THE PYRAZINES

G. B. Barlin

THE AUSTRALIAN NATIONAL UNIVERSITY CANBERRA



AN INTERSCIENCE[®] PUBLICATION

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THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER AND EDWARD C. TAYLOR

Editors



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ARNOLD WEISSBERGER

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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 Professor A. Albert advised in many ways and provided unpublished data.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, $\mathbb{R}^1 = \mathbb{R}^2 = \mathbb{R}^3 = \mathbb{R}^4 = \mathbb{P}h$), 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."

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

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

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,



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.



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.



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.



Introduction to Pyrazines

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).



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-2,5dimethylpyrazine, 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),

Occurrence

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 $162.7^{\circ}C$ (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-3methoxypyrazine has been characterized in the vacuum steam volatile oil of potatoes (64), 2-ethyl-3-methoxypyrazine in cooked potato (65), and 3-ethyl-2,5dimethylpyrazine 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).

