THE PYRAZINES

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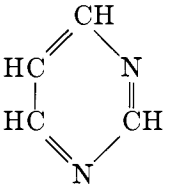
I. Introduction

There are three possible ways in which two nitrogen atoms may be combined with four carbon atoms to form the system of six-membered heterocyclic rings known as diazines.

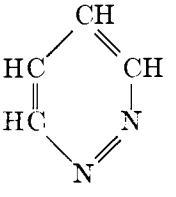
The most familiar class of this system is that in which the two nitrogen atoms are meta to each other, the pyrimidines. These are of importance because of



Pyrimidine

their occurrence in such diverse natural products as the purines (caffeine, uric acid, etc.), vitamins (thiamin, riboflavin), and nucleic acids, as well as in the synthetic barbiturates. T. B. Johnson and coworkers have made extensive investigations of these compounds, and valuable discussions by them may be found in Gilman's *Organic Chemistry* (92) and *Chemical Reviews* (115).

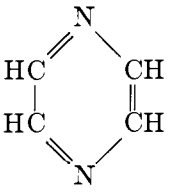
The *o*-diazines, the pyridazines, are a more obscure class. For a unified



Pyridazine

account of their chemistry the reader is referred to Meyer and Jacobson's *Lehrbuch der organischen Chemie.*

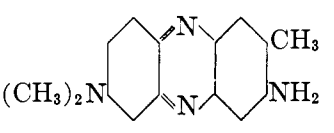
The final class of diazines are the pyrazines, in which the ring nitrogens are situated para to each other. Stoehr and Wolff (*cf.* references) were the first to



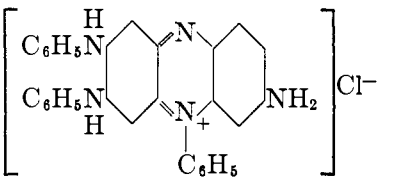
Pyrazine

work intensively in this field, and it is only comparatively recently that further integrated investigations of these compounds were undertaken. This lack of interest was no doubt due to the difficulties which obtained in the synthetic procedures, as well as to the lack of a convenient natural source of supply.

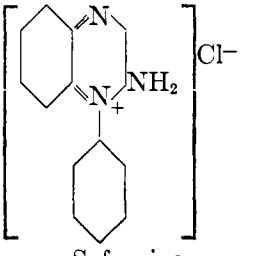
It is worthy of note that Hilditch (103) considered pyrazine to be the most important of the diazines because of its relationship as the parent of those condensed systems which constitute the azine dyes, e.g., the eurhodines, indulenes, and safranines:



Toluylene red
(a eurhodine)

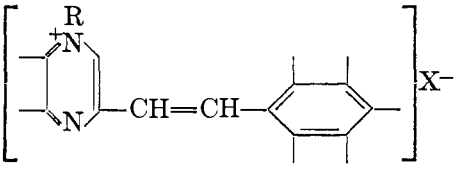


Indulene

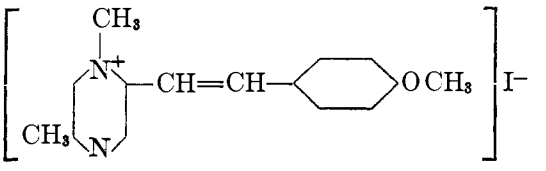


Safranine

More recently (1933), Riesz (182) patented compounds of the type



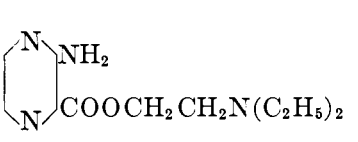
claiming that they possess the property of desensitizing photographic emulsions in aqueous medium. A specific example is 1,5-dimethyl-2-[4′-methoxystyryl]-pyrazinium iodide,

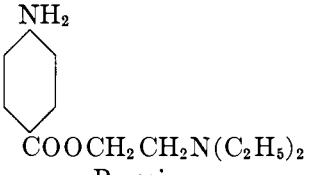


The preparation of pyrazine "phthalein" dyes was recorded by De and Dutta (59) in 1934, when they were successful in condensing *o*-pyrazinedicarboxylic acid with various phenols and amines.

The renewed interest in pyrazine chemistry may be largely traced to the great advances of chemotherapy, in which heterocycles have been particularly prominent. The successful application of sulfapyridine, sulfathiazole, and sulfadiazine led to the development of sulfapyrazine, which has had very favorable clinical reports (132). The indexes of *Chemical Abstracts* for the past four years list over twenty references to clinical investigations and related topics involving sulfapyrazine and its derivatives.

Attempts to improve the action of the procaine type of anesthetic resulted in the synthesis of the β-diethylaminoethyl ester of 2-amino-3-pyrazinoic acid (73):



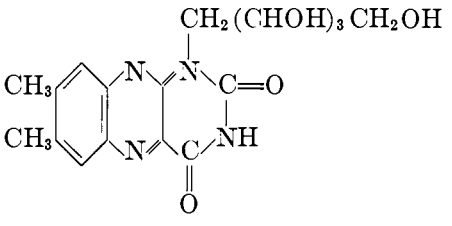


Procaine

The β-diethylaminoethyl ester of 2-amino-5-pyrazinoic acid, which would be more analogous to procaine, was not prepared because of greater difficulties inherent in its synthesis.

Amidopyrazines have been patented by E. Merck (56), with the claim that they are valuable analeptics.

The importance of the pyrazine nucleus in life processes is indicated in its condensed derivative, riboflavin or vitamin B_2.



In addition, the simple pyrazinoic and 2,3-pyrazinedicarboxylic acids have both been found to possess antipellagric action (13, 19).

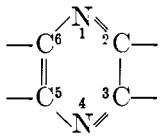
In view of the increasing importance of these substances, the following survey of the chemistry of the *uncondensed* pyrazines is presented with the hope of affording a modern unified picture of this field. We have made no attempts to include the hydro derivatives exhaustively, and these substances are discussed only when they are in some measure concerned with either the synthesis or the reaction of a pyrazine proper.

II. Nomenclature

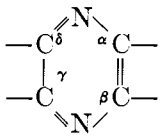
As will be indicated in the following historical section, the development of the nomenclature was beset with difficulties, owing to the confusion of the early

workers with regard to the structure of pyrazine. In addition to understandable trivial names given to compounds discovered before their structure was elucidated, there arose such terms for pyrazine as aldine, paradiazine, and piazine. At one time, 2,5-dimethylpyrazine was thought to be the parent of the class, with the result that it was given the generic name "ketine."

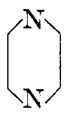
We shall follow the *Ring Index* (169), giving preference to the class name "pyrazine" and numbering the nucleus as follows:



An alternative scheme is that used by Victor v. Richter in his *Lehrbuch der organischen Chemie:*



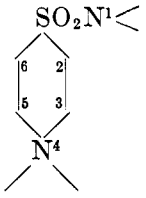
As an abbreviation for the pyrazine nucleus, we shall use the hexagonal skeleton, except where possible ambiguity may occur.



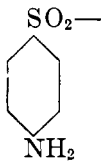
Since the carboxylic acids are among the more widely discussed compounds, it was suggested by Daniels and Iwamoto (57) that for convenience the single monocarboxylic acid be given the name of pyrazinoic acid.

In considering the sulfanilamide derivatives, advantage was taken of the scheme developed by Crossley, Northey, and Hultquist (50) for a systematic nomenclature. For the sake of the unfamiliar reader we quote the more salient features of the system.

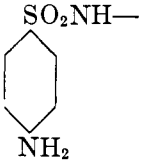
The following numbering sequence is utilized for the substituted sulfanilamides:



The radical names, sulfanilyl

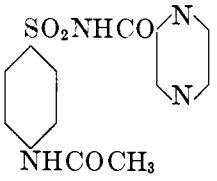


and sulfanilamido

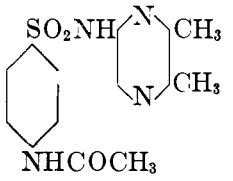


are also found to be very convenient.

We give two examples:



N^4-Acetyl-N^1-pyrazinoyl-sulfanilamide

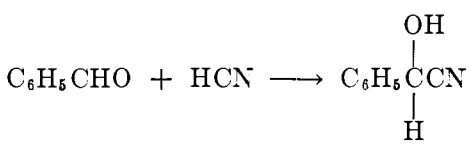


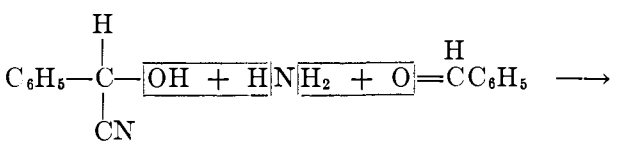
2-[N^4-Acetylsulfanilamido]-5,6-dimethylpyrazine

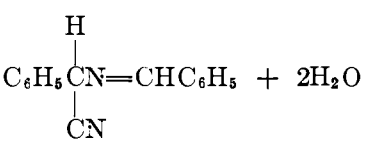
III. Historical

In recording the development of pyrazine chemistry, we have attempted to preserve the original historical plan, presenting the facts in almost the same manner as they were exposed. This treatment may initially appear somewhat awkward, but it will be seen that the early and apparently unrelated observations form an important part of the entire pattern.

The first procedure for the synthesis of a pyrazine derivative was published by Laurent in 1844 (134). Starting with crude benzaldehyde, i.e., benzaldehyde containing some hydrogen cyanide, he treated it with ammonia to obtain what was then known as "benzoylazotid"—actually α-benzalaminophenylacetonitrile:



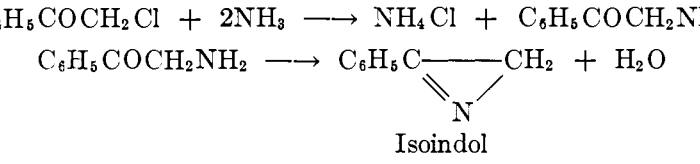




Then, in a fashion typical of that period, he more or less destructively distilled "benzoylazotid," and was able to isolate amongst the products a substance which he called amarone.

Twenty-one years later Erdmann (74) reported an apparently new substance, benzoinimide, which he obtained, along with some others, by the action of ammonia on benzoin.

No further progress was made until 1876, when Stadel and Rügheimer (200) published a paper describing the formation of a new compound, isoindol, by the action of ammonia on ω-chloroacetophenone. They postulated that isoindol was the inner anhydride of an amino ketone and was formed according to the following sequence:

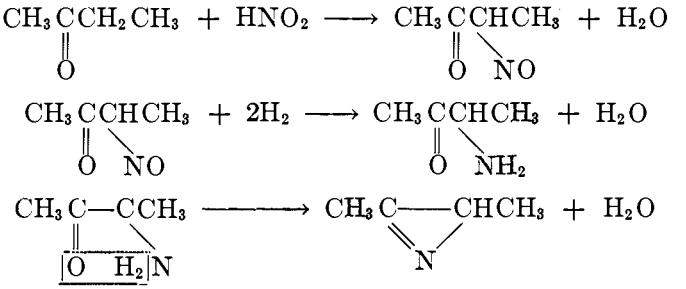


Isoindol

This is of interest since it represents the first recorded instance of a structural formula for a pyrazine.

In 1881 Etard (78) made what was seemingly an uncorrelated observation when he published the fact that a new substance, which he named glycolin, could be isolated from the distillate which resulted from heating a mixture of glycerol and an ammonium salt.

Two years prior to the appearance of Etard's article, work was progressing in Victor Meyer's laboratory at Zurich which was to be of great value in the elucidation of the nature of these compounds. At that time Meyer was interested in the study of nitroso derivatives. To H. Gutknecht he assigned the task of reducing the product of the action of nitrous acid on ethyl methyl ketone. We now know that this nitrous acid product was the oxime, but these investigators believed that they were dealing with a true nitroso compound. The results were published in 1879 (99), with the conclusion that an inner anhydride of the amino ketone was obtained from the reduction, in exact analogy to the hypothesis of Stadel and Rügheimer:

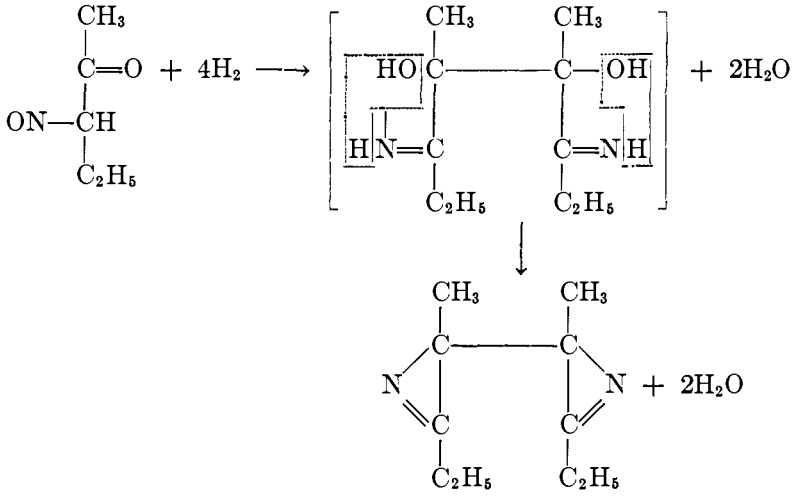


Analyses of the crystalline product were not too satisfactory because of difficulties in obtaining it in an absolutely anhydrous state. After consideration of the data, Gutknecht advanced the possibility that the compound might contain one less hydrogen atom than was indicated by the formula.

This point was finally clarified by F. P. Treadwell (of analytical fame) in the

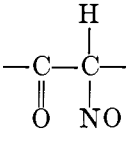
same laboratory in 1881 (221). He had carried out a reduction of (iso) "nitrosoethylacetone" and had isolated a crystalline hydrate. After placing these crystals in a desiccator over calcium chloride he noted that an anhydrous oil had formed. Analysis of this oil proved that it possessed one hydrogen atom less than would be anticipated from the formula of the simple "inner anhydride" of an amino ketone. Vapor-density determinations further indicated that the molecular weight was about twice that which would be expected for such a compound.

Using the reduction of acetone to pinacol as a model, Treadwell assumed that the reaction for (iso) "nitrosoethylacetone" proceeded as follows:

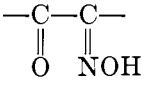


The name "ketine" was applied to this new series of nitrogenous compounds to indicate their derivation from ketones. The simplest member, according to the Treadwell theory, would be that obtained from acetone; and this was specifically termed ketine. The other members were named as derivatives of ketine, so that Gutknecht's compound was called dimethylketine, and Treadwell's diethylketine.

The next year V. Meyer submitted a paper (151) in which he contributed two important suggestions. He first pointed out that although the products of the action of nitrous acid on the ketones were presumably nitroso compounds, they failed to respond to the Liebermann nitroso test. This led to the hypothesis that they were not true nitroso compounds but rather the isomeric oximes:



Nitroso ketone

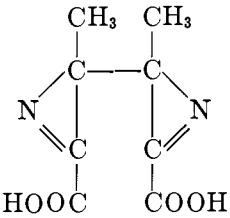


Oximino ketone

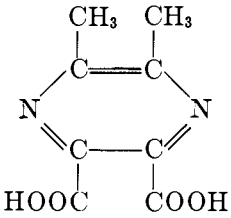
He then considered the reduction of these compounds. After making careful

comparisons with the corresponding processes for nitro-amine and ketone-pinacol reductions, he concluded that the former was more analogous. This led to the abandonment of the Treadwell theory.

The first conception of the ketines as ring compounds was put forth, almost immediately, by Wleugel in an article concerned with the reduction of (iso) "nitrosoacetoacetic" ester (234). Thus, instead of writing the structure for the "ketine" which was obtained as

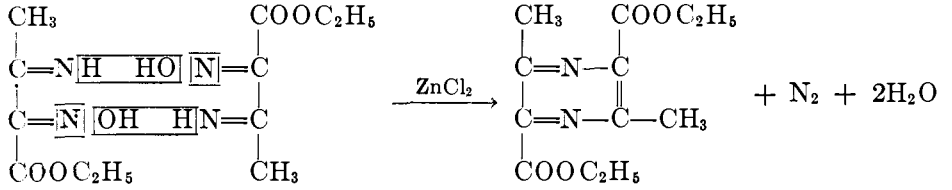


he closed the six-membered ring by utilizing the C—C bonds involved in the two inner anhydride rings:



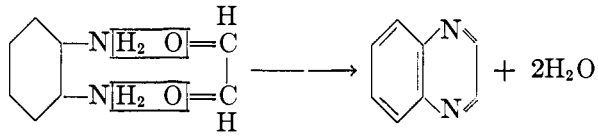
This resulted in the formulation of a heterocycle which, as Wleugel stated, could be conceived to be a pyridine in which the CH group para to the nitrogen atom was replaced by another nitrogen atom. This is our modern concept of the pyrazine nucleus; but there remained a flaw in its derivation, since Wleugel had still utilized the ketine(pinacol) mechanism.

It remained for L. Oeconomides in 1886 (167) to demonstrate experimentally that this mechanism was untenable. He attempted to dehydrate Wleugel's diacid to the acid anhydride, a reaction which should have been clearly possible if the two carboxyls were ortho to one another. This was unsuccessful, and the natural conclusion was that these functional groups had been assigned to incorrect positions on the ring. Verification came, together with a proof that the carboxyls were actually para, from the following experiment. Iminoisonitrosobutyric ester was heated with fused zinc chloride. An examination of the only plausible mechanism which could yield a "ketine" indicated that the carboxyl groups in such a compound would unambiguously be situated at the para positions:

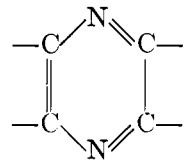


A small amount of free acid was isolated and compared with Wleugel's; the two were found to be identical.

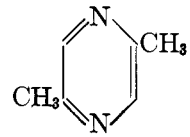
Oeconomides further called attention to the fact that Hinsberg (105) had synthesized quinoxaline, a condensed pyrazine, from *o*-phenylenediamine and glyoxal:



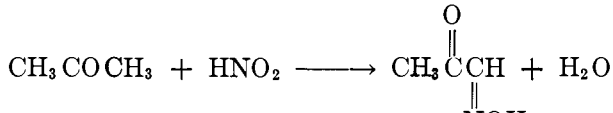
Thus, the ketine nucleus was firmly established as

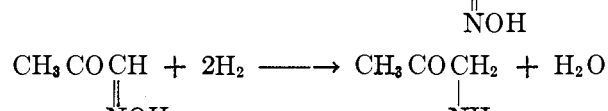


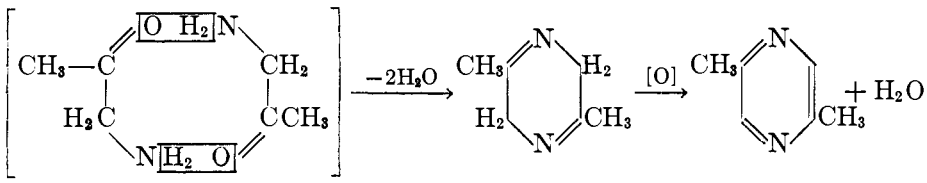
and what was previously thought to be the simplest member, ketine, in fact was the dimethyl derivative.



The name "pyrazine" was independently suggested for the nucleus in the following year by Mason (145) and Wolff (236), in order to point up the correlation with pyridine. It is interesting to note that, in the same paper, Wolff acknowledged that the mechanism, first inferred by Meyer, for the preparation of a pyrazine by the reduction of an isonitroso ketone involved an intermediate amino ketone which immediately condensed with itself to yield a dihydropyrazine that was oxidized to the desired pyrazine. Thus, starting with acetone:





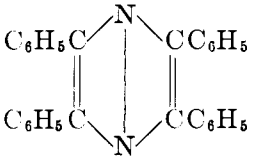


V. Meyer (152) objected to the term "pyrazine" on the grounds that Knorr (126) had already used it for pyrazole tetrahydride, and, in its stead, proposed the generic name "aldine," since the simplest member would result from the self-condensation of the hypothetical aminoacetaldehyde.

Widman (228) finally resolved the issues with a systematic nomenclature. He classified as azines those compounds which contained a six-membered ring consisting of nitrogen and carbon atoms. Hence, substances containing two nitrogen atoms in the ring were called *di*azines. These were further classified, according as to whether the nitrogens were ortho, meta, or para, as *o*-diazines, *m*-diazines, or *p*-diazines. Mason condensed these names, respectively, into oiazines, miazines, and piazines; but it seems that he and his associates were the only ones to use this terminology consistently.

In the light of the newly elucidated structures of the pyrazines, the results of the early workers were finally clarified. Thus, Wolff in 1887 demonstrated that what Stadel and Rügheimer had called isoindol was 2,5-diphenylpyrazine. Stoehr (202) improved Etard's procedure for glycolin and showed that this was identical with 2,5-dimethylpyrazine.

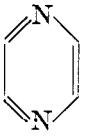
Japp and Wilson (114) undertook the task of determining the true nature of Erdman's benzoinimide, which they renamed ditolanazotide, by repeating the original experiments. In the following year Japp and Burton (110) concluded that the compound was an azine, and assigned to it the structure,



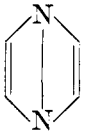
together with the name "tetraphenylazine."

Snape and Brooke thereupon repeated Laurent's original work and in 1897 published a paper (195) in which they revealed that amarone, benzoinimide, ditolanazotide, and tetraphenylazine were all one and the same substance: tetraphenylpyrazine.

There yet remained doubt as to the exact location of the double bonds in the pyrazine molecule. The Kekulé type with its conjugated double bond system (I) and the Dewar type (II) with the long para bond, each had its adherents (147, 212, 246).



I

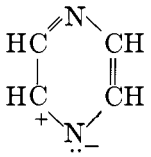


II

Bruhl (32) finally established the validity of I after a study of the molecular refractions of a number of pyrazine derivatives.

Recently, Pauling and his collaborators (170) have made electron-diffraction studies on some cyclic systems, including pyrazine. Their results showed that pyrazine and benzene have almost identical structures. Further, although the C—C distances for the two molecules were almost identical, 1.39 A., the value for the C—N distance in pyrazine, 1.36 A., was greater than expected for the Kekulé resonance, which would give this bond 50 per cent double-bond character.

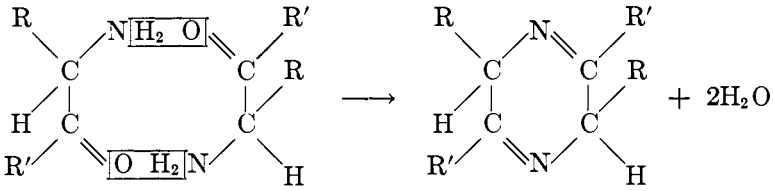
This is interpreted as being due to the large electronegativity of the nitrogen atom, which results in the introduction of additional resonating ionic structures, as:



IV. Methods of Preparation

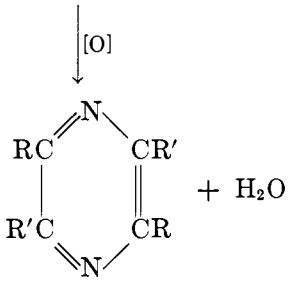
A. Autocondensation of α-primary aminocarbonyls

The most general procedure for the synthesis of symmetrical pyrazines depends on the fact that α-primary aminocarbonyl compounds can rarely be isolated because of their strong tendency to condense and form dihydropyrazines. Thus, although the ammonium salts, such as the hydrochlorides, of these compounds are perfectly stable and may be obtained as crystalline solids, most attempts to isolate the free bases by treating with excess alkali yield only the dihydropyrazines. These are easily oxidized by such mild reagents as mercuric or cupric ions, or even air, to the desired pyrazines.



Condensation of 2 moles of aminocarbonyl; R and R′ may each be alkyl, aryl, or hydrogen

Dihydropyrazine derivative



Pyrazine derivative

It is clear that the essence of this method lies in the preparation of the pertinent α-primary aminocarbonyl derivatives. A detailed discussion of these compounds is not inappropriate here, since they are of great importance in pyrazine chemistry. It may be pointed out that in a recent lengthy review paper dealing with amino ketones (49), the primary α-amino type received only cursory mention.

1. Reduction of oximino ketones

The first step of this important classical synthesis, discovered by Gutknecht (99), generally involves the formation of the oximino ketone from the ketone:

$$RCH_2COR' + HNO_2 \rightarrow RC{=}NOHCOR' + H_2O$$

R = alkyl, aryl, or hydrogen; R' = alkyl or aryl.

These oximino compounds were improperly referred to by the early workers as isonitroso ketones on the assumption that an equilibrium existed between these and the true nitroso compounds:

$$RC{=}(NOH)COR' \rightleftarrows R{-}\underset{\displaystyle NO}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}{-}COR'$$

However, in most cases the species on the right is non-existent (192). Wherever we have used the prefix "isonitroso," it is to avoid possible confusion when reference is made to original papers.

The most direct approach utilizes the action of free nitrous acid on the ketone. This is most often accomplished by dissolving the ketone in acetic acid and then slowly adding, with agitation, a concentrated aqueous solution of sodium nitrite to the well-cooled reaction mixture. The oximino ketone may then be extracted with ether to effect its separation; however, it has been found in our laboratories (15) that a great improvement in manipulation and yield resulted when no attempt was made to isolate the compound for the next step in the synthesis.

Unless the ketones are β-diketones or β-ketonic esters, the reaction may be unsuccessful. Recourse may then be had to the method of Claisen and Manasse (42), which has been found to work in every case. Instead of sodium nitrite, a nitrous acid ester, usually amyl nitrite or occasionally methyl or ethyl nitrite (193), is used in conjunction with either an alkaline catalyst such as sodium ethylate, or an acid catalyst such as hydrogen chloride.

Certain of the oximino compounds may be prepared in better yield by the procedure of Charrier (38) and Freon (86). A β-ketonic ester is dissolved in a cold caustic solution and permitted to hydrolyze to the alkali salt. The mixture is then treated with sodium nitrite and acid to form the oximino ketonic acid, which is unstable and loses carbon dioxide. Oximinoacetone prepared in this way was obtained in 95 per cent yield, as compared to the 40 per cent yield from the Claisen method with acetone (135).

The reduction of the oximino ketone ordinarily is effected in acid medium with either stannous chloride or zinc:

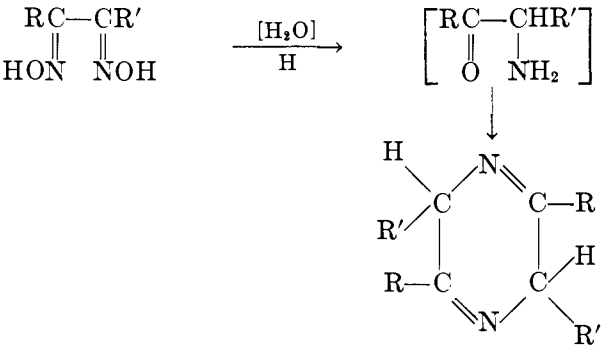
$$RC(=NOH)COR' + 2H_2 + H^+ \rightarrow RCH\overset{+}{N}H_3COR' + H_2O$$

Other reduction techniques have been recorded. Cerchez and Colesiu (39) used an aluminum amalgam to reduce oximinoacetoacetic ester. Satisfactory catalytic reductions were carried out by Diels and Poetsch (63) with a palladium catalyst and by Adkins and associates (3, 229, 230) using Raney nickel. The latter further observed that the yield of pyrazines was a function of the hydrogen pressure, higher pressures favoring the formation of the aminohydroxy derivatives. This is interpreted to mean that at higher pressures there is not sufficient time for the self-condensation to occur, since reduction to the hydroxyamines is so much more rapid. It has been reported that the conditions of the catalytic reduction may be modified so as to favor the formation of piperazines (94).

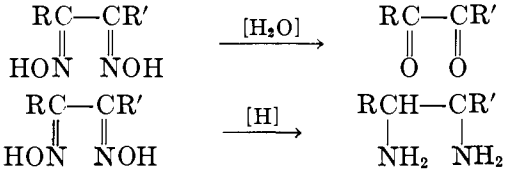
With catalytic hydrogenation the reduction to the aminopyrazine takes place directly, whereas in the acid reduction process the product is the salt of the amino ketone. In the latter case treatment with alkali is necessary to release the free amino ketone, which then undergoes condensation.

The oxidation of the dihydropyrazine is simple and proceeds with great ease. Customarily mercuric oxide or chloride or copper sulfate has been used, but in some cases even atmospheric oxygen has been found to be sufficient.

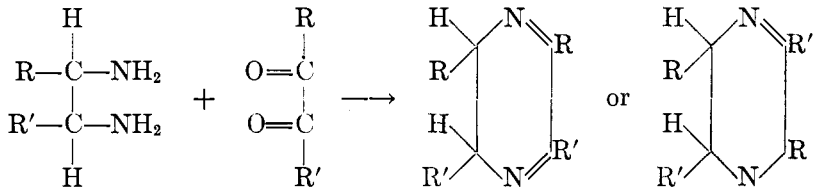
A number of examples have been recorded where the reduction of diketone dioximes has yielded pyrazine derivatives (table 1). There are two possible ways of picturing the mechanism. Either we may consider that simultaneous hydrolysis and reduction occur in the same molecule:



or one molecule undergoes complete hydrolysis and another complete reduction:



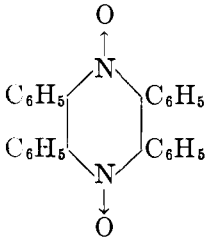
followed by condensation of the two different molecules:



(If R = R′ only one possibility arises.)

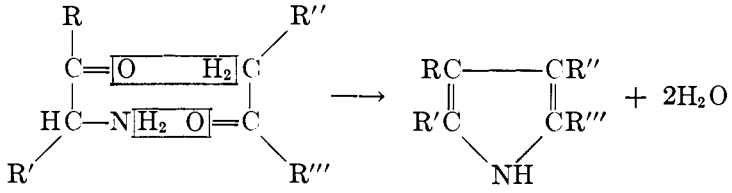
It should be possible to distinguish between the two mechanisms from a study of the dihydropyrazines, since a different one would be obtained in each case; but so far as is known, this task has as yet not been undertaken.

An interesting variation was developed by Durio and Bissi (66), based on the treatment of α-benzil dioxime with alkaline ferrocyanide. This experiment was first performed by von Auwers and Meyer (9), who were able to isolate diphenyl peroxide and a small quantity of an unidentified compound. Durio and Bissi demonstrated that this substance was dioxotetraphenylpyrazine:



and were able to modify the conditions so as to improve its yield. They also found that the other isomers of benzil dioxime were capable of forming only diphenyl peroxide; and, further, that the reaction was not general for the α-aryl dioximes, since α-*p*-tolyl dioxime and α-anisil dioxime yielded no pyrazines.

Before closing our discussion of the reduction of the oximino ketones we should indicate its value in the Knorr pyrrole synthesis (125). The latter is carried out in essentially the same manner, with the exception that after the reduction of the oximino ketone, an equimolar quantity of a ketone (or, better, a β-diketone) is added before the mixture is made alkaline:



It is easily perceived how pyrazines may be obtained as by-products from this reaction, since there is always the possibility of autocondensation of some

TABLE 1

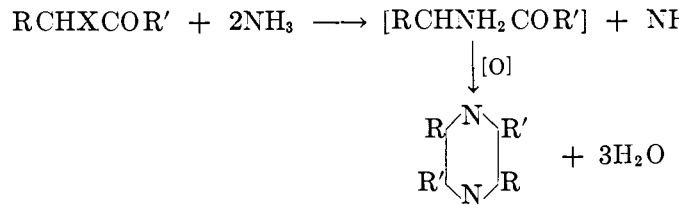
Pyrazines prepared by reduction of oximino ketones

OXIMINO KETONE	PYRAZINE DERIVATIVE	REFERENCES
Oximinoacetone	2,5-Dimethylpyrazine	(4, 87, 106, 114, 223)
Oximinoacetoacetic ester	2,5-Dicarbethoxy-3,6-dimethylpyrazine	(3, 39, 88, 97, 230, 234)
Oximino ethyl methyl ketone	Tetramethylpyrazine	(26, 28, 78, 99, 165)
Oximino methyl propyl ketone	2,5-Diethyl-3,6-dimethylpyrazine	(88, 221)
Oximino methyl butyl ketone	2,5-Dimethyl-3,6-dipropylpyrazine	(131, 222)
Oximino isoamyl methyl ketone	2,5-Dimethyl-3,6-diisobutylpyrazine	(133)
Oximino *n*-hexyl methyl ketone	2,5-Dimethyl-3,6-diamylpyrazine	(14)
Oximinoacetophenone	2,5-Diphenylpyrazine	(29, 172, 230)
Benzyloximinoacetone	2,5-Dibenzyl-3,6-dimethylpyrazine	(196)
Benzil monoxime	Tetraphenylpyrazine	(30, 230)
Dimethylglyoxime	Tetramethylpyrazine	(230)
Acetylbenzoyl dioxime	2,5-Dimethyl-3,6-diphenylpyrazine	(127)
β-Hydroxy-γ-oximino-*n*-valeric acid	Tetramethylpyrazine	(242)
Benzaldiacetyl monoxime	2,5-Dimethyl-3,6-di[β-phenylethyl]pyrazine	(63)
Phenyloximinoacetone	2,5-Dimethyl-3,6-diphenylpyrazine	(218)
Anisyloximinoacetone	2,5-Dimethyl-3,6-dianisylpyrazine	(218)
α-*p*-Tolyloximinoacetone	2,5-Dimethyl-3,6-di-*p*-tolylpyrazine	(218)
Oximinoacetylacetone	2,5-Dimethyl-3,6-diacetylpyrazine	(84, 164)
Benzil dioxime	Tetraphenylpyrazine Dioxotetraphenylpyrazine	(80, 176, 229)
Oximino-3,4-dimethoxyphenyl-3,4-methylenedioxy-β-phenyl ethyl ketone	2,5-Di[3,4-dimethoxyphenyl]-3,6-di[3,4-methylenedioxyphenyl]-pyrazine	(36)

of the amino ketone. Thus, in the preparation of 3,5-diacetyl-2,4-dimethylpyrrole, some 3,6-diacetyl-2,5-dimethylpyrazine was obtained (84). Indeed, in some circumstances the formation of pyrazines is favored, as was shown by Ochiai, Tsuda, and Ikuna, when they found much tetramethylpyrazine after a reduction of oximino ethyl methyl ketone in the presence of ethyl 2-picoloylacetate (165).

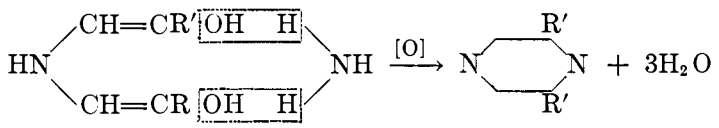
2. Replacement of the halogen in a halocarbonyl with an amino group

Stadel and Rügheimer (200) were the first to use this method, which has since proved of wide utility.



R' and R = alkyl, aryl, or hydrogen.

Ammonia, either aqueous or anhydrous, has been employed most often to effect the replacement of the halogen. This, of course, necessitates the use of sealed tubes or autoclaves, since the reaction normally proceeds at elevated temperatures. It might be anticipated that the use of ammonia would give rise to secondary and tertiary amino derivatives: $HN(RCHCOR')_2$ and $N(RCHCOR')_3$. However, the cyclization of the primary aminocarbonyl in most cases is much more rapid. The occasional occurrence of a 2,6-derivative (224) may be explained by the formation of such a secondary amino derivative, which reacts further:



The use of ammonia may lead to other complications, such as resin formation. This was found true in the attempted conversions of *p*-methoxy-ω-chloroacetophenone (224) and α-chloromethyl ethyl ketone (128) to the corresponding pyrazines. In such cases the amination may successfully be accomplished by the Gabriel phthalimide method.

It is found true here, as in other homologous series, that the application of a general method to the first member leads to anomalous results. Many attempts have been made to obtain pyrazine by the action of ammonia on a haloacetaldehyde, but the yields have always been poor (16, 40, 87, 97, 201). Chichibabin and Schukina (40) made a careful study of the conditions and concluded that the

TABLE 2

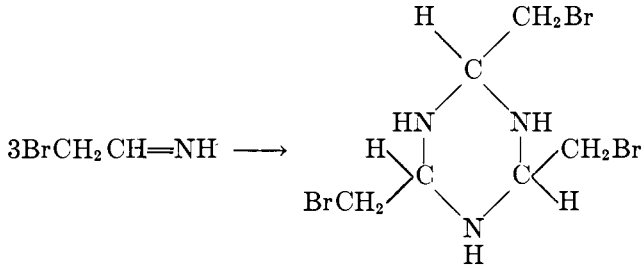
Pyrazines prepared by the replacement of the halogen in a halocarbonyl with an amino group

HALOCARBONYL	PYRAZINE DERIVATIVE	REFERENCES
ω-Chloro(or bromo)acetophenone	2,5-Diphenylpyrazine; also some 2,6-diphenylpyrazine	(27, 172, 200, 224, 239)
Methyl α-chloroethyl ketone	Tetramethylpyrazine	(61)
Methyl α-chloropropyl ketone	2,5-Dimethyl-3,6-diethylpyrazine	(128)
α-Chlorodiethyl ketone	2,5-Dimethyl-3,6-diethylpyrazine	(61)
β-Bromolevulinic acid	Tetramethylpyrazine	(237)
Bromophenylacetone	2,5-Dimethyl-3,6-diphenylpyrazine	(127)
Phenyl α-bromoethyl ketone	2,5-Dimethyl-3,6-diphenylpyrazine	(43, 188)
Phenyl α-bromopropyl ketone	2,5-Diethyl-3,6-diphenylpyrazine	(43)
ω-Chloro-*p*-methoxyacetophenone	2,5-Di-*p*-methoxyphenylpyrazine (also some 2,6-di-*p*-methoxyphenylpyrazine)	(224)
ω-Chloro-*p*-hydroxyacetophenone	2,5-Di-*p*-hydroxyphenylpyrazine (also some 2,6-di-*p*-hydroxyphenylpyrazine)	(224)
ω-Dibromoacetophenone	3,6-Diphenyl-2-hydroxypyrazine (isoindileucin)	(71)
α-Chloromethyl ethyl ketone	2,5-Diethylpyrazine	(128)
Indacyl bromide	2,5-Diindolylpyrazine	(184)
Bromoacetylskatole	Bis(3-methyl-2-indolyl)pyrazine	(184)
α-Methylindacyl chloride	Bis(2-methyl-3-indolyl)pyrazine	(183)
ω-Chloro-*m*,*p*-dimethoxyacetophenone	2,5-Di[m,*p*-dimethoxyphenyl]-pyrazine	(224)
ω-Chloro-*o*,*p*-dihydroxyacetophenone	2,5-Di[*o*,*p*-dihydroxyphenyl]-pyrazine	(224)

reaction is a function of the temperature, the solvent, and the speed with which the ammonia is passed into the reaction mixture. In addition, they indicated that it may proceed in two directions. The ammonia may add to the carbonyl group to yield the aldehyde ammonia, which loses water to form an imine that polymerizes into a tri[bromomethyl]hexahydrotriazine:

$$BrCH_2CHO + NH_3 \longrightarrow BrCH_2CHOHNH_2$$

$$BrCH_2CHOHNH_2 \longrightarrow BrCH_2CH{=}NH + H_2O$$



On the other hand, the bromine of the bromoaldehyde may be replaced by ammonia to form a mixture of various amino derivatives. The best yield of pyrazine, after oxidation of the reaction mixture with mercuric salts, was about 16 per cent.

TABLE 3

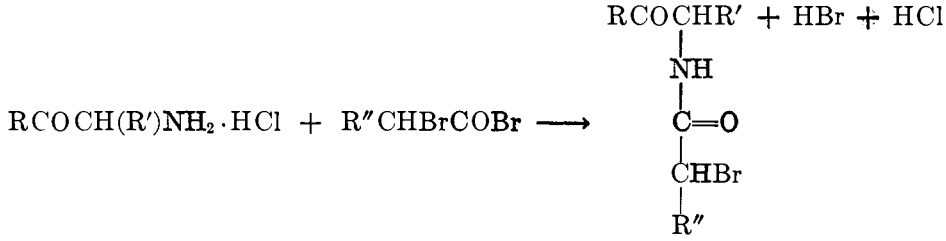
Pyrazines prepared according to the scheme of Tota and Elderfield (220)

R	R′	R″	PYRAZINE
CH_3	CH_3	H	2,3-Dimethyl-5-hydroxypyrazine
C_6H_5	CH_3	H	2-Phenyl-3-methyl-5-hydroxypyrazine
C_6H_5	CH_3	CH_3CH_2	2-Phenyl-3-methyl-6-ethyl-5-hydroxypyrazine
CH_3	$CH_2CH_2OC_2H_5$	H	2-Methyl-3(β-ethoxyethyl)-5-hydroxypyrazine

A more effective method might be to hydrolyze aminoacetal, which may be prepared either from chloroacetal and ammonia (235, 240) or by the reduction of nitroacetal (143). Woodward and Doering (249) improved the former procedure and were able to obtain 72.5 per cent of aminoacetal in addition to 10 per cent of diacetalylamine.

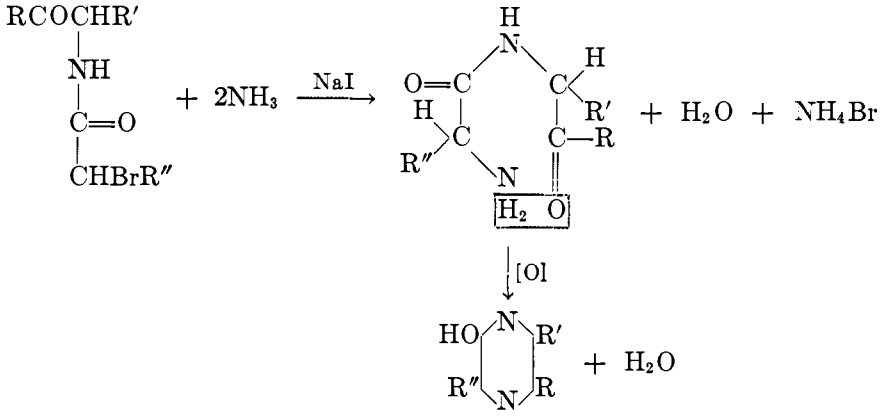
Tota and Elderfield (220) have recently reported a general synthesis for 2,3-disubstituted or 2,3,6-trisubstituted 5-hydroxypyrazines (see table 3).

The hydrochloride of a primary α-amino ketone is first treated with a bromoacyl bromide. The more reactive acyl halogen attacks the amino group to form the amide derivative:



R,R′ = alkyl or aryl; R″ = H or alkyl.

The second bromine atom is then replaced with an amino group by ammonia in the presence of sodium iodide. The resultant molecule then cyclizes by the elimination of water to form a dihydropyrazine, which is oxidized by atmospheric oxygen to the pyrazine:



3. Reduction of amino acids

Neuberg (161) reduced the hydrochlorides of the ethyl esters of glycine and alanine to the salts of the corresponding aminocarbonyls with sodium amalgam in acid medium. Subsequent treatment with excess alkali and mercuric chloride yielded fair amounts of pyrazine and 2,5-dimethylpyrazine.

4. Oxidation of amino alcohols

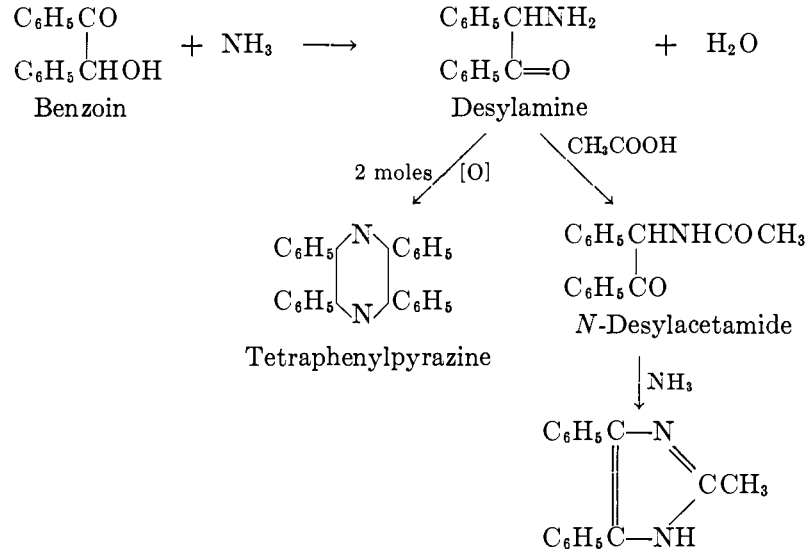
Aston and his collaborators used this approach for the synthesis of pyrazine (6). Ethanolamine was passed over a copper catalyst at 300°C. to effect dehydrogenation. The aminoacetaldehyde produced cyclized to dihydropyrazine, which underwent oxidation to pyrazine. The best yield of several experiments was 5.6 per cent, most of the aminoacetaldehyde being consumed by side reactions to form resins. The latter further interfered by inactivating the catalyst.

5. Replacement of the hydroxyl in a hydroxycarbonyl with an amino group

This method was first applied by Erdmann (74) for the synthesis of tetraphenylpyrazine by the action of ammonia on benzoin in a sealed tube at elevated temperatures. Japp and Wilson (114) reported a 55 per cent yield with fused ammonium acetate.

Davidson, Weiss, and Jelling (58) simply refluxed benzoin and ammonium acetate in glacial acetic acid. In addition to 20–30 per cent of tetraphenylpyrazine, they obtained equivalent quantities of 2-methyl-4,5-diphenylgly-

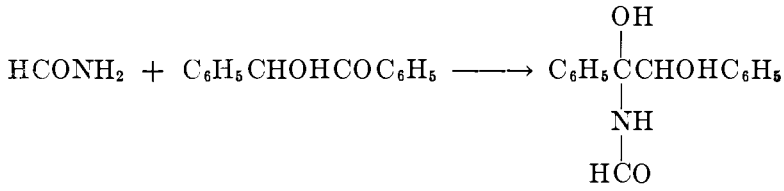
oxaline. To account for these facts, they proposed the intermediate formation of desylamine:



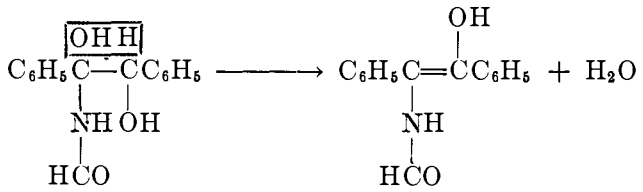
In support of this mechanism, they demonstrated that replacing benzoin by an equivalent quantity of desylamine hydrochloride gave identical results. Furthermore, although the substitution of propionic acid for acetic acid did not influence the yield of tetraphenylpyrazine, it did lead to the formation of a different imidazole: 2-ethyl-4,5-diphenylglyoxaline. However, when formic acid was the solvent, no pyrazines could be detected.

Leuckart (137) had reported that by heating a mixture of ammonium formate and benzoin at 230°C. (quite different conditions from Davidson's) he obtained quantitative conversions to tetraphenylpyrazine.

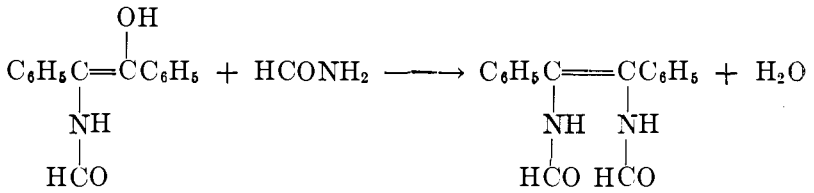
Ingersoll *et al.* (108) had shown that formamide was the active agent in the formation of primary amines from ketones heated with ammonium formate. However, when Novelli (162) attempted to apply this result to the Leuckart reaction, by heating formamide with benzoin or its derivatives, he could only obtain about 10 per cent of the tetraarylpyrazines. In contrast, this reaction simultaneously produced about 80 per cent of glyoxalines. The following mechanism was suggested. First, there occurs the formation of an unstable addition compound:



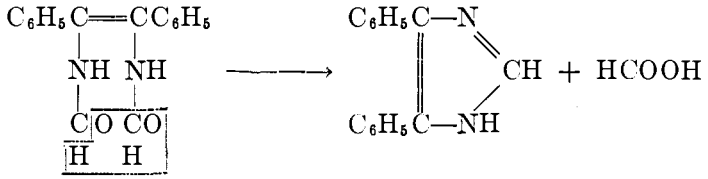
followed by loss of water:



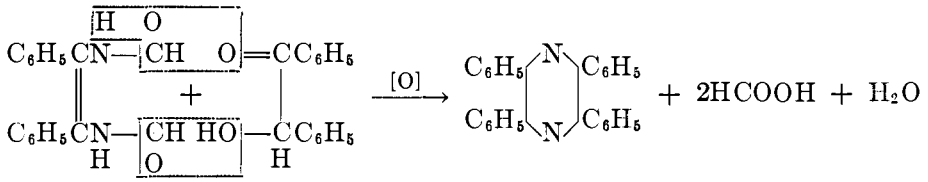
The product reacts with another mole of formamide:



4,5-Diphenylglyoxaline (80 per cent) then results by the elimination of formic acid:



Pyrazines are formed (10 per cent) by condensation with a mole of unchanged benzoin.



It is now interesting to speculate why Davidson and his students found no pyrazines when operating in formic acid. There is little doubt that under their experimental conditions very little formamide would be formed, thus invalidating Novelli's hypothesis. On the other hand, the fact that 4,5-diphenylglyoxaline was obtained would indicate the presence of the intermediate desylamine, in accordance with their mechanism. However, it would also be anticipated that some autocondensation would take place to yield tetraphenylpyrazine. Since this was not observed, it is reasonable to assume that the reaction of formic acid with desylamine to form *N*-desylformamide, the glyoxaline intermediate, occurs more readily than the autocondensation of desylamine. A study of the kinetics of these reactions should be of aid in resolving these issues.

We must further examine the reason for Leuckart's quantitative yields of tetraphenylpyrazine, when Novelli, presumably employing the intermediate formamide, could get only 10 per cent. This apparent discrepancy becomes clear when it is remembered that Leuckart conducted his experiment at a temperature of 230°C., when any formamide resulting from the ammonium formate would have dissociated to yield ammonia. Thus, Novelli's, Davidson's, and Leuckart's conditions are not at all comparable, and the mechanism for each is apparently different.

TABLE 4

Pyrazines prepared by the replacement of the hydroxyl in a hydroxycarbonyl with an amino group

REACTANTS	PYRAZINE DERIVATIVE	REFERENCES
Benzoin	Tetraphenylpyrazine	(58, 74, 114, 134, 137, 162, 189, 202, 203, 204, 209)
Anisoin	Tetra-*p*-methoxyphenylpyrazine	(162)
Benzanisoin	Diphenyl-di-*p*-methoxyphenylpyrazine	(162)
p-Toluoin	Tetra-*p*-tolylpyrazine	(162)
β-Hydroxylevulinic acid	Tetramethylpyrazine	(237)
Fructose	Fructosazine	(141, 142)
Glucose	Fructosazine	(141, 142)
α-Keto-β-acetyl(or benzoyl)anilino-α,β-diphenylethane	Tetraphenylpyrazine	(79)
Benzil, benzylamine	Tetraphenylpyrazine	(111)

In table 4 we have listed not only those pyrazines whose preparation directly involves the replacement of the hydroxyl in a hydroxycarbonyl compound with an amino group, but also those for which this mechanism operates only indirectly. Thus, when benzil is treated with benzylamine under the influence of zinc chloride, tetraphenylpyrazine is obtained as a result of the intermediate formation of benzoin and ammonia.

6. Treatment of the bisulfite compounds of oximino ketones with potassium cyanide

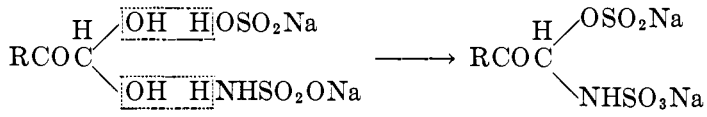
This synthesis was originated by Gastaldi (90). When an oximino ketone is treated with a strong solution of sodium bisulfite saturated with sulfur dioxide,

there are apparently formed the short-lived intermediates, sulfamic acid and a hydrated glyoxal:

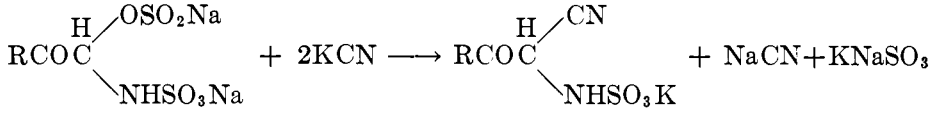
$$RCOCH{=}NOH + H_2SO_3 + H_2O \rightarrow RCOCH(OH)_2 + H_2NSO_3H$$

R = aryl or alkyl (specifically phenyl or methyl).

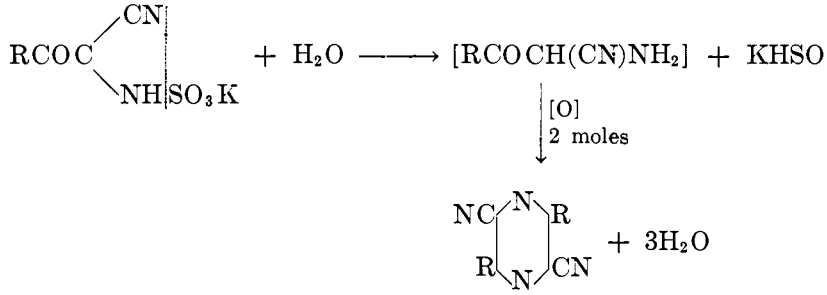
The hydrated glyoxal immediately reacts with the bisulfite and sulfamic acid (or sodium sulfamate) present, yielding a sulfite sulfamate:



Addition of a strong aqueous solution of potassium cyanide results in the replacement of the sulfite group with a cyano group:



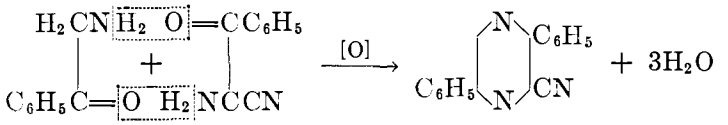
Hydrolytic cleavage at the nitrogen-sulfur bond of the cyano sulfamate yields potassium acid sulfate and the cyanoamino ketone. Finally, the latter cyclizes and undergoes oxidation to the pyrazine:



It should be noted that Gastaldi states that potassium acid sulfite results from the nitrogen-sulfur cleavage. This clearly cannot be the case if the process is only hydrolysis, as it undoubtedly is. He makes a somewhat similar statement concerning the hydrolysis of sodium sulfamate, maintaining that the products are ammonia and sodium bisulfite. Actually, they are ammonia and sodium bisulfate.

In this manner, 2,5-dimethyl-3,6-dicyanopyrazine and 2,5-diphenyl-3,6-dicyanopyrazine were synthesized. In the latter preparation some 2,5-diphenyl-3-cyanopyrazine was also isolated. This is explained by the formation of some ω-aminoacetophenone, possibly by reduction of the starting oximino compound

with sulfite. This can then condense with the more normal cyanoamino ketone present in the reaction mixture:

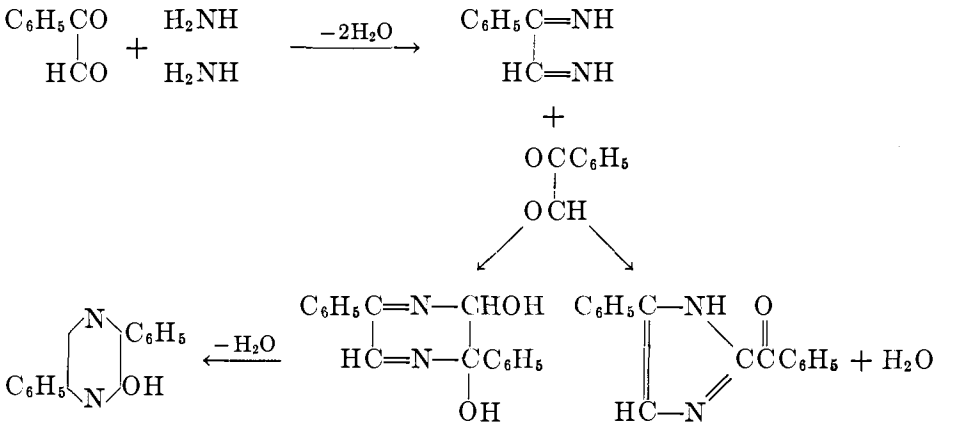


The formation of some 2,5-diphenylpyrazine by the condensation of 2 moles of ω-aminoacetophenone might also be anticipated. This was probably not detected because of the extremely limited quantity in which it would be formed.

7. Replacement of one carbonyl group in a dicarbonyl compound with an amino group

The reaction between phenylglyoxal and ammonia was first studied by Müller and von Pechmann (156), and later was more thoroughly investigated by Pinner (175). He pointed out that one of the products isolated by the earlier workers was 2,5-diphenyl-3-hydroxypyrazine and showed that benzoylphenylglyoxaline was produced as well.

According to Pinner an intermediate diimine was first produced, which then condensed with some of the diketone present in one of two ways:



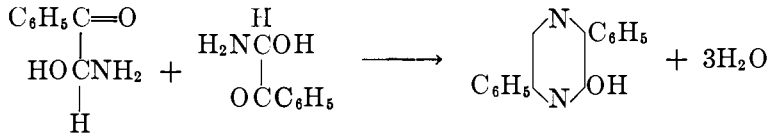
However, if this mechanism be true it is difficult to see why some 2,6-diphenyl-3-hydroxypyrazine should not form by the alternative condensation:

Furthermore, it was never possible to isolate any such intermediate diimine.

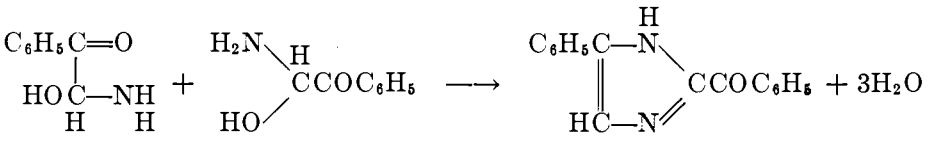
It would seem at least equally, if not more, probable that an aldehyde ammonia would first form:

$$C_6H_5COCHO + NH_3 \rightarrow C_6H_5COCHOHNH_2$$

followed by autocondensation and dehydration:



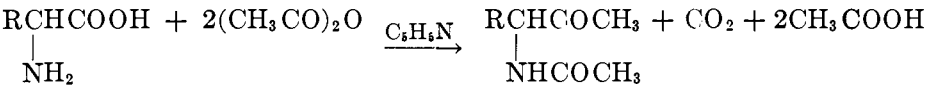
Glyoxaline formation may be accounted for as follows:



For completeness, we mention another reaction that may possibly fall in this category: that between benzil and potassium amide in the presence of ammonium chloride, from which traces of tetraphenylpyrazine have been isolated (136).

8. The action of acetic anhydride and pyridine on amino acids

When an α-primary amino acid containing an unsubstituted hydrogen on the α-carbon is treated with acetic anhydride in the presence of pyridine, an acetylaminoacetone is formed (54, 138):



R = hydrogen, alkyl, or aryl.

Upon hydrolysis of the acetylaminoacetone and subsequent treatment with mercuric chloride in excess alkali, the pyrazine results:

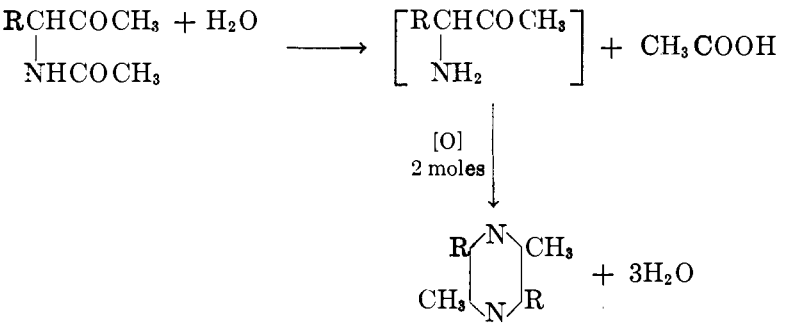


TABLE 5

Pyrazines prepared by the action of acetic anhydride and pyridine on amino acids

AMINO ACID	PYRAZINE DERIVATIVE	REFERENCES
Glycine	2,5-Dimethylpyrazine	(54)
Hippuric acid	2,5-Dimethylpyrazine	(54)
Aspartic acid	Tetramethylpyrazine	(54)
Glutamic acid	2,5-Dimethylpyrazine-3,6-dipropionic acid	(54)
Phenylalanine	2,5-Dibenzyl-3,6-dimethylpyrazine	(54, 138)
Tyrosine	2,5-*p*-Dihydroxybenzyl-3,6-dimethylpyrazine	(54, 138)
Phenylaminoacetic acid	2,5-Diphenyl-3,6-dimethylpyrazine	(138)

9. *Rearrangement of certain oximes*

In the course of their researches on the Beckmann rearrangement, Neber and his associates (157, 158, 159, 160) discovered an interesting rearrangement of oximes (see table 6), that resulted in the formation of amino ketones.

TABLE 6

Pyrazines and dihydropyrazines prepared by the rearrangement of certain oximes

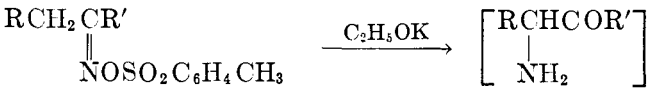
OXIME	PYRAZINE DERIVATIVE	REFERENCES
Bibenzyl ketoxime	2,5-Diphenyl-3,6-dibenzyldihydropyrazine	(160)
Benzylacetone oxime	3,6-Dibenzyl-2,5-dimethyl-3,6-dihydropyrazine	(160)
o-Nitrobenzyl methyl ketoxime	2,5-Dimethyl-3,6-di-(*o*-nitrophenyl)-dihydropyrazine	(159)
Benzyl methyl ketoxime	2,5-Dimethyl-3,6-diphenylpyrazine	(159)
Acetoacetanilide oxime	2,5-Dimethyl-3,6-(dicarboxanilide)-dihydropyrazine	(157)
2,4-Dinitrobenzyl methyl ketoxime	2,5-Dimethyl-3,6-di(2,4-dinitrophenyl)-dihydropyrazine	(158)

The oxime is first converted into the *p*-toluenesulfonic ester.

$$RCH_2CR' + CH_3C_6H_4SO_2Cl \longrightarrow \underset{\underset{NOSO_2C_6H_4CH_3}{\|}}{RCH_2CR'} + HCl$$
$$\underset{\underset{NOH}{\|}}{}$$

R,R' = aryl or alkyl.

Upon saponification with potassium ethoxide, rearrangement occurs with the formation of the amino ketone:

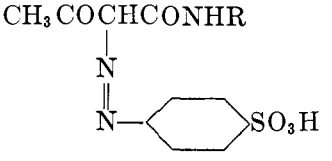


In most cases the amino ketones condense without further treatment into the dihydropyrazines. Although these may be oxidized to the pyrazines, this step was not carried out.

The method is claimed to be quite superior for the preparation of certain amino ketones, but there have been a number of instances where it has met with failure. Thus, negative results were reported with 3,4-dihydroxy-, 3,4-diacetoxy-, 3,4-dibenzoyloxy-, and 3,4-dimethoxyacetophenone oximes. In other cases certain modifications were found necessary. For example, the oxime of ethyl acetoacetate gave rise to methylisoxazolone, but the desired product was obtained when the anilide rather than the ester was used.

10. Reduction of diazoacetoacetanilides

Fierz-David and Ziegler (83) discovered this reaction during an investigation of certain dyestuffs. They prepared acetoacetanilides from ethyl acetoacetate and various aromatic amines. When coupled with diazotized sulfanilic acid, dyes of the form



R = aryl.

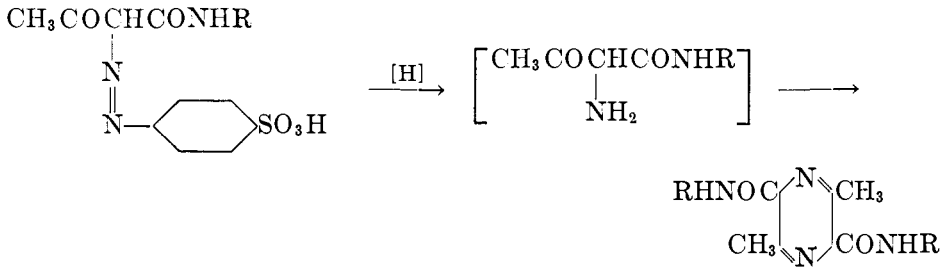
were obtained.

After reduction with stannous chloride in hydrochloric acid, the azo bond cleaved to yield the corresponding anilides of aminoacetoacetic acid. As usual, cyclization to the dihydropyrazines took place when the free bases were released with excess alkali (see table 7).

TABLE 7

Dihydropyrazines resulting from the reduction of diazoacetoanilides (83)

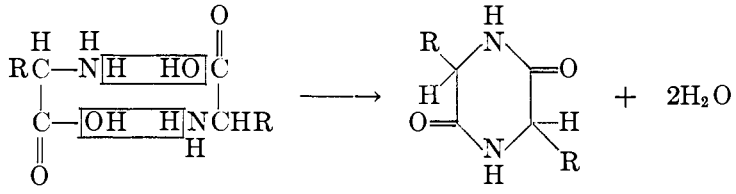
ANILIDE	DIHYDROPYRAZINE
Anilide	2,5-Dimethyl-3,6-dihydropyrazine-3,6-dicarboxanilide
o-Toluide	2,5-Dimethyl-3,6-dihydropyrazine-3,6-*o*-toluide
p-Toluide	2,5-Dimethyl-3,6-dihydropyrazine-3,6-*p*-toluide
m-Xylide	2,5-Dimethyl-3,6-dihydropyrazine-3,6-*m*-xylide
o-Anisidide	2,5-Dimethyl-3,6-dihydropyrazine-3,6-*o*-anisidide
o-Chloroanilide	2,5-Dimethyl-3,6-dihydropyrazine-3,6-*o*-chloroanilide
2,5-Dichloroanilide	2,5-Dimethyl-3,6-dihydropyrazine-3,6-2,5-dichloroanilide



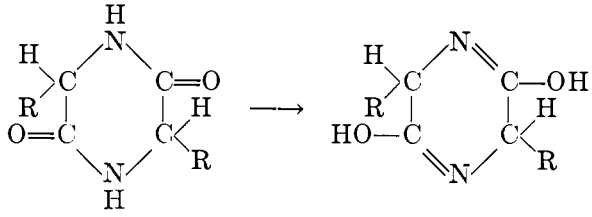
These workers did not attempt to oxidize the dihydropyrazines to the pyrazines.

11. Enolization of diketopiperazines

Although the diketopiperazines (or dipeptide anhydrides) which may be formed by the condensation of 2 moles of amino acid (generally as the ester)

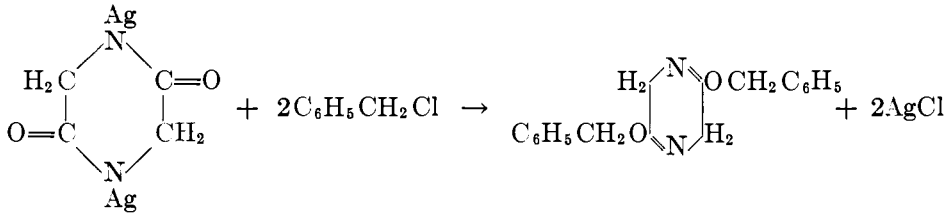


are not directly within our scope, they nevertheless enter the discussion, since it was observed that they may be made to enolize into the dihydropyrazines:



Other enolization products are possible, but experimental evidence favors this particular species. The investigators have not reported any attempts to oxidize these compounds to the pyrazine derivatives.

Two methods have been used to induce enolization. Karrer and his coworkers (120, 121) refluxed the silver salt of glycine anhydride with benzyl chloride to obtain 2,5-dibenzyloxydihydropyrazine.



When *p*-carbethoxybenzyl chloride was employed as the halide, the corresponding 2,5-di(*p*-carbethoxy)benzyloxydihydropyrazine resulted (121).

Abderhalden and his associates (1, 2) simply refluxed the diketopiperazines with aniline and then removed the aniline with ether. They reported successful conversions for the anhydrides of glycine, alanine, sarcosine, and leucylglycine. In one instance (alanine), they were able to form the dihydropyrazine directly, by heating the amino acid ester with aniline.

12. Miscellaneous

We have included in this category a number of assorted reactions which apparently depend upon the intermediate formation of α-primary aminocarbonyl

TABLE 8

Miscellaneous methods for preparing pyrazines

REACTANTS	CONDITIONS	PRODUCTS	REFERENCES
α,β-Dichlorostyrene and ammonia	Elevated temperature and pressure	2,5-Diphenylpyrazine	(130)
α-Methyl-α,β-dichlorostyrene and ammonia	Elevated temperature and pressure	2,5-*p*-Ditolylpyrazine	(130)
Dypnone ($C_6H_5(CH_3)C{=}CHCOC_6H_5$) and hydroxylamine	Large excess of hydroxylamine at room temperature for several days	2,5-Diphenylpyrazine	(102)
α-(4-Morpholinyl)propiophenone and ammonium carbonate	105°C.; 15 hr. under pressure	2,5-Dimethyl-3,6-diphenylpyrazine	(45)

compounds. In many cases the production of these substances is unexpected. Without experimental verification it would be pointless to attempt any detailed interpretation of the chemistry involved. Therefore, we present only the salient information as embodied in table 8.

B. AUTOCONDENSATION OF α-HYDROXYIMINES

When Minovici (153) treated mandelonitrile with dry hydrogen chloride in anhydrous ether, he obtained a yellow crystalline substance which Japp and his associates (112, 113) proved to be 3-keto-2,5-diphenyl-3,4-dihydropyrazine (or its tautomer, 2,5-diphenyl-3-hydroxypyrazine). Ingham (109) studied the reaction more closely and provided the following scheme for its mechanism.

As would be expected from the conditions an iminochloride first forms:

$$HCl + RCH(OH)CN \xrightarrow{\text{ether}} RCH(OH)CCl{=}NH$$

Cyclization then occurs by the loss of two molecules of water:

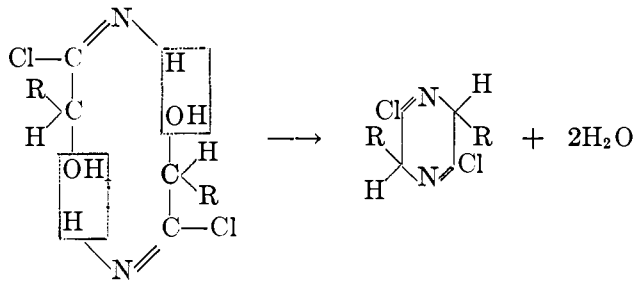
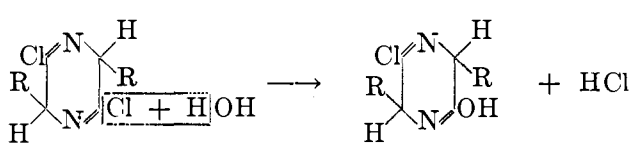


TABLE 9

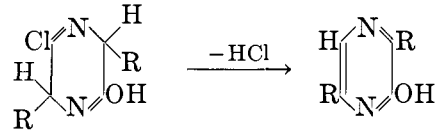
Pyrazines prepared by the autocondensation of α-hydroxyimines

REACTANTS	PYRAZINE DERIVATIVE	REFERENCES
Mandelonitrile and α-naphthylmagnesium bromide	2,5-Diphenyl-3,6-di-α-naphthylpyrazine	(150)
Benzoin oxime and hydrogen	Tetraphenylpyrazine	(229)
Mandelonitrile	3-Keto-2,5-diphenyl-3,4-dihydropyrazine	(112, 113, 153)
Anisaldehyde cyanohydrin	3-Keto-2,5-di-*p*-methoxyphenyl-3,4-dihydropyrazine	(148)
Cinnamaldehyde cyanohydrin	3-Keto-2,5-distyryl-3,4-dihydropyrazine	(148)
m-Nitrobenzaldehyde cyanohydrin	3-Keto-2,5-di-*m*-nitrophenyl-3,4-dihydropyrazine	(109)
p-Nitrobenzaldehyde cyanohydrin	3-Keto-2,5-di-*p*-nitrophenyl-3,4-dihydropyrazine	(109)

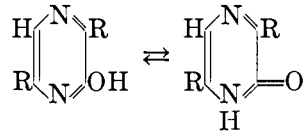
Interaction with one molecule of water leads to the elimination of a molecule of hydrogen chloride:



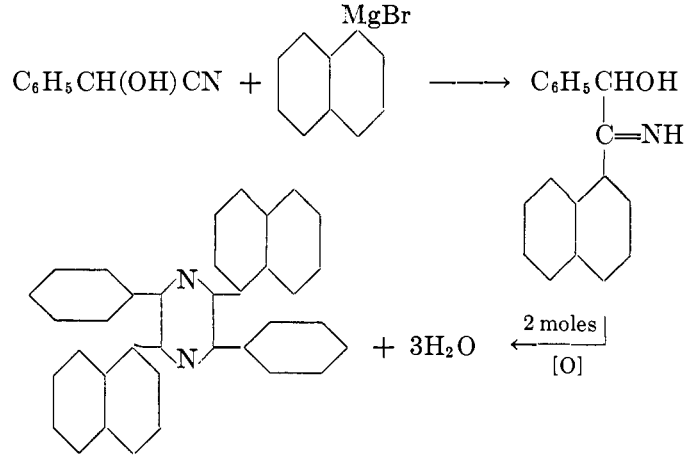
Finally, another mole of hydrogen chloride is lost to yield the product:



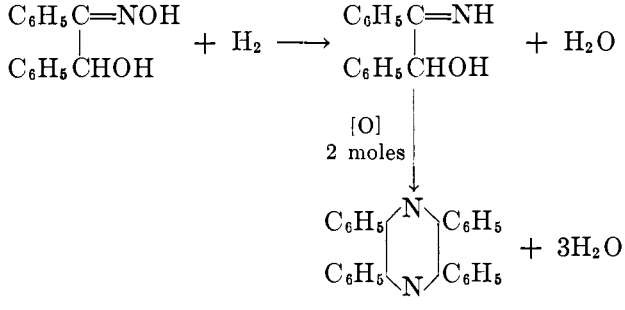
The hydroxypyrazine is a tautomer of the keto dihydropyrazine, as Japp and Knox (112) have shown:



McKenzie and Kelman (150) modified the procedure by treating the aldehyde cyanohydrin with the Grignard reagent instead of hydrogen chloride. They thus prepared 2,5-diphenyl-3,6-di[α-naphthyl]pyrazine from mandelonitrile and α-naphthylmagnesium bromide.



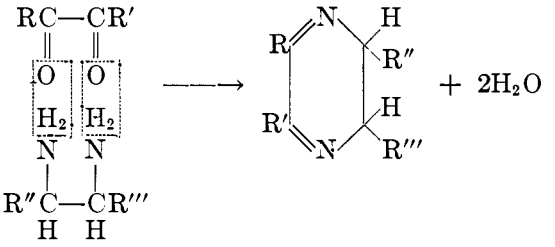
A similar cyclization mechanism is ostensibly in operation in the hydrogenation of benzoin oxime (229):



C. CONDENSATION OF α,β-DIAMINES WITH α,β-DICARBONYLS

1. The direct formation of pyrazines

This method of forming the pyrazine ring has proved of wide utility. The general procedure is to react the dicarbonyl with the diamine in a mutual solvent.



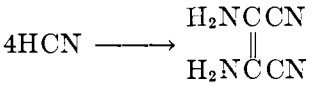
R,R',R'',R''' = aryl, alkyl, or hydrogen.

The resulting 2,3-dihydropyrazines may be isolated, or oxidized directly to the pyrazines (see table 10).

If R and R' are aryl, the reaction proceeds smoothly and the yields are uniformly good. Again, difficulties are encountered (15) when attempts are made to prepare the first member of the series by the condensation of glyoxal with ethylenediamine (118). Apparently with those low-molecular-weight substances, the conditions as ordinarily employed favor the formation of polymers, e.g.:

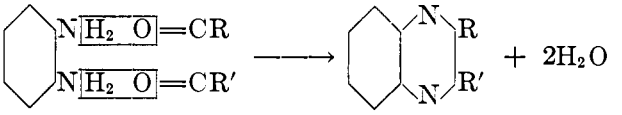
$$=NCH_2CH_2N=CHCH=NCH_2-$$

A novel method for the preparation of 2,3-dicyanopyrazines depends on the use of the tetramer of hydrogen cyanide, diaminomaleonitrile, as the diamine (96, 140):



2. The oxidation of quinoxaline or its derivatives

The value of the method may be extended by means of quinoxaline and its derivatives prepared by the condensation of *o*-phenylenediamine with various dicarbonyl compounds.



These compounds are important, since they may be easily oxidized with dilute alkaline permanganate to pyrazinedicarboxylic acids in good yields (see table 11):

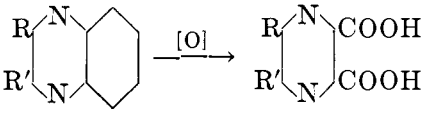


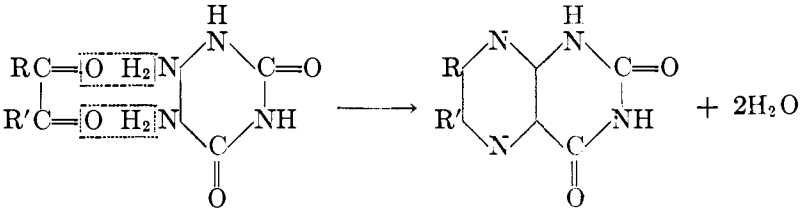
TABLE 10

Pyrazines prepared by the condensation α,β-diamines with α,β-dicarbonyls

REACTANTS	PYRAZINE DERIVATIVE	REFERENCES
Diaminomaleonitrile and glyoxal	2,3-Dicyanopyrazine	(96, 140)
Diaminomaleonitrile, glyoxal, and hot water	6-Hydroxy-2,3-dicyanopyrazine	(104)
Diacetyl and ethylenediamine	2,3-Dimethylpyrazine	(118)
Benzil and ethylenediamine	2,3-Diphenylpyrazine; also some tetraphenylpyrazine	(5, 145, 146, 147)
Benzil and propylenediamine	2,3-Diphenyl-5-methylpyrazine	(145, 146, 147)
Anisil and ethylenediamine	2,3-Dimethoxyphenylpyrazine; also some tetra[dimethoxyphenylpyrazine]	(146, 147)
Methyl propyl diketone and ethylenediamine	2-Methyl-3-propylpyrazine	(31)
Stilbenediamine and benzil	Tetraphenylpyrazine	(81)
Diaminomaleonitrile and diacetyl	5,6-Dimethyl-2,3-dicyanopyrazine	(96, 140)
Diaminomaleonitrile and benzil	5,6-Diphenyl-2,3-dicyanopyrazine	(96, 140)
Phenylethylenediamine and benzil	2,3,5-Triphenylpyrazine	(81)
α-Dicyanodibenzyl diketone and ethylenediamine	2,3-Di[α-cyanobenzyl]-5,6-dihydropyrazine	(67)
3-Chlorotrimethylene-1,2-diamine dihydrochloride and benzil	5,6-Diphenyl-2-chloromethyl-2,3-dihydropyrazine	(174)
1,2-Diaminocyclobutane and benzil	Tetraphenylpyrazine	(33)

3. The cleavages of lumazines

As a further application of this general reaction we may consider the formation of lumazines by the reaction of 4,5-diaminouracil with various dicarbonyl compounds:



R, R′ = alkyl, aryl, or hydrogen.

Weijlard, Tishler, and Erickson (227) found that these derivatives could be split with rupture of the pyrimidine nucleus, the pyrazine nucleus remaining intact (see table 12).

Alkaline cleavage led to the formation of 2-amino-3-pyrazinoic acid derivatives:

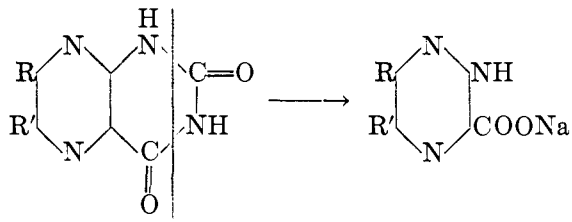
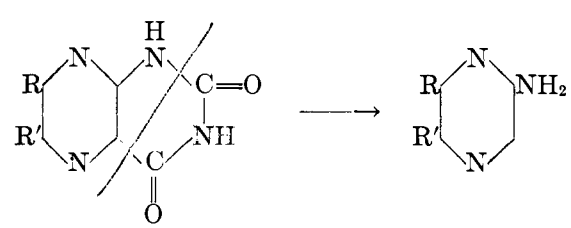


TABLE 11

Pyrazinecarboxylic acids prepared by the oxidation of quinoxalines

QUINOXALINE	PYRAZINE ACID	REFERENCES
Quinoxaline	2,3-Pyrazinedicarboxylic acid	(20, 21, 60, 73, 89, 116, 117)
α,β-Diphenyl-1,2-naphthoquinoxaline (or its quinone)	2,3-Diphenyl-5-carboxypyrazine-6-*o*-benzoic acid	(46)
β-Phenyl-1,2-naphthoquinoxaline-3,4-quinone	Pyrazine-3-phenyl-5-carboxy-6-*o*-benzoic acid	(48)
Naphtho-1,2-quinoxalyl-β-acetic acid	6-Carboxy-5-(*o*-carboxyphenyl)-2-pyrazineacetic acid	(47)
2-Methylquinoxaline	5-Methyl-2,3-pyrazinedicarboxylic acid	(22, 135)
2,3-Dimethylquinoxaline	5,6-Dimethylpyrazinedicarboxylic acid	(89)
2-Ethoxymethylquinoxaline	Pyrazinetricarboxylic acid	(23)
2,3-Quinoxalinedicarboxylic acid anhydride	Pyrazinetetracarboxylic acid	(37)

With sulfuric acid, on the other hand, further decarboxylation occurred, resulting in aminopyrazines:



D. THE ACTION OF AMMONIA OR ITS SALTS ON POLYHYDROXY COMPOUNDS

Etard (78) and Stoehr (202) discovered independently that 2,5-dimethylpyrazine (together with much smaller quantities of 2,5-dimethyl-3-ethylpyrazine) could be obtained by distilling glycerol with a mixture of ammonium chloride and ammonium phosphate. If only ammonium phosphate was used the distillate was found to consist primarily of pyridines, predominantly β-picoline.

The postulated mechanism for both cases involves the intermediate formation of acrolein:

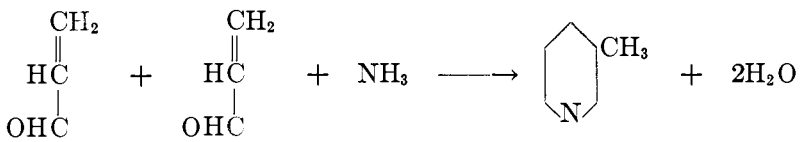
$$CH_2OHCHOHCH_2OH \rightarrow CH_2{=}CHCHO + 2H_2O$$

TABLE 12

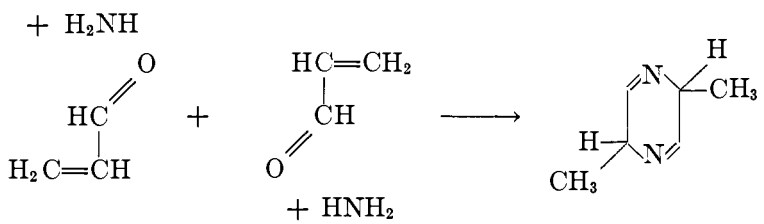
Pyrazine derivatives prepared by Weijlard, Tishler, and Erickson (227)

R	R'	CLEAVAGE MEDIUM	PRODUCT
H	H	NaOH	2-Amino-3-pyrazinoic acid (2-hydroxy-3-pyrazinoic acid under more stringent conditions)
CH_3	H	NaOH	2-Amino-6-methyl-3-pyrazinoic acid
C_6H_5	C_6H_5	NaOH	2-Amino-5,6-diphenyl-3-pyrazinoic acid
CH_3	CH_3	NaOH	2-Amino-5,6-dimethyl-3-pyrazinoic acid
H	H	H_2SO_4	Aminopyrazine
CH_3	H	H_2SO_4	2-Amino-6-methylpyrazine
C_6H_5	C_6H_5	H_2SO_4	2-Amino-5,6-diphenylpyrazine
CH_3	CH_3	H_2SO_4	2-Amino-5,6-dimethylpyrazine
C_6H_5	H	H_2SO_4	2-Amino-5(or 6)phenylpyrazine

Two molecules of acrolein may combine with one of ammonia to form β-picoline:



On the other hand, if 2 molecules of acrolein combine with 2 molecules of ammonia, pyrazines result:



The 2,5-dimethyl-2,5-dihydropyrazine is further oxidized under the reaction conditions to yield finally 2,5-dimethylpyrazine. A possible explanation for the occurrence of 2,5-dimethyl-3-ethylpyrazine may be found in Stoehr's observation that the addition of acetaldehyde increases the yield of this compound (209).

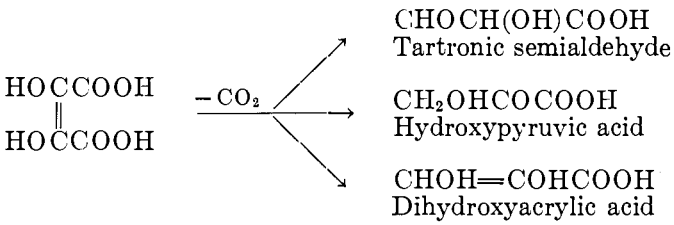
Baeyer (10) has obtained β-picoline from the dry distillation of acrolein ammonia; however, support of the mechanism for the production of dimethylpyrazine is lacking.

The yield of dimethylpyrazine is poor (5–10 per cent). Attempts to improve it by variation of conditions and the use of catalysts such as charcoal and copper sulfate have not been substantially effective (12, 62, 78, 97, 98, 129, 202, 203, 204).

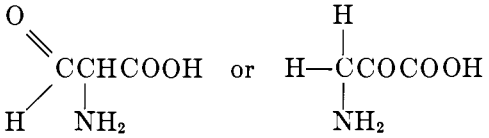
The method has been modified by employing polyhydroxy compounds other than glycerol. Dori and Mohring (65) have patented a procedure requiring the treatment of sucrose with ammonia or ammonium salts at 200°C. and 50 atm. in the presence of a sulfite, bisulfite, animal charcoal, or a copper sulfate catalyst. The process was claimed to yield "basic mixtures including pyrazines."

A similar reaction appears to be that of ammonium hydroxide and glucose at 100°C. (25, 215, 217). Amongst the products identified were pyrazine, methylpyrazine, and 2,6-dimethylpyrazine. Since pyrazines other than 2,5-dimethylpyrazine were obtained, it would seem to indicate that mechanisms other than that postulated for glycerol might also be involved.

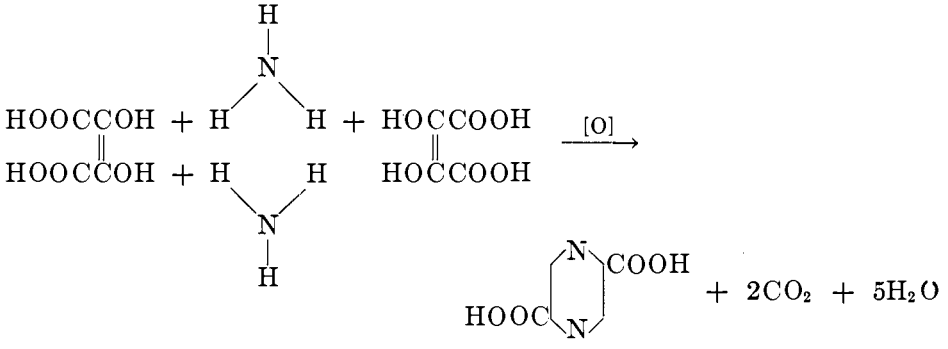
Fenton (82) discovered that when ammonium dihydroxymaleate was allowed to remain in contact with aqueous ammonia at 50–60°C. for half an hour, 2,5-pyrazinedicarboxylic acid was formed. He pointed out that there were several routes by which such a change could take place. Thus, by the loss of carbon dioxide, dihydroxymaleic acid may give one of several products:



Condensation of any of these with ammonia could lead to an α-primary aminocarbonyl carboxylic acid such as



Cyclization and oxidation would then yield the 2,5-pyrazinedicarboxylic acid. Fenton indicates another possibility in the formation of a tetracarboxylic acid which could give the product by oxidation and loss of carbon dioxide:



This, however, seems more remote, since we know that the pyrazinecarboxylic acids require much more drastic conditions than those present in order to undergo decarboxylation.

It is noteworthy that when the esters were used instead of the free acids, oxamide was formed with no traces of any pyrazines.

E. CERTAIN REACTIONS OF THE PHENACYLBENZYLAMINES

Mason and his students (147) carried out a series of studies on the preparation and properties of the phenacylbenzylamines, which led to the synthesis of a number of pyrazine derivatives.

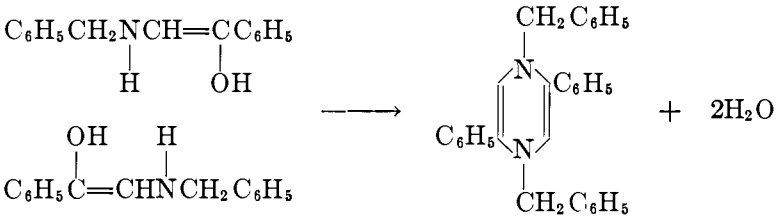
The mono- and diphenacylamines may be prepared by heating a mixture of benzylamine and ω-bromoacetophenone:

$$2C_6H_5CH_2NH_2 + 3C_6H_5COCH_2Br \longrightarrow$$

$$C_6H_5COCH_2NHCH_2C_6H_5 \cdot HBr + (C_6H_5COCH_2)_2NCH_2C_6H_5 \cdot HBr + HBr$$

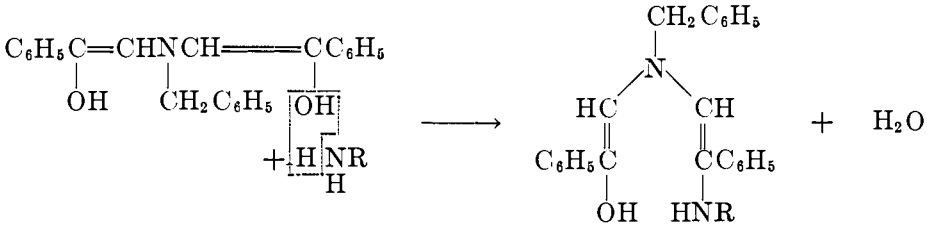
Monophenacylbenzylamine — Diphenacylbenzylamine

When monophenacylbenzylamine hydrobromide is treated with potassium hydroxide at 100°C., 1,4-dibenzyl-2,5-diphenylpyrazine dihydride is formed:



Boiling this product causes debenzylation, resulting in 2,5-diphenylpyrazine and 2 molecules of toluene.

The formation of pyrazine from diphenacylbenzylamine occurs in a somewhat different manner. The latter in its enolic form may react with an amine:

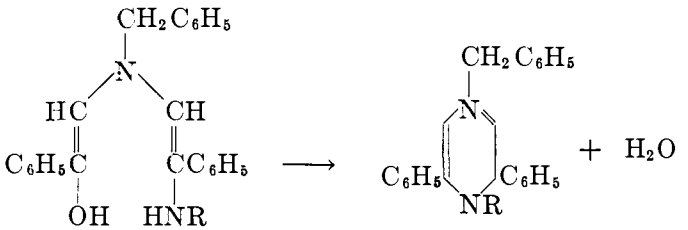


R = aryl or hydrogen.

Aminodiphenacylbenzylamine

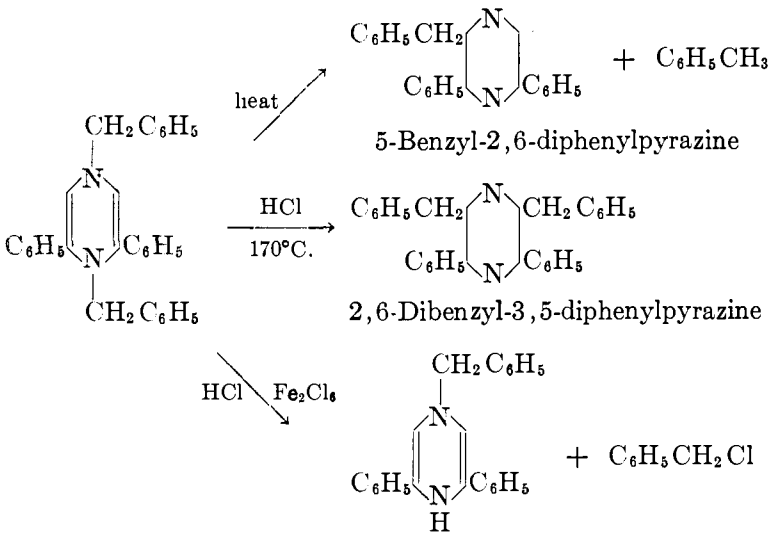
Such an intermediate was actually isolated when the amine reagent was cold ammonia (R = H).

With heat, another molecule of water is eliminated, effecting cyclization:



Compounds thus prepared were 1-benzyl-3,4,5-triphenyldihydropyrazine (R = phenyl); 1,4-dibenzyl-3,5-diphenyldihydropyrazine (R = benzyl); and 1-benzyl-3,5-diphenyldihydropyrazine (R = H). 1-Benzyl-3,5-diphenyldihydropyrazine may be converted by heat to 3,5-diphenylpyrazine with the loss of a molecule of toluene (see, also, reference 172).

Depending on the reagent, 1,4-dibenzyl-3,5-diphenyldihydropyrazine may undergo debenzylation and/or rearrangement:



5-Benzyl-2,6-diphenylpyrazine

2,6-Dibenzyl-3,5-diphenylpyrazine

1-Benzyl-3,5-diphenyldihydropyrazine

F. THE ACTION OF HYDRAZINE OR HYDROXYLAMINE ON DIHYDROXYMORPHOLINE

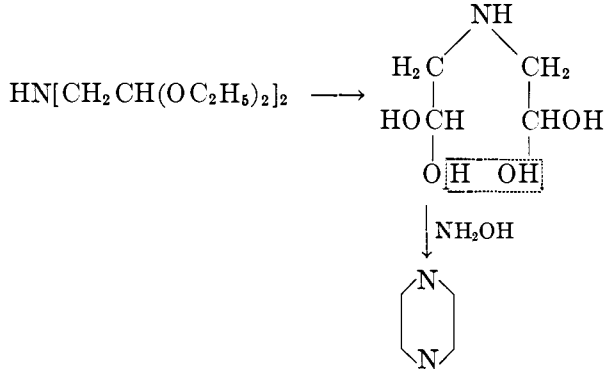
Wolff and Marburg (247) discovered that the heterocyclic oxygen atom in a morpholine could be replaced with nitrogen, thus affording a means of transition to the pyrazine series.

They first prepared diacetalylamine by heating chloroacetal with ammonia in a sealed tube:

$$2ClCH_2CH(OC_2H_5)_2 + NH_3 \rightarrow HN[CH_2CH(OC_2H_5)_2]_2 + 2HCl$$

Conversion to pyrazine was then accomplished by heating this substance with the hydrochloride of either hydrazine or hydroxylamine under pressure.

The dihydroxymorpholine which is formed (and which may be isolated) is thereby transformed into pyrazine:



Although inconvenient because of the long periods of heating in closed vessels in both steps, this method remains the best of the published pyrazine syntheses with regard to yield—78 per cent based on diacetalylamine (107).

G. THE OXIDATION OF PIPERAZINES

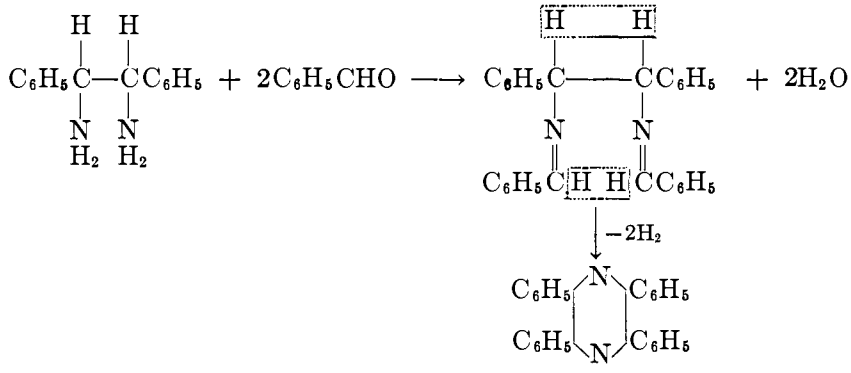
In order to oxidize piperazine to pyrazine, Stoehr (207) found it necessary to distill either the base or its hydrochloride over zinc dust. He attributed the oxidizing action of the zinc to the fact that it contained zinc oxide, and indeed found that the best results were obtained by using a mixture of zinc dust and lime. As might be expected the yields were very poor, not exceeding 10 per cent.

Recently, Dixon (64) obtained a patent based on the vapor-phase dehydrogenation of piperazine. The piperazine in the form of a dilute solution in benzene was passed in the vapor phase over copper chromite at 215–500°C. Yields of 35–40 per cent pyrazine were reported.

H. THE ACTION OF STILBENEDIAMINE ON BENZALDEHYDE

Grossman (95) showed that the primary product of the reaction between stilbenediamine and benzaldehyde is dibenzylidenestilbenediamine.

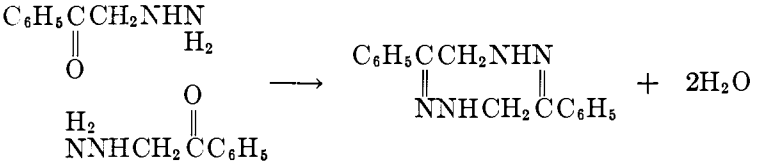
If the reaction is forced, dehydrogenation may occur, forming tetraphenylpyrazine:



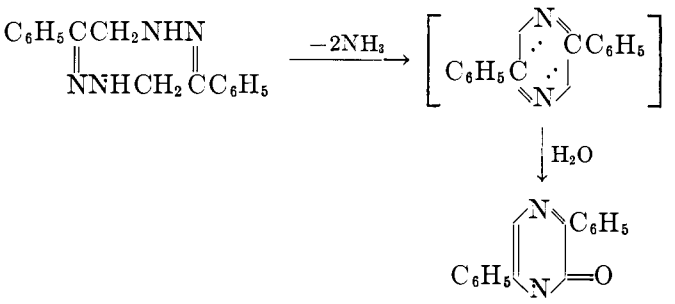
To obtain the final product from the initial reactants, it was found necessary to heat the mixture in ethanol at 180°C. for 10 hr. in a sealed tube.

I. THE CONDENSATION OF PHENACYLHYDRAZINES

Phenacylhydrazine apparently possesses the property of autocondensation, in a manner resembling that of the α-primary aminocarbonyl compounds, to form an eight-membered heterocycle (35).



This is followed by a spontaneous ring contraction with elimination of two molecules of ammonia and the addition of one of water:



p-Bromophenacylhydrazine after a similar course of reactions yields 2,5-di-*p*-bromophenyl-3-keto-3,4-dihydropyrazine.

J. BIOLOGICAL SYNTHESES

In the introduction we mentioned the condensed pyrazine derivative, riboflavin. There are also indications that the simple nucleus may take part in life processes. Scattered throughout the literature are a number of reports by various workers concerning the occurrence of such derivatives in the fusel oils resulting from the fermentation of various carbohydrate products. Table 13 presents a résumé of the data.

The exact mechanism for the production of these products is as yet unknown, but even disregarding possible degradations of riboflavin, the fact that they do occur should not occasion surprise. In the previous sections we have seen how many biologically important substances may serve in pyrazine syntheses. We may cite the action of ammonia on various polyhydroxy compounds such as glycerol and sugars, as well as the formation of pyrazines from amino acids.

In this connection we may recall an interesting experiment performed by Kikoji and Neuberg (122), in which they fed rabbits doses of aminoacetaldehyde hydrochloride. Examination of the urine revealed that cyclization had occurred *in vivo*, resulting in the formation of pyrazine which could be isolated.

Stolte (215) reported the biological oxidation of the pyrazine derivative fructosazine. This was fed to rabbits, which oxidized it to 2-methylol-5-pyrazinoic acid. The oxidation product was isolated from the urine.

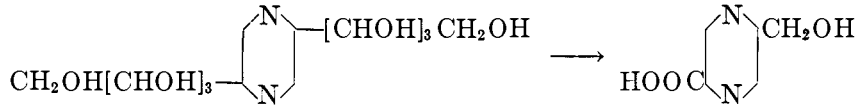


TABLE 13

Pyrazine derivatives isolated from fusel oil

PYRAZINE DERIVATIVE	CARBOHYDRATE SOURCE OF THE FUSEL OIL	REFERENCE
2,5-Dimethylpyrazine	(Kahlbaum's amyl alcohol)	(11)
Trimethylpyrazine	Molasses	(155)
Trimethylpyrazine	Potatoes	(191)
Tetramethylpyrazine	Potatoes	(191)
Diethylpyrazine	Potatoes	(191)
Triethylmethylpyrazine	Potatoes	(191)
2,5-Diethylpyrazine	Beet molasses	(219)

K. UNCLASSIFIED

There are a number of reactions found in the literature that are productive of pyrazine derivatives but for which the mechanisms are obscure. These will be found grouped in table 14.

V. Properties

A. GENERAL

The simple alkylpyrazines, like the corresponding pyrimidines and pyridazines, are low-melting solids which yield colorless mobile liquids. If not carefully purified they darken rapidly on standing. The compounds possess distinctive odors which generally have been described as narcotic.

A characteristic property is the extreme solubility of the lower members in the solvents alcohol, ether, and water. These same compounds are hygroscopic and form hydrates with great ease. At least in one case the difficulty of removing the final traces of water has led to incorrect analytical results with consequent misinterpretation of structure (Gutknecht's work reported in the historical section).

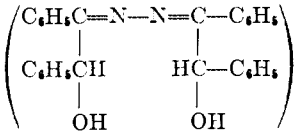
Because of their volatility with steam, codistillation with steam is of great aid in the separation of these bases from reaction mixtures. Pfann (173) has reported the existence of a water–pyrazine azeotrope.

Although no quantitative measurements have been made, the behavior of the pyrazines indicates that they are weaker bases than the pyridines. This might have been anticipated from a consideration of the negative inductive effects of

the nitrogen atoms in the ring, which would mutually bind each basic lone pair of electrons more tightly to the ring. Since the inductive effect is exerted more effectively in the ortho and para positions, it would be anticipated that pyridazine and pyrazine would be less basic than pyrimidine. Such a relationship holds

TABLE 14

Unclassified methods for the preparation of pyrazines

REACTANTS	CONDITIONS	PRODUCTS	REFERENCES
Benzaldehyde and formamide	Reflux equal quantities	Tetraphenylpyrazine	(34)
Benzaldehyde and magnesium nitride	Heat under pressure	Tetraphenylpyrazine	(195)
α-Aminophenylacetonitrile ($C_6H_5CH(CN)NH_2$) and chloral	Anhydrous ether	2,3-Dichloro-6-phenylpyrazine	(154)
α-Aminophenylacetonitrile and bromal	Anhydrous ether	2,3-Dibromo-6-phenylpyrazine	(154)
α-Amino-*p*-methoxyphenylacetonitrile and chloral	Anhydrous ether	2,3-Dichloro-6-*p*-methoxyphenylpyrazine	(154)
α-Amino-*p*-methoxyphenylacetonitrile and bromal	Anhydrous ether	2,3-Dibromo-6-*p*-methoxyphenylpyrazine	(154)
Bisbenzoinketazine  and hydrazine	Heat	Tetraphenylpyrazine	(52, 53)
Bis-*p*-toluoinketazine	Heat	Tetra-*p*-tolylpyrazine	(53)
Amarine(4,5-dihydro-2,4,5-triphenylimidazole)	Reduction with amalgams in ethanol	Tetraphenylpyrazine (a minor product)	(216)

true in the five-membered nitrogen heterocycles, where the basic dissociation constants of pyrazole and imidazole have been reported as 3×10^{-12} and 1.2×10^{-7}, respectively (188a).

In contrast, the methyl-substituted compounds are more basic because of the positive inductive effect of the alkyl group. The completely reduced piperazines

are much stronger bases than the parent pyrazines, which possess an aromatic system of conjugated double bonds.

Advantage is taken of the basicity for the isolation of these compounds from aqueous solutions by adding excess alkali, whereby they may be forced into another phase, despite their extreme solubility in pure water.

Notwithstanding the two basic nitrogen atoms in the ring, the early workers generally considered the pyrazines to be monoacid bases, since only one molecule of an alkyl halide was found to react with one of a pyrazine to form a mono-quaternary salt. However, Tutin and Caton (226) later reported, on spectroscopic and chemical evidence, that the two series of salts could be formed. Studies based on potentiometric titrations are lacking.

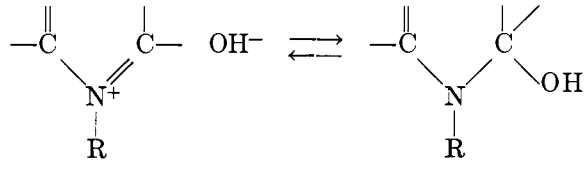
Durio and Bissi (66) have shown that both nitrogens may coördinate with oxygen in the compound which they prepared by the action of alkaline ferrocyanide on α-benzil dioxime, dioxotetraphenylpyrazine. This compound may be deoxygenated to tetraphenylpyrazine and some tetraphenylpiperazine with zinc in glacial acetic acid. Cripps and Perroncito (48) presumably were able to prepare a derivative in which only one of the nitrogens was oxygenated by treating 2,3-diphenyl-5-carboxypyrazine-6-*o*-benzoic acid with hydrogen peroxide in glacial acetic acid.

The complex salts formed with mercuric chloride are of importance. These are white insoluble products which may be easily decomposed by acid or alkali to liberate the bases, so that they may serve as a means for the isolation and purification of these compounds.

For detailed methods of the preparation and properties of many of the salts of the simple pyrazines the reader is referred to the various papers of Stoehr and Wolff (bibliography) in addition to that of Tutin and Caton previously cited.

B. THE QUATERNARY SALTS

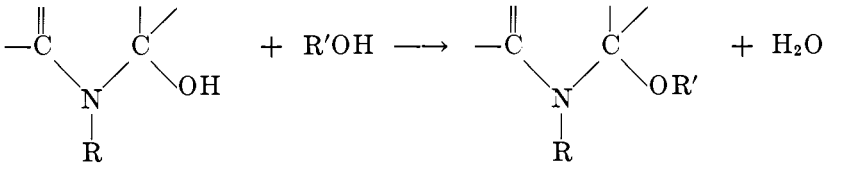
Aston carried out a series of investigations of the quaternary salts designed to give a more thorough insight into the structures of these compounds (7, 8). It is well known in the pyridine and quinoline series (192) that a quaternary hydroxide may undergo one of two possible changes, depending upon the nuclear substituents. There may be formed a pseudo base (II):



I
True base

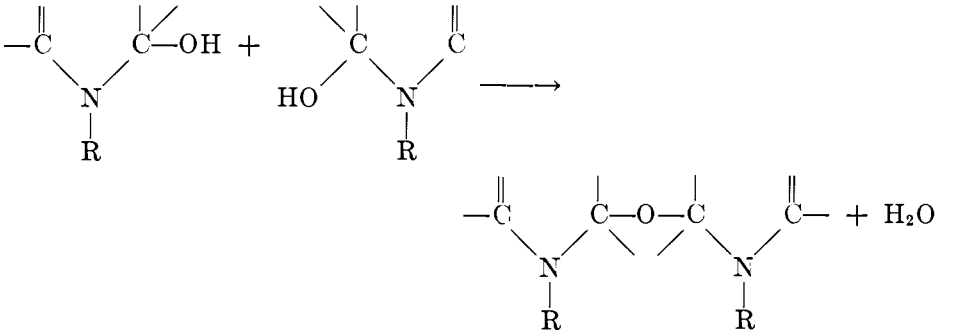
II
Pseudo base

As is shown, an equilibrium may exist between the electrolyte (I) and the non-electrolyte (II). There is a further difference between I and II in that the latter possesses one less double bond than the former. The pseudo base may then react with an alcohol to give an ether (III):



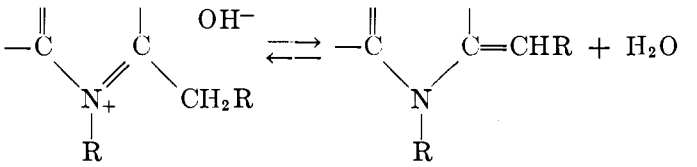
III
Ether

And in some cases another molecule of the pseudo base may function as the alcohol, yielding the dimeric ether (IV):



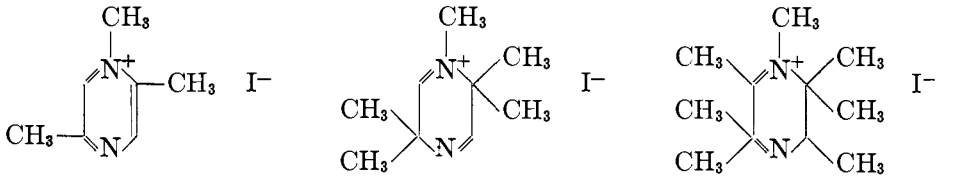
IV
Dimeric ether

However, if the substituent on the carbon carrying the hydroxyl of the pseudo base is not hydrogen and is attached by a methylene group, an anhydro base (V) may also be formed by the elimination of water:



I V
Anhydro base

Aston worked with three quaternary salts of the pyrazine series: 1,2,5-trimethylpyrazinium iodide (A), 1,2,2,5,5-pentamethyldihydropyrazinium iodide (B), and 1, 2,2,3,5,5,6-heptamethyldihydropyrazinium iodide (C):

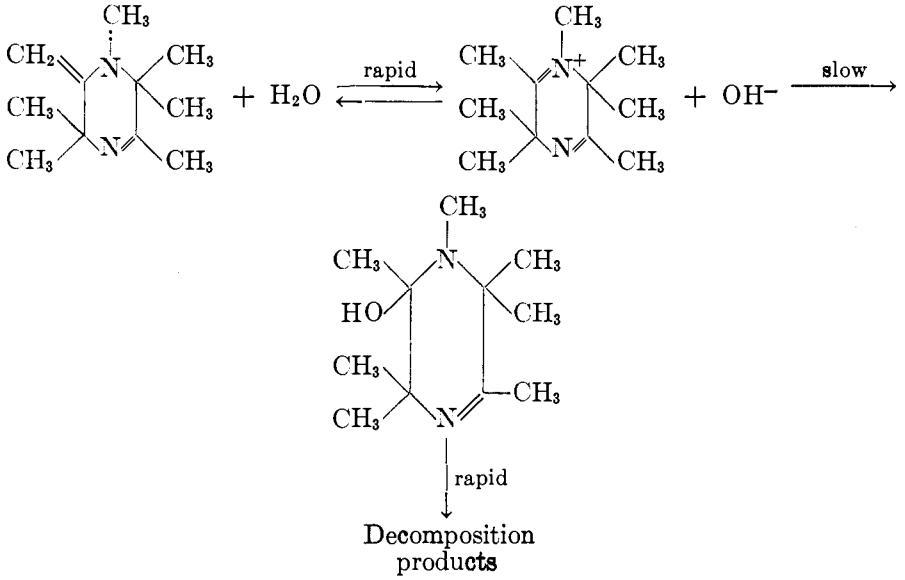


A B C

Upon the addition of potassium hydroxide to these iodides, B was found to yield the pseudo base (II), and C the anhydro base (V), but no base could be isolated from A. The reaction rates and basic dissociation constants of the equilibrium mixtures were determined from conductance measurements in aqueous solution. It was shown that for B an equilibrium between forms I and II is reached extremely rapidly, and is in favor of II.

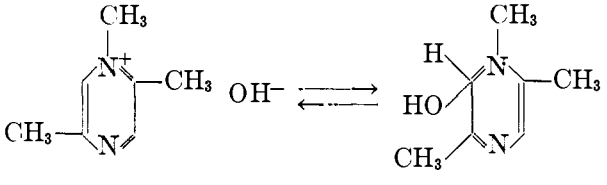
In the case of C an equilibrium between I and V is also attained very rapidly. Although the solution was strongly basic ($K = 4 \times 10^{-3}$) when freshly prepared, the basicity diminished in time simultaneously with the formation of decomposition products. Furthermore, a kinetics study revealed that the decomposition rate was proportional to the first power of the concentration of the pyrazinium and hydroxide ions. Consideration of these facts led to the conclusion that the formation of the pseudo base is the controlling step.

These transformations may be indicated as follows:



The failure of the attempts to isolate a base from A was further probed kinetically. Experiments showed that the disappearance of strong base from a mixture of 1,2,5-trimethylpyrazinium iodide and sodium hydroxide proceeds in two main directions.

In both cases there first occurs a rapid equilibrium favoring the left:

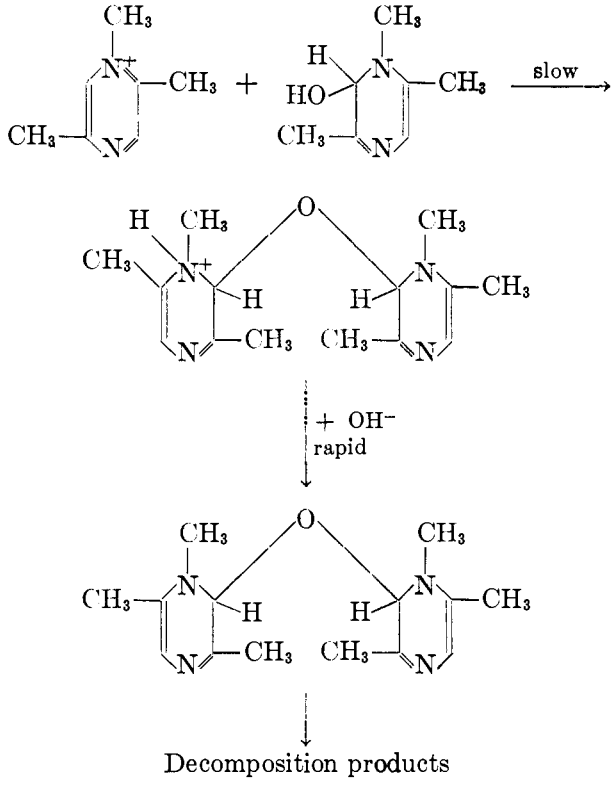


(Py$^+$) (POH) (1)

The equilibrium constant, K_1, is given by:

$$K_1 = \frac{[POH]}{[Py^+][OH^-]}$$

Consider now the formation of a dimeric ether in accordance with the following mechanism:



(2)

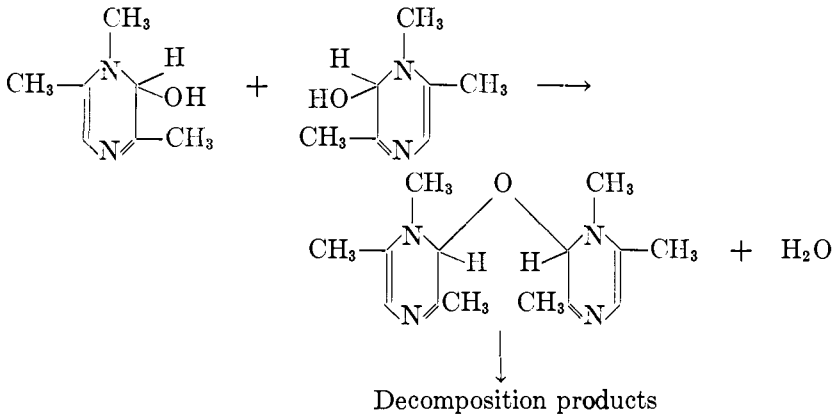
Reaction 2 is thus the rate-controlling step. The differential equation is:

$$-\frac{d[Py^+]}{dt} = k_2[POH][Py^+]$$

Substituting for [POH] from the expression for K_1, there results:

$$-\frac{d[Py^+]}{dt} = K_1 k_2[Py^+]^2[OH^-] = k'[Py^+]^2[OH^-]$$

On the other hand, if the slow reaction takes place by the direct condensation of two molecules of the pseudo base:



(3)

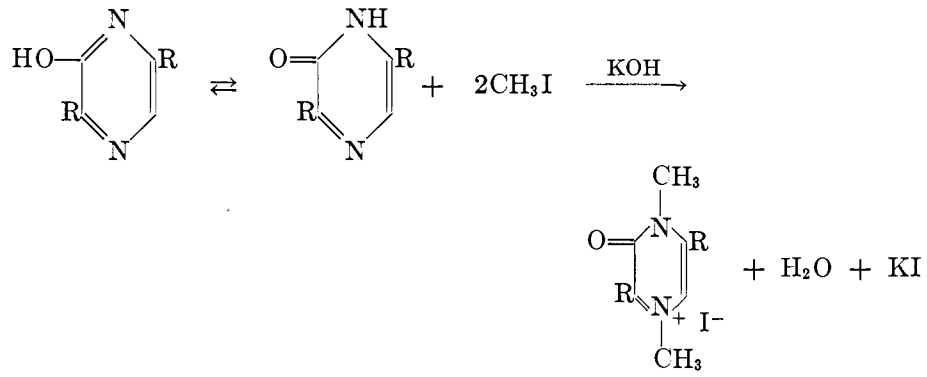
the kinetics will be represented by:

$$-\frac{d[Py^+]}{dt} = -\frac{d[POH]}{dt} = k_3[POH]^2 = K_1^2 k_3 [Py^+]^2[OH^-]^2$$
$$= k''[Py^+]^2[OH^-]^2$$

These two mechanisms are supported by the data, the latter one predominating in solutions which contain an excess of hydroxide ion.

These results were interpreted by Aston in the light of ring conjugation. Since the —N=C— double bond of B will be more prone to add the hydroxyl ion than that of the fully conjugated system A, the I–II equilibrium will be displaced more to the side of II in the former case. Analogously, the non-conjugation of C leads to the rapid establishment of the I–V equilibrium, and again the fact that this does not occur in the case of A, although the possibility exists, is attributed to its aromatic nature.

The observations of Gastaldi and Princivalle (91, 178) may also be explained on the basis of these hypotheses. When 2,5-diphenyl(or dimethyl)-6-hydroxypyrazine was treated in a sealed tube for 10 hr. at 100°C. with potassium hydroxide and methyl iodide in methanol, 1,4-dimethyl-2,5-diphenyl(or dimethyl)-6-keto-1,6-dihydropyrazinium iodide was obtained.



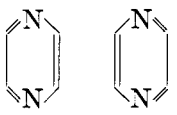
R = phenyl or methyl.

The 1,2,4,5-tetramethyl-6-keto-1,6-dihydropyrazinium iodide, when treated with alkali, may further react to form the anhydro base 1,2,4-trimethyl-5-methylene-6-keto-1,6,4,5-tetrahydropyrazine, analogous to the behavior of 1,2,2,3,5,5,6-heptamethyldihydropyrazinium iodide (C). It was also noted that 1,2,5-trimethylpyrazinium iodide did not form an anhydro base under similar circumstances but underwent another change. This we have seen was identified by Aston as the formation of the unstable dimeric ether.

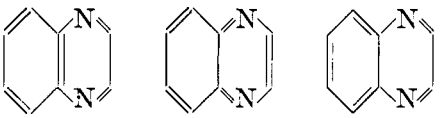
Before closing our discussion of the quaternary salts we should mention a reaction of these compounds which has received much attention in the pyridine series, *viz.*, the migration of *N*-substituted radicals. An example of this type has been recorded by Brandes and Stoehr (24). They observed that when the methobromide of dimethylpyrazine was heated in a sealed tube, trimethylpyrazine and tetramethylpyrazine were obtained. The formation of the latter compound indicates that the migration is intermolecular, in accord with our knowledge of similar migrations in the pyridine series.

Bergstrom and Ogg (17) have made an interesting interpretation of the pyrazine molecule, based on the ammonia system of compounds. Since it contains the linkage —N=CH—CH=N—, pyrazine is formally an ammono glyoxal; the same is of course true of quinoxaline. These concepts were tested by treating these compounds with typical aldehyde reagents in liquid ammonia. Quinoxaline formed aldehyde addition compounds with bisulfite, hydrogen cyanide, and the Grignard reagent, whereas pyrazine, if it reacted at all, yielded undefined products.

An explanation of this behavior may be formulated on the basis of resonance phenomena similar to Pauling's treatment of benzene and the polynuclear hydrocarbons (171). Considering the following resonating structures involving double bond shifts:

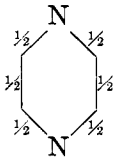


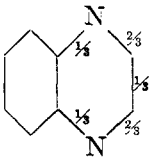
Pyrazine



Quinoxaline

we can assign values for double-bond character:

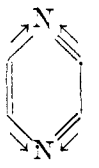




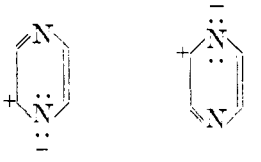
In the case of quinoxaline, therefore, the —N—C— bonds in the 1,2- and 3,4-positions possess more double-bond character than those in the other positions of either quinoxaline or pyrazine. Hence, we should expect these positions to exhibit greater aldehydic properties, a conclusion which is in conformity with the observed facts.

C. DIRECT NUCLEAR SUBSTITUTION

The structure of the pyrazine molecule seems particularly unsuited for direct substitution with the usual electrophilic reagents. In addition to the inductive effects of the negative nitrogen atoms which reduce the electron density of all carbons equally,



the deactivation is intensified by the effects of such resonating structures as:



Of the three diazines, it is only pyrazine which is rendered so thoroughly inactive, for in pyrimidine and pyridazine there is at least one carbon atom which is not adjacent to both nitrogens.

However, just as the nucleus is deactivated with respect to attempted electrophilic substitutions, so may substitutents on the ring be activated for certain reactions. Thus, we may point to the relatively large values for the dissociation constants of two of the carboxylic acids as determined by Sausville and Spoerri (186) from the half-neutralization points of electrometric titrations with the hydrogen electrode: pyrazinoic acid, $K_a = 1.2 \times 10^{-3}$; 2,3-pyrazinedicarboxylic acid, $K_1 = 1.7 \times 10^{-3}$, K_2 "too weak to measure." Further evidence will be presented in the discussions of the ammonolysis, hydrolysis, and alcoholysis of the nuclear-substituted halides and the condensation of alkyl derivatives with aldehydes.

1. Halogenation

Until recent times all attempts at halogenation, as shown in table 15, were unsatisfactory, giving rise to products of varying stability and uncertainty of structure.

The first successful direct halogenations of pyrazine have been reported in patents issued within the past year to Sayward (187) and Winnek (231). Both employed vapor-phase reactions reminiscent of the methods used for the halopyridines. The former simply passed a mixture of pyrazine and water vapors with chlorine through a tube at 400°C.; whereas the latter diluted the pyrazine vapor with nitrogen instead of water, and was able to operate at lower temperatures by using a copper–cuprous chloride catalyst. A patent just issued to Dixon

and Sayward (64a) claims the preparation of bromopyrazine from the reaction between pyrazine hydrochloride (or hydrobromide) and bromine in carbon tetrachloride at 150–250°C. for 3½ hr.

Certain substituents on the ring apparently modify the character sufficiently to permit a successful direct halogenation under ordinary conditions. Thus Ellingson and Henry (69) found that whereas they could obtain nothing but tars from the action of bromine on aminopyrazine, the same reagent was successful in converting 2-amino-3-carbomethoxypyrazine to 2-amino-3-carbomethoxy-5-bromopyrazine in 90 per cent yields.

Almost simultaneously with the introduction of these direct methods, Erickson and Spoerri (76, 77) prepared pure chloropyrazine by the treatment of hydroxy-

TABLE 15

Early attempts at the direct halogenation of pyrazines

PYRAZINE	REAGENT	PRODUCT	REFERENCES
Pyrazine	Bromine	Unstable addition compound	(209)
Pyrazine	Iodine and potassium iodide	"Periodide"; structure undetermined	(209)
Trimethylpyrazine	Iodine and potassium iodide	"Periodide"; structure undetermined	(24)
Tetramethylpyrazine	Bromine	Unstable addition compound	(99)
2,5-Dimethylpyrazine	Bromine	Unstable addition compound	(203, 205)
2,5-Dimethylpyrazine	Iodine and potassium iodide	"Periodide"; structure undetermined	(203)
3-Keto-2,5-diphenyl-3,4-dihydropyrazine	Bromine in glacial acetic acid	Fairly stable crystalline monobromo derivative; structure not proven	(109, 153)

pyrazine with a mixture of phosphorus pentachloride and phosphorus oxychloride. When the corresponding phosphorus bromides were employed, one of the dibromopyrazines was obtained in addition to the monobromo derivative. More recently, McDonald and Ellingson (149) treated 2-amino-3-hydroxypyrazine with phosphorus oxychloride under pressure to obtain 2-amino-3-chloropyrazine.

Durio and Bissi (66) found that when they subjected 1,4-dioxotetraphenylpyrazine to the action of phosphorus pentachloride, deoxygenation occurred together with the halogenation of one of the phenyl groups to yield 2-chlorophenyl-3,5,6-triphenylpyrazine.

2. Nitration

Minovici (109, 153) apparently obtained a nitro derivative of 3-keto-2,5-diphenyl-3,4-dihydropyrazine by the action of fuming nitric acid. The structure of this compound was not proven. Generally when aryl-substituted pyrazines are treated with nitric acid, it is found, as expected, that if nitration does take place, it is the aryl nucleus which is primarily affected. Thus 2,5-di[*m*-nitrophenyl]pyrazine was obtained from the nitration of diphenylpyrazine (163). Similar treatment of tetraphenylpyrazine resulted in the formation of tetra(nitrophenyl)pyrazine (30), which was capable of being reduced to tetra(aminophenyl)pyrazine by tin and hydrochloric acid (190).

3. Sulfonation

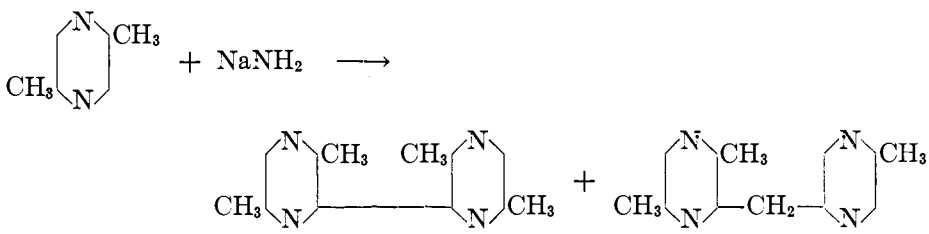
The subject of sulfonation may be dismissed with the brief statement that no pyrazinesulfonic acids have been reported. Some idea of the resistance of the pyrazine nucleus to sulfuric acid may be gained from the fact that lumazine may be cleaved to aminopyrazine by heating in 100 per cent sulfuric acid at 250°C. There is little apparent detriment to the aminopyrazine, since it may be recovered in 80 per cent yields (227).

4. Amination

Since those electronic conditions which discourage electrophilic substitutions aid the attack of nucleophilic reagents, one would anticipate favorable results from a direct amination with sodium amide. When this reaction is carried out in the pyridine series, it is observed that it is the 2- and 4-positions which are first substituted, contrary to the action of the electrophilic reagents which preferentially attack the electron-richer 3-position.

Bergstrom and Ogg (17) attempted to react pyrazine with potassium amide in liquid ammonia, but they could isolate no products. However, a patent has just been obtained by Crossley and English (51), in which they claimed to have modified the conditions sufficiently to permit successful results.

Chichibabin and Schukina (41) treated sodium amide with 2,5-dimethylpyrazine in xylene, and obtained only 10 per cent yields of 3-amino-2,5-dimethylpyrazine. In addition, coupling induced by the aminating agent occurred, as in the pyridine series (168), yielding bipyrazyls:



With dimethylaniline as the solvent, Joiner and Spoerri (116, 117) were able to raise the yield of 3-amino-2,5-dimethylpyrazine to 35 per cent.

Most of the aminopyrazines that appear in the literature have been prepared

by the Hofmann degradation of the acid amides. This will be further considered in Section D,4,d, dealing with the properties of the acid amides.

5. Cyanation

Another example of an anionoid reagent successful in the pyrazine series is potassium cyanide. Mason *et al.* (147) refluxed 2,3-diphenyl-5,6-dihydropyrazine with potassium cyanide in 80 per cent ethanol. After preliminary oxidation to the pyrazine, cyanation followed by partial hydrolysis occurred, resulting in the amide of 2,3-diphenyl-5-pyrazinoic acid. 2,3-Dimethoxyphenyl-5,6-dihydropyrazine yielded the corresponding amide under similar treatment.

D. REACTIONS OF RING SUBSTITUENTS

1. Hydrolysis, ammonolysis, and alcoholysis of halopyrazines

As previously mentioned, the halopyrazines are fairly reactive. Bromopyrazine gives a positive halogen test with alcoholic silver nitrate (76). This resembles the behavior of the 2- and 4-halopyridines. Spoerri and Erickson (76, 77) hydrolyzed chloropyrazine to hydroxypyrazine by heating with aqueous alkali in a sealed tube for 7 hr. Similarly, the ammonolysis of chloropyrazine was accomplished with concentrated ammonia, to produce 2-aminopyrazine (76, 77, 232). 2,3-Diaminopyrazine was obtained by the analogous treatment of 2-amino-3-chloropyrazine with ammonia (149).

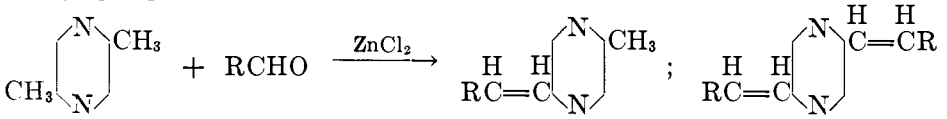
Metanilamidopyrazine and orthanilamidopyrazine were both prepared by treating chloropyrazine with either metanilamide or orthanilamide, in nitrobenzene in the presence of potassium carbonate (72). Winnek (232a) has patented the preparation of 2-N^4-[acetylsulfanilamido]pyrazine from chloropyrazine and N^4-acetylsulfanilamide by a similar method.

An example of the alcoholysis of a halopyrazine is the preparation of ethoxypyrazine by refluxing chloropyrazine in an alcoholic solution of sodium ethoxide (76, 77).

2. Condensation of alkylpyrazines with aldehydes

The enhanced activity of the alkyl groups on the pyrazine nucleus may be illustrated by the condensation of the methyl derivatives with various aldehydes. This reaction is entirely analogous to that of other activated methyl groups such as occur in 2,4-dinitrotoluene, the α- and β-picolines, and the 2- and 4-alkylquinolines.

Franke (85) published the results of an investigation in which he condensed various aldehydes with 2,5-dimethylpyrazine in the presence of zinc chloride. Depending upon the conditions and the particular aldehyde, one and/or both methyl groups were found to react:



A summary will be found in table 16.

Riesz (182) extended this work to the quaternary salts of the methylpyrazines, employing a piperidine catalyst. The condensation products were stated to have the property of desensitizing silver halide emulsions. The compounds specifically prepared in the patent also appear in table 16.

3. Hydrolysis of aminopyrazines

An example of this reaction which also depends on activation by the ring nitrogens has been furnished by Weijlard, Tishler, and Erickson (227). By

TABLE 16

Condensation of methylpyrazines with aldehydes

REACTANTS	PRODUCTS	REFERENCES
2,5-Dimethylpyrazine and benzaldehyde	2-Methyl-5-styrylpyrazine and 2,5-distyrylpyrazine	(85)
2,5-Dimethylpyrazine and chloral	2,5-Bistrichloropropenylpyrazine	(85)
2,5-Dimethylpyrazine and *p*-toluylaldehyde	2,5-Di(*p*-methylstyryl)pyrazine	(85)
2,5-Dimethylpyrazine and anisaldehyde	2,5-Di(*p*-methoxystyryl)-5-methylpyrazine	(85)
2,5-Dimethylpyrazine and *p*-nitrobenzaldehyde	2-*p*-Nitrostyryl-5-methylpyrazine	(85)
1,2,5-Trimethylpyrazinium nitrate and benzaldehyde	1,5-Dimethyl-2-styrylpyrazinium nitrate	(182)
1-Ethyl-2,5-dimethylpyrazinium iodide and *p*-dimethylaminobenzaldehyde	1-Ethyl-5-methyl-2(4'-dimethylaminostyryl)pyrazinium iodide	(182)
1,2,5-Trimethylpyrazinium iodide and *p*-methoxybenzaldehyde	1,5-Dimethyl-2(4'-methoxystyryl)-pyrazinium iodide	(182)
1-Ethyl-2,5-dimethylpyrazinium iodide and *m*-nitrobenzaldehyde	1-Ethyl-5-methyl-2(3'-nitrostyryl)-pyrazinium iodide	(182)

heating 2-amino-3-pyrazinoic acid with 20 per cent sodium hydroxide in a sealed tube they were able to obtain 2-hydroxy-3-pyrazinoic acid.

4. Oxidation of side chains—the carboxylic acids and their derivatives

It thus appears that the standard methods for the introduction of substituents into the benzene nucleus which have been used with some measure of success in such heterocycles as pyridine, quinoline, and even the two other diazines are not at all applicable to the pyrazines under similar circumstances. As was indicated, it is only within the past few years that efforts have been made to

modify the techniques suitably to make them practical for use in the pyrazine series.

The classical syntheses of pyrazine derivatives generally hinged on the preparation of the carboxylic acids. These could be treated by usual methods to

TABLE 17

Oxidation of pyrazine side chains

PYRAZINE DERIVATIVE	OXIDATION PRODUCT	REFERENCES
Methylpyrazine	Pyrazinoic acid	(211)
2,5-Dimethylpyrazine	2,5-Pyrazinedicarboxylic acid and/or 2-methyl-5-pyrazinoic acid, depending on conditions	(75, 93, 129, 206, 208, 210, 214, 238)
2,5-Dimethyl-3-ethylpyrazine	Pyrazinetricarboxylic acid and/or 2,5-dimethyl-3-pyrazinoic acid, depending on conditions	(196, 214)
2,5-Dimethyl-3,6-diethylpyrazine	2,5-Dimethyl-3,6-pyrazinedicarboxylic acid	(119)
Tetramethylpyrazine	Pyrazinetetracarboxylic acid. As the permanganate concentration is reduced there is obtained an increasing quantity of 3,6-dimethyl-2,5-pyrazinedicarboxylic acid	(228, 243)
Phenazine and substituted phenazines	Pyrazinetetracarboxylic acid	(181)
2-Methyl-6-pyrazinoic acid	2,6-Pyrazinedicarboxylic acid	(196)
Copper 2-methylol-5-pyrazinoate	2,5-Pyrazinedicarboxylic acid	(215)
Fructosazine	2,5-Pyrazinedicarboxylic acid	(215)
2,2',5,5'-Tetramethyl-3,3'-bipyrazyl	2,5-Dimethyl-3-pyrazinoic acid and 2,5-dimethyl-2'-methyl-5'-carboxyl-3,3'-bipyrazyl	(41)
(2,5-Dimethyl-5'-methyl)bipyrazyl-3,3'-methane	2,5-Pyrazinedicarboxylic acid and 2,5-dimethyl-3-pyrazineglyoxalic acid	(41)

yield esters, amides, nitriles, etc., which were then made the starting materials for further derivatives, such as the amino, hydroxy, and halogen compounds.

We first concern ourselves, therefore, with the carboxylic acids. In Section IV, we have noted a few cases where these compounds were obtained directly

as the result of a pyrazine synthesis. However, the most important method for the preparation of the pyrazine acids is dependent on the oxidation of the side chains of those alkyl derivatives that are available (see table 17).

The reagent most commonly selected for this task is dilute (2 per cent) alkaline permanganate. This works very well for quinoxaline and its derivatives, resulting in the formation of the corresponding 2,3-dicarboxylic acids in yields of the order of 70 per cent. However, when applied to the oxidation of other side chains, yields are considerably poorer, the total varying from 5 to 10 per cent, because of additional destruction of the nucleus. Rather futile efforts have been made to improve the situation by the control of variables such as the permanganate and alkylpyrazine concentrations, pH, and reaction time. The use of other

TABLE 18

Pyrazinecarboxylic acids obtained by the hydrolysis of amides or nitriles

AMIDE OR NITRILE	ACID	CONDITIONS	REFERENCES
2,5-Dimethyl-3,6-pyrazinediamide	2,5-Dimethyl-3,6-pyrazinedicarboxylic acid	Nitrous acid	(91)
2,3-Dimethoxyphenyl-5-pyrazinamide	2,3-Dimethoxyphenyl-5-pyrazinoic acid	Heat with aqueous alkali or acid	(147)
2,3-Diphenyl-5-pyrazinamide	2,3-Diphenyl-5-pyrazinoic acid	Heat with aqueous alkali or acid	(147)
Cyanopyrazine	Pyrazinoic acid	Heat with aqueous alkali	(21)
2,5-Diphenyl-3,6-dicyanopyrazine	2,5-Diphenyl-6-hydroxy-3-pyrazinoic acid	Heat with aqueous alkali	(90)
2,5-Diphenylcyanopyrazine	2,5-Diphenylpyrazinoic acid	Heat with aqueous alkali	(90)

oxidants, such as nitric acid and acid dichromate mixtures, has also been of little avail (93, 129).

Several of the carboxylic acids have also been obtained by the hydrolysis of the amides or nitriles. These are listed in table 18.

A characteristic property of the pyrazinecarboxylic acids is their reaction with ferrous salts to give reddish-colored compounds. This is also true of the pyridine- and quinolinecarboxylic acids (Skraup's test). It has been established that the necessary condition for a positive test is the group, —C=N, in which the dotted portion signifies the remainder of a cyclic system (139).

a. Decarboxylation

In common with the carboxylic acids of other heterocycles, e.g., the pyridines, quinolines, and the other diazines, those of the pyrazines may be decarboxylated

in good yields. This has proven a lucrative device for the preparation of derivatives otherwise unobtainable.

There are a number of ways in which the decarboxylation may be effected,

TABLE 19

Decarboxylations of pyrazinecarboxylic acids

PYRAZINECARBOXYLIC ACID	PRODUCT	CONDITIONS	REFERENCES
Pyrazinoic acid	Pyrazine	Sublimation; dibutyl phthalate	(180, 206)
2,3-Pyrazinedicarboxylic acid	Pyrazinoic acid	Vacuum sublimation	(16, 21, 60, 89, 100, 101, 116, 180)
2,3-Pyrazinedicarboxylic acid	Pyrazine	Vacuum sublimation; dibutyl phthalate	(16, 89, 93, 116)
2,5-Pyrazinedicarboxylic acid	Pyrazinoic acid	Sublimation; glacial acetic acid	(238, 243)
2,5-Pyrazinedicarboxylic acid	Pyrazine	Sublimation; glacial acetic acid	(166, 206, 208, 210, 214, 238)
Pyrazinetricarboxylic acid	2,5-Pyrazinedicarboxylic acid; also some 2,6-pyrazinedicarboxylic acid	Boiled in water for 2 to 3 days; dibutyl phthalate	(180, 206, 214)
Pyrazinetetracarboxylic acid	2,5-Pyrazinedicarboxylic acid; also some pyrazine	Fuse dipotassium salt; dibutyl phthalate	(180, 238, 243)
2-Methylpyrazinoic acid	Methylpyrazine	Sublimation	(206, 208, 210)
2,5-Dimethylpyrazine-3,6-dicarboxylic acid	2,5-Dimethylpyrazine	Glacial acetic acid	(206, 208, 210, 214)
5,6-Dimethylpyrazine-2,3-dicarboxylic acid	5,6-Dimethylpyrazine	Glacial acetic acid	(89)
2,5-Dimethyl-6-hydroxy-3-pyrazinecarboxylic acid	2,5-Dimethyl-6-hydroxypyrazine	Fuse sodium salt	(90)
2-Hydroxy-3-pyrazinoic acid	2-Hydroxypyrazine	Carbitol acetate	(227)
2-Amino-5,6-dimethyl-3-pyrazinoic acid	2-Amino-5,6-dimethylpyrazine	80 per cent sulfuric acid	(227)
2-Amino-5,6-diphenyl-pyrazinoic acid	2-Amino-5,6-diphenylpyrazine	80 per cent sulfuric acid	(227)

TABLE 19—*Continued*

PYRAZINECARBOXYLIC ACID	PRODUCT	CONDITIONS	REFERENCES
2-Amino-6-methyl-3-pyrazinoic acid	2-Amino-6-methylpyrazine	80 per cent sulfuric acid	(227)
2,5-Diphenyl-6-hydroxy-3-pyrazinoic acid	2,5-Diphenyl-6-hydroxypyrazine	Fuse sodium salt	(90)
2,5-Diphenylpyrazinoic acid	2,5-Diphenylpyrazine	Fuse sodium salt	(90)
2-Amino-3-pyrazinoic acid	2-Aminopyrazine	Fuse	(89, 227)
5-Methylpyrazine-2,3-dicarboxylic acid	6-Methyl-2-pyrazinoic acid	Vacuum sublimation	(135)
2,3-Diphenyl-5-carboxypyrazine-6-*o*-benzoic acid	2,3,5-Triphenylpyrazine	Distill over calcium oxide	(48)
Pyrazine-3-phenyl-5-carboxy-6-*o*-benzoic acid	2,5-Diphenylpyrazine	Distill over calcium oxide	(46)

as is indicated in table 19. The general procedure is to reflux the acid in glacial acetic acid. This has been varied by employing other media such as carbitol acetate, 80 per cent sulfuric acid, and dibutyl phthalate—the major effect being the increase in temperature due to the higher boiling point. Some acids undergo this reaction so easily that it may be conducted in boiling water. Sublimation has also been found to be effective, and this process was further improved for some cases by operating under reduced pressures. Occasionally, heating the alkali salt to the state of fusion was sufficient to induce decarboxylation.

An example of the decarboxylation of a cyano derivative was furnished by Gastaldi (90), who found that phosphorus and hydrogen iodide converted 2,5-diphenyl-3,6-dicyanopyrazine into 2,5-diphenyl-3,6-dihydropyrazine.

b. Esters

Esterification with methanol and ethanol takes place smoothly when carried out in the customary fashion. Generally, the acid is dissolved in an excess of the alcohol which contains either hydrogen chloride or sulfuric acid as a catalyst. After warming and/or allowing to stand for a period of time, the esters usually crystallize out when the solvent is partially evaporated. The yields are good, ranging from 80–90 per cent.

These derivatives have been largely utilized for the preparation of the acid amides.

The β-diethylaminoethyl ester of 2-amino-3-pyrazinoic acid was prepared by

the reaction of silver 2-amino-3-pyrazinoate with diethylaminoethyl chloride (73). It was thought that this compound might possess anesthetic activity because of its resemblance to procaine.

TABLE 20

Esterifications of pyrazinecarboxylic acids

PYRAZINECARBOXYLIC ACID	PRODUCT	CONDITIONS	REFERENCES
2,3-Pyrazinedicarboxylic acid	Dimethyl 2,3-pyrazinedicarboxylate	Methanol; hydrogen chloride	(73, 89, 166)
5-Methylpyrazine-2-pyrazinoic acid	5-Methyl-2-methyl pyrazinoate	Methanol; hydrogen chloride	(227)
Pyrazinoic acid	Methyl pyrazinoate	Methanol; hydrogen chloride	(21, 144)
Pyrazinoic acid	Ethyl pyrazinoate	Ethanol; hydrogen chloride	(116, 117)
2,5-Pyrazinedicarboxylic acid	Dimethyl 2,5-pyrazinedicarboxylate	Methanol; hydrogen chloride	(75, 129)
2-Amino-3-pyrazinoic acid	2-Amino-3-methyl pyrazinoate	Methanol; sulfuric acid	(70)
5,6-Dimethyl-2,3-pyrazinedicarboxylic acid	Dimethyl 5,6-dimethyl-2,3-pyrazinedicarboxylate	Methanol; hydrogen chloride	(89)
Pyrazinetetracarboxylic acid	Tetraethyl pyrazinetetracarboxylate	Ethanol; hydrogen chloride	(37)
3-Hydroxy-2-pyrazinoic acid	3-Hydroxy-2-methyl pyrazinoate	Methanol; sulfuric acid	(139)

c. Acid chlorides

The literature records the preparation of two pyrazine acid chlorides. These are pyrazinoyl chloride (57) and the diacid chloride of 2,5-pyrazinedicarboxylic acid (75), both of which were made by the action of phosphorus pentachloride on the free acids. Thionyl chloride was found to be an ineffective reagent for this transformation (75).

d. Amides and hydrazides

The acid chlorides and esters have been used to prepare the amides and hydrazides by the standard procedure of treating them with ammonia, hydrazine, or their derivatives. Yields are good: 80–90 per cent. For some of the higher

N-substituted amides, it was found sufficient to reflux the pyrazine acid directly with the amine in xylene (18).

The hydrolytic action of 95 per cent sulfuric acid on nitriles has also served for the preparation of the amides.

The appearance of the large number of these compounds may be attributed

TABLE 21

Amides and hydrazides

PYRAZINE REACTANT	PRODUCT	CONDITIONS	REFERENCES
Methyl or ethyl pyrazinoate	Pyrazinamide	Alcoholic ammonia	(21, 116)
Dimethyl 2,3-pyrazinedicarboxylate	2,3-Pyrazinediamide	Alcoholic ammonia	(73, 89, 166)
Dimethyl 2,5-pyrazinedicarboxylate	2,5-Pyrazinediamide	Alcoholic ammonia	(75, 88, 129)
2-Amino-3-carbomethoxypyrazine	2-Amino-3-pyrazinamide	Alcoholic ammonia	(70)
2-Methyl-5-carbomethoxypyrazine	2-Methyl-5-pyrazinamide	Alcoholic ammonia	(227)
2,3-Pyrazinedicarboxylic acid	*N*,*N*′-Dibenzyl-2,3-pyrazinediamide	Benzylamine refluxed with the diacid in xylene	(18)
2,3-Pyrazinedicarboxylic acid	*N*,*N*′-Diamyl-2,3-pyrazinediamide	Amylamine refluxed with the diacid in xylene	(18)
Diethyl 2,5-pyrazinedicarboxylate	2,5-Pyrazine dihydrazide	Hydrazine hydrate	(75)
3-Hydroxy-2-carbomethoxypyrazine	3-Hydroxy-2-pyrazine amide	Alcoholic ammonia	(149)
2,5-Dimethyl-3,6-dicyanopyrazine	2,5-Dimethyl-3,6-pyrazinediamide	Heat with sulfuric acid	(91)
2-Amino-3-cyanopyrazine	2-Amino-3-pyrazinamide	Heat with sulfuric acid	(70)

in part to their importance as intermediates for the Hofmann and Curtius degradations. The majority of them, however, have been synthesized by Dalmer and Walter (56) because of their purported physiological behavior as analeptics.

The following derivatives were claimed in the patent issued to Dalmer and Walter (56). They were synthesized by the action of ethyl pyrazinoate or pyrazinoyl chloride on ammonia, hydrazine, or their derivatives: *N*-β-amino-

ethylpyrazinamide; *N*-β-hydroxyethylpyrazinamide, *N*-butylpyrazinamide, *N*,*N*-dibenzylpyrazinamide, *N*,*N*-di(β-hydroxyethyl)pyrazinamide, *N*,*N*-dibutylpyrazinamide, *N*,*N*-diisopropylpyrazinamide, *N*,*N*-dimethylpyrazinamide, *N*,*N*-dipropylpyrazinamide, *N*-ethylpyrazinamide, *N*-heptylpyrazinamide, *N*-methylpyrazinamide, *N*-methylbenzoylpyrazinamide, *N*-methylpyrazinhydrazide, *N*-phenylpyrazinhydrazide, pyrazinanilide, pyrazinhydrazide.

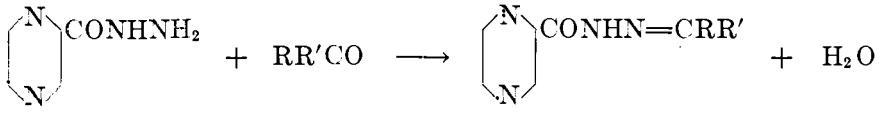
Several sulfanilamide derivatives have been prepared by reacting pyrazinoyl chloride with the appropriate sulfanilamide (57). These are illustrated in table 22.

TABLE 22

Pyrazinoyl sulfanilamide derivatives (57)

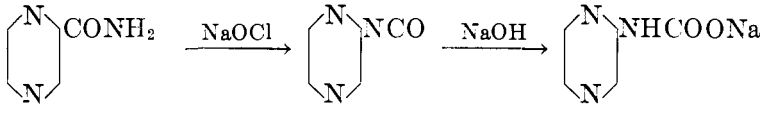
REACTANTS	PRODUCTS
Pyrazinoyl chloride and sulfanilamide	N^4-Pyrazinoylsulfanilamide
N^4-Pyrazinoylsulfanilamide and acetic anhydride	N^1-Acetyl-N^4-pyrazinoylsulfanilamide
N^4-Pyrazinoylsulfanilamide and pyrazinoyl chloride	N^1,N^4-Dipyrazinoylsulfanilamide
N^4-Acetylsulfanilamide and pyrazinoyl chloride	N^4-Acetyl-N^1-pyrazinoylsulfanilamide
N^4-Acetyl-N^1-pyrazinoylsulfanilamide and sodium hydroxide	N^1-Pyrazinoylsulfanilamide

The hydrazino groups of the hydrazides are reactive, readily combining with aldehydes and ketones to form the alkylidenepyrazinoyl hydrazides (55):



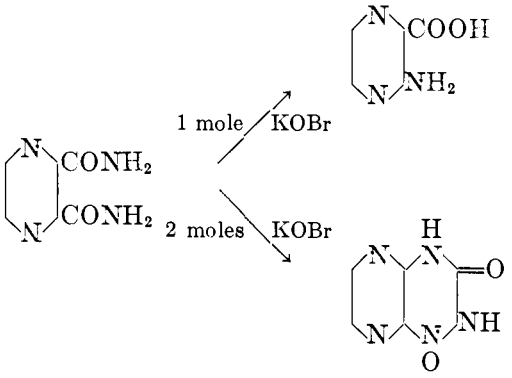
The following derivatives were thus prepared, pyrazinoylhydrazide being condensed with the appropriate carbonyl compound: isopropylidenepyrazinoyl hydrazide (R = R′ = CH_3), ethylidenepyrazinoyl hydrazide (R = CH_3, R′ = H), and trichloroethylidenepyrazinoyl hydrazide (R = CCl_3, R′ = H).

With the few exceptions already noted, all the reported aminopyrazines have been prepared by the Hofmann degradation. There are several points of interest with regard to this reaction. For example, the pyrazine nucleus may exert a stabilizing influence on some of the intermediates. Thus, the sodium salt of the intermediate carbamate could be isolated when the reaction was carried out with pyrazinamide (101):



In addition to the preparation of aminopyrazine (21, 101, 116), the method has been successfully applied to two other pyrazine monoamides, 2-methyl-5-pyrazinamide (227) and 2-hydroxy-3-pyrazinamide (149), for the preparation of the corresponding 2-methyl-5-aminopyrazine and 2-hydroxy-3-aminopyrazine.

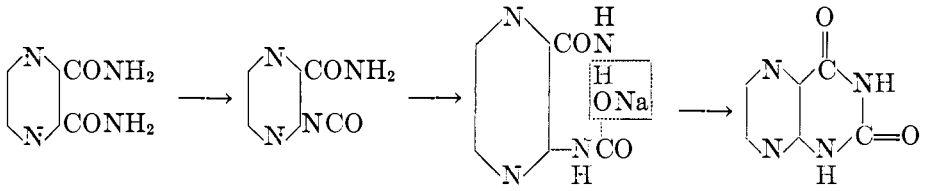
Gabriel and Sonn (89) investigated the diamide of the ortho diacid. They discovered that, although 1 mole of hypobromite reacted with 1 mole of the diamide to give the expected 2-amino-3-pyrazinoic acid, 2 moles of the hypobromite effected cyclization:



A similar course of events was observed in the pyridine series.

The condensed heterocycle was subsequently synthesized in other ways and given the name of lumazine. As has been already noted, use has been made of this compound and its derivatives in the synthesis of other pyrazines.

The formation of lumazine may be accounted for on the basis of the intermediate formation of a carbamate which is sufficiently stable under the conditions of the reaction to undergo intramolecular condensation:



It would seem, therefore, that the yields of lumazine and 2-amino-3-pyrazinoic acid are functions of the relative rates at which the carbamate group reacts either intramolecularly with the amide group or intermolecularly with the alkaline medium. Furthermore such rates, from the observations of Gabriel and Sonn, apparently depend upon the concentration of the hypobromite.

Ellingson, Henry, and McDonald (70) were unsuccessful in an attempt to prepare the 2,3-diamine by the Hofmann degradation of 2-amino-3-pyrazinecarboxamide. When the acetyl derivative was employed, two unexpected products were obtained which were not identified.

Further evidence of the stabilizing effect of the pyrazine nucleus is found in the work of Erickson and Spoerri (75) on 2,5-pyrazinedicarboxamide. After failing to obtain the diamine by the normal Hofmann degradation, they prepared the intermediate compounds, using the Curtius reactions. In this way they could determine at which stage the sequence was halted. The diazide of 2,5-pyrazinedicarboxylic acid was synthesized by treating the dihydrazide with nitrous acid (it could not be obtained by reacting the diacid chloride with sodium azide). After either heating the diazide in benzene or treating it with ethanol, the diisocyanate or the diurethan was respectively obtained.

Now, in the normal Hofmann and Curtius reactions the isocyanate which is formed immediately hydrolyzes under the conditions to the amine. In this case, however, the diisocyanate (and the diurethan) was found to be extremely stable toward both alkaline and acid hydrolysis. Heating the diisocyanate (or diurethan) with fuming hydrochloric acid at 210°C. in a sealed tube or fusing it with solid potassium hydroxide had slight effect. It is of interest to add that the diamine sought could not be prepared according to Gabriel's method, for the diphthalimide which was made by the action of phthalic anhydride on the diazide proved incapable of hydrolysis.

In addition to the Hofmann degradation, the amides undergo the other reactions characteristic of these compounds. An example of the Bouveault reaction with nitrous acid is given in table 18.

The dehydration of the amides to the nitriles requires the most vigorous dehydrating agents. The syntheses of cyanopyrazine (21, 60) and 3-amino-2-cyanopyrazine (70) were achieved only by distilling the corresponding amides with phosphorus pentoxide.

Gabriel and Sonn (89, 166) formed the imide of 2,3-pyrazinedicarboxylic acid by heating the 2,3-diamide in vacuum.

The 2,5-dicarboxamide was observed to be quite refractory toward the standard dehydrating agents (129). After refluxing the compound in acetic anhydride in an attempt to dehydrate one of the amide groups, it was found that acetylation had taken place after 48 hr., forming the diacetyldiamide of 2,5-pyrazinedicarboxylic acid. To obtain the 2,5-dicyanopyrazine it was necessary to reflux the diamide with phosphorus pentoxide in nitrobenzene, the solvent being necessary to avoid extensive decomposition.

e. Cyanopyrazines

There is little that need be said concerning the cyanopyrazines. They have been prepared by the dehydration of amides, by direct cyanation, and by the cyclization of certain nitriles. The hydrolytic reactions have already been discussed under the carboxylic acids and amides. An investigation was made to determine whether these compounds undergo any of the typical addition reactions (21, 60). Cyanopyrazine was successfully converted into the pyrazinoyl methyliminoether hydrochloride by the action of hydrogen chloride in methanol.

This addition compound was then treated with ammonia to form the pyrazinoylamidine hydrochloride.

f. Acid anhydrides—pyrazine "phthaleins"

The ortho diacid in many ways resembles phthalic acid. Thus it is easily converted to the anhydride by heating with either acetic anhydride or thionyl chloride.

De and Dutta (59) have synthesized a number of the phthalein-type dyes by condensing the *o*-pyrazinedicarboxylic acid with various phenols and amines. The use of such condensing agents as zinc chloride was not essential, but in some cases did improve the yields. Compared with the corresponding benzene derivatives, the pyrazine "phthaleins" were found to possess greater intensity of color but less fluorescence.

Table 23 summarizes the compounds which have been thus prepared. In

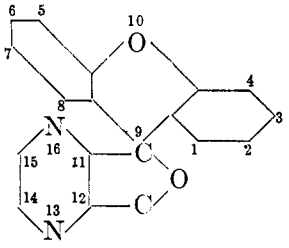
TABLE 23

Pyrazine dicarboxyleins (59)

COMPOUND CONDENSED WITH 2,3-PYRAZINEDICARBOXYLIC ACID	PRODUCT
Resorcinol	3,6-Dihydroxypyrazine dicarboxylein*
Orcinol	2,7-Dimethylpyrazine dicarboxylein
Phloroglucinol	1,3,6,8-Tetrahydroxypyrazine dicarboxylein
m-Aminophenol	3,6-Diaminopyrazine dicarboxylein
N-Dimethylamino-*m*-phenol	3,6-Di(*N*-dimethylamino)pyrazine dicarboxylein
N-Diethylamino-*m*-phenol	3,6-Di(*N*-diethylamino)pyrazine dicarboxylein
m-Phenylenediamine	3,6-Diamino-10-iminopyrazine dicarboxylein

* The bromination of 3,6-dihydroxypyrazine dicarboxylein resulted in the formation of 2,4,5,7-tetrabromo-3,6-dihydroxypyrazine dicarboxylein.

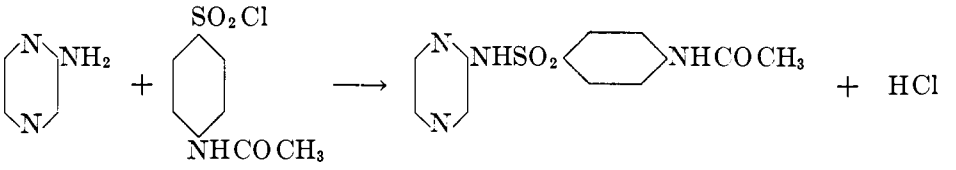
order to facilitate the naming of these compounds we shall use the following skeleton, which will be termed pyrazine dicarboxylein in accordance with the usage of De and Dutta:



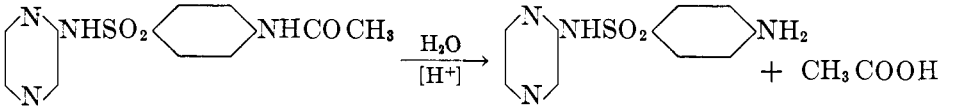
5. Aminopyrazines

We have seen that the aminopyrazines may be prepared directly by amination, by ammonolysis of the halopyrazines, or more widely by the Hofmann degradation of the amides.

The most important practical application of these substances has been in the syntheses of various sulfapyrazines. Generally, the aminopyrazine is first treated with acetylsulfanilyl chloride:

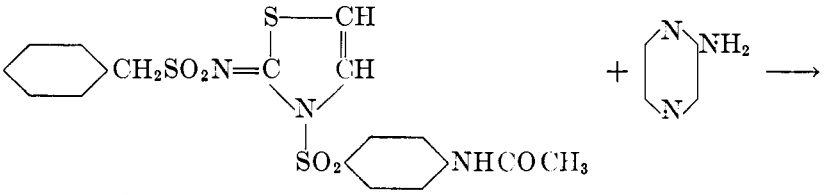


The N^4-acetylsulfanilamidopyrazine is then hydrolyzed to split off the protecting acetyl group:

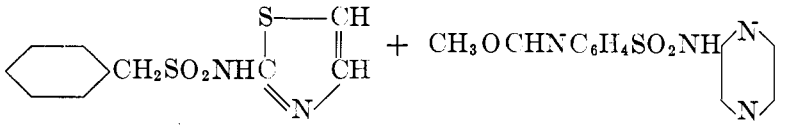


In table 24 there will be found a summary of the sulfanilamidopyrazines that have been made in this manner.

A novel method of preparing sulfanilamidopyrazine from aminopyrazine is that reported in the patent of Hartmann, Cueni, Druey, and von Meyenberg (102a). It is stated that when aminopyrazine is reacted with 2-[benzylsulfonimido]-3-[*p*-acetylaminobenzenesulfonyl]thiazoline (I) an exchange takes place to form acetylsulfanilamidopyrazine (II) and 2-benzylsulfonamidothiazole (III).



I



III II

The latter may be treated with *p*-acetylsulfanilyl chloride to regenerate the sulfanilamide donor (I). Such a technique further suggests itself for the preparation of those sulfanilamidopyrazine derivatives which may be otherwise inaccessible (*vide infra*).

While investigating the sulfanilamidopyrazines, Ellingson and his coworkers (70, 149) discovered certain peculiarities evidently due to the electronic effects of the two ring nitrogens. They found it impossible, for example, to prepare

3-sulfanilamido-2-pyrazinoic acid directly by the condensation of 3-amino-2-pyrazinoic acid with sulfanilyl chloride. To obtain the desired product it was necessary to proceed by way of the hydrolysis of 3-sulfanilamido-2-pyrazinamide (table 24).

TABLE 24

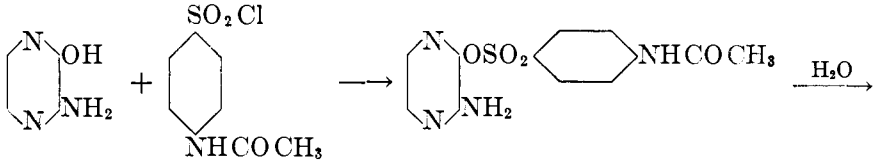
Sulfanilamidopyrazines

AMINOPYRAZINE	N^4-ACETYLSULFANILAMIDOPYRAZINE	SULFANILAMIDOPYRAZINE	REFERENCES
2,5-Dimethyl-3-aminoaminopyrazine	3-[N^4-Acetylsulfanilamido]-2,5-dimethylpyrazine	3-Sulfanilamido-2,5-dimethylpyrazine	(116)
Aminopyrazine	2-[N^4-Acetylsulfanilamido]pyrazine	2-Sulfanilamidopyrazine	(68, 70, 179, 185, 186)
2-Amino-5,6-dimethylpyrazine	2-[N^4-Acetylsulfanilamido]-5,6-dimethylpyrazine	2-Sulfanilamido-5,6-dimethylpyrazine	(227)
2-Amino-5,6-diphenylpyrazine	2-[N^4-Acetylsulfanilamido]-5,6-diphenylpyrazine	2-Sulfanilamido-5,6-diphenylpyrazine	(227)
2-Amino-6-methylpyrazine	2-[N^4-Acetylsulfanilamido]-6-methylpyrazine	2-Sulfanilamido-6-methylpyrazine	(227)
2-Amino-5-methylpyrazine	2-[N^4-Acetylsulfanilamido]-5-methylpyrazine	2-Sulfanilamido-5-methylpyrazine	(227)
2-Amino-5(or 6)-phenylpyrazine	2-[N^4-Acetylsulfanilamido]-5 (or 6)-phenylpyrazine	2-Sulfanilamido-5(or 6)-phenylpyrazine	(227)
2-Amino-3-carbomethoxypyrazine	2-[N^4-Acetylsulfanilamido]-3-carbomethoxypyrazine	2-Sulfanilamido-3-carbomethoxypyrazine	(90)
3-Amino-2-pyrazinamide	3-[N^4-Acetylsulfanilamido]-2-pyrazinamide	3-Sulfanilamido-2-pyrazinamide	(90)

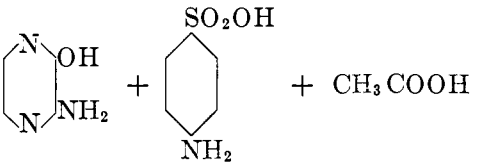
In attempting to prepare the sulfanilamido derivatives of some bifunctionally substituted pyrazines, further interesting behavior was brought to light (149).

When 2-hydroxy-3-aminopyrazine (I) was treated with acetylsulfanilyl chloride the hydroxyl group was preferentially esterified to yield 3-amino-2-pyrazinyl *p*-acetamidobenzenesulfonate (II). However, when it was desired to

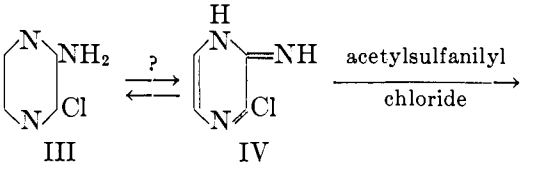
cleave the protecting acetyl group, this could not be done without hydrolyzing the sulfonic ester linkage as well:



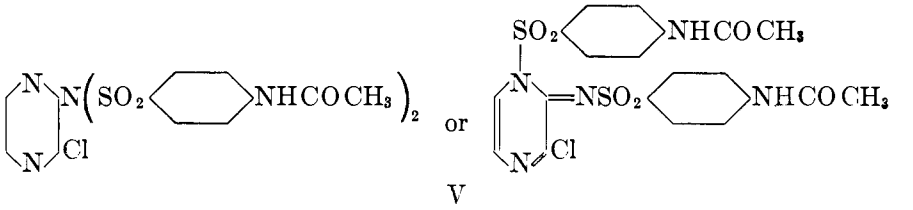
I II



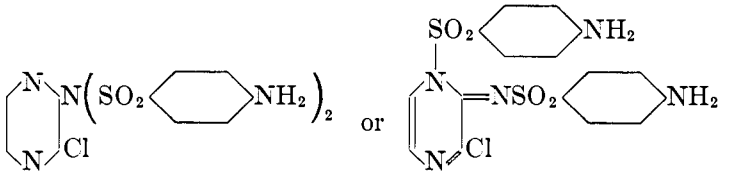
2-Amino-3-chloropyrazine (III) with acetylsulfanilyl chloride yielded a 2-(?)-di-N^4-acetylsulfanilylamido-3-chloropyrazine (V). The question mark appears since there are two possible ways in which the condensation may have occurred: either both acetylsulfanilyl groups reacted with both hydrogens of the amino nitrogen or, with one hydrogen atom on each of two of the nitrogens of the tautomeric imino form (IV).



III IV



V



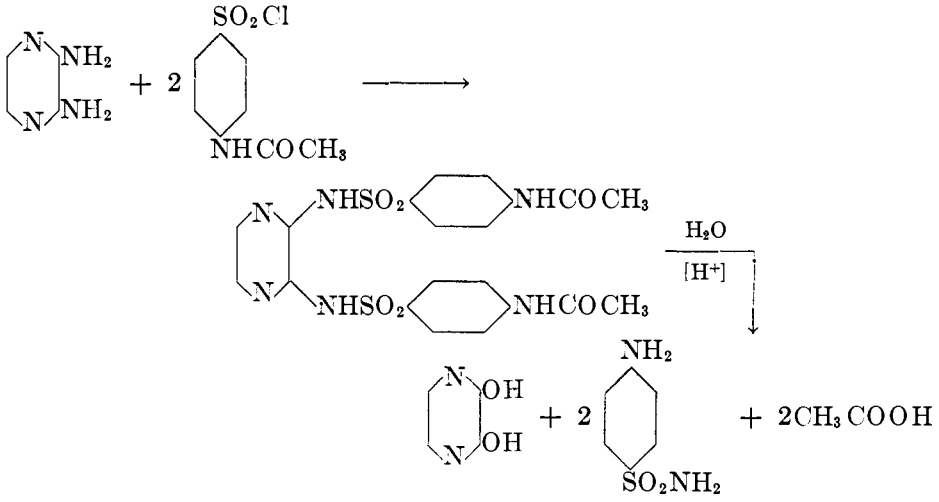
VI

All efforts to induce monocoupling only, by proper adjustment of reagent concentrations, failed. Nor could the monocoupled compound be obtained by

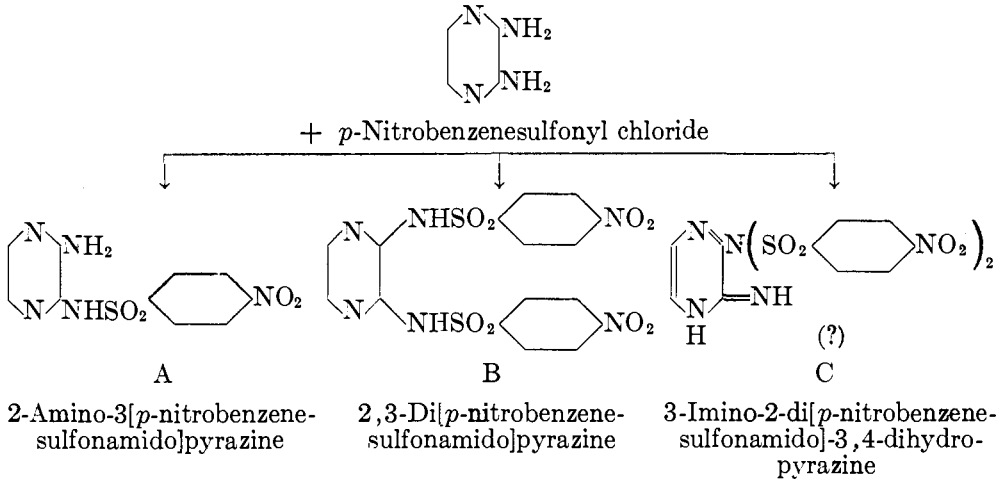
the controlled hydrolysis of the dicoupled compound; the only effect was to cleave the protecting acetyl groups, resulting in 2-(?)-disulfanilylamino-3-chloropyrazine (VI).

When acetylsulfanilyl chloride was reacted with 2,3-diaminopyrazine, one hydrogen atom of each of the amino groups was replaced, forming 2,3-di-[N^4-acetylsulfanilamido]pyrazine. The evidence for this was the solubility of the resulting compound in dilute alkali, for the only other alternative, 2-amino-3-di-[N^4-acetylsulfanilamido]pyrazine, would be expected to be more basic because of its free amino group.

Again, attempts to remove the protecting acetyl groups resulted in the cleavage of the sulfanilamido residue.



The action of *p*-nitrobenzenesulfonyl chloride on 2,3-diaminopyrazine resulted in the formation of three substances:



A — 2-Amino-3[*p*-nitrobenzenesulfonamido]pyrazine

B — 2,3-Di[*p*-nitrobenzenesulfonamido]pyrazine

C — 3-Imino-2-di[*p*-nitrobenzenesulfonamido]-3,4-dihydropyrazine

The reduction of B gave several products which could not be characterized.

Because of the weak bascity of the aminopyrazines, the usual methods of diazotization are not very efficient. In order to consummate the reaction it has been found necessary to use nitrosylsulfuric acid in concentrated sulfuric acid. By such means the diazotization of aminopyrazine and 2-amino-3-pyrazinoic acid was accomplished. These diazonium compounds were not isolated, but immediately hydrolyzed into hydroxypyrazine and 2-hydroxy-3-pyrazinoic acid, respectively (76, 77).

6. Hydroxypyrazines

In addition to the above device of hydrolyzing the diazonium compounds, the hydroxypyrazines have been prepared by the hydrolysis of the halopyrazines and the aminopyrazines.

The hydroxypyrazines may be easily esterified by acetic anhydride and

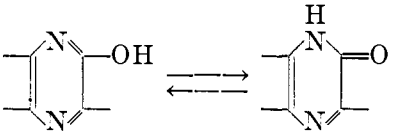
TABLE 25

Esterification of hydroxypyrazines

REACTANTS	ESTER	REFERENCES
Fructosazine and acetic anhydride	Fructosazine octaacetate	(140)
2-Methylol-5-pyrazinoic acid and acetic anhydride	Acetic ester of 2-methylol-5-pyrazinoic acid	(215)
Hydroxypyrazine and acetic anhydride	Acetoxypyrazine	(76, 77)
Di-*o*-hydroxyphenylpyrazine and benzoyl chloride	Di-*o*-benzoyloxy-2,5-diphenylpyrazine	(224)
o,o',p,p'-Tetrahydroxy-2,5-diphenylpyrazine	*o,o',p,p'*-Tetrabenzoyloxy-2,5-diphenylpyrazine	(224)

benzoyl chloride. These reactions are listed in table 25. For completeness we have also included those pyrazines which contain hydroxyl groups on the side chains.

The hydroxypyrazines are formally capable of tautomerizing into ketodihydropyrazines:

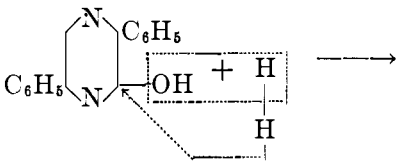


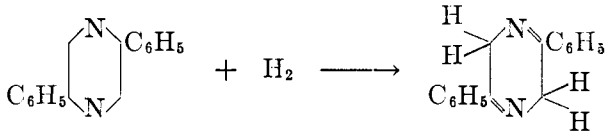
In some instances, for example, 2,5-diphenyl-3-hydroxypyrazine (112), the keto form seems to predominate completely. This conclusion is based on such behavior as the inability of the hydroxyl group to undergo acetylation.

Japp and Knox (112) offered as further evidence the fact that this substance

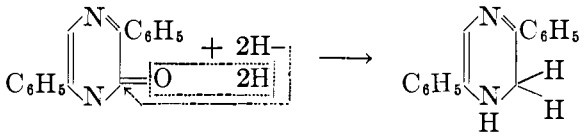
is reduced to 2,5-diphenyl-3,4-dihydropyrazine with phosphorus and hydrogen iodide. Their reasoning was that if the compound existed in the keto modification the oxygen atom would be replaced by the two atoms of hydrogen simultaneously, leading to the 3,4-dihydropyrazine. In the case of the enol however, it was thought that the hydroxyl group would be replaced by hydrogen, forming a pyrazine which could not be further reduced. Now, this is not a strictly valid argument, for it is based upon the premise that phosphorus and hydrogen iodide will not reduce 2,5-diphenylpyrazine. That it could be reduced by this reagent was shown by the work of Gastaldi (90), who obtained 2,5-diphenyl-3,6-dihydropyrazine as the result of such a reaction. The argument of Japp and Knox may be revised, however, to bring it into conformity with the evidence. One must first note that the dihydropyrazines obtained by Japp and Knox and Gastaldi differ in the location of the saturating hydrogen atoms.

It is a plausible assumption that on reduction a hydroxypyrazine will give the same dihydropyrazine as a pyrazine, for it doubtless passes through the latter stage:





On the other hand, a keto pyrazine may yield a different dihydropyrazine, for the carbonyl carbon may be reduced without passing through a pyrazine stage:



Thus, it is seen that the enol form should give a 3,6-dihydropyrazine identical with that obtained by Gastaldi from 2,5-diphenylpyrazine, whereas the keto form should yield a 3,4-dihydropyrazine. Since the latter compound was actually obtained, it must be concluded that the ketonic formulation is correct.

Gastaldi and Princivalle have attacked this problem for the alkylhydroxypyrazines by studying the behavior of these compounds with diazonium salts. It was observed that coupling took place in a normal manner, and this was considered as good evidence that the alkylhydroxypyrazines possessed the enolic configuration.

The reaction was successfully carried out with 2,5-dimethyl-3-hydroxy-

pyrazine and the phenyldiazonium, *o*-tolyldiazonium, and *p*-tolyldiazonium salts to yield the corresponding azo dyes: 3-phenylazo-2,5-dimethyl-6-hydroxypyrazine, 3-*o*-tolylazo-2,5-dimethyl-6-hydroxypyrazine, and 3-*p*-tolylazo-2,5-dimethyl-6-hydroxypyrazine (178). The necessity for the enol form in coupling is further shown by the inability of 1,2,5-trimethyl-6-keto-1,6-dihydropyrazine to couple with diazonium compounds (178).

The coupling of *p*-hydroxypyrazinecarboxylic acids is unusual in that it is accompanied by the elimination of the carboxyl group. Thus 2,5-dimethyl-6-hydroxy-3-pyrazinoic acid, coupled with either benzenediazonium chloride or *p*-tolyldiazonium chloride, yields either 3-phenyl-2,5-dimethyl-6-hydroxypyrazine or 3-*p*-tolylazo-2,5-dimethyl-6-hydroxypyrazine (178).

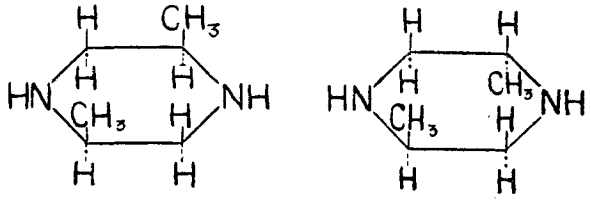
Similar behavior has been observed in the coupling of certain other hydroxycarboxylic acids, among which may be mentioned α-hydroxynaphthoic acid, *p*-hydroxybenzoic acid, and acetoacetic ester.

E. REDUCTION OF PYRAZINES

The pyrazine nucleus resembles that of pyridine in its behavior toward reducing agents. They are both much more easily reduced then benzene; in fact, sodium and ethanol, which do not affect benzene, are very effective for the reduction of pyridine and pyrazine to the fully saturated piperidines and piperazines. The analogy with pyridine cannot be carried too far for the other diazines; for, although some pyridazine derivatives may be smoothly reduced, others, including pyridazine itself, are cleaved at the N—N bond.

Other methods have been applied toward the reduction of the pyrazines. Analgams of various types, tin and hydrochloric acid, and catalytic hydrogenation have been employed for the conversion into the piperazines. Red phosphorus and hydrogen iodide is a reagent which will effect partial reduction. This is illustrated in its action on 2,5-diphenylpyrazine, which is reduced to 2,5-diphenyl,3,6-dihydropyrazine (90). Table 26 is a compilation of the reductions carried out in the pyrazine series.

It is perhaps not amiss to point out that in the case of the substituted piperazines the possibilities of geometrical and optical isomerism may arise. Thus for 2,5-dimethylpiperazine *cis* and *trans* forms may result, of which the former would constitute a racemic pair, and the latter an internally compensated meso form.



Kipping (123, 124) has reinvestigated the reduction of tetramethylpyrazine. There are five possible geometric isomers, of which two will be racemic pairs (II to V), and three will be meso forms (I, III, and IV).

Attempts were made to isolate all five of the isomers by using various reducing agents (table 26) and then separating the products by fractional crystallization.

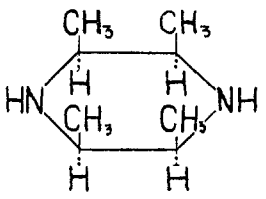
TABLE 26

Reduction of pyrazines

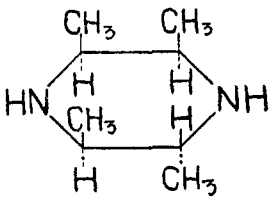
PYRAZINE	REDUCED PYRAZINE	REDUCING AGENT	REFERENCES
2,5-Dimethylpyrazine	2,5-Dimethylpiperazine (*cis* and *trans*)	Sodium in ethanol	(177, 207)
2,5-Dimethylpyrazine	2,5-Dimethylpiperazine (*trans*)	Hydrogen over nickel	(94)
Trimethylpyrazine	Trimethylpiperazine (two stereoisomers)	Sodium in ethanol	(207)
Pyrazine	Piperazine	Sodium in ethanol	(238)
2-Methylpyrazine	2-Methylpiperazine	Sodium in ethanol	(211)
2,5-Dimethyl-3-ethylpyrazine	2,5-Dimethyl-3-ethylpiperazine (two stereoisomers)	Sodium in ethanol	(207)
2,3-Diphenylpyrazine	2,3-Diphenylpiperazine (two stereoisomers)	Sodium in amyl alcohol	(146)
2,5-Diphenylpyrazine	2,5-Diphenyl-3,6-dihydropyrazine	Phosphorus and hydrogen iodide	(90)
Tetramethylpyrazine	Tetramethylpiperazine (two stereoisomers)	Sodium in ethanol	(207)
Tetramethylpyrazine	β- and γ-tetramethylpiperazines	Hydrogen over platinum	(123)
Tetramethylpyrazine	α-, β-, and γ-tetramethylpiperazines	Aluminum amalgam in neutral solution	(123)
Tetramethylpyrazine	α- and β-tetramethylpiperazines	Sodium amalgam in neutral solution	(123)
Tetramethylpyrazine	α-, β-, γ-, and δ-tetramethylpiperazines	Tin and hydrochloric acid	(123)
Tetramethylpyrazine methiodide	2,3,4,5,6-Pentamethylpiperazine	Hydrogen over platinum	(124)

In order to determine the configuration of each of the stereoisomeric fractions, the following approach was used. II and V could be differentiated from the

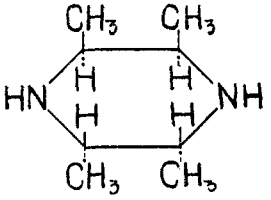
meso forms by the fact that they were capable of resolution. It was further noted that in II the environment of the two ring nitrogen atoms was different,



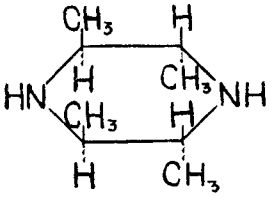
I



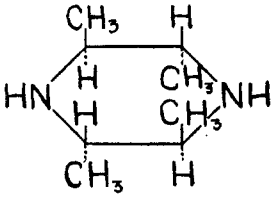
II



III



IV



V

whereas in V it was the same. Hence, if each of the nitrogens were substituted with a different group, II would give two different compounds whereas V would give one and the same compound. This could therefore be used as a means for distinguishing II from V.

In the case of the meso forms, III could be differentiated from the other two by the fact that if one of the nitrogens were substituted by another group, III would become asymmetrical and therefore resolvable.

As a result of his experiments Kipping was able to isolate four of the five possible isomers, which he designated as α, β, γ, and δ.

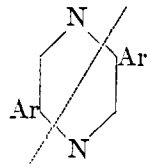
He was further able to correlate β with the structure of II, by proceeding along the lines indicated above. In the other cases structural correlation proved too difficult, because the properties of the substances were unsuitable for the operations necessary to effect the requisite separations and resolutions.

F. DEGRADATIONS OF THE NUCLEUS

Pyrazine and its alkyl and aryl homologues are stable toward the action of acids such as sulfuric and hydrochloric, as well as alkalies. They are also quite inert to heat, since even the higher-boiling members may be distilled at atmospheric pressure without decomposition.

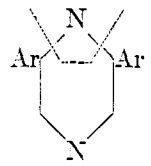
In contrast to pyridine, which may serve as an inert solvent for permanganate, pyrazine is susceptible to the action of this oxidizing agent (210). This is further demonstrated in most of the side-chain oxidations, where the yields are very poor because of the extensive nuclear destruction (exception: quinoxalines).

Hydrogen iodide in glacial acetic acid has been observed by Tutin (224) to cleave the nucleus of substituted pyrazines in one of two ways, depending on the orientation of the substituents. The 2,5-diarylpyrazines, as exemplified by *p,p'*-dimethoxy-2,5-diphenylpyrazine and *m,m',p,p'*-tetramethoxy-2,5-diphenylpyrazine, were found to yield the hydroiodides of *ω*-amino-*p*-hydroxyacetophenone and *ω*-amino-*m,p*-dihydroxyacetophenone, respectively:



$$\xrightarrow[CH_3COOH]{HI} ArCOCH_2NH_3I$$

In the case of the 2,6-diarylpyrazines, the cleavage took another course, forming the hydroiodides of the diphenacylamines:



$$\xrightarrow[CH_3COOH]{HI} (ArCOCH_2)_2NH_2I$$

Thus, with 2,6-diphenylpyrazine, *p,p'*-dimethoxy-2,6-diphenylpyrazine, and *m,m',p,p'*-tetramethoxy-2,6-diphenylpyrazine there resulted the corresponding hydroiodides of diphenacylamine, *p,p'*-dihydroxydiphenacylamine, and *m,m',p,p'*-tetrahydroxydiphenacylamine. These two types of cleavage are interesting in that they may be viewed as being the reverse of the cyclizations leading to the formation of the pyrazines.

Gastaldi and Princivalle (91) have shown that the quaternary salts of certain hydroxypyrazines may be split with alkalies to yield the *N*-alkylamines. Specifically, methylamine, equivalent to both nitrogen atoms, was obtained when the methiodides of both 1-methyl-2,5-diphenyl- and 1-methyl-2,5-dimethyl-6-keto-1,6-dihydropyrazine were treated with alkali. This is analogous to the situation in the imidazole series, where alkalies cause the cleavage of the *N*-alkyl quaternary salts into the *N*-alkylamines (Rung–Behrend–Pinner reaction).

G. UNCLASSIFIED

Tota and Elderfield (220) cleaved the ether 2-methyl-3-ethoxyethyl-5-hydroxypyrazine with hydrogen bromide in glacial acetic acid. There resulted a compound which was believed to have the structure of 2-methyl-3,*β*-bromoethyl-5-hydroxypyrazine. The probability of the correctness of this structure was increased by the observation that the compound could be dehydrohalogenated with 5 per cent sodium carbonate to yield 2-methyl-3-vinyl-5-hydroxypyrazine.

In conclusion the authors wish to acknowledge the active interest of Mr. Bernard Klein during the writing of this paper.

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