2,4-dinitrophenylhydrazone) (729). Similarly 2-amino-3-cyano-5-pyridiniomethylpyrazine chloride (**69**) (prepared from 2-amino-5-chloromethyl-3-cyanopyrazine) treated with *p*-nitrosodimethylaniline and potassium carbonate in aqueous ethanol gave *N*-[*p*-(dimethylamino)phenyl]-α-(2-amino-3-cyanopyrazin-5-yl)nitrone (**68**, $R^1 = NH_2$, $R^2 = CN$), which was hydrolyzed in cold 6*N* hydrochloric acid to 2-amino-3-cyano-5-formylpyrazine (1030).



(**68**)



(**69**)

2-Methylpyrazine added to sodium amide in liquid ammonia and treated with butyl nitrite gave 2-hydroxyiminomethylpyrazine (727, 728); and 2,3,5-trimethyl-6-pentylpyrazine similarly treated gave 2-hydroxyiminomethyl-3,6-dimethyl-5-pentylpyrazine (648).

Formylpyrazines have been isolated from acetals by hydrolysis. Thus 2-acetamido-3-dimethoxymethylpyrazine refluxed with aqueous pyridine hydrochloride gave 2-acetamido-3-formylpyrazine (1075), and 2-dimethoxymethyl-3-ethoxycarbonylaminopyrazine was hydrolyzed similarly (1075); 2-dimethoxymethyl-3-formamidopyrazine with toluene-*p*-sulfonic acid monohydrate and sodium sulfate in acetone at room temperature gave 2-formamido-3-formylpyrazine (1075), and 2-dimethoxymethyl-3-ethoxalylaminopyrazine refluxed with the same reagents gave 2-ethoxalylamino-3-formylpyrazine (1075).

B. Reactions of Formylpyrazines

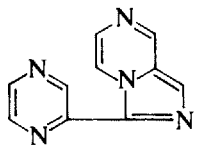
(1) *Oxidation and Reduction*

2-Formylpyrazine, which is light sensitive, undergoes the Cannizzaro reaction with aqueous sodium hydroxide to give 2-carboxypyrazine and 2-hydroxymethylpyrazine (1077). The direct oxidation of 2-formylpyrazine to 2-carboxypyrazine has not been described; but 2-amino-3-formylpyrazine was oxidized by aqueous potassium permanganate to 2-amino-3-carboxypyrazine (423).

(2) *Formation of the Usual Aldehyde Derivatives*

2-Amino-3-formylpyrazine in boron trifluoride–methanol complex at room temperature gave 2-amino-3-dimethoxymethylpyrazine (1075), and 2-amino-

3-cyano-5-formylpyrazine was converted to its dimethyl acetal in methanol with anhydrous hydrogen chloride, *p*-toluenesulfonic acid, or Dowex 50W-X4 cation-exchange resin (hydrogen form) (1030). 2-Formylpyrazine with trimethyl orthoformate catalyzed by ammonium chloride gave 2-dimethoxymethylpyrazine (40%) and 3-(pyrazin-2′-yl)imidazo[1,5-*a*]pyrazine (**70**) (1027); 2-formylpyrazine with sulfur dioxide in aqueous chloroform gave α-sulfo-α-hydroxymethylpyrazine (1077), and with aq. potassium cyanide gave pyrazoin (1,2-dipyrazinyl-1,2-ethanediol) (1077); 2-amino-3-formylpyrazine with hydroxylamine hydrochloride and sodium acetate in aqueous solution formed the oxime (423), and 2-formamido-3-formylpyrazine similarly treated gave 2-hydroxyiminomethyl-3-hydroxyiminomethylaminopyrazine (1166). 2-Formylpyrazine with aqueous isonicotinoylhydrazine gave 2-(isonicotinoylhydrazonomethyl)pyrazine (1201), and similar derivatives were prepared with nicotinoylhydrazine and picolinoylhydrazine (1201). 2-Formyl-3-methylpyrazine formed a Schiff base with ethyl *p*-aminobenzoate (1185), and this was reduced by sodium borohydride to 2-(*p*-ethoxycarbonylphenylaminomethyl)-3-methylpyrazine (1185).



(70)

6. PYRAZINE KETONES AND DERIVATIVES

A. Preparation of *C*-Acyl Derivatives

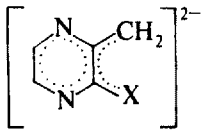
(1) *By Primary Synthesis*

Preparations of *C*-acylpyrazines by primary syntheses have been described in Section II.1B by reduction of α-hydroxyimino carbonyl compounds (226–230). In addition to these preparations, reduction of 3-nitrosopentane-2,4-dione (prepared by nitrosation of pentane-2,4-dione) over Pd/C in an autoclave gave 2,5-diacetyl-3,6-dimethylpyrazine, and 2-nitroso-1-phenylbutane-1,3-dione (from 1-phenylbutane-1,3-dione) similarly treated gave 2,5-dibenzoyl-3,6-dimethylpyrazine (1064).

Cleavage of pteridines and related ring systems have been reported in Section II.5 (423, 456), and ring opening of 6-methylpteridine by acid gave 2-acetyl-3-aminomethyleneaminopyrazine (1167).

(2) *From Methylpyrazines*

Preparations of acylpyrazines from methylpyrazines have been described in Sections IV.2A(2) (635) and IV.2A(3) (634, 642, 645–647, 650–651). Recently it has been shown that 2-hydroxy(or mercapto)-3-methylpyrazine with two equivalents of butyllithium in dry tetrahydrofuran gave the colored dilithium salt (**71**, X = O or S), which reacted with alkyl benzoates and gave 2-benzoylmethyl-3-hydroxy(or mercapto)pyrazines (**72**, X = O or S, Y = O). Similar reactions occurred with thio esters to give the thiocarbonyl compounds (**72**, X = O or S, Y = S) (1446).



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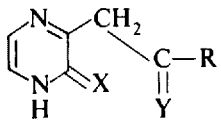


(72)

(3) *From Cyanopyrazines*

The preparation of acetylpyrazines from cyanopyrazines and Grignard reagents proceeded in the usual manner. 2-Cyanopyrazine with methylmagnesium bromide in ether followed by treatment with dilute hydrochloric acid gave 2-acetylpyrazine (138, 1447). In a similar way the following pyrazines were prepared: 2-acetyl-5-methyl (1327); 2-acetyl-6-methyl (1327); 5-acetyl-2,3-diphenyl (866); 2-acetyl-3,5,6-trimethyl (886); and 2-benzoyl (1447).

(4) *By Oxidation*

Acylpyrazines have been prepared by various oxidations as follows. Oxidation of 2,5-dibenzyl-3,6-dimethylpyrazine with chromic oxide in acetic acid gave 2,5-dibenzoyl-3,6-dimethylpyrazine (212); 2-ethyl-3-methylpyrazine with sodium dichromate in acetic acid at 80° gave 2-acetyl-3-methylpyrazine in good yield (678, 1448), 2,3-diethylpyrazine similarly treated but at 118° gave 2-acetyl-3-ethylpyrazine (678, 1448), and a mixture of 2-ethyl-3,5-dimethyl- and 3-ethyl-2,5-dimethylpyrazines similarly treated at 80° gave a mixture of 2-acetyl-3,5-dimethyl- and 3-acetyl-2,5-dimethylpyrazine (678, 1448); but oxidation of 2-ethylpyrazine and 2-ethyl-5-methylpyrazine under similar conditions gave only low yields of the corresponding ketones (678).

2-(1′-Bromoethyl)-3-methylpyrazine was oxidized to 2-acetyl-3-methylpyrazine by sodium 2-propanenitronate (from 2-nitropropane and sodium ethoxide in ethanol) at reflux (66.5% yield) and by pyridine 1-oxide in acetonitrile at reflux (25% yield) (691), and 2-(1′-bromoethyl)-3-ethylpyrazine similarly oxidized with

sodium 2-propanenitronate gave 2-acetyl-3-ethylpyrazine (54%) (691, 692). 2-Ethyl-3-(1′-methoxyethyl)pyrazine was oxidized in dimethyl sulfoxide–acetic anhydride at room temperature for 24 hours to 2-acetyl-3-ethylpyrazine (691), also prepared from 2-(1′-acetoxyethyl)-3-ethylpyrazine by hydrolysis followed by a similar oxidation (692).

(5) *From Acid Chlorides and Esters*

2-Chlorocarbonylpyrazine, and Grignard solution from magnesium and ethyl bromide in ether, and pulverized cadmium chloride gave 2-propionylpyrazine (1449).

3-Chlorocarbonyl-2-methoxy-5-methylpyrazine with lithium dimethyl copper reagent in ether gave 3-acetyl-2-methoxy-5-methylpyrazine; 2-acetyl-3-methoxypyrazine and 2-acetyl-3,6-dimethoxy-5-methylpyrazine were prepared similarly (844), but 2-chlorocarbonyl-3-methoxy-5-methylpyrazine with lithium dimethyl copper in ether gave a mixture of 2-acetyl-3-methoxy-5-methylpyrazine and 2-(1′-hydroxy-1′-methylethyl)-3-methoxy-5-methylpyrazine (844).

Addition of 2-chlorocarbonylpyrazine to diazomethane in ether gave 2-diazomethylcarbonylpyrazine (1332), which treated with hydrogen chloride in ether gave 2-(chloroacetyl)pyrazine (138, 1332).

The formation of ketones from esters has been described in Section 2C(4).

(6) *By Other Methods*

Homolytic acylation of the pyrazine cation with aldehyde radicals have been reported (616). A mixture of pyrazine, acetaldehyde, aqueous acetic acid, sulfuric acid, *t*-butyl hydroperoxide, and ferrous sulfate gave 2,5-diacetylpyrazine, and similar reactions occurred with propionaldehyde and benzaldehyde (616).

2-Amino-5-bromomethyl-3-cyanopyrazine with ethyl acetoacetate and sodium hydride in tetrahydrofuran gave 5-[(2′-acetyl-2′-ethoxycarbonyl)ethyl]-2-amino-3-cyanopyrazine (1031) [which with sodium chloride in aqueous dimethyl sulfoxide at 155–170° for 6 hours gave 5-(2′-acetylethyl)-2-amino-3-cyanopyrazine] and a similar reaction with ethyl γ-ethoxyacetoacetate gave 2-amino-3-cyano-5-[(2′-ethoxycarbonyl-2′-ethoxymethylcarbonyl)ethyl]pyrazine [which with sodium chloride in aqueous dimethyl sulfoxide at 155–170° for 6 hours gave 2-amino-3-cyano-5-(2′-ethoxymethylcarbonyl)ethylpyrazine] (1031).

2-Vinylpyrazine undergoes a Michael condensation with cyclohexanone, cyclopentanone, and acetophenone; for example, 2-vinylpyrazine with cyclohexanone and sodium gave 2-[2′-(1″-oxocyclohexan-2″-yl)ethyl]pyrazine, and with acetophenone and sodamide in liquid ammonia gave low yields of 2-(3′-benzoylpropyl)pyrazine (monopyrazylethylation) and the bis Michael adduct (731).

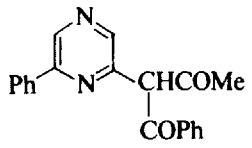
B. Properties of Acetylpyrazines

The occurrence of acetylpyrazines in cocoa products, roasted peanuts, roast beef, and other gastronomic delicacies has been reported (55, 69, 844). The pK_a of *N*-(4′-nitrophenacyl)pyrazinium bromide has been determined as 4.1 (1450).

C. Reactions of *C*-Acylpyrazines

2-Acetylpyrazine undergoes the Willgerodt reaction with ammonium polysulfide in aqueous dioxane to give 2-carbamoylmethylpyrazine in poor yield, but 2-acetylpyrazine with sulfur and morpholine gives a good yield of 2-*N*-morpholino(thiocarbamoyl)methylpyrazine (138). 2-Acetyl-5-methylpyrazine with hydrazine hydrate and potassium hydroxide in ethylene glycol at 240° gave 2-ethyl-5-methylpyrazine (1327), and sodium borohydride reduction of 5-(2′-acetylethyl)-2-amino-3-cyanopyrazine in methanol formed 2-amino-3-cyano-5-(3′-hydroxybutyl)pyrazine (1031). 2-Acetonyl- and 2-phenacylpyrazines treated with aqueous potassium hypochlorite gave 2-dichloromethylpyrazine (694); and 2-diazomethylcarbonylpyrazine warmed with glacial acetic acid and then potassium acetate at 100° gave 2-(acetoxyacetyl)pyrazine (138).

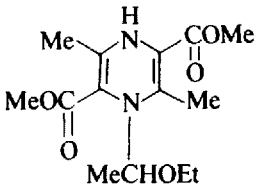
The reaction of 2-acetonylpyrazine with phenyllithium in bromobenzene gave 2-acetonyl-6-phenylpyrazine, and with phenyllithium and methyl benzoate gave a mixture of 2-acetonyl-6-phenylpyrazine and 2-(1′-benzoylacetonyl)-6-phenylpyrazine (73) (639). 2-Phenacylpyrazine with *p*-chlorobenzyl chloride and sodium hydride in dimethylformamide gave 2-[1′-(*p*-chlorobenzyl)phenacyl]-pyrazine (1451). 2,6-Dimethyl-3,5-diphenacylpyrazine with nitrous acid gave 2,6-bis(1′-hydroxyiminophenacyl)-3,5-dimethylpyrazine (647), and 2-(pyridin-2′-ylcarbonylmethyl)pyrazine gave 2-(1′-hydroxyimino-2′-oxo-2′-pyridin-2″-yl)pyrazine [$C_5H_4NCOC(NOH)C_4H_3N_2$]; and other pyrazines were prepared similarly (642).



(73)

Irradiation of 2,5-bis(methoxycarbonyl)-3,6-dimethylpyrazine in diethyl ether with a 450-W high-pressure mercury lamp (330 nm) gave two significant photoproducts 2-hydroxy-5-methoxycarbonyl-3,6-dimethylpyrazine and 1-(1′-ethoxyethyl)2,5-dimethoxycarbonyl-3,6-dimethyl-1,4-dihydropyrazine (74). Similar products were isolated when tetrahydrofuran was used as solvent. Corresponding reactions were observed with 2,5-bis(ethoxycarbonyl)-3,6-dimethylpyrazine, 2,5-diacetyl-3,6-dimethylpyrazine, and 2,5-dibenzoyl-3,6-dimethylpyrazine. The mechanism of these reactions were investigated and the initial stage was found to be

reversible and involved a dihydropyrazine (1064). 2-Diazomethylcarbonylpyrazine or 2-chloroacetylpyrazine refluxed with thiourea in ethanol gave 2-(2′-aminothiazol-4′-yl)pyrazine (75) (1409).



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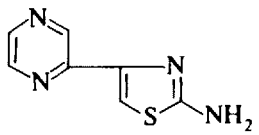
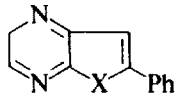


(75)

2-Hydroxy-3-phenacylpyrazine was cyclized with concentrated sulfuric acid at 70–80° to 2-phenylfuro[2,3-*b*]pyrazine (76, X = O), and 2-mercapto-3-thiophenacylpyrazine with methanolic hydrogen chloride at reflux to 2-phenylthieno[2,3-*b*]pyrazine (76, X = S) (1446).

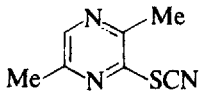


(76)

Typical preparations have been described for 2-(1′-hydroxyiminomethyl)pyrazine (138); 2-(4′-dimethylamino-1′-hydroxyiminobutyl)pyrazine (1186); 2-(2′-hydroxyiminopentyl)-6-methylpyrazine (645); 2-(2′-hydroxyimino-3′,3′-dimethylbutyl)-6-methylpyrazine (645); 2-[1′-hydroxyimino-2′-(pyridin-2″-yl)ethyl]pyrazine (642); 2-[2′-hydroxyimino-2′-(pyridin-2″-yl, pyrazin-2″-yl, or pyrimidin-4″-yl)ethyl]pyrazine (642); 2-[1′,2′-bishydroxyimino-2′-(pyridin-2″-yl)ethyl]pyrazine (642); 2-[2′-(2″,4″-dinitrophenylhydrazono)-3′-methylbutyl]-6-methylpyrazine (645); 2-[1-(substituted hydrazono)ethyl]pyrazine (1196); 2-[1′-phenyl-1′-(substituted hydrazono)methyl]-pyrazine (1196); 2-(1′-thiosemicarbazonoethyl)pyrazine (138); 2-(2′-chloro-1′-thiosemicarbazonoethyl)pyrazine (138); and 2,5-dimethyl-3,6-bis(1′-semicarbazonoethyl)pyrazine (1196).

7. ISOCYANATO- AND THIOCYANATOPYRAZINES

Two isocyanatopyrazines and one thiocyanatopyrazine have been reported in the literature, but cyanato- and isothiocyanatopyrazines appear unknown. 2,5-Diazidocarbonylpyrazine refluxed in benzene gave 2,5-diisocyanatopyrazine (**50**) (1172), which was stable to hydrolytic agents (1172); and 2-amino-3,5-6-trichloropyrazine with oxalyl chloride in boiling benzene or toluene until the evolution of gas was complete gave 2,3,5-trichloro-6-isocyanatopyrazine [γ_{max} 2250 cm^{-1} (NCO)] (1240–1242). 3-Mercapto-2,5-dimethylpyrazine with alkali and cyanogen bromide gave 2,5-dimethyl-3-thiocyanatopyrazine (77) (1139).



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8. CARBOXYPYRAZINE *N*-OXIDES

A. Preparation of Carboxypyrazine *N*-Oxides

(1) *By Primary Synthesis*

Ring opening reactions to give carboxypyrazine *N*-oxides have been described in Sections II.5 (462) and VIII.3A(2) (1222, 1256).

(2) *By Hydrolysis of Amides and Esters*

Carboxypyrazine *N*-oxides have been prepared by hydrolysis of carbamoyl- and alkoxycarbonylpyrazine *N*-oxides as follows (reagent and conditions): 2-carbamoylpyrazine 1-oxide (10% NaOH/reflux/12 h) (838); 3-carbamoylpyrazine 1-oxide (10% NaOH/reflux/30 min) (1266, cf. 838); 3-*N*-acetylcarbamoylpyrazine 1-oxide (10% NaOH/heat) (1057); 3-morpholinocarbonylpyrazine 1-oxide (18% HCl/reflux/8 h) (870); 2-hydroxy-5-methoxycarbonylpyrazine 1-oxide (2.5 *N* NaOH/20–25°/20 min) (739); 3-hydroxy-5-methoxycarbonylpyrazine 1-oxide (KOH/22°/2 h gave 3-carboxy-5-hydroxypyrazine 1-oxide, which interfered with the growth of *Streptococcus faecium* and *Escherichia coli* at 6×10^{-7} and 4×10^{-4} *M*, respectively) (1035); 2-amino-3-benzyloxycarbonyl-5-methylpyrazine 1-oxide (2 *N* NaOH/reflux/30 min) (365c); and 2-amino-5-chloro-3-methoxycarbonylpyrazine 1-oxide (2.5 *N* NaOH/heat) (876, 1222).

(3) *By Oxidation*

Although 3-carboxypyrazine *N*-oxides could not be prepared by direct oxidation of 2-carboxypyrazine (no reaction took place under mild conditions whereas drastic conditions resulted in decarboxylation) (1266), some substituted 3-carboxypyrazine 1-oxides have been prepared by oxidation (and used as hypoglycemic and hypolipemic substances in rats) (1452).

2-Carboxy-3-(*o*-carboxyphenyl)-5,6-diphenylpyrazine has been reported to be oxidized by hydrogen peroxide in boiling acetic acid to 2-carboxy-3-(*o*-carboxyphenyl)-5,6-diphenylpyrazine *N*-oxide (399). Oxidation of 3-(D-*arabo*-tetrahydroxybutyl)pyrazine 1-oxide with potassium permanganate in aqueous potassium hydroxide gave 3-carboxypyrazine 1-oxide (543).

B. Reactions of Carboxypyrazine *N*-Oxides

(1) *Decarboxylation*

Carboxypyrazine *N*-oxides may be readily decarboxylated. 3-Carboxypyrazine 1-oxide, boiled with acetic anhydride for 2 hours (1057), or on sublimation (744), gave pyrazine 1-oxide; 2-carboxy-3,5-bismethylamino-6-*N*-methylcarbamoylpyrazine 1-oxide with trifluroacetic acid at room temperature gave 3,5-bis(methylamino)-2-*N*-methylcarbamoylpyrazine 1-oxide (462); and 2-amino-3-carboxy-5-methylpyrazine 1-oxide heated at 190–195° gave 2-amino-5-methylpyrazine 1-oxide (365c).

(2) *Esterification*

3-Carboxypyrazine 1-oxide heated in a sealed tube at 60° with methanol and a little thionyl chloride (870, 1266), or refluxed in methanol with thionyl chloride until the acid dissolved (3 hours) (839), gave 3-methoxycarbonylpyrazine 1-oxide, and the ethyl ester was prepared similarly (839, 1266). 3-Carboxypyrazine 1-oxide with diazomethane also gave 3-methoxycarbonylpyrazine 1-oxide (1266).

(3) *Deoxygenation*

3-Carboxypyrazine 1-oxide heated with phosphoryl chloride at 40–50° for 15 minutes gave 2-carboxy-6-chloropyrazine (868–870), but Nováček et al. (839) claim that 3-carboxypyrazine 1-oxide refluxed with thionyl chloride for 5.5 hours, and the product treated with ammonia, gave 2-carbamoyl-5-chloropyrazine (?). 2-Carboxy-3-(*o*-carboxyphenyl)-5,6-diphenylpyrazine *N*-oxide was deoxygenated by stannous chloride (399) and 2-carboxy-3,5-bis(methylamino)-6-*N*-methylcarbamoylpyrazine 1-oxide with sodium dithionite in aqueous ethanol at 90° for 3 hours (462).

(4) *Other Reactions*

Ring closures of aminocarboxypyrazine *N*-oxides to bicyclic heterocycles have been described in Section VIII.3C(3).

9. ALKOXYCARBONYLPYRAZINE *N*-OXIDES

A. Preparation

Primary syntheses of alkoxycarbonyl-2-aminopyrazine 1-oxides from α-amino nitriles and α-hydroxyimino carbonyl compounds have been described in Section III.1 (Table III.1) (531, 537–541).

Alkoxycarbonylpyrazines have been oxidized to alkoxycarbonylpyrazine *N*-oxides as follows: 2-ethoxycarbonylpyrazine with "perhydrol" gave 3-ethoxycarbonylpyrazine 1-oxide (575); 2-amino-3-methoxycarbonylpyrazine refluxed with *m*-chloroperoxybenzoic acid in chloroform gave 2-amino-3-methoxycarbonylpyrazine 1-oxide (876, 880, 1222); the 5-bromo (808, 877, 878, 1222) and 5-chloro (875, 876, 879, 1222) derivatives were prepared similarly; and some 3-ethoxycarbonylpyrazine 1-oxides have been prepared by oxidation (reagent not stated) of 2-ethoxycarbonylpyrazines (1452).

Alkoxycarbonylpyrazine *N*-oxides have been prepared by esterification of the corresponding acids. 3-Methoxycarbonylpyrazine 1-oxide was prepared from 3-carboxypyrazine 1-oxide in methanol with a little thionyl chloride in a sealed tube at 60° (the ethyl ester was prepared similarly) (739, 1266) and also from 3-carboxypyrazine 1-oxide and diazomethane (1266). 5-Carboxy-2-hydroxypyrazine 1-oxide with methanolic hydrogen chloride gave 2-hydroxy-5-methoxycarbonylpyrazine 1-oxide (739).

B. Reactions

Deoxygenation and halogenation of alkoxycarbonylpyrazine *N*-oxides by phosphoryl chloride (and other acid halides) to alkoxycarbonylhalogenopyrazines have been described in Section V.1G.

Acetoxylative deoxygenations are as follows. 3-Methoxycarbonylpyrazine 1-oxide refluxed with acetic anhydride for 30 hours gave 2-acetoxy-6-methoxycarbonylpyrazine (838), but Nováček et al. (839) claim that the product (prepared with acetic anhydride at 160°) after hydrolysis with water was 2-hydroxy-5(?)-methoxycarbonylpyrazine; and 2-amino-3-ethoxycarbonylpyrazine 1-oxide refluxed with acetic acid–acetic anhydride gave 3-acetamido-2-ethoxycarbonyl-5-hydroxypyrazine (538).

Hydrolyses of alkoxycarbonylpyrazine *N*-oxides to carboxypyrazine *N*-oxides have been described in Section 8A(2).

The preparation of the following carbamoylpyrazine 1-oxides (and derivatives) from the corresponding methoxycarbonylpyrazine 1-oxide (reagent and conditions) have been described: 3-carbamoyl (ammonium hydroxide heated to boil) (1266); 3-*N*-hydroxycarbamoyl (hydroxylamine in methanol at room temperature) (1266); 3-hydrazinocarbonyl (refluxed with 50% hydrazine hydrate) (1266); 2-amino-5-chloro-3-methylcarbamoyl (methylamine in ethanol) (876); 2-amino-5-chloro-3-hydrazinocarbonyl (hydrazine in ethanol) (876, 1257); 2-amino-3-guanidinocarbonyl (guanidine in methanol) (876, 1222); 2-amino-5-chloro(and bromo)-3-guanidinocarbonyl (876, 1222); 2-amino-3-guanidinocarbamoyl (aminoguanidine in methanol) (876, 1257); 2-amino-5-chloro(and bromo)-3-guanidinocarbamoyl (876, 1257); and 2-amino-3-guanidinocarbonyl-5-methyl (ethyl ester with guanidine and sodium methoxide in methanol) (537). 2-Amino-3-ethoxycarbonyl-5-hydroxyiminomethylpyrazine 1-oxide with guanidine hydrochloride and sodium

methoxide in methanol, followed by heating the product in dimethylformamide, gave 2-amino-4-hydroxy-6-hydroxyiminomethylpteridine-8-oxide (539).

10. CARBAMOYLPYRAZINE *N*-OXIDES AND RELATED COMPOUNDS (HYDRAZIDES, GUANIDINOCARBONYL COMPOUNDS, ETC.)

A. Preparation of Carbamoylpyrazine *N*-Oxides

(1) *By Primary Synthesis*

The preparations of carbamoylpyrazine *N*-oxides by primary syntheses have been described in Sections II.5 (450, 462), III.1 (531, 535, 537), III.3 (547) (and 1453), and VIII.3A(2) (450, 462, 1256).

(2) *From Esters*

Carbamoylpyrazine *N*-oxides are also prepared from the corresponding esters. 3-Methoxycarbonylpyrazine 1-oxide with ammonium hydroxide at reflux gave 3-carbamoylpyrazine 1-oxide (1266) and similarly with hydroxylamine gave 3-*N*-hydroxycarbamoylpyrazine 1-oxide (1266). 2-Amino-5-chloro-3-methoxycarbonylpyrazine 1-oxide with methylamine gave 2-amino-5-chloro-3-*N*-methylcarbamoylpyrazine 1-oxide (876).

(3) *By Partial Hydrolysis of Nitriles*

2-Cyanopyrazine 1-oxide and 3-cyanopyrazine 1-oxide each with alkaline 3% hydrogen peroxide at 55° gave 2-carbamoylpyrazine 1-oxide and 3-carbamoylpyrazine 1-oxide, respectively (838). 3-Amino-2-cyanopyrazine 1-oxide refluxed with trifluoroacetic anhydride in trifluoroacetic acid for 5 hours gave 3-amino-2-carbamoylpyrazine 1-oxide (538), and 2-amino-3-cyano-5-methylpyrazine 1-oxide with sulfuric acid (d. 1.8) at 100° gave 2-amino-3-carbamoyl-5-methylpyrazine 1-oxide (1255). 2-Amino-6-chloro-3-cyano-5-methylpyrazine 1-oxide with 0.5*N* sodium hydroxide at room temperature for 48 hours formed a mixture of 2-amino-3-cyano-6-hydroxy-5-methylpyrazine 1-oxide (56%) and 2-amino-3-carbamoyl-6-chloro-5-methylpyrazine 1-oxide (22%) (533). 3-*N*-Acetylcarbamoylpyrazine 1-oxide was hydrolyzed by hot 10% sodium hydroxide to 3-carboxypyrazine 1-oxide (1057).

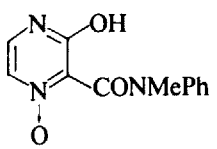
(4) *By Oxidation*

Oxidation of 2-carbamoylpyrazine with hydrogen peroxide in acetic acid gave a mixture containing mainly 3-carbamoylpyrazine 1-oxide (138, 575, 757, 839, 840,

1266), with some 2-carbamoylpyrazine 1-oxide (839, 840); and 2-cyanopyrazine with hydrogen peroxide in aqueous sodium hydroxide at 70° gave 3-carbamoylpyrazine 1-oxide (and some 2-carbamoylpyrazine) (839). 2-Carbamoyl-3-methoxypyrazine with hydrogen peroxide in acetic acid at 80° has been reported to give 3-carbamoyl-2-methoxypyrazine 1-oxide and 3-methoxypyrazine 1-oxide (881), and the following *N*-oxides have been prepared by similar oxidation: 3-*N*-morpholinocarbonylpyrazine 1-oxide (870); 3-hydroxy-2-*N*-methyl-*N*-phenyl(and *p*-tolyl)-carbamoylpyrazine 1-oxide (1055); and 4-methyl-2-*N*-methyl-*N*-phenylcarbamoyl-3-oxo-3,4-dihydropyrazine 1-oxide (1055); and a series of 3-carbamoylpyrazine 1-oxides have been prepared by oxidation (unspecified) of 2-carbamoylpyrazines (1452). 2-*N*-Hydroxycarbamoylpyrazine was oxidized by hydrogen peroxide in acetic acid at room temperature to 3-*N*-hydroxycarbamoylpyrazine 1-oxide (1266). 2-Amino-5-chloro-3-*N*-methylcarbamoylpyrazine refluxed with *m*-chloroperoxybenzoic acid in chloroform gave 2-amino-5-chloro-3-*N*-methylcarbamoylpyrazine 1-oxide (1222).

B. Reactions of Carbamoylpyrazine *N*-Oxides

Hydrolyses of carbamoylpyrazine *N*-oxides to carboxypyrazine *N*-oxides have been described in Section 8A(2), deoxygenation and chlorination of carbamoylpyrazine *N*-oxides (*N*-unsubstituted carbamoyl compounds gave the nitrile) in Section V.1G, and deoxygenation of carbamoylpyrazine *N*-oxides (which also contained amino groups) in Section VIII.3C(4). In addition, 4-methyl-2-*N*-methyl-*N*-phenylcarbamoyl-3-oxo-3,4-dihydropyrazine 1-oxide refluxed with aqueous ethanolic sodium dithionite gave 4-methyl-2-*N*-methyl-*N*-phenylcarbamoyl-3-oxo-3,4-dihydropyrazine (1137), and 3,5-bis(methylamino)-3-*N*-methylcarbamoylpyrazine 1-oxide was deoxygenated by heating at 190–200° and 0.25 mm (462). 3-Hydroxy-2-(*N*-methyl-*N*-phenyl)carbamoylpyrazine 1-oxide (**78**) heated in concentrated sulfuric acid at 55° for 2 hours underwent reaction to give 2-hydroxy-3-*o*-methylaminophenylpyrazine (**79**), 4-methyl-2-(*N*-methyl-*N*-phenyl)carbamoyl-3-oxo-3,4-dihydropyrazine 1-oxide similarly treated gave 1-methyl-3-*o*-methylaminophenyl-2-oxo-1,2-dihydropyrazine (but no "crossed products" could be isolated from mixed reactants) (1055, 1454), and 3-hydroxy-2-(*N*-methyl-*N*-*p*-tolyl)carbamoylpyrazine 1-oxide gave 2-hydroxy-3-(5-methyl-2-methylamino)-phenylpyrazine (1055). 3-Carbamoylpyrazine 1-oxide underwent the Hofmann degradation with sodium hypobromite (at 60–70°) and gave 3-aminopyrazine 1-oxide (108, 547a). 3-Carbamoylpyrazine 1-oxide refluxed with acetic anhydride



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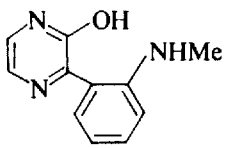


(79)

gave 3-*N*-acetylcarbamoylpyrazine 1-oxide (1057), which heated with concentrated sulfuric acid at 80–90° produced 3-carbamoylpyrazine 1-oxide (1057). 3-Carbamoylpyrazine 1-oxide, aqueous formaldehyde, and diethylamine refluxed in ethanol (Mannich reaction) gave 3-(diethylaminomethyl)carbamoylpyrazine 1-oxide, and similar preparations were observed with other amines (1455).

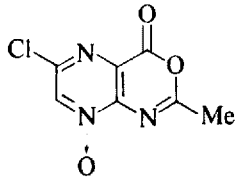
Various bicyclic heterocycles have been prepared from carbamoylpyrazine *N*-oxides: 2-amino-5-chloro-3-*N*-methylcarbamoylpyrazine 1-oxide refluxed with triethyl orthoformate and acetic anhydride gave 6-chloro-3-methyl-4-oxo-3,4-dihydropteridine 8-oxide (1222); 2-amino-3-carbamoyl-5-methyl(or phenyl)pyrazine 1-oxide with triethyl orthoformate, or with ethyl chloroformate followed by cyclization of the intermediate urethane, gave 6-methyl(or phenyl)-4-hydroxypteridine 8-oxide (537).

C. Preparation and Reactions of Hydrazinocarbonyl-, Guanidinocarbamoyl-, and Guanidinocarbonylpyrazine *N*-Oxides

3-Methoxycarbonylpyrazine 1-oxide refluxed with 50% hydrazine hydrate gave 3-hydrazinocarbonylpyrazine 1-oxide (1266), and similar treatment of 2-amino-5-chloro-3-methoxycarbonylpyrazine 1-oxide with hydrazine in ethanol gave 2-amino-5-chloro-3-hydrazinocarbonylpyrazine 1-oxide (876, 1257).

2-Hydrazinocarbonylpyrazine was oxidized by 30% hydrogen peroxide in acetic acid to 2-hydrazinocarbonylpyrazine 1,4-dioxide (1266). 2-Amino-5-chloro-3-hydrazinocarbonylpyrazine 1-oxide in dimethyl sulfoxide with *S*-methylthiourea hydriodide and sodium methoxide gave 2-amino-5-chloro-3-guanidinocarbamoylpyrazine 1-oxide (1257), and 2-amino-5-chloro-3-hydrazinocarbonylpyrazine 1-oxide refluxed with cyanamide in ethanolic hydrogen chloride gave 2-amino-5-chloro-3-guanidinocarbamoylpyrazine 1-oxide (1257).

The preparation of guanidinocarbonylpyrazine *N*-oxides by ring opening reactions has been described in Section VIII.3A(2), and from alkoxycarbonylpyrazine *N*-oxides in Section 9B. 6-Chloro-2-methyl-4*H*-pyrazino[2,3-*d*][1,3]oxazin-4-one 8-oxide (**80**) with aminoguanidine hydrochloride and sodium methoxide in



(80)

methanol gave 2-acetamido-5-chloro-3-guanidinocarbamoylpyrazine 1-oxide, and the 5-dimethylamino analogue was prepared similarly (1257). 2-Amino-3-guanidinocarbonyl-5-methylpyrazine 1-oxide was cyclized by heating in dimethylformamide to 2-amino-4-hydroxy-6-methylpteridine 8-oxide (537).

11. CYANOPYRAZINE *N*-OXIDES

A. Preparation

Cyanopyrazine *N*-oxides have been prepared from α-amino nitriles and α-hydroxyimino carbonyl compounds as summarized in Section III.1 (528–530, 532–534, 537, 540, 542). Oxidation of 2-cyanopyrazine with perhydrol gave 3-cyanopyrazine 1-oxide (575), 2-cyano-5-ethoxy-3,6-dimethylpyrazine with 30% hydrogen peroxide in acetic acid at 55° gave 2-cyano-5-ethoxy-3,6-dimethylpyrazine *N*-oxide (288), and the oxidations of 2-amino-3-cyanopyrazine 1-oxide (538) and 2-amino-3-cyano-5-methylpyrazine 1-oxide (532) to their dioxides have been described in Section VIII.3A(4). The sodium salts of 2-sulfopyrazine 1-oxide and 3-sulfopyrazine 1-oxide each heated with potassium cyanide at 290–310° under reduced pressure gave 2-cyanopyrazine 1-oxide and 3-cyanopyrazine 1-oxide, respectively (838). Attempts to convert 3-chloropyrazine 1-oxide to 3-cyanopyrazine 1-oxide with cuprous cyanide in *N*-methylpyrrolidine or dimethylformamide were unsuccessful (838).

B. Reactions

The oxidations of 2-amino-3-cyanopyrazine 1-oxides to the 1,4-dioxides are described in Section VIII.3A(4) and deoxygenations of some 2-amino-3-cyanopyrazine 1-oxides and 1,4-dioxides with phosphorus trichloride or sodium dithionite in Section VIII.3C(4). Deoxygenation and chlorination of aminocyanopyrazine 1-oxides are reported in Section V.1G, and deoxygenation and acetoxylation or alkoxylation of 2-amino-3-cyano-5-methylpyrazine 1,4-dioxide in Section VIII.3C(5). Hydrolysis of cyanopyrazine *N*-oxides to carbamoylpyrazine *N*-oxides are given in Section 10A(3) and ring closure reactions of 2-amino-3-cyanopyrazine 1-oxides to pteridine 8-oxides in Section VIII.3C(3).

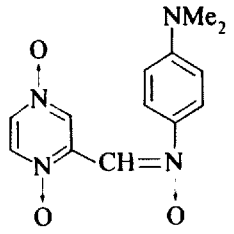
C. Properties

Hydrogen–deuterium exchange rates of H2 in 3-cyanopyrazine 1-oxide (pK_a 1.12; k_{H_2} 2.8×10^2 l/mol · min) and of H2 and H6 in other 3-substituted pyrazine 1-oxides have been correlated with σ-constants, and the logarithm of the H2 exchange rates has been shown to be linearly related to the pK_a values of these compounds (745).

12. FORMYL- AND ACETYLPYRAZINE *N*-OXIDES AND DERIVATIVES

A. Preparation

Treatment of the 2-*p*-dimethylaminophenyliminomethylpyrazine tri-*N*-oxide (81) with aqueous alcoholic hydrogen chloride and addition of hydrogen peroxide



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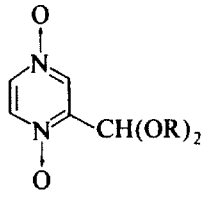

(82)

gave 2-formylpyrazine hydrate 1,4-dioxide (**82**, R = H) (50.4%) (739), and compound (**81**) with a solution of hydrogen chloride (13.5%) in anhydrous ethanol at 20–25° for 40 hours gave 2-diethoxymethylpyrazine 1,4-dioxide (**82**, R = Et) (77%) and 2-carboxypyrazine 1,4-dioxide (12.6%) (739). 2-Acetoxymethylpyrazine 1,4-dioxide on treatment with phenylhydrazine and aqueous sodium hydroxide gave 3-phenylhydrazonomethylpyrazine 1-oxide (1138), and oxidation of 2-acetylpyrazine with "perhydrol" gave 3-acetylpyrazine 1-oxide (575).

B. Reactions

2-Formylpyrazine hydrate dioxide in alkaline solution (with or without hydrogen peroxide) formed a mixture of 3-carboxypyrazine 1-oxide and 5-carboxy-2-hydroxypyrazine 1-oxide (739), and it formed derivatives with 2,4-dinitrophenylhydrazine, semicarbazide, or hydroxylamine (739).

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CHAPTER X

The Ionization and Spectra of Pyrazines

1. IONIZATION OF PYRAZINES

Ionization constants of heterocyclic substances may be readily determined by potentiometric titration, spectroscopy (ultraviolet or visible), or conductivity (1456) and by p.m.r. spectroscopy (1457, 1458). Estimates of ionization constants may be obtained by calculation (1459–1461). They are essential data in practical heterocyclic chemistry and of immense use in the establishment of structures in potential tautomeric compounds. Albert (1462) gives a simple treatment of ionization constants as applied to heterocyclic chemistry.

The first basic ionization constant of pyrazine (in water at 20–27°) has been determined as 0.65 (122), 0.60 (123, 125), and 1.1 (124); and the second as −5.78 (122), −6.25 (126), and −6.6 (1463). They should be compared with the first basic pK_a values of 5.23 for pyridine (123), 1.30 for pyrimidine (123), and 2.33 for pyridazine (123). The lower basic strength (about 4.6 units) of pyrazine relative to pyridine is due to the electron-attracting (and base-weakening) doubly bound ring nitrogen atom at the para position, which effect approximates that of a nitro group [the pK_a value of 4-nitropyridine at 20° is 1.61 (1464) and at 25° is 1.39 (1465)]. Ionization constants for mono- and diprotonation have been determined for pyrazine, methylpyrazine, 2,5- and 2,6-dimethylpyrazine, and tetramethylpyrazine (122). The basicity was increased by methyl groups; the effect was additive and the same for pyrazine as for pyridine (122). Each methyl group increased the basicity by 0.72 pH units (122), and there is an approximate linear relation between pK_1 and pK_2 for the pyrazines (122). The pK_a values of pyrazine and derivatives are given in Table X.1. References for the table are 94, 122–126, 140, 370, 400, 422, 424, 430, 431, 448, 449, 745, 746, 820, 821, 834, 853, 1060, 1075, 1079, 1080, 1082, 1100, 1136, 1167, 1183, 1190, 1463 and 1466–1472.

2-Aminopyrazine is a stronger base than pyrazine; moreover, 2-amino-, 2-methylamino-, and 2-dimethylaminopyrazine have closely similar basic strengths, which supports the conclusion that, in aqueous solution, 2-aminopyrazine exists mainly in the amino form (1) (821). Ultraviolet spectral evidence (see Section VIII.1C) indicates that the protonation does not take place at the extranuclear amino group (821). This and other evidence (p.m.r.) (1136) are consistent with monoprotonation of 2-aminopyrazine at N_1, and the second protonation at N_4. 2,3-Diaminopyrazine (pK_a 4.88) is a much stronger base than 2-aminopyrazine, but

TABLE X.1 SOME pK_a VALUES OF PYRAZINES[a]

Pyrazine	Basic pK_a	Acidic pK_a	Refs.
Unsubstituted[b]	1.1, 0.65, 0.6, −5.78, −6.25, −6.6		122–126, 1463
2-Acetoxymethyl-3-amino	2.42		1075
2-Acetyl-3-aminomethyleneamino	5.51		1167
2-Amidino-5,6-dimethyl-3-methylamino	9.45		431
2-Amidino-3-methylamino	8.98		431
2-Amino	3.14, 2.96, 1.8 (?)		123, 821, 1190
2-Amino-3-aminomethyl	8.40, 2.05		1183
5-Amino-2-carbamoyl-3-methylamino	2.53		448
2-Amino-3-carboxy	1.1, < 1	3.8, 3.70	422, 1190
2-Amino-3-carboxy-5,6-dimethyl	< 1	4.46	431
2-Amino-5-carboxy-3-formyl-6-hydroxy		7.63, 3.71	1466
2-Amino-5-chloro-3-formyl	−0.68		430
3-Amino-5-chloro-2-formyl	−1.64		430
2-Amino-3-cyano	−0.43		1183
5-Amino-2,3-dimethyl	3.89		370
2-Amino-3-dimethylamino	4.29, −0.24		370
2-Amino-3-dimethylamino-5,6-dimethyl	4.88, −0.18		370
2-Amino-3-ethoxalylaminomethyl	2.61		1183
2-Amino-3-ethoxycarbonylaminomethyl	2.80		1183
2-Amino-5-ethoxycarbonyl-3-formyl-6-hydroxy		6.09	1466
3-Amino-2-formyl-5-hydroxy	−1.34	6.61	448, 449
2-Amino-3-formyl-6-hydroxy-3-methylcarbamoyl		6.01	1466
2-Amino-3-hydrazinocarbonyl	3.10, 1.06		424
2-Amino-3-hydrazinocarbonyl-5,6-dimethyl	2.96, 1.38		424
2-Amino-3-hydrazinocarbonyl-5-methyl	3.07, 1.13		424
3-Amino-2-hydrazinocarbonyl-5-methyl	3.05, 1.28		424
2-Amino-3-hydroxymethyl	3.11		1075
2-Aminomethyleneamino-3-formyl	5.17		1167
2,5-Bis(D-*arabo*-tetrahydroxybutyl)	0.7		125
2,3-Bismethoxycarbonyl	< −2.0		1467
2-Carbamoyl	−0.5		140
2-Carbamoyl-5,6-dimethyl-3-methylamino	2.70		431
2-Carbamoyl-5-hydroxy-3-methylamino	−0.92	7.48	449
2-Carbamoyl-3-methylamino	2.11		431
2-Carboxy		2.92	400
2-Carboxy-5,6-dimethyl-3-methylamino		4.82	431
2-Carboxy-5-methyl		2.85	1468
2,3-Diamino	4.88, 0.76		370
2,3-Diamino-5,6-dimethyl	5.36, 1.23		370
3,5-Diamino-2-formyl	1.57		448
2,3-Dicarboxy	< −2.0	3.57, 2.77, 2.20, 0.9	400, 1467, 1468
2,5-Dicarboxy		2.29	1468
5,6-Dichloro-1-cyclohexyl-3-hydroxy-2-oxo-1,2-dihydro		5.66 (4.66)	653

TABLE X.1 *Continued*

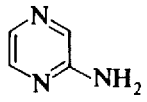
Pyrazine	Basic pK_a	Acidic pK_a	Refs.
2,3-Dimethoxycarbonyl	< 2.0		1467
2,5-Dimethyl	2.1, 1.97, 1.9, 1.85, − 4.60		122, 124, 125, 1467
2,6-Dimethyl	2.5, 1.90, − 4.57		122, 124
2-Dimethylamino	3.27		821
2-Formyl-5-hydroxy-3-methylamino	− 1.05	6.44	448, 449
3-Guanidino-6-hydroxymethyl-1-methyl-2-oxo-1,2-dihydro	11.9		1060
2-Hydroxy	− 0.1	8.23	820, 1082
2-Hydroxycarbamoyl		8.1	1469
3-Hydroxy-2,5-diisobutyl	1.7		125
2-Mercapto	− 0.24, − 0.73	6.72,[c] 6.32	821, 1100
5-Mercapto-2,3-diphenyl		7.3	834
2-Methoxy	0.75		820
2-Methyl	1.5, 1.47, 1.45, 1.4, − 5.25		122, 124, 125, 1467
2-Methylamino	3.42		821
1-Methyl-2-oxo-1,2-dihydro	− 0.04		820
2-Methylsulfinyl	− 1.48		1080
2-Methylsulfonyl	− 2.47		1079
2-Methylthio	0.55, 0.48		821, 1100
1-Methyl-2-thio-1,2-dihydro	− 0.18, − 0.45		821, 1100
2-Phenacyl		12[d]	1470
2-(Pyridin-2′-ylcarbonylmethyl)	2.98	10.21	1470
2-Sulfanilamido	12.22[b]	6.04	1471
2-(D-*arabo*-Tetrahydroxybutyl)-5-methyl	1.4		125
Tetramethyl	3.7, 3.6, 3.55, 2.8, − 2.7		122, 124, 125
Unsubstituted/1-oxide	0.05		745
2-Amino/1-oxide	0.79		1136
3-Amino/1-oxide	1.50, − 1.92		745
6-*s*-Butyl-2-hydroxy-3-isobutyl/1-oxide		5.5	94
2-Chloro/1-oxide	− 1.31		1136
3-Chloro/1-oxide	− 1.05		745
3-Cyano/1-oxide	− 1.12		745
3-Dimethylamino/1-oxide	1.34, − 1.77		745
2-Hydroxy-6-(1′-hydroxy-1′-methylpropyl)-3-isobutyl/1-oxide		4.9	94
2-Methoxy/1-oxide	− 0.51		1136
3-Methoxy/1-oxide	− 0.45		745
3-Methyl/1-oxide	0.46		745
3-Piperidino/1-oxide	1.34, − 1.80		745
Tetramethyl/1,4-dioxide	− 4.01, − 4.56		746

[a] Ionization constants have been determined mostly at 20 or 25° in water unless otherwise specified.

[b] The protonation of pyrazine has been studied by p.m.r. techniques (1472).

[c] Determined in 50% ethanol.

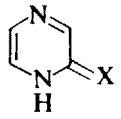
[d] Determined in 50% dioxane–water.



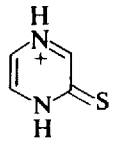
(1)

the first pK_a for protonation of 2-amino-3-methylaminopyrazine is significantly lower than 2,3-diaminopyrazine, presumably due to steric hindrance (370). The orientation of the ethoxalyl group in 2-amino-3-ethoxalylaminomethylpyrazine was supported by the low basic strength (pK_a 2.66) (1183) and the orientation of the acetyl group in 2-amino-3-acetoxymethylpyrazine was established (in part) by comparison of its basic strength (pK_a 2.42) with that of 2-amino-3-hydroxymethylpyrazine (pK_a 3.11) (1075).

Comparison of the basic ionization constants of 2-hydroxypyrazine and its *O*- and N_1-methyl derivatives (Table X.1 and Section VI.5) indicates that in aqueous solution the amide form (**2**, X = O) is the predominant tautomer (820, 821). Similarly the basic strength of 2-mercaptopyrazine approximates that of its N_1-methyl derivatives but differs from 2-methylthiopyrazine, thus indicating that in aqueous solution, 2-mercaptopyrazine exists mainly in the thione form (**2**, X = S) (821, 1100) (see also Section VII.3). The basic center of 2-mercaptopyrazine is presumably N_4, giving the cation (**3**). 2-Mercaptopyrazine is a weaker base and stronger acid than 2-hydroxypyrazine (821, 1100), but 2-methylthiopyrazine (pK_a 0.48 (1100)] has only a slightly lower (weaker) basic strength than 2-methoxypyrazine (0.75), in agreement with the known similarity of the inductive effect of the methylthio and methoxy groups (1100).



(2)

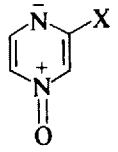


(3)

2-Methylsulfinyl- and 2-methylsulfonylpyrazines were weaker bases by 2.13 (1080) and 3.12 (1079) pH units, respectively, than pyrazine; the electron withdrawal was thought to operate by the inductive and mesomeric mechanism. Protonation occurred at N_4. Proton magnetic resonance studies show that 2-methoxycarbonylpyrazine also protonates at N_4 (1136).

As expected, amidinopyrazines (431) and guanidinopyrazines (1060) are relatively strong bases. 2-Carboxypyrazine has pK_a 3.92 (400); and Brown and Jacobsen (431) remark that the possibility that 2-amino-3-carboxypyrazines are zwitterionic cannot be excluded.

The strong base-weakening effect of an *N*-oxide group upon a para-situated sp^2 nitrogen atom is exemplified by comparison of the pK_a of pyrazine (0.65) (122) with that of pyrazine *N*-oxide (pK_a 0.05) (745). Thus there is no significant contribution of resonance structures such as (**4**) to the ground state of pyrazine *N*-oxide (745). The major effect that a 3-substituent has upon the basicity of the



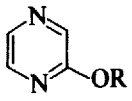
(4)

ring nitrogen atom (N_4) in 3-substituted pyrazine 1-oxides appears to involve the inductive contribution of the substituents only (745). Paudler and Humphrey (745) claim that 2-aminopyrazine 1-oxide is monoprotonated at the extranuclear amino group and diprotonated at the ring nitrogen atom. A p.m.r. study of protonation (in D_2SO_4/D_2O) has revealed that 2-amino-, 2-chloro-, and 2-methoxypyrazine 1-oxides protonate first at the ring nitrogen atom, N_4 (1136, 1473); the first protonation of 2-aminopyrazine 1,4-dioxide takes place at the oxygen atom of the *N*-oxide group in position 1, and that of 2-methoxypyrazine 1,4-dioxide at the oxygen of the *N*-oxide group in position 4 (1136).

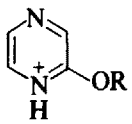
Thermodynamic parameters for the protonation of 2,3,5,6-tetramethylpyrazine 1,4-dioxide have been obtained from basicity measurements at 25, 40, 60, 80, and 90° using a spectroscopic method (746).

2. ULTRAVIOLET SPECTRA OF PYRAZINES

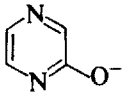
Ultraviolet spectra of numerous pyrazines have been recorded, but in many cases without regard to the effects of ionization, and in various solvents. All pyrazines are basic and thus have both neutral (e.g., **5**) and cationic (e.g., **6**) forms. Pyrazines with a substituent containing an ionizable hydrogen, such as a carboxy, hydroxy, or mercapto group, may also exist in the anionic form (e.g., **7**), the tautomeric neutral form (e.g., **2**, R = H), a potentially zwitterionic form (**8**, R = H) or an isomeric cationic form (e.g., **9**, R = H). Many published spectra are in fact of mixed ionic species: to determine the spectrum of each ionic form it is necessary to measure its spectrum in a solution buffered at least two units above or below the pK_a value (or values) of the substance. In nonaqueous solvents, the neutral (uncharged) species are favored. The ultraviolet spectra of pure species may then serve to characterize the pyrazine, may permit the correlation of spectra with structure, and may be used in quantitative determinations.



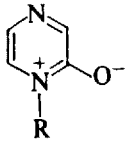
(5)



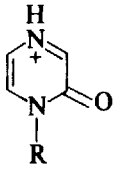
(6)



(7)



(8)



(9)

Published ultraviolet spectra of some simple pyrazines, measured in the solvent specified, are recorded in Table X.2. References for the table are 86, 89, 98, 108,

TABLE X.2 ULTRAVIOLET SPECTRA OF SOME SIMPLE PYRAZINES[a]

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
Unsubstituted	0.6	pH 7.0	0	261 (3.77), 300 (2.98)	1467, cf. 122
	− 5.78	$H_0 - 1.1$	+	266 (3.86)	1467, cf. 122
		Aq. H_2SO_4	++	284 (–)	122
		C_6H_{12}		260 (3.75), 328 (3.02)	1467, cf. 1474
		EtOH		261 (3.78), 310 (2.93)	1467, cf. 1212, 1474–1477
2-Acetamido		pH 7.0		231 (4.16), 280 (3.81), 296 (3.81)	1478
2-Acetamido-5-ethyl		H_2O		237 (4.06), 304 (3.87)	376
2-Acetoxy		EtOH		265 (3.83)	738
2-Acetoxymethyl		EtOH		264.5 (3.88), 271 (3.81)	738
2-Acetoxymethyl-3-amino	2.42	pH 6.0	0	231 (4.03), 310 (3.78)	1075
2-Acetoxymethyl-5-methyl		H_2O		274 (3.99)	760
2-Acetoxymethyl-6-methyl		H_2O		273 (3.99)	760
2-Acetyl-5-hydroxy-3,6-dimethyl		EtOH		285 (4.14)	1064
2-Amidino-3-methylamino	8.98	pH 11.0	0	256 (4.13), 361 (3.76)	431
		pH 7.0	+	264 (3.93), 359 (3.69)	
2-Amino	3.14	pH 7.0	0	230 (4.02), 285 (3.33), 316 (3.70)	1478, cf. 821, 1479
		pH 0.1	+	230 (4.05), 325 (3.77)	821, cf. 1478, 1479
		EtOH	–	230 (4.03), *285* (–), 316 (3.70)	86, 921
2-Amino/MeI		pH 6.9		244 (4.155), 353 (3.7)	821
2-Amino-3-aminomethyl	8.40	pH 11.0	0	230 (3.96), 313 (3.73)	1183
	2.05	pH 4.0	+	229 (4.07), 313 (3.78)	1183
2-Amino-3-carbamoyl		pH 6.1		246 (4.06), *305* (*3.26*), 350 (3.80)	1478
3-Amino-2-carbamoyl-5-methyl		pH 13		249 (4.04), 349 (3.90)	435
		pH 1		244 (4.07), 356 (3.97)	435

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
2-Amino-3-carboxy	3.7	pH 6.1	0	244 (4.01), *295 (3.29)*,	1478, cf. 424
	< 1			340 (3.76)	
2-Amino-5-carboxy		H_2O		262 (4.15), 319 (3.86)	408
2-Amino-3-carboxy-5,6-dimethyl	4.11	pH 7.0	0	248 (4.00), 343 (3.87),	431
				350 (4.08), 372 (4.01)	
2-Amino-3-cyano	− 0.43	pH 2	0	245 (4.13), 350 (3.82)	1183
		$H_0 - 3.0$	+	240 (4.18), 356 (3.96)	1183
3-Amino-2,5-dimethyl		EtOH		234 (4.08), 319 (3.88)	478[b]
5-Amino-2,3-dimethyl	3.89	H_2O	0	233 (3.99), 323 (3.79)	376
2-Amino-5-ethyl		H_2O		233.5 (4.05), 314 (3.72)	376
2-Amino-6-ethyl		H_2O		232 (3.89), 384 (3.36),	376
				319.5 (3.73)	
2-Amino-3-hydroxymethyl	3.11	pH 6.0	0	231 (4.00), 316 (3.78)	1075
		pH 0.0	+	231 (4.00), 326 (3.84)	1075
2-Amino-3-mercapto-5-methyl		95% EtOH		236 (3.60), 278 (3.63),	1101
				387 (3.80)	
3-Amino-2-methoxycarbonyl-5-methyl		pH 13.0		244 (3.96), 340 (3.86)	435
		pH 1.0		247 (3.99), 357 (3.95)	435
2-Amino-5-methyl		H_2O		233 (4.03), 324.5 (3.71)	376
2-Amino-5-phenyl		H_2O		271.5 (4.26), 339 (3.88)	376
2-Amino-3,5,6-trifluoro		EtOH		222 (3.82), 317 (3.56)	851
2-Bromo		C_6H_{12}		274 (3.9), 282 (3.9),	1474
				308 (3.1) [cv]	
2-Bromo-3,5,6-trifluoro		C_6H_{12}		242.5 (2.91), 289 (3.93)	851
2-Carbamoyl	− 0.5	H_2O	0	268.5 (6.06, ?)	1398
		MeOH		268 (6.28, ?)	1398
2-Carbamoyl-3-methylamino	2.11	pH 5.0	0	256 (4.15), 371 (3.74)	431
		pH 0.0		247 (4.15), 361 (3.77)	431
2-Carboxy-3-chloro		MeOH		277.5 (3.83)	838

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
5-Carboxy-2,3-diphenyl		EtOH		222 (4.34), 305 (4.09)	352
2-(2′-Carboxyhydrazino) (?)		MeOH		229.3 (3.7), 277.3 (3.8), 323 (3.98), 332.6 (3.97)	971
2-Carboxy-3-hydroxy		NaOH		Cv	1056
		HCl		Cv	1056
		EtOH		Cv	1056
5-Carboxy-2-methylamino-3-*N*-methylcarbamoyl		pH 7.0		281 (4.32), 367 (3.81)	442
		pH 1.0		288 (4.26), 362 (3.80)	442
2-Carboxy-5-phenyl		H_2O		255 (4.03), 301 (4.19)	352
2-Carboxy-6-phenyl		H_2O		251 (4.08), 298 (3.96)	352
2-Chloro		C_6H_{12}		270 (3.8), 303 (–) [cv]	1474
		EtOH		268 (3.80), 274 (3.80)	737
2-Chloro-5-methoxy		H_2O		221.5 (–), 306 (–)	838
2-Chloro-6-methoxy		MeOH		219.5 *277–280* (–), 297.5 (–)	838
2-Chloro-5-methoxycarbonyl		H_2O		225 (4.05), 278 (3.94), 281 (3.99), *296* (*3.55*)	838
2-Chloro-3-methyl		MeOH		275.5 (413), *295* (–)	737
2-Chloro-3-morpholinocarbonyl		MeOH		278.1 (3.83)	838
2-Chloro-3,5,6-trifluoro		C_6H_{12}		288 (3.46)	851
2.3-Diamino	4.88	pH 7.0	0	239 (3.95), 321 (3.90)	370
	0.76	pH 2.8	+	245 (3.99), 331 (3.96)	370
		$H_0 - 1.38$	++	242 (3.97), 341 (3.99)	370
2,3-Dicarboxy	3.57	pH 7.0	−−	281 (3.89), *315* (*2.99*)	1467
	0.9	pH 2.2	−	274 (3.81), *305* (*2.91*)	1467
	< -2.0	$H_0 - 1.1$	0	270 (3.84), *310* (*2.85*)	1467
		EtOH		269 (3.79), 314 (2.84)	1467
2,5-Dicarboxy	2.29			Cv	1176
2,3-Dichloro		C_6H_{12}		213 (3.8), 278 (3.6), *303* (*3.4*) [cv]	1474

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
2,5-Dichloro		C_6H_{12}		217 (3.9), 273 (3.6), *303 (3.4)* [cv]	1474
		MeOH		215 (4.03), 278 (3.84)	737
2,6-Dichloro		C_6H_{12}		217 (3.8), 273 (3.6), *303 (3.4)* [cv]	1474
		MeOH		214.5 (4.03), 278 (3.84)	737
2,6-Dichloro-3,5-difluoro		C_6H_{12}		248 (2.89), 294 (3.86)	851
2-Dichloromethyl		MeOH		215 (3.95), 278 (3.81), 292 (–)	737
2,3-Dihydroxy		95% EtOH		234 (3.71), 380 (3.69)	483
2,3-Dihydroxy-5-methyl		95% EtOH		234 (3.83), 315 (3.81)	483
2,3-Dimethoxycarbonyl	< – 2.0	pH 7	0	268 (3.85), 303 (2.87)	1467
		C_6H_{12}		268 (3.83), 319 (2.82)	1467
		EtOH		268 (3.85), 313–315 (2.78)	1280, cf. 1467
2,5-Dimethyl		H_2O	0	276 (–)	122
		Aq. H_2SO_4	+	286 (–)	122
		Aq. H_2SO_4	++	308 (–)	122
2,6-Dimethyl		H_2O	0	275 (–)	122
		Aq. H_2SO_4	+	282 (–)	122
		Aq. H_2SO_4	++	306 (–)	122
2-Dimethylamino	3.27	7.2	0	252 (4.13), 287 (2.75), 346 (3.64)	821
		0.3	+	244 (4.00), 352 (3.65)	821
		MeOH		252 (4.23), *293* (–), 345 (3.72)	921
2-Dimethylamino/MeI[c]		4.9		234 (3.84), 262 (4.22), 392 (3.575)	821
2-Diphenoxyphosphinothioyloxy		MeOH (?)		270 (3.78)	1117
2-Ethoxy		EtOH		211 (4.05), 279 (3.74), *295* (–)	668a, cf. 978

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
5-Ethoxycarbonylamino-2,3-diphenyl		EtOH		226.5 (4.44), 276.5 (4.12), 326 (4.08)	971
3-Ethoxy-2,5-dimethyl		EtOH		298 (3.92)	872
2-Ethylthio		EtOH		252 (3.99), *300* (–), 322 (3.96)	668a
2-Fluoro		EtOH		261 (3.72), 265 (3.72), *295* (–)	882, cf. 884
3-Hydrazino-2,5-dimethyl		MeOH		261 (4.23), *263* (*4.22*), 330 (3.98)	775
5-Hydrazino-2,3-diphenyl		EtOH		228 (4.11), 293 (4.20), 350 (3.85)	846
2-Hydrazino-3-methyl		MeOH		258 (3.88), *263* (*3.85*), 329 (3.56)	775
2-Hydroxy	8.23 − 0.1	pH 10.5		227 (4.05), 316 (3.75)	1480, cf. 821
		5.1	0	221 (3.96), 316 (3.74)	1480, cf. 821 1081
		$H_0 - 2.3$	+	222 (4.02), 342 (3.79)	1480, cf. 821
		EtOH		224 (3.95), 321 (3.74)	1081, cf. 89, 108
3-Hydroxy-2,5-dimethyl		EtOH		227 (3.88), 323 (3.55)	89
2-Hydroxy-3-methoxycarbonyl		pH 12.3		Cv	1056
		pH 1.7		Cv	1056
		95% EtOH		Cv	1056
2-Hydroxy-5-methoxycarbonyl		H_2O		259 (–), 312 (–)	838
2-Hydroxy-6-methoxycarbonyl		H_2O		242 (3.90), 329 (3.93)	838
2-Hydroxy-5-methoxycarbonyl-3,6-dimethyl		EtOH		264 (4.14), 307 (3.82)	1064

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
2-Hydroxymethyl		95% EtOH		220 (3.62), 265 (3.86), *300 (3.04)*	625
		EtOH		220.5 (3.04), 265.5 (3.83), 272 (3.77)	738
2-Hydroxy-3-methyl		H_2O		222 (3.92), 311 (3.83)	737
2-Hydroxy-6-methyl		H_2O		233 (3.62), 324 (3.97)	737
2-Hydroxymethyl-5-methyl		H_2O		274 (3.87)	760
2-Hydroxymethyl-6-methyl		H_2O		274 (3.83)	760
2-Mercapto	6.32 −0.73	pH 9.0	−	226 (3.72), 270 (4.05), 344 (3.70)	1100, cf. 821
		pH 3.48		227 (3.53), 279 (4.09), 382 (3.82)	1100, cf. 821
		$H_0 - 3.1$	+	291 (4.25), 450 (3.66)	821, cf. 1100
2-Methoxy		C_6H_{12}	−	210 (4.06), 277 (3.76)	1480
	0.75	pH 7.0	0	209 (3.98), 290 (3.72)	1081, cf. 821
		$H_0 - 2.25$	+	217 (3.96), 305 (3.84)	821, cf. 1106
		MeOH		211 (3.96), 276 (3.62), 288 (3.59)	1106
2-Methoxycarbonyl		EtOH		267.5 (3.90), 316.5 (2.72)	1280
2-Methoxy-3-methoxycarbonyl		EtOH		221.2 (3.99), 297.5 (3.90)	867
2-Methoxy-3-(morpholinocarbonyl)		MeOH		213 (4.08), 284.7 (3.87)	867
2-Methyl	1.47	C_6H_{12}	−	266 (3.76), 320 (2.92)	1467
		pH 7	0	271 (3.77), *295 (3.05)*	1467, cf. 122, 1470
		$H_0 - 0.3$	+	276 (3.82)	1467, cf. 122, 1470
		Aq. H_2SO_4	++	295 (−)	122
		95% MeOH		266 (3.79), 273 (3.74), 308 (−)	1470

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
2-Methylamino	3.42	7.2	0	242 (4.10), *285* (*2.91*), 332 (3.64)	821
		0.4	+	237 (4.04), 331 (3.71)	821
1-Methyl-2-oxo-1,2-dihydro	− 0.04	pH 7.0	0	223 (3.97), 323 (3.75)	1081, cf. 821
		$H_0 - 2.3$	+	225 (4.04), 345 (3.81)	1480, cf. 821
2-Methylsulfinyl	− 1.48	pH 6.0	0	272 (3.76), 308–309 (2.90)	1080
		$H_0 - 4.0$	+	*233* (*3.52*), 269–271 (3.61), 287 (3.58)	1080
2-Methylsulfonyl	− 2.47	pH 6.0	0	*259* (*3.80*), 264 (3.86), *270* (*3.74*), 310 (2.78)	1079
		$H_0 - 5.0$	+	273 (3.90)	1079
2-Methylthio	0.55	pH 7.0	0	251 (3.89), *300* (*3.51*), 322 (3.73)	1100, cf. 821
		$H_0 - 2.2$	+	237 (3.80), 266 (4.02), 360 (3.69)	821, cf. 1100
1-Methyl-2-thio-1,2-dihydro	− 0.18	7.0	0	222 (3.56), 279 (4.07), 375 (3.81)	1100, cf. 821
		$H_0 - 2.95$	+	*260* (*3.56*), 2.91 (4.17), 436 (3.64)	1100, cf. 821
2-Phenacyl	12[d]	pH 13.0	−	239 (4.43), 271 (3.70), 330 (4.03), 383 (4.10)	1470
		N $HClO_4$		250 (4.11), 273 (4.07)	1470
		95% MeOH		247 (3.99), 265 (3.93), *271* (−), 310 (3.17), 360 (3.18)	1470
2-Sulfo (sodium salt)		H_2O		204 (3.87), 267 (3.91), *274* (−), 309 (2.92)	882
Tetrabromo		C_6H_{12}		246 (4.09), 288.5 (3.49), *302* (*3.78*), 312.5 (4.05), 323 (3.96)	851

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
Tetrachloro		C_6H_{12}		231.5 (4.07), 234 (4.07), 272.5 (3.20), 305 (3.97) 309.5 (4.01), 314.5 (3.93)	851
Tetraethoxycarbonyl		EtOH		277–279 (3.93)	1280
Tetrafluoro		C_6H_{12}		280.5 (4.01)	851
Tetramethyl		H_2O	0	280 (–)	122
		Aq. H_2SO_4	+	302 (–)	122
		Aq. H_2SO_4	++	322 (–)	122
2,3,5-Trichloro-6-fluoro		C_6H_{12}		298.5 (3.97)	851
2,3,5-Trifluoro-6-hydrazino		EtOH		310 (–)	851
2,3,5-Trifluoro-6-hydroxy		C_6H_{12}		*225 (2.83)*, 293.5 (3.83)	851
2,3,5-Trifluoro-6-methoxy		C_6H_{12}		225.5 (2.81), 293 (3.83)	851
2,3,5-Trifluoro-6-methyl		C_6H_{12}		247.5 (2.95), 280.5 (3.84)	851
2,3,5-Trimethoxycarbonyl		EtOH		276 (3.96), 321 (2.72)	1280
2-Vinyl		EtOH		229.5 (4.11), 286.5 (3.84)	656
Unsubstituted/1-oxide	0.05	H_2O	0	213 (3.87), 263 (4.10)	745, cf. 626
		$H_0 - 1.7$	+	228 (4.01), 285 (4.1)	745
		n-Heptane		222 (4.1), 275 (4.0), 300 (3.5), 308 (3.3)	627, 1481
2-Acetoxymethyl/1-oxide		EtOH		222.5 (4.15), 270 (4.10)	738
3-Acetoxymethyl/1-oxide		H_2O		219 (4.23), 260 (4.18)	760
		EtOH		223.5 (4.18), 271 (4.11)	738
5-Acetoxymethyl-2-methyl/1-oxide		H_2O		215 (4.03), 264 (4.00)	760
3-Amino/1-oxide	1.50 – 1.92	H_2O	0	232 (3.38), 260 (3.89), 331 (3.62)	745, cf. 921
		$H_0 - 1.7$		225 (4.28), 278 (3.90), 338 (3.69)	745
		$H_0 - 8.8$	++	221 (4.32), 348 (3.78)	745
		MeOH		235 (4.45), 267 (3.93), 337 (3.62)	108

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
2-Amino-3,5-dimethyl/1-oxide		EtOH		234 (4.34), 339 (3.87)	524
3-Benzoyloxy/1-oxide		95% EtOH		233 (4.31), 270 (4.18)	1035
2-Carbamoyl/1-oxide		H_2O		228.5 (4.35), 270 (4.06), *300 (3.46)*	838
3-Carbamoyl/1-oxide		H_2O		225 (4.23), 265 (3.99), *300 (3.31)*	745, cf. 838
		$H_0 - 8.8$		208 (4.27), 277 (3.78)	745
2-Carboxy/1-oxide		H_2O		224 (4.10), 270 (4.06), *300 (3.59)*	838
3-Carboxy/1-oxide		H_2O		223.5 (4.16), 266.5 (4.02), *300* (–)	838, cf. 543
3-Carboxy-5-hydroxy/1-oxide		H_2O		233 (4.33), 285 (3.71), 336 (3.77)	1035
2-Chloro/1-oxide	− 1.31	H_2O	0	223 (4.23), 265 (4.01), *295 (3.45)*	838
3-Chloro/1-oxide	− 1.05	H_2O	0	225 (4.17), 268 (4.18), *295* (–)	838, cf. 737, 745
		$H_0 - 8.8$	+	203 (4.19), 238 (3.88), 282 (4.00), *300 (3.98)*	745
3-Chloro-2-methyl/1-oxide		H_2O		219 (4.14), 266 (4.01), *305* (–)	737
		N HCl		223 (4.15), 265 (4.03)	793
3-Chloro-5-methyl/1-oxide		H_2O		222.5 (4.03), 268 (4.02), 300 (3.53), 309 (3.46)	737
2-Cyano/1-oxide		H_2O		232 (4.40), 274 (4.06), *310 (3.28)*	838

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
3-Cyano/1-oxide	− 1.12	H_2O	0	230 (4.35), 274 (3.23), *310 (3.38)*	838, cf. 745
		$H_0 - 7.2$	+	204 (4.21), 244 (4.03), *250 (3.98)*, 290 (3.95), *315 (3.47)*	745
2,6-Diamino/1-oxide		EtOH		230.5 (4.34), 282 (3.34), 336 (3.98)	465
3-Dimethylamino/1-oxide	1.34 − 1.77	EtOH		254 (4.39), 280 (–), 360–365 (3.62)	921
3-Ethoxy/1-oxide		H_2O		217.5 (4.31), 261 (4.05), 305 (3.68)	978
2-Formyl/1-oxide, phenylhydrazone		EtOH		234 (4.20), 254 (4.24), 387 (4.39)	1138
2-Hydroxy/1-oxide		MeOH		232 (4.59), 330 (4.55)	838
3-Hydroxy/1-oxide		H_2O		222.5 (4.23), 276 (3.83), 331 (3.63)	838, cf. 108
		pH 12		262 (3.93), 337 (3.72)	1035
		95% EtOH		222 (4.32), 278 (3.86), 331 (3.60)	1035
2-Hydroxy-6-benzyl/1-oxide		EtOH		235 (4.12), 333 (3.99)	546
2-Hydroxy-3,6-diisobutyl/1-oxide		EtOH		236 (3.96), 328 (4.02)	98
2-Hydroxy-3,5-dimethyl/1-oxide		EtOH		234 (3.90), 330 (3.73)	546[b]
3-Hydroxy-2,5-dimethyl/1-oxide		EtOH		225 (4.18), 272 (3.79), 327 (3.68)	872
2-Hydroxy-3,6-dimethyl/1-oxide		EtOH		234 (3.91), 326.5 (3.85)	548
2-Methoxy/1-oxide	− 0.51	H_2O	0	221 (4.18), 260 (3.83), 309 (3.65)	838

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
3-Methoxy/1-oxide	− 0.45	H_2O	0	216 (4.43), 261 (4.15), 304 (3.83)	838, cf. 745
		$H_0 - 3.7$	+	202 (4.17), *221 (3.78)*, 281 (3.98), *305 (3.87)*	745
3-Mercapto/1-oxide		95% EtOH		284 (4.23), 315 (3.67), 418 (3.44)	1035
3-Mercapto-2-methyl/1-oxide		pH 9.0		211 (4.12), 259 (4.27), 365 (3.71)	905
		pH 3.0		220 (4.03), 272 (4.37), 395 (3.83)	905
3-Methoxycarbonyl/1-oxide		H_2O		229 (4.32), 270.5 (4.08) *305* (−)	838
2-Methyl/1-oxide		EtOH		220.5 (4.14), 266.5 (3.97)	738
3-Methyl/1-oxide	0.46	H_2O	0	215 (4.08), 262 (4.14), *288 (3.61)*, *297 (3.48)*	745
		$H_0 - 1.1$	+	232 (4.01), 285 (4.15)	745
		EtOH		222.5 (4.10), 269 (4.08)	738
4-Methyl-3-oxo-3,4-dihydro/1-oxide		95% EtOH		224 (4.37), 282 (3.92), 336 (3.64)	1035
2-Sulfo/1-oxide		H_2O		225 (4.34), 270.5 (4.10), *300 (3.45)*	838
3-Sulfo/1-oxide		H_2O		224 (4.21), 270 (4.09), *300 (3.42)*	838
3-(D-*arabo*-Tetrahydroxybutyl)/1-oxide		H_2O		217 (4.04), 265 (4.08)	543
Unsubstituted 1,4/dioxide		?		222 (3.78), 302 (4.34)	626, cf. 627
2-Acetoxymethyl/1,4-dioxide		EtOH		227 (4.24), 313.5 (4.32)	738
2-Acetoxymethyl-5-methyl/1,4-dioxide		EtOH		269 (3.84)	760
2-Amino/1,4-dioxide		H_2O		Cv	1189

TABLE X.2 *Continued*

Pyrazine	pK_a	Solvent	Species	λ_{max} (nm) (log ϵ)	Refs.
		$H_0 - 4.7$		Cv	1189
2-Ethoxy/1,4-dioxide		H_2O		212 (4.05), 234 (4.30), 256 (3.74), 296 (4.31), 337.5 (4.08)	978
2-Methyl/1,4-dioxide		EtOH		228 (4.27), 311 (4.34)	738, cf. 626

[a] Spectral data recorded in this table have been selected from the literature in the preferred order of the pure species (0, neutral, +, cation; ++, dication; −, anion; −−, dianion) in aqueous solution at specific pH (or H_0) values, and solutions in cyclohexane (C_6H_{12}), alcohols, and other solvents. Published λ_{max} (nm) and log ϵ values are quoted, except that some values have been estimated from the spectral curves. The letters "cv" in the table indicate the existence of a published spectral curve. Values in italics refer to shoulders and inflections.

[b] Spectra of more complex compounds are also given in this reference.

[c] Spectrum compensated for iodide ion.

[d] Determined in 50% dioxane–water.

122, 352, 370, 376, 408, 424, 431, 435, 442, 465, 478, 483, 524, 543, 546, 548, 625–627, 656, 668a, 737, 738, 745, 760, 775, 793, 821, 838, 846, 851, 872, 882, 884, 905, 921, 971, 1035, 1056, 1064, 1075, 1079, 1080, 1081, 1100, 1101, 1106, 1117, 1138, 1176, 1183, 1189, 1212, 1280, 1398, 1467, 1470, 1474, and 1475–1481.

The spectra of pyrazine, pyrimidine, and pyridazine, all in cyclohexane, are compared by Albert (1462). They show two bands with associated fine structure, the peaks for pyrazine center around 260 and 328 nm. The near-ultraviolet spectrum of pyrazine has been measured in several solvents [and at various pH values (1463)] and the transitions assigned (1474, 1482). The diffuse system at 260 nm has been attributed to $\pi \rightarrow \pi$ transitions whereas the sharp system at 328 nm has been ascribed to $n \rightarrow \pi$ transitions (1467, 1474). Semiempirical calculations have been made on the electronic structure of pyrazine with reference to its $n \rightarrow \pi$ transition (1483–1486), calculations have been made of $n \rightarrow \pi^*$ transition energies in *N*-heterocyclic molecules (including pyrazine) by a one-electron approximation (1487), and solvent effects on $n \rightarrow \pi^*$ transitions in pyrazine have been examined (1488). Relative to pyridine, the $n \rightarrow \pi$ transition of pyrazine (like other di- or polyazines) is displaced to longer wavelengths, and for pyrazine (and azines) a change of solvent from cyclohexane to aqueous solutions leads to a shift to shorter wavelengths (1489). The $n \rightarrow \pi$ bands of pyrazines are shifted to shorter wavelengths by electron-donating substituents and toward longer wavelengths by electron-accepting substituents, but the $\pi \rightarrow \pi$ bands undergo bathochromic shifts with both types of substituent (1467). Ultraviolet absorption spectra of pyrazine vapor (1490, 1491) and chloropyrazine vapor (1491) have been recorded and discussed. Absorption spectra have been measured of crystalline pyrazine and pyrazine in crystalline hydrogen, argon, krypton, and xenon all at 4.2°K, as well as pyrazine vapor (1492).

The connection between electronic structure and u.v. spectra of pyrazine and protonated pyrazine has been examined; the electronic distributions were calculated using a Pariser–Parr–Pople method employing an electrostatic model (proton bounded to the unshared electron pair of the nitrogen atom by electrostatic forces) (1493). The electronic absorption of a number of alkyl-substituted pyrazines in neutral and in acid solvents have also been measured (1476).

Whereas pyrazine and alkylpyrazines exhibit an absorption at about 260–270 nm in water, their mono *N*-oxides show two peaks, one about 215 nm, and the other about 260 nm, which are characteristic of the presence of an *N*-oxide function (838). The u.v. absorption maxima of pyrazine *N*-oxide moved to shorter wavelengths from that in heptane as the polarity was increased in ethanol and water (1481). Band analyses of pyrazine mono- and di-*N*-oxides have been carried out (627).

Ultraviolet spectra have been used extensively in a study of tautomerism in 2-hydroxy- (821, 1081) and 2-mercaptopyrazines (821, 1100) (see Sections VI.5 and VII.3, respectively) and both compounds have been shown to exist predominantly in the form (2, X = O, S). The wavelengths of the first and second absorption maxima of the different species of 2-mercaptopyrazine (neglecting the effect of methyl substitution) follow the sequence, cation > thioamide > anion > thiol

(821). This sequence was also observed for the long wavelength maxima of the corresponding species of 2-hydroxypyrazine (821) and was in accord with a molecular-orbital theory developed by Mason (1480). Cullen and Harrison (905) have found a broad maximum in the 380–400 nm region for a series of *C*-methyl 2-mercaptopyrazines and 3-mercaptopyrazine 1-oxides. This was shifted to shorter wavelengths by about 40 nm in the spectrum of the anion.

Cheeseman (821) has shown from a study of ultraviolet spectra (and ionization constants) that 2-aminopyrazine exists mainly in the amino form (1) and that it protonates at N_1 and is quaternized by methyl iodide at N_4 (see Section VIII.1C).

Ultraviolet spectra have been used for qualitative determinations of the positions of the keto–enol equilibria in phenyl pyrazylmethyl ketone (2-phenacylpyrazine) and the three isomeric pyridinyl pyrazinylmethyl ketones (1470).

3. NUCLEAR MAGNETIC RESONANCE SPECTRA OF PYRAZINES

The nuclear magnetic resonance spectra of simple heterocycles, including pyrazines, to about 1970 have been described by Batterham (1494), and these data are not discussed further here.

Published data on proton magnetic resonance spectra of pyrazines, pyrazine mono- and di-*N*-oxides, and methiodides are recorded in Table X.3. References for the table are 98, 314, 331, 365a, 377, 465, 483, 610, 614, 616, 666, 668a, 678, 685–687, 733a, 733b, 734, 739, 744, 764, 775, 838, 844, 846, 851, 867, 900, 905, 906, 936, 971, 979, 1034, 1064, 1075, 1079, 1080, 1086, 1094, 1136, 1183, 1230, 1261, and 1495–1499. Further data are described below.

Proton magnetic resonance techniques have been used for the measurement of rates of hydrogen–deuterium exchange of pyrazine (in CH_3OD–CH_3ONa at 164.6°) (591); for a study of protonation of pyrazine (1472); for analysis of the reaction mixture from quaternization of 2-substituted pyrazines with methyl iodide (666); for elucidation or confirmation of the structures of alkylpyrazines obtained by alkylation of pyrazines with aldehydes and ketones in the presence of a solution of an alkali or alkaline earth metal in liquid ammonia, or a suspension of these metals in other solvents (614); for a study of changes in chemical shifts produced on ionization of 2-methyl and 2-amino derivatives of pyrazine in liquid ammonia (665); for characterization of methoxymethylpyrazines (686); for the determination of the position of the *N*-oxide function in monosubstituted pyrazine *N*-oxides and the analysis of *N*-oxidation reactions (838); for a study of the structure of the cations of *N*-oxides of monosubstituted pyrazines (1136); and for the determination of the structure of the products of peroxyacetic and peroxysulfuric acid *N*-oxidation of phenyl- and chlorophenylpyrazines (733b).

Benzylic coupling in substituted methylpyrazines (687) and the influence of side chain alkyl substitution on benzylic coupling constants (1500) have been examined. On the basis of the methyl replacement technique, within its inherent limitations, the *para*-benzylic coupling appeared to be π-electron transmitted,

TABLE X.3 PROTON NUCLEAR MAGNETIC RESONANCE SPECTRA OF PYRAZINES

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
Unsubstituted	DMSO	8.63	1495, cf. 1094
	$CDCl_3$	8.63	1496
2-Acetamido-3-formyl	$CDCl_3$	2.46($COCH_3$), 8.53 and 8.62(H5,6), 10.18(CHO), 10.76(NH)	1075
2-Acetyl	N.s.g.	2.69($COCH_3$), 8.60 and 8.71(ArH), 9.22(ArH)	678[b]
	CCl_4	2.63(CH_3), 8.56, 8.68, 9.13	844, cf. 1497
2-Acetyl-3,5-dimethyl/3-acetyl-2,5-dimethyl mixture	N.s.g.		678
2-Acetyl-3-ethyl	N.s.g.	1.28(CH_2CH_3), 2.68($COCH_3$), 6.15(CH_2CH_3), 8.46, 8.60(ArH)	678
2-Acetyl-5-hydroxy-3,6-dimethyl	$CDCl_3$	2.45(CH_3), 2.28(CH_3), 2.69(CH_3), 12.8(ArH)	1064
2-Acetyl-3-methyl	N.s.g.	2.71($COCH_3$), 2.82(CH_3), 8.46, 8.60(ArH)	678
2-Acetyl-5-methyl	N.s.g.	2.60(CH_3), 2.64($COCH_3$), 8.46, 9.08(ArH)	678
2-Amino	DMSO	6.32(NH_2), 7.71(H5), 7.90(H6), 7.94(H3)	1086, cf. 1495
	D_2O	7.82(H5), 7.95(H6), 8.04(H3)	1136
	$N\ D_2SO_4$	7.86(H6), 7.97(H5), 8.53(H3)	1136
	$22N\ D_2SO_4$	8.16(H5), 8.54(H6), 9.06(H3)	1136
1-Amino/iodide	DMSO		610
2-Amino-3-aminomethyl	DMSO	2.36(CH_2NH_2), 3.87(CH_2), 6.51(NH_2), 7.80 and 7.96(H5 and H6)	1183
2-Amino-6-*s*-butyl	CCl_4	0.83(CH_2CH_3), 1.22($CHCH_3$), 1.4–2.0(CH_2CH_3), 2.58($CHCH_3$), 4.83(NH_2), 7.68(ArH), 7.71(ArH)	614
2-Amino-5-carboxy	DMSO	7.94(H3), 8.57(H6)	867
2-Amino-3-chloro	$CDCl_3$	5.05(NH_2), 7.70, 7.92(ArH)	838
	$CDCl_3$	7.92(H5), 8.59(H6)	867

TABLE X.3 *Continued*

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
2-Amino-3-dimethoxymethyl	$CDCl_3$	3.48(OCH_3), 5.32(OCHO), 5.63(NH_2), 7.91 and 8.09(ArH)	1075
2-Amino-3-ethoxyalylaminomethyl	DMSO	1.26(CH_2CH_3), 4.24(CH_2CH_3), 4.31(CH_2NH), 6.3(NH_2), 7.71 and 7.87(H5,6), 9.13(CONH)	1183
2-Amino-3-guanidinomethyl/sulphate	DMSO	4.43(CH_2), 6.54($ArNH_2$), 7.82(guan. H), 7.85(H5,6)	1183
2-Amino-3-methoxycarbonyl	$CDCl_3$	8.00(H5), 8.21(H6)	867
2-Amino-3-methyl	DMSO	2.33(CH_3), 6.12(NH_2), 7.64(H6), 7.79(H5)	979
	TFA	2.85(CH_3), 8.08(H6), 8.15(H5)	979
2-Amino-5-methyl	DMSO	2.26(CH_3), 6.02(NH_2), 7.81	1230
2-Amino-3-(methylthio)carbonyl	DMSO	2.32(SCH_3), 7.56(NH_2), 7.99, 8.42(ArH)	1075[b]
2-Amino-5-phenyl	DMSO	5.20(NH_2), 8.03(H6), 8.41(H3)	365a, cf. 377
2-Amino-6-phenyl	$CDCl_3$	4.77(NH_2), 7.86(H5), 8.31(H3)	365a
2,5-Bis(acetoxymethyl)	$CDCl_3$	8.63(H3,6)	867
2-Bromo-6-methoxycarbonyl	$CDCl_3$	8.89(H3), 9.22(H5)	867
2-*s*-Butyl-6-methoxy	CCl_4	0.85(CH_2CH_3), 1.27($CHCH_3$), 1.4–2.0(CH_2CH_3), 2.70($CHCH_3$), 3.94(OCH_3), 7.88 and 7.95(ArH)	614
2-Carbamoyl	DMSO	7.90 and 8.28($CONH_2$), 8.76(H6), 8.90(H5), 9.25(H3)	1086, cf. 1495
2-Carboxy	DMSO	8.76(H5), 8.83(H6), 9.15(H3)	1495
2-Carboxy-3-chloro	$CDCl_3$	8.69(H6), 8.72(H5)	867
	DMSO	8.68(H6), 8.75(H5)	867
2-Carboxy-5-methoxy	DMSO	8.29(H6), 8.71(H3)	867
2-Chloro	CCl_4	8.34(H6), 8.45(H5), 8.57(H3)	687, cf. 900
	$CDCl_3$	8.44(H6), 8.55(H5), 8.66(H3)	733b
	DMSO	8.46(H6), 8.60(H5), 8.71(H3)	1086, cf. 1495

TABLE X.3 *Continued*

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
2-Chloro-6-cyano	$CDCl_3$	8.87, 8.90	744
3-Chloro-2,5-dimethyl	$CDCl_3$	2.50(2-CH_3), 2.60(5-CH_3), 8.24(H6)	979
	TFA	2.82(2-CH_3), 2.93(5-CH_3), 8.51(H6)	979
2-Chloro-3-methoxy	$CDCl_3$	7.90(H5), 8.00(H6)	867
2-Chloro-6-methoxy	$CDCl_3$	8.15(H3,5)	867
2-Chloro-3-methoxycarbonyl	$CDCl_3$	8.59(H5), 8.65(H6)	867
2-Chloro-5-methoxycarbonyl	$CDCl_3$	4.07(CH_3), 8.71 and 9.08(ArH)	838, cf. 867
2-Chloro-6-methoxycarbonyl	$CDCl_3$	8.79(H3), 9.20(H5)	867
2-Chloro-3-methyl	CCl_4	8.14(H6), 8.30(H5)	687
	$CDCl_3$	2.66(CH_3), 8.20(H5), 8.38(H6)	979, cf. 775
	TFA	3.01(CH_3), 8.71(H5), 9.05(H6)	979
2-Chloro-6-methyl	$CDCl_3$	2.56(CH_3), 8.17(H3,5)	775
	CCl_4	8.29(H5), 8.34(H3)	687
2-Chloro-3-morpholinocarbonyl	$CDCl_3$	8.46(H5), 8.56(H6)	867
2-Chloro-6-morpholinocarbonyl	$CDCl_3$	8.63(H3), 8.84(H5)	867
2-Cyano	DMSO	8.86(H5), 8.97(H6), 9.18(H3)	1495
2-Deutero-3-methyl	CCl_4	8.30(H5), 8.37(H6)	687
2-Deutero-6-methyl	CCl_4	8.30(H5), 8.38(H3)	687
2,5-Diacetyl	N.s.g.	2.8, 9.3	616
2,5-Diacetyl-3,6-dimethyl	$CDCl_3$	2.67 and 2.79	1064
2,5-Dicarboxy	DMSO	9.30(H3,6)	867
2,6-Dicarboxy	DMSO	7.34(H3,5)	867
2-Dichloromethyl-5-methoxy	N.s.g.	4.00(OCH_3), 6.70($CHCl_2$), 8.07(H6), 8.52(H3)	685
2,5-Diethoxy	CCl_4	1.35(CH_2CH_3), 4.28(CH_2CH_3), 7.63(ArH)	314
2,3-Difluoro-5-methoxy-6-methyl	CCl_4	2.35(CH_3), 3.95(OCH_3)	851
2,5-Difluoro-3-methoxy-6-methyl	CCl_4	2.35(CH_3), 4.00(OCH_3)	851
2,3-Dihydroxy-5-methyl	DMSO	1.90(CH_3), 6.02(ArH)	483
2,3-Dimethoxycarbonyl	$CDCl_3$	8.68(H5,6)	867

TABLE X.3 *Continued*

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
2,6-Dimethoxycarbonyl	$CDCl_3$	9.46(H3,5)	867
2,3-Dimethoxy-5-methoxymethyl	N.s.g.	3.40(CH_2OCH_3), 3.95($ArOCH_3$), 4.34(CH_2OCH_3), 7.55(H6)	685
3,5-Dimethoxy-2-methoxymethyl	N.s.g.	3.29(CH_2OCH_3), 3.90 and 3.95($ArOCH_3$), 4.38($ArCH_2$), 7.65(ArH)	685
2-Dimethoxymethyl-5-methoxy	N.s.g.	3.31[$CH(OCH_3)_2$], 3.93($ArOCH_3$), 5.25[$CH(OCH_3)_2$], 8.08(H6), 8.20(H3)	685
2,3-Dimethyl	N.s.g.	2.47(CH_3), 8.14(ArH)	331
2,5-Dimethyl	TFA	3.00(CH_3), 9.22(ArH)	98, cf. 979
	$CDCl_3$	2.51(CH_3), 8.33(ArH)	979, cf. 867
2,5-Dimethyl-3-propylthio	Neat	1.02($CH_2CH_2CH_3$), 1.64($CH_2CH_2CH_3$), 2.35 and 2.38($ArCH_3$), 3.10($SCH_2CH_2CH_3$), 7.83(ArH)	764
2,3-Dimorpholinocarbonyl	$CDCl_3$	8.58(H5,6)	867
2-Ethoxy	$CDCl_3$	1.37(CH_3), 4.33(CH_2), 8.05, 8.18	668a
2-Ethoxycarbonyl	DMSO	8.78(H5), 8.86(H6), 9.15(H3)	1495
5-Ethoxycarbonylamino-2,3-diphenyl	$CDCl_3$	1.2(CH_3), 4.27(CH_2), 7.32(Ph), 7.80(NH), 9.36(ArH)	971
2-Ethylamino	CCl_4	1.19(CH_3), 3.33(CH_2CH_3), 5.83(NH), 7.63, 7.79, 7.87(ArH)	668a
2-Ethyl-3-methyl	CCl_4	1.27(CH_2CH_3), 2.50(CH_3), 2.78(CH_2CH_3), 8.20, 8.25(ArH)	614
2-Ethyl-6-methyl	CCl_4	1.30(CH_2CH_3), 2.48(CH_3), 2.75(CH_2CH_3), 8.19(ArH)	614
2-Ethylthio	CCl_4	1.33(CH_3), 3.12(CH_2), 8.08, 8.23, 8.34	668a
2-Fluoro	DMSO	8.43(H6), 8.70(H5), 8.73(H3)	1086, cf. 1495
2-Fluoro-5,6-dimethoxy-3-methyl	CCl_4	2.3(CH_3), 3.95(OCH_3)	851
2-Formyl	DMSO	8.82(H5), 8.88(H6), 9.03(H3)	1495
5-Hydrazino-2,3-diphenyl	MeCN	8.13(ArH), 7.22(Ph)	846

TABLE X.3 *Continued*

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
2-Hydroxy	DMSO	7.30(H5), 7.40(H6), 7.92(H3), 9.79(OH)	1086
3-Hydroxy-2,5-dimethyl	$CDCl_3$	2.30(CH_3-2), 2.41(CH_3-5), 7.15(H6)	979
	TFA	2.67(CH_3-2), 2.90(CH_3-5), 7.63(H6)	98, cf. 979
2-Hydroxy-3-methoxycarbonyl	$CDCl_3$	8.11(H5), 8.24(H6)	867
2-Hydroxy-5-methoxycarbonyl	$CDCl_3$	8.23(H3,6)	867
2-Hydroxy-6-methoxycarbonyl	DMSO	8.29(H3), 8.45(H5)	867
2-Hydroxy-5-methoxycarbonyl-3,6-dimethyl	$CDCl_3$	2.49, 2.73, 3.94, 12.93	1064
2-Hydroxy-3-methyl	DMSO	2.29(CH_3), 7.17(H6), 7.25(H5)	979
	TFA	2.89(CH_3), 7.60(H6), 8.08(H5)	979
2-Hydroxy-5-phenyl	DMSO	7.26–7.65, 7.89–8.05, 8.06, 8.14	377
	DMSO	8.03(H6), 8.13(H3), 12.46(OH)	365a
2-Hydroxy-6-phenyl	DMSO	8.04(H5), 8.32(H3), 12.00(OH)	365a
2-Iodo	DMSO	8.48(H5), 8.64(H6), 8.90(H3)	1495
3-Mercapto-2,5-dimethyl	TFA	2.60(CH_3), 2.85(CH_3), 7.55(ArH)	905
2-Methoxy	DMSO	3.96(CH_3), 8.22(H5), 8.22(H6), 8.31(H3)	1086, cf. 1094, 1495
	CCl_4	8.02(H6), 8.07(H5), 8.19(H3)	687
2-Methoxycarbonyl	DMSO	3.99(OCH_3), 8.86(H6), 8.93(H5), 9.22(H3)	1086, cf. 1495
	D_2O	4.02(OCH_3), 8.78(H6), 8.88(H5), 9.27(H3)	1136
	12 *N* D_2SO_4	4.14(OCH_3), 9.16(H5), 9.51(H3), 9.60(H6)	1136
3-Methoxy-2,5-dimethyl	$CDCl_3$	2.39(CH_3), 2.40(CH_3), 3.94(OCH_3), 7.83(ArH)	979
2-Methoxy-3-methoxycarbonyl	$CDCl_3$	8.26(H5), 8.33(H6)	867
	DMSO	8.33(H5), 8.48(H6)	867
2-Methoxy-5-methoxycarbonyl	$CDCl_3$	8.26(H3), 8.86(H6)	867
	DMSO	8.93(H3), 9.03(H6)	867

TABLE X.3 *Continued*

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
2-Methoxy-6-methoxycarbonyl	$CDCl_3$	8.37(H3), 8.81(H5)	867
2-Methoxy-3-methyl	CCl_4	7.79(H6), 7.88(H5)	687
	N.s.g.	2.42(CCH_3), 3.91(OCH_3), 7.87, 7.95	686
	DMSO	2.40(CH_3), 3.94(OCH_3), 8.02(H5), 8.04(H6)	979
	TFA	2.80(CH_3), 4.27(OCH_3), 8.09(H6), 8.72(H5)	979
2-Methoxy-5-methyl	CCl_4	7.83(H6), 8.05(H3)	687
	N.s.g.	2.40(CCH_3), 3.86(OCH_3), 7.86 and 8.04(H3,6)	686
2-Methoxy-6-methyl	CCl_4	7.91(H5), 7.96(H3)	687
	N.s.g.	2.37(CH_3), 3.86(OCH_3), 7.88 and 7.94(H3,5)	686
2-Methoxy-3-morpholinocarbonyl	$CDCl_3$	8.18(H5,6)	867
	DMSO	8.28(H5), 8.36(H6)	867
2-Methoxy-6-morpholinocarbonyl	$CDCl_3$	8.29(H3), 8.47(H5)	867
	DMSO	8.40(H3,5)	867
2-Methyl	$CDCl_3$	2.57(CH_3), 8.38(H5), 8.45(H6), 8.57(H3)	1086, cf. 733b
	TFA	3.12(CH_3), 9.40(H5,6), 9.5(H3)	98
	DMSO	8.40(H5), 8.46(H6), 8.50(H3)	1495
2-Methylamino	DMSO	7.65(H5), 7.94(H3,6)	1495
2-Methyl-3-methylamino	CCl_4	2.28(CH_3), 2.98($NHCH_3$), 4.35(NH), 7.62, 7.83(ArH)	844
1-Methyl-2-oxo-1,2-dihydro	$CDCl_3$	3.53(CH_3), 7.12, 7.33, 8.15	666
2-Methylsulfinyl	$CDCl_3$	2.90(CH_3), 8.60(H6), 8.71(H5), 9.23(H3)	1080
	DCl–D_2O	3.25(CH_3), 9.08(H5), 9.35(H3), 9.70(H6)	1080
2-Methylsulfonyl	$CDCl_3$	3.31(CH_3), 8.84(H6), 9.01(H5), 9.45(H3)	1079
	9 *M* D_2SO_4	3.57(CH_3), 9.32(H5), 9.61(H3), 9.86(H6)	1079

TABLE X.3 *Continued*

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
2-Methyl-3-propyl	CCl_4	0.99(CH_2CH_3), 1.75(CH_2CH_3), 2.50(CH_3), 2.74($CH_2CH_2CH_3$), 8.19 and 8.21(ArH)	614
2-Methyl-6-propyl	CCl_4	0.97(CH_2CH_3), 1.75(CH_2CH_3), 2.49(CH_3), 2.70($CH_2CH_2CH_3$), 8.17 and 8.18(ArH)	614
2-Methylthio	$CDCl_3$	2.61(CH_3), 8.29(H5), 8.46(H6), 8.58(H3)	1079
	5 *N* DCl	2.81(CH_3), 8.68(H5), 9.03(H3), 9.3(H6)	1079
2,3,5-Trifluoro-6-methyl	CCl_4	2.5	851
2,3,5-Trimethoxy-6-methyl	N.s.g.	2.21, 3.83, 3.85, 3.88	685
Unsubstituted/1-oxide	$CDCl_3$	8.11(H3,5), 8.44(H2,6)	1498
2-Amino/1-oxide	D_2O	7.85(H5), 8.11(H6), 8.33(H3)	1136
	3 *N* D_2SO_4	8.05(H5), 8.51(H3), 8.62(H6)	1136
	30 *N* D_2SO_4	8.23(H5), 8.90(H6), 9.13(H3)	1136
4-Amino/1-oxide iodide	DMSO	8.66(NH_2), 8.83	610
2-Amino-3-chloro/1-oxide	DMSO	7.38(NH_2), 7.72(H5), 8.36(H6)	906
2-Amino-5-methyl/1-oxide	DMSO	2.26(CH_3), 6.68(NH_2), 8.04	1230
2-Amino-5-phenyl/1-oxide	DMSO	7.05(NH_2), 7.23–7.62, 7.78–8.05, 8.22, 8.74	377
2-Azido/1-oxide	$CDCl_3$	8.08(H5), 8.16(H3), 8.25(H6)	1261
2-Carbamoyl/1-oxide	DMSO	8.48(H6), 8.68(H5), 9.17(H3)	838
3-Carbamoyl/1-oxide	DMSO	8.47(H6), 8.55(H2), 8.59(H5)	838
2-Carboxy/1-oxide	DMSO	8.60(H6), 8.85(H5), 9.17(H3)	838
3-Carboxy/1-oxide	DMSO	8.51(H6), 8.64(H2,5)	838
2-Chloro/1-oxide	DMSO	8.51(H6), 8.58(H5), 8.90(H3)	838
	$CDCl_3$	8.22(H6), 8.36(H5), 8.62(H3)	900, cf. 733b
	D_2O	8.48(H6), 8.57(H5), 8.87(H3)	1136
	12 *N* D_2SO_4	8.74(H5), 8.91(H6), 9.13(H3)	1136
3-Chloro/1-oxide	DMSO	8.38(H6), 8.44(H5), 8.70(H2)	838
	$CDCl_3$	7.96(H6), 8.12(H2), 8.22(H5)	900, cf. 733b
2-Cyano/1-oxide	DMSO	8.58(H6), 8.77(H5), 9.15(H3)	838

TABLE X.3 *Continued*

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
3-Cyano/1-oxide	DMSO	8.61(H6), 8.69(H5), 9.12(H2)	838
2,6-Diamino/1-oxide	DMSO	6.6(NH_2), 7.33(H3,5)	465
2-Methoxy/1-oxide	DMSO	8.18(H6), 8.36(H5), 8.50(H3)	838
	D_2O	4.25(OCH_3), 8.32(H6), 8.33(H5), 8.61(H3)	1136
	7 *N* D_2SO_4	4.33(OCH_3), 8.53(H5), 8.74(H3), 8.84(H6)	1136
	35 *N* D_2SO_4	4.74(OCH_3), 8.90(H5), 9.25(H3), 9.29(H6)	1136
3-Methoxy/1-oxide	DMSO	7.97(H6), 8.06(H2), 8.16(H5)	838
3-Methoxycarbonyl/1-oxide	DMSO	8.62(H6), 8.67(H5), 8.78(H2)	838
2-Methyl/1-oxide	$CDCl_3$	8.27(H6), 8.36(H5), 8.49(H3)	733b, cf. 733a
	D_2O	2.36(estimated)(CH_3)	734
3-Methyl/1-oxide	$CDCl_3$	8.04(H5), 8.09(H2), 8.40(H6)	733b
	D_2O	2.49(estimated)(CH_3)	734
2-Sulfo/1-oxide	DMSO	8.43(H6), 8.60(H5), 8.95(H3)	838
3-Sulfo/1-oxide	DMSO	8.33(H5,6), 8.51(H2)	838
3-Trimethylsilyloxy/1-oxide	$CDCl_3$	0.39[$Si(CH_3)_3$], 7.73, 7.80, 7.98	1034
2-Amino/1,4-dioxide	D_2O	7.72(H5), 8.13(H3), 8.22(H6)	1136
	5 *N* D_2SO_4	7.77(H5), 8.33(H6), 8.34(H3)	1136
	30 *N* D_2SO_4	8.20(H5), 8.76(H6), 9.03(H3)	1136
2-Carboxy/1,4-dioxide	D_2O	8.27(H5), 8.31(H6), 8.46(H2)	739
2,5-Dimethyl/1,4-dioxide	$CDCl_3$	2.40(CH_3), 8.06(ArH)	733a[b]
2-Diethoxymethyl/1,4-dioxide	$CDCl_3$	1.26(CH_3), 2.05(H6), 3.78(CH_2), 5.82(CH), 7.96(5H), 8.36(3H) (?)	739
2-Methoxy/1,4-dioxide	D_2O	2.90(OCH_3), 7.62(H5), 7.81(H3), 8.02(H6)	1136
	3 *N* D_2SO_4	2.90(OCH_3), 7.69(H5), 7.95(H6), 8.20(H3)	1136

TABLE X.3 *Continued*

Pyrazine	Solvent[a]	Chemical shift (δ)	Refs.
2-Methyl/1,4-dioxide	D_2O	2.40(CH_3), 8.25(H5), 8.38(H6), 8.46(H3)	739
Unsubstituted/MeI	DMSO	4.60(CH_3)	666
(CD_3I)	DMSO	9.16(H2,6), 9.52(H3,5)	1499
2-Amino/1-MeI	DMSO	3.82(CH_3)	666
3-Amino/1-MeI	DMSO	4.34(CH_3)	666
	D_2O	4.27(CH_3), 7.90(H6), 8.12(H2), 8.57(H5)	704
3-Carbamoyl/1-MeI	DMSO	4.64(CH_3)	666
3-Chloro/1-MeI	DMSO	4.54(CH_3)	666
3-Dimethylamino/1-MeI	D_2O	3.22[$N(CH_3)_2$], 4.30(CH_3), 7.84(H5), 8.22(H2), 8.63(H6)	936
3-Fluoro/1-MeI	DMSO	4.58(CH_3)	666
3-Methoxy/1-MeI	DMSO	4.47(NCH_3)	666
2-Methyl/1-MeI	DMSO	4.42(NCH_3)	666
3-Methyl/1-MeI	DMSO	4.50(NCH_3)	666

[a] Solvents: DMSO, hexadeuterodimethylsulfoxide; TFA, deuterotrifluoroacetic acid; n.s.g., no solvent given.
[b] Proton magnetic spectra of more complex molecules are given in this reference.

whereas a σ-electron contribution of ~ 30% appeared likely for the *meta*-benzylic coupling (687). Proton chemical shifts have been correlated with Hammett–Taft σ-constants in 2-substituted pyrazines in carbon tetrachloride (1501) and in dimethyl sulfoxide (1495). A substituent-ring "second-order" mesomeric interaction was proposed to explain the correlation of the proton meta to electron-donating substituents (1495).

Nuclear magnetic resonance parameters of disubstituted pyrazines have been correlated with chemical structures (867). The coupling constants of 2,3-, 2,5-, and 2,6-disubstituted pyrazines were found to be 2.5–3.0, 1.1–1.4, and 0 Hz, respectively, and the values were not influenced by the kind of substituents (867). Methyl–methyl proton spin–spin coupling constants in 2,5- and 2,6-dimethylpyrazines have been determined (1502).

Kinetics of hydrogen–deuterium exchange in pyrazine *N*-oxide dissolved in liquid trideuteroammonia or a solution of potassium dideuteroamide in trideuteroammonia have been studied (747). The relative sign of the proton–proton couplings in diazine *N*-oxides (including pyrazine *N*-oxide) (1498) and the n.m.r. spectra of *N*-methyldiazonium iodides (1499) have been investigated. In the p.m.r. spectra of some 2,5-dialkylpyrazine *N*-oxides (except 2,5-dimethylpyrazine 1-oxide) the signals of the α-protons of the side chain at C_2 appeared at lower field than that of pyrazine, and this was attributed to the anisotropic effect of the *N*-oxide group (733a). Lanthanide induced shift (LIS) reagents have been used in an n.m.r. study to unambiguously identify isomers from *N*-oxidations of chloropyrazines with peroxysulfuric acid (900).

The ^{2}H and ^{14}N relaxation rates and the deuterium quadrupole coupling constant for pyrazine have been reported (1503) but the motion of this molecule could not be analyzed. ^{14}N–H Spin couplings in pyrazine methiodides have been determined (704).

The ^{13}C nuclear magnetic resonance spectra have been obtained for pyrazine (1504), and 10 monosubstituted pyrazines (1505); and a ^{13}C n.m.r. study has been made on the adduct of phenyllithium with pyrazine (720a).

^{19}F Nuclear magnetic resonance spectroscopy has been applied to a number of fluoropyrazines (494–496, 850, 851, 885, 888, 914) and fluorohydropyrazines (796).

4. INFRARED, MASS, AND OTHER SPECTRA OF PYRAZINES

Some references to published infrared and mass spectra of simple pyrazines are presented without discussion in Table X.4. They are references 51, 53, 61, 69a, 76, 80, 98, 108, 183, 184, 314, 331, 355, 365a, 367, 368, 377, 433a, 465, 500, 543, 575, 625, 626, 652, 668a, 678, 679, 681, 686, 738, 739, 744, 760, 775, 831, 832, 834, 838, 839, 844, 846, 851, 867, 884, 905, 906, 971, 975, 985, 986, 1034, 1035, 1075, 1084, 1117, 1146, 1183, 1189, 1230, 1261, 1266, 1278, 1280, 1327, 1435, and 1506–1511. References to some other spectra are summarized briefly as follows. Raman spectra have been measured for pyrazine (1506, 1512), for 2,3-,

TABLE X.4 REFERENCES TO INFRARED AND MASS SPECTRA OF PYRAZINES

Pyrazine	References	
	Infrared Spectra	Mass Spectra
Unsubstituted	626, 1506	53, 69a, 76, 975, 1507
2-Acetamido-3-formyl	1075	
2-Acetamido-3-hydrazinocarbonyl	433a	
2-Acetamido-3-methoxycarbonyl	433a	
2-Acetoxy	738	
2-Acetoxymethyl	738	
2-Acetoxymethyl-5-methyl	760	
2-Acetoxymethyl-6-methyl	760	
2-Acetyl	575, 844[a]	69a, 678, 844
2-Acetyl-3-ethyl		678
2-Acetyl-3-methoxy	844	844
2-Acetyl-3-methyl		678
2-Acetyl-5-methyl		678
2-Amino	575, 1508, cf. 1189	975
2-Amino-3-aminomethyl	1183	
2-Amino-5-carboxy	744	
2-Amino-6-carboxy	744	
2-Amino-3-chloro	838	
2-Amino-6-chloro	744	
2-Amino-3-cyano	1183	
2-Amino-3-ethoxyalylaminomethyl	1183	
2-Amino-5-ethoxycarbonyl	744	
2-Amino-6-ethoxycarbonyl	744	
2-Amino-3-hydroxy	832	
2-Amino-3-methoxycarbonyl	433a	
2-Amino-5-methyl	1230	
2-Amino-3-(methylthio)carbonyl	1075	
2-Amino-5-phenyl	365a, 377	
2-Amino-6-phenyl	365a	
2-Amino-3,5,6-trifluoro	851	
2-Benzyl-3-chloro	80	80
2-Benzyl-3-methoxy	80	80
6-Benzyloxy-1-methyl-2-oxo-1,2-dihydro	832	
2,6-Bis(ethoxymethyl)	679	
2-Bromo-6-methoxycarbonyl	867	
2-Bromo-3,5,6-trifluoro	851	
2-Carbamoyl	575	975
2-Carbamoyl-6-chloro	744	
2-Carbamoyl-6-methoxy	985	
2-Carboxy	575, 1266, 1278, 1509	975
2-Carboxy-3-chloro	838	
2-(2′-Carboxyhydrazino) (?)	971	
2-Carboxy-6-methoxy	985	
2-Carboxy-3-methoxycarbonyl	1278, 1509	
2-Chloro	575	
2-Chlorocarbonyl-3-methoxycarbonyl	1278	
2-Chloro-6-cyano	744	
2-Chloro-5-methoxycarbonyl	838	

TABLE X.4 *Continued*

Pyrazine	References	
	Infrared Spectra	Mass Spectra
2-Chloro-6-methoxycarbonyl	744	
2-Chloro-3-methyl	681	
2-Chloro-6-methyl	681	
2-Chloro-3-morpholinocarbonyl	838	
2-Chloro-5-phenyl	377	
2-Chloro-6-phenyl	365a	
2-Chloro-3,5,6-trifluoro	851	
2-Cyano	575	
2-Cyano-3-ethoxalylamino	1183	
2-Cyano-5(and 6)-methyl	1327	
2-Deuterocarboxy	1509	
2-Deuterocarboxy-3-methoxycarbonyl	1509	
2,5-Diacetoxymethyl	760	
2,3-Diamino-5,6-diphenyl	834	
2,3-Dicarboxy	1278, 1509	
2,3-Dicarboxy(anhydride)	1278	
2,3-Dichloro	831	
2,5-Dichloro	831	
2,6-Dichloro	831	
2,6-Dichloro-3,5-difluoro	851	
2,3-Dicyano	355	
2,3-Dicyano-5-methyl	355, 1435	
2,3-Dideuterocarboxy	1509	
2,5-Diethoxy	314[a]	
2-Diethoxyphosphinothioyloxy	1117	
2,3-Dihydroxy	832	
2,5-Di(hydroxy-*t*-butyl)	500	
2,3-Dimethoxycarbonyl	183, 184, 1278	
2,5-Dimethoxycarbonyl	184	
2,3-Dimethyl	51, 53, 686	53, 69a, 331, 1507
2,5-Dimethyl	51, 53, 686	53, 69a, 76, 975, 1510
2,6-Dimethyl	51, 53, 686	53, 69a, 76, 1510
2-Ethoxy	668a	668a
2-Ethoxycarbonyl	575	
5-Ethoxycarbonylamino-2,3-diphenyl	971	
2-Ethoxy-3-ethyl	368	368
2-Ethoxy-3-methyl	679	
2-Ethyl	53	53, 69a, 76
2-Ethylamino	668a	668a
2-Ethyl-3-hydroxy	367[a]	367
2-Ethyl-3-methoxy	367[a]	367
2-Ethyl-1-methyl-2-oxo-1,2-dihydro		367
2-Ethylthio	668a	668a
2-Fluoro	884	
2-Formyl	1077	
2-Hydrazinocarbonyl-6-methoxy	986	
3-Hydrazino-2,5-dimethyl	775	
5-Hydrazino-2,3-diphenyl	846	
2-Hydrazino-3-methyl	775	

TABLE X.4 *Continued*

Pyrazine	References	
	Infrared Spectra	Mass Spectra
2-Hydroxy	108, 1084	
2-Hydroxy-6-methoxy	738, 832	
2-Hydroxy-5-methoxycarbonyl	838	
2-Hydroxy-6-methoxycarbonyl	838	
2-Hydroxymethyl	625	
2-Hydroxymethyl-5-methyl	760	
2-Hydroxymethyl-6-methyl	760	
2-Hydroxy-5-phenyl	365a, 377	
2-Hydroxy-6-phenyl	365a	
2-Hydroxy-3-propyl	367	367
2-Isobutyl-3-methoxy		61
2-Mercapto	1146	
2-Mercapto-3-methyl	905	
2-Methoxy		975
2-Methoxycarbonyl	1278	
2-Methoxy-6-methoxycarbonyl	839, 867, 985	
2-Methoxy-6-(*C*-methoxy-*C*-iminomethyl)	986	
2-Methoxy-3(5 and 6)-methyl	686	69a, 1511
2-Methoxy-3-morpholinocarbonyl	867[a]	
2-Methyl	51, 575, 626, 652	53, 69a, 76, 975, 1510
2-Methyl-3-methylamino	844[a]	844
2-Methyl-6-methylamino	844[a]	
2-Methyl-3-methylthio		69a, 1511
2-Methyl-6-methylthio		1511
2-Methylthio	1146	
1-Methyl-2-thio-1,2-dihydro	1146	
Tetrabromo	851	
Tetrachloro	851	
Tetrafluoro	851	
2,3,5-Trichloro-6-fluoro	851	
2,3,5-Trifluoro-6-hydrazino	851	
2,3,5-Trifluoro-6-hydroxy	851	
2,3,5-Trifluoro-6-methoxy	851	
2,3,5-Trifluoro-6-methyl	851[a]	
Trimethoxycarbonyl	1280	
Trimethyl		69a
2-Vinyl		69a
Unsubstituted/1-oxide	575, 625, 626	975
2-Acetoxymethyl/1-oxide	738	
3-Acetoxymethyl/1-oxide	738, 760	
2-Acetyl/1-oxide	575	
2-Amino/1-oxide	1189	975
3-Amino/1-oxide	1189	975
2-Amino-3-chloro/1-oxide	906	
2-Amino-5-methyl/1-oxide	1230	
2-Amino-5-phenyl/1-oxide	377	
2-Azido/1-oxide	1261	
2-Carbamoyl/1-oxide	838	975

TABLE X.4 *Continued*

Pyrazine	References	
	Infrared Spectra	Mass Spectra
3-Carbamoyl/1-oxide	838, 839	975
2-Carboxy/1-oxide	838	975
3-Carboxy/1-oxide	543, 838, 1266	838, 975
2-Chloro/1-oxide	838	
3-Chloro/1-oxide	575	
2-Cyano/1-oxide	838	
3-Cyano/1-oxide	575, 838	
2,3-Diamino/1-oxide	906	
2,6-Diamino/1-oxide	465	
2,5-Dimethyl/1-oxide	625	
3-Ethoxycarbonyl/1-oxide	575	
3-Hydroxy/1-oxide	838, cf. 108	
2-Hydroxy-3,6-diisobutyl/1-oxide	98	
3-Hydroxymethyl/1-oxide	738	
3-Mercapto/1-oxide	1035	
3-Mercapto-2-methyl/1-oxide	905	
2-Methoxy/1-oxide	838	975
3-Methoxy/1-oxide	838	975
3-Methoxycarbonyl/1-oxide	838	
2-Methyl/1-oxide	575, 625, 626, 738, 838	975
3-Methyl/1-oxide	575, 625, 738, 838	975
4-Methyl-3-oxo-3,4-dihydro/1-oxide	1035	
3-(D-*arabo*-Tetrahydroxybutyl)/1-oxide	543	
3-Trimethylsilyloxy/1-oxide	1034	
Unsubstituted/1,4-dioxide	575, 625, 626	975
2-Acetoxymethyl/1,4-dioxide	738	
2-Amino/1,4-dioxide	1189	
2-Carboxy/1,4-dioxide	739	
2,5-Dimethyl/1,4-dioxide		975
2-Methyl/1,4-dioxide	575, 625, 626	975

[a] Spectra of additional, more complex pyrazines also given.

2,5-, and 2,6-dimethylpyrazines and 2-methoxy-3(5 or 6)-methylpyrazine (686), and for pyrazine absorbed on silica (1513). Raman spectra of pyrazine on a series of alkali and alkali earth cation exchange X-type zeolites have been recorded (1514). Electron spin resonance studies have been made of pyrazine anion radical (583, 596, 752, 1515) pyrazine 1-oxide and 1,4-dioxide anion radicals (750a, 751), the cation radical of pyrazine 1,4-dioxide (753), cation and anion radicals of pyrazine 1-oxide and 1,4-dioxide (750b), the anion radicals of 2,3-dimethylpyrazine and 2,5-di-*t*-butyl-3-isopropylpyrazine (596a), and diprotopyrazine cation radical (1516).

Phosphorescence (1477, 1492, 1517) and fluorescence (1518) spectra of pyrazine have been studied. Magnetic circular dichroism (1519) and induced circular dichroism (1520) of pyrazine have been measured. The photoelectron spectra of pyrazine, 2,6-dimethylpyrazine, and tetramethylpyrazine have been compared

(585); the multiphoton ionization spectra of pyridine and pyrazine have been taken and assigned (1521, 1522); and the radiationless decay in pyrazine has been studied by opto-acoustic spectroscopy (1523).

Photoelimination reactions of 2-butylpyrazine and 2-β-hydroxyethylpyrazine to give 2-methylpyrazine have been examined (722).

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CHAPTER XI

The Reduced Pyrazines

The chemistry of hydropyrazines (including piperazines) has not been treated in the comprehensive manner used for the pyrazines in this volume because it is, strictly speaking, beyond the scope of this work. To provide an entry to the literature, references to reviews of the older literature are summarized in Table XI.1 (35–39, 1524–1534), and a selection of preparations and reactions, drawn from more recent publications are discussed.

Pratt (36) in 1957 published a comprehensive review which included reduced pyrazines (di- and tetrahydropyrazines, piperazines, and piperazinones), and the literature prior to 1957 is generally not further examined.

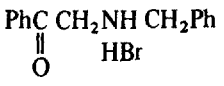
1. DI- AND TETRAHYDROPYRAZINES

Early publications in this area have been reviewed by Pratt (1957) (36) and Ramage and Landquist (1959) (37), and updated to about 1971 by Cheeseman and Werstiuk (39). Generally only significant publications since, or not mentioned in, these reviews are discussed below.

A. 1,2-Dihydropyrazines

(1) *Preparation*

Mason and Winder (26) reported that the base-catalyzed cyclodehydration of *N*-phenacylbenzylamine hydrobromide (**1**) gave 1,4-dibenzyl-2,5-diphenyl-1,4-dihydropyrazine (**2**) but Chen and Fowler (1535) showed that the product was 1,2-dibenzyl-3,6-diphenyl-1,2-dihydropyrazine (**3**) (20%). Further investigation by



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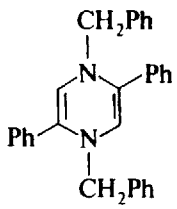

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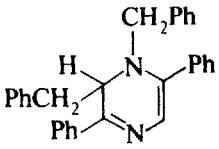

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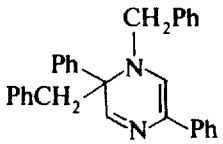
TABLE XI.1 REVIEWS OF REDUCED PYRAZINES

Author(s) (Total References Cited)	Year Published	Reduced Pyrazines Reviewed	Refs.
Krems and Spoerri	1947	2,5-Dihydropyrazines, piperazines	35
Pratt (170)	1957	1,2-, 2,3-, 2,5-, and 1,4-Dihydropyrazines, tetrahydropyrazines, piperazin-2-ones, piperazine-2,3-, 2,5-, and 2,6-diones, piperazinetetraones, piperazines	36
Ramage and Landquist	1959	1,2-, 2,3-, 2,5-, and 1,4-Dihydropyrazines, tetrahydropyrazines, piperazin-2-ones, piperazine-2,3- and 2,5-diones, piperazinetri- and tetraones, piperazines	37
Augustyniak (101)	1966	Piperazine-2,5-diones	1524
Augustin (520)	1966	Piperazine-2,5-diones	1525
Mjos (39)	1968	Piperazines	1526
Cheeseman and Werstiuk	1972	1,2-, 2,3-, 2,5-, and 1,4-Dihydropyrazines, tetrahydropyrazines	39
Sammes (258)	1975	Piperazine-2,5-diones	1527
Schmidt	1975	1,4-Dihydropyrazines	1528
Kubo (31)	1976	Piperazine-2,5-diones	1529
Johne and Groger (256)	1977	Piperazine-2,5-diones	1530
Armarego (54, all brief)	1977	2,3- and 1,4-Dihydropyrazines, piperazine-2,5-diones, piperazines	1531
Mjos (153)	1978	Piperazines (and morpholines)	1532
Anteunis (160)	1978	Piperazine-2,5-diones	1533
Porter (all very brief)	1979	1,2-, 2,3-, 2,5-, and 1,4-Dihydropyrazines, tetrahydropyrazines, piperazine-2,5-diones	1534

Lown and Akhtar (1536) revealed a second product from this reaction, namely 1,2-dibenzyl-2,5-diphenyl-1,2-dihydropyrazine (59%) (**4**). Lown and Akhtar (1537) also showed that the self-condensation of *N*-isopropylphenacylamine at room temperature gave 1,2-diisopropyl-2,5-diphenyl-1,2-dihydropyrazine (and proposed 1,4-diisopropyl-2,5-diphenyl-1,4-dihydropyrazine as an intermediate). In a similar series of reactions of *N*-alkylphenacylamines, the thermally induced self-condensations were followed by regiospecific 1,3-shifts to substituted carbon atoms to give in good yields 1,2-dialkyl-2,5-diphenyl-1,2-dihydropyrazines at temperatures ranging from ambient to 140° (1536).

The reactions of *N*-benzyl-*N*,*N*-diphenacylamine hydrobromide with benzylamine at 120–130° was also reported to give 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine



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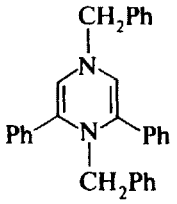

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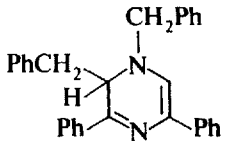
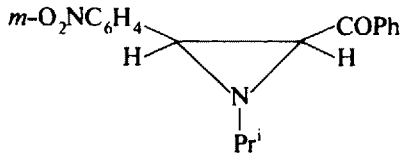


(6)

(5) (26), but Chen and Fowler (1535) showed it to be 1,2-dibenzyl-3,5-diphenyl-1,2-dihydropyrazine (6), and 1,3-benzyl migration from the initially formed but unisolated 1,4-dibenzyl-1,4-dihydro isomer was postulated (1535). By working at lower temperatures (40°), Lown and Akhtar (1538) were able to isolate the reactive intermediate, 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine (5), as in the case of more stable 1,4-dialkyl-1,4-dihydropyrazines (1540); this intermediate (5) rearranged in degassed benzene at 55° to give compound (6) (> 95%) and the kinetics and mechanism were examined (1538, 1539).

Heating of a solution of pure *cis*-2-benzoyl-1-isopropyl-3-(*m*-nitrophenyl)aziridine (7) in dry acetonitrile under reflux for 24 hours gave 1,2-diisopropyl-2,5-diphenyl-1,2-dihydropyrazine (10%) (8) together with other products; and the pure trans isomer similarly treated also gave the dihydropyrazine (12.5%) (1537). Reaction of 3-phenylazirine (9) with an equimolar amount of molybdenum hexacarbonyl in tetrahydrofuran at room temperature of 24 hours gave 2,5-diphenyl-1,6-dihydropyrazine (together with 2,5-diphenylpyrazine and 2,5-diphenyl-3,6-dihydropyrazine) (505b, cf. 1541).



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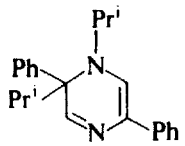

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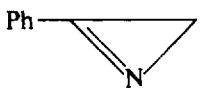
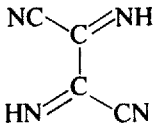


(9)

Condensation of diiminosuccinonitrile (10) with 3-methylbutan-2-one gave 5,6-dicyano-2,2,3-trimethyl-1,2-dihydropyrazine (11) (11%) and 4,5-dicyano-1-isopropyl-2-methylimidazole (7.6%) (383). Cyclization of α-cyanoalkyldiaminomaleonitriles (12, e.g., R = Me) with phosphorus pentoxide in refluxing ethanol has been shown to give 5,6-dicyano-3-hydroxy(-2-substituted)-1,2-dihydropyrazines (13, e.g., R = Me) (489, 490) and the conversion of benzylidenediaminomaleonitrile to 5-carbamoyl-6-cyano- and 6-carbamoyl-5-cyano-2,3-diphenyl-1,2-dihydropyrazines has been described in Section II.3 (395a).



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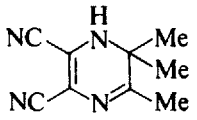

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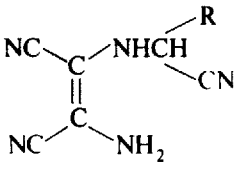

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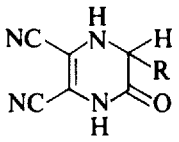

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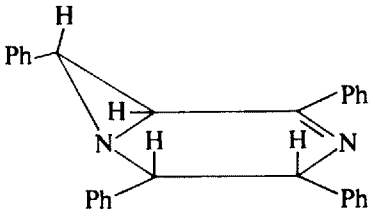


(14)

Treatment of (2α,3α,6α,7α)-2,3,5,7-tetraphenyl-1,4-diazabicyclo[4,1,0]hept-4-ene (**14**) with potassium *t*-butoxide in benzene has been reported to give 1-benzyl-2,3,5-triphenyl-1,2-dihydropyrazine (1542).

Catalytic reduction (Pd/C) of di-, tri-, and tetraalkoxycarbonylpyrazines [see Section IX.2C(3)] afford 1,2-, not 1,4-dihydropyrazines, as the major products (1326).

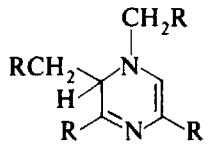
The reactions of pyrazine with sodium amide in liquid ammonia to give the anion of 2-amino-1,2-dihydropyrazine (608), and of 3-substituted 1-methylpyrazinium ions with liquid ammonia to give 3(or 5)-substituted 2-amino-1-methyl-1,2-dihydropyrazines (609) have been described in Section IV.1C. Similar reactions of pyrazine with phenyllithium at -45° in tetrahydrofuran (720a) and of 1,2,5-trimethylpyrazinium salts in liquid ammonia with nitromethide and ethanethiolate anions (721) have been described in Section IV.2C(8).

(2) *Reactions*

Pyrolysis of 1,2-dibenzyl-3,6-diphenyl-1,2-dihydropyrazine (**3**) gave a mixture of 2,5-diphenylpyrazine, 3-benzyl-2,5-diphenylpyrazine, 2,5-dibenzyl-3,6-diphenylpyrazine, and toluene (1535), and pyrolysis of 1,2-dibenzyl-3,5-diphenyl-1,2-dihydropyrazine formed a mixture of 2,6-diphenylpyrazine and 2-benzyl-3,5-diphenylpyrazine (1535). 1-Benzyl-2,3,5-triphenyl-1,2-dihydropyrazine refluxed with palladium on charcoal in benzene gave 2,3,5-triphenylpyrazine (1542) and the

lithium salt of 2-phenyl-1,2-dihydropyrazine was oxidized by air to give 2-phenylpyrazine (720a). Several reactions of some 1,2-dihydropyrazines with dimethyl acetylenedicarboxylate have been described (1543–1545).

Under anion-generating conditions the 1-benzyl-1,2-dihydropyrazines (**15**) avoid the formation of systems with formally delocalized 8π-electrons (1546).

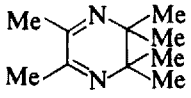


(**15**)

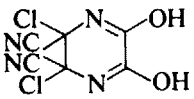
B. 2,3-Dihydropyrazines

(1) *Preparation*

The preparation of some 2,3-dihydropyrazines from α,β-dicarbonyl compounds with α,β-diamino compounds has been recorded in Section II.2 (330, 330a, 331, 333, 334, 338–344, 349, 356, 357), with further data given in references 6, 337, 345, and 1547–1549. In addition hexamethyl-2,3-dihydropyrazine (**16**) has been prepared from 2,3-diamino-2,3-dimethylbutane and butane-2,3-dione (1550). Condensation of oxalyl chloride with diiminosuccinonitrile (**10**) in ether has been shown to give 2,3-dichloro-2,3-dicyano-5,6-dihydroxy-2,3-dihydropyrazine (**17**) (383).



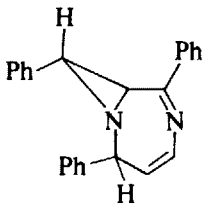
(**16**)



(**17**)

Ultraviolet irradiation (1551, 1552) and thermolysis (1552) of 2,6,8-triphenyl-1,5-diazabicyclo[5,1,0]octa-3,5-diene (**18**) formed a mixture containing 2,5-diphenyl-*trans*-3-styryl-2,3-dihydropyrazine; and irradiation of *endo*- and *exo*-2,4,6-triphenyl-1,3-diazabicyclo[3,1,0]hex-3-ene in benzene at 50° gave *cis*-2,3,5-triphenyl-2,3-dihydropyrazine (**19**) (1553, cf. 1554), whereas in methanol almost no dihydropyrazine (**19**) was formed (1555). Irradiation of a solution of *endo*-2,4,6-triphenyl-1,3-diazabicyclo[3,1,0]hex-3-ene (**20**) in benzene at 50° formed *cis*-2,3,5-triphenyl-2,3,-dihydropyrazine (1556); and irradiation of *cis*-amarine (**21**) in acetonitrile gave a mixture of products from which *trans*-2,3,5,6-tetraphenyl-2,3-dihydropyrazine (2%) was isolated (1557).

Fluorination of tetrafluoropyrazine with a mixture of cobalt and calcium fluorides at 80° gave 2,2,3,3,5,6-hexafluoro-2,3-dihydropyrazine (**22**) (886), and chlorination of tetrafluoropyrazine gave 10% 5,6-dichloro-2,2,3,3-tetrafluoro-2,3-



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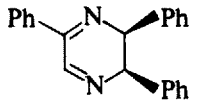

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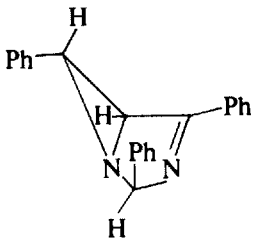

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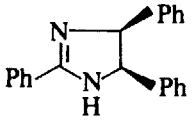
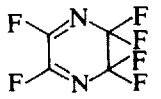


(21)

dihydropyrazine (**23**) [and 50% 3,6-dichloro-2,2,5,5-tetrafluoro-2,5-dihydropyrazine (**24**)] (796). The bromination of 2-methoxy-3-sulfanilamidopyrazine in methanol to 5-(4′-amino-3′,5′-dibromobenzene)sulfonimido-6-hydroxy-2,3-dimethoxy-2,3,4,5-tetrahydropyrazine (**25**) has been reported in Section V.5D(2) (815, 816).



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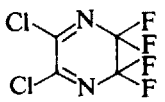

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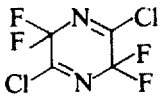

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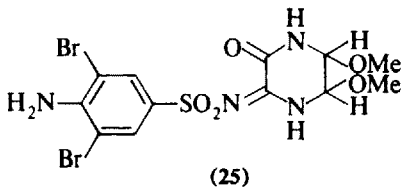


(25)

(2) *Reactions*

Dehydrogenations of some 2,3-dihydropyrazines to the corresponding pyrazines have been effected as follows: 2,3-dimethyl-5,6-dihydro [reflux with potassium hydroxide in ethanol (333); heat in ethylene glycol at 197° (653, 1558); reflux with potassium hydroxide and manganous oxide in ethanol (633a); vapor phase reaction in the presence of a catalyst, such as copper chromite, and clay (472); heat

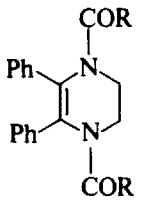
with aqueous potassium hydroxide and mercuric chloride (635); heat with copper chromite (331)]; 2,3,5-trimethyl-5,6-dihydro (reflux with potassium hydroxide and cupric oxide or manganese dioxide in ethanol) (1559); 2,3-diphenyl-5,6-dihydro (reflux with nickel peroxide in benzene gave 92% 2,3-diphenylpyrazine) (1560); 2,3-di(fur-2′-yl)-5,6-dihydro (and its 5-methyl derivative) (introduction of air into a solution containing sodium hydroxide in 80% ethanol) (338); and 2-(*o*-methoxyphenyl)-3-phenyl-5,6-dihydro (heat at 145°) (262). Methods of dehydrogenation of 2,3-dihydropyrazines have been reviewed (331, 1559).

2,3-Diphenyl-5,6-dihydropyrazine reacts with alcoholic alkali to form 2,3-diphenylpyrazine and 5,5′,6,6′-tetraphenyl-2,2′-bipyrazinyl [not 2,3,6,7-tetraphenyl-1,4,5,8-tetraazabiphenylene (25, 401)], and 2,3-bis-(*p*-methoxyphenyl)-5,6-dihydropyrazine undergoes an analogous reaction, but 2,3-bis-(*p*-nitrophenyl)-5,6-dihydropyrazine yields only an apparently polymeric material (1548). A new aromatization technique based on deprotonation–hydride elimination has been tested experimentally by allowing dihydroarenes to react with various base–hydride acceptor pairs; and in this potassium fencholate–fenchone was particularly suitable. Thus 2,3-diphenyl-5,6-dihydropyrazine with this reagent in DMSO at 95° gave 2,3-diphenylpyrazine (1561). 2,3-Diphenyl-5,6-dihydropyrazine refluxed with chloranil in xylene afforded 2,3-diphenylpyrazine and the *p*-methoxyphenyl and *p*-nitrophenyl analogues were prepared similarly (1548). This method with chloranil is superior to the thermal dehydrogenations previously used (6). 2,5-Diphenyl-3-styryl-2,3-dihydropyrazine is oxidized by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to 2,5-diphenyl-3-styrylpyrazine (1551, 1552) [also prepared from 3-methyl-2,5-diphenylpyrazine (1551)], and *cis*-2,3,5-triphenyl-2,3-dihydropyrazine was converted similarly to 2,3,5-triphenylpyrazine (1556).

Irradiation of *trans*-2,3,5,6-tetraphenyl-2,3-dihydropyrazine in benzene gave *cis*-2,3,5,6-tetraphenyl-2,3-dihydropyrazine (1556).

It has been claimed (25) that 2,3-diphenyl-5,6-dihydropyrazine when heated with acetic or benzoic anhydride gives a derivative of the 1,4-dihydropyrazine ring system, but this has been shown by Chen and Fowler (1562) to be in error [the products have been shown to be 1,4-diacetyl(or dibenzoyl)-5,6-diphenyl-1,2,3,4-tetrahydropyrazine (**26**, R = Me or Ph), respectively, together with 2,3-diphenylpyrazine]. Hexamethyl-2,3-dihydropyrazine cannot undergo oxidation to a pyrazine, but it rapidly dimerized in air in the presence of hydrochloric acid to give compound (**27**, X = Cl) (also prepared as the iodide with iodine in ether) (1550).

The photorearrangement of 2,3-dihydropyrazines to imidazoles has been described (1547, 1563, 1564). For example, 2,3-dimethyl-5,6-dihydropyrazine gave



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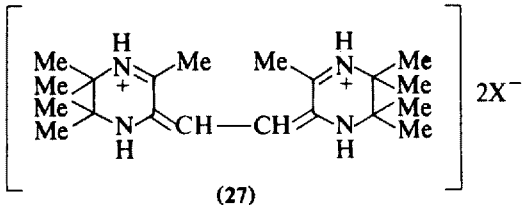

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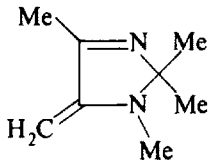
1,4,5-trimethylimidazole (1547) and other imidazoles (1564). Irradiation of a benzene solution of 2,3,5,5-tetramethyl-5,6-dihydropyrazine at room temperature has been shown to give 80% 1,2,2,4-tetramethyl-5-methylene-2,5-dihydroimidazole (**28**) and a mixture containing mostly dimer (**29**); the mechanism of the reaction was discussed (1565). Irradiation of 2,2,3,3-tetramethyl-5,6-diphenyl-2,3-dihydropyrazine gave *cis*- and *trans*-2,7-dimethyl-4,5-diphenyl-3,6-diazaocta-2,4,6-triene (1566) and *trans*-2,3,5,6-tetraphenyl-2,3-dihydropyrazine stirred with perbenzoic acid in chloroform gave the oxaziridine (**30**) (1557).



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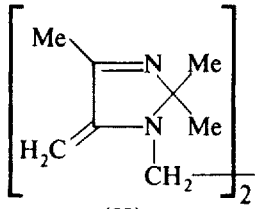

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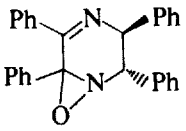

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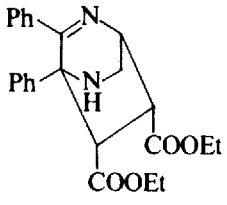
Electrochemical reductions of 2,3-dihydropyrazines have been investigated (1549, 1567); 2,3-diphenyl-5,6-dihydropyrazine was reported to give 2,3-diphenyl-1,4,5,6-tetrahydropyrazine and the 2,3-dimethyl analogue was prepared similarly (1549).

Catalytic hydrogenation of hexamethyl-2,3-dihydropyrazine occurred in two distinct steps (the first fast, the second slow) to give hexamethylpiperazine (1550); reduction of 2,5,6-triphenyl-2,3-dihydropyrazine with sodium and isoamyl alcohol gave two isomeric piperazines (330a); reduction of 2,3-dimethyl-5,6-dihydropyrazine with sodium ethanol or lithium aluminum hydride gave *trans*- or *cis*-2,3-dimethylpiperazine (333), and the heat of hydrogenation of 2,3-dimethyl-5,6-dihydropyrazine has been determined as 40.5 kcal/mol for comparison with those of compounds containing isolated and conjugated double bonds (597).

2,3-Diphenyl-5,6-dihydropyrazine reacts with diethyl fumarate to give diethyl 1,2-diphenyl-1,3-dihydro-3,7-diazabicyclo[2,2,2]octane-5,6-dicarboxylate (**31**) (1568), and a similar reaction was observed with *N*-methylmaleimide (1569). 2,3-Diphenyl-5,6-dihydropyrazine reacts with diphenylketene to give the azetidinone, 7,7a-dihydro-1,7,7,7a-tetraphenyl-6*H*-azeto[1,2-a]pyrazin-6-one (**32**) (1570). The reactions of 2,3-diphenyl-5,6-dihydropyrazine and 2,3-di(*p*-fluorophenyl)-5,6-



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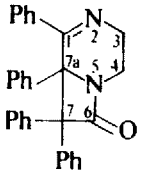

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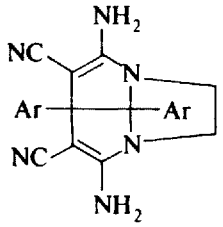
dihydropyrazine with malononitrile gave 2,6-diamino-3,5-dicyano-4,10-diphenyl-1,7-diazatricyclo[5,2,1,$0^{4,10}$]deca-2,5-diene (**33**, Ar = Ph) (1571, cf. 1572) and 2,6-diamino-3,5-dicyano-2,10-di(*p*-fluorophenyl)-1,7-diazatricyclo[5,2,1,$0^{4,10}$]deca-2,5-diene (**33**, Ar = *p*-FC_6H_4), respectively (1571).



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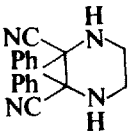

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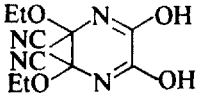

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2,3-Diphenyl-5,6-dihydropyrazine reacts with 2 mol of hydrocyanic acid to give 2,3-dicyano-2,3-diphenylpiperazine (**34**) (1573, 1574, cf. 1575), not 1,4-dicyano-2,3-diphenylpiperazine (25, 1572). 2,3-Di(fur-2′-yl)-5,6-dihydropyrazine when refluxed with potassium cyanide in dilute ethanol has been reported to give 5-carbamoyl-2,3-di(fur-2′-yl)pyrazine, and the 6-methyl derivative was prepared similarly (338). 2,3-Dichloro-2,3-dicyano-5,6-dihydroxy-2,3-dihydropyrazine with ethanol in acetonitrile gave 2,3-dicyano-2,3-diethoxy-5,6-dihydroxy-2,3-dihydropyrazine (**35**), but the former with ethanethiol in acetonitrile produced 2,3-dicyano-5,6-dihydroxypyrazine (383).

2,3-Bis(pyridin-2′-yl)-5,6-dihydropyrazine and 2,3-bis(6′-methylpyridin-2′-yl)-5,6-dihydropyrazine both show high sensitivity and characteristically high selectivity in their reactions with iron(II) and copper(I), respectively (1576). The ease with which the highly colored metal chelates can be extracted into immiscible solvents to give stable solutions makes these reagents useful for the determination of traces of iron and copper (1576).

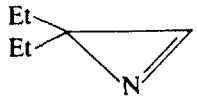
C. 2,5-Dihydropyrazines

(1) *Preparation*

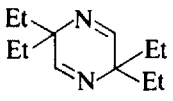
2,5-Dihydropyrazines may be prepared by the self-condensation of α-(primary amino)carbonyl compounds and some of these syntheses have been described in Sections II.1A (169, 172, 178, 186, 190), II.1J (294–298), and II.1L (306). The conversion of α-amino acids through piperazine-2,5-diones (2,5-dihydroxy-3,6-dihydropyrazines) to pyrazines has been described in Section II.1N (93, 95, 101, 282, 312–314a) and Section II.6 (314, 314a) and ring transformations to 2,5-dihydropyrazines in Section II.9 (302, 505a, cf. 1541). 3-Phenylazirine dimerizes on standing to 2,5-diphenyl-3,6-dihydropyrazine (1577).

2-Hydroxy-5,6-diphenylpyrazine and its N_1-methyl derivative are electrochemically reduced to the 3,4-dihydro derivatives, which isomerize into the 3,6-

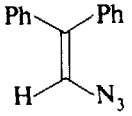
dihydro derivatives, and electrochemical reduction of these latter compounds leads to 3,4,5,6-tetrahydro derivatives (1097). Two kinds of azirine oligomers have been isolated as intermediates in the formation of 2,2,5,5-tetraethyl-2,5-dihydropyrazines (**37**) by heating of 2,2-diethylazirine (**36**) (1578). 2-Chloro-2,2-diphenylacetaldehyde when heated with ammoniacal ethanol gave 2,2,5,5-tetraphenyl-2,5-dihydropyrazine [also obtained together with 3-phenylindole by decomposition of 2-azido-1,1-diphenylethylene (**38**) in ethanol], and 2,5-dimethyl-2,5-diphenyl-2,5-dihydropyrazine was prepared similarly (1579).



(**36**)



(**37**)

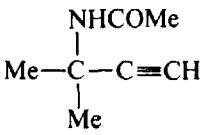


(**38**)

The chlorination of tetrafluoropyrazine to 3,6-dichloro-2,2,5,5-tetrafluoro-2,5-dihydropyrazine and 5,6-dichloro-2,2,3,3-tetrafluoro-2,3-dihydropyrazine has been described in Section V.1A(3) (796), and the conversion of 2,5-difluoro-3,6-bis(heptafluoroisopropyl)pyrazine to perfluoro-2,5-diisopropyl-3,6-dihydropyrazine in Section V.5J (1025).

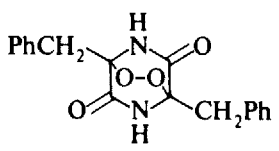
The method first described by Conant (1580) for preparing hexamethyl-2,5-dihydropyrazine from 3-methylbutanone with warm aqueous alkaline potassium ferricyanide has been expanded into a simple one-step selective way of preparing α-amino-α,α-dialkyl ketones and/or their self-condensation products, hexaalkyl-2,5-dihydropyrazines, in moderate yields (1581). In this way the corresponding 2,5-dihydropyrazines were prepared from methyl cyclopentyl ketone, methyl cyclohexyl ketone, and other compounds (1581).

N-(2-Methylbut-3-yn-2-yl)acetamide (**39**) (prepared by the Ritter reaction of acetonitrile with 3-hydroxy-3-methylbut-1-yne) on hydrolysis with sulfuric or hydrochloric acid in methanol, basified and steam distilled, gave 2,2,3,5,5,6-hexamethyl-2,5-dihydropyrazine (1582) (probably through 3-amino-3-methylbutan-2-one) (1582). 2-Dimethylaminobut-2-enylamine on treatment with aqueous hydrochloric and at room temperature followed by neutralization with potassium hydroxide afforded 2,5-diethyl-2,5-dihydropyrazine (1583).



(**39**)

2,5-Dibenzyl-3,6-dihydroxypyrazine with singlet oxygen gave 2,5-dibenzyl-2,5-epidioxy-3,6-dihydroxy-2,5-dihydropyrazine (3,6-dibenzyl-3,6-epidioxypiperazine-2,5-dione) (**40**), which was reduced by sodium borohydride to the 2,5-dibenzyl-2,3,5,6-tetrahydroxy-2,5-dihydropyrazine (**41**), and this subjected to acid catalyzed dehydration gave 2,5-dibenzylidene-3,6-dihydroxy-2,5-dihydropyrazine (**42**) (1128).



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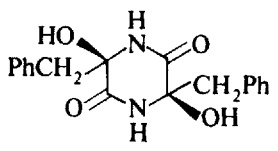

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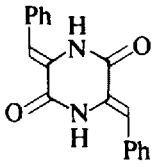

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2,5-Diethoxy-3,6-dimethylpyrazine similarly gave 3,6-diethoxy-2,5-dimethyl-2,5-epidioxy-2,5-dihydropyrazine, which was reduced by sodium borohydride to 3,6-diethoxy-2,5-dihydroxy-2,5-dimethyl-2,5-dihydropyrazine (1127).

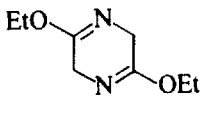
(2) *Reactions*

Oxidation of 2,5-diethoxy-3,6-dihydropyrazine with dichlorodicyanobenzoquinone (DDQ) formed 2,5-diethoxypyrazine (314), and the 3,6-dimethyl analogue reacted similarly (314). 2,5-Diisopropyl-3,6-dimethyl-2,5-dihydropyrazine was oxidized in alkaline solution to 2,5-diisopropyl-3,6-dimethylpyrazine (225). Oxidation of 2,5-diethoxy-3,6-dimethyl-3,6-dihydropyrazine with lead tetraacetate in refluxing benzene gave both 2,5-diethoxy-3,6-dimethylpyrazine (minor product) and 2,5-diacetoxy-3,6-diethoxy-2,5-dimethyl-2,5-dihydropyrazine (1068).

Pyrolysis of 2,5-diethoxy-3,6-dihydropyrazine in the range 250–270° *in vacuo* gave only unchanged starting material and no sign of 2,5-diethoxypyrazine (314), and the thermal instability of 2,5-dimethyl-3,6-dihydropyrazine has been reported to be due to its dimerization (190). Pyrolysis of *trans*-2,5-dibenzyl-3,6-diethoxy-2,5-dihydropyrazine at 250–270° resulted in the clean formation of 3-benzyl-2,5-diethoxypyrazine (ca. 90% yield) along with traces of 2,5-dibenzyl-3,6-diethoxypyrazine. Heating of the cis isomer at 120° resulted in gradual epimerization into the trans isomer, and heating at 250–270° for 12 hours resulted in the formation of the same products as for the trans isomer (314). Pyrolysis of racemic 3,6-diethoxy-2,5-dimethyl-2,5-dihydropyrazine at 250–270° for 12 hours gave a low yield of 2,5-diethoxy-3-methylpyrazine (314). 2,2,5,5-Tetramethyl-2,5-dihydropyrazine was unchanged on pyrolysis at 350°, whereas decomposition to carbonaceous products occurred at higher temperatures (314).

2,5-Diethoxy-3,6-dihydropyrazine (**43**), metalated with lithium diisopropylamide and alkylated with allyl bromide, gave 3-allyl-2,5-diethoxy-3,6-dihydropyrazine (314a). The conditions employed for generating the imidate anion were also suitable in the condensations of aldehydes and ketones with the dihydropyrazine. Condensation of (**43**) with benzaldehyde gave 2,5-diethoxy-3-(α-hydroxybenzyl)-3,6-dihydropyrazine (**44**) (314a) and the process may be repeated (314a). Compound (**44**) with DDQ gave 2,5-diethoxy-3-(α-hydroxybenzyl)pyrazine (and smaller quantities of the benzoyl-substituted pyrazine) (314a). Certain α-amino ketone hydrochlorides and the corresponding 2,5-dihydropyrazines can be quantitatively interconverted with mild aqueous base and warm dilute hydrochloric acid (1581).

2-Ethoxy-5-hydroxy-3,6-dihydropyrazine coupled with 2,3,4,6-tetra-*O*-acetyl-



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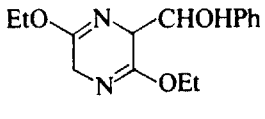

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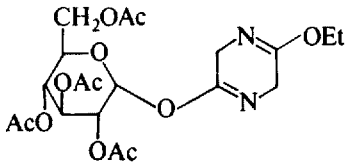


(45)

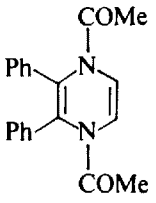
α-D-glucopyranosyl bromide to give the 2-*O*-glycoside [2-ethoxy-5-(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyloxy)-3,6-dihydropyrazine] (**45**). An attempted *O*- to *N*-glycoside rearrangement of (**45**) with mercuric acetate resulted in aromatization of the dihydropyrazine ring (1584).

D. 1,4-Dihydropyrazines

(1) *Preparation*

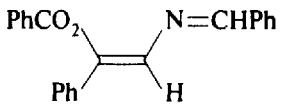
Lown and Akhtar (1538, 1539) have shown that *N*-benzyl-*N*,*N*-diphenacylamine reacts with benzylamine at 40° to give 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine (**5**), which rearranged at higher temperatures to 1,2-dibenzyl-3,5-diphenyl-1,2-dihydropyrazine (**6**) [Mason and Winder (26) reported that *N*-benzyldiphenacylamine hydrobromide with benzylamine at 120–130° gave 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine, but Chen and Fowler (1535) found that under the same conditions the product was 1,2-dibenzyl-3,5-diphenyl-1,2-dihydropyrazine and they (1535) postulated that the 1,4-dihydropyrazine was an intermediate in the reaction; see Section 1A(1)]. Stable 1,4-dialkyl-1,4-dihydropyrazines have been readily prepared by reaction of benzyldiphenacylamine hydrobromide with primary aliphatic amines provided the alkyl group has low migratory aptitude (1540) and/or care is taken to avoid the subsequent rearrangement (1539) to the 1,2-dihydropyrazine. For example, treatment of *N*-benzyldiphenacylamine hydrobromide with two equivalents of cyclohexylamine under nitrogen in refluxing toluene gave 4-benzyl-1-cyclohexyl-2,6-diphenyl-1,4-dihydropyrazine (1540), and the reaction of phenacyl bromide with anhydrous methylamine (gas) in benzene gave (through *N*-methyldiphenacylamine) the reactive 1,4-dimethyl-2,6-diphenyl-1,4-dihydropyrazine (1536).

The 1,4-dihydropyrazine ring system was first characterized by Chen and Fowler using n.m.r. (1562). Slow addition of acetyl chloride to 2,3-diphenyl-5,6-dihydropyrazine in benzene containing two equivalents of pyridine gave 1,4-diacetyl-2,3-diphenyl-1,4,dihydropyrazine (**46**) (30%) together with 1,4-diacetyl-5,6-diphenyl-1,2,3,4-tetrahydropyrazine and 2,3-diphenylpyrazine (1562, cf. 25).



(46)

Treatment of 2-benzylideneamino-1-phenylvinyl benzoate (**47**) with sodium methoxide produced one major product which was assigned as 2,5-dibenzoyl-3,6-diphenyl-1,4-dihydropyrazine (**48**) (1585). Dimerization of a series of α-arylamino ketones (**49**) in toluene with *p*-toluenesulfonic acid gave the symmetrical 1,4-diaryl-1,4-dihydropyrazine (**50**), not the corresponding 1,4-diaryl-1,4-dihydropyrazines (**51**) or 1-aryl-1,2-dihydropyrazines (**52**). Thus ω-(4-chloroanilino)acetophenone gave 1,4-bis(*p*-chlorophenyl)-2,6-diphenyl-1,4-dihydropyrazine (1546).



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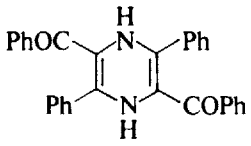

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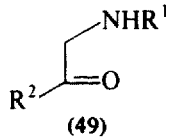

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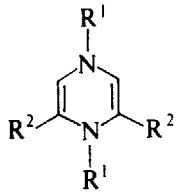

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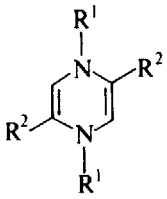

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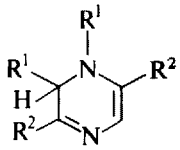
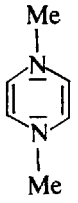


(52)

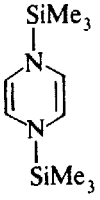
Ethyl β-ethoxy-α-nitroacrylate with 1,1-diphenylhydrazine in ethanol followed by heating has been shown to give 1,4-bis(diphenylamino)-2,5-diethoxycarbonyl-1,4-dihydropyrazine (1586). A small amount of 2,5-dicyano-1,4-bis(dimethylamino)-1,4-dihydropyrazine was obtained from the reaction of 2-chloro-3-(2′,2′-dimethylhydrazino)propionitrile [$(Me)_2NNHCH_2CH(Cl)CN$] with sodium hydride (1587). Hexaalkyl-1,4-dihydropyrazines and other 1,4-dialkyl-1,4-dihydropyrazines can be obtained by thermolysis of the products of reaction of α-(alkylamino)carboxylic acid esters with alkylmagnesium bromide. Thus the reaction of ethyl α-*s*-butylaminopropionate with ethylmagnesium bromide, followed by heating *in vacuo* to 250–300°, gave 2,5-dimethyl-3,6-diethyl-1,4-di-*s*-butyl-1,4-dihydropyrazine (1588).

The reaction mixture of *N,N′*-dimethylethylenediamine with butyllithium, when examined by electron paramagnetic resonance (e.p.r.), was consistent with the formation of the radical anion of 1,4-dimethyl-1,4-dihydropyrazine (**53**) (1589).



(53)

The electrochemical reduction of several pyrazines has been reported (125, 702, 703, 1096, 1097, 1190, 1549, 1567). Many of these reductions involve unstable 1,4-dihydropyrazines (703, 1096, 1190). Reductive silylation of pyrazine with alkali metals and halogenosilanes gave 1,4-bis(trimethylsilyl)-1,4-dihydropyrazine (**54**), which decomposes spontaneously in the presence of air (623).



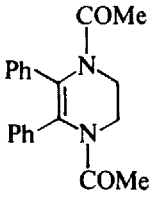
(54)

The irradiation of pyrazine derivatives with an α-carbonyl substituent under an atmosphere of nitrogen gave hydroxypyrazines and 1,4-dihydropyrazines (solvent adducts). Thus irradiation of 2,5-dimethoxycarbonyl-3,6-dimethylpyrazine in diethyl ether with a 450-W high-pressure mercury lamp gave two significant photoproducts, 2-hydroxy-5-methoxycarbonyl-3,6-dimethylpyrazine and 1(1′-ethoxyethyl)-2,5-dimethoxycarbonyl-3,6-dimethyl-1,4-dihydropyrazine (1064). The mechanism of the reaction has been investigated and discussed (1064).

(2) *Reactions (and Properties)*

Catalytic hydrogenation of 1,4-diacetyl-2,3-diphenyl-1,4-dihydropyrazine (**46**) over palladium–charcoal resulted in the rapid uptake of 1 mol of hydrogen with formation of 1,4-diacetyl-5,6-diphenyl-1,2,3,4-tetrahydropyrazine (**55**); this addition of only one equivalent of hydrogen under these conditions is characteristic of a 1,4-dihydropyrazine (1562). Similar catalytic hydrogenation of 4-benzyl-1-cyclohexyl-2,6-diphenyl-1,4-dihydropyrazine gave 4-benzyl-1-cyclohexyl-2,6-diphenyl-1,2,3,4-tetrahydropyrazine (1539, 1540), and 1,4-dimethyl-2,6-diphenyl-1,4-dihydropyrazine gave 1,4-dimethyl-2,6-diphenyl-1,2,3,4-tetrahydropyrazine (1536).

The 1,4-dialkyl-1,4-dihydropyrazines are stable in the crystalline state but are reactive in solution (e.g., reaction as enamines toward chloroform and carbon tetrachloride) and most significantly are readily oxidized by air to stable free



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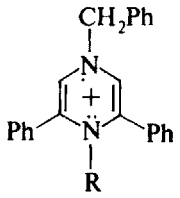
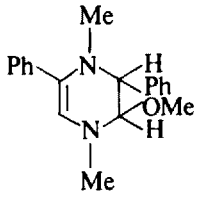


(56)

radical cations which give persistent e.s.r. signals that have been assigned to the radical cations (**56**). Their sensitivity to oxygen results in considerable paramagnetic n.m.r. line broadening in the case of many 1,4-dialkyl-1,4-dihydropyrazines (1540).

Hydrolysis of 1,4-diacetyl-2,3-diphenyl-1,4-dihydropyrazine with potassium hydroxide in ethylene glycol produced 2,3-diphenylpyrazine (probably formed by air oxidation of the dihydropyrazine) (1562). 1,4-Dimethyl-2,6-diphenyl-1,4-dihydropyrazine reacts with methanol to give 2-methoxy-1,4-dimethyl-3,5-diphenyl-1,2,3,4-tetrahydropyrazine (**57**) (1536).



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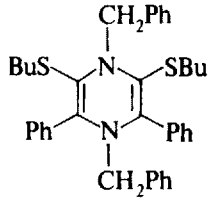


(58)

1,4-Dibenzyl-2,6-diphenyl-1,4-dihydropyrazine reacts with a large excess of butanethiol in benzene to form 1,4-dibenzyl-3,5-dibutylthio-2,6-diphenyl-1,4-dihydropyrazine (**58**) (42%); the reaction may involve disproportionation or air oxidation (1539). 1,4-Dibenzyl-2,6-diphenyl-1,4-dihydropyrazine rearranges in degassed benzene at 55° to 1,2-dibenzyl-3,5-diphenyl-1,2-dihydropyrazine (1538); the reaction obeys first-order kinetics over 80% of its course and the mechanism has been examined (1538). The corresponding rearrangement of 2,5-diphenyl-1,4-dihydropyrazines has also been studied (1545).

An X-ray analysis of 1,4-bis(*p*-chlorophenyl)-2,6-diphenyl-1,4-dihydropyrazine has been reported (1590) and bond lengths and net atom changes have been calculated for 1,4-dihydropyrazine (and pyrazine) (1591).

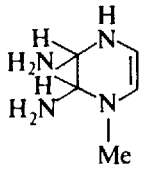
E. Tetrahydropyrazines

(1) *Preparation*

The preparation of tetrahydropyrazines from dihydropyrazines has been reported in Sections 1B(2) (1549, 1562), 1C(1) (1097), and 1D(2) (1536, 1539, 1540,

1562), and reduction of alkoxycarbonylpyrazines to the tetrahydropyrazines has been discussed in Section IX.2C(3) (1280, 1326).

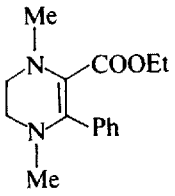
1-Methylpyrazinium ion in liquid ammonia at $-28°$ forms a 2,3-diadduct, 2,3-diamino-1-methyl-1,2,3,4-tetrahydropyrazine (**59**) (609), and 1,4-diacetyl-2,3-di(indol-3′-yl)-1,2,3,4-tetrahydropyrazine has been prepared by refluxing pyrazine with indole in acetic anhydride (1592).



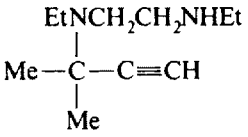
(**59**)

Heating of "1,4-dicyano-2,3-dinitroso-2,3-diphenylpiperazine" (?) (1572, cf. 1573) in mesitylene is claimed to give 1,4-dicyano-2,3-diphenyl-1,4,5,6-tetrahydropyrazine (1572), and "1-carbamoyl-3-hydroxy-2,3-diphenylpiperazine" (?) (1572, cf. 1573) with methyl iodide and potassium carbonate in methanol is claimed to give 4-carbamoyl-1,1-dimethyl-2,3-diphenyl-1,4,5,6-tetrahydropyrazinium iodide (1572). 2-Diethylamino-1,4-dimethylpiperazine on thermal treatment gives 1,4-dimethyl-1,2,3,4-tetrahydropyrazine, which was methoxycarbonylated to 5-methoxycarbonyl-1,4-dimethyl-1,2,3,4-tetrahydropyrazine (1593).

1,4-Dimethylethylenediamine with ethyl α-benzoyl-α-chloroacetate afforded 2-ethoxycarbonyl-1,4-dimethyl-3-phenyl-1,4,5,6-tetrahydropyrazine (**60**) (1594), and *N,N′*-diethyl-*N*-(1′,1′-dimethylpropynyl)ethylenediamine (**61**) refluxed with mercuric oxide in aqueous methanolic sulfuric acid is reported to give 4-ethyl-2,3,3-trimethyl-2,3,4,5-tetrahydropyrazine (?) (1595).



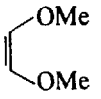
(**60**)



(**61**)

Diiminosuccinonitrile (DISN) (**10**) reacts exothermically with *cis*-1,2-dimethoxyethylene (**62**) in acetonitrile to give 5,6-dicyano-2,3-dimethoxy-1,2,3,4-tetrahydropyrazine (**63**) (386, 1596). Styrene and *p*-halogenostyrenes reacted with DISN in acetonitrile at room temperature to form 2-amino-3-(2′-arylaziridin-1′-yl)maleonitrile (**64**) (50–80%), whereas the more electron-rich *p*-methoxystyrene and 2-vinylfuran gave 5-aryl-2,3-dicyano-1,4,5,6-tetrahydropyrazine (**65**) (60–80%). *p*-Methylstyrene gave both types of products (1597).

The dianil of diacetyl with dimethylketene ($Me_2C{=}C{=}O$) afforded 2,2,5,6-tetramethyl-3-oxo-1,4-diphenyl-1,2,3,4-tetrahydropyrazine (**66**) (1598), and with



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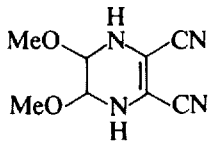

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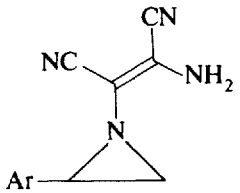

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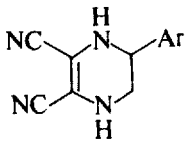

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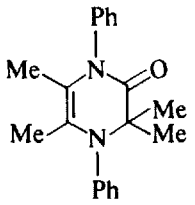

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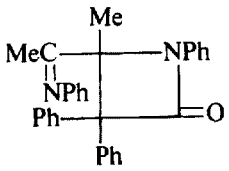
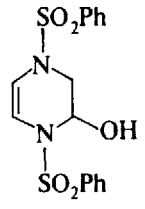


(67)

phenylketene and diphenylketene gave 1,2,4-triphenyl- and 1,2,2,4-tetraphenyl-5,6-dimethyl-3-oxo-1,2,3,4-tetrahydropyrazine, respectively (1599), but the dianil of diphenylglyoxal with diphenylketene has been shown to give 4-methyl-1,3,3-triphenyl-4-[1′-(phenylimino)ethyl]azetidin-2-one (**67**) (1570). Hydrolysis of poly(3-ethoxy-1-tosyl-1-azapropane-1,3-diyl) $[-CH(OEt)CH_2N(Ts)-]_n$ with ethanolic hydrogen chloride (1600, 1601) or of 2,5-diethoxy-1,4-ditosylpiperazine with hydrochloric acid (1601) gave 2-ethoxy-1,4-ditosyl-1,2,3,4-tetrahydropyrazine [also obtained from hydrolysis of poly(3-methoxy-1-tosyl-1-azapropane-1,3-diyl) with aqueous ethanol; and the methoxy analogue was obtained when methanol was used] (1601). The 1,4-bisbenzenesulfonyl-2-ethoxy-1,2,3,4-tetrahydropyrazine did not add alcohols but with thiophenol and boron trifluoride etherate it gave 1,4-bisbenzenesulfonyl-2,5-(?)-bisphenylthiopiperazine (1600).

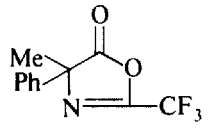
Cyclization of *N*-(2′,2′-dimethoxyethyl)benzenesulfonamide $[PhSO_2NHCH_2CH(OMe)_2]$ has been shown to give 1,4-dibenzenesulfonyl-2-hydroxy-1,2,3,4-tetrahydropyrazine (**68**) or 1,4-dibenzenesulfonyl-2,5-dihydroxypiperazine according to the conditions (1602, cf. 1603) and the latter was readily dehydrated to (**68**) (1602). A similar preparation of the tosyl analogue was also reported (1602).



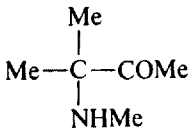
(68)

A synthesis of 3-mono- and 3,3-disubstituted-1,5,6,6-tetramethyl-2-oxo-1,2,3,6-tetrahydropyrazines has been reported (1604). For example, *N*-trifluoroacetyl-α-

methyl-α-phenylglycine with thionyl chloride gave 4-methyl-4-phenyl-5-oxo-2-trifluoromethyl-4,5-dihydrooxazole (**69**), which was condensed with 3-methyl-3-(methylamino)butan-2-one (**70**) in dry acetonitrile to give crude (**71**), and this with methanolic hydrogen chloride formed 1,3,5,6,6-pentamethyl-2-oxo-3-phenyl-1,2,3,6-tetrahydropyrazine (**72**) (1604).



(69)



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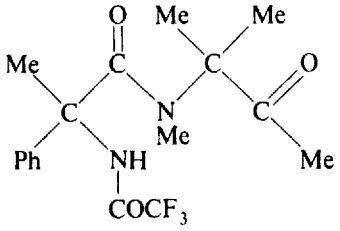

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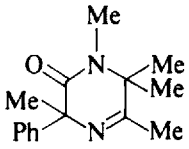
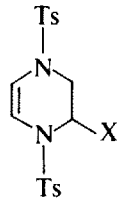


(72)

(2) *Reactions*

Reduction of 1,4-diacetyl-5,6-diphenyl-1,2,3,4-tetrahydropyrazine with lithium aluminum hydride formed 1,4-diethyl-5,6-diphenyl-1,2,3,4-tetrahydropyrazine (1562). Both 1,4-dibenzenesulfonyl-2-hydroxy-1,2,3,4-tetrahydropyrazine and 1,4-dibenzenesulfonyl-2,5-dihydroxypiperazine reacted with hot acidic methanol to produce 1,4-dibenzenesulfonyl-2-methoxy-1,2,3,4-tetrahydropyrazine (1602). The tosyl analogue behaved similarly. Reaction of 2-hydroxy-1,4-ditosyl-1,2,3,4-tetrahydropyrazine (**73**, X = OH) with benzenethiol in acidified acetone gave 2-phenylthio-1,4-ditosyl-1,2,3,4-tetrahydropyrazine (**73**, X = SPh) (1602).

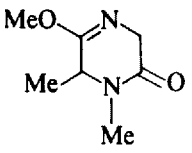


(73)

Treatment of 2-hydroxy-1,4-ditosyl-1,2,3,4-tetrahydropyrazine (**73**, X = OH) or 2,5-dihydroxy-1,4-ditosylpiperazine with thionyl chloride gave 2,5-dichloro-1,4-

ditosylpiperazine which on brief heating in toluene gave 2-chloro-1,4-ditosyl-1,2,3,4-tetrahydropyrazine, and this with water or ethanol gave 2-hydroxy or 2-ethoxy-1,4-ditosyl-1,2,3,4-tetrahydropyrazine (1602). Compound (73) (or 2-chloro-1,4-ditosyl-1,2,3,4-tetrahydropyrazine) with bromine underwent addition elimination with the formation of *trans*-2,3-dibromo-1,4-ditosyl-1,2,3,4-tetrahydropyrazine, which with water and ethanol readily gave trans-2,3-dihydroxy-1,4-ditosyl-1,2,3,4-tetrahydropyrazine.

Oxidation of 2-hydroxy-1,4-ditosyl-1,2,3,4-tetrahydropyrazine with Jones reagent surprisingly resulted in hydroxylation of the double bond with the formation of 2,3,5-trihydroxy- and 2,3-dihydroxy-1,4-ditosylpiperazine (1602). Despite numerous attempts, Eisner and Williams (1602) were unable to convert a series of 1,2,3,4-tetrahydropyrazines to 1,4-dihydropyrazines. 5-Methoxy-1,6-dimethyl-2-oxo-1,2,3,6-tetrahydropyrazine (74) was oxidized by lead tetraacetate at reflux in benzene to give 6-acetoxy-6-acetoxymethyl-5-methoxy-1-methyl-2-oxo-1,2,3,6-tetrahydropyrazine (75) (1068).



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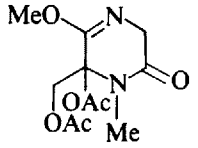


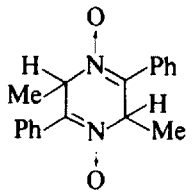
(75)

F. Dihydropyrazine *N*-Oxides

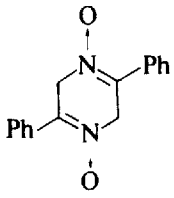
(1) *Preparation*

Some primary syntheses of dihydropyrazine *N*-oxides have been included in Section III.6 (555–556a).

N-(1′-Benzoylethyl)hydroxylamine, PhCOCHMeNHOH, on standing for one day is reported to give 2,5-dimethyl-3,6-diphenyl-2,5-dihydropyrazine 1,4-dioxide (76) and *N*-(benzoylmethyl)hydroxylamine hydrochloride when neutralized gave 3,6-diphenyl-2,5-dihydropyrazine 1,4-dioxide (77) (1605).



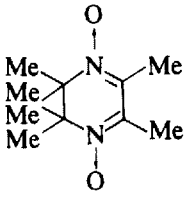
(76)



(77)

(2) *Reactions*

Reduction of 2,2,3,3,5,6-hexamethyl-2,3-dihydropyrazine 1,4-dioxide (**78**) with sodium borohydride gave 1,4-dihydroxy-2,2,3,3,5,6-hexamethylpiperazine (555) and attempted deoxygenation of (**78**) by zinc and hydrochloric acid gave the bishydroxylamine (**79**) (555). Compound (**78**) did not form benzylidene derivatives with benzaldehyde (555) and it was only slowly attacked by selenium dioxide; one equivalent of selenium dioxide required 5 days' boiling under reflux before the nitrone was completely reacted, and the product was thought to be 6-formyl-2,2,3,3,5-pentamethyl-2,3-dihydropyrazine 1,4-dioxide (**80**) (555). The reaction of (**78**) with methyl magnesium iodide gave a complex mixture (555).



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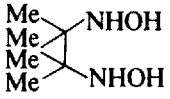

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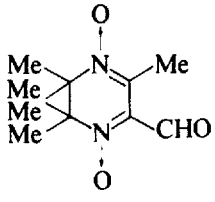


(80)

The photochemical isomerization of hexamethyl-2,3-dihydropyrazine 1,4-dioxide has been investigated (1606).

The reactions of 2,5-dimethyl-3,6-diphenyl-2,5-dihydropyrazine 1,4-dioxide and 3,6-diphenyl-2,5-dihydropyrazine 1,4-dioxide with acetic anhydride and a small amount of sulfuric acid afforded 2,5-dimethyl-3,6-diphenylpyrazine 1-oxide and 2,5-diphenylpyrazine 1-oxide (1605), respectively. Ring opening of perfluoro-2,5-diisopropyl-3,6-dihydropyrazine by photolysis has been described (1607).

2. PIPERAZINONES

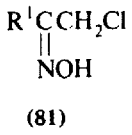
A number of reviews of piperazinones, particularly piperazin-2,5-diones, has been published. These are listed in Table XI.1 and some references to other data are recorded below.

A. Piperazin-2-ones

(1) *Preparation*

The preparation of piperazin-2-ones by reduction of 2-oxo-1,2-dihydropyrazines has been described in Section V.5A(1) (853).

3,6-Disubstituted piperazin-2-ones (**83**) were first synthesized by the reaction of α-chloro oximes (**81**) with esters of amino acids, followed by reductive cyclization



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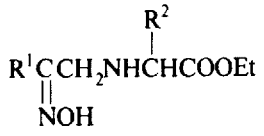

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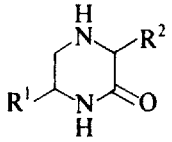
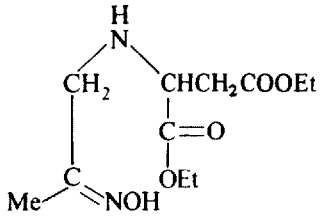


(83)

of the product (**82**) (1608). For example, 1-chloro-2-hydroxyiminopentane with leucine ethyl ester gave *N'*-(2'-hydroxyiminopentyl)leucine ethyl ester, which afforded 3-isobutyl-6-propylpiperazin-2-one (1608).

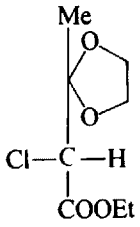
Condensations of chloroacetyl chloride (and similar compounds) with substituted ethylenediamines to give 1,4-disubstituted piperazin-2-ones have been described, and a number of 4-alkyl(or aralkyl)-1-arylpiperazin-2-ones has been prepared either by catalytic debenzylation or pyrolytic debenzylation (or demethylation) of 1,1-dialkyl(or 1,1-diaralkyl)-3-oxo-4-arylpiperazinium halides (1609). 3-Ethoxycarbonylmethylene-6-methylpiperazin-2-one has been synthesized by the reaction of diethyl acetylenedicarboxylate with propylenediamine (1610), and treatment of diethyl fumarate with propylenediamine has been shown to give 3-ethoxycarbonylmethyl-6-methylpiperazin-2-one, also prepared from the diethyl ester of *N*-(2'-hydroxyiminopropyl)aspartic acid (**84**) (1611).



(84)

The reaction of 1-phenylethylenediamine with ethyl α-bromo-β-phenylpropionate and of propylenediamine with ethyl α-bromopropionate gave 3-benzyl-6-phenylpiperazin-2-one (together with a small amount of 3-benzyl-5-phenylpiperazin-2-one) and 3,6-dimethylpiperazin-2-one, respectively (1133). Similarly ethyl α-bromo-α-phenylacetate with ethylenediamine gave 3-phenylpiperazin-2-one (1612); condensation of 2-amino-1-benzylaminopropane with ethyl α-bromopropionate followed by heating at 200° gave a mixture of *cis* and *trans*-1-benzyl-3,5-dimethylpiperazin-2-ones (1613) (which were reduced by lithium aluminum hydride to 1-benzyl-3,5-dimethylpiperazine) (1613) and 4-benzyl-3,6-dimethylpiperazin-2-one; and ethyl 2-chloro-3-ethylenedioxybutyrate (**85**) with *N,N'*-dimethylethylenediamine (**86**) gave 3-(1',1'-ethylenedioxy)ethyl-1,4-dimethylpiperazin-2-one (**87**) (1594) and with ethylenediamine gave 3-(1',1'-ethylenedioxy)ethylpiperazin-2-one (1594).

The reaction mixture of ethylenediamine and glycolonitrile ($HOCH_2CN$) when treated with an excess amount of hydroxylamine in methanol gave 2-hydroxyiminopiperazine (1614) [which with 3*N* hydrochloric acid and methanol afforded the dihydrochloride of *N*-(2'-aminoethyl)glycine methyl ester] (1614).



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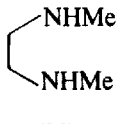

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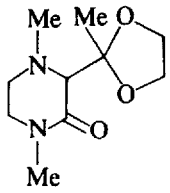
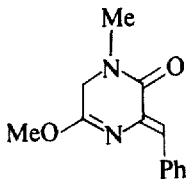


(87)

(2) *Reactions*

Piperazin-2-one with benzyl chloride and sodium carbonate gave 4-benzylpiperazin-2-one, which with acrylonitrile gave 4-benzyl-1-cyanoethylpiperazin-2-one or with butyl bromide and sodium in toluene formed 4-benzyl-1-butylpiperazin-2-one (1615); but (*Z*)-3-benzylidene-1-methylpiperazine-2,5-dione methylated with methyl iodide and silver carbonate produced (*Z*)-3-benzylidene-5-methoxy-1-methyl-2-oxo-1,2,3,6-tetrahydropyrazine (**88**) and a small amount of (*Z*)-3-benzylidene-1,4-dimethylpiperazine-2,5-dione (**89**) (1616).



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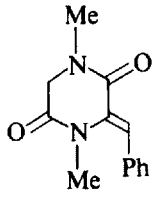
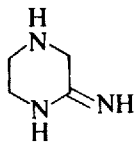


(89)

Catalytic reduction of 2-hydroxyiminopiperazine over Raney nickel afforded 2-iminopiperazine (**90**) (1614). This was converted by methanolic hydroxylamine at room temperature to 2-hydroxyiminopiperazine, and by hydrogen sulfide to piperazine-2-thione (1614). Reduction of 4-benzoylpiperazin-2-one with sodium borohydride in pyridine formed 1-benzylpiperazine and 4-benzylpiperazin-2-one, but reduction with sodium borohydride in triethylamine gave only some 1-benzoylpiperazine (1617). Piperazin-2-one with amyl nitrite in butanol produced 4-nitrosopiperazin-2-one (1614), and 3-(1′,1′-ethylenedioxy)ethyl-1,4-dimethylpiperazin-2-one (**87**) with ethanolic hydrogen chloride gave 3-acetyl-1,4-dimethylpiperazin-2-one (**91**) (1594).



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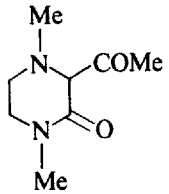


(91)

B. Piperazine-2,3-diones

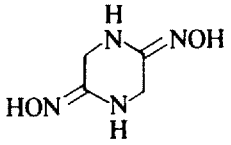
Reaction of diiminosuccinonitrile (**10**) with oxalyl chloride (ClOCCOCl) afforded 5,6-dichloro-5,6-dicyanopiperazine-2,3-dione (**17**) (383), which with ethanol gave 5,6-dicyano-5,6-diethoxypiperazine-2,3-dione but with ethanethiol was reported to give 2,3-dicyano-5,6-dihydroxypyrazine (383). Diisobutyl oxalate heated with dihydrazinoethane in dimethylformamide gave 1,4-diaminopiperazine-2,3-dione (1618), which with lithium aluminum hydride formed 1,4-diaminopiperazine (1618), and 1,2-bis(methylamino)ethane with diisobutyl oxalate gave 1,4-dimethylpiperazine-2,3-dione (1618). Hydrogenation of 1,4-diphenyl-2,3-dioxo-1,2,3,4-tetrahydropyrazine in acetic acid over palladium–charcoal formed 1,4-diphenylpiperazine-2,3-dione (853).

C. Piperazine-2,5-diones

(1) *Preparation*

The preparation and reactions of piperazine-2,5-diones has been much discussed in the reviews mentioned above and in papers by Sammes and co-workers (314, 314a, 1066–1068, 1078, 1127, 1128, 1616).

Some preparations are described in Section 1C(1) and additional preparative data are as follows. Aminoacetonitrile with hydroxylamine gave 2,5-bishydroxyiminopiperazine (**92**) (465), which was hydrolyzed with dilute hydrochloric acid to the monoxime; in contrast, nitrous acid converted the dioxime (**92**) into piperazine-2,5-dione (465). *N*-(Aminoacyl)aminoacetonitrile with hydroxylamine formed 5-hydroxyiminopiperazin-2-one (1619). Reduction of diethyl hydroxyiminomalonate in ethanol with hydrogen over palladium–charcoal gave diethyl aminomalonate and 3,6-diethoxycarbonylpiperazine-2,5-dione (821); and heating of diethyl *N*-methylaminomalonate formed 3,6-diethoxycarbonyl-1,4-dimethylpiperazine-2,5-dione (1620), which with sodium hydride in dioxane followed by treatment with sulfur monochloride gave 3,6-epidithio- (**93**) and 3,6-epitetrathio-3,6-diethoxycarbonyl-1,4-dimethylpiperazine-2,5-dione (1620). Reduction of 2,5-dihydroxy-3,6-diisobutylpyrazine with hydrogen over platinum gave 3,6-diisobutylpiperazine-2,5-dione (99), and treatment of 2-bromo-5-hydroxypyrazines with zinc dust and aqueous acetic acid produced piperazine-2,5-diones (113c, 113e).



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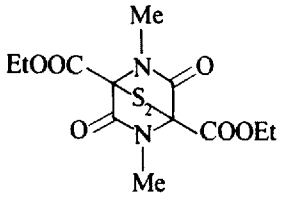
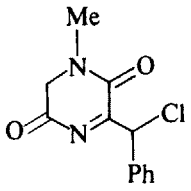


(93)

The chemical degradation of oligopeptides to cyclic dipeptides and identification of the latter by gas chromatography – mass spectroscopy has been investigated as a method of amino acid sequencing (1621). Treatment of 3-(α-chlorobenzyl)-1-methyl-2,5-dioxo-1,2,5,6-tetrahydropyrazine (**94**) or its 3-(α-acetoxybenzyl) analogue with aluminum chloride in nitromethane followed by pouring into dichloromethane and washing with water gave (*Z*)-3-benzylidene-6-hydroxy-1-methylpiperazine-2,5-dione (**95**) (1616).



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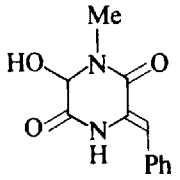


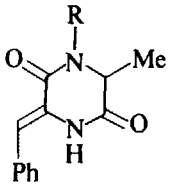
(95)

Sterically pure piperazinediones have been prepared from formate salts of dipeptide methyl esters (1622). The conformation of piperazine-2,5-diones has been reviewed (1623).

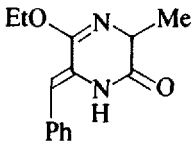
(2) *Reactions*

Reactions of piperazine-2,5-diones with phosphorus pentachloride and phosphorus pentabromide have been described in Sections V.1D and V.1F, respectively. Aromatic aldehydes condense with 3-methylpiperazine-2,5-dione in the presence of acetic anhydride to form mainly mono-*N*-acetyl derivatives of *trans*-3-arylidene-6-methylpiperazine-2,5-diones (e.g., **96**, R = Ac) (1066). In these products the acetyl group was shown to be attached to position 1 and the 4,5-amide group was found to be sterically hindered. Photolysis formed the cis isomers. Both isomers were deacetylated with methanolic potassium hydroxide (1066). Condensation of 1,4-diacetylpiperazine-2,5-diones with aldehydes has been applied to the synthesis of unsymmetrical 3,6-diarylidenepiperazine-2,5-diones; and the reaction has been extended to 1,4-diacetyl-3,6-dimethylpiperazine-2,5-diones (1624). Treatment of (**96**, R = H) with triethyloxonium tetrafluoroborate in dichloromethane gave the monoimino ether, 5-benzylidene-6-ethoxy-3-hydroxy-2-methyl-2,5-dihydropyrazine (**97**) (1066). 1-Methylpiperazine-2,5-dione similarly treated gave 5-ethoxy-1-methyl-2-oxo-1,2,3,6-tetrahydropyrazine (which was condensed with anthranilic acid at 150° to 2-methyl-1,2-dihydropyrazino[2,1-*b*]quinazoline-3(4*H*),6-dione (**98**) (1625), and 1,4-dimethylpiperazine-2,5-dione gave 5-ethoxy-1,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyrazine and 5,5-diethoxy-1,4-dimethylpiperazin-2-one (1626).

1,2,4,5-Tetramethylpiperazine-2,5-dione brominated with *N*-bromosuccinimide formed 3,6-dibromo-3,6-bis(bromomethyl)-1,4-dimethylpiperazine-2,5-dione, which with sodium acetate in methanol at room temperature gave 3,6-bis(bromomethyl)-3,6-dimethoxy-1,4-dimethylpiperazine-2,5-dione, and this with tri-*n*-butyltin hydride



(96)



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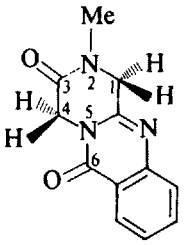

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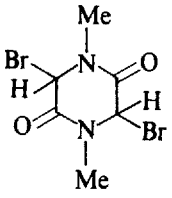

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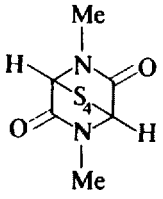
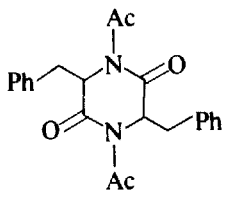


(100)

and 2,2'-azobisisobutyronitrile gave 3,6-dimethoxy-1,3,4,6-tetramethylpiperazine-2,5-dione (1627). 3,6-Dibromo-1,4-dimethylpiperazine-2,5-dione (**99**) (of unknown configuration) reacted with sodium ethanethiolate to give 3,6-bisethylthio-1,4-dimethylpiperazine-2,5-dione. Compound (**99**) with Na_2S_2 gave 7,9-dimethyl-2,3,4,5-tetrathia-7,9-diazabicyclo[4,2,2]decane[8,10]dione (**100**), which was reduced by sodium borohydride and then methylated with methyl iodide to 1,4-dimethyl-3,6-*cis*-bis(methylthio)piperazine-2,5-dione (1628).

A solution of sulfur in dimethylformamide can act as an oxidant of certain *N*-blocked piperazine-2,5-dione derivatives, resulting in net dehydrogenation (1068). For example, (*cis trans*)-1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione (**101**) reacted with sulfur in dimethylformamide and triethylamine to form, after hydrolytic removal of the acetyl groups, 3-benzyl-6-benzylidenepiperazine-2,5-dione (**102**) (1968). Oxidation of 1,3,4,6-tetramethylpiperazine-2,5-dione (**103**) with lead tetraacetate in benzene gave 3,6-diacetoxy-3-acetoxymethyl-1,4,6-trimethylpiperazine-2,5-dione (**104**) and 3-acetoxy-3-acetoxymethyl-1,4,6-trimethylpiperazine-2,5-dione (**105**) (1068). Heating of the dipotassium salt of 3,6-dicarboxy-1,4-dimethylpiperazine-2,5-dione with sulfur monochloride (S_2Cl_2) in dioxane gave 1,4-dimethyl-3,6-epidithiopiperazine-2,5-dione; when the reaction mixture from the above preparation was reduced with sodium borohydride and ethylated with ethyl iodide



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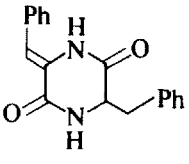

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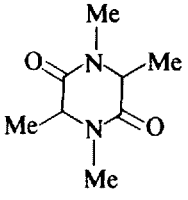

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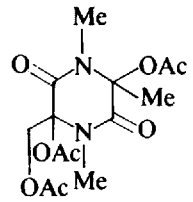

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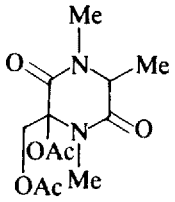
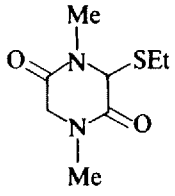


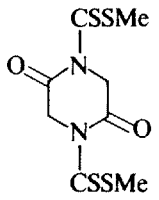
(105)



(106)

it gave *cis*-3,6-bis(ethylthio)-1,4-dimethylpiperazine-2,5-dione (1629), together with a trace of trans isomer and the monoethylthio derivative (**106**) (1629).

Piperazine-2,5-dione treated with sodium hydride in *N,N*-dimethylacetamide and carbon disulfide followed by esterification with methyl iodide gave 1-methylthio(thiocarbonyl)piperazine-2,5-dione (methyl 2,5-dioxopiperazine-1-dithiocarboxylate) and 1,4-bis[methylthio(thiocarbonyl)]piperazine-2,5-dione (**107**), but when the reaction was carried out in dimethyl sulfoxide containing tetrahydrofuran it afforded (**107**) plus 3-[bis(methylthio)methylene]-1-methylthio(thiocarbonyl)piperazine-2,5-dione (**108**) (1630).



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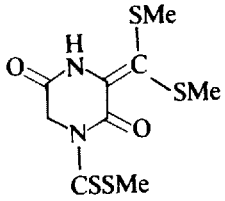

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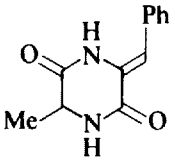


(109)

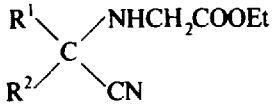
Prolonged treatment of *cis*- or *trans*-3-benzylidene-6-methylpiperazine-2,5-diones (**109**) with sodium hydroxide formed 2-benzyl-3,6-dihydroxy-5-methylpyrazine (1066), and 2-benzylidene-3-ethoxy-6-hydroxy-5-methyl-2,5-dihydropyrazine similarly treated gave 2-benzyl-3-ethoxy-6-hydroxy-5-methylpyrazine. The effect of *p*-substituted benzylidene analogues on the course of this reaction was studied (1066). Oxidations of 3-benzylidenepiperazine-2,5-diones with singlet oxygen have been shown to give piperazinetriones. For example, (*Z*)-3-benzylidene-1-methylpiperazine-2,5-dione in dichloromethane gave 1-methylpiperazine-2,3,5-trione (1616). The peptide radical ($\underline{\text{NHĊHCONHCH}_2\text{CO}}$) has been produced from the reaction of hydroxyl radicals with glycine anhydride and its reactions have been discussed (1631).

D. Piperazine-2,6-diones

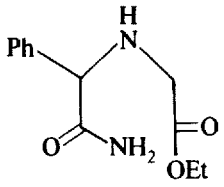
(1) *Preparation*

Piperazine-2,6-diones have been prepared as follows. A group of 3,3-dialkylpiperazine-2,6-diones were obtained by treating *N*-(1-cyanoalkyl)glycine esters

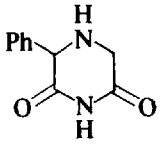
(**110**) or the corresponding amido acids or amido esters with polyphosphoric acid (1632), and *N*-(α-carbamoylbenzyl)glycine ethyl ester (**111**) with sodium hydride in xylene gave 3-phenylpiperazine-2,6-dione (**112**) (1612). A series of piperazine-2,6-diones have been prepared from aminodiacetic acids (**113**, X = COOH). Methyliminodiacetic acid heated with urea at 160–170° gave 4-methylpiperazine-2,6-dione which was benzylated at N_1 by refluxing with benzyl chloride and potassium carbonate in acetone (1633); and treatment of alkyliminodiacetic acid monoamides with acetic anhydride produced the corresponding piperazine-2,6-diones (1634, 1635). Similar methods of preparation have been reviewed (1634).



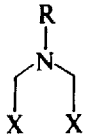
(**110**)



(**111**)

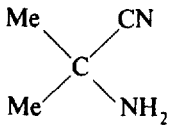


(**112**)

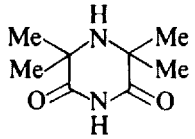


(**113**)

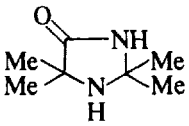
The aminonitrile (**114**) with potassium hydroxide in refluxing methanol gave 3,3,5,5-tetramethylpiperazine-2,6-dione (**115**) [plus 2,2,5,5-tetramethyl-4-oxotetrahydroimidazole (**116**)] (1636). Hydroxylamine and iminodiacetonitrile (**113**, R = H, X = CN) gave 2,6-bishydroxyiminopiperazine (**117**) (465, 1637); and sodamide in formamide effected addition of ammonia to *N*-benzyliminodiacetonitrile (**113**, R = CH_2Ph, X = CN) to yield 4-benzyl-2,6-diiminopiperazine, which underwent displacement reactions with water and hydroxylamine, the former



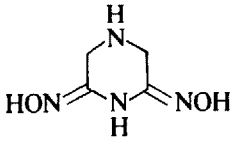
(**114**)



(**115**)



(**116**)



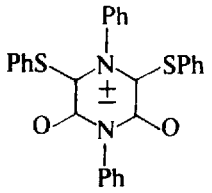
(**117**)

giving 4-benzylpiperazine-2,6-dione, and the latter giving 4-benzyl-2,6-dihydroxyiminopiperazine (1637). Sodamide in formamide with iminodiacetonitrile provided 2,6-bisformyliminopiperazine (1637).

Diiminosuccinonitrile reacts with oxalyl chloride to form 5,6-dichloro-5,6-dicyanopiperazine-2,3-dione (383) and 2,6-dibenzyloxypyrazine was reduced with hydrogen over palladium–charcoal to piperazine-2,6-dione (832).

(2) *Reactions*

Piperazine-2,6-diones are reduced to piperazines with borane–tetrahydrofuran (1634), and 3,3,5,5-tetramethylpiperazine-2,6-dione was reduced by lithium aluminum hydride to 2,2,6,6-tetramethylpiperazine (1636). 1,4-Diphenylpiperazine-2,6-dione with benzenesulfonyl chloride in pyridine was said to give anhydro-2,6-dihydroxy-1,4-diphenyl-3,5-bisphenylthiopyrazinium dihydroxide (**118**) (476a, 1635); and 1,4-diphenylpiperazine-2,6-dione with tosyl chloride in pyridine in the presence of benzoyl chloride gave anhydro-3-benzoyl-2,6-dihydroxy-1,4-diphenyl-5-(*p*-tolylthio)pyrazinium dihydroxide (476b). 3,3,5,5-Tetramethylpiperazine-2,6-dione as the sodium salt reacted with benzyl chloride or ethyl chlorocarbonate to give the corresponding 4-benzyl- or 4-ethoxycarbonyl derivative which were oxidized by *m*-chloroperoxybenzoic acid or 30% hydrogen peroxide to the free radical *N*-oxyls (**119**, R = CH_2Ph, COOEt) (1636); the corresponding 4-unsubstituted 1-oxyls were prepared by hydrolysis of the 4-ethoxycarbonyl compounds followed by spontaneous decarboxylation (1636).



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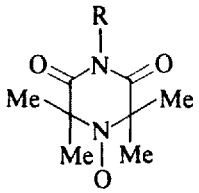


(119)

Oxidation of 1,4-diphenylpiperazine-2,6-dione with selenium dioxide in dioxane afforded 1,4-diphenylpiperazinetetraone (476b); and treatment of 1,4-diphenylpiperazine-2,6-dione with either nitrobenzene or tosyl chloride and triethylamine in benzene gave a cyclic dimer (476b).

Hydrogenolysis of 4-benzylpiperazine-2,6-diones over palladium–charcoal produced 4-unsubstituted piperazine-2,6-diones in high yield. The amino group in 1-phenylpiperazine-2,6-dione underwent alkylation with benzyl chloride and phenacyl bromide, but not with simple alkyl halides (1638). Oxidative dimerizations of piperazine-2,6-diones in nitrobenzene have been studied (1639). 2,6-Bis(hydroxyimino)piperazine heated with palladium–charcoal in *o*-dichlorobenzene gave 2,6-diaminopyrazine (465).

E. Piperazine-2,3,5-triones and Piperazinetetraones

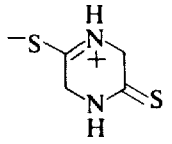
Piperazine-2,3,5-trione has been prepared from aminoacetamide and diethyl oxalate in methanolic sodium methoxide (365b). Oxanilic acid (PhNHCOCOOH) refluxed with thionyl chloride gave 1,4-diphenylpiperazinetetraone (identical with authentic material obtained by chromic acid oxidation of 1,4-diphenylpiperazine-2,5-dione) (1640). Hydrolysis of 3,3,5,5,6,6-hexachloro-4-cyclohexyl-1-phenylpiperazin-2-one by heating at 100° with aqueous acetic acid gave 1-cyclohexyl-4-phenylpiperazinetetraone (probably) (853).

Piperazine-2,3,5-trione heated with phosphorus pentachloride produced 2,3,5-trichloropyrazine (365b). Electrochemical reduction of piperazinetetraone to piperazine-2,5-dione has been studied (1641).

F. Piperazinethiones

2-Iminopiperazine when treated with hydrogen sulfide gives piperazine-2-thione (1614), and *N*-(aminoacyl)aminoacetonitrile with ammonium hydrogen sulfide gave 5-thiopiperazin-2-one (1619). Piperazine-2,5-dithione may be prepared from aminoacetonitrile and hydrogen sulfide in ammoniacal solution (1642).

Piperazine-2,5-dithiones, thio analogues of cyclic dipeptides, have been shown to have a flattened boat configuration (1643), and infrared spectroscopic studies indicate that in the trans tautomer **(120)** the C–N bond has a more pronounced double bond character than that of the trans amide tautomer (1644).



(120)

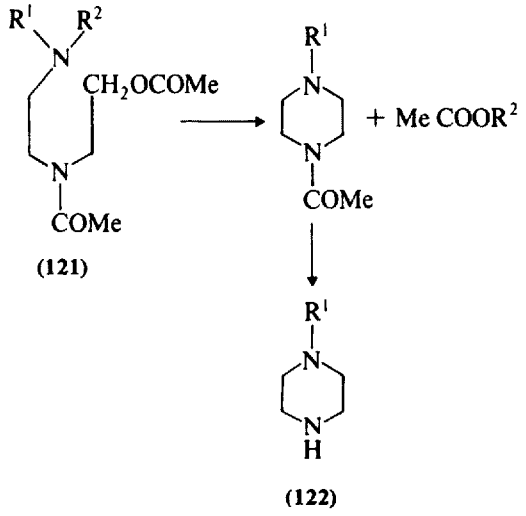
3. PIPERAZINES

Previous reviews of piperazines are listed in Table XI.1, and Kurgan et al. (1645) have also covered various aspects of piperazine chemistry. Some more recent literature is described below.

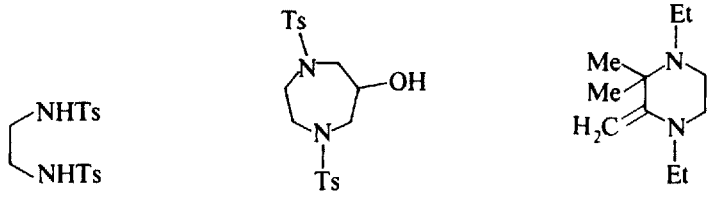
A. Preparations

The preparation of piperazines from ethylenediamines has been dealt with in earlier reviews; some additional references are as follows: heating of 1,2-bis(diethylamino)ethylene with *N*,*N*′-dimethylethylenediamine at 120° gives 2-diethylamino-

1,4-dimethylpiperazine and diethylamine (1593). A method has been described for the preparation of monoalkyl(or aryl)piperazines (**122**) from substituted ethylenediamines (e.g., **121**) by elimination of an ester by heating at 200–300° followed by deacetylation (1646); similar preparations of 1,4-disubstituted piperazines were also described (1647). *N,N'*-Disubstituted ethylenediamines with ethyl α,β-dibromopropionate gave 2-ethoxycarbonylpiperazines (1391, 1648, 1649). The disodium salt of *N,N'*-ethylenebis-*p*-toluenesulfonamide (**123**) with ethyl 2,3-dibromopropionate formed 2-ethoxycarbonyl-1,4-ditosylpiperazine (1650), whereas with 2,3-dibromopropan-1-ol it has been shown to give hexahydro-1,4-ditosyl-1*H*-1,4-diazepin-6-ol (**124**) (1651) as the major product. *N,N'*-Diethyl-*N*-(2-methylbut-3-yn-2-yl)ethylenediamine (**61**) with mercuric oxide and sulfuric acid formed 1,4-diethyl-3,3-dimethyl-2-methylenepiperazine (**125**), which was reduced with hydrogen over palladium–charcoal to 1,4-diethyl-2,3,3-trimethylpiperazine (1595).



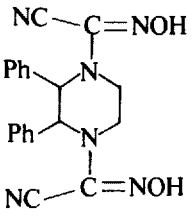
(**121**) (**122**)



(**123**) (**124**) (**125**)

Heating of alkylenediamines with various glycols at high pressures in an autoclave, using Raney nickel as a catalyst, affords *C*-alkylated piperazines in good yield. The reaction of propylenediamine with ethylene glycol, propylene glycol, and 2,3-butanediol, respectively, formed 2-methylpiperazine, *cis*- and *trans*-2,5-dimethylpiperazine, and α-, β-, and γ-2,3,5-trimethylpiperazine. *C*-Alkylated piperazines

were also prepared by cyclization of *N*-(2′-hydroxyalkyl)alkylenediamines under a high pressure and in the presence of a catalyst (343). *N,N′*-Bis(α-cyanobenzyl)-ethylenediamine, $[PhCH(CN)NHCH_2]_2$, with sodium nitrite in acetic acid is reported to give 1,4-bis(*C*-cyano-*C*-hydroxyiminomethyl)-2,3-diphenylpiperazine (**126**) or 1,4-bis(*C*-cyano-*C*-hydroxyiminomethyl)-2,3-diphenyl-1,4,5,6-tetrahydropyrazine (**127**) (1572). Bis(β-hydroxyethyl)amines react with primary amines to give aryl-, aralkyl-, and alkylpiperazines (1652); and diethanolamine with phosphorus pentafluoride gave 1,4-bis(hydroxyethyl)piperazine (1653).



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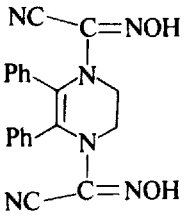
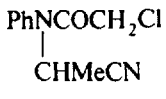


(127)

The product obtained by heating *N,N*-bis(2-chloroethyl)amine (1654) has been shown to be 1,4-bis(2′-chloroethyl)piperazine (1655–1657) and bis(2-chloroethyl)amine with anilines gave 4-arylpiperazine (1658). Reduction of *N*-chloroacetyl-1-cyanoethylaniline (**128**) with lithium aluminum hydride gave 2-methyl-1-phenylpiperazine (1659). Sodamide in formamide effected addition of ammonia to *N*-benzyliminodiacetonitrile (**113**, R = CH_2Ph, X = CN) to yield 4-benzyl-2,6-diiminopiperazine (**129**), which underwent a displacement reaction with hydroxylamine to 4-benzyl-2,6-dihydroxyiminopiperazine (1637). Aminoacetonitrile with hydroxylamine in aqueous sodium carbonate gave 2,5-bishydroxyiminopiperazine (465).



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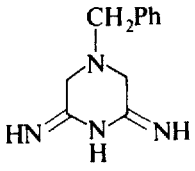
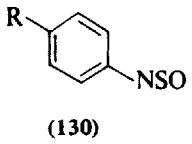


(129)

When bis(2-anilinoethyl) phenylphosphonite $[PhP(OCH_2CH_2NHPh)_2]$ (from 2,3-diphenyl-1,3,2-oxazaphospholidine with 2-anilinoethanol) was heated at 200° for 1 hour it gave 1,4-diphenylpiperazine (1660). The reaction of *p*-substituted *N*-sulfinylanilines (**130**) with styrene oxide in the presence of tetraethylammonium bromide produced the corresponding 1,2,4,5- (**131**) and 1,2,4,6-tetraarylpiperazines, whose configurations have been established on the basis of the n.m.r. spectral studies (1661). Heating of *N*-sulfinylaniline (**130**, R = H) with ethylene carbonate (**132**) and lithium bromide at 140° for 6 hours gave 50% 1,4-diphenylpiperazine (1662).



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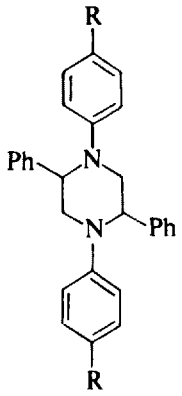

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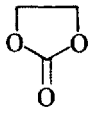
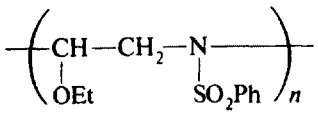


(132)

Benzenesulfonyl azide ($PhSO_2N_3$) reacted with ethyl vinyl ether (CH_2=CHOEt) to yield a 1:1 polymer (**133**) and a small amount of 1,4-bisbenzenesulfonyl-2,5-diethoxypiperazine (**134**) (1600). A similar reaction was observed between tosyl azide and ethyl vinyl ether (1601) and between benzenesulfonyl azide and butyl vinyl ether (1600).



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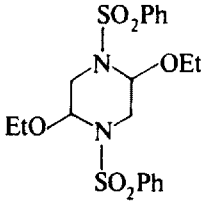


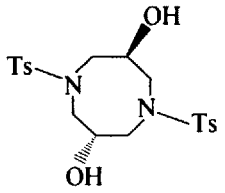
(134)

The base-catalyzed additions of glyoxal to formamide and methanesulfonamide afforded 1,4-diformyl- (895, 1663) and 1,4-bis(methylsulfonyl) derivatives (895) of 2,3,5,6-tetrahydroxypiperazines, respectively, in addition to the corresponding *N,N'*-disubstituted 1,2-diamino-1,2-ethanediols (895). Salts of 2,3,5,6-tetrahydroxypiperazine-1,4-disulfonic acid were similarly prepared by the addition of aqueous glyoxal to sulfamic acid in the presence of base (1664). Ethylene dichloride with hydrazine in ethanol gave ethylene dihydrazine, 1,4-diaminopiperazine, and poly(ethylenehydrazine) (1665).

N-Benzyl-2-methylaziridine with phenol and dimethylformamide at 60° formed (2*S*,5*S*)-dimethyl-1,4-dibenzylpiperazine (1666), 1-cyclohexylaziridine with phenylmagnesium bromide gave 1,4-dicyclohexylpiperazine (1667), and some 1-alkylaziridines with alkyl, alkenyl, or benzyl halides, as well as with dialkylchloroethylamines, have been found to give nearly quantitative yields of the corresponding 1,1,4-trialkylpiperazinium halides (1668). Dimerization of dimethyl 1-(*p*-methoxyphenyl)aziridine-2,3-dicarboxylate gave two isomers of 2,3,5,6-

tetramethoxycarbonyl-1,4-bis(*p*-methoxyphenyl)piperazine (1669), and heating of methyl 1-phenylaziridine-2-carboxylate gave *trans*-2,3-dimethoxycarbonyl-1,4-diphenylpiperazine (1669).

Treatment of *trans*-1,5-bis(*p*-toluenesulfonyl)-3,7-dihydroxyoctahydro-1,5-diazocine (**135**) with thionyl chloride gave *trans*-1,4-di(*p*-toluenesulfonyl)-2,5-di(chloromethyl)piperazine (**136**) and *trans*-1,4-bis(*p*-toluenesulfonyl)-6-chloro-2-chloromethylhexahydro-1,4-diazepine (**137**) (507), and treatment of *cis*-1,5-diphenyl-3,7-dihydroxyoctahydro-1,5-diazocine with phosphorus tribromide yielded a mixture of *cis*-2,6-bis(bromomethyl)-1,4-diphenylpiperazine and *cis*-2,5-bis(bromomethyl)-1,4-diphenylpiperazine (1670).



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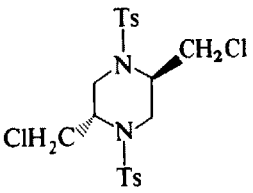

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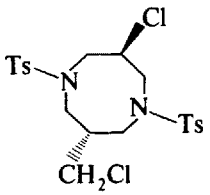


(137)

Some reported reductions of pyrazines (reagents given) to the corresponding piperazines are as follows: 2-(2′-hydroxyethyl) (H_2/Pt/MeOH) (1671), 2-carbamoyl-6-chloro (?) (839, cf. 985) (red phosphorus and hydriodic acid) (839), carboxy, carbamoyl, dicarboxy, dicarbamoyl, and dialkoxycarbonyl (H_2/Pd/C/KOH) (1269, 1352), and tetramethoxycarbonyl (H_2/Pd/C) (1326). Reduction of 1-benzyl-3-methyl-, 1-benzyl-3,5-dimethyl-, and 1-benzyl-2,5-dimethylpyrazinium salts with sodium borohydride gave the corresponding piperazines (1672), and catalytic reduction of 1,4-diethylpyrazinium difluoroborate gave 1,4-diethylpiperazinium dihydrofluoroborate (621). The reduction of 2,3-dihydropyrazines to piperazines has been described in Section 1B(2).

Reductions of a series of pyrazine *N*-oxides with sodium borohydride in water or methanol at room temperature gave *N*-hydroxypiperazines; for example, 2,3,4-trimethylpyrazinium 1-oxide iodide gave 1-hydroxy-2,3,4-trimethylpiperazine (766). When tosylated diethanolamine was allowed to react with hydroxylamine, detosylation and methylation occurred to afford 1-hydroxy-4-methylpiperazine (1673).

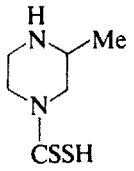
B. Properties

Dipole moments have been measured in the piperazine series in an attempt to correlate those of noncyclic nitramines and nitrosamines with the moments of some homologous dinitroso- and dinitropiperazines (1674), to examine the conformation of certain 1,4-disubstituted piperazines (1675), and to examine the effective size of the lone pair on nitrogen (1676). Infrared spectral measurements of the ν_{NH} first overtone and electronic dipole moment measurements indicate that the N–H in a

piperazine prefers the equatorial position by about the same amount as in piperidine (1677).

Proton magnetic resonance measurements have been used to determine the inversion rates of some substituted piperazinium chlorides (1678), the predominant conformation of the five isomeric 1,4-dinitroso-2,3,5,6-tetramethylpiperazines (1679), and conformational statics and dynamics of 1,4-disubstituted piperazines (1680). The chemical shift of the *N*-methyl group of various 1,4-dimethylpiperazinium dichlorides has been examined in the presence of α-substituents; and the basicities of nitrogens 1 and 4 and the nitrogen 1 inversion rate, in H_2O and D_2O at 33°, have been determined by analysis of this signal in the case of 1,4-*cis*-(2,6)-tetramethylpiperazine (1681). Carbon-13 chemical shifts have been measured for a number of substituted nitrosopiperazines (1682), and the population ratio of the *ee* and *ae* + *ea* conformations in 1,4-dichloropiperazine at −45°C was determined as 3 : 1 (AG° = 0.5 kcal/mol) (1683).

Ionization constants of 2-carboxypiperazine and the three dicarboxylic acids have been determined (1684), and the nucleophilic reactivity of piperazine compared to other amines in reactions with 1-chloro-2,4-dinitrobenzene has been measured (1685). The rate of quaternization of 1-ethoxycarbonyl-4-methylpiperazine with allyl bromide (k = 2.25 l/mol · min) and methyl iodide ($10k$ = 1.22) have been measured in acetone–water solution (1686). The composition and structure of the 2-methylpiperazine–carbon disulfide complex has been investigated: it was a mixture of 1-dithiocarboxy-3-methylpiperazine **(138)** and the 2-methylpiperazine salt of 1,4-bis(dithiocarboxy)-2-methylpiperazine (1687).

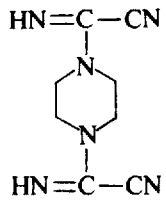


(138)

A study has been made of anti-pinworm activity of many quaternary piperazines (1688). In general, it has been found that the presence of the piperazine nucleus in drugs makes their activity more effective and decreases their toxicity (1689).

C. Reactions

Piperazine reacts with benzyl chloroformate to give 1-(benzyloxycarbonyl)-piperazine (1690), with benzyl chloride (1 mol) (and piperazine dihydrochloride) to 1-benzylpiperazine (1691–1693), with ethyl chloroformate and sodium hydroxide to 1,4-diethoxycarbonylpiperazine, which with sodium benzyl oxide gave 1,4-dibenzyloxycarbonylpiperazine (1694), and with cyanogen to 1,4-bis(*C*-cyano-*C*-iminomethyl)piperazine **(139)** (1695). The piperazine–chlorotrimethylsilane adduct with triethylamine gave 1,4-bis(trimethylsilyl)piperazine (1696), and piperazine in



(139)

tetrahydrofuran with triphenylsilyllithium formed 1,4-bis(triphenylsilyl)piperazine (1697).

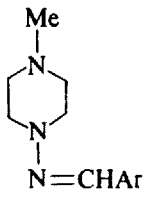
Piperazine treated with methyl acrylate in methanol gave 1,4-bis(2′-methoxycarbonylethyl)piperazine, and a similar reaction occurred with 2-methylpiperazine (1698). 1-Methylpiperazine in chloroform with phosgene formed 1-chlorocarbonyl-4-methylpiperazine hydrochloride, which with diethylamine in chloroform gave 1-diethylcarbamoyl-4-methylpiperazine (1699). 1-Ethylpiperazine with ethylene sulfide gave 1-ethyl-4-(2′-mercaptoethyl)piperazine (1700). The alkylation of alkyl(and aryl)piperazines with, for example, chloroacetonitrile and potassium carbonate in dimethylformamide to produce 1,4-disubstituted piperazines has been described (1701).

Syntheses of some unsymmetrical 1,4-disubstituted 2-methylpiperazines from 2-methylpiperazine first by monoalkylation and then by reaction with ethylene chlorohydrin have been reported (1702); also 1-substituted piperazines with halogenonitriles (1703). Alkylation of 1-benzylpiperazine with β-methoxyethyl toluene-*p*-sulfonate gave 1-benzyl-4-(2′-methoxyethyl)piperazine, which was debenzoylated with palladium–charcoal in acetic acid (1693). Alkylation of 1-methyl(and phenyl)piperazine by ethyl benzoate and lithium aluminum hydride to give 1-benzyl-4-methyl(and phenyl)piperazine has been reported (1704).

A series of mono- and disulfonyl β-aminoethylpiperazines has been prepared, in most cases by a modified Schotten–Baumann reaction. The benzyloxycarbonyl blocking group was employed in the preparation of the monosubstituted compounds and was removed by catalytic hydrogenation without cleavage of the sulfonyl group (1705). 1-Benzyloxycarbonyl-4-trifluoroacetylpiperazine with acetic acid saturated with hydrogen bromide gave 1-trifluoroacetylpiperazine (1706). The use of various protecting groups in the synthesis of unsymmetrical piperazines has been discussed (1707). 1,4-Dibenzyl-2-hydroxymethylpiperazine hydrogenated over palladium–charcoal in acetic acid gave 2-hydroxymethylpiperazine (1651).

Hydrazones (**140**) derived from 4-amino-1-methylpiperazine can be reduced by sodium borohydride to 1-arylmethylamino-4-methylpiperazine (**141**) (1708). 1-Methylpiperazine vacuum distilled with formalin gave bis-(1-methylpiperazinyl)-methane, which refluxed with methyl iodide in methanol formed 1,4-dimethylpiperazine dimethiodide (1709). 1-Methylpiperazine with carbon disulfide in ethanol produced 1-dithiocarboxy-4-methylpiperazine, which was reduced by lithium aluminum hydride to 1,4-dimethylpiperazine (1709).

Piperazine with nitrous acid gave 1,4-dinitrosopiperazine, which was reduced by lithium aluminum hydride to 1,4-diaminopiperazine (1710); the electrochemical



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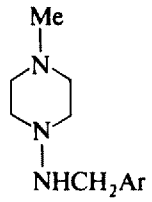
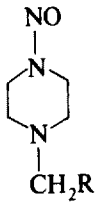


(141)

reduction with a mercury cathode has also been described (1711). 1-Methylpiperazine with aqueous nitrous acid formed 1-methyl-4-nitrosopiperazine (1712). 1-Nitrosopiperazine with 33% formaldehyde (CH_2O) gave the unstable 1-hydroxymethyl-4-nitrosopiperazine (**142**, R = OH), which was hydrolyzed by refluxing in 92% formic acid to mainly 1-methyl-4-nitrosopiperazine (**142**, R = H) and some 1-methylpiperazine (1713). *trans*-1-Benzyl-3,5-dimethylpiperazine with nitrous acid gave the 4-nitroso derivative, which with lithium aluminum hydride in tetrahydrofuran produced *trans*-1-amino-4-benzyl-2,6-dimethylpiperazine (1613). Transnitrosation by nitrosopiperazines has been studied (1714) and the kinetics and mechanism examined (1715).



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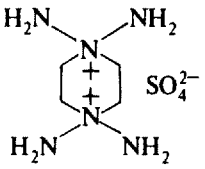


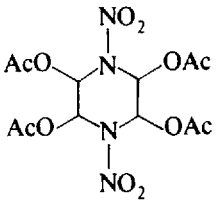
(143)

1,1,4,4-Tetraaminopiperazinium sulfate (**143**) has been prepared by exhaustive amination of 1,4-diaminopiperazine with the sodium salt of hydroxylamido-*O*-sulfuric acid (H_2NOSO_3Na) (1716). 1-Methylpiperazine heated with palladium in the presence of moisture formed 1-formyl-4-methylpiperazine (1717).

Dehydrogenations of piperazines to pyrazines have been described in Section II.6, and the conversion of piperazine over catalysts (e.g., CuO) to give mostly pyrazine (90–94%) has been studied (1718). The oxidation of 1,4-diphenylpiperazine with manganese dioxide in chloroform at 20° to yield *N,N'*-diformyl-*N,N'*-diphenylethylenediamine has been reported (1719). Formylpiperazines have been reported as formylating agents. Thiophene, 1,4-diformylpiperazine, and phosphoryl chloride are reported to give 2-formylthiophene (1720).

1,4-Diformyl-2,3,5,6-tetrahydroxypiperazine was readily acetylated by a 1:1 mixture of acetic acid and acetic anhydride in the presence of an acid catalyst to give 2,3,5,6-tetraacetoxy-1,4-diformylpiperazine (895) [the 1,4-bis(methanesulfonyl) analogue was prepared similarly (895)] and in like manner benzoyl chloride in pyridine gave 2,3,5,6-tetrabenzoyloxy-1,4-diformylpiperazine (895). 1,4-Diformyl-2,3,5,6-tetrahydroxypiperazine was nitrated for 1 hour at 0° in a mixture of nitric acid and acetic anhydride to give 1,4-diformyl-2,3,5,6-tetranitratopiperazine [and

the 1,4-bis(methylsulfonyl) analogue was prepared similarly] (895). Salts of 2,3,5,6-tetrahydroxypiperazine-1,4-disulfonic acid treated with nitric acid and acetic anhydride gave 2,3,5,6-tetraacetoxy-1,4-dinitropiperazine (**144**) and 2,5-diacetoxy-3,6-dinitrato-1,4-dinitropiperazine (**145**) (1664).



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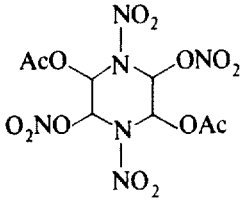
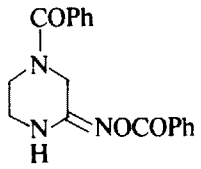


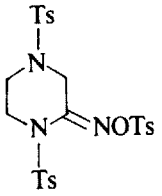
(145)

1-Cyclohexyl-2-oxo-4-tosylpiperazine allowed to stand with phenol and 35% hydrobromic acid at 37° in acetic acid formed 1-cyclohexyl-2-oxopiperazine (853). 2-Ethoxycarbonyl-1,4-di-*p*-tosylpiperazine refluxed with 47.5% hydrobromic acid gave 2-carboxypiperazine which with ethanol, benzene, and sulfuric acid on distillation gave 2-ethoxycarbonylpiperazine, which with concentrated ammonium hydroxide at room temperature or with hydrazine hydrate formed the amide or hydrazide, respectively (1391, 1648). The preparation of mono-*N*-alkyl(and acyl)piperazines by (nonhydrolytic) cleavage of the 4-substituted 1-ethoxycarbonyl-piperazines with hydrogen bromide in acetic acid has been described (1721).

Hydrolysis of 3-ethoxycarbonylpiperazine-2,5-dione gave 3-carboxypiperazine-2,5-dione (pK_a 2.5) (1722) and 3-ethoxycarbonylpiperazine-2,5-dione with primary and secondary amines gave the expected amides (1722). 2-Hydroxyiminopiperazine with benzoyl chloride gave the dibenzoyl derivative (**146**) and with tosyl chloride gave a tritosyl derivative (**147**) (926). Reduction of 3-phenylpiperazin-2-one with lithium aluminum hydride gave 2-phenylpiperazine, also obtained by similar reduction of 3-phenylpiperazine-2,6-dione (1612).



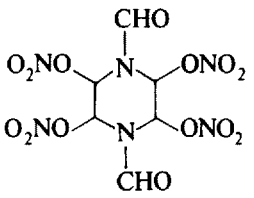
(146)



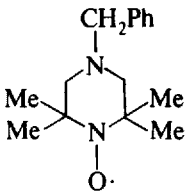
(147)

Chlorinations of nuclear and extranuclear hydroxyl groups by thionyl chloride have been described in the following piperazines: 1,4-diformyl-2,3,5,6-tetrahydroxy (thionyl chloride and pyridine at reflux) (895), 2,3,5,6-tetrahydroxy-1,4-bis-(methanesulfonyl) (895), 2-hydroxymethyl-1,4-di(?)methyl (thionyl chloride in carbon tetrachloride at 70°) (1649), 2-(2′-hydroxyethyl) (1671), and 1-benzyl-4-(2′-hydroxyethyl) (1723). Treatment of 2-hydroxymethyl-1,4-ditosylpiperazine with dibromotriphenylphosphorane gave 2-bromomethyl-1,4-ditosylpiperazine (1650).

Thermal decomposition of 2,3,5,6-tetrachloro-1,4-diformylpiperazine gave 2-chloropyrazine (Section V.10) (895). 2,3,5,6-Tetrachloro-1,4-diformylpiperazine stirred with silver nitrate in acetonitrile formed 1,4-diformyl-2,3,5,6-tetranitratopiperazine (**148**) (895) and the 1,4-bis(methanesulfonyl) analogue was prepared similarly (895). 2,3,5,6-Tetrachloro-1,4-diformylpiperazine refluxed with ethanol and barium carbonate gave 2,3,5,6-tetraethoxy-1,4-diformylpiperazine (895), and the methoxy analogue was prepared likewise (895). Hydrogenation of 3,6-dibromo-1,4-diphenylpiperazine-2,5-dione in dioxane over palladium gave 1,4-diphenylpiperazine-2,5-dione (853); 3,6-dibromo-1,4-diphenylpiperazine-2,5-dione stirred with aniline formed 3,6-dianilino-1,4-diphenylpiperazine-2,5-dione (853), and boiled with ethanol produced 3,6-diethoxy-1,4-diphenylpiperazine-2,5-dione (853). *cis*-2,6-Bis(bromomethyl)-1,4-diphenylpiperazine was converted with lithium aluminum hydride to the *cis*-2,6-dimethyl-1,4-diphenylpiperazine (1670). 2-(Bromomethyl)-1,4-ditosylpiperazine with phenol and hydrobromic acid at reflux gave 2-(bromomethyl)piperazine, which with sodium hydrogen sulfide produced 2-mercaptomethylpiperazine (1724), and 1-(2′-bromoethyl)piperazine with potassium hydrogen sulfide formed 1-(2′-mercaptoethyl)piperazine (1700).



(148)



(149)

Anhydrous piperazine refluxed with methyl formate produced 1-formylpiperazine (1725), which was reduced with lithium aluminum hydride to 1-methylpiperazine (1703). 1-Nitroso-4-phenylpiperazine in tetrahydrofuran with diisopropylamine, methyllithium, and carbon dioxide formed 2-carboxy-1-nitroso-4-phenylpiperazine, which was cleaved by dry hydrogen chloride in benzene to 3-carboxy-1-phenylpiperazine (1726). Distillation of the calcium salt of *trans*-2,3-dicarboxy-1,4-diphenylpiperazine gave 1,4-diphenylpiperazine (1669). Reduction of 1-ethoxycarbonyl-4-trifluoroacetylpiperazine with borane in tetrahydrofuran formed 1-ethoxycarbonyl-4-(2′,2′,2′-trifluoroethyl)piperazine (1706), and 1-trifluoroacetylpiperazine similarly treated gave 1-(2′,2′,2′-trifluoroethyl)piperazine (1706). 2-Ethoxycarbonyl-1,4-ditosylpiperazine with lithium aluminum hydride in tetrahydrofuran gave 2-hydroxymethyl-1,4-ditosylpiperazine (1651).

Oxidation of 4-benzyl-2,2,6,6-tetramethylpiperazine with 30% hydrogen peroxide in methanol gave the free radical 4-benzyl-2,2,6,6-tetramethylpiperazine 1-oxyl (**149**) (1636).

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APPENDIX

Systematic Tables of Simple Pyrazines

INTRODUCTION

The Tables (A.1 to A.35) contain as complete a list as possible of the simple pyrazines described through 1978, with the addition of some compounds to 1980. The tables were prepared from *Beilstein* to 1929 and the index of *Chemical Abstracts* to 1978 (Volume 89), with the addition of some data from original papers thereafter. Melting (or boiling) points are given for most of the pyrazines listed with a selection of the best references; in other cases references to preparations or alternative physical data are also recorded.

PYRAZINES EXCLUDED FROM THE TABLES

The tables of simple pyrazines have been prepared usually after exclusion of the following compound types, which were not classified as simple:

Pyrazines reduced in the nucleus (hydropyrazines)
Pyrazines with heterocyclic substituents (except piperidino)
Pyrazines fused with other ring systems
Pyrazines with more than six carbon atoms in a substituent (except benzyl)
Pyrazines with substituted phenyl groups
Pyrazines with difunctional groups
Pyrazines with substituted ureido, thioureido, or guanidino groups.

TERMS USED IN THE TABLES

The title of each table makes use of inclusive terms (for brevity) for the type of substituent, arranged in alphabetical order.

Alkyl includes alkyl, aryl, aralkyl, alkenyl, alkynyl, and cycloalkyl groups.

Amino includes amino, imino, alkylamino, dialkylamino, anilino, hydrazino, acylamino, sulfanilamido, trialkylammonio, ureido, thioureido, and guanidino groups.

Carboxy includes carboxy (carboxylic acids), alkoxycarbonyl (esters), carbamoyl (amides), thiocarbamoyl, hydrazinocarbamoyl (hydrazides), guanidinocarbonyl, azidocarbonyl (azides), chlorocarbonyl (acid chlorides), amidino, *C*-hydrazino-*C*-iminomethyl, *C*-alkoxy-*C*-iminomethyl (imino ethers), *C*-alkylthio-*C*-iminomethyl (iminothioethers), cyano (nitriles), *C*-formyl(aldehydes), dialkoxymethyl (acetals of aldehydes), *C*-acyl (ketones), isocyanato, and thiocyanato groups.

Halogeno includes only the four halogens.

Nitro includes nitro and azo groups.

Oxy includes hydroxy (and hydroxyalkyl), alkoxy (and alkoxyalkyl), aryloxy, acyloxy (e.g., acetoxy), and oxo groups.

Sulfonyl includes alkylsulfonyl (sulfones), alkylsulfinyl (sulfoxides), sulfo (sulfonic acids), and sulfamoyl (sulfonamides) groups.

Thio includes mercapto, thioxo (thiones), alkylthio (thioethers or sulfides), and acylthio groups.

USE OF THE TABLES

All tables include relevant *C*-alkyl derivatives of the type of pyrazine listed. For example, Table A.2 (aminopyrazines) contains aminopyrazines and *N*-substituted analogues, as well as *C*-alkyl derivatives; and Table A.21 (carboxy halogenopyrazines) lists 2,6-dichloro-3-cyano-5-methylpyrazine.

There is a separate table for each class of pyrazine with one type of substituent, a table for each combination containing two types of substituents, and appropriate tables for three and four types of substituents. Thus, for example, 2-amino-3-ethoxypyrazine is listed in Table A.12 (amino oxypyrazines), 3-amino-2-methoxycarbonyl-5-methylsulfinylpyrazine in Table A.16 (amino carboxy sulfonylpyrazines), and 2-amino-5-chloro-6-ethoxy-3-ethoxycarbonylpyrazine in Table A.20 (amino carboxy halogenopyrazines with other functional groups).

For the pyrazine *N*-oxides, there is a table for each substituent type, and compounds are listed (once only) at the first opportunity. For example, 2-amino-6-chloromethyl-3-cyanopyrazine 1-oxide is listed in Table A.31 (aminopyrazine *N*-oxides) and 2-hydroxy-5-methoxycarbonylpyrazine 1-oxide in Table A.32 (carboxypyrazine *N*-oxides).

In the melting point and boiling point column, boiling points are indicated by a pressure in mm Hg or atm. (atmospheric) e.g., 154°/atm. or 58/21. A m.p. given, for example, as 97–98°, indicates the range of melting; one given, for example, as 114 to 116°, indicates the limits of variation in the literature; and an entry given, for example, as 200–205°, 212–213°, indicates a divergence of figures in the literature. Abbreviations for derivatives are self-explanatory (such as pic. for picrate, HCl for hydrochloride, H_2O for hydrate). No distinction has been made between "melting point," "melting with decomposition at," "decomposing at," etc., because of markedly different usage by various authors. The use of "greater

than" (e.g., $> 180°$) in the melting point column indicates that the substance either melted above, or did not melt below this temperature. In some instances melting points or boiling points have not been given in the literature but the compounds have been included in the tables for reference, and (where available) other physical properties used for characterization such as infrared spectra (i.r.), mass spectra (m.s.), nuclear magnetic resonance (n.m.r.), and analyses (anal.) may have been noted. Satisfactory analyses have generally been reported for compounds listed in the tables but in some instances compounds have been included for which analyses have not been provided.

To facilitate the use of the tables, references should be made to the table of contents in the front of the book. Entries in the tables are not repeated in the index.

TABLE A.1 ALKYL- AND ARYLPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
Unsubstituted	47, 48, 50 to 55, 57; 112–114/730, 115.5–115.8/755, 118/768.4; H_2SO_4 136–137; $HgCl_2$ 270 to 273; Pic. 155 to 157; MeI 136; MeI · $6HgCl_2$ 217–218; EtI 162; 2ICl 177	22, 28, 30, 31, 32, 237, 249, 272, 397, 464, 559–562, 564, 565, 573, 578, 619, 1727
2-Allyl	I.r., m.s., n.m.r.	618
2-Benzyl	107–108/1.3	643
3-Benzyl-2,5-diphenyl	98–99	1535
2-Benzyl-3,5-dimethyl	95, 98–99	26, 1535
2,3:5,6-Bishexamethylene	115–116; 134–138/0.01	253
2-(1′-Butenyl)	90–91/12; pic. 100–101	1020
2-Butyl	84/19, 90–92/20; pic. 39–42	612, 643
2-*s*-Butyl	I.r., m.s., n.m.r.	640, 693
2-*t*-Butyl	G.l.c., anal., n.m.r.	638
2-Butyl-3,5-dimethyl	M.s.	72
3-Butyl-2,5-dimethyl	67/1	612
5-Butyl-2,3-dimethyl	G.l.c., anal., n.m.r.	635
2-Butyl-3-methyl	83–84/9	331
2-Butyl-6-methyl	105–108/22	645
2-*s*-Butyl-5-methyl	G.l.c., n.m.r.	614
2-*s*-Butyl-6-methyl	G.l.c., n.m.r.	614
2-*t*-Butyl-5-methyl	I.r., m.s.	329
2-*t*-Butyl-6-methyl	I.r., m.s.	329
2-Butyl-3,5,6-trimethyl	65–66/0.3	648
2-Butyl-3,5,6-triphenyl	109	330a
2-(But-3′-ynyl)-6-methyl	103–104/12	645
2-Cyclopentyl-6-methyl	–	640
2,5-Dibenzyl	76	303
2,5-Dibenzyl-3,6-dimethyl	97–98 or 100–100.5; pic. 125–126; H_2PtCl_6 197–198	212, 290, 292
2,5-Dibenzyl-3,6-diphenyl	145–147	1535

TABLE A.1 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,6-Dibenzyl-3,5-diphenyl (?)	146–147	26, cf. 1535
2,5-Dibutyl	95/11.5	668a
2,5-Di-*s*-Butyl	112–117/13; H_2PtCl_6 183	87, 89, 668a
2,6-Di-*s*-Butyl	I.r.,m.s., n.m.r.	614
2,5-Di-*t*-Butyl	108–109	233
2,5-Dibutyl-3,6-dimethyl	82–83/0.3	648
2,3-Diethyl	G.l.c., anal.	635
2,5-Diethyl	185.5–186/767; 64/12; pic. 93, 97–98	43, 53, 165, 487
2,6-Diethyl	70/20	53
2,5-Diethyl-3,6-diisobutyl	106–107/12; HCl 82–84	1728
2,6-Diethyl-3,5-dimethyl	N.m.r.	637
2,5-Diethyl-3,6-dimethyl	$8H_2O$, 48–50; 215–217 (corr.)/atm., 65/2, 81/7.6	8, 218, 306, 512
2,5-Diethyl-3,6-diphenyl	140 to 145–146	175, 240, 328
2,3-Diethyl-5-methyl	M.s.	67
3,5-Diethyl-2-methyl	M.s.	67
2,5-Di-*n*-hexyl-3,6-dimethyl	113–114/0.3	648
2,5-Diisobutyl	103/13	668a
2,5-Diisobutyl-3,6-dimethyl	242–244/atm., 110–112/12, 74–75/0.5	210, 648, 1728
2,5-Diisopentyl-3,6-dimethyl	96–98/0.45	648
2,5-Diisopropyl	206–207/atm.	174
2,5-Diisopropyl-3,6-dimethyl	44–46	225
2,3-Dimethyl	157/760, 47/10; pic. 150, 151–153	332, 333, 397, 654, 687
2,5-Dimethyl	15, 154/atm., 155/760, 160.2/atm., 58/21; Pic, 154, 157; MeI 230, 235; MeBr 222; EtBr 182	23, 32, 196, 197, 255, 271, 289, 306, 411, 512, 655, 659, 1316
2,6-Dimethyl	39, 47–48; 155.6/atm.; pic. 175–176	33, 659
2-(2′,3′-Dimethylbut-1′-enyl)-6-methyl	86–89/2	657
2,5-Dimethyl-3,6-dipentyl	108–109/0.6; H_2PtCl_6 231	211, 648
2,3-Dimethyl-5,6-diphenyl	97–98	513, 514
2,5-Dimethyl-3,6-diphenyl	124 to 128; pic. 153–154	166, 176, 191, 192, 207, 209, 211, 232, 240, 241, 292, 294, 328, 505a, 512, 743, 1290
2,6-Dimethyl-3,5-diphenyl (?)	102	242
2,5-Dimethyl-3,6-dipropyl	235–240/atm.; pic. 95	201, 208
2,5-Dimethyl-3-pentyl	96.5/7	612
3,5-Dimethyl-2-pentyl	M.s.	72
2,5-Dimethyl-3-phenyl	124–126/1.4; pic. 154–155	612, 636
2,5-Dimethyl-3-propyl	63/4	394
3,5-Dimethyl-2-propyl	47	72, 394

TABLE A.1 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,3-Diphenyl	118 to 121	6, 25, 337, 703, 1548
2,5-Diphenyl	191 to 198	3, 10, 26, 166, 169, 170, 193, 202, 209, 236, 246, 286, 303, 305, 317, 321, 406, 505a, 1729, 1730
2,6-Diphenyl	88 to 92	26, 236, 1731
2-(1',3'-Diphenyl-2'-propyl)	65.2–66.2; 180–184/2	643
2-Ethyl	152 to 155/760	53, 669
2-Ethyl-3,5-dimethyl	64–66/8	53, 637
3-Ethyl-2,5-dimethyl	178 to 181/atm., 80–81/19; pic. 142	32, 612, 637, 695
5-Ethyl-2,3-dimethyl	76/15	635, 637, 1732
5-Ethyl-2,3-diphenyl	102–104	824, 825
2-Ethyl-3-methyl	57/10, 69–70/16	331, 635
2-Ethyl-5-methyl	79–80/56	51, 53, 1327
2-Ethyl-6-methyl	57–63/13	53
2-(2'-Ethylbut-1'-enyl)-6-methyl	69–72/0.7	657
2-(1'-Ethylpropyl)	–	693
2-Ethyl-3,5,6-trimethyl	85–90/101	330
2-Ethyl-3,5,6-triphenyl	122	330a
2-Ethyl-3-vinyl	–	653
2-Ethynyl-3-methyl	–	653
2-Hexyl	104–106/12	643
3-Hexyl-2,5-dimethyl	100.5–104/5.1	612
2-Hexyl-3-methyl	113–115/9	331
2-Hexyl-6-methyl	88–89/2.3	645
2-Hexyl-3,5,6-trimethyl	92–94/0.8	648
2-Isobutyl	67–70/10	643
2-Isobutyl-5-isopropyl	89–90/4	740a
2-Isobutyl-3-methyl	74/10	53, 331
2-Isobutyl-6-methyl	57–58/2.3	645
2-Isobutyl-3,5,6-trimethyl	55–56/0.7	648
2-Isopentyl	90–95/12	643
3-Isopentyl-2,5-dimethyl	M.s.	72
2-Isopentyl-6-methyl	98–100/12	645
2-Isopentyl-3,5,6-trimethyl	65–67/0.4	648
2-Isopropenyl	–	1497
2-Isopropyl	Anal., n.m.r.	638
2-Isopropyl-3-methyl	59/10	331
2-Isopropyl-5-methyl	M.s.	53, 329
2-Isopropyl-6-methyl	I.r., m.s., n.m.r.	329, 614
2-Isopropyl-3,5,6-triphenyl	163	330a
2-Methyl	135/761; pic. 133; 1-MeI 126–128; 4-MeI 126–128	33, 272, 405, 470, 652, 666, 671
2-Methyl-3-deutero		687
2-Methyl-6-deutero		687
5-Methyl-2,3-diphenyl	86–87	24
2-Methyl-6-(2'-methylbut-1'-enyl	112–113/13	657

TABLE A.1 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Methyl-6-(2'-methylprop-1'-enyl)	109–111/19.5	657
2-Methyl-3-pentyl	98/10	331
2-Methyl-6-pentyl	82–84/4	645
2-(2'-Methylprop-1'-enyl)	104–107/25	657
2-Methyl-3-propyl	71–72/10; 189–190.5/763	331, 334
2-Methyl-6-propyl	186–187/739	645
2-Methyl-3,5,6-triphenyl	185	330a
2-Methyl-5-vinyl	65–66/12	53
2-Methyl-6-vinyl	74–75/22	53
2-Pentyl	94–96/11	643
2-Phenyl	72–73	390, 733b, 761
2-Phenylethyl	118–121/2	643
2-Prop-1'-enyl (cis and trans)	I.r., m.s., n.m.r.	618
2-Propyl	172–174	643
Tetramethyl	$3H_2O$ 74–78; anhyd. 86–88; 189–190/atm.; MeI 212	3, 8, 15, 16, 198, 199, 201, 202, 203, 205, 239, 290, 326, 396, 562, 660, 669, 701, 1733
Tetraphenyl	241 to 256	1, 12, 14, 193, 195, 202, 220, 259, 261, 265, 268, 269, 270, 309, 328, 395, 516, 517, 554, 1734
2,3,5-Tri-*t*-butyl	61–62	233
2,3,5-Triethyl-6-methyl	232/atm.; pic. 101–102	43
Trimethyl	172–172.5/atm.; 86–88.5/35; pic. 138–141; MeI 231	43, 612, 636, 660
2,3,5-Trimethyl-6-(2',4'-dimethylpent-1'-enyl)	115–119/2	648
2,3,5-Trimethyl-6-pentyl	73–74/0.6	648
2,3,5-Triphenyl	143, 149, 152–153	330a, 339(?), 1554, 1556
2-Vinyl	60–62/20; pic. 99.2–100.2; MeI 126	470, 657

TABLE A.2 AMINOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetamido	133	1171, 1478
2-Acetamido-3-amino-5,6-dimethyl	191–193	374
2-Acetamidoethyl	150–154/0.54	731
2-Acetamido-5-ethyl	135	376
2-Acetamido-6-ethyl	98–100	376
2-Acetamidomethyl	64	690
2-Acetamido-5-methyl	211–212.5	673

TABLE A.2 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C)	Refs.
2-Acetamido-6-methyl	168–169, 170	434, 673
2-Acetamido-5-phenyl	161–162	532
2-(1′-Acetyl-3′-dimethylaminopropyl)	103–106/0.6	645
3-*N*(4′)-Acetylsulfanilamido-2,5-di-*s*-butyl	187–189	1207
2-Amino	117 to 122; acet. 133; pic. 243; MeI 176–178	397, 420, 422, 477, 575, 606, 607, 804, 818, 821, 887, 920, 1171
1-Amino/iodide	178–180	610
2-Amino-3-aminomethyl	84 to 85	1183, 1184, 1219
2-Amino-3-aminomethyl-5-methyl	81.5–82.5	1183, 1184, 1219
2-Amino-3-benzylamino-5,6-dimethyl	144.5–145.5	907
2-Amino-6-*s*-butyl	–	640
3-Amino-5-*s*-butyl-2-isobutyl	Pic. 120–121	92
3-Amino-2-*s*-butyl-5-isobutyl	–	93
3-Amino-2,5-di-*s*-butyl	112–114/0.5; pic. 134–136; *d*-camphor-β-sulfonate 109–111; *d*-bromocamphor-π-sulfonate 167–169	89
3-Amino-2,5-diethyl	42; pic. 157	478
2-Amino-3,5-dimethyl	94–95, 96; H_2O 44–45	524, 887
3-Amino-2,5-dimethyl	111 to 114; 109 to 122/10; pic. 205, 206	92, 478, 491, 680, 718, 719, 887, 921
5-Amino-2,3-dimethyl	140 to 151	420, 433, 812, 887
1-Amino-2,5-dimethyl/iodide	145–146	610
2-Amino-3-dimethylamino	110–111	370
2-Amino-5-dimethylamino	84–86	432
2-Amino-3-(3′-dimethylaminopropyl)-amino	–	1225
2-Amino-5,6-dimethyl-3-dimethylamino	108–109	370
2-Amino-5,6-dimethyl-3-methylamino	157.5–158.5	907
3-Amino-2,5-diphenyl	186	478, 491
5-Amino-2,3-diphenyl	224 to 228	420, 433, 887, 1155
2-Aminoethyl	102–103/9; 2HCl 159–161	405, 730
2-Amino-3-ethyl	56–57	887
2-Amino-5-ethyl	95	376
2-Amino-6-ethyl	88	376
2-[2′-(Amino)ethane]sulfonamido	220–222	1209
2-Amino-3-guanidinomethyl	HCl *ca.* 219	1183
3-Amino-2-isobutyl-5-isopropyl	pic. 121–122	103, 525
2-Aminomethyl	87–88/3; HCl 183–184	1029
2-Amino-3-methyl	165–167, 170–171	535, 679, 680, 887
2-Amino-5-methyl	108 to 112; 115 to 118	362, 373, 376, 420, 446, 535, 673, 1173, 1230

TABLE A.2 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C)	Refs.
2-Amino-6-methyl	121–122, 124 to 128	362, 373, 420, 433, 434, 673
1-Amino-3-methyl/iodide	132–134	610
2-Amino-3-methyl-5,6-diphenyl	150–151	887
2-Amino-3-phenyl	110	535
2-Amino-5-phenyl	140–141, 143, 144, 150	365a, 376, 532
2-Amino-6-phenyl	125–126, 126–127, [130–131(?)]	352, 365a, 420(?), 429
2-Amino-3,5,6-trimethyl	133	933
2-Anilino	132–133, 135–136	882, 921, 1614
2-Anilino-3-methyl	78–79	929
2-Azidomethyl	65/1.0	690
2-Benzamido	171	1201
2-Benzylamino	68–69, 71–71.5; pic. 139.5–140	882, 884, 921
3-Benzylamino-2,5-dimethyl	95–96.5	921
2-Benzyloxycarbonylamino-5-phenyl	192	376
2,5-Bis[bis(dimethylaminomethyl)-methyl]	92–94; $4HCl \cdot H_2O$ 235–238	715
2,5-Bis[bis(trimethylammoniomethyl)-methyl]/tetrabromide	> 360	715
2,5-Bis(dimethylamino)-3,6-dimethyl	2HCl 176–178	689, 793
2,6-Bis(dimethylamino)-3,5-diphenyl	160	937
2,5-Bis-(2′-dimethylaminoethyl)	2HCl 201–204	715
2-Bis(2′-hydroxyethyl)aminomethyl	160–162/0.2; 2HCl 131–133	1029
5-Bis(methylthio)methylenehydrazino-2,3-diphenyl	212–214	971
2-Butylamino	148–151/17; pic. 142	921, 1063
3-Butylamino-2,5-dimethyl	127–128/5	921
2-Butylaminomethyl	76–78/0.5	679
2-*s*-Butylidenehydrazino	106.5–108	1195
2-Carboxyamino (sodium salt)	Brown 257; black 275	1171
2-(*N*′-Carboxyhydrazino)	220–222	971
2,5-Diacetamido	365–366	461, 1176
2,6-Diacetamido	> 300	465
3-Diacetamido-2,5-diphenyl	117	478
2,3-Diamino	195–200, 203, 205, 205.6	369, 370, 804, 833, 921
2,5-Diamino	215, 223–224 (evac. tube)	461, 1176
2,6-Diamino	133–136	460, 465, 865
2,3-Diamino-5,6-dimethyl	212.5–213.5, 216	379, 812, 907
2,5-Diamino-3,6-dimethyl	210–211	887
2,6-Diamino-3,5-dinitro	356 (sealed tube) (darkens 300)	1180
2,3-Diamino-5,6-diphenyl	275–282, 282–283; pic. 246–247	829, 834
2,3-Diamino-5-methyl	178	483

TABLE A.2 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C)	Refs.
2,3-Diamino-5-methyl-6-phenyl	167–168, 169–170	483, 829
2,3-Diamino-5-phenyl	172–173	483, 829
2,5-Di-*s*-butyl-3-phthalamido	130	89
2,5-Di-*s*-butyl-3-phthalimido	111–112	89
2,5-Di-*s*-butyl-3-succinamido	121–122	89
2,5-Di-*s*-butyl-3-succinimido	99–101	89
2,5-Di-*s*-butyl-3-sulphanilamido	161	1207
2,5-Diethoxycarbonylamino	> 270	1172
2-Diethylamino	125/26	668a
2-Diethylaminoethyl	70–72/0.6, 83–84/1.55; pic. 103–105	716, 730
2,5-Diethyl-3-piperidino	86–94/0.04–0.05	931
2,5-Diethyl-3-propionamido	98	478
2-Dimethylamino	25.7; 64/1.2, 88–90/8; HCl 184.2–185.8; pic. 158–160; MeI 133–134, 136–137	821, 922, 936
3-Dimethylamino-2,5-diethyl	100–102/8	937
3-Dimethylamino-2,5-diisobutyl	150/20	937
3-Dimethylamino-2,5-dimethyl	100/20	680, 921
2-Dimethylamino-3,5-diphenyl	95–96	937
3-Dimethylamino-2,5-diphenyl	79	937
5-Dimethylamino-2,3-diphenyl	133	937
2-Dimethylaminoethyl	93–94/10, 114–122/20	657, 730
2-(2'-Dimethylaminoethyl)amino	120–124/4; pic. 157–159	924
2-Dimethylamino-3-isobutyl	–	844
2-Dimethylamino-6-isobutyl	–	844
2-Dimethylamino-3-methyl	HCl 228–230(?), 238–240	681, 844, cf. 680(?)
2-Dimethylamino-6-methyl	HCl 222–225	681, 844
2-(*N,N*-Dimethylaminomethyleneamino)-3-methyl	105/0.3	1254
2-(*N,N*-Dimethylaminomethylene-hydrazino)	141	973
2-[Di(*N,N*-dimethylaminomethyl)-methyl]	138–144/20	657
2-Dimethylamino-5-phenyl	96–98	937
2-Dimethylaminopropyl	80–82/2	643
2-Dimethylaminopropyl-6-methyl	90–91/2.3	645
2-Dimethylamino-3,5,6-trimethyl	162–164	935
2,5-Dimethyl-3-methylamino	HCl 228.5–229	680
2,5-Dimethyl-3-piperidino	HCl 136.2–137.4	931
2,5-Dimethyl-3-propionamido	106–108	478, 720
2-(*S,S*-Dimethylsulfimido)	pic. 148–150	1235
2,3-Diphenyl-5-piperidino	127–129	741
2,5-Diphenyl-3-propionamido	212.5	478
5-(*N'*-Dithiocarboxyhydrazino)-2,3-diphenyl	272–273	971

TABLE A.2 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C)	Refs.
3-Ethoxycarbonylamino-2,5-diphenyl	212.5	478
5-Ethoxycarbonylamino-2,3-diphenyl	126–128	971
5-(*N'*-Ethoxycarbonylhydrazino)-2,3-diphenyl	147–149; HCl 195–198	971
2-Ethoxymethyleneamino-3-methyl	106–108/8	1195
2-Ethylamino	90.5/2.5	668a
2-Ethylaminoethyl	65–68/0.55	730
2-(1'-Ethylamino-2'-methylpropyl)-3-methyl	–	614
2-(1'-Ethylamino-2'-methylpropyl)-6-methyl	–	614
3-Ethylcarbonylamino-2,5-dimethyl	106–108	478
2-Ethylidenehydrazino	106–108	1195
2-Ethyl-3-piperidino	85/0.25	931
2-Formamidomethyl	39–40; 113–114/0.06	690
2-Formamido-3-methyl	–	1200
2-Hexylamino	32; 134/2.0	921
3-Hexylamino-2,5-dimethyl	90–91/0.02	921
2-Hydrazino	108 to 114; pic. 155–156	846, 971, 972
5-Hydrazinocarbonylamino-2,3-diphenyl	188–191	971
2-Hydrazino-3,5-dimethyl	137–140	826
3-Hydrazino-2,5-dimethyl	121	775
5-Hydrazino-2,3-dimethyl	119–120; pic. 169–170	846, 971
2-Hydrazino-5,6-dimethyl-3-propyl	77–79	826
5-Hydrazino-2,3-diphenyl	154 to 156; pic. 157	846, 971
2-Hydrazino-3-methyl	140	775
2-Hydrazino-6-methyl	86	775
2-Hydrazino-5-methyl-3-propyl	98–100	826
3-Hydrazino-5-methyl-2-propyl	2HCl 199–200	826
2-Hydrazino-3,5,6-trimethyl	115–116	826
2-Hydroxyamino-5,6-dimethyl-3-phenyl	144	346
3-(2'-Hydroxyethylamino)-2,5-dimethyl	119.5–120.5	680
5-(2'-Hydroxyethylamino)-2,3-diphenyl	140.5–141.5	834
2-(2'-Hydroxyethyl)aminomethyl	98–100/0.1; 2HCl 128–132	1029
2-(1'-Iminoethylamino)	127	1198
2-Isopropylamino	82.5/2.0	668a
2-Isopropylaminoethyl	86–88/3	730
2-Methylamino	49–50; 76/1; pic. 181–182	821
2-Methyl-3-methylamino	53–55; HCl 236–240	680, 681, 844
2-Methyl-6-methylamino	63–66	681
2-Methyl-3-(*N*-Methyl-*N*-phenylamino)-methyleneamino	83–83.5	1735
2-Methyl-3-piperidino	HCl 112–114.2	681, 931
2-Methyl-6-piperidino	HCl 171–172	681
2-Piperazinyl	141–146/2; HCl 244–248, 250–251.5	759, 923, 1736

TABLE A.2 *Continued*

Pyrazine	M.P. (°C) or B.p. (°C)	Refs.
2-Propylamino	Pic. 176–177	1062
2-Sulfanilamido	251–251.5, 253, 255 to 259	400, 1175, 1204, 1205
Tetraamino	Dec. < 360 (sealed tube)	1180
2-Thioureido	128	138
2,3,5-Triamino-6-nitro	300 (sealed tube) (darkens 260)	1180
2,3,5-Trimethyl-6-dimethylamino	HCl 162–164	934

TABLE A.3 CARBOXYPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-*N*-(2'-Acetamidoethyl)carbamoyl	187–188	1319
2-Acetonyl	113–114/9	642
2-Acetonyl-6-methyl	50–52/4.5	645
2-Acetonyl-6-phenyl	133–135/0.5	639
2-Acetyl	75 to 80	138, 575, 678, 844
2-*N*-Acetylcarbamoyl	92–97	138
2-Acetyl-3,5-dimethyl	N.m.r., m.s.	678
3-Acetyl-2,5-dimethyl	N.m.r., m.s.	678
5-Acetyl-2,3-diphenyl	152–153	866
2-Acetyl-3-ethyl	55/1.1, 77/6	678, 691, 692
2-Acetyl-3-methyl	56/0.5, 71/6	678, 691
2-Acetyl-5-methyl	55–56, 57	678, 1327
2-Acetyl-6-methyl	32–34	1327
2-Acetyl-3,5,6-trimethyl	61–62	866
2-Amidino	HCl 215–218	138
5-Amidino-2,3-diphenyl	HCl 260–265	866
2-Amidino-3,5,6-trimethyl	HCl 170–171	866
2-(Aminoamidino)	123–124, 132–133	1439, 1441
2[(*C*-Amino-*C*-hydroxyimino)methyl]	185–187	1334, 1424
2-Anilinocarbamoyl	167–168	1333, 1360
2-Azidocarbonyl-5-carbamoyl		1368
2-Azidocarbonyl-5-ethoxycarbonyl	108.5–109.5	676
2-Azidocarbonyl-5-phenyl	125	376
2-(*N*-Benzenesulfonamido)carbamoyl	175.5–176	1323
2-Benzoyl	190–200/20	1447
2-(*N*-Benzoylhydrazino)carbonyl	217	1201
2-Benzoylmethyl-5-methyl	104.5–106.5	635
2-Benzylamidino	118	1334
2-*N*-Benzylcarbamoyl	116–118	138, 1737
2-(Benzylthio)carbonyl	56–57	1355
2,3-Bis(*N*-benzylcarbamoyl)	171–171.5	1737
2,5-Bis(chlorocarbonyl)	143–144	1172
2,5-Bis(chlorocarbonyl)-3,6-diphenyl	174–175	192

TABLE A.3 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,5-Bis(*N*,*N*-dimethylcarbamoyl)-3,6-dimethyl	186–187	215
2-[1′,1′-Bis(ethoxycarbonyl)ethyl]	114–118/0.5	824
2,5-Bis(hydrazinocarbonyl)	270	1172
2,3-Bis(hydroxyaminocarbonyl)	163	1469
2,6-Bis(isobutyrylmethyl)	154–156/0.9	646
2,5-Bis(*N*-methyl)thiocarbamoyl	307–310	1433
2,3-Bis(*N*-pentylcarbamoyl)	145.5–146	1737
2,5-Bisphenylhydrazonomethyl	266	729
2,6-Bis(pivaloylmethyl)	146–147/0.4	646
2,6-Bis(propionylmethyl)	64.5–65.4	646
2-*N*-Butylcarbamoyl	41, 43, 63–64, 141	138, 1268, 1333, 1360
2-(*N*-Butylthio)carbamoyl)	61	1268
2-(Butylthio)carbonyl	122–123/2	1738
2-*t*-(Butylthio)carbonyl	87–88/2	1738
2-Carbamoyl	188–191; 4-Mel 192–202	138, 985, 1171, 1188, 1270, 1312, 1318, 1360, 1390, 1395
2-Carbamoyl-3-carboxy	156, 170–171	1269, 1270, 1271, 1312
5-Carbamoyl-2,3-diphenyl	197–198	25
2-Carbamoyl-5-ethoxycarbonyl	188–189	676
2-(1′-Carbamoylethyl)	96–98	364, 365, 824
2-(2′-Carbamoylethyl	125–126	405
2-Carbamoyl-3-ethyl	119–120	866
2-Carbamoyl-5-ethyl	165	376
2-Carbamoyl-6-ethyl	143	376
5-(1′-Carbamoylethyl)-2,3-diphenyl	123–125	364, 365, 824, 825
2-(1′-Carbamoylethyl)-5-phenyl	152–153	364, 824, 825
2-Carbamoyl-5-hydrazinocarbonyl	299–299.5	676, 1368
2-Carbamoyl-3-methyl	164–165	866
2-Carbamoyl-5-methyl	206, 210–211.5	138, 420, 673, 1327
2-Carbamoyl-6-methyl	163.5–164	673
2-Carbamoyl-3-phenyl	171–172	866
2-Carbamoyl-3-propyl	98–99	866
2-Carbamoyl-3,5,6-trimethyl	165–166	866
2-Carboxy	217 to 222, 229–230	22, 32, 272, 353, 397, 669, 1171, 1268
2-Carboxy-3-(2′-diethylaminoethoxy)-carbonyl	157–158	1278
3-Carboxy-2,5-dimethyl	114–115, 117	32, 1015
5-Carboxy-2,3-dimethyl	180–182	351, 397
2-Carboxy-3-(2′-dimethylaminoethoxy)-carbonyl	186–187	1278
3-Carboxy-2,5-diphenyl	197	286
5-Carboxy-2,3-diphenyl	174 to 179	25, 351, 352
2-(1′-Carboxyethyl)	95–96	364, 365, 824

TABLE A.3 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(2′-Carboxyethyl)	91.5–92	405
2-Carboxy-5-ethyl	123	352
2-Carboxy-6-ethyl	112	352
5-(1′-Carboxyethyl)-2,3-diphenyl	127–128	364, 365, 824
2-(1′-Carboxyethylidene)hydrazinocarbonyl	201–202	1201
2-(1′-Carboxyethyl)-5-phenyl	105–107	364, 365, 824
2-Carboxy-3-hydrazinocarbonyl	250–252, > 300	1340, 1349
3-Carboxy-2-hydroxycarbamoyl	151–152	1174
2-Carboxy-3-methoxycarbonyl	115–116, 117–118	1278, 1312
2-Carboxy-3-methoxycarbonyl-5,6-dimethyl	107–107.5	654
2-Carboxy-3-methyl	177	671
2-Carboxy-5-methyl	160, 166–167	352, 673, 1327, 1739
2-Carboxy-6-methyl	197, 200–202	351, 352, 673, 1740, cf. 32, 272, 404
2-(*N*-Carboxymethyl)carbamoyl	229	1201
2-Carboxy-3-phenyl	141–144; H_2O 74–76	1024, 1274
2-Carboxy-5-phenyl	190	351, 352
2-Carboxy-6-phenyl	205	351, 352
2-(1′-Carboxypropyl)-5-phenyl	90–91	364, 365, 824, 825
2-(2′-Carboxyvinyl)	183.5–184	405
2-Chlorocarbonyl	55–56, 59–61, 110–117	1278, 1332, 1336
2-Chlorocarbonyl-3-methoxycarbonyl	94–96/0.2	1278
2-Cyano	20; 87/6–7, 116–117/50, 95–100/15	138, 726, 866, 1334 1409
2-(1′-Cyanobutyl)	136–138/14	644
2-Cyano-3,5-dimethyl	113–115/20	866
3-Cyano-2,5-dimethyl	49–50	1015
5-Cyano-2,3-dimethyl	29–30; 119–120/17	866
3-Cyano-2,5-diphenyl	119–121	286, 288
5-Cyano-2,3-diphenyl	153–154	866
2-Cyano-3-ethoxycarbonyl-5,6-dimethyl	99	1044
2-Cyano-3-ethoxyformidoyl-5,6-dimethyl	HCl 225–227	1044
2-Cyano-3-ethyl	102–103/15	866
2-{2′-[2″-(Cyanoethyl)hydrazino]-carbonyl}	121–122	1317
2-(Cyanomethoxy)carbonyl	68–69; 136–140/2–3	1317
2-Cyanomethyl	34–36; 134–137.5/14	644
2-Cyano-3-methyl	125–126/50	866
2-Cyano-5-methyl	–	1327
2-Cyano-6-methyl	–	1327
2-Cyano-3-methyl-5,6-diphenyl	173–174	866
2-(1′-Cyano-1′-methyl)ethyl	112–113/14	644
2-(1′-Cyano-2′-methyl)propyl	69/0.2	644
2-(1′-Cyanopentyl)	95–98/0.5	644
2-Cyano-3-phenyl	77–78, 94–96; 117–118/0.2	866, 1024

TABLE A.3 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(1′-Cyanopropyl)	72–74/0.06, 95/3	644, 1421
2-Cyano-3-propyl	112–113/15	866
2-Cyano-3,5,6-trimethyl	68–69; 120–121/17	866
2-Cyano-3,5,6-triphenyl	255–256	866
2,5-Diacetyl	158	616
2,5-Di-(*N*-acetylcarbamoyl)	270–272	672
2,5-Diacetyl-3,6-dimethyl	98–99, 101–102	226, 227, 229, 1064, 1741
2,5-Diazidocarbonyl	133–134	1172
2-Diazomethylcarbonyl	85.5–86	1332
2,5-Dibenzoyl	176	616
2,5-Dibenzoyl-3,6-dimethyl	159–160, 167–169	212, 1064
2-*N*,*N*-Dibenzylcarbamoyl	90	1333, 1360
2-*N*-[(Dibutylamino)methyl]carbamoyl	46–47	1413
2-(*N*,*N*-Dibutylcarbamoyl)	167/8	1333, 1360
2,3-Dicarbamoyl	230, 240	138, 397, 477, 1392
2,5-Dicarbamoyl	> 270, > 300	676, 1172
2,6-Dicarbamoyl	300, > 355	138, 865
2,3-Dicarbamoyl-5,6-dimethyl	227	403
2,5-Dicarbamoyl-3,6-dimethyl	290, 297–298	287, 1104
2,5-Dicarbamoyl-3,6-diphenyl	338–340	505
2,3-Dicarbamoyl-5-methyl	215–217	138
2,3-Dicarboxy	179 to 187; anhyd. 193; $2H_2O$ 186; pic. 156–157	138, 353, 354, 397, 398, 400, 1276–1278, 1348
2,3-Dicarboxy, anhydride of	170–175 (darkening), 207–210, 224–225	397, 1174, 1278, 1312, 1338
2,3-Dicarboxy, imide of	243 to 245	138, 397, 1338
2,3-Dicarboxy, methylimide of	183–184	1338
2,5-Dicarboxy	253, 255 to 265, 269; $2H_2O$ 255–256	22, 27, 32, 45, 46, 48, 273, 278, 411, 672, 676, 867, 1071, 1287, 1348
2,6-Dicarboxy	217–218 (anhyd.); 225	27, 411, 865
2,3-Dicarboxy-5,6-dimethyl	190, 192–193, 200	357, 397, 403, 654
2,3-Dicarboxy-5,6-dimethyl, anhydride of	170–171.5	654
2,5-Dicarboxy-3,6-dimethyl	190 to 195, 200–201	18, 19, 674, 1104
2,5-Dicarboxy-3,6-diphenyl	185–186	192, 209
2,5-Di(2′-carboxyethyl)-3,6-dimethyl	209–213	177, 290, 293
2,3-Dicarboxy-5-methyl	174–175, 196	398, 403–405
2,3-Dicarboxy-5-phenyl	$1.5H_2O$ 225–227	1742
2,3-Dicyano	132, 132.5–133, 135	353–355, 357, 1411, 1434
2,5-Dicyano	188–189	672
2,6-Dicyano	162–163	865
2,5-Dicyano-3,6-diethyl	115	287
2,3-Dicyano-5,6-dimethyl	166, 169–170, 171	353, 355, 357, 383
2,5-Dicyano-3,6-dimethyl	207, 210, 210.5–211.5	286, 287

TABLE A.3 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,3-Dicyano-5,6-diphenyl	245 to 247	353, 355, 357
2,5-Dicyano-3,6-diphenyl	202, 203	286, 288
2,3-Dicyano-5-methyl	94–96, 97	385, 1435
2,3-Dicyano-5-methyl-6-phenyl	129, 133–135	355, 386a, 1435
2,3-Dicyano-5-phenyl	164 to 171	355, 386a, 387, 1435
2,3-Diethoxycarbonyl	138–140/2	1269
2,5-Diethoxycarbonyl	62.5–63.5	676
2,5-Diethoxycarbonyl-3,6-dimethyl	85.5 to 88; 315–317/atm.	18, 194, 202, 213–215, 287, 674, 1104
2,5-Diethoxycarbonyl-3,6-diphenyl	104	209
2-(1′,1′-Diethoxycarbonylethyl)	114–118/0.5	364, 365
2-(1′,1′-Diethoxycarbonylethyl)-5-phenyl		364
2,5-Diethoxycarbonylmethyl-3,6-diphenyl	105–107	232
2-(2′-Diethylaminoethoxy)carbonyl	HCl 139–140	1278
2-(2′-Diethylaminoethoxy)carbonyl-3-methoxycarbonyl	HCl 113–115	1278
2-*N*-[(Diethylamino)methyl]carbamoyl	47–50, cf. 127–130	1413–1415, cf. 1416
2-(*N*,*N*-Diethylcarbamoyl)	130–131/6–7	1360
2-(Diformylmethyl)	207–208.5	717
2,3-Di(hydrazinocarbonyl)	> 300	1310, 1367
2,5-Di(hydrazinocarbonyl)	270	1172
2,5-Diisocyanato	250	1172
2-(*N*,*N*-Diisopropylcarbamoyl)	74	1360
2,3-Dimethoxycarbonyl	50, 55 to 57, 59.5–60, 62–63	397, 401, 798, 1278, 1280, 1325
2,5-Dimethoxycarbonyl	168 to 170.1; 120–140/10^{-3}	183, 676, 798, 1072, 1172
2,6-Dimethoxycarbonyl	119–120, 128.5–129.5	411, 867
2,5-Dimethoxycarbonyl-3,6-dimethyl	131–133, 137–138	215, 323, 501
2,3-Dimethoxycarbonyl-5-methyl	32–34	138
2,3-Dimethoxycarbonyl-5-phenyl	113–115	1742
2-(1′,1′-Dimethoxymethyl) (?)	90–94/10	694
2-(2′-Dimethylaminoethoxy)carbonyl	HCl 184–185	1278
2-[2′-(Dimethylamino)ethoxy]carbonyl-3-methoxycarbonyl	HCl 138–139	1278
2,5-Dimethyl-3,6-bis(*N*-methylcarbamoyl)	286	215
2-*N*,*N*-Dimethylcarbamoyl	70–72	138, 1188, 1333, 1360
2,6-Dimethyl-3,5-bis(3′-methyl-2′-oxobutyl)	101–104	647
2-(3′,3′-Dimethyl-2′-oxobutyl)	114–114.5/5	642
2-(3′,3′-Dimethyl-2′-oxobutyl)-6-methyl	114–115/4; oxime 93.2–94	645
2,5-Dimethyl-3-propionamido	106–108	478, 720
2-(*N*,*N*-Dimethyl)thiocarbamoyl	65–66, 67; 140–150/3	1268, 1422
2,5-Dimethyl-3-thiocyanato	95–97/0.4	1139
2,5-Diphenyl-3,6-bis(*N*-phenylcarbamoyl)	301–303	192
2,5-Dipropionyl	115	616

TABLE A.3 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-*N*-[(Dipropylamino)methyl]carbamoyl	58–59	1413
2-(*N*,*N*-Dipropylcarbamoyl)	158–159/8	1360
2-Ethoxalylmethyl	72–73	1187
2-Ethoxycarbonyl	49, 52–53; 120–122/6	575, 1269
2-Ethoxycarbonylacetyl	66–67, 75; 116–120/2	1382, 1383
5-Ethoxycarbonyl-2,3-diphenyl	91–92	25
2-[1′-(Ethoxycarbonyl)ethyl]	71–73/0.4	364, 365, 824
2-[1′-(Ethoxycarbonyl)ethyl]-5-phenyl	38–40	364, 365, 824
2-Ethoxycarbonyl-5-hydrazinocarbonyl	141.5	676
2-Ethoxycarbonyl-3-methyl	49.5–51.5	1185
2-Ethoxycarbonylmethyl-3-methyl	G.l.c.	635
2-(Ethoxycarbonylmethylthio)carbonyl	65–68	1355, 1738
2-(2′-Ethoxycarbonylprop-2′-yl)-5-phenyl	–	364, 365
2-(*C*-Ethoxyformidoyl)	49–50	1334, 1440
2-*N*-Ethylcarbamoyl	67, 68	1268, 1360
2-*N*-Ethyl(thiocarbamoyl)	84	1268
2-(Ethylthio)carbonyl	95–98/1, 100–108/5	1355, 1738
2-Formyl	31–33; 57–57.8/6	732, 1077
2-(2′-Formylhydrazino)carbonyl	162.5	1201
2-Formyl-3-methyl	184–185/742	1185
2-Heptylcarbamoyl	42–43	1333, 1360
2-Hydrazinocarbonyl	161–164, 167–169, 171–172, 176–177	138, 1266, 1323, 1333, 1360, 1425, 1743
2-Hydrazinocarbonyl-5-methyl	128–130	1426
2-Hydrazinocarbonyl-5-phenyl	212	376
2-Hydrazinocarbonyl-6-phenyl	142	356
2-*N*-Hydroxycarbamoyl	163–165, 168, 177–179	138, 1266, 1469
2-*N*-(2′-Hydroxyethyl)carbamoyl	118	1360
2-Hydroxyiminomethyl	90–97	727
2-Hydroxyiminomethyl-3,6-dimethyl-5-pentyl	127–128.2	648
2-*N*-(Hydroxymethyl)carbamoyl	129–136.5	138
2-*N*-Isobutylcarbamoyl	61	1268
2-*N*-Isobutyl(thiocarbamoyl)	62.5	1268
2-(Isobutylthio)carbonyl	101/3	1738
2-*N*-Isopropylcarbamoyl	85.5	1268
2(2′-Isopropylhydrazino)carbonyl	80–82; 97/0.05, 105–106/0.1	1366
2-Isopropylidenehydrazinocarbonyl	142–144	1366
2-*N*-Isopropyl(thiocarbamoyl)	79.5	1268
2-(Isopropylthio)carbonyl	90/2	1738
2-Methoxycarbonyl	59–62; HCl 46	138, 1016, 1171, 1263, 1312, 1319, 1323, 1324
5-Methoxycarbonyl-2,3-diphenyl	115–116	25
2-Methoxycarbonylethyl	–	405
2-Methoxycarbonyl-5-methyl	–	1327
2-Methoxycarbonyl-6-methyl	–	1327

TABLE A.3 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Methoxycarbonyl-5-phenyl	138	352
2-Methoxycarbonyl-6-phenyl	79	352
2-(*C*-Methoxyformidoyl)	2HCl 180	138
2-*N*-Methylcarbamoyl	105	138, 1268, 1333, 1360
2-(2′-Methylhydrazino)carbonyl	99–100	1333, 1360
2-Methyl-6-(3′-methyl-2′-oxobutyl)	92–96/0.9, 109–109.5/4	645, 646
2-(3′-Methyl-2′-oxobutyl)	115–116/6	642
2-Methyl-6-(2′-oxobutyl)	82–88/0.7, 106–108/4	645, 646
2-(3′-Methyl-2′-oxobutyl)-3,5,6-trimethyl	50–50.5	647
2-Methyl-6-(2′-oxopentyl)	115–116/5	645
2-Methyl-6-pivaloylmethyl	102–106/1.0	646
2-*N*-Methyl(thiocarbamoyl)	207	1268
2-(Methylthio)carbonyl	65–66	1355, 1738
2-(2′-Oxopentyl)	121.5–122/6	642
2-(Pentylthio)carbonyl	114–118/2	1738
2-Phenacyl	82–83, 82–84	642, 651
2-Phenylamidino	104–105	1334, 1410
2-*N*-Phenylcarbamoyl	123–125, 127–130	138, 1333, 1335, 1360
2-(Phenylthio)carbonyl	145 to 151, 154	1355, 1356, 1738
2-Pivaloylmethyl-6-propionylmethyl	146–149/0.5	646
2-Propionyl	25; 77–82/4	1449
2-Propionylmethyl	111–112/6	642
2-*N*-Propylcarbamoyl	56	1268
2-*N*-Propyl(thiocarbamoyl)	66	1268
2-(Propylthio)carbonyl	131/3, 155–180/*in vacuo*	1355, 1738
2-Semicarbazidocarbonyl	204–205	1201
2-Sulfanilylcarbamoyl	247–248	1336
Tetracarbamoyl	390–391, > 400	384, 412
Tetracarboxy	198–202, 204–205, 206–208	3, 22, 27, 384, 413, 415–418, 1290, 1292
Tetracarboxy, dianhydride	Dec. > 180	1342
Tetracyano	274–276	384, 386, 1180
Tetraethoxycarbonyl	102–104	267, 412, 413, 1320
Tetrahydrazinocarbonyl	> 400	412
Tetramethoxycarbonyl	181–184	269, 418, 629, 1326
2-Thiocarbamoyl	195–196	138, 1409
2-α-(Thiocarbamoyl)benzyl	142–143	1420
2-Thiocarbamoylmethyl	112–114	1419–1421
2-(1′-Thiocarbamoylpropyl)	88–90	1420, 1421
2-Thiosemicarbazidocarbonyl	230–231	1201
2-Thiosemicarbazonomethyl	237–239	138
2,3,5-Tricarbamoyl	300–305	412
2,3,5-Tricarboxy	Anhyd. 180; $2H_2O$(?) 190–191	27, 32, 410, 411, 865

TABLE A.3 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,3,5-Triethoxycarbonyl	135–137/0.4	412
2,3,5-Trimethoxycarbonyl	80.5	411
2,3,5-Trimethyl-6-(2′-oxopentyl)	61–63; 130–134/2	647
2,3,5-Trimethyl-6-pivaloyl	66–70	647
2-Ureidocarbonyl	210–212	1322
2-Valerylmethyl	130–130.5/6	642

TABLE A.4 HALOGENOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Benzyl-3-chloro	134–138/2	80, 366
2,3-Bis(chloromethyl)		654
2,5-Bis(chloromethyl)	N.m.r.	756
2,6-Bis(chloromethyl)		679
2,5-Bis(dichloromethyl)-3,6-diphenyl	261–262	192
2,5-Bis(3′,3′,3′-trichloroprop-1′-enyl)	$4H_2O$ 89	708
2-Bromo	57–58/9, 61–64/9–10	598, 603, 818, 866
2-Bromo-3,5-dimethyl	91–92/14	866
5-Bromo-2,3-dimethyl	94–96/14	866
3-Bromo-2,5-diphenyl	119–120	866
5-Bromo-2,3-diphenyl	149–150	866
2-Bromo-5,6-diphenyl-3-propyl	135–140/0.001	866
2-Bromo-3-ethyl	85–87/14	866
2-Bromo-3-ethyl-5,6-diphenyl	99–100	866
2-(1′-Bromoethyl)-3-ethyl	I.r., m.s., n.m.r.	691, 692
2-(1′-Bromoethyl)-3-methyl	I.r., m.s., n.m.r.	691
2-Bromo-3-isopropyl-5,6-diphenyl	118–119	866
2-Bromo-3-methyl	105–107/50	866
2-Bromo-3-methyl-5,6-diphenyl	155–156	866
2-Bromo-3-phenyl	88 to 91; 110–115/0.5	866, 1024
2-Bromo-3-propyl	101–102/14	866
2-Bromo-3,5,6-trichloro	85–86	888
2-Bromo-3,5,6-trifluoro	37–39	851
2-Bromo-3,5,6-trimethyl	53–54; 105–110/20	866
2-Bromo-3,5,6-triphenyl	178–180°	866
2-*s*-Butyl-3-chloro	123–130/64.5	80
2-*s*-Butyl-3-chloro-5-isobutyl	94–95/2	313
5-*s*-Butyl-3(or 2)-chloro-2(or 3)-isobutyl(?)	93/31	313
2-Butyl-3,5,6-trifluoro	170/760	851
2-Chloro	130–158.5/atm., 150–153/atm., 52/20, 62–63/31; N_4 MeI 175–176, 182–183	362, 599, 600, 612, 666, 737, 818, 819, 821, 912
2-Chloroacetyl	85–86, 89–89.5	138, 1332
2-Chlorocarbonyl-3-phenyl	142–145/4	1024

TABLE A.4 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
3-Chloro-2-chloromethyl-5-methyl	70/3	842
2-Chloro-5-deutero-3-methyl		687
2-Chloro-3-dichloromethyl	46–47; 152/41	685, 687, 688
3-Chloro-2,5-diethyl	81/5–91/6	680, 682, 683
2-Chloro-3,5-dimethyl	92–94/42, 111–112/70	362, 687
3-Chloro-2,5-dimethyl	66–69/8.6, 64/10–65/12, 78/12–15, 112–113/70	312, 362, 612, 679, 680, 683, 740
5-Chloro-2,3-dimethyl	86–88/60	362
2-Chloro-5,6-dimethyl-3-propyl	121–122/20	362
2-Chloro-3,5-diphenyl	108–109	827
3-Chloro-2,5-diphenyl	103–104	827
5-Chloro-2,3-diphenyl	125 to 127; 140–145/10^{-3}	362, 741, 827, 846
2-Chloro-5,6-diphenyl-3-propyl	155–160/10^{-3}	362
2-Chloro-3-ethyl	110–111/72	362
2-Chloro-3-ethyl-5,6-dimethyl	106–107/20	362
2-Chloro-3-ethyl-5,6-diphenyl	77–78; 145–150/10^{-3}	362
2-Chloro-3-ethyl-5-methyl	93–94/20	362
2-Chloro-6-fluoro	41–50/17; pic. 114–115	883
2-Chloroformyl	59–61	138, 1278, 1330
2-Chloro-3-hydroxymethyl	120–123/10	737
2-Chloro-3-isobutyl	125–130/70	80,
2-Chloro-5-isobutyl	–	693
3-Chloro-2-isobutyl-5-isopropyl	89–90/2	740a
3-Chloro-5-isobutyl-2-isopropyl	75–80/2	740a
2-Chloro-3-isopropyl	106–107/64, 112–113/65	80, 362
2-Chloro-3-isopropyl-5,6-dimethyl	105–106/15	362
2-Chloro-3-isopropyl-5,6-diphenyl	96–97; 155–160/10^{-3}	362
2-Chloro-3-isopropyl-5-methyl	95–96/18	362
2-Chloromethyl		679, 690
2-Chloro-3-methyl	55–65/15, 78/25, 94–96/65	362, 535, 626, 680, 687
2-Chloro-5-methyl	94–96/60	362
2-Chloro-6-methyl	49–51, 84–85/40	362, 681
2-Chloro-3-methyl-5,6-diphenyl	136–137, 140–150/10^{-3}	362
2-Chloromethyl-3-methyl		654
2-Chloromethyl-5-methyl		679
2-Chloro-5-methyl-3-propyl	106–107/20	362, cf. 826
2-Chloro-3-phenyl	65–67; 92–93/0.3, 135–137/0.5	535, 817
2-Chloro-5-phenyl	96 to 99	363–365, 761, 824, 825, 827
2-Chloro-6-phenyl	30–31, 34–35; 99–100/0.3	365a, 827
2-Chloro-3-propyl	124–125/65	362

TABLE A.4 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Chloro-3-trichloromethyl	167/40	688
2-Chloro-3,5,6-trifluoro	61–63	850–852
2-Chloro-2-trifluoromethyl	135/atm.	759
2-Chloro-3,5,6-trimethyl	56–57; 100–101/25	362
2,3-Dibromo	58 to 61	603, 768, 797
2,5-Dibromo	6.5–8.0	603, 768, cf. 798
2,6-Dibromo	49 to 52.5; 97/10	603, 768, 818, 865
2,5-Dibromo-3-chloro	50	807
Dibromodifluoro	51–52	851
2,3-Dibromo-5,6-dimethyl	87–88	817
2,3-Dibromo-5,6-diphenyl	204–205, 212–214	817, 834
2,5-Dibromo-3,6-diphenyl	197–198	817
2,3-Dibromo-5-phenyl	115	829
2,5-Dibromo-3-phenyl	71–72, 83–84	817, 829
3,5-Dibromo-2-phenyl	66–67	829
2,5-Di-*s*-butyl-3-chloro	116/12	312, 740
2,5-Di-*s*-butyl-3,6-dichloro	58–61	312, 740
2,5-Dibutyl-3,6-difluoro	49–50/0.025	851
2,3-Dichloro	23–24; 82–85/14, 125–130/30	474, 481, 483, 603, 757, 771, 828
2,5-Dichloro	ca. 0, 13–14; 72/12, 90–91/44	603, 737, 768, 831
2,6-Dichloro	51 to 58; 120–122/40	737, 757, 768–772, 832
2,5-Dichloro-3,6-bischloromethyl	65–67	756
2,5-Dichloro-3-chloromethyl-6-methyl	45–47	756
2,5-Dichloro-3,6-difluoro	80–82, 89–90	493, 888
2,6-Dichloro-3,5-difluoro	69–71	850, 851
2,5-Dichloro-3,6-diisobutyl	112–113/3, 134–137/5	101, 843
2,3-Dichloro-5,6-dimethyl	79–81; 122–123/15	483, 817
2,5-Dichloro-3,6-dimethyl	70 to 73	312, 740, 756, 817, 842, 872
2,3-Dichloro-5,6-diphenyl	178–180	817, 834
2,5-Dichloro-3,6-diphenyl	159–160	282, 817
2,5-Dichloro-3-isobutyl-6-isopropyl	96–98/2	740a
2,3-Dichloro-5-methyl	12; 100–101/20	483
3,5-Dichloro-2-methyl	99–100/1	535
2-Dichloromethyl	87–90/10, 105–108/18	694, 737
2,3-Dichloro-5-methyl-6-phenyl	69–70	483
2,3-Dichloro-5-phenyl	106–107	483, 829
2,5-Dichloro-3-phenyl	58–60; 115–116/0.3	817, 829
3,5-Dichloro-2-phenyl	57–58; 122–123/0.1	829
2,6-Difluoro	90–92	883
2,5-Difluoro-3,6-di(heptafluoroisopropyl)	149/760	496
2,6-Difluoro-3,5-di(heptafluoroisopropyl)	G.l.c., anal., m.s., n.m.r.	494
2,5-Difluoro-3,6-di(nonafluoro-*s*-butyl)	165/760	494
2,6-Difluoro-3,5-di(nonafluoro-*s*-butyl)	G.l.c., anal., m.s., n.m.r.	494
2,6-Difluoro-3,5-di(pentafluoroethyl)	G.l.c., anal., m.s., n.m.r.	495
2,5-Difluoro-3,6-di(pentafluoroethyl)	G.l.c., anal., m.s., n.m.r.	494

TABLE A.4 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Ethyl-3-iodo	152–153/72	887
2-Fluoro	108–110/atm.	882–884
3-Fluoro	MeI 142–143	666
3-Fluoro-2,5-dimethyl	146–148	883
2-Iodo	109–110/34	887
2-Iodo-3,5-dimethyl	154–155/70	887
3-Iodo-2,5-dimethyl	61–62; 140–141/47	887
5-Iodo-2,3-dimethyl	55–57; 120–121/20	887
5-Iodo-2,3-diphenyl	141–142	887
2-Iodo-3-methyl	40–41; 137–138/65	887
Tetrabromo	148 to 154	851, 889
Tetrachloro	97 to 100.5; 100/0.1	601, 684, 773, 774, 850–852
Tetrafluoro	50.5 to 54	850–852
Tetra(trifluoromethyl)	129/20	899
Tribromo	40–46	603, 807
2,3,5-Tributyl-6-fluoro	70/760	851
2,3,5-Trichloro	31.5 to 33; 80/3	365b, 845, 888
2,3,5-Trichloro-6-fluoro	76–77	851
2,3,5-Trichloro-6-methyl	49–50	1018
2-Trichloromethyl	Anal., n.m.r.	685
2,3,5-Trichloro-6-phenyl	42–43	1018
2,3,5-Trichloro-6-trichlorovinyl		777
2,3,5-Trifluoro	0–1; 89/atm.	885
2,3,5-Trifluoro-6-heptafluoroisopropyl	G.l.c., anal., m.s., n.m.r.	494
2,3,5-Trifluoro-6-methyl	115/760	851
2-Trifluoromethyl	118/atm.	759
2,3,5-Trifluoro-6-(nonofluoro-*s*-butyl)	G.l.c., anal., m.s., n.m.r.	494
2,3,5-Trifluoro-6-pentafluoroethyl	G.l.c., anal., m.s., n.m.r.	494

TABLE A.5 OXYPYRAZINES WITHOUT *C*- OR *N*-ALKYL GROUPS

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetoxy	115–120/10–12	738
2-Acetoxymethyl	93–95/5–6	738
2-Acetoxymethyl-3-ethoxy	100–102/0.4	978
2-Benzyloxy-6-hydroxy	184–185, 190–191	832, 873
2-Benzyloxy-6-methoxy	136–140/40	832
2,3-Bis(acetoxymethyl)	72–74, 143–145/3	739
2,5-Bis(acetoxymethyl)	68–70, 77–77.5, 80–81; 105/5, 123–124/0.5	625, 760, 867
2-[Bis(diethylamino)phosphinothioyloxy]	43	1113
2-[Bis(dimethylamino)phosphinothioyloxy]	54–55	1113
2,3-Bis(ethoxymethyl)	115–116/10	654
2,6-Bis(ethoxymethyl)	130–133/20	679

TABLE A.5 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,5-Bis(2′-hydroxy-1,1′-dimethylethyl)	173	500
2,5-Bis(hydroxymethyl)	88–89	625
2,3-Bis(trimethylsilyloxy)	70/5	1111
2-Chloromercurioxy	220	1106
2,3-Dibenzyloxy	47–48	883
2,6-Dibenzyloxy	62–63	832
2-Dichlorophosphinothioyloxy	37–38; 101–105/5	1112, 1113
2,5-Diethoxy	30–31	314
2,6-Diethoxy	27–27.5; 68–70/5, 112–114/26	865, 883
2,5-Diethoxy-3,6-bis(ethoxymethyl)	139–140	756
2,5-Diethoxy-3,6-bis(methoxymethyl)	51–53	756
2-Diethoxyphosphinothioyloxy		1114
2,3-Dihydroxy	300–303, > 320, > 350, 370–380	481, 482, 757, 797, 832, 833, 1055
2,6-Diisopropoxy	105–106/10	865
2,3-Dimethoxy	108–110/50	797
2,6-Dimethoxy	31–31.5, 47, 48–49	832, 865
2,5-Dimethoxy-3,6-bis(methoxymethyl)	80–81	756
2-(2′-Dimethylaminoethoxy)	80–89/5; pic. 136–138	924
2-(Diphenoxyphosphinothioyloxy)		1117
2-Ethoxy	58/13, 72–73/30, 90–92/90	668a, 818, 978
2-Ethoxy-5-hydroxy	263–264	1069
2-Ethoxy-3-hydroxymethyl	46–47	978
2-Ethoxymethyl	110–112/53	679
2-(2′-Ethyl-2′-hydroxybutyl)-6-methyl	111–113/0.8	707
2-Hydroxy	185 to 190	86, 361, 362, 420, 477, 818, 821, 846, 887, 1048
2-(2′-Hydroxy-2′,3′-dimethylbutyl)	121–123/15	706
2-(2′-Hydroxyethyl)	128.5–129/10; pic. 73–74	470, 656
2-Hydroxy-6-methoxy	190–195	832
2-Hydroxymethyl	35–36; 59–62/0.1, 64–66/0.3, 83–85/4–6	625, 738, 1077
2-(2′-Hydroxy-2′-methylbutyl)	117–118/5.5	706
2-(2′-Hydroxy-3′-methylbutyl)	110–112/2.5	706
2-Isopropoxy	74.5/22	668a
2-Methoxy	60–61/29; 4-MeI 129–130, 133–135; 4-$C(CN)_2$ 205–206	666, 912, 1094, 1744
2-(*p*-Methoxy-*p*-methylamino)phosphinothioyloxy	57–58	1113
2-Methoxy-6-phenyl	46–48; 113–114/1	365a
2-Phenoxy	50–52	138
2,3,5-Trihydroxy	240, 240–242	365b, 1745

TABLE A.6 OXYPYRAZINES WITH *C*- BUT WITHOUT *N*-ALKYL GROUPS

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(1'-Acetoxyethyl)-3-ethyl	107–110/0.4	691, 692
3-Acetoxy-2-methoxy-5-methyl	53–54	844
3-Acetoxymethyl-2-hydroxy-5-phenyl	187–188	873
5-Acetoxymethyl-2-hydroxy-3-phenyl	186–187	873
2-Acetoxymethyl-5-methyl	70–71/0.4, 123–125/10	625, 760
2-Acetoxymethyl-6-methyl	127–130/14; pic. 201–202	760
2-Acetoxymethyl-3,5,6-trimethyl	145–147/17; pic. 96–97	760
2-Allyloxy-3-methyl	61–62	680
3-Benzyl-2,5-diethoxy	130–140/0.1	314
2-Benzyl-3,6-diethoxy-5-methyl	$100/10^{-4}$	1066
2-Benzyl-3,6-dihydroxy-5-methyl	250, 335	1066, 1746
2-Benzyl-3-ethoxy-6-hydroxy-5-methyl	138	1066
2-Benzyl-6-ethoxy-3-hydroxy-5-methyl	124–125	1066
2-Benzyl-3-hydroxy	146–150, 151–152.5	80, 366
2-Benzyl-3-methoxy	123–130/2	80, 366
5-Butoxy-2-hydroxy-3-phenyl	135–140/0.01	797
5-Butoxy-2-methoxy-3-phenyl	137–140/0.3	797
2-Butoxy-3-methyl	98/14	680
2-Butyl-3-hydroxy	140–160/0.45	80
3-*s*-Butyl-2-hydroxy-6-(1'-hydroxy-1'-methylpropyl)	120–120.5	110
2-*s*-Butyl-3-hydroxy-5-isobutyl	97–98	93
5-*s*-Butyl-3-hydroxy-2-isobutyl (deoxyaspergillic acid)	96 to 104; 197–199/10, 305–310/760	86, 90, 92, 94, 313, 480, 551
2-*s*-Butyl-3-methoxy	105–115/54	49, 59, 80, 693
2-*s*-Butyl-6-methoxy		640
5-Deutero-2-methoxy-3-methyl		687
3-Deutero-5-methoxy-2-monodeuteromethyl		687
2,6-Diacetoxy-3,5-diphenyl	170–171	873
2,5-Dibenzyl-3,6-diethoxy	48–49; 120–130/0.1	314
2,5-Dibenzyl-3,6-dihydroxy	258, 259–261	1067, 1126
2,5-Dibenzyloxy-3,6-dimethyl	91–92, 108	224, 756
2,5-Di-*s*-butyl-3-hydroxy	122–123, 122–124; HCl 173–175	89, 171, 312
5-Diethoxyphosphinothioyloxy-2,3-dimethyl		1114
2-Diethoxyphosphinothioyloxy-5-phenyl		1114
2-Diethoxyphosphinothioyloxy-3,5,6-trimethyl		1114
2,5-Diethoxy-3,6-dimethyl	73–75, 77 to 80	314, 756, 872
2,5-Diethyl-3-hydroxy	135	287, 478
2,5-Dihydroxy-3,6-diisobutyl	315	99
2,3-Dihydroxy-5,6-dimethyl	> 340, > 360	483, 817
2,5-Dihydroxy-3,6-dimethyl	> 320	797, 887
2,3-Dihydroxy-5,6-diphenyl	335–340, 338–339, 340–342	483, 817, 863, 1065
2,5-Dihydroxy-3,6-diphenyl	295–300	797
2,6-Dihydroxy-3,5-diphenyl	258–259	873

TABLE A.6 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,5-Dihydroxy-3-isobutyl	290	1092
2,3-Dihydroxy-5-methyl	301–303	483
2,3-Dihydroxy-5-methyl-6-phenyl	327–328	483
2,3-Dihydroxy-5-phenyl	288–290	483
2,5-Diisobutyl-3-methoxy	102–103/3	980
2,5-Diisopropyl-3,6-dimethoxy	M.s., i.r., n.m.r.	844
2,3-Dimethoxy-5,6-dimethyl	62–63; 105–110/15	797
2,5-Dimethoxy-3,6-dimethyl	63 to 70; 103–104/14	756, 797, 883
2,3-Dimethoxy-5,6-diphenyl	140–141	797
2,5-Dimethoxy-3,6-diphenyl	146–147	797
2,6-Dimethoxy-3,5-diphenyl	98–99	873
3,5-Dimethoxy-2-methyl	75–76	535
2,5-Dimethoxy-3-phenyl	107–108/0.1	817
5-Dimethoxyphosphinothioyloxy-2,3-dimethyl		1118
5-(1′,2′-Epoxy-2′-methylpropyl)-2-isobutyl-3-methoxy	< 105/4	113b
3-Ethoxy-2,5-dimethyl	81/15, 86–88/20, 96–98/31; pic. 108–109	312, 679
3-Ethoxy-2-ethoxymethyl-5-methyl	112/10; H_2PtCl_6 170	872
2-Ethoxy-3-ethyl	M.s., i.r.	367
2-(1′-Ethoxyethyl)-3-ethyl	44–50/0.5	691
3-Ethoxy-2-hydroxymethyl-5-methyl	45–46	872
2-Ethoxy-3-methyl	83–88/38–40, 88–90/48	679, 978
2-Ethoxy-6-methyl	–	981
2-Ethoxymethyl-5-methyl	98–104/20	679
2-Ethyl-3-hydroxy	96–97, 102–103, 105–106	362, 367, 887
2-Ethyl-3-hydroxy-5,6-dimethyl	149–150	362
2-Ethyl-5-hydroxy-3,6-dimethyl	155–155.5	615
2-Ethyl-3-hydroxy-5,6-diphenyl	207–208	362
2-Ethyl-3-(1′-hydroxyethyl)	70–71/1.5	691
3-Ethyl-2-hydroxy-5-methyl	99–100	362
2-Ethyl-3-methoxy	M.s., i.r.	65, 367
3-Ethyl-2-methoxy-5-methyl	89/16	844
2-Hexyl-3-hydroxy	83.5–84	367
2-Hexyl-3-methoxy	M.s., i.r.	367
2-Hydroxy-2,5-diisobutyl	144.5 to 151	95, 98, 101, 479, 980, 1747
2-Hydroxy-3,5-dimethyl	145 to 152	361, 362, 524, 546, 978
3-Hydroxy-2,5-dimethyl	207 to 215	98, 286, 312, 362, 470, 477, 548, 887, 978
5-Hydroxy-2,3-dimethyl	199–200, 201–202	248, 361, 362
2-(2′-Hydroxy-2′,3′-dimethylbutyl)-6-methyl	99.5–100/0.9	707

TABLE A.6 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(2′-Hydroxy-2′,4′-dimethylpentyl)-3,5,6-trimethyl	109/0.6	648
2-Hydroxy-5,6-dimethyl-3-phenyl	222–226, 235–238, 242–243	361, 546, 817
2-Hydroxy-5,6-dimethyl-3-propyl	119–120	362
2-Hydroxy-3,5-diphenyl	270–272, 272–273, 273–274	546, 873, 1042
3-Hydroxy-2,5-diphenyl	286, 292–293	282, 866
5-Hydroxy-2,3-diphenyl	225–227, 238–240, 243–244	361, 362, 980, 1047
2-Hydroxy-5,6-diphenyl-3-propyl	205–206	362
2-(2′-Hydroxyethoxy)-3-methyl	100–106/2	680
3-Hydroxy-5-(1′-hydroxy-1′-methylpropyl)-2-isobutyl (deoxyhydroxyaspergillic acid)	104–105, 107	94, 113
3-Hydroxy-5-(2′-hydroxy-2′-methylpropyl)-2-isobutyl	118–119.5, 122.5–123	113b, 1061
2-Hydroxy-3-isobutyl	90–92.5, 93–94	80, 367
3-Hydroxy-2-isobutyl-5-isopropyl) (deoxymuta-aspergillic acid)	106 to 109, 113–115	103, 525, 740a
3-Hydroxy-5-isobutyl-2-isopropyl	141–142	740a
2-Hydroxy-3-isobutyl-5-methyl		368
3-Hydroxy-2-isobutyl-5-methyl		368
3-Hydroxy-2-isobutyl-5-(1′-methylprop-1′-enyl) (dehydrodeoxyaspergillic acid)	158	94
3-Hydroxy-2-isobutyl-5-(2′-methylprop-1′-enyl)	95–96.5	113b
3-Hydroxy-2-isobutyl-5-phenyl	167–168.5	479, 551
3-Hydroxy-2-isobutyl-5-propyl	136.5–137	479
2-Hydroxy-3-isopropyl	74.5 to 78	80, 362, 367
2-Hydroxy-3-isopropyl-5,6-dimethyl	144–145	362
2-Hydroxy-3-isopropyl-5,6-diphenyl	234–235	362
3-(α-Hydroxyisopropyl)-2-methoxy-5-methyl	56/1–2	844
2-Hydroxy-3-isopropyl-5-methyl	91–92	362
2-Hydroxy-3-methoxy-5,6-dimethyl	234–235	797
2-Hydroxy-5-methoxy-3,6-dimethyl	180–181	797
2-Hydroxy-3-methoxy-5,6-diphenyl	266–268	797
2-Hydroxy-5-methoxy-3,6-diphenyl	194–196	797
2-Hydroxy-3-methoxy-5-phenyl	249–250	365a
5-Hydroxy-2-methoxy-3-phenyl	208–209	797
2-Hydroxy-3-methyl	140 to 152	361, 362, 680, 681, 887, 1047
2-Hydroxy-5-methyl	126–128	362, cf. 734
2-Hydroxy-6-methyl	240 to 251	362, 372, 434, 681
2-(2′-Hydroxy-2′-methylbutyl)-6-methyl	102–103/2	707
2-(2′-Hydroxy-3′-methylbutyl)-6-methyl	128–130/0.8	707
2-(2′-Hydroxy-3′-methylbutyl)-3,5,6-trimethyl	96–97/1	648

TABLE A.6 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Hydroxy-3-methyl-5,6-diphenyl	212.5–214	362, 1047
2-Hydroxy-5-methyl-3,6-diphenyl	229–231	817
2-Hydroxy-6-methyl-3,5-diphenyl	277–279	817
2-(1′-Hydroxy-1′-methyl)ethyl-3-methoxy-5-methyl	I.r., m.s., n.m.r.	844
2-(1′-Hydroxy-1′-methyl)ethyl-6-methyl	116/15	614
2-Hydroxymethyl-5-methyl	36–39; 137–138/21	625, 760
2-Hydroxymethyl-6-methyl	43–45	760
2-Hydroxy-3-methyl-5-phenyl	212–213, 222–223	361, 546
2-Hydroxy-5-methyl-3-phenyl	160–161	817
3-Hydroxy-5-methyl-2-phenyl	206–208	365b, 817
5-Hydroxy-3-methyl-2-phenyl	254	248
2-Hydroxy-5-methyl-3-propyl	Anhyd. 75–76.5 hyd. 83.5–85.5	362, 826
3-Hydroxy-5-methyl-2-propyl	127–128	826
5-(1′-Hydroxy-2′-methylpropyl-2-isobutyl-3-methoxy	133–135.5/5	113b
5-(2′-Hydroxy-2′-methylpropyl)-2-isobutyl-3-methoxy	< 110/2	113b
2-(2′-Hydroxy-2′-methylpropyl)-6-methyl	83–85/1.2	707
2-(2′-Hydroxy-2′-methylpropyl)-3,5,6-trimethyl	89–90/1	648
2-Hydroxymethyl-3,5,6-trimethyl	65–66	760
2-Hydroxy-3-phenyl	172–173, 172–174	361, 817, 1024
2-Hydroxy-5-phenyl	208–210, 212–214	364, 365, 824, 827
2-Hydroxy-6-phenyl	239–241, 243–244	365a, 827
2-Hydroxy-3-propyl	79–80, 86–86.5	362, 367
2-Hydroxy-3,5,6-trimethyl	193–194, 197–199, 200–201, 204–205	89, 361, 362, 546, 1047
2-Hydroxy-3,5,6-triphenyl	279–281	866
2-Isobutyl-5-isopropyl-3-methoxy	65/1.5	740a
5-Isobutyl-2-isopropyl-3-methoxy	80/7	740a
2-Isobutyl-3-methoxy	120–126; m.s., i.r., n.m.r.	60, 80, 311, 367
2-Isobutyl-5-methoxy	N.m.r.	693
2-Isobutyl-3-methoxy-5,6-dimethyl	M.s., i.r.	368
2-Isobutyl-3-methoxy-5-methyl	M.s., i.r.	368
3-Isobutyl-2-methoxy-5-methyl	M.s., i.r.	368
2-Isobutyl-3-methoxy-5-(2′-methylprop-1′-enyl)	108/3	113b
2-Isopropyl-3,5-dimethoxy-6-methyl	M.s., i.r., n.m.r.	50, 844
2-Isopropyl-3,6-dimethoxy-5-methyl	M.s., i.r., n.m.r.	844
2-Isopropyl-3-methoxy	94–100/61.5	80, 367
2-Isopropyl-3-methoxy-5-methyl	M.s., i.r., n.m.r.	844
3-Isopropyl-2-methoxy-5-methyl	89/16	50, 844
5-Isopropyl-2-methoxy-3-methyl	G.l.c., n.m.r.	50
2-Methoxy-3,5-dimethyl	G.l.c., n.m.r.	687
3-Methoxy-2,5-dimethyl	86/22, 85/25	978, 979
5-Methoxy-2,3-diphenyl	128–129	837

TABLE A.6 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Methoxy-3-methyl	70/25, 87/60	686, 687, 979, 1511
2-Methoxy-5-methyl	N.m.r.	686, 687
2-Methoxy-6-methyl	80/45	686, 687, 1511
2-Methoxy-3-phenyl	143–145/14	817
2-Methoxy-3-propyl	M.s., i.r.	367
2-Methyl-3-[2′-(2″-methylpyrazin-3″-yloxy)ethoxy]	84–85; 150/3	680
2-Methyl-3-myristyloxy	175–179/2	680
2-Methyl-3-phenoxy	90/0.5	929
2-(D-*arabo*-tetrahydroxybutyl)-5-methyl	201	48
2-(D-*arabo*-tetrahydroxybutyl)-6-methyl	170	48
2,3,5-Tri-*t*-butyl-6-hydroxy	222–224	233

TABLE A.7 OXYPYRAZINES WITH ANY *N*-SUBSTITUENT

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
1-Benzyl-3-hydroxy-2-oxo-1,2-dihydro	226–228	1111
3-Benzyl-5-methoxy-1,6-dimethyl-2-oxo-1,2-dihydro		1078
1-Benzyl-2-oxo-3-trimethylsilyloxy-1,2-dihydro		1111
1-(1′-Carboxybutyl)-3-methyl-2-oxo-1,2-dihydro	M.s., u.v., i.r.	381
1-(1′-Carboxyethyl)-3-methyl-2-oxo-1,2-dihydro	M.s., u.v., i.r.	381, 382
1-(1′-Carboxyethyl)-2-oxo-1,2-dihydro	M.s., u.v., i.r.	381
1-(1′-Carboxy-3′-methylbutyl)-3-isobutyl-2-oxo-1,2-dihydro	M.s., u.v., i.r.	381
1-(1′-Carboxy-3′-methylbutyl)-3-methyl-2-oxo-1,2-dihydro	M.s., u.v., i.r.	381
1-(1′-Carboxy-3′-methylbutyl)-2-oxo-1,2-dihydro	M.s., u.v., i.r.	380
1-(1′-Carboxymethyl)-3-isobutyl-2-oxo-1,2-dihydro	M.s., u.v., i.r.	381, 382
1-(1′-Carboxymethyl)-3-methyl-2-oxo-1,2-dihydro	M.s., u.v., i.r.	382
1-(Carboxymethyl)-2-oxo-1,2-dihydro	M.s., u.v., i.r.,	381, 382
1-(1′-Carboxy-2′-methylpropyl)-3-methyl-2-oxo-1,2-dihydro	M.s., u.v., i.r.	381
1-(1′-Carboxypentyl)-3-methyl-2-oxo-1,2-dihydro	M.s., u.v., i.r.	381
1,4-Dibenzyl-2,3-dioxo-1,2,3,4-tetrahydro	221–223	883
Anhydro base of 2,6-dihydroxy-1,4-diphenyl-3,5-bisphenylthiopyrazinium dihydroxide	251–253	476a
3,6-Diisobutyl-1-methoxy-2-oxo-1,2-dihydro		980
1,4-Dimethyl-2,3-dioxo-1,2,3,4-tetrahydro	257–259	832
1,5-Dimethyl-2-oxo-1,2-dihydro	112–115	365c
2,3-Dioxo-1,4-diphenyl-1,2,3,4-tetrahydro	287–290	853
5-Ethoxy-1,3-dimethyl-2-oxo-1,2-dihydro	61–75	1067
3-Ethyl-1-methyl-2-oxo-1,2-dihydro	M.s.	367
3-Hexyl-1-methyl-2-oxo-1,2-dihydro	M.s.	367
3-Hydroxy-6-hydroxymethyl-1-methyl-2-oxo-1,2-dihydro	175–178	1060
3-Hydroxy-1-methyl-2-oxo-1,2-dihydro	210–211, 233–234	832, 1111

TABLE A.7 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
6-Hydroxy-1-methyl-2-oxo-3,5-diphenyl-1,2-dihydro	HCl 230–231	873
3-Isobutyl-1-methyl-2-oxo-1,2-dihydro	M.s.	367
3-Isopropyl-1-methyl-2-oxo-1,2-dihydro	I.r., m.s.	367
3-Methoxy-1-methyl-2-oxo-1,2-dihydro	136–137	832
6-Methoxy-1-methyl-2-oxo-1,2-dihydro	112–115	832
5-Methoxy-1-methyl-2-oxo-3,6-diphenyl-1,2-dihydro	183–185	832
2-Methylene-1,4,5-trimethyl-3-oxo-1,2,3,4-tetrahydro	HCl 203; HI 220	1105
1-Methyl-2-oxo-1,2-dihydro	80–81, 83–84, 84–85	86, 821, 1102
1-Methyl-2-oxo-3,6-diphenyl-1,2-dihydro	168; MeI 216	281, 1104
1-Methyl-2-oxo-3-propyl-1,2-dihydro	M.s.	367
1,3,5,6-Tetramethyl-2-oxo-1,2-dihydro	77–78	1131
1,4,6-Trimethyl-2,3-dioxo-1,2,3,4-tetrahydro	170	1105
1,3,6-Trimethyl-2-oxo-1,2-dihydro	HCl 227; MeI 215, 220; MeCl 203	1104, 1105, 1122

TABLE A.8 SULFONYLPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,6-Bismethylsulfonyl	186–188	759
2-Chlorosulfonyl	–	1006
2,6-Dibenzylsulfonyl	158–159	883
2-Methylsulfinyl	66–67	1080
2-Methylsulfonyl	47–48	1079
2-Sulfamoyl	166–166.5	1006, 1153
2-Sulfo	Na salt H_2O 290–292, 295, 298–300	819, 882, 884

TABLE A.9 THIOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Benzylthio	56–57	1738
2,3-Bis(butoxycarbonylthio)		1144, 1145
2,3-Bis(butylthiothiocarbonylthio)		1145
2,3-Bis(dimethylaminocarbonylthio)		1144, 1145
2,3-Bis(methoxycarbonylthio)-5,6-dimethyl	58–63	1143, 1144
2,3-Bis(methylthiothiocarbonylthio)		1144, 1145
2,6-Dibenzylthio	70–71	883
2,3-Dimercapto		1143, 1144
2,3-Dimercapto-5,6-dimethyl		1143, 1144
2,5-Dimethyl-3,6-dipropylthio	34–35	764

TABLE A.9 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,5-Dimethyl-3-propylthio	73–75/0.2	764
2-Ethylthio	87/10.5	668a
2-Isobutyl-3-methylthio	118–120/12	844
2-Isopropylthio	79/6	668a
2-Mercapto	210–215, 215–218, 229	821, 1006, 1100
3-Mercapto-2,5-dimethyl	180–181, 181–184, 224–225	905, 1007, 1013
5-Mercapto-2,3-diphenyl	165, 186–188	834, 1008
2-Mercapto-3-methyl	180–182, 210–214	905, 1013
2-Mercapto-3-phenyl	148–149	1008
2-Mercapto-3,5,6-trimethyl	HCl 235	933
2-Methyl-3-methylthio	M.s.	1511, cf. 735
2-Methyl-5-methylthio (?)		735
2-Methyl-6-methylthio	M.s.	1511, cf. 735
2-Methyl-3-phenylthio	70–71	929
2-Methylthio	44–47, 45–47.5; MeI 162–163	821, 912, 1100
1-Methyl-2-thioxo-1,2-dihydro	132, 133–134	821, 1100

TABLE A.10 AMINO-CARBOXYPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetamido-5-benzylamino-3-guanidinocarbonyl	225–228	432
2-Acetamido-3-*N*-benzylcarbamoyl	–	457
2-Acetamido-3-*N*-benzylcarbamoyl-5,6-diphenyl	149–150	1165
2-Acetamido-3-carbamoyl	218.7	1175
2-Acetamido-6-carbamoyl	> 300	434
2-Acetamido-3-carbamoyl-5,6-diphenyl	207–208	1165
2-Acetamido-6-carboxy	173	434
2-Acetamido-3-cyano-5-methyl	182	532
5-Acetamido-2,3-dicarboxy	Mono K salt 293	408
2-Acetamido-3-dimethoxymethyl	132/0.1	1075
2-Acetamido-5-dimethylamino-3-guanidinocarbonyl	196.5; nitr. 236, 236.5	432, 778, 783, 784
2-Acetamido-3-formyl	70	1075
2-Acetamido-3-guanidinocarbonyl-5-isopropylamino	203–205	432
2-Acetamido-3-guanidinocarbonyl-5-methoxyamino	225	786
2-Acetamido-3-hydrazinocarbonyl	147–149	433a
2-Acetamido-6-methoxycarbonyl	159	434
2-Acetyl-3-aminomethyleneamino	200; sulf. 110	423

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(*N'*-Acetylhydrazino)carbonyl-5,6-dimethyl-3-methylamino	211–212	428
2-(*N'*-Acetylhydrazino)carbonyl-5-methyl-3-methylamino	144–146	428
2-*N*-Allylcarbamoyl-3,5-bismethylamino-6-methylcarbamoyl	194–195.5	1192
2-Amidinoamidino-3-amino	310, 312	792, 1218
2-Amidino-5,6-dimethyl-3-methylamino	131–132	431
2-Amidino-3-methylamino	108–110; HCl 204	431
3-Amino-5-anilino-2-methoxycarbonyl	171.5–173	855
2-Amino-5-benzylamino-3-carboxy	130–132	432
3-Amino-5-benzylamino-2-guanidino-carbonyl	HCl 231–233	809, 855
3-Amino-5-benzylamino-2-methoxy-carbonyl	189.5–191.5, 157–158(?)	780, 809, 855, 858
2-Amino-5,6-dicarbamoyl-3-dimethylamino	230–231	409
2-Amino-3-butylcarbamoyl-5,6-diphenyl	146–147	455
2-Amino-3-*N*-butyl(thiocarbamoyl)-5,6-diphenyl	168–169	455
2-Amino-3-carbamoyl	234 to 245	138, 378, 458, 1175, 1212
2-Amino-5-carbamoyl	266–267, 274 to 279	408, 798, 1177
2-Amino-6-carbamoyl	203–205	870
2-Amino-3-carbamoylcarbamoyl	288	1152
2-Amino-3-carbamoyl-5-cyclohexyl	185.5–187	802
2-Amino-3-carbamoyl-5-cyclopropyl	185.5–187.5	780, 802
2-Amino-3-carbamoyl-5,6-dimethyl	243–245, 255	378, 458, 459, 812
2-Amino-3-carbamoyl-5,6-diphenyl	202 to 205	451, 454, 458, 459
2-Amino-3-carbamoyl-5-ethyl	160 to 168.5	778, 780, 802
2-Amino-3-carbamoyl-5-methyl	203–204	378, 458
3-Amino-2-carbamoyl-5-methyl	235 to 242	435, 458
5-Amino-2-carbamoyl-3-methylamino	218–219	448
2-Amino-3-carbamoyl-3-phenyl	239–240	378
2-Amino-3-carboxy	196 to 210; NH_4^+ salt 232	397, 420, 423, 433, 452, 477, 947
2-Amino-5-carboxy	278 to 283	408, 744, 798, 1177
2-Amino-6-carboxy	120–121, 283–285(?)	434, 744
2-Amino-3-carboxy-5-cyclohexyl	118–121, 138.5–139.5	378a, 802
3-Amino-2-carboxy-5-cyclohexyl	182.5–183.5	780, 802
2-Amino-3-carboxy-5-cyclopropyl	169–172	780, 802
2-Amino-3-carboxy-5,6-dimethyl	208–211	378, 420, 431, 433
2-Amino-3-carboxy-5-dimethylamino	164.5–165.5	432, 432a, 778
3-Amino-2-carboxy-5-dimethylamino	231–232	432
2-Amino-3-carboxy-5,6-diphenyl	189	420, 433
2-(2'-Amino-2'-carboxy)ethyl	240–243	1187
2-Amino-3-carboxy-5-ethyl	149–152	778, 780, 802
3-Amino-2-(2'-carboxyethyl)carbamoyl-5-methyl	207–209	435
2-Amino-3-carboxy-5-methyl	171–174	378, 432a, 446, 783, 785

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
3-Amino-2-carboxy-5-methyl	210 to 212	420, 421, 433, 435, 446a
2-Amino-3-carboxy-5(or 6)-methyl-6(or 5)-phenyl	193.5–194.5	780, 802
2-Amino-3-carboxy-6(or 5)-methyl-5(or 6)-phenyl	155–156	780, 802
2-Amino-3-carboxy-5-phenyl	118–121, 196	378, 782
3-Amino-2-carboxy-5-phenyl	225; Na salt 295	429
2-Amino-3-cyano	189–191.9	1175, 1183
2-Amino-3-(*N*-cyano)carbamoyl	–	1375
2-Amino-3-cyano-5-cyanomethyl	169–170	1031
2-Amino-3-cyano-5-cyclopropyl	172–173	1218
3-Amino-2-cyano-5-dedihydrotriphenyl-phosphoranylmethyl	249–250; HCl 271	534
2-Amino-3-cyano-5-(2',2'-diethoxy-carbonylethyl)	115–116	1031
2-Amino-3-cyano-5-(*N*,*N*-diethylamino-methyl)	90–92	542
2-Amino-3-cyano-5-dimethoxymethyl	91–93	1030
2-Amino-3-cyano-5,6-diphenyl	160–163	454, 848
2-Amino-3-cyano-5-(2'-ethoxycarbonyl)-ethyl	85–86	1031
2-Amino-3-cyano-5-(2'-ethoxycarbonyl-3'-oxobutyl)	96–97	1031
2-Amino-3-cyano-5-(4'-ethoxy-3'-oxobutyl)	89–91	1031
3-Amino-2-[*N*-(2'-cyanoethyl)carbamoyl]-5-methyl	135–137	435
2-Amino-3-cyano-5-formyl	202–204	1030
2-Amino-5-cyano-3-(*C*-imino-*C*-methoxy-methyl)-6-methoxy	230	484
2-Amino-3-cyano-5-methoxycarbonyl-6-methyl	191	488
2-Amino-3-cyano-5-methyl	171–172, 174.5–175	532, 1218, 1255
3-Amino-2-cyano-5-methyl	212–213	534
2-Amino-3-cyano-5-methyl-6-phenyl	168	488
2-Amino-3-cyano-5-(3'-oxobutyl)	130–131	1031
2-Amino-3-cyano-5-phenyl	182	532
2-Amino-3-cyano-5-(prop-1'-enyl)	186–187	529
3-Amino-2-cyano-5-(prop-1'-enyl)	184–185	534
2-Amino-3-cyano-5-propyl	138	532
3-Amino-2-cyano-5-propyl	115–116	1031
2-Amino-3-cyano-5-(pyridiniomethyl)/chloride	> 300	1030
3-Amino-2-cyano-5-styryl	222–223	534
2-Amino-3-cyano-5-vinyl	175–176	529
2-Amino-5-cyclohexyl-3-guanidinocarbonyl	228–230	778, 786, 802
3-Amino-5-cyclohexyl-2-guanidinocarbonyl	221–222	780, 802, 855, 859
2-Amino-5-cyclohexyl-3-methoxycarbonyl	126.5–128	378a, 778, 780, 786, 802, 854, 858

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
3-Amino-5-cyclohexyl-2-methoxycarbonyl	173–174.5	780, 802, 855, 858, 859
2-Amino-3-cyclopentylcarbamoyl	73	1213
2-Amino-5-cyclopropyl-3-guanidinocarbonyl	196.5–199	778, 780, 786, 802
2-Amino-5-cyclopropyl-3-methoxycarbonyl	112–114.5	778, 780, 786, 802
3-Amino-5-cyclopropylmethylamino-2-guanidinocarbonyl	–	859
3-Amino-5-cyclopropylmethylamino-2-methoxycarbonyl	132–133	855
5-Amino-2,3-dicarboxy	262	408
2-Amino-3,5-dicyano-6-diethylamino	157–159	484
2-Amino-3,5-dicyano-6-dimethylamino	–	158
2-Amino-5,6-dicyano-3-phenyl	166–167	490
5-Amino-2,3-diethoxycarbonyl	125	412
2-Amino-5,6-dimethoxycarbonyl-3-dimethylamino	181–182.5	409
2-Amino-3-dimethoxymethyl	–	1075
2-Amino-5-dimethylamino-3-guanidinocarbonyl	195–197	432, 778, 786
3-Amino-5-dimethylamino-2-guanidinocarbonyl	224–225	780, 791, 809, 855, 858, 859
2-Amino-6-dimethylamino-3-guanidinocarbonyl-5-methyl	262(?); 2HCl 262	780, 802, 1371
2-Amino-6-dimethylamino-3-guanidinocarbonyl-5-phenyl	205–206	780, 802, 1371
2-Amino-6-dimethylamino-3-hydrazinocarbonyl-5-phenyl	153–154	1370, 1371
3-Amino-5-dimethylamino-2-methoxycarbonyl	242.5–243.5	780, 809, 855
2-Amino-6-dimethylamino-3-methoxycarbonyl-5-methyl	108.5–110.5	802, 858
2-Amino-6-dimethylamino-3-methoxycarbonyl-5-phenyl	167.5–169.5	780, 802
2-Amino-5,6-dimethyl-3-(*N*,*N*'-dimethylhdyrazinocarbonyl)	166–168	426
2-Amino-3-(*N*',*N*'-dimethylhydrazinocarbonyl)	138	426
2-Amino-3-(*N*',*N*'-dimethylhydrazinocarbonyl)-5-methyl	136–138	426
3-Amino-2-(*N*',*N*-dimethylhydrazinocarbonyl)-5-methyl	146–147	426
2-Amino-5,6-diphenyl-3-thiocarbamoyl	158–160	454, 455
2-Amino-3-ethoxyalylaminomethyl	161	1183
2-Amino-5-ethoxycarbonyl	172–173, 174–175	408, 1177
2-Amino-6-ethoxycarbonyl	145–147	744
2-Amino-3-ethoxycarbonylaminomethyl	131.5–132.5	1183, 1184, 1219
2-Amino-3-ethoxycarbonyl-5-hydroxyiminomethyl	267.9	539

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-3-ethoxycarbonyl-5-trifluoro-methyl	91.5–93.5	802
2-Amino-3-(*C*-ethoxy-*C*-iminomethyl)	HCl 205	878, 1218
3-Amino-5-ethylamino-2-hydrazinocarbonyl	–	880
3-Amino-5-ethylamino-2-methoxycarbonyl	–	880
2-Amino-5-ethyl-3-guanidinocarbonyl	207–209.5	778, 780, 786, 802
2-Amino-5-ethyl-3-methoxycarbonyl	85–87.5	778, 780, 786, 802, 858
2-Amino-3-formyl	117, 119–120	423, 1075
2-Amino-3-(*N'*-formylhydrazino)carbonyl	227–229	1214
2-Amino-3-guanidinocarbamoyl	HCl 286–287, 288.5–290	781, 1058
2-Amino-3-guanidinocarbonyl	200–202	787, 802
2-Amino-3-guanidinocarbonyl-5,6-dimethyl	245, 247	780, 802
2-Amino-3-guanidinocarbonyl-5,6-diphenyl	234.5–235.5	780, 802
2-Amino-3-guanidinocarbonyl-5-methoxy-amino	–	786
2-Amino-3-guanidinocarbonyl-5-methyl	218–219	780, 786, 802
3-Amino-2-guanidinocarbonyl-5-methyl	210	780, 802, 855
2-Amino-3-guanidinocarbonyl-5-methyl-6-phenyl	212–213	780, 802
2-Amino-3-guanidinocarbonyl-6-methyl-5-phenyl	218–219	780, 802
2-Amino-3-guanidinocarbonyl-5-phenyl	194.5–195.5	778, 780, 786, 802
3-Amino-2-guanidinocarbonyl-5-phenyl	224–226	780, 802, 855
2-Amino-3-(*C*-guanidino-*C*-iminomethyl)	312	878
2-Amino-3-hydrazinocarbonyl	207 to 214	1203, 1212, 1214
2-Amino-3-hydrazinocarbonyl-5,6-dimethyl	209	424
2-Amino-3-hydrazinocarbonyl-5,6-diphenyl	250–251	451
2-Amino-3-hydrazinocarbonyl-5-methyl	> 140	424
3-Amino-2-hydrazinocarbonyl-5-methyl	190	424
2-Amino-3-(*C*-hydrazino-*C*-iminomethyl)	176	803
2-Amino-3-hydroxyaminocarbonyl	185–189, 196	1215, 1406
3-Amino-2-hydroxyaminocarbonyl-5-methyl	204–206	425
2-Amino-3-hydroxyiminomethyl	201–202	423
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-diethylamino	134–136	1424
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-dimethylamino	226–228	1424
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-(*N'*,*N*-dimethylhydrazino)	225–227	945
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-ethylamino	130–132	1424
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-isopropylamino	135–136	1424
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-methylamino	156–157	1424
2-Amino-3-isopropylcarbamoyl	134	1213

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-3-isopropylidenehydrazino-carbonyl	166–167	1214
2-Amino-5-isopropyl-2-methoxycarbonyl	125.5–126.5	855
2-Amino-3-methoxyaminocarbonyl	129	427
2-Amino-3-methoxyaminocarbonyl-5,6-dimethyl	170–172	426
3-Amino-2-methoxyaminocarbonyl-5-methyl	167–168	426
2-Amino-3-methoxycarbonyl	170 to 178	433a, 867, 1174, 1175, 1212, 1322, 1328
2-Amino-5-methoxycarbonyl	228–229, 230–231	408, 1057
2-Amino-6-methoxycarbonyl	192–194	744
2-Amino-3-methoxycarbonyl-5,6-dimethyl	170–171	812
2-Amino-3-methoxycarbonyl-5,6-diphenyl	204–206	451
2-Amino-3-methoxycarbonyl-5-methyl	138.5–140.5	378a, 778, 780, 782, 786, 802, 858
3-Amino-2-methoxycarbonyl-5-methyl	165–167, 167–169	435, 780, 854, 855
2-Amino-3-methoxycarbonyl-5-methyl-6-phenyl	162	488
2-Amino-3-methoxycarbonyl-5(or 6)-methyl-6(or 5)-phenyl	162.5–163.5, 163–164	780, 802, 858
2-Amino-3-methoxycarbonyl-5-phenyl	126.5–128(?), 140–141	378a, 778, 780, 782, 786, 802, 858
3-Amino-2-methoxycarbonyl-5-phenyl	230, 231–232	488, 780, 802, 854, 855
2-Amino-3-methylcarbamoyl	131–134	421, 423
2-Amino-3-methylcarbamoyl-5,6-diphenyl	195 to 198	439, 1250, 1363
2-Aminomethyleneamino-3-formyl	Pic. 116.5	1167
2-Aminomethyleneamino-3-(*C*-hydrazino-*C*-imino)methyl	173–174	452
2-Aminomethyleneamino-3-hydroxy-iminomethyl	165	423
2-Amino-3-(*N'*-methylhydrazinocarbonyl)	105–106	426
2-Amino-5-methyl-2-*N*-methylcarbamoyl	126–128	435
3-Amino-5-methyl-2-(*N'*-methylhydrazino-carbonyl)	143–145	426
2-Amino-3-(methylthio)carbonyl	151–153	1075
2-Amino-3-(*C*-methylthio-*C*-iminomethyl)	123	1075
2-Amino-3-*N*-phenylcarbamoyl	106–107	458
2-Amino-3-thiocarbamoyl	168–170	1212
2-Amino-3,5,6-tricyano	225	384
2-Amino-3-ureidocarbonyl	285	1322
2-Anilino-3-carbamoyl	175–176	458
5-Anilino-3-guanidinocarbonyl-2-isopropylideneamino	214–216	432, 778, 780, 786, 858
5-Anilino-2-isopropylideneamino-3-methoxycarbonyl	195.5–197.5	432, 778, 780, 786, 858
2-Benzylamino-3-carbamoyl	125–216	379, 458, 1203

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Benzylamino-3-carbamoyl-5,6-dimethyl	186–187	379
2-Benzylamino-3-carbamoyl-5,6-diphenyl	177–178	379
2-Benzylamino-3-carboxy	166.5–168	458
2-Benzylamino-3-methoxycarbonyl	183.5	1203
2-*N*-Benzylcarbamoyl-3-(*N*-benzyl-carbamoyl-*N*-methylamino)-5-phenyl	255–256	453
2-*N*-Benzylcarbamoyl-3,5-bismethyl-amino-6-methylcarbamoyl	218.5–220	1192
2-*N*-Benzylcarbamoyl-5,6-diphenyl-3-(*N'*-isopropylthioureido)	170	1165
2-*N*-Benzylcarbamoyl-5,6-diphenyl-3-(*N'*-phenylureido)	210	1165
2-*N*-Benzylcarbamoyl-3-methylamino-5-phenyl	96–97	453
2,6-Bisbutylamino-3,5-bis-(*N*-butyl-carbamoyl)	89–91	1169
2,6-Bis(ethylamino)-3-*N*-ethylcarbamoyl-5-*N*-phenylcarbamoyl	146.5–147.5	1192
2,5-Bis(methylamino)-3,6-bis-*N*-methyl-carbamoyl	253–254	461
2,6-Bis(methylamino)-3,5-bis-*N*-methyl-carbamoyl	231 to 235	444, 460, 462, 1192
3,5-Bis(methylamino)-3-*N*-methylcarbamoyl	151–152	462
2,6-Bis(methylamino)-3-*N*-methyl-carbamoyl-5-*N*-propylcarbamoyl	218–219	1192
2,6-Bis(propylamino)-3,5-bis-*N*-propyl-carbamoyl	96–97	1169
2-Butylamino-6-thiocarbamoyl	117–119	945
2-*N*-Butylcarbamoyl-3,5-bis(methylamino)-6-*N*-methylcarbamoyl	194–196	1192
2-*N*-*t*-Butylcarbamoyl-3,5-bis(methylamino)-6-*N*-methylcarbamoyl	204–205	1192
2-*N*-Butylcarbamoyl-3-ethoxycarbonyl-amino-5,6-diphenyl	110–111	455
2-(*N'*-Butylhydrazinocarbonyl)-3,5-bis-(methylamino)-6-*N*-methylcarbamoyl	194–196	1192
2-(*N'*-*s*-Butylhydrazinocarbonyl)-3,5-bis-(methylamino)-6-*N*-methylcarbamoyl	188–190	1169
2-(*N'*-*t*-Butylhydrazinocarbonyl)-3,5-bis-(methylamino)-6-*N*-methylcarbamoyl	204–205	1169
2-Butyramido-3-hydrazinocarbonyl	122–124	433a
2-Carbamoyl-3,5-bis(methylamino)-6-*N*-methylcarbamoyl	290–292	1192
2-Carbamoyl-3-cyclohexylamino	128–129	379
2-Carbamoyl-3-cyclohexylamino-5,6-dimethyl	159–161	379
2-Carbamoyl-3-cyclohexylamino-5,6-diphenyl	185–186	379
2-Carbamoyl-6-diethylamino	191–192	942

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Carbamoyl-6-dimethylamino	222–224	942
2-Carbamoyl-6-(*N'*,*N'*-dimethylhydrazino)	224–226	945
2-Carbamoyl-5,6-dimethyl-3-methylamino	164	431
2-Carbamoyl-5,6-diphenyl-3-(*N'*-phenylthioureido)	233	1165
2-Carbamoyl-5,6-diphenyl-3-(*N'*-phenylureido)	240.5–241.5	1165
2-Carbamoyl-5-ethylamino-6-ethylcarbamoyl-3-methylamino	223–224	1169
2-Carbamoyl-3-(*N'*-isopropylthioureido)-5,6-diphenyl	251–252	1165
2-Carbamoyl-3-methylamino	196, 198–201	423, 431, 458, 459
2-Carbamoyl-6-methylamino	257–258	940
2-Carbamoyl-3-methylamino-5-phenyl	188–189	453
2-Carbamoyl-5-methyl-3-methylamino	149	428
2-Carbamoyl-6-piperidino	221–222	942
2-Carbamoyl-3-propionamido	–	457
2-Carbamoyl-3-sulfanilamido	203	1175
2-Carboxy-3,5-bis(ethylamino)-6-*N*-ethylcarbamoyl	174–175	1169
2-Carboxy-3,5-bis(methylamino)-6-*N*-methylcarbamoyl	190	462
2-Carboxy-3-(2'-carboxyethylamino)-5,6-dimethyl	177–179	443
2-Carboxy-6-diethylamino	180–181	942
2-Carboxy-6-dimethylamino	214–216	942
2-Carboxy-6-(*N'*,*N'*-dimethylhydrazino)	202–203	945
2-Carboxy-5,6-dimethyl-3-methylamino	146	431
2-(2'-Carboxyethylamino)-3-(2'-carboxyethylcarbamoyl)-5,6-dimethyl	174–175	443
2-Carboxy-5-ethylamino-6-*N*-ethylcarbamoyl-3-methylamino	160–162	1169
2-Carboxy-3-formamido-5-methyl	184–185	435
2-Carboxy-5-hydrazino	–	1098
3-Carboxy-2-hydroxyiminomethylamino-5-methyl	219–221	425
2-Carboxy-3-methylamino	182	1164
2-Carboxy-6-methylamino	250–251	940
2-Carboxy-5-methylamino-6-(*N*-methylcarbamoyl)	306–307	442
2-Carboxy-3-methylamino-5-phenyl	178–179	375
2-Carboxy-3-methylamino-6-phenyl	173–174	375
2-Carboxy-6-piperidino	179–180	942
2-Carboxy-3-sulfanilamido	178–180	1175
3-Cyano-5-cyclopropyl-2-dimethylaminomethyleneamino	118–120	1218
2-Cyano-6-diethylamino	123–124	941, 942
2-Cyano-6-dimethylamino	92–93	942
2-Cyano-3-dimethylaminomethyleneamino	86	803

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Cyano-3-(dimethylaminomethyleneamino)-5-methyl	182.5–183	1031
3-Cyano-2-dimethylaminomethyleneamino-5-methyl	102.5–103.5	1031
2-Cyano-6-*N'*,*N'*-dimethylhydrazino	105–107	945
2-Cyano-3-ethoxalylamino	160–161	1183, 1184
2-Cyano-3-(*N*-ethoxycarbonyl-*N*-methylamino)-5-phenyl	66–67	453
2-Cyano-3-ethoxymethyleneamino	105	803
2-(2'-Cyanoethylamino)-3-(2'-cyanoethylcarbamoyl)-5,6-dimethyl	163–166	443
2-Cyano-3-formamido	210	803
2-Cyano-6-isopropylamino	126–128	945
3-Cyano-2-methoxymethylamino-5-vinyl	161–162	529
2-Cyano-6-methylamino	155–157	940, 945
2-Cyano-6-piperidino	72–74	941
2-(*N*-Cyclopropyl-*N*-methylamino)-3-methoxycarbonyl	128–134/2	857
2-Diacetamido-5,6-dimethoxycarbonyl-3-dimethylamino	139–139.5	409
2,3-Diamino-5,6-dicarbamoyl	< 300	409
2,5-Diamino-3,6-dicarboxy	*ca.* 220	461
2,6-Diamino-3,5-dicarboxy	–	1180
2,3-Diamino-5,6-dicyano	332	384
2,6-Diamino-3,5-dicyano	> 400	1180
2,3-Diamino-5,6-dimethoxycarbonyl	268.5–269.5	409
3,5-Diamino-2-formyl	245–247	448
3,5-Diamino-2-guanidinocarbonyl	200.5–203.5, 286(?); HCl 186–188, 286–288	780, 791, 809, 885, 858, 859
3,5-Diamino-2-methoxycarbonyl	252–254	780, 809, 855, 858, 859
2-Diethylamino-6-*N*,*N*-diethylcarbamoyl	125–127/0.01	870
2-Diethylamino-6-ethoxycarbonyl	–	942
2-Diethylamino-6-hydrazinocarbonyl	143–145	942
2-Diethylamino-6-*N*-hydroxycarbamoyl	171–175	942
2-(*C*-Diethylamino-*C*-iminomethyl)-6-dimethylamino	198–201	1424
2-(*C*-Diethylamino-*C*-iminomethyl)-6-piperidino	198–200	1424
2-Diethylamino-6-thiocarbamoyl	210–212	941
2-(*N'*,*N'*-Diethylhydrazino)-6-thiocarbamoyl	174–175	945
2-Dimethoxymethyl-3-ethoxalylamino	56	1075
2-Dimethoxymethyl-3-trifluoroacetamido	49	1075
2-(2'-Dimethylamino-1'-formyl)vinyl	107.5–108	717
2-Dimethylamino-6-hydrazinocarbonyl	205–206	942
2-Dimethylamino-6-hydroxycarbamoyl	218–220	942
2-Dimethylamino-6-(*C*-imino-*C*-piperidinomethyl)	233–235	1424

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Dimethylamino-6-methoxycarbonyl	106–107	942
2-(*N*,*N*-Dimethylcarbamoyl)-3,5-bismethylamino-6-*N*-methylcarbamoyl	128–129	1192
2-(*N'*,*N'*-Dimethylhydrazinocarbonyl)-3,5-bis(methylamino)-6-*N*-methylcarbamoyl	128–129	1169
2-(*N'*,*N'*-Dimethylhydrazino)-6-*N*-hydroxymethyl(thiocarbamoyl)	175–176	945
2-(*N'*,*N'*-Dimethylhydrazino)-6-thiocarbamoyl	194–196	945
2,3-Dimethyl-5-methylamino-6-*N*-methylcarbamoyl	96–98	443
2-Ethoxalylamino-3-formyl	124	1075
2-Ethoxycarbonylamino-3-formyl	73	1075
2-Ethoxycarbonylamino-5,6-diphenyl-3-piperidinocarbonyl	174–175	455
2-Ethoxycarbonylamino-3-*N*-methylcarbamoyl-5,6-diphenyl	153	1250
2-(*N*-Ethoxycarbonyl-*N*-methylamino)-3-*N*-methylcarbamoyl-5,6-diphenyl	190	439
2-Ethoxycarbonyl-6-piperidino	91–93	942
2-Ethylamino-3,5-bis(*N*-ethylcarbamoyl)-6-methylamino	162–164	1169
2-Ethylamino-3-*N*-ethylcarbamoyl-6-methylamino-5-*N*-methylcarbamoyl	169–170	1169, 1192(?)
2-Ethylamino-3-*N*-ethylcarbamoyl-6-methylamino-5-*N*-propylcarbamoyl	84–86	1169
2-Ethylamino-3-*N*-ethylcarbamoyl-6-propylamino-5-*N*-propylcarbamoyl	91–92	1169, 1192(?)
2-Ethylamino-6-thiocarbamoyl	188–189	945
2-*N*-Ethylcarbamoyl-3,5-bis(methylamino)-6-*N*-methylcarbamoyl	197–198.5	1192
2-(*N'*-Ethylhydrazinocarbonyl)-3,5-bis-(methylamino)-6-*N*-methylcarbamoyl	197–198.5	1169
2-(*N*-Ethyl-*N*-methylcarbamoyl)-3,5-bis-(methylamino)-6-*N*-methylcarbamoyl	188–190	1192
2-Formamido-3-dimethoxymethyl	70	1075
2-Formamido-3-formyl	125–127, 126–128	423, 1075
3-Formamido-5-methyl-2-*N*-methylcarbamoyl	225–231, 232–235	435
2-Hydrazinocarbonyl-3,5-bis(methylamino)-6-*N*-methylcarbamoyl	290–292	1169
2-Hydrazinocarbonyl-5,6-dimethyl-3-methylamino	161	428
3-Hydrazinocarbonyl-2-isopropylideneamino-5-methyl	178	424
2-Hydrazinocarbonyl-6-methylamino	225–227	940
2-Hydrazinocarbonyl-6-piperidino	134–136	942
2-Hydrazinocarbonyl-3-methylamino-5-phenyl	215–216.5	453

TABLE A.10 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(*C*-Hydrazino-*C*-iminomethyl)-3-hyrazinomethyleneamino	*ca.* 240	803
2-Hydroxyaminocarbonyl-6-methylamino	205–207	940
2-*N*-Hydroxycarbamoyl-6-piperidino	200–202	942
2-Isobutylamino-6-thiocarbamoyl	122–123	945
2-(*N'*-Isopropylhydrazinocarbonyl)-3,5-bis-(methylamino)-6-*N*-methylcarbamoyl	175–177	1169
2-*N*-Methoxycarbamoyl-3-methoxyimino-methylamino	166	426
2-*N*-Methoxycarbamoyl-3-methoxyimino-methylamino-5-methyl	167	426
3-*N*-Methoxycarbamoyl-2-methoxyimino-methylamino-5-methyl	168–169	426
2-Methoxycarbonyl-3-methylamino	–	861
2-Methoxycarbonyl-6-methylamino	145–146	940
2-Methoxycarbonyl-3-methylamino-5-phenyl	134–135	375, 453
3-Methoxycarbonyl-2-methylamino-5-phenyl	140–141	375
2-Methoxycarbonyl-3-propionamido	–	457
2-Methoxycarbonyl-3-sulfanilamido	193.5–194	1175
2-Methylamino-3-*N*-methylcarbamoyl	73	423
2-Methylamino-6-*N*-methylcarbamoyl	172	940
2-Methylamino-3-*N*-methylcarbamoyl-5,6-diphenyl	159–161, 163–164	438, 439
2-Methylamino-3-*N*-methylcarbamoyl-5-phenyl	92–94	375
3-Methylamino-2-*N*-methylcarbamoyl-5-phenyl	112–114	375
2-Methylamino-3-*N*-methylcarbamoyl-6-propylamino-5-*N*-propylcarbamoyl	136–137	1192
2-Methylamino-6-thiocarbamoyl	207–209	945
2-Piperidino-6-thiocarbamoyl	197–199	941
2-Propylamino-6-thiocarbamoyl	148–150	945
2,3,5-Tricarboxy-6-ureido	265	1748
2,3,5-Tricyano-6-dimethylamino	–	158
2-(2'-Trimethylammonioethyl)/iodide	–	657

TABLE A.11 AMINO-HALOGENOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Allylamino-6-chloro	HCl 110	1749
2-Allyloxycarbonylamino-3,5,6-trichloro	80	1240
2-Amino-3-bromo	137	807
2-Amino-5-bromo	113.6	798

TABLE A.11 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-bromo-3-chloro	128	806, 807
2-Amino-3-bromo-5,6-dimethyl	114–117	812
2-Amino-5-bromo-3-dimethylamino	Variable	804
2-Amino-3-bromo-5-phenyl	153–154	365a
2-Amino-5-bromo-3-piperidino	128.5	804
2-Amino-3-chloro	167 to 169	369, 370, 481, 483, 547a, 833, 838, 984
2-Amino-5-chloro	129 to 132	831, 838
2-Amino-6-chloro	152–154	757, 870, cf. 744
2-Amino-3-chloro-5,6-dimethyl	98	374, 812
2-Amino-3-chloro-5,6-diphenyl		1010
2-Amino-3-chloro-5-methyl	58–62, 65	373, 835
3-Amino-2-chloro-5-methyl	113	373, 483, 835
5-Amino-3-chloro-2-methyl	58–60	535
3-Amino-2-chloro-5-phenyl	191–192	365a
2-Amino-3,5-dibromo	114 to 116	757, 804–807, 810 811
2-Amino-3,5-dibromo-6-phenyl	127–128	365a
2-Amino-3,5-dichloro (?)	140–142	845, cf. 365b
3-Amino-2,5-dichloro	140–141	365b, cf. 845
3-Amino-2,5-difluoro	Sublimes ca. 170	885
2-Amino-5-fluoro-3,6-bisheptafluoroisopropyl	59–61	496
2-Amino-5-iodo-3,6-dimethyl	129–130	887
2-Amino-5-iodo-3-methyl	95–96	887
2-Amino-3,5,6-trichloro	138	773
2-Amino-3,5,6-trifluoro	73–75	850–852
2-Benzamido-5-bromo	235	987
2-Benzylidenehydrazino-6-chloro	223	973
2,3-Bis(dimethylamino)-5,6-difluoro	52–53	885
2,5-Bis(dimethylamino)-3,6-difluoro	34	885
2,6-Bis(dimethylamino)-3,5-difluoro	70	885
2-Bromo-5-dimethylamino-3,6-difluoro	30–33	885
2-Chloro-5,6-bis(dimethylamino)-3-fluoro	50–51	888
2-Chloro-3,6-difluoro-5-hydrazino	137	888
2-Chloro-6-dimethylamino	44–45	759
2-Chloro-5-dimethylamino-3,6-difluoro	14–15	885
2-Chloro-6-dimethylamino-3,5-difluoro	6–7	888
2-Chloro-5-dimethylamino-3,6-dimethyl	HCl 155–157	689, 793
2-Chloro-5-dimethylamino-3,6-diisobutyl	145/5	937
2-Chloro-5-dimethylamino-3,6-diisopropyl	150/10	937
2-Chloro-5-dimethylamino-3,6-dipropyl	160/10	937
2-Chloro-6-(*N*,*N*-dimethylaminomethylenehydrazino)	168–170	973
2-Chloro-3-hydrazino	152–153	828
2-Chloro-6-hydrazino	136–139	973
2-Chloro-3-methylamino		1004
2,3-Diamino-5-bromo	217–218	804
2,3-Diamino-5,6-dibromo	252	684, 970

TABLE A.11 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,6-Diamino-3,5-dibromo	160–165	684
2,6-Diamino-3,5-dichloro	218–220	773
2,3-Diamino-5,6-dichloro	270	773
2,3-Diamino-5,6-difluoro	237–239	684
2,6-Diamino-3,5-difluoro	*ca.* 243	966
2,5-Diazido-3,6-difluoro	105–106	852
3,5-Dibromo-2-dimethylaminomethylene-amino	121–123	1252
3,5-Dibromo-2-hydroxyiminomethylamino	170	1252
2,6-Dichloro-3,5-bis(dimethylamino)	88.5–89.5	888
2,3-Dichloro-5,6-bis(dimethylamino)	86.5–87	888
2,5-Dichloro-3,6-bis(dimethylamino)	64–65	888
2,5-Dichloro-3-dimethylamino-6-fluoro	Anal., m.s., n.m.r.	888
2,6-Dichloro-3-dimethylamino-5-fluoro	52–60	888
2,5-Difluoro-3-dimethylamino	16	885
2-Dimethylamino-3,5,6-trifluoro	−23	885
2,3,5-Trichloro-6-dimethylamino	85–86	794, 888
2,3,5-Trichloro-6-hydrazino	172	888
2,3,5-Trichloro-6-methylamino	88.5	888
2,3,5-Trifluoro-6-hydrazino	48–50	851

TABLE A.12 AMINO-OXYPYRAZINES

Pyrazines	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetamido-3-acetoxymethyl	102	1075
2-Acetamido-3-hydroxy	215–217, 224–225; pic. 165–168	834, 1111
2-Acetoxymethyl-3-amino	79.5	1075
2-Amino-3,5-dimethoxy	75	881
3-Amino-2,5-dimethoxy	73	881
5-Amino-2,3-dimethoxy	127	535
2-Amino-3,5-dimethoxy-6-methyl	115–117	535
2-Amino-3-ethoxy	44	984
2-Amino-3-hydroxy	292–298, 300–301	369, 370, 833
2-Amino-3-hydroxy-5,6-dimethyl	300–303	374
2-Amino-5-hydroxy-3,6-dimethyl	225–230	872
2-Amino-3-hydroxy-5,6-diphenyl	309–311	1065
2-Amino-3-hydroxymethyl	118–119.5	1074, 1075
2-Amino-3-hydroxy-5-methyl	335–337	369
2-Amino-5-hydroxy-3-methyl	> 300	434
3-Amino-2-hydroxy-5-methyl	300	373
3-Amino-2-hydroxy-5-phenyl	310	365a
2-Amino-3-methoxy	80–82, 85, 85–86	773, 804, 810, 811, 832

TABLE A.12 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-methoxy	110–111	805, 1011
2-Amino-6-methoxy	112	805
2-Amino-3-methoxy-5,6-dimethyl	122	373, 835
2-Amino-3-methoxy-5-methyl	77–78	373, 835
3-Amino-2-methoxy-5-methyl	96	373, 835
5-Amino-3-methoxy-2-methyl	105–106	535
2-Amino-3-methoxy-5-phenyl	138–139	365a
3-Amino-1-methyl-2-oxo-1,2-dihydro	172; MeI 286–287	832
2-Benzylamino-3-hydroxy-5,6-dimethyl	171.5–172	907
2,5-Bis(ethoxycarbonylmethylcarbamoylmethyl-amino)-3,6-dihydroxy	2HCl 156	849
2,3-Diamino-5-hydroxy (?)	168–170; pic. 240	1049
2-Dimethylamino-5-hydroxy-3,6-dimethyl	HCl 235–240	689, 793
3-Dimethylamino-2-hydroxymethyl-5-methyl	HCl 141–142	793
2-Dimethylamino-5-methoxy-3,6-dimethyl	HCl 154–156 and remelt 232–234	689, 793
3-Guanidino-6-hydroxymethyl-1-methyl-2-oxo-1,2-dihydro (stizolamine)	208; HCl 294–296	1060
2-Hydrazino-3-hydroxy-5,6-diphenyl	222–223	1124
2-Hydroxy-5,6-dimethyl-3-methylamino	223–224	907
6-Hydroxymethyl-1-methyl-2-oxo-3-ureido-1,2-dihydro	200	1060

TABLE A.13 AMINO-THIOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-3-(*C*-carboxy-*C*-ethyl)methylthio-5,6-diphenyl		1010
2-Amino-3-(*C*-carboxy-*C*-methyl)methylthio-5,6-dimethyl		1010
2-Amino-3-carboxymethylthio-5,6-dimethyl		1010
2-Amino-3-carboxymethylthio-5,6-diphenyl		1010
2-Amino-3-cyanomethylthio-5,6-dimethyl	176–177	1229
2-Amino-3-cyanomethylthio-5,6-diphenyl	179–180	1229
2-Amino-3-(*C*-cyano-*C*-phenyl)methylthio-5,6-diphenyl	156–157	1229
2-Amino-6-ethylthio	96–97.5	994, 1208
2-Amino-3-mercapto	245–255, 260–261	535, 1009
2-Amino-3-mercapto-5,6-dimethyl	231, 259–261	1009, 1101
2-Amino-3-mercapto-5,6-diphenyl	259–261	1010, 1142
2-Amino-3-mercapto-5-methyl	219	1101
2-Amino-5-methyl-3-methylthio	75	535
2-Amino-3-methylthio	93	535
2-Amino-6-methylthio	96.5–98	994, 1208
2-Amino-3-phenacylthio	119–120	1009
2-Amino-3-phenacylthio-5,6-diphenyl	147–151	1142

TABLE A.14 AMINO-CARBOXY-HALOGENOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetamido-3-(*N'*-acetylamidinocarbamoyl)-5-chloro	194.5–196	150, 783–785
2-Acetamido-5-bromo-3-carbamoyl	216	987
3-Acetamido-2-bromo-5-carboxy	173	434
2-Acetamido-5-chloro-3-(2'-dimethylamino-ethylcarbamoyl)	142–144	1160
2-Acetamido-5-chloro-3-(*N',N''*-diphenyl-guanidinocarbonyl)	211–212	432a
2-Acetamido-5-chloro-3-guanidinocarbamoyl	204–205	783, 784, 1058, 1059
2-Acetamido-5-chloro-3-guanidinocarbonyl	204–206	781
2-Allylamino-6-amino-3-chloro-5-cyano	103–105	808, 877, 879, 1217, 1218, 1253
2-Allylamino-6-amino-3-chloro-5-(*N',N'*-dimethylguanidinocarbonyl)	212.5–215	780, 809, 858, 1350, 1371, 1372, 1412, 1432, 1433
2-Allylamino-6-amino-3-chloro-5-guanidino-carbamoyl	HCl 182–183	781, 1058
2-Allylamino-6-amino-3-chloro-5-guanidino-carbonyl	213–214	780, 809, 858, 1350, 1371, 1372, 1412, 1430, 1432, 1433
2-Allylamino-6-amino-3-chloro-5-hydrazino-carbonyl	158–160	963, 1370, 1371
2-Allylamino-6-amino-3-chloro-5-methoxy-carbonyl	105–106.5	780, 781, 809, 858
2-Allylamino-5-chloro-6-ethylamino-3-guanidino-carbonyl	132–135	799
2-Allylamino-5-chloro-6-ethylamino-3-methoxy-carbonyl	100–102	799
2-(*N*-Allyl-*N*-ethylamino)-6-amino-3-chloro-5-guanidinocarbonyl	208–209	780, 809, 858
2-(*N*-Allyl-*N*-ethylamino)-6-amino-3-chloro-5-methoxycarbonyl	43.5–45.5	781, 809
2-(*N*-Allyl-*N*-methylamino)-6-amino-3-chloro-5-guanidinocarbonyl	207–208	780, 809, 858, 1371, 1431
2-(*N*-Allyl-*N*-methylamino)-6-amino-3-chloro-5-methoxycarbonyl	90.5–92	780, 809, 858
2-Amidinoamidino-3-amino-6-chloro-5-dimethylamino	115	1218
2-Amino-6-(2'-aminoethylamino)-5-chloro-3-guanidinocarbonyl	HCl 311	780, 858
2-Amino-6-(2'-aminoethylamino)-5-chloro-3-methoxycarbonyl	265	780, 781, 858
2-Amino-3-(2'-aminoethylcarbamoyl)-5-chloro	153–155	1160
2-Amino-3-(*N'*-aminoguanidinocarbamoyl)-5-chloro	HCl 266–267	781
2-Amino-6-anilino-5-chloro-3-guanidinocarbonyl	224–226, 246.5 to 250.5	780, 809, 858
2-Amino-6-anilino-5-chloro-3-hydrazinocarbonyl	168–170, 194–195	963, 1370
2-Amino-6-anilino-5-chloro-3-methoxycarbonyl	171.5–174	780, 809, 858, 859

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-3-azidocarbonyl-5-chloro		1226
2-Amino-6-benzylamino-5-chloro-3-guanidinocarbonyl	206–209	780, 809, 858
2-Amino-6-benzylamino-5-chloro-3-methoxycarbonyl	157–158	780, 809, 855, 858, 859
2-Amino-3-(*N'*-benzylguanidinocarbamoyl)-5-chloro	241–243	1058
2-Amino-5-bromo-3-carbamoyl	213; 215–217	138, 803, 1218
2-Amino-5-bromo-3-carboxy	185–186	798
3-Amino-2-bromo-5-carboxy	153–154	434
2-Amino-5-bromo-6-chloro-3-methoxycarbonyl	225–228	792, 808, 875, 877–879
2-Amino-5-bromo-3-cyano	181–183	808, 877, 879, 1218, 1253
2-Amino-6-bromo-3,5-dicyano	236–238	484
2-Amino-5-bromo-3-(*N',N'*-dimethylguanidinocarbonyl)	205.5–206.5	150, 800, 801
2-Amino-5-bromo-3-guanidinocarbamoyl	HCl 268–269, 270–271	781, 1058
2-Amino-5-bromo-3-guanidinocarbonyl	234–234.5; HCl 265	150, 787, 1376
2-Amino-5-bromo-3-guanidinocarbonyl-6-methyl	288; HCl 290	780, 802
2-Amino-5-bromo-3-guanidinocarbonyl-6-phenyl	234–236	780, 802
2-Amino-5-bromo-3-hydrazinocarbonyl-6-methyl	202–205	1370, 1371
2-Amino-5-bromo-3-methoxycarbonyl	175.3–175.9	798
2-Amino-5-bromo-3-methoxycarbonyl-6-methyl	178–181	780, 802, 858
2-Amino-5-bromo-3-methoxycarbonyl-6-phenyl	217–221	780, 802, 858
2-Amino-6-(*N*-bromo-*N*-methylamino)-5-chloro-3-guanidinocarbonyl	HCl 288	858
2-Amino-5-bromomethyl-3-cyano		1031
2-Amino-6-(*N*-bromo-*N*-phenylamino)-5-chloro-3-guanidinocarbonyl	234–236	858
2-Amino-6-butylamino-5-chloro-3-(*N',N'*-dimethylguanidinocarbonyl)	187.5	780, 809, 858, 1361, 1433
2-Amino-6-butylamino-5-chloro-3-guanidinocarbonyl	219.5	780, 809, 858
2-Amino-6-*s*-butylamino-5-chloro-3-guanidinocarbonyl	208–209	809, 858
2-Amino-6-*t*-butylamino-5-chloro-3-guanidinocarbonyl	222–223	780, 809, 858
2-Amino-6-butylamino-5-chloro-3-hydrazinocarbonyl	162–165, 166–168	963, 1370, 1371
2-Amino-6-butylamino-5-chloro-3-methoxycarbonyl	140–142	780, 809, 858
2-Amino-6-*s*-butylamino-5-chloro-3-methoxycarbonyl	106–108	780, 809, 858
2-Amino-6-*t*-butylamino-5-chloro-3-methoxycarbonyl	98–108	780, 809, 858
2-Amino-6-(*N*-butyl-*N*-ethylamino)-5-chloro-3-guanidinocarbonyl	200.5–201.5	780, 809, 858

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-6-(*N*-butyl-*N*-ethylamino)-5-chloro-3-methoxycarbonyl	77.5–79.5	780, 809
2-Amino-6-(*N*-butyl-*N*-methylamino)-5-chloro-3-guanidinocarbonyl	208–209, 214–215	780, 809, 858
2-Amino-6-(*N*-butyl-*N*-methylamino)-5-chloro-3-methoxycarbonyl	59.5–61.5	780, 809, 858
2-Amino-6-(*N*-butyl-*N*-propylamino)-5-chloro-3-guanidinocarbonyl	215–217	780, 858
2-Amino-6-(*N*-butyl-*N*-propylamino)-5-chloro-3-methoxycarbonyl		780
2-Amino-3-carbamoylcarbamoyl-5-chloro	240	1152
2-Amino-3-carbamoyl-5-chloro	131–132, 227–230, 231–232	379, 432, 432a, 778, 780, 783, 786, 808, 858, 877, 1218, 1253
2-Amino-3-carbamoyl-5-chloro-6-dimethylamino	182–183	792, 808, 877, 878
2-Amino-3-carbamoyl-5-chloro-6-ethylamino	195–198	963
2-Amino-3-carbamoyl-5-chloro-6-isopropylamino	140–141	808, 877
2-Amino-3-carbamoyl-6-chloro-5-methyl	280	535
2-Amino-3-carbamoyl-5,6-dichloro	291–293.5	792, 808, 809, 877
3-Amino-2-carbamoyl-5-trifluoromethyl	195–196	802, cf. 781, 1376
2-Amino-3-carbamoyl-5-trifluoromethyl	220–221	802
2-Amino-3-carboxy-5-chloro	177 to 180; 228–230 (?)	150, 432a, 781, 783–785, 831
2-Amino-3-carboxy-5-chloro-6-(prop-2'-ynyl-amino)		961
2-Amino-3-carboxy-5,6-dichloro	227, 228.5	809, 854
3-Amino-2-carboxy-5-trifluoromethyl	185–186	802, cf. 781, 787, 1376
2-Amino-6-chloro-5-chloromethyl-3-cyano	190–191	874
2-Amino-5-chloro-6-(*N*-chloro-*N*-phenylamino)-3-guanidinocarbonyl	214–216	858
2-Amino-5-chloro-3-cyano	151 to 154	538, 807, 877, 879, 1218, 1253
3-Amino-5-chloro-2-cyano	194–196	538
2-Amino-5-chloro-3-*N*-cyanocarbamoyl		1375
2-Amino-5-chloro-3-*N*-cyanocarbamoyl-6-dimethylamino		1375
2-Amino-5-chloro-3-*N*-cyanocarbamoyl-6-ethylamino		1375
2-Amino-5-chloro-3-cyano-6-diethylamino	114–116	877, 879, 1217, 1218, 1253
2-Amino-5-chloro-3-cyano-6-dimethylamino	118 to 122.5	792, 808, 877–879, 1217, 1218, 1253
2-Amino-5-chloro-3-cyano-6-dimethylamino-ethylamino	135–137	879
2-Amino-5-chloro-3-cyano-6-ethylamino	107–109	808, 877, 879, 1218, 1253
2-Amino-5-chloro-3-cyano-6-isopropylamino	126–128	792, 808, 877, 879, 1217, 1218, 1253

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-6-chloro-3-cyano-5-methyl	228–229	538
2-Amino-5-chloro-6-cyclohexylamino-3-guanidinocarbonyl	221–222	858
2-Amino-5-chloro-6-cyclopentylamino-3-guanidinocarbonyl	219–220	809, 858, 1371
2-Amino-5-chloro-6-cyclopentylamino-3-hydrazinocarbonyl	143–145	1370, 1371
2-Amino-5-chloro-6-cyclopentylamino-3-methoxycarbonyl	119.5–121.5	780, 781, 809, 858
2-Amino-5-chloro-6-cyclopropylamino-3-guanidinocarbonyl	213–215, 220–221.5	809, 858, 1432
2-Amino-5-chloro-6-cyclopropylamino-3-methoxycarbonyl	167–169	780, 781, 809
2-Amino-5-chloro-6-(*N*-cyclopropylmethyl)-amino-3-(*N'*,*N'*-dimethylguanidinocarbonyl)	196–197	780, 809, 858, 1371
2-Amino-3-chloro-6-(*N*-cyclopropyl-*N*-methyl-amino)-5-guanidinocarbonyl	260	857
2-Amino-5-chloro-6-(*N*-cyclopropylmethyl)-amino-3-guanidinocarbonyl	219–220, 220–221.5	780, 809, 858, 1350, 1361, 1371, 1372, 1412, 1431, 1433
2-Amino-3-chloro-6-(*N*-cyclopropyl-*N*-methyl-amino)-5-methoxycarbonyl	114–120	857
2-Amino-5-chloro-6-(*N*-cyclopropylmethyl)-amino-3-methoxycarbonyl	132–133	780, 781, 809, 858, 859
2-Amino-5-chloro-3-(*N'*,*N''*-diacetylguanidino-carbonyl)	187.5–188.5	150
2-Amino-5-chloro-3-(*N'*,*N'*-dibutylguanidino-carbonyl)	143.5–145	150
2-Amino-5-chloro-6-dichloroamino-3-guanidino-carbonyl	HCl 259–261	858
2-Amino-6-chloro-3,5-dicyano	234–236	484, 486
2-Amino-5-chloro-6-diethylamino-3-(*N'*,*N'*-dimethylguanidinocarbonyl)	212–214	809, 858, 1350, 1361, 1371, 1372, 1412, 1431–1433
2-Amino-5-chloro-6-diethylamino-3-guanidino-carbonyl	215	780, 809, 858, 1371
2-Amino-5-chloro-6-diethylamino-3-hydrazino-carbonyl	141 to 145	963, 1371
2-Amino-5-chloro-6-diethylamino-3-methoxy-carbonyl	99–101	780, 809, 858
2-Amino-3-chloro-5,6-dimethoxycarbonyl	127–128	409
2-Amino-5-chloro-6-dimethylamino-3-(*N'*,*N'*-dimethylguanidinocarbonyl)	214, 219	780, 809, 858, 1371
2-Amino-5-chloro-6-[2'-(dimethylamino)ethyl]-amino-3-guanidinocarbonyl	192.4–194.5	780, 1371
2-Amino-5-chloro-6-[2'-(dimethylamino)ethyl]-amino-3-hydrazinocarbonyl	161–163	1370, 1371
2-Amino-5-chloro-6-[2'-(dimethylamino)ethyl]-amino-3-methoxycarbonyl	257	780, 781, 858

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-chloro-3-[2′-(dimethylamino)ethyl]-carbamoyl	94–96	1160
2-Amino-5-chloro-6-dimethylamino-3-guanidino-carbamoyl	221; HCl 221	781, 791, 1058, 1361, 1432, 1433
2-Amino-5-chloro-6-dimethylamino-3-guanidino-carbonyl	216–217; HCl 298	780, 783, 789, 791, 809, 854, 858, 1350, 1361, 1371, 1372, 1412, 1431–1433
2-Amino-5-chloro-6-dimethylamino-3-guanidino-(*C*-iminomethyl)	115	792, 878
2-Amino-5-chloro-6-dimethylamino-3-hydrazino-carbonyl	132–134, 142–145	1370, 1371
2-Amino-5-chloro-6-dimethylamino-3-methoxy-carbonyl	142–144, 145.5–146.5	779–781, 809, 855, 858, 859, 891, 1322
2-Amino-5-chloro-6-dimethylamino-3-ureido-carbonyl	209–211	1322, 1375
2-Amino-5-chloro-3-(*N*′,*N*′-dimethylguanidino-carbamoyl)	HCl 279–280	780, 918, 1058
2-Amino-5-chloro-3-(*N*′,*N*′-dimethylguanidino-carbonyl)	198–199	150, 800, 801, 918
2-Amino-5-chloro-3-(*N*′,*N*′-dimethylguanidino-carbonyl)-6-(*N*-ethyl-*N*-methylamino)	218	780, 809, 858, 1371
2-Amino-5-chloro-3-(*N*′,*N*′-dimethylguanidino-carbonyl)-6-isopropylamino	238.5–240	780, 809, 858, 1350, 1361, 1371, 1372, 1412, 1431–1433
2-Amino-5-chloro-3-(*N*′,*N*′-dimethylguanidino-carbonyl)-6-(*N*-isopropyl-*N*-methylamino)	209–211	780, 858, 1350, 1412, 1432, 1433
2-Amino-5-chloro-3-(*N*′,*N*′-dimethylguanidino-carbonyl)-6-(*N*-methyl-*N*-propylamino)	209–211	809, 1361, 1372
2-Amino-5-chloro-3-(*N*′,*N*″-diphenylguanidino-carbonyl)	224–226	432a
2-Amino-5-chloro-6-(dipropylamino)-3-guanidinocarbonyl	221–222	780, 858
2-Amino-5-chloro-6-(dipropylamino)-3-methoxy-carbonyl	68.5–71.5	780, 858
2-Amino-5-chloro-6-ethylamino-3-guanidino-carbonyl	207.5–209.5; 217–218	809, 858, 1371
2-Amino-5-chloro-6-ethylamino-3-hydrazino-carbonyl	168–170	963, 1371
2-Amino-5-chloro-6-ethylamino-3-(*N*-hydroxycarbamoyl)	185–186	957
2-Amino-5-chloro-6-ethylamino-3-methoxy-carbonyl	149–150	780, 809, 858, 957
2-Amino-5-chloro-6-(1′-ethylethylamino)-3-guanidinocarbonyl	208–209	780
2-Amino-5-chloro-6-(*N*-ethyl-*N*-isopropylamino)-3-guanidinocarbonyl	207–208	780, 809, 858
2-Amino-5-chloro-6-(*N*-ethyl-*N*-isopropylamino)-3-methoxycarbonyl		780

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-chloro-6-(*N*-ethyl-*N*-methylamino)-3-guanidinocarbonyl	229–230	780, 809, 858, 1350, 1361, 1371, 1372, 1412, 1432, 1433
2-Amino-5-chloro-6-(*N*-ethyl-*N*-methylamino)-3-hydrazinocarbonyl	134–136	963, 1370, 1371
2-Amino-5-chloro-6-(*N*-ethyl-*N*-methylamino)-3-methoxycarbonyl	102–104	780, 781, 809, 858
2-Amino-5-chloro-6-(*N*-ethyl-*N*-propylamino)-3-guanidinocarbonyl	224–225	780, 809, 858
2-Amino-5-chloro-6-(1′-ethylpropylamino)-3-guanidinocarbonyl	209–211	809, 858
2-Amino-5-chloro-6-(*N*-ethyl-*N*-propylamino)-3-methoxycarbonyl		780
2-Amino-5-chloro-6-(1′-ethylpropylamino)-3-methoxycarbonyl	82.5–84.5	780, 809
2-Amino-5-chloro-3-formyl	158–159	430
3-Amino-5-chloro-2-formyl	151–152	430
2-Amino-5-chloro-3-guanidinocarbamoyl	300, 333–334; HCl 277–278	779, 781, 783, 784, 918, 1058, 1159, 1370
2-Amino-5-chloro-3-guanidinocarbamoyl-6-isopropylamino	HCl 229–231	780, 781, 1058
3-Amino-5-chloro-2-guanidinocarbonyl	250	876
2-Amino-5-chloro-3-guanidinocarbonyl	238; HCl 286	150, 787, 1376
2-Amino-5-chloro-3-guanidinocarbonyl-6-hexylamino	194.5–196.5	780, 809
2-Amino-5-chloro-3-guanidinocarbonyl-6-(2′-hydroxyethylamino)	HCl 272–273	780, 809, 858
2-Amino-5-chloro-3-guanidinocarbonyl-6-isobutylamino	221	780, 809, 858, 1371
2-Amino-5-chloro-3-guanidinocarbonyl-6-isopropylamino	215	780, 783, 809, 858, 1371
2-Amino-5-chloro-3-guanidinocarbonyl-6-(*N*-isopropyl-*N*-methylamino)	207–208	780, 809, 858, 1350, 1361, 1372, 1412, 1432, 1433
2-Amino-5-chloro-3-guanidinocarbonyl-6-(*N*-methoxy-*N*-methylamino)	203.5–204.5	809
2-Amino-5-chloro-3-guanidinocarbonyl-6-methylamino	238–239	780, 809, 858, 1371
2-Amino-3-chloro-5-guanidinocarbonyl-6-methylamino		789
2-Amino-5-chloro-3-guanidinocarbonyl-6-(1′-methylbutylamino)	186.5–188.5	780, 809
2-Amino-5-chloro-3-guanidinocarbonyl-6-(1′-methylhydrazino)	234	780, 809
2-Amino-5-chloro-3-guanidinocarbonyl-6-(2′-methylhydrazino)	234	858
2-Amino-5-chloro-3-guanidinocarbonyl-6-(1′-methylpentylamino)	186.5–188.5	858

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-chloro-3-guanidinocarbonyl-6-(*N*-methyl-*N*-propylamino)	214–215	809, 1350, 1361, 1371, 1372, 1432, 1433
2-Amino-5-chloro-3-guanidinocarbonyl-6-pentylamino	215–216	780, 809, 858
2-Amino-6-chloro-3-guanidinocarbonyl-5-phenyl	214–216	780, 802
2-Amino-5-chloro-3-guanidinocarbonyl-6-propylamino	221–222	780, 809, 858, 1371
2-Amino-5-chloro-3-guanidinocarbonyl-6-(2′,2′,2′-trifluoroethylamino)	232–233	780, 809, 858, 1371
2-Amino-5-chloro-3-guanidinocarbonyl-6-(3′,3′,3′-trifluoropropylamino)	221–222.5	780, 809, 858
2-Amino-5-chloro-3-guanidinocarbonyl-6-trimethylhydrazino	2HCl 262	858
2-Amino-5-chloro-6-guanidino-3-guanidinocarbonyl	2HCl > 340	780, 809, 858
2-Amino-5-chloro-6-guanidino-3-hydrazinocarbonyl	300	963
2-Amino-5-chloro-6-hexylamino-3-methoxycarbonyl	72.5–75.5	780, 858
2-Amino-5-chloro-3-hydrazinocarbonyl	218–220	779, 781, 1058, 1226
2-Amino-5-chloro-3-hydrazinocarbonyl-6-(2′-hydroxyethylamino)	184–185	963, 1370, 1371
2-Amino-5-chloro-3-hydrazinocarbonyl-6-[*N*-(2′-hydroxyethyl)-*N*-methylamino]	122–125	963
2-Amino-5-chloro-3-hydrazinocarbonyl-6-isopropylamino	132–134	963, 1370
2-Amino-5-chloro-3-hydrazinocarbonyl-6-(2′-methoxyethylamino)	151–154	963
2-Amino-5-chloro-3-hydrazinocarbonyl-6-methylamino	257–260; monoacetyl 230–231	963, 1370, 1371
2-Amino-5-chloro-3-hydrazinocarbonyl-6-(*N*-methyl-*N*-propylamino)	133–136	963, 1370, 1371
2-Amino-5-chloro-3-hydrazinocarbonyl-6-pentylamino	HCl 265–267	1371
2-Amino-5-chloro-3-hydrazinocarbonyl-6-propylamino	171–173	963, 1370, 1371
2-Amino-5-chloro-6-hydrazino-3-hydrazinocarbonyl	238–239	891
2-Amino-5-chloro-3-(*C*-hydrazino-*C*-iminomethyl)	169–171	1218
2-Amino-5-chloro-6-(2′-hydroxyethylamino)-3-methoxycarbonyl	155–157	780, 781, 809, 858
2-Amino-5-chloro-3-(*C*-imino-*C*-methylthiomethyl)	192–194	877, 1218
2-Amino-5-chloro-6-isobutylamino-3-methoxycarbonyl	113.5–115.5	780, 809, 858

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-chloro-6-isopropylamino-3-methoxycarbonyl	122.5–126.5	780, 781, 809, 858, 859
2-Amino-5-chloro-6-isopropylamino-3-(*N'*-methylguanidinocarbonyl)	216.5–219, > 300	809, 1350, 1361, 1372, 1412, 1432
2-Amino-5-chloro-6-(*N*-isopropyl-*N*-methylamino)-3-methoxycarbonyl	73–75, 75.5–77.5	780, 809, 858, 1322
2-Amino-5-chloro-6-(*N*-isopropyl-*N*-methylamino)-3-ureidocarbonyl	196–198	1322
2-Amino-5-chloro-3-methoxycarbonyl	142, 154–157, 159–161	150, 779–782, 858, 1322, 1376
3-Amino-5-chloro-2-methoxycarbonyl	185–187	876, 880
2-Amino-5-chloro-3-methoxycarbonyl-6-(*N*-methoxy-*N*-methylamino)	144–146	781, 809
2-Amino-6-chloro-3-methoxycarbonyl-5-methyl	108.5–110.5, 176.5 to 179.5	780, 782, 802, 854, 858
2-Amino-5-chloro-3-methoxycarbonyl-6-methylamino	221–222	780, 809, 858
2-Amino-3-chloro-5-methoxycarbonyl-6-methylamino		789, 861
2-Amino-5-chloro-3-methoxycarbonyl-6-(1'-methylbutyl)	74.5–75.5	809
2-Amino-5-chloro-3-methoxycarbonyl-6-(1'-methylhydrazino)	136.5–138.5	780, 809
2-Amino-5-chloro-3-methoxycarbonyl-6-(2'-methylhydrazino)	136.5–138.5	858
2-Amino-5-chloro-3-methoxycarbonyl-6-(*N*-methyl-*N*-propylamino)	83.5–85.5	780, 809, 858
2-Amino-5-chloro-3-methoxycarbonyl-6-pentylamino	100.5–102.5	780, 781, 809, 858
2-Amino-6-chloro-3-methoxycarbonyl-5-phenyl	187.5 to 191.5	780, 782, 802, 854, 858
2-Amino-5-chloro-3-methoxycarbonyl-6-phenylamino	138–140	780, 809, 858
2-Amino-5-chloro-3-methoxycarbonyl-6-(prop-2'-ynylamino)		961
2-Amino-5-chloro-3-methoxycarbonyl-6-(2',2',2'-trifluoroethylamino)	153–154	780, 781, 809, 858, 859
2-Amino-5-chloro-3-methoxycarbonyl-6-(3',3',3'-trifluoropropylamino)	124.5–125.5	780, 809, 858
2-Amino-5-chloro-3-methylcarbamoyl	152 to 154.5	432, 778, 783, 1222
2-Amino-5-chloromethyl-3-cyano	156–157	529
3-Amino-5-chloromethyl-2-cyano	174	534
2-Amino-5-chloro-3-(*N'*-methylguanidinocarbamoyl)	263–265; HCl 252–253	781, 918, 1058
2-Amino-5-chloro-3-(*N'*-methylguanidinocarbonyl)	235–236	150, 800, 801, 918
2-Amino-5-chloro-3-(*N'*-methyl-*N''*-methylguanidinocarbonyl)	226–227	150, 800, 801, 918
2-Amino-5-chloro-3-(*N'*-phenylguanidinocarbamoyl)	HCl 254–255	1058

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-chloro-3-semicarbazidocarbonyl	249–251	1058
2-Amino-5-chloro-3-thiocarbamoyl	193–195	1218
2-Amino-5-chloro-3-ureidocarbonyl	240	1322, 1375
2-Amino-5,6-dicarbamoyl-3-chloro	227–228	409
2-Amino-5,6-dichloro-3-cyano	213–215, 295	792, 808, 877–879, 1218, 1253
2-Amino-5,6-dichloro-3-formyl	154	430
2-Amino-5,6-dichloro-3-guanidinocarbonyl	216–217; HCl 259–261	780, 782, 809, 854
2-Amino-5,6-dichloro-3-methoxycarbonyl	233–234	432a, 779–781, 809, 854
2-Amino-3-ethoxycarbonyl-5-trifluoromethyl	91.5–93.5	802
2-Amino-3-guanidinocarbamoyl-5-iodo	254–255, 256–257	781, 1058
3-Amino-2-guanidinocarbamoyl-5-trifluoromethyl	HCl 249–250	1058, cf. 781
2-Amino-3-guanidinocarbonyl-5-iodo	226–227, 228–229	150
2-Amino-3-guanidinocarbonyl-5-trifluoromethyl	222–223, 230–232	787, 1376, cf. 802
3-Amino-2-guanidinocarbonyl-5-trifluoromethyl	222–223	802
2-Amino-5-iodo-3-methoxycarbonyl	200–202	150, 781, 782, 787, 854, 1376
2-Amino-3-methoxycarbonyl-5-trifluoromethyl	195.5–196.5	781, 787, 802, 1376
3-Amino-2-methoxycarbonyl-5-trifluoromethylamino	153–154	855
2-Azidocarbonyl-6-chloro-5-dimethylamino-3-ethylamino	110	891
2-Benzamido-5-bromo-3-carbamoyl		987
2-Bromo-5-chloro-6-dimethylamino-3-methoxycarbonyl	98–99	799, 891
2-Bromo-5-chloro-6-ethylamino-3-methoxycarbonyl	160–162	799
5-Bromo-2-cyclopropylamino-3-guanidinocarbonyl	265	955, 1377
5-Bromo-2-cyclopropylamino-3-methoxycarbonyl	91–93	955, 1377
5-Bromo-2-dimethylamino-3-guanidinocarbonyl	216–218	799–801
5-Bromo-2-dimethylamino-3-methoxycarbonyl	80–82, 105–108	799–801
5-Bromo-3-guanidinocarbonyl-2-methylamino	230–232	799–801
5-Bromo-3-methoxycarbonyl-2-methylamino	181.5–183.5	799–801
3-Carbamoyl-5-chloro-2-methylamino	152.5–154.5	786
5-Chloro-2-chloroamino-3-methoxycarbonyl	142	150, 432a, 779, 781, 784, 787, 854
5-Chloro-2-cyano-3-(dimethylaminomethyleneamino) (?)	114–116	808
5-Chloro-3-cyano-2-(dimethylaminomethyleneamino)	114–116, 117–119	877, 879, 1218, 1253
2-Chloro-6-cyano-3-isopropylamino-5-dimethylaminomethyleneamino	144–145	877

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
5-Chloro-2-cyclopropylamino-3-guanidinocarbonyl	260–265	955, 956, 1377
5-Chloro-2-cyclopropylamino-3-methoxycarbonyl	78–80	955, 956, 1377
5-Chloro-2-(cyclopropylmethyl)amino-3-guanidinocarbonyl	265	1377
5-Chloro-2-(cyclopropylmethyl)amino-3-methoxycarbonyl	94–95	955, 1377
2-Chloro-3-dimethylamino-5-ethylamino-6-guanidinocarbonyl	241–242	799
5-Chloro-2-(2′-dimethylaminoethyl)amino-3-guanidinocarbonyl	210–213	799, 800
2-Chloro-3-dimethylamino-5-ethylamino-6-methoxycarbonyl	93–95	799, 891
5-Chloro-2-(2′-dimethylaminoethyl)amino-3-methoxycarbonyl	105–108, 116–118	790, 799–801
2-Chloro-3-dimethylamino-6-guanidinocarbonyl-5-(2′-hydroxyethylamino)	242–244	799
2-Chloro-3-dimethylamino-5-(2′-hydroxyethyl)-amino-6-methoxycarbonyl	103–105	799, 891
2-Chloro-3-ethylamino-6-guanidinocarbonyl-5-(2′-methoxyethyl)amino	219–220	799
2-Chloro-3-ethylamino-6-methoxycarbonyl-5-(2′-methoxyethyl)amino	89–90	799
5-Chloro-2-formamido-3-formyl	163	430
5-Chloro-3-formamido-2-formyl	140–141	430
2,6-Diamino-3-azidocarbonyl-5-chloro	160 (explodes)	1371
2,6-Diamino-5-benzimidoylcarbamoyl-3-chloro	221–224	1331
2,6-Diamino-3-(*N*′-benzylguanidinocarbamoyl)-5-chloro	244–247	1058
2,6-Diamino-3-(*N*′-benzylguanidinocarbonyl)-5-chloro	215–216	1433
2,6-Diamino-3-(*N*′-benzyl-*N*′-methylguanidino)-carbonyl-5-chloro	HCl 274.5	1433
2,6-Diamino-3-benzylthiocarbonyl-5-chloro	145–146.5	1331
2,6-Diamino-3-bromo-5-guanidinocarbonyl	232.5–235.5	780, 809, 858, 1361, 1372, 1432, 1433
2,6-Diamino-3-bromo-5-methoxycarbonyl	217–219	780, 781, 809, 858
2,6-Diamino-3-*t*-butylcarbamoyl-5-chloro	219–221	1331
2,6-Diamino-3-(*N*′-*t*-butylguanidino)carbamoyl-5-chloro	160 (resolidifies) 275	1370
2,6-Diamino-3-(butylthio)carbonyl-5-chloro	129.5–130.5	1161
2,6-Diamino-3-(*N*′-*t*-butylureidocarbamoyl)-5-chloro	275	1369
2,6-Diamino-3-carbamoylcarbamoyl-5-chloro	260	1152
2,6-Diamino-3-carbamoyl-5-chloro	218.5–220.5	809, 877, 1361, 1412
2,6-Diamino-3-carboxy-5-chloro	228–230, 272	783, 784, 1058, 1265
2,6-Diamino-3-chloro-5-cyano	290 to 295	808, 877–879, 1218, 1253, 1361, 1432
2,6-Diamino-3-chloro-5-cyanocarbamoyl	> 330	1374, 1375

TABLE A.14 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,6-Diamino-3-chloro-5-(*N'*,*N'*-dibutylguanidinocarbonyl)	148–149	780, 1371
2,6-Diamino-3-chloro-5-(*N*,*N'*-dicyclohexylureidocarbonyl)	218–220	1331
2,6-Diamino-3-chloro-5-(*N'*,*N'*-diethylguanidiocarbonyl	265	780, 791, 809, 858, 1350, 1361, 1371, 1372, 1432, 1433
2,6-Diamino-3-chloro-5-(*N'*,*N'*-dimethylguanidinocarbamoyl)	305–309; HCl H_2O 277 to 280	791, 1058, 1361, 1370, 1432
2,6-Diamino-3-chloro-5-(*N'*,*N'*-dimethylguanidinocarbonyl)	240, 295; HCl H_2O 275 to 277	780, 791, 809, 858, 1350, 1371, 1372, 1412, 1432, 1433
2,6-Diamino-3-chloro-5-(*N*,*N'*-dimethylhydrazinocarbonyl)		1344
2,6-Diamino-3-chloro-5-ethylcarbamoyl	205–206	1331
2,6-Diamino-3-chloro-5-guanidinocarbamoyl	278 to 282; HCl 276.5–277.5, 281–282	781, 783, 784, 791, 1058, 1331, 1361, 1433
2,6-Diamino-3-chloro-5-guanidinocarbonyl	239 to 241.5; HCl 293.5	780, 783, 791, 809, 858, 1161, 1331, 1350, 1361, 1371, 1372, 1412, 1431, 1432
2,6-Diamino-3-chloro-5-hydrazinocarbonyl	266–268	779, 1058, 1331
2,6-Diamino-3-chloro-5[2(*C*-imino-*C*-methylthiomethyl)]hydrazinocarbonyl	> 300	1331
2,6-Diamino-3-chloro-5-(*N'*-isopropylguanidinocarbamoyl)	271–274	1058
2,6-Diamino-3-chloro-5-methoxycarbonyl	212–213	432a, 463a, 779–781, 783, 808, 809, 854–856, 858, 859, 1330, 1345
2,6-Diamino-3-chloro-5-(*N'*-methylguanidinocarbonyl)	252–254.5	791, 809, 1350, 1361, 1372, 1412, 1432, 1433
2,6-Diamino-3-chloro-5-(*N*-methylhydrazinocarbonyl)	176–177.5	1369
2,6-Diamino-3-chloro-5-(*N*-phenylcarbamoyl)	198–202	1331, 1345, 1346
2,6-Diamino-3-chloro-5-(*N'*-phenylguanidinocarbonyl)	272	1371
2,6-Diamino-3-chloro-5-ureidocarbonyl		1375
2,6-Diamino-3-guanidinocarbonyl-5-iodo	HCl 273–274	780, 809, 858
2,6-Diamino-3-iodo-5-methoxycarbonyl	200–202	780, 809
2,3-Dichloro-5-cyano-6-dimethylamino methyleneamino	117–119	808, 878, 879, 1218
2,3-Dichloro-5-(*N*-cyclopropyl-*N*-methylamino)-6-methoxycarbonyl	130–131	857
2,3-Dichloro-5-formamido-6-formyl	153–154	430
2,3-Dichloro-5-methoxycarbonyl-6-methylamino		789, 861

TABLE A.15 AMINO-CARBOXY-OXYPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
3-Acetamido-2-carbamoyl-5-hydroxy	257–259	538
2-Acetamido-3-carbamoyl-6-hydroxy-5-methyl	238–239	538
3-Acetamido-2-ethoxycarbonyl-5-hydroxy	158–160	538
2-Acetamido-3-guanidinocarbonyl-5-methoxy	Nitrate 225, 225–229	432, 786
5-Acetoxymethyl-2-amino-3-cyano	140–141	542
2-Amino-3-carbamoyl-5-cyano-6-hydroxy	147–150	484
2-Amino-3-carbamoyl-5-cyano-6-methoxy	240–244	484
2-Amino-3-carbamoyl-5-hydroxy	338	538
2-Amino-3-carbamoyl-6-hydroxy-5-methyl	276–278	538
2-Amino-3-cyano-5-(3′-hydroxybutyl)	101.5–103	1031
2-Amino-5-cyano-6-methoxy-3-methoxycarbonyl	238	484
2-Amino-3-cyano-5-methoxymethyl	142–143	529
2-Amino-3,5-dicyano-6-ethoxy	225	484
2-Amino-3,5-dicyano-6-methoxy	191–192	484
2-Amino-5,6-dicyano-3-methoxy	211.5–213	385
3-Amino-2-ethoxycarbonyl-5-hydroxy	228–230	538
3-Amino-2-formyl-5-hydroxy	*ca.* 222	448, 449
3-Amino-2-guanidinocarbonyl-5-hydroxy	HCl > 310	780, 809, 855, 858, 859
3-Amino-2-guanidinocarbonyl-5-methoxy	HCl 229–230	780, 809, 855, 858, 859
2-Amino-3-hydroxy-5,6-dimethoxycarbonyl	238.5–239.5	409
3-Amino-5-hydroxy-2-methoxycarbonyl	220–260, 260	780, 809, 855, 858, 859
3-Amino-5-methoxy-2-methoxycarbonyl	205.5–207.5	780, 790, 809, 855, 858, 859
2-Carbamoyl-5-hydroxy-3-methylamino	*ca.* 300	449
2-Carbamoyl-5-hydroxy-6-methyl-3-trifluoroacetamido	280–290	538
2-Carboxy-3-hydroxy-6-methylamino-5-methylcarbamoyl	208–210	440
2-Carboxy-3-hydroxy-5-methylamino-6-(*N*-methylcarbamoyl)	270–275	441
2-(2′-Carboxyprop-1′-enyl)-3-hydroxy-6-methylamino-5-(*N*-methylcarbamoyl)	220–223	445
2,6-Dicyano-3-dimethylaminomethyleneamino-5-ethoxy	223–225	484
3-(*N*-Ethoxycarbonyl-*N*-methylamino)-5-hydroxy-2-(*N*-methylcarbamoyl)	166–168	441
2-Formyl-5-hydroxy-3-methylamino	290–295	448
2-Hydroxy-6-methylamino-3,5-bis(*N*-methylcarbamoyl)	188	440
2-Hydroxy-5-methylamino-3,6-bis(*N*-methylcarbamoyl)	252–254	440
5-Hydroxy-3-methylamino-2-(*N*-methylcarbamoyl)	270–280	441
2-Hydroxy-3-methyl-6-methylamino-5-(*N*-methylcarbamoyl)	285–286	445
2-Methoxy-6-methylamino-3,5-bis(*N*-methylcarbamoyl)	198	440

TABLE A.16 AMINO-CARBOXY-SULFONYLPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-benzylsulfonyl-3-carboxy		786
2-Amino-3-carboxy-5-methylsulfonyl	239–242	432, 432a, 778, 780, 783, 784, 786, 858
2-Amino-3-guanidinocarbonyl-5-methylsulfonyl	222 to 226	432, 778, 780, 783, 784, 786, 858
3-Amino-2-methoxycarbonyl-5-methylsulfinyl	237.5–240.5	855

TABLE A.17 AMINO-CARBOXY-THIOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetamido-3-guanidinocarbonyl-5-methylthio	220–222	432, 778, 780, 783, 784, 786, 858
2-Amino-5-benzylthio-3-carboxy	127 to 139	432, 778, 783, 784, 786, cf. 780
2-Amino-5-benzylthio-3-guanidinocarbonyl	171–173	432, 778, 780, 783, 784, 786, 858
2-Amino-3-carboxy-5-methylthio	182–184	432, 432a, 778, 780, 783, 784, 858
2-Amino-3-guanidinocarbonyl-5-methylthio	202–205	432, 778, 780, 783, 786, 858
3-Carboxy-2-hydroxyamino-5-methylthio	182–184	786

TABLE A.18 AMINO-HALOGENOPYRAZINES WITH OTHER FUNCTIONAL GROUPS EXCEPT CARBOXY

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-bromo-3-hydroxy	255–256, 270–280	804, 807
2-Amino-5-bromo-3-mercapto	190–192	805, 1011
2-Amino-5-bromo-3-methoxy	138, 139	804, 810, 811, 814, 984
2-Amino-5-chloro-6-ethylamino-3-nitro	136–138	1181
2-Amino-5-chloro-3-methoxy	128–131	845
3-Amino-5-chloro-2-methoxy	138	365b
3-Amino-2-chloro-5-methoxy	115	365b
2-Amino-5,6-dichloro-3-methoxy	195	773
2-Amino-5,6-difluoro-3-methoxy	127	885
5,6-Dichloro-1-cyclohexyl-3-ethylamino-2-oxo-1,2-dihydro	142–144	853

TABLE A.18 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,3-Dichloro-5-dimethylamino-6-methoxy	93–94	888
2,6-Dichloro-3-dimethylamino-5-methoxy	68.5–70	88
2,3-Dichloro-5-ethylamino-6-methoxy		916
5,6-Dichloro-3-ethylamino-2-oxo-1-phenyl-1,2-dihydro	191–192	853
5,6-Dichloro-1-ethyl-3-ethylamino-2-oxo-1,2-dihydro	130–132	853
2,3-Dichloro-5-methoxy-6-methylamino	164	888
2,3-Difluoro-5-hydrazino-6-methoxy	155	885
2-Dimethylamino-5,6-difluoro-3-methoxy	21	885

TABLE A.19 AMINO-OXY-THIOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-3-mercapto-5-methoxy	185–190	805, 1011
2-Amino-5-methoxy-3-methylthio	75	535

TABLE A.20 AMINO-CARBOXY-HALOGENOPYRAZINES WITH OTHER FUNCTIONAL GROUPS

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetoxymethyl-5-amino-3-chloro-6-cyano	172–173	874
2-Amino-3-carbamoylcarbamoyl-5-chloro-6-methyl sulfonyl	215	1152
2-Amino-3-carbamoylcarbamoyl-5-chloro-6-methyl-thio	225	1152
2-Amino-3-carbamoyl-5-chloro-6-methoxy		877
2-Amino-3-carboxy-5-chloro-6-hydroxy	210	809
2-Amino-3-carboxy-5-chloro-6-methoxy	222–224	790, 963
2-Amino-5-chloro-6-(2′-dimethylaminoethoxy)-3-methoxycarbonyl	134.5–136.5	780, 858
2-Amino-5-chloro-6-ethoxy-3-ethoxycarbonyl	124–215	809
2-Amino-5-chloro-6-ethoxy-3-guanidinocarbonyl	215–216	780, 809
2-Amino-5-chloro-6-ethoxy-3-methoxycarbonyl	123–125	780, 858
2-Amino-5-chloro-6-ethylthio-3-hydrazinocarbonyl	196–199	963, 1370, 1371
2-Amino-5-chloro-3-guanidinocarbonyl-6-hydroxy	< 310; HCl > 300	780, 809, 1371
2-Amino-5-chloro-3-guanidinocarbonyl-6-mercapto	236.5	780, 809, 1371
2-Amino-5-chloro-3-guanidinocarbonyl-6-methoxy	HCl 257	809
2-Amino-5-chloro-3-guanidinocarbonyl-6-methylthio	234.5–236.5	809, 1371
2-Amino-5-chloro-3-hydrazinocarbonyl-6-hydroxy	> 300	963, 1370, 1371
2-Amino-5-chloro-3-hydrazinocarbonyl-6-(2′-hydroxyethylthio)	200–203	963

TABLE A.20 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-5-chloro-3-hydrazinocarbonyl-6-mercapto	218–220	963, 1370, 1371
2-Amino-6-chloro-3-hydrazinocarbonyl-5-mercapto	218–220	790
2-Amino-5-chloro-3-hydrazinocarbonyl-6-methoxy	228–230	963
2-Amino-5-chloro-3-hydrazinocarbonyl-6-methylthio	240–242	963, 1370, 1371
2-Amino-5-chloro-3-hydrazinocarbonyl-6-pentylthio	HCl 265–267	963, 1370
2-Amino-5-chloro-3-hyrazinocarbonyl-6-propylthio	166–168	963, 1370, 1371
2-Amino-5-chloro-6-hydroxy-3-methoxycarbonyl	245	780, 809, 855, 858, 859
2-Amino-5-chloro-6-mercapto-3-methoxycarbonyl	207–208	780, 809, 858
2-Amino-6-chloro-2-methoxycarbonyl-5-methylsulfinyl	237.5–240.5	780, 809, 858, 859
2-Amino-5-chloro-3-methoxycarbonyl-6-methylsulfonyl	206.5–209	809
2-Amino-5-chloro-3-methoxycarbonyl-6-methylthio	212 to 216	780, 790, 809, 855, 858, 859
2-Amino-5-chloro-3-methoxycarbonyl-6-phenoxy	188–189	809
2-Amino-5-chloro-6-methoxy-3-methoxycarbonyl	255–257	780, 790, 809, 855, 858, 859
2-Chloro-3-dimethylamino-6-guanidinocarbonyl-5-hydroxy	231.5–233.5; HCl 228–230	799, 892
2-Chloro-3-dimethylamino-5-hydroxy-6-methoxycarbonyl	140–141	799, 892
2-Chloro-3-ethylamino-5-hydroxy-6-methoxycarbonyl	182–184	892
2-Chloro-3-ethylamino-5-mercapto-6-methoxycarbonyl	136–138	892

TABLE A.21 CARBOXY-HALOGENOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-chloro	154–155	1424
2-Bromo-5-carbamoyl	168.5–169.5	839, 1098
2-Bromo-5-chloro-3-methoxycarbonyl	35–36, 38–40	799–801, 892
2-Bromo-6-cyano	72–73	865
2-Bromo-3-cyano-5,6-diphenyl	229–231	837
2-Bromo-5-ethoxycarbonyl	69–73/0.8	839
2-Bromo-3-methoxycarbonyl	44	798
2-Bromo-6-methoxycarbonyl	59–59.5; 115–120/5	867
2-Carbamoyl-3-chloro	186–187	423
2-Carbamoyl-5-chloro (?)	171 to 173.5	840, cf. 839
2-Carbamoyl-6-chloro	172 to 177	744, 757, 840, 870, 985, cf. 839
2-Carbamoyl-3-chloro-5,6-diphenyl	218–219	837
2-Carboxy-3-chloro	116–118.5	838, 867, 947

TABLE A.21 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Carboxy-6-chloro	154–155, 158–159, 162.5–165	868–870, cf. 839
2-Chloro-6-chlorocarbonyl		1389
2-Chloro-3-cyano	47.5, 48	810, 840
2-Chloro-5-cyano (?)	90–91/7–8	840, cf. 744, 839
2-Chloro-6-cyano	75–76/3, 100–102/12, 125–127/40	744, 757, 840, 1439
2-Chloro-5-cyano-3,6-dimethyl	79–80	288
2-Chloro-3-cyano-5,6-diphenyl	210–212	837, 848
2-Chloro-6-diethylcarbamoyl		1389
5-Chloro-2-dimethylaminoethyl(?)-3-guanidinocarbonyl	211–213	801, cf. 799
2-Chloro-3-hydrazinocarbonyl-5,6-diphenyl		848
2-Chloro-6-(*C*-hydrazino-*C*-iminomethyl)	155–157	1439
2-Chloro-3-methoxycarbonyl	31–32; 50–52/0.04; 87–89/2	371, 423, 867
2-Chloro-5-methoxycarbonyl	90.5–91.5	838, 867, cf. 839
2-Chloro-6-methoxycarbonyl	41–44.5; 108–109/5	744, 838, 868–870, cf. 839
2-Chloro-3-methoxycarbonyl-5,6-diphenyl	116–117	371, 837
3-Chloro-2-methoxycarbonyl-5-methyl	84–85	371
3-Chloro-2-methoxycarbonyl-5-phenyl	81–83	375
2-Chloro-6-(*N*-methylamidino)	111–117	940
2-Chloro-6-thiocarbamoyl	203–205	941
2,5-Dibromo-3-methoxycarbonyl	66–68	799, 801
2,6-Dichloro-3-cyano-5-methyl	95–96	535
2,3-Dichloro-5,6-dimethoxycarbonyl	81–82.5	409
2,3,5-Trichloro-6-isocyanato	100/0.07	1240, 1242

TABLE A.22 CARBOXY-OXYPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetoxy-6-methoxycarbonyl	58 to 60.5	838, 1057
2-Acetoxymethyl-5-carboxy		1277
2-Acetyl-3,6-dimethoxy-5-methyl	M.s., i.r., n.m.r.	844
2-Acetyl-5-hydroxy-3,6-dimethyl	180	1064
2-Acetyl-3-methoxy	43–44	844
2-Acetyl-3-methoxy-5-methyl	M.s., i.r., n.m.r.	844
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-ethoxy	112–114	1424
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-phenoxy	109–110	1424
2-Benzoyl-5-hydroxy-3,6-dimethyl		1064
2-Benzoylmethyl-3-hydroxy	230	1446
3-Carbamoyl-2,5(6)-dihydroxy-6(5)-methyl	*ca.* 360	369

TABLE A.22 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
3-Carbamoyl-2,5-dimethoxy	149–150	881
2-Carbamoyl-3,5-dimethoxy-6-methyl	199–200	535
2-Carbamoyl-6-ethoxy	172–173	986
2-Carbamoyl-3-hydroxy	263 to 270	138, 361, 369, 833
2-Carbamoyl-5-hydroxy	292–295	1057
2-Carbamoyl-6-hydroxy	289–292	1057
2-Carbamoyl-3-hydroxy-5,6-dimethyl	231–232, 232–234	361, 369, 374
2-Carbamoyl-3-hydroxy-5,6-diphenyl	123–125, 174–175	361, 837
2-Carbamoyl-3-hydroxymethyl	156–158	1076
2-Carbamoyl-3-hydroxy-5-methyl	219–220, 227	369, 371–373, cf. 361
3-Carbamoyl-2-hydroxy-5-methyl	262–264, 243–244	373, cf. 361
2-Carbamoyl-3-hydroxy-5-phenyl	252–253, 262	365a, 375
3-Carbamoyl-2-hydroxy-5-phenyl	213–216(?), 257	361, 365a
2-Carbamoyl-6-isopropoxy	148–150	986
2-Carbamoyl-3-methoxy	146	810
2-Carbamoyl-5(?)-methoxy	214–215	839
2-Carbamoyl-6-methoxy	220, 220–221, 235–235.5	805, 839, 986
2-Carbamoyl-6-propoxy	158–160	986
2-Carboxy-3,6-diethyl-5-hydroxy	166	287
2-Carboxy-3,6-dimethoxy-5-methyl		844
2-Carboxy-6-ethoxy	176–178	986
2-Carboxy-3-hydroxy	215 to 225	361, 371, 420, 433, 818, 1056
2-Carboxy-5-hydroxy	> 300	408
2-Carboxy-6-hydroxy	> 360	1057
2-Carboxy-3-hydroxy-5,6-dimethyl	172–174	361
2-Carboxy-5-hydroxy-3,6-dimethyl	265, 270	286, 288
2-Carboxy-3-hydroxy-5,6-diphenyl	216–217, 225–227	371, 797, 837
2-Carboxy-5-hydroxy-3,6-diphenyl	263, 264–265	286, 797
2-Carboxy-3-hydroxy-5-methyl	182–183, 183–184, 188–189, 205	361, 369, 371, 372
3-Carboxy-2-hydroxy-5-methyl	155–157	361
2-Carboxy-5-hydroxymethyl		1277
2-Carboxy-3-hydroxy-5-phenyl	208–209, 217, 219–220, 224	365a, 375, 378, 429
3-Carboxy-2-hydroxy-5-phenyl	200–210	375, 378, 429
2-Carboxy-6-isopropoxy	174–175	986
2-Carboxy-3-methoxy	169–171	867
2-Carboxy-5-methoxy	197.5–199.5	867
2-Carboxy-6-methoxy	176–177.5, 182–183	869, 986
2-Carboxy-3-methoxy-5,6-diphenyl	179–181, 180–181; Na salt 254–256	371, 837
3-Carboxy-2-methoxy-5-methyl		844

TABLE A.22 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Carboxy-6-propoxy	135–136	986
2-Cyano-3,6-diethyl-5-hydroxy	129–130	288
3-Cyano-2,5-dimethoxy	140	881
2-Cyano-3,5-dimethoxy-6-methyl	116–117	535
2-Cyano-5-ethoxy-3,6-dimethyl	61	288
2-Cyano-5-hydroxy-3,6-dimethyl	220–221	288
2-Cyano-3-hydroxy-5,6-diphenyl	230–232	797
2-Cyano-3-methoxy	56	810
2,3-Dicarboxy-5,6-dihydroxy	270	1051
2,3-Dicyano-5,6-dihydroxy	*ca.* 270	1044
2,3-Dihydroxy-5,6-dimethoxycarbonyl	240–241	409
3,5-Dimethoxy-2-methoxycarbonyl	98	685, 881
2-Ethoxycarbonyl-5-hydroxy-3,6-dimethyl	220.5–221	1064
3-Ethoxycarbonyl-2-hydroxy-5-phenyl	158–159	375, 429
2-Ethoxycarbonyl-3-hydroxy-5-phenyl	112, 112–114	375, 429
2-Ethoxy-6-ethoxycarbonyl		986
2-Ethoxy-6-(*C*-ethoxyformidoyl)	55–57	985, 986
2-Ethoxy-6-hydrazinocarbonyl	176–177	986
2-Hydrazinocarbonyl-3,5-dimethoxy	153	881
3-Hydrazinocarbonyl-2,5-dimethoxy	180	881
2-Hydrazinocarbonyl-6-isopropoxy	138–140	986
2-Hydrazinocarbonyl-6-methoxy	180–181	986
2-Hydrazinocarbonyl-6-propoxy	90–92	986
2-Hydroxy-3-methoxycarbonyl	148–149, 154	423, 833, 1056
2-Hydroxy-5-methoxycarbonyl	181.5–185	838, 1057, cf. 839
2-Hydroxy-6-methoxycarbonyl	196–197, 205–206	838, 1057, cf. 839
2-Hydroxy-5-methoxycarbonyl-3,6-dimethyl	230	1064
2-Hydroxy-3-methoxycarbonyl-5,6-diphenyl	204–205	371, 837
2-Hydroxy-3-methoxycarbonyl-6-methyl	174–175	371
3-Hydroxy-2-methoxycarbonyl-5-phenyl	172–173	375
2-Hydroxy-3-(*N*-methylcarbamoyl)	95	1076
2-Hydroxy-3-(*N*-methyl-*N*-phenylcarbamoyl)	217.5	1055
2-Hydroxy-3-phenylcarbamoyl	287–288	1055
2-Isopropoxy-6-isopropoxycarbonyl	I.r.	986
2-Isopropoxy-6-(*C*-isopropoxyformidoyl)	I.r.	986
2-Methoxy-3-methoxycarbonyl	58–60	867
2-Methoxy-5-methoxycarbonyl	98.5–99.5	867
2-Methoxy-6-methoxycarbonyl	74–75, 74.5–75.5; 82/3, 112/6	869, 870, 986
2-Methoxy-3-methoxycarbonyl-5,6-diphenyl	118.5–119	371
2-Methoxy-6-(*C*-methoxyformidoyl)	100–101	985, 986
1-Methyl-2-oxo-3-*N*-phenylcarbamoyl-1,2-dihydro	186	1055
2-Propoxy-6-propoxycarbonyl	I.r.	986
2-Propoxy-6-(*C*-propoxyformidoyl)	I.r.	986

TABLE A.23 CARBOXY-SULFONYLPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Benzylsulfonyl-3-carbamoyl	251–253	992
2-Benzylsulfonyl-6-cyano	143–144	992
2-Carbamoyl-6-ethylsulfonyl	196–199	992
2-Carbamoyl-5-phenylsulfinyl	167–168	840, 993
2-Carbamoyl-6-phenylsulfinyl	172–173	992
2-Carbamoyl-5-phenylsulfonyl	164–165	840, 993
2-Carbamoyl-6-propylsulfonyl	186–188	992
2-Cyano-6-ethylsulfinyl	80–84	992
2-Cyano-6-ethylsulfonyl	121–123	992
2-Cyano-5-phenylsulfonyl	127	840, 993
2-Cyano-6-phenylsulfonyl	117–119	992
2-Cyano-6-propylsulfinyl	60–63	992

TABLE A.24 CARBOXY-THIOPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-benzylthio	145–146	992
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-ethylthio	130–132	992
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-phenylthio	163–164	992
2-(*C*-Amino-*C*-hydroxyiminomethyl)-6-propylthio	110–112	992
2-Benzoylmethyl-3-mercapto	214	1446
2-Benzylthio-6-carbamoyl	170–172	992
2-Benzylthio-6-carboxy	188–190	992
2-Benzylthio-6-cyano	78–83	992
2-Benzylthio-6-(*N*-hydroxycarbamoyl)	150–152	992
2-Benzylthio-6-hydrazinocarbonyl	128–129	992
2-Benzylthio-6-methoxycarbonyl		992
2-Benzylthio-6-thiocarbamoyl	140–142	992
2-Carbamoyl-6-ethylthio	149–150	992
2-Carbamoyl-5-phenylthio	171–172	840
2-Carbamoyl-6-phenylthio	166–167	992
2-Carbamoyl-6-propylthio	108–110	992
2-Carboxy-6-ethylthio	134–135	992
2-Carboxy-3-mercapto	203–204	1264
2-Carboxy-6-phenylthio	122–124	992
2-Carboxy-6-propylthio	93–96	992
2-Cyano-6-ethylthio	42–44	992
2-Cyano-5-phenylthio	72; 150–170/0.05	840, 993
2-Cyano-6-phenylthio	75–78	992
2-Cyano-6-propylthio	130–131/0.2	992
2-Ethoxycarbonyl-6-ethylthio		992
2-(*C*-Ethoxy-*C*-iminomethyl)-6-ethylthio		992
2-Ethylthio-6-hydrazinocarbonyl	105–107	992
2-Ethylthio-6-(*N*-hydroxycarbamoyl)	136–138	992
2-Ethylthio-6-thiocarbamoyl	112–114	992

TABLE A.24 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Guanidinocarbonyl-3-mercapto	244–246	799
2-Hydrazinocarbonyl-6-phenylthio	155–156	992
2-Hydrazinocarbonyl-6-propylthio	70–82	992
2-(*N*-Hydroxycarbamoyl)-6-phenylthio	157–159	992
2-(*N*-Hydroxycarbamoyl)-6-propylthio	145–147	992
2-Mercapto-3-methoxycarbonyl	124–125	799, 892
2-Mercapto-3-phenyl(thiocarbonyl)methyl	169–170	1446
2-Methoxycarbonyl-6-phenylthio	64–65	992
2-Methoxycarbonyl-6-propylthio		992
2-Phenylthio-6-thiocarbamoyl	153–154	992
2-Propoylthio-6-thiocarbamoyl	120–122	992

TABLE A.25 CARBOXY-HALOGENOPYRAZINES WITH OTHER FUNCTIONAL GROUPS EXCEPT AMINO

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
5-Bromo-3-guanidinocarbonyl-2-hydroxy	> 290	799, 892
5-Bromo-3-guanidinocarbonyl-2-methylthio	HCl 275 to 279.5	799, 892
5-Bromo-2-hydroxy-3-methoxycarbonyl	120.5–121.5	799
5-Bromo-3-methoxycarbonyl-2-methylthio	135 to 137	799, 892
2-Carbamoyl-5-chloro-3-hydroxy-6-methyl	239–240	535
3-Carbamoyl-5-chloro-2-methoxy	184	881
5-Chloro-3-cyano-2-methoxy	91	881
2-Chloro-5,6-diethoxycarbonyl-3-methoxy	57–57.5	409
2-Chloro-3,5-dimethoxy-6-methoxycarbonyl	117	881
5-Chloro-3-guanidinocarbamoyl-2-hydroxy	257–259, 259–260	799, 892, 1058
5-Chloro-3-guanidinocarbonyl-2-mercapto	$0.5H_2O$ 260	799
5-Chloro-3-guanidinocarbonyl-2-methoxy	HCl 214–216	799, 892
5-Chloro-2-hydroxy-3-methoxycarbonyl	127–129	1058
2-Chloro-5-hydroxy-3-methoxy-6-methoxycarbonyl	187	881
5-Chloro-2-mercapto-3-methoxycarbonyl	80–82	799
2-Chloro-3-methoxy-5,6-dimethoxycarbonyl	71.5–72.5	409
5-Chloro-2-methoxy-3-methoxycarbonyl	45	799

TABLE A.26 HALOGENO-NITRO(AND OXY)PYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Chloro-5-nitro-3-phenyl	89–91	817
2-Acetoxymethyl-*x*-chloro	124–126/9–10	738
2-(1'-Acetoxy-2'-methylpropyl)-3-chloro-5-isobutyl	113–123/2	760a
5-(1'-Acetoxy-2'-methylpropyl)-3-chloro-2-isobutyl	149/3, < 125/1	113b, 760a

TABLE A.26 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Benzyloxy-6-chloro	44–45	832
2,5-Bischloromethyl-3,6-diethoxy	85	756
2,5-Bischloromethyl-3,6-dimethoxy	117–118	756
2-Bromo-3-*s*-butyl-5-hydroxy-6-isobutyl (bromodesoxyaspergillic acid)	129–130	87
2-Bromo-6-*s*-butyl-5-hydroxy-3-isobutyl	150–151	93
5-Bromo-3-chloro-2-hydroxy	190	807
2-Bromo-6-chloro-3-hydroxy-5-phenyl	210–211	817
5-Bromo-2-chloro-3-methoxy	107	535
5-Bromo-2,3-dimethoxy	65	535
2-Bromo-5-ethoxy-3,6-diphenyl	100–101	797
5-Bromo-3-ethyl-2-hydroxy	125–126	817
2-Bromo-6-ethyl-5-hydroxy-3-methyl	179–180	817
2-Bromo-6-hydroxy	209	865
2-Bromo-5-hydroxy-3,6-dimethyl	237–239	817
2-Bromo-3-hydroxy-5,6-dimethyl	227–228	817
2-Bromo-3-hydroxy-5,6-diphenyl	223–224	817, 841
2-Bromo-5-hydroxy-3,6-diphenyl	245	282
2-Bromo-5-hydroxy-6-isobutyl-3-isopropyl (monobromodeoxymuta-aspergillic acid)	113	104
5-Bromo-2-hydroxy-3-isopropyl	119–121	817
5-Bromo-2-hydroxy-3-methoxy	228	535
5-Bromo-2-hydroxy-3-methyl	185–187	817
2-Bromo-5-hydroxy-3-methyl-6-phenyl	270–271	817
3-Bromo-2-hydroxy-5-phenyl	227–228	365a
5-Bromo-2-hydroxy-3-phenyl	192–193	817
2-Bromo-3-methoxy-5,6-dimethyl	74–75; 125–127/14	797
2-Bromo-3-methoxy-5,6-diphenyl	182–183	797
2-Bromo-5-methoxy-3,6-diphenyl	137–138	797
2-*t*-Butoxy-3,5,6-trifluoro	42/0.05	851
2(or 5)-*s*-Butyl-6-chloro-3-ethoxy-5(or 3)-isobutyl	115/1	93
2(or 5)-*s*-Butyl-6-chloro-3-hydroxy-5(or 2)-isobutyl	139–140	93
2-Chloro-3-chloromethyl-5-methoxy		688
2-Chloro-5-chloromethyl-3-methoxy		688
3-Chloro-2-chloromethyl-5-methoxy		687
3-Chloro-5-chloromethyl-2-methoxy		688, 756
2-Chloro-6-diethoxyphosphinothioyloxy		1114
2-Chloro-3,6-difluoro-5-methoxy	156–157/760	851
6-Chloro-1,5-dimethyl-2-oxo-3-phenyl-1,2-dihydro	92–93	873
6-Chloro-1,3-dimethyl-2-oxo-5-phenyl-1,2-dihydro	132–133	873
2-Chloro-5-ethoxy-3,6-dimethyl	24, 30; 65/1	756, 872
2-Chloro-5-ethoxy-3,6-diphenyl	102–103	797
2-Chloro-5-hydroxy	128–129	831
2-Chloro-6-hydroxy	200–205, 212–213	832, 883
2-Chloro-5-hydroxy-3,6-diisobutyl	141–142	101
2-Chloro-5-hydroxy-3,6-dimethyl	222–224, 229–230	312, 756, 842, 872, 883
2-Chloro-3-hydroxy-5,6-diphenyl	(212)–219, 229–231	817, 834, 841

TABLE A.26 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Chloro-5-hydroxy-3,6-diphenyl	260–261	817
2-Chloro-6-hydroxy-3,5-diphenyl	244–246	873
2-Chloro-6(2′-hydroxyethoxy)	103–104/0.1	989
3-Chloro-2-hydroxy-5-methyl	174–175	373, 835
2-Chloro-3-hydroxy-5-methyl	187	373
3-Chloro-5-hydroxy-2-methyl	163–164	535
2-Chloro-6-hydroxy-3-methyl-5-phenyl	185–186	873
2-Chloro-6-hydroxy-5-methyl-3-phenyl	181–182	873
3-Chloro-5-(1′-hydroxy-2′-methyl)propyl-2-isobutyl	140–142/5	113b
2-Chloro-5-hydroxy-3-phenyl	142–144	817
3-Chloro-5-hydroxy-2-phenyl	235–236	829
5-Chloro-2-hydroxy-3-phenyl	174–176	817
2-Chloro-3-methoxy	31.5–32; 92–93/40	867
2-Chloro-5-methoxy	105/105	838
2-Chloro-6-methoxy	27.5–28.5; 68–70/12; 105/103	838, 867, 883
2-Chloro-5-methoxy-3,6-dimethyl	59, 64–65	756, 883
2-Chloro-6-methoxy-3,5-diphenyl	95–96	873
2-Chloro-5-methoxy-3,6-diphenyl	108–109	817
2-Chloro-6-methoxy-3-methyl-5-phenyl	55–56	873
2-Chloro-6-methoxy-5-methyl-3-phenyl	80–81	873
2-Chloro-3-methoxy-5-phenyl	86–87	365a
2-Chloro-5-methoxy-3-phenyl	73–74	817
5-Chloro-2-methoxy-3-phenyl	111–113/0.3	817
2-Chloromethyl-3-ethoxy-5-methyl	106/10; HCl 115	872
6-Chloro-1-methyl-2-oxo-3,5-diphenyl-1,2-dihydro	159–160	873
3,5-Dibromo-2-hydroxy	180–182	807
2,5-Di-*s*-butyl-3-chloro-6-hydroxy	105–106	312
5,6-Dichloro-1-cyclohexyl-3-ethoxy-2-oxo-1,2-dihydro	89	853
5,6-Dichloro-1-cyclohexyl-3-methoxy-2-oxo-1,2-dihydro	149	853
2,5-Dichloro-3,6-dihydroxy	83	849
2,3-Dichloro-5,6-dimethoxy	131.5–132	888
2,5-Dichloro-3,6-dimethoxy	151–152	888
2,6-Dichloro-3,5-dimethoxy (?)	138.5	888
5,6-Dichloro-2,3-dioxo-1,4-diphenyl-1,2,3,4-tetrahydro	247–249	853
5,6-Dichloro-3-ethoxy-2-oxo-1-phenyl-1,2-dihydro	158–160	853
5,6-Dichloro-3-hydroxy-2-oxo-1-phenyl-1,2-dihydro	171–173	853
2,5-Dichloro-3-methoxy	79–81	915
2,3-Difluoro-5,6-bis(2′-hydroxyethoxy)	80–81	851
2,3-Difluoro-5,6-dimethoxy	79–81	851
2,5-Difluoro-3,6-dimethoxy	67–68	852
2,3-Difluoro-5-ethoxy-6-methoxy	26–28	851
2,3-Difluoro-5-methoxy		885
2,5-Difluoro-3-methoxy	1–3	885

TABLE A.26 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,3-Difluoro-5-methoxy-6-methyl	48/0.5	851
2,5-Difluoro-3-methoxy-6-methyl	55/0.5	851
2-Ethoxy-3,5,6-trifluoro	148–152/760	851
5-Fluoro-2,3-dimethoxy	63.5–64.5	885
2-Fluoro-6-hydroxy	217	883
2-Fluoro-5,6-dimethoxy-3-methyl	77–79	851
3,5,6-Trichloro-1-cyclohexyl-2-oxo-1,2-dihydro	124.5–126	853
2,3,5-Trichloro-6-ethoxy	< 50	898
3,5,6-Trichloro-1-ethyl-2-oxo-1,2-dihydro	61–62	853
2-(3',3',3'-Trichloro-2'-hydroxypropyl)	106–107	405
2,3,5-Trichloro-6-isopropoxy	< 50	898
2,3,5-Trichloro-6-methoxy	29 to 35	888, 898
2,3,5-Trichloro-2-oxo-1-phenyl-1,2-dihydro	163	853
2,3,5-Trichloro-6-phenoxy	76–77	898
2,3,5-Trifluoro-6-hydroxy	79–81	851
2,3,5-Trifluoro-6-(2'-hydroxyethoxy)	165–170/760	851
2,3,5-Trifluoro-6-methoxy	142/760	851

TABLE A.27 HALOGENO-SULFONYL(AND THIO)PYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Ref.
2-Benzylsulfonyl-6-chloro	86–87	883
2-Benzylthio-6-chloro	145–146/0.6	883
3-Chloro-2-chloromethyl-5-methylthio		688
2-Chloro-3-chloromethyl-5-methylthio		688
2-Chloro-5-chloromethyl-3-methylthio		688
3-Chloro-5-chloromethyl-2-methylthio		688
2-Chloro-6-(2'-mercaptoethylthio)	91	989
2-Chloro-6-methylthio	105/20	759
2-Chloro-6-phenylthio	121–122/0.2	759
2,5-Difluoro-3,6-diphenylthio	182–183	852
2,3,5-Tribromo-6-methylthio	96–98	898
2,3,5-Trichloro-6-methylthio	43–44	898
2,3,5-Triiodo-6-methylthio	202–204	898

TABLE A.28 NITRO-OXYPYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-*s*-Butyl-6-hydroxy-5-isobutyl-3-phenylazo	188–190	90, 92
2-*s*-Butyl-3-hydroxy-5-isobutyl-6-phenylazo	203–205	93
2,5-Di-*s*-butyl-3-hydroxy-6-phenylazo	200	90

TABLE A.28 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Hydroxy-3,6-dimethyl-3-phenylazo	208	1125
2-Hydroxy-5,6-dimethyl-3-phenylazo	Chars < 100	817
2-Hydroxy-3-nitro-5,6-diphenyl	210–213	1065
2-Hydroxy-5-nitro-3,6-diphenyl	274–276	817
2-Hydroxy-5-nitro-3-phenyl	254–256	817
1,4,6-Trimethyl-2-oxo-3-phenylazomethylene-1,2,3,4-tetrahydro	201; HI 228	1132

TABLE A.29 OXY-SULFONYL(AND THIO)PYRAZINES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Ref.
2-(*C*-Hydroxy-*C*-sulfo)methyl	159–159.5	1077
2-Hydroxy-5,6-dimethyl-3-(2′-methylthioethyl)	128–129	361
2-Hydroxy-3-(2′-methylthioethyl)	96–97	361

TABLE A.30 ALKYL- AND ARYLPYRAZINE *N*-OXIDES

Pyrazine *N*-Oxide	M.p. (°C) or B.p. (°C/mm)	Refs.
Unsubstituted/1,4-dioxide	260, 285–295, 300, > 300	575, 625, 626, 628, 744
Unsubstituted/1-oxide	104, 108, 113–114, 114–116	575, 625, 626, 628, 744, 1057
3-Butyl-2,5-dimethyl/1,4-dioxide	105–106	626
2-*s*-Butyl-5-isobutyl/1-oxide	85–90/0.025	313
2,5-Di-*s*-butyl/1,4-dioxide	159–161	740
2,5-Di-*t*-butyl/1,4-dioxide	Sublimes at 285	233
2,5-Di-*t*-butyl/1-oxide	Sublimes at 202–203	233
2,3-Dimethyl/1,4-dioxide	212–214	739
2,5-Dimethyl/1,4-dioxide	> 300, darkens at 280° mp > 360	626, 740
2,6-Dimethyl/1,4-dioxide	227	626
2,3-Dimethyl/1-oxide	MeI 201–203	766
2,5-Dimethyl/1-oxide	105–108; 120–134/0.5–1.5; HCl 166–168; 4-MeCl 190; 4-MeI 229–231, 234, 237; 4-$PhCH_2Cl$ 210–220	625, 626, 740, 766
2,6-Dimethyl/1-oxide	55; 134–135/17; pic. 199–203; 4-MeI 224	626, 766
3,5-Dimethyl/1-oxide	108–110, 125–127, 130–132; 4-MeI 235	626, 663, 760, 766
2,5-Dimethyl-3,6-dipentyl/1-oxide	138–140/0.6	648

TABLE A.30 *Continued*

Pyrazine *N*-Oxide	M.p. (°C) or B.p. (°C/mm)	Refs.
2,5-Dimethyl-3,6-diphenyl/ 1,4-dioxide	259–260	191, 1605
2,5-Dimethyl-3,6-diphenyl/ 1-oxide	192–193	743
2,5-Dimethyl-3-pentyl/ 1,4-dioxide	123	626
2,5-Dimethyl-3-phenyl/ 1,4-dioxide	165	626
2,3-Diphenyl/1,4-dioxide	262	741
2,3-Diphenyl/1-oxide	171–172; 4-MeI 230	741, 766
2,5-Diphenyl/1-oxide	193–195, 204–205	326, 742
3,5-Diphenyl/1-oxide (?)	200–201	741
3-Hexyl-2,5-dimethyl/1,4-dioxide	111	626
2-Isobutyl-5-isopropyl/1,4-dioxide	170–171	740a
2-Isobutyl-5-isopropyl/1-oxide	155/7	740a
5-Isobutyl-2-isopropyl/1-oxide	134–136/3	740a
2-Methyl/1,4-dioxide	230–231 to 242–244	625, 626, 737, 738
2-Methyl/1-oxide	90 to 92, 93–95	625, 733b, 734, 738, cf. 626
3-Methyl/1-oxide	64 to 71, eutectic with isomer 43–45	626, 686, 733b, 734, 738, cf. 625
2-Phenyl/1-oxide	132–133	733b
3-Phenyl/1-oxide	141–142	733b, 761
Tetramethyl/1,4-dioxide	220, 224	626, 713, 1750
Tetramethyl/1-oxide	100–101.5	626, 760
Tetraphenyl/1,4-dioxide	322	554

TABLE A.31 AMINOPYRAZINE *N*-OXIDES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetamido/1,4-dioxide	215–216	1259
2-Acetamido/1-oxide	220–221	1259
3-Acetamido/1-oxide	256–257	1259
3-Acetamido-2-cyano-5-hydroxy-6-methyl/ 1-oxide	245	532
2-Acetamido-3-cyano-5-methyl/1,4-dioxide	203	532
2-Acetamido-3-cyano-5-methyl/1-oxide	174	532
2-Amino/1,4-dioxide	256–257, 263	1189, 1259
2-Amino/1-oxide	178–180, 186–187	1258, 1259
3-Amino/1-oxide	174 to 178	108, 547a, 921, 1259
4-Amino/1-oxide iodide	144–145	610
2-Amino-3-benzyloxycarbonyl-5-methyl/1-oxide	158–160	540
2-Amino-3-bromo-5,6-dimethyl/1-oxide	145.5–146	907
2-Amino-5-bromo-3-methoxycarbonyl/1-oxide	200–202	792, 808, 875, 877–879, 1222

TABLE A.31 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-3-*s*-butyl-6-isobutyl/1-oxide	84–86	93
2-Amino-6-*s*-butyl-3-isobutyl/1-oxide	150–155/0.5	92
3-Amino-2-carbamoyl/1-oxide	230–232	538
2-Amino-3-carbamoyl-6-chloro-5-methyl/1-oxide	244–245	533
2-Amino-3-carbamoyl-5-methyl/1-oxide	218.3, 230–230.5, 235–236	535, 537, 1255
2-Amino-3-carbamoyl-5-phenyl/1-oxide	280–282	531, 537
2-Amino-3-carboxy-5-chloro/1-oxide	240	876, 1222
2-Amino-3-carboxy-5-methyl/1-oxide	193–195	365c
2-Amino-6-(2'-carboxyvinyl)-3-cyano/1-oxide	> 234	534
2-Amino-3-chloro/1-oxide	147–148	906
2-Amino-6-(1'-chlorobutyl)-3-cyano/1-oxide	155–157	534
2-Amino-6-chloro-3-cyano-5-methyl/1-oxide	257–258	533
2-Amino-6-(1'-chloroethyl)-3-cyano/1-oxide	222	534
2-Amino-5-chloro-3-guanidinocarbamoyl/1-oxide	H_2O 205	876, 1257
2-Amino-5-chloro-3-guanidinocarbonyl/1-oxide	260	876, 1222
2-Amino-5-chloro-3-hydrazinocarbonyl/1-oxide	228–230	876, 1257
2-Amino-5-chloro-3-methoxycarbamoyl/1-oxide	170–172	876, 1222
2-Amino-5-chloro-3-methoxycarbonyl/1-oxide	200–202	875, 876, 1222
2-Amino-5-chloromethyl-3-cyano/1-oxide	143–144	529
2-Amino-6-chloromethyl-3-cyano/1-oxide	250	534
2-Amino-5-chloromethyl-3-cyano-6-methyl/1-oxide	191–201	762
2-Amino-3-cyano/1,4-dioxide	255	538
2-Amino-3-cyano/1-oxide	267	532
3-Amino-2-cyano/1-oxide	262–263	538
2-Amino-3-cyano-6-dedihydrotriphenylphosphoranylmethyl/1-oxide	243–244; HCl 239–240	534
2-Amino-3-cyano-5-ethyl/1-oxide	139–140	532
3-Amino-2-cyano-5-guanidino-6-methyl/1-oxide	> 280	532
2-Amino-3-cyano-5-hydroxyiminomethyl/1-oxide	300	532
2-Amino-3-cyano-6-hydroxy-5-methyl/1-oxide	260–261	533
2-Amino-3-cyano-6-(3'-hydroxyprop-1'-enyl)/1-oxide	117	534
2-Amino-3-cyano-5-isobutyl/1-oxide	140–142	532
2-Amino-3-cyano-5-isopropyl/1-oxide	126–128	532
3-Amino-2-cyano-5-methoxy-6-methyl/1-oxide	> 235	532
2-Amino-3-cyano-5-methoxymethyl/1-oxide	137–138	529
2-Amino-3-cyano-5-methyl/1,4-dioxide	221	532
2-Amino-3-cyano-5-methyl/1-oxide	186–188.1	532, 537, 542
2-Amino-3-cyano-6-methyl/1-oxide	244–245	534
2-Amino-3-cyano-5-pentyl/1-oxide	103–104	532
2-Amino-3-cyano-5-phenyl/1-oxide	214	532

TABLE A.31 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Amino-3-cyano-5-(prop-1'-enyl)/1-oxide	214–215	529
2-Amino-3-cyano-6-(prop-1'-enyl)/1-oxide	187–188	534
2-Amino-3-cyano-5-propyl/1-oxide	145–146	532
2-Amino-3-cyano-6-styryl/1-oxide	280–281	534
2-Amino-3,5-dimethyl/1-oxide	156; H_2O 76	524
2-Amino-3,6-dimethyl/1-oxide	165; pic. 220	92
3-Amino-2,5-dimethyl/1-oxide	239–240	921
4-Amino-2,5-dimethyl/1-oxide iodide	172–174	610
2-Amino-5,6-dimethyl-3-methylamino/1-oxide	222–223	907
2-Amino-3-ethoxycarbonyl/1-oxide	194–195	538
2-Amino-3-ethoxycarbonyl-6-isopropenyl-5-methyl/1-oxide	121–122	531
2-Amino-3-ethoxycarbonyl-5-methyl/1-oxide	132–133.5, 134.8	531, 537
2-Amino-3-ethoxycarbonyl-5-(2'-methylprop-1'-enyl)/1-oxide	–	537
2-Amino-3-ethoxycarbonyl-5-phenyl/1-oxide	135–137	531, 537
2-Amino-3-ethoxycarbonyl-5-propyl/1-oxide	89–90	531
2-Amino-3-ethoxycarbonyl-5-styryl/1-oxide		537
2-Amino-5-ethyl-3-methyl/1-oxide	109–110, H_2O 80–81	524
2-Amino-3-guanidinocarbonyl/1-oxide	> 300	876, 1257
2-Amino-6-hydroxyamino/1-oxide	H_2O 161; pic. H_2O 158	465
2-Amino-3-isobutyl-6-isopropyl/1-oxide	130/0.25	103, 525
2-Amino-3-methoxycarbonyl/1-oxide	235–237	876, 1222
2-Amino-5-methyl/1-oxide	216–218, 221–223	535, 1230
2-Amino-3-methyl-5-phenyl/1-oxide	188 to 190.5	524, 526, 527
2-Amino-5-methyl-3-phenyl/1-oxide	163–164	524
2-Amino-3-methyl-6-phenyl/1-oxide	172.5–174.5	526, 527
3-Anilino/1-oxide	165–166	921
2-Azido/1-oxide	85–88	1261, 1262
3-Benzylamino/1-oxide	124–126	921
3-Benzylamino-2,5-dimethyl/1-oxide	195–196	921
3,5-Bis(dimethylamino)/1-oxide	170–172	663
3,5-Bis(methylamino)-2,6-bis(*N*-methylcarbamoyl)/1-oxide	158–159	462
3,5-Bis(methylamino)-2-*N*-methylcarbamoyl/1-oxide	235–236	462
3-Butylamino/1-oxide	64.5–66	921
3-Butylamino-2,5-dimethyl/1-oxide	104–105	921
2-Carboxy-3,5-bis(methylamino)-6-*N*-methylcarbamoyl/1-oxide	218	462
2,6-Diacetamido/1-oxide	272–273	465
2,3-Diamino-/1-oxide	170	906
2,6-Diamino/1-oxide	294–295	465
2,3-Diamino-5,6-dimethyl/1,4-dioxide	257–258	907
3-Dimethylamino/1-oxide	149–150	921
3-Dimethylamino-2,5-dimethyl/1-oxide	72–74	921
3-Dimethylamino-2-methyl/1-oxide	89–91	793

TABLE A.31 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,3-Dimethyl-5-methylamino-6-*N*-methylcarbamoyl/1-oxide	117	1256
3-Hexylamino/1-oxide	83.5–84	921
3-Hexylamino-2,5-dimethyl/1-oxide	82.5–83.5	921
5-Methoxy-3-methylamino-2-methoxycarbamoyl/1-oxide	108–109	450
2-Sulfanilamido/1-oxide	222	1032, 1033
3-Sulfanilamido/1-oxide	240–241	1032, 1033

TABLE A.32 CARBOXYPYRAZINE *N*-OXIDES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
3-Acetyl/1-oxide	184	575
3-*N*-Acetylcarbamoyl/1-oxide	199–200.5	1057
3-Benzoyloxy-5-methoxycarbonyl/1-oxide	144–145.5	1035
2-Carbamoyl/1-oxide	205–206.5	838
3-Carbamoyl/1-oxide	291–293, 300–303, 309–311	138, 575, 757, 838, 839, 1057, 1266
3-Carbamoyl-2-methoxy/1-oxide	234	881
2-Carboxy/1,4-dioxide	268	739
2-Carboxy/1-oxide	138.5–139.5	838
3-Carboxy/1-oxide	188–188.5, 202, 212–213	543, 838, 1057, 1266
3-Carboxy-5-hydroxy/1-oxide	> 250	1035
5-Carboxy-2-hydroxy/1-oxide	234–235	739
2-Cyano/1-oxide	156–157	838
3-Cyano/1-oxide	153, 153.5–154.5	575, 838
2-Cyano-5-ethoxy-3,6-dimethyl/*N*-oxide	104	288
3-Diethoxymethyl/1-oxide		739
3-*N*-(Diethylaminomethyl)carbamoyl/1-oxide	122–123	1455
2-Dihydroxymethyl/1,4-dioxide	110–112 oxime 208–209 diethylacetal 94–94.5	739
3-Dihydroxymethyl/1-oxide	–	739
3-Ethoxycarbonyl/1-oxide	140–148, 149–150	575, 839, 1266
3-Formyl/1-oxide	Phenylhydrazone 239–241	1138
2-Hydrazinocarbonyl/1,4-dioxide	247–248	1266
3-Hydrazinocarbonyl/1-oxide	265–268	1266
3-Hydroxycarbamoyl/1-oxide	243–244	1266
2-Hydroxy-3-hydroxyaminocarbonyl/1-oxide	183–186	547, 1453
2-Hydroxy-3-hydroxyaminocarbonyl-5,6-dimethyl/1-oxide	212–214, 220–222	547, 1453

TABLE A.32 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs
2-Hydroxy-3-hydroxyaminocarbonyl-5,6-diphenyl/1-oxide	215–217	1453
2-Hydroxy-5-methoxycarbonyl/1-oxide	173–174	739
3-Hydroxy-5-methoxycarbonyl/1-oxide	206–212	1035
3-Methoxycarbonyl/1-oxide	166.5–170, 172–173	739, 839, 870, 1266

TABLE A.33 HALOGENOPYRAZINE *N*-OXIDES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-(1′-Acetoxy-2′-methylpropy)-3-chloro-5-isobutyl/1-oxide	145–150/3	760a
5-(1′-Acetoxy-2′-methylpropyl)-3-chloro-2-isobutyl/1,4-dioxide	111–112	760a
5-(1′-Acetoxy-2′-methylpropyl)-3-chloro-2-isobutyl/1-oxide	175–180/3	760a
2,3-Bis(bromomethyl)/1,4-dioxide	170–171	739
3-Bromo-2-*s*-butyl-6-hydroxy-5-isobutyl/1-oxide	129–130	87
2-Bromomethyl/1,4-dioxide	165.5–166	739
2-Bromomethyl-3-methyl/1,4-dioxide	140–141	739
2-*s*-Butyl-3-chloro-5-isobutyl/1-oxide	99–102/0.12	313
5-*s*-Butyl-3-chloro-2-isobutyl/1-oxide	49–51	313
2-Chloro/1-oxide	131–132, 133–134.5, 140–146	733b, 757, 758, 838, 900
3-Chloro/1-oxide	94 to 98	575, 733b, 737, 757, 900
3-Chloro-2-dichloromethyl/1-oxide		688
3-Chloro-2,5-diisobutyl/1,4-dioxide	134–136	843
2-Chloro-3,6-diisobutyl/1-oxide	33–34	113b
3-Chloro-2,5-diisobutyl/1-oxide	56.5–57	843
3-Chloro-2,5-dimethyl/1,4-dioxide	203–204	842
3-Chloro-2,5-dimethyl/1-oxide	113 to 117.5	756, 842, 872, 978
2-Chloro-3,6-dimethyl/1-oxide	105 to 109	842, 900
3-Chloro-2(1′-hydroxy-2′-methylpropyl)-5-isobutyl/1-oxide	134–134.5	760a
3-Chloro-2-isobutyl-5-isopropyl/1,4-dioxide	94–95	740a
3-Chloro-5-isobutyl-2-isopropyl/1,4-dioxide	95–96	740a
3-Chloro-2-isobutyl-5-isopropyl/1-oxide	76.5–77.5	740a
3-Chloro-5-isobutyl-2-isopropyl/1-oxide	120–123/1	740a
2-Chloro-3-methyl/1-oxide (?)	51–52	737
3-Chloro-2-methyl/1-oxide	71 to 76	737, 793
3-Chloro-5-methyl/1-oxide	109–110	737
5-Chloromethyl-2-methyl/1-oxide	89	756
2-Chloro-3-phenyl/1-oxide	188–189	733b

TABLE A.33 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
3-Chloro-2-phenyl/1-oxide	151–152	733b
2-Chloro-5-phenyl/1-oxide	146	733b, 761
5-Chloro-2-phenyl/1-oxide	151	733b
3-Chloro-5-phenyl/1-oxide	121–122	733b
2-Chloro-6-phenyl/1-oxide	128	733b
2-Chloro-3-trichloromethyl/*N*-oxide		688
2,3-Di(bromomethyl)/1,4-dioxide	170–171	739
2,3-Dichloro/1-oxide	104–106	900
2,6-Dichloro/1-oxide	122–123	900
3,5-Dichloro/1-oxide	119–120, 123–125	365b, 663, 900
2,5-Dichloro-3-chloromethyl-6-methyl/1-oxide	Anal., n.m.r.	756
3,5-Dichloro-2,6-difluoro/1-oxide	80–89	901
2,5-Dichloro-3,6-diisobutyl/1,4-dioxide	192–193	101
2,5-Dichloro-3,6-diisobutyl/1-oxide	35–35.5	101
2,5-Dichloro-3,6-dimethyl/1,4-dioxide	231, 248	756, 842
2,5-Dichloro-3,6-dimethyl/1-oxide	122	756
3,5-Dichloro-2-methoxy/1-oxide	92–96	901
Tetrabromo/1-oxide	230	901
Tetrachloro/1,4-dioxide	310, 315	900, 903, 904
Tetrachloro/1-oxide	200, 216–218	900–902
2,3,5-Tribromo/1-oxide	129–132	901
2,3,5-Trichloro/1-oxide	102–105	901
3-Trifluoromethyl/1-oxide	57–59	759

TABLE A.34 OXYPYRAZINE *N*-OXIDES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Acetoxymethyl/1,4-dioxide	250	738
2-Acetoxymethyl/1-oxide	225–226	738
3-Acetoxymethyl/1-oxide	104–105, 111–112; 174–177/8–10	738, 760
2-Acetoxymethyl-5-methyl/1,4-dioxide	239–243	625, 760
2-Acetoxymethyl-5-methyl/?-oxide	96–97	625
5-Acetoxymethyl-2-methyl/1-oxide	73–74.5	760
2-(1′-Acetoxy-2′-methylpropyl)-5-isobutyl/1-oxide	42–43	760a
3-Benzoyloxy/1-oxide	106–107	1035
5-Benzoyloxy-2-methyl/1-oxide	139–140	1035
3-Benzoyloxy-5-methyl/1-oxide	123–124.5	1035
6-Benzyl-3-ethyl-2-hydroxy/1-oxide	137–138	546
6-Benzyl-2-hydroxy/1-oxide	171	546
3-Benzyl-2-hydroxy-5-phenyl/1-oxide	165–166	1133
2-Benzyloxy-5-hydroxy-3,6-dimethyl/1,4-dioxide	158–160, 163–165	756, 842
2,3-Bis(acetoxymethyl)/1,4-dioxide	160–162	739

TABLE A.34 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2,5-Bis(acetoxymethyl)/1-oxide	113–114	625
2,3-Bis(hydroxymethyl)/1,4-dioxide		739
3-*s*-Butyl-2-hydroxy-5,6-dimethyl/1-oxide	83–85, 87–90	547, 1453
3-*s*-Butyl-2-hydroxy-6-(1′-hydroxy-1′-methylpropyl)/1-oxide		112
6-*s*-Butyl-2-hydroxy-3-isobutyl/1-oxide (aspergillic acid)	93 to 99	90, 313, 551, 1751, cf. 83–86
5-*s*-Butyl-3-hydroxy-2-isobutyl/1,4-dioxide	128.5–131	313
3-*s*-Butyl-2-hydroxy-6-isopropyl/1-oxide	Cu salt 205–207	104a
6-*s*-Butyl-2-hydroxy-3-(2′-methylthioethyl)/1-oxide	74–76	1134
6-*s*-Butyl-2-hydroxy-3-propyl/1-oxide	80–81	96
6-*s*-Butyl-3-isobutyl-1-methoxy-2-oxo-1,2-dihydro		86
2,5-Dibenzyloxy-3,6-dimethyl/1,4-dioxide	108–110, 125–127	756, 842
3,6-Di-*s*-butyl-2-hydroxy/1-oxide		111, 982
2,5-Diethoxy-3,6-dimethyl/1,4-dioxide	158–159	756, 842
3,6-Diethyl-2-hydroxy/1-oxide	95–97	548
2,5-Dihydroxy-3,6-diisobutyl/1,4-dioxide (pulcherriminic acid)	> 200	99, 100, 1752
2,5-Dihydroxy-3,6-dimethyl/1,4-dioxide	200	842
2,3-Di(hydroxymethyl)/1,4-dioxide	123–124	739
2,5-Diisobutyl-4,6-dimethoxy-3-oxo-3,4-dihydro/1-oxide	81	99
2,5-Diisobutyl-3-methoxy/1,4-dioxide		980
2,5-Diisobutyl-4-methoxy-3-oxo-3,4-dihydro/1-oxide	128–129.5	843
2,5-Dimethoxy-3,6-dimethyl/1,4-dioxide	170–171	756
4,6-Dimethoxy-2,5-dimethyl-3-oxo-3,4-dihydro/1-oxide	151–152	842
5-(1′,2′-Epoxy-2′-methyl)propyl-2-isobutyl-3-methoxy/1-oxide	66–68	113b
3-Ethoxy/1,4-dioxide	180–180.5	978
3-Ethoxy/1-oxide	76–77	978
3-Ethoxy-2,5-dimethyl/1-oxide	92–94, 96–97	872, 978
2-Ethoxy-5-hydroxy-3,6-dimethyl/1,4-dioxide	164–165	756, 842
3-Ethoxy-2-methyl/1-oxide	121–122	978
2-Hydroxy/1-oxide	*ca.* 225–230	1753
3-Hydroxy/1-oxide (emimycin)	225, 255	108, 547a, 838
2-Hydroxy-3,6-bismethylthioethyl/1-oxide	106–107	1134
3-Hydroxy-2,5-diisobutyl/1,4-dioxide	195–195.5	843, 980
3-Hydroxy-2,5-diisobutyl/1-oxide	237–238	101
2-Hydroxy-3,6-diisobutyl/1-oxide (neoaspergillic acid)	122 to 129	96, 98, 113a, 550, 551, 843, 980, 1061, 1747
2-Hydroxy-3,6-diisopropyl/1-oxide	74–75	96
2-Hydroxy-3,5-dimethyl/1-oxide	135	524, 546
3-Hydroxy-2,5-dimethyl/1-oxide	> 250, 270–272	872, 978
2-Hydroxy-3,6-dimethyl/1-oxide	194–195	548

TABLE A.34 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
2-Hydroxy-5,6-dimethyl-3-phenyl/1-oxide	154–156	37, 546
2-Hydroxy-3,5-diphenyl/1-oxide	165–166	546
2-Hydroxy-3,6-dipropyl/1-oxide	106–107	96
2-Hydroxy-6-(1′-hydroxy-1′-methylethyl)-3-isobutyl/1-oxide	167–168, 173–174	102, 553
2-Hydroxy-6-(1′-hydroxy-1′-methylpropyl)-3-isobutyl/1-oxide (hydroxyaspergillic acid)	149–150	94
3-Hydroxy-5-(1′-hydroxy-2′-methylpropyl)-2-isobutyl/1,4-dioxide	177–178	760a
2-Hydroxy-6-(1′-hydroxy-2′-methylpropyl)-3-isobutyl/1-oxide (neohydroxyaspergillic acid)	170–171	98, 760a, 1747
2-Hydroxy-6-(2′-hydroxy-2′-methylpropyl)-3-isobutyl/1-oxide	143–144	113a
2-Hydroxy-3-isobutyl-5,6-dimethyl/1-oxide	69–71, 95–98	547, 1453
2-Hydroxy-3-isobutyl-5,6-diphenyl/1-oxide	217–220	547
3-Hydroxy-2-isobutyl-5-isopropyl/1,4-dioxide	156	740a
3-Hydroxy-5-isobutyl-2-isopropyl/1,4-dioxide	144.5–145	740a
2-Hydroxy-3-isobutyl-6-isopropyl/1-oxide	92–94, 99–100	96, 112, 740a
2-Hydroxy-6-isobutyl-3-isopropyl/1-oxide	86–87	740a
2-Hydroxy-3-isobutyl-6-(1′-methylprop-1′-enyl)/1-oxide (dehydroaspergillic acid)	116–117	94
2-Hydroxy-3-isobutyl-6-methylthioethyl/1-oxide	114–116	1134
2-Hydroxy-6-isobutyl-3-methylthioethyl/1-oxide	114–116	1134
2-Hydroxy-3-isobutyl-6-propyl/1-oxide	129–131, 130–131	96, 549
2-Hydroxy-6-isopropyl-3-methylthioethyl/1-oxide	69–75	1134
2-Hydroxy-5-methoxy-3,6-dimethyl/1,4-dioxide	195–197	756
3-Hydroxymethyl/1-oxide	Pic. 117–118	738
3-Hydroxy-2-methyl/1-oxide	216–218	978
3-Hydroxy-5-methyl/1-oxide	> 250	1035
5-Hydroxy-2-methyl/1-oxide	214–216	1035
2-Hydroxymethyl-5-methyl/1,4-dioxide	226–228, 229–230	625, 760
2-Hydroxy-3-methyl-5-phenyl/1-oxide	185	546
2-Hydroxy-5-methyl-3-phenyl/1-oxide	144–145	873
2-(1′-Hydroxy-2′-methylpropyl)-5-isobutyl/1-oxide	114–115	760a
5-(2′-Hydroxy-2′-methylpropyl)-2-isobutyl-3-methoxy/1-oxide	< 158/4	113b
2-Hydroxymethyl-3,5,6-trimethyl/1,4-dioxide	152.5–154.5	760
2-Hydroxymethyl-3,5,6-trimethyl/*N*-oxide	83–85.5	760
2-Hydroxy-5-phenyl/1-oxide	194–196	546
2-Hydroxy-3,5,6-trimethyl/1-oxide	176–177	546
2-Methoxy/1-oxide	159.5–160.5	838
3-Methoxy/1-oxide	75, 80–81.5	108, 838, 881
3-Methoxy-2-phenyl/1-oxide	94–96	817

TABLE A.34 *Continued*

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Refs.
4-Methyl-3-oxo-3,4-dihydro/1-oxide	190–191	1035
2-Sulfo/1-oxide	252.5–253	838
3-Sulfo/1-oxide	230–235	838
3-(Trimethylsilyl)oxy/1-oxide	140/8.8	1034

TABLE A.35 THIOPYRAZINE *N*-OXIDES

Pyrazine	M.p. (°C) or B.p. (°C/mm)	Ref.
3-Mercapto/1-oxide	204–206	1035
3-Mercapto-2,5-dimethyl/1-oxide	231–232	905
3-Mercapto-2-methyl/1-oxide	216–217	905

Chemistry of Heterocyclic Compounds, Volume 41
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Author Index

Numbers in *italics* indicate where references appear.

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Subject Index

The index covers the text and Tables of Chapters I – XI in detail except for the contents of the Tables of Chapter X (Ionization Constants and Spectra). The Appendix Tables have not been indexed. Only the names of authors actually mentioned in the text appear in the Index.

Information recorded in this volume is therefore available through the Index, through the Tables of Chapter X, or from the Systematic Tables of Simple Pyrazines in the Appendix.

Page numbers which immediately follow the primary entry refer to syntheses or general information. Numbers in parentheses indicate that, although the subject is treated on that page, the actual name will not be found in full (or perhaps not at all) in the relevant text. For example, on p. 134 a paragraph begins "Replacement of the chloro substituent by methoxide has been observed in the following pyrazines: 2-chloro-3-methoxycarbonyl....." The product (2-methoxycarbonylpyrazine) is not mentioned, but only implied, and the index entry is shown as (134).

The general term chlorination has been used in the Index for replacement of hydrogen by chlorine and for the conversion of hydroxypyrazines (with phosphoryl chloride, phosphorus pentachloride, thionyl chloride, etc.) to chloropyrazines. Aminolysis refers to reactions with amines (and hydrazines) such as replacement of halogen by amines, and the conversion of esters to amides.


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