Glyoxal Bishydrazones through
Facile Ring Cleavage of Hydrazinopyrazine by Hydrazines

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The reaction of chloropyrazine and hydrazine was reinvestigated and was shown to produce hydrazinopyrazine and glyoxal bishydrazone. The latter was obtained also when hydrazine hydrochloride was allowed to react with hydrazinopyrazine. The fusion of hydrazinopyrazine at 160° produced glyoxal bis(pyrazinylhydrazone). The interconversions of glyoxal bishydrazone with hydrazinopyrazine were studied. Mechanisms to explain the various transformations are discussed.

In our previous paper, we reported the degradative ring cleavage of 3-benzenesulfonyloxylumazine with sodium methoxide in methanol to give the ester **1a**. Subsequent hydrolysis of **1a** afforded the corresponding acid **1b**, which was decarboxylated to give s-triazolo[4,3-a]pyrazine-3-(2H)one, **1c**.

1, a, R CO₂CH₃,
   b, R CO₂H
   c, R H
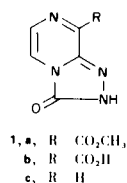
Our attempts to synthesize **1c** by reacting hydrazinopyrazine with either urea, or ethyl chloroformate, or phosgene, failed. We did observe, however, when hydrazinopyrazine was fused with urea, a new compound was isolated, whose mass spectrum differed considerably from that expected for **1c**. Furthermore, the new compound isolated proved to be identical with a byproduct which was also formed during the synthesis of hydrazinopyrazine from chloropyrazine from chloropyrazine and hydrazine. This prompted us to investigate the structure of this new compound, its origin and its possible involvement in preventing the formation of **1c** from hydrazinopyrazine and the various carbonic acid derivatives mentioned above.

The Reaction of Chloropyrazine and Hydrazine.

When chloropyriazine and hydrazine were refluxed in ethanol for several hours, and the solvent removed, hydrazine was isolated by extracting the residual mixture with benzene. The benzene-insoluble residue was triturated with water to permit isolation of a yellow substance. This solid proved to be identical to one described by Mallett and Rose

(2), who had isolated it previously as a byproduct from their synthesis of hydrazinopyrazine. The only difference in their synthesis of hydrazinopyrazine was that they used water as the solvent for their reaction, while we had used ethanol. However, we repeated their experiment in water and reisolated their compound which was identical to our "new compound". They assigned structure **2** to this compound based on their elemental analysis and unfortunately, an incorrect interpretation of the pmr spectrum.
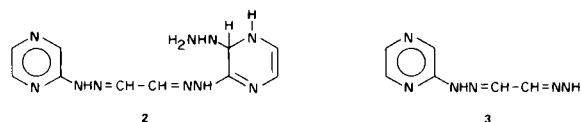
None of the spectral data fit the proposed structure, **2**. The mass spectrum of the compound shows a molecular ion, m/e 164, which is too small for **2**. The pmr spectrum in DMSO-d_6 shows a broad peak at δ 7.23, which integrated for 2 protons and is exchangeable with deuterium oxide, and AB quartet at δ 7.47 and 7.76, three pyrazine ring protons with the expected coupling constants, and another exchangeable proton downfield at δ 10.90. On the basis of our data we assign structure **3** to this compound. Furthermore, we were able to synthesize this compound from glyoxal bishydrazone and hydrazinopyrazine, by amine exchange (see below). The mass spectra fragmentation pattern agreed with the proposed structure **3** and is discussed below.

The possibility that **3** originated from the attack of one molecule of hydrazinopyrazine on another was ruled out on the basis of the following experiment.

When hydrazinopyrazine, hydrazinopyrazine hydrochloride, or an equal mixture of the base and salt, were refluxed in ethanol for 6 hours, only starting material could be

recovered. In the same vein, when a mixture of hydrazino-pyrazine and hydrazine was boiled in ethanol, hydrazino-pyrazine was recovered and the presence of 3 could not be detected. However, a reaction took place when hydrazino-pyrazine and hydrazine hydrochloride was reacted in hot ethanol and 3 was formed. It then became apparent that proton catalysis is essential in promoting a reaction between hydrazine and hydrazinopyrazine. This fact is rather logical since during the formation of hydrazinopyrazine from chloropyrazine, hydrogen chloride is formed and could then act as a catalyst for the formation of 3. Actually, when the benzene-insoluble residue from the reaction of chloropyrazine and hydrazine was examined further, it was obvious that 3 was not originally present. The pmr spectrum, in DMSO or deuterium oxide solution, presented signals due to some (expected) hydrazinopyrazine and (residual) hydrazine, and a singlet at δ 7.58. However, with time, this peak increased, in relation to the other signals. Later, it was found that glyoxal bishydrazone, 4, gave rise to a singlet at δ 7.58 and its presence in the reaction mixture was proved by isolation and comparison to an authentic specimen (tlc, ir). However, the residue from the chloropyrazine-hydrazine reaction, when dissolved in water at 25° for several hours, did furnish 3. It was surmised, and later on substantiated, that 3 was formed by amine exchange from glyoxal bishydrazone, 4, and hydrazino-pyrazine. This is elaborated on further below.

Fusion of Hydrazinopyrazine.

In our attempts to synthesize 1c equal quantities of hydrazinopyrazine and urea were fused originally at 160°. The only product which could be isolated was 5. Its structure was established by comparison with an authentic sample synthesized from glyoxal bisulfite and hydrazino-pyrazine (2). Later, we found that if urea was omitted, 5

NH₂N CH-CH NNH₂

4

5
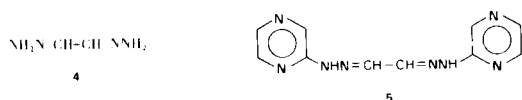
was obtained in good yield. This pyrolysis was accompanied by the evolution of a basic gas. It is suggested that the mechanism of this reaction is analogous to the one with hydrazine but proceeds only at elevated temperature. In summary, it appears that hydrazinopyrazine reacts with itself only at high temperature, but fails to react in ethanol, with or without hydrogen chloride as catalyst. Hydrazine fails to attack hydrazinopyrazine in boiling ethanol, unless hydrogen chloride is present to catalyze the reaction.
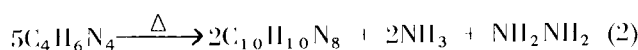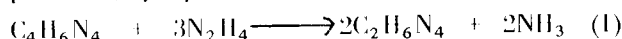
The Mechanism for Ring Opening.

The mechanism of the two pertinent reactions is discussed in one scheme, where R is either H or the pyrazinyl

group. The products arise if hydrazinopyrazine, 6, is attacked initially at either its 5 or 6 position by the requisite hydrazine, RNHNH₂. The proposed mechanism is illustrated only by starting with nucleophilic attack at C-6 to form the dihydropyrazine, 7. This kind of intermediate 7,
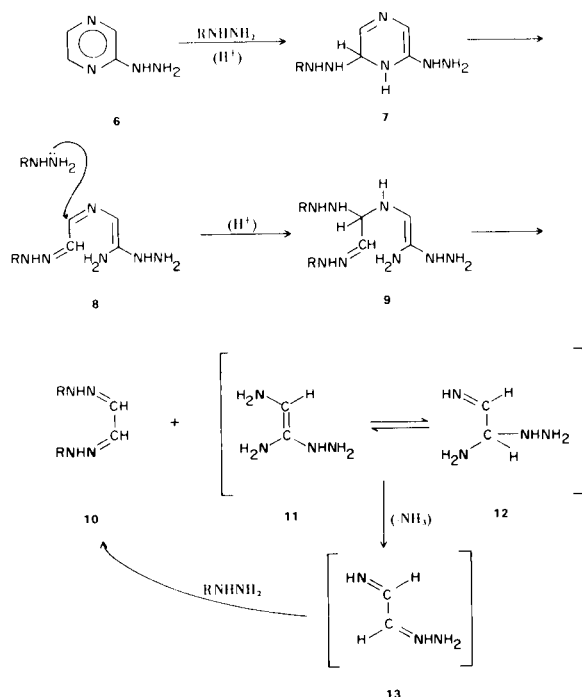
resembles the one postulated for the first step for the Dimroth Type of reactions in the pyrimidine series. Ring opening of 7 can lead to 8, which may add another molecule of hydrazine across the imine double bond. Subsequent elimination of a molecule like 11, from 9, would give rise to glyoxal bishydrazone, 10. The tautomer of 11, viz., 12, could lose ammonia, to form another molecule of glyoxal bishydrazone. This can be accomplished from 12, either by the elimination of ammonia (as shown) or hydrazine, followed by amine interchange of 13 with RNHNH₂ to give this other molecule of 10.

On the basis of these mechanisms, the stochiometry for the acid-catalyzed reaction of hydrazine with hydrazino-pyrazine to form glyoxal bishydrazone, 4, is governed by equation 1, and that of fusion of hydrazinopyrazine to provide 5, by equation 2:

$$C_4H_6N_4 + 3N_2H_4 \longrightarrow 2C_2H_6N_4 + 2NH_3 \quad (1)$$

$$5C_4H_6N_4 \xrightarrow{\Delta} 2C_{10}H_{10}N_8 + 2NH_3 + NH_2NH_2 \quad (2)$$

Interconversion of Glyoxal Bishydrazones.

A number of pH-dependent conversions of glyoxal bishydrazone, 4, with 6 were observed in aqueous media. In essence, 3 and 4 undergo amine exchange reactions with

6 at various pH's and these are summarized below. It has been reported that 4 polymerized at pH < 5 (12), but in the presence of 6, it formed, 5. However, 4 reacted with 6 at pH ~ 8 to form 3. The latter can then react at various pH's to give 5 and the glyoxal polymer.
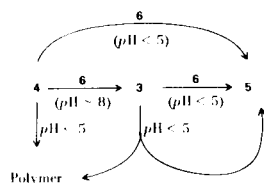

General Conclusions on the Reaction of 2-Hydrazinopyrazine and Carbonic Acid Derivatives.

A number of anomalies in this area remain to be explained. Cyclization of several 2-hydrazinopyridines with either urea, ethyl chloroformate or ethyl allophanate $(H_2NCONHCO_2C_2H_5)$ provided the corresponding s-triazolopyridines, based on structure 1c, (11). Our attempts to apply these and related methods to the conversion of 6 to 1c, failed. The clear-cut transformation of 3,6-dimethyl-2-hydrazinopyrazine with urea to form the 5,8-dimethyl derivative of 1c is reported and the compound is characterized by its spectra. Such detailed spectra data are not available for a series of related compounds. It is reported the 5,6-dimethyl-, 5,6-diphenyl-, 3-n-propyl-, 3,5,6-trimethyl- and 3-n-propyl-5-methyl-2-hydrazinopyrazines reacted and cyclized with phosgene to provide additional members of the series based on 1c (2,9).

On the basis of the mechanisms advanced above, it is reasonable to speculate that those 2-hydrazinopyrazines which have either substituents at C-6 or C-5 might react with carbonic acid derivatives and cyclize to compounds based on 1c. Such reactions, leading to structures based on 1c, would compete with any involving nucleophilic attack at C-6. It is somewhat more difficult to rationalize why 3-n-propyl- and 3-n-propyl-5-methyl-2-hydrazinopyrazines can be converted by phosgene (9) to compounds based on 1c, while 2-hydrazinopyrazine apparently fails to yield 1c. However, for the reactions involving the 3-n-propyl and 3-n-propyl-5-methyl analogs of 6, the authors did not
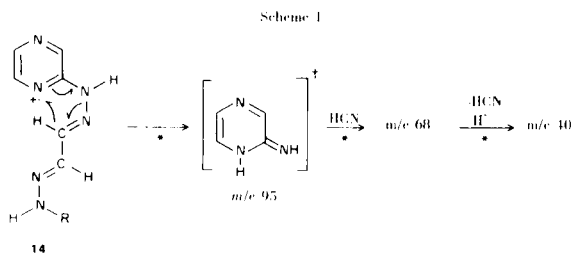
specify reaction times and reported either low or no percentage yields of these alkyl derivatives of 1c. The
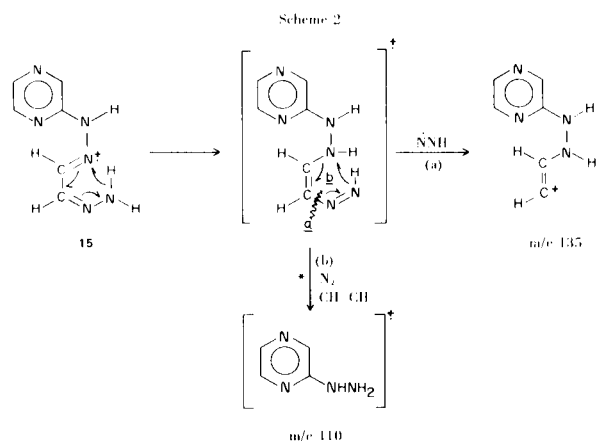
structure proof of the derivatives of 1c rested on elemental analyses and unfortunately no definitive spectral data are provided (9).

Furthermore, it was claimed that 6 reacted with phosgene to give a "carbamic acid" based on 6. However, the elemental analysis for this "carbamic acid" was unsatisfactory and only ir and uv spectral data are reported (9). Our attempts to repeat this reaction of 6 with phosgene in pyridine (25°), boiling benzene or boiling toluene (containing triethylamine) gave us only starting hydrazinopyrazine.

Mass Spectra of Glyoxal Bishydrazones.

The fragmentation pattern of the three relevant glyoxal hydrazones deserve some discussion. The dominant fragmentation from the molecular ions of 3, 4 and 5 arises from successive losses of RNH^* (R = H or pyrazinyl), and then HCN (twice). Metastable ions to support these transitions are listed in the appropriate section in the Experimental.

It had been established by means of a pmr spectral study (4), perchloric acid titrations (5) and dipole moment measurements (6) that glyoxal osazones exist in the non-chelating E-E conformation in solutions or in the crystalline state. Although these molecules are free to rotate about the C-C bond between connecting the hydrazone groups, the non-chelating E-E conformation apparently predominates in the gaseous state since their mass spectra are best interpreted from such a conformation. The fragment ion,

Scheme 4
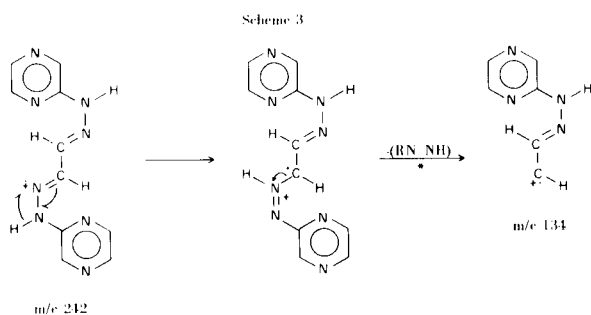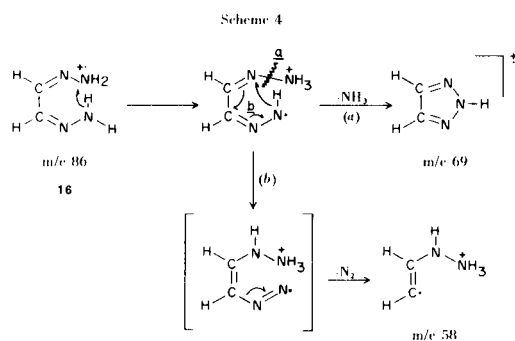
m/e 95, which is present to a considerable extent in the mass spectra of 3 and 5 can be explained if an E-E conformation is involved. The molecular ion 3 and 5, represented by 14 (R = H and 2-pyrazinyl, respectively) can lose RNH-N=CH-C≡N by a McLafferty rearrangement to give rise to m/e 95 as shown in Scheme 1. This ion may then lose HCN, and H⁺ + HCN) to produce ions, m/e 68 and 40.

The E-Z and Z-Z conformation of the molecular ions as represented by 15 and 16, may fragment to give rise to the ions m/e 135, 110 from 15 and 69, 58 from 16, respectively by mechanisms indicated in Schemes 2 and 4. The absence of ions m/e 135, 110 in the fragmentation of the molecular ion of 3 can be explained if one assumes that the bulky pyrazinyl groups would prefer to keep the molecule in the E-E conformation and the molecular ion gives rise to a fragment, m/e 134. This transition is explained in Scheme 3 and it is postulated that the ion m/e 242 (from 3) initially undergoes a hydrogen shift prior to the loss of RNNH⁺.

EXPERIMENTAL

Melting point apparati, spectrometers, tlc determinations have been described at the beginning of a previous Experimental Section (1).

Glyoxal Bishydrazone (4).

This compound was prepared in 60% yield from the reaction of 30% aqueous glyoxal with 95+% hydrazine (Eastman) according to the precedure of Bayer et al. (3). Recrystallization from chloroform provided the sample for this study; m.p. 93-95°, lit. m.p. (3) 100-102°, (10) 97-99°; pmr (DMSO): δ 7.58, lit. (5) δ 7.57; mass spectrum, (70 eV): m/e (rel intensity) 86 (66), 70 (20), 69 (20), 58 (15), 44 (6), 43 (100), 42 (37), 41 (39), 40 (12), 39 (6); metastable peaks 57.0 (86 → 70), 55.4 (86 → 69), 39.1 (86 → 58).

Glyoxal Bispyrazinylhydrazone (5).

This compound was synthesized by the modification of the published procedure (2). A solution of hydrazinopyrazine (0.22 g., 0.002 mole) and glyoxal bisulfite (0.24 g., 0.0009 mole) in 15 ml. of water was heated at 60° for 0.5 hour to yield a precipitate, which proved to be 5 (0.2 g., 91%), m.p. 335° dec., lit. m.p. (2) 320°; Its uv spectrum and its pmr spectrum in trifluoroacetic acid were identical with those in the literature (2); ir (Nujol): 3200 (NH), 1590, 1580 cm⁻¹; pmr (DMSO): δ 7.80 (s, CH=N), 7.95

(d, H-6), 8.10 (dd, H-5), 8.32 (d, H-3) (J$_{5,6}$ = 2.4, J$_{3,5}$ = 1.8 Hz), 11.1 (s, NH, broad); mass spectrum (70 eV): m/e (rel intensity) 242 (32), 148 (56), 135 (7), 134 (42), 121 (45), 120 (8), 96 (15), 95 (60), 94 (13), 81 (12), 80 (15), 79 (19), 69 (9), 68 (70), 67 (50), 65 (15), 54 (7), 53 (20), 52 (33), 43 (8), 42 (15), 41 (22), 40 (100), 39 (11); metastable peaks, 98.9 (148 → 121), 90.6 (242 → 148), 74.2 (242 → 134), 73.0 (121 → 94), 48.8 (95 → 68), 37.3 (242 → 95), 23.8 (68 → 40).

The same compound, 5, was also obtained by acidifying a suspension of 3 (0.2 g.) in 20 ml. water with concentrated hydrochloric acid (1 ml.). The mixture was cooled at 0° and then filtered. The filtrate was neutralized with sodium carbonate to pH 5. The precipitate was filtered, triturated with 10 ml. boiling ethanol and refiltered to give 5 (0.05 g.).

Glyoxal Hydrazone Pyrazinylhydrazone (3).

To a solution of 4 (0.5 g.) in 20 ml. water and added hydrazinopyrazine, 6, (0.3 g.) in one portion. The slightly turbid solution was kept at 25° for 24 hours, during which time 3 separated as yellow crystals (0.25 g., 56%), m.p. 335° dec. (sintered at 236°), lit. m.p. (2) 236-237°; recrystallization from DMSO (100°) did not change the m.p.; ir (Nujol): 3340, 3200 (NH's), 1580 cm⁻¹; pmr (DMSO-d$_6$): δ 7.23 (2, s, NH$_2$, broad), 7.47, 7.76 (2, AB quartet, 2 CH, J = 8.4 Hz), 7.95 (d, H-6 of pyrazine ring), 8.10 (dd, H-5), 8.38 (d, H-3) (J$_{5,6}$ = 2.5, J$_{3,5}$ = 1.4 Hz), 10.90 (1, s, broad, NH); uv max (ethanol): nm (log ε), 315 (4.42), 238-240 (3.77), lit. (2) uv max, 317.5 (4.69), 240-242 (4.00); mass spectrum (70 eV): m/e (rel intensity) 165 (10), 164 (71), 148 (38), 135 (15), 122 (8), 121 (100), 120 (10), 110 (34), 109 (10), 96 (11), 95 (37), 94 (17), 81 (6), 80 (6), 79 (12), 78 (10), 69 (12), 68 (57), 67 (34), 66 (12), 53 (13), 52 (22), 43 (33), 42 (16), 41 (23), 40 (54), 39 (9); metastable peaks, 133.6 (164 → 148), 98.9 (148 → 121), 73.7 (164 → 110), 73.0 (121 → 94), 48.8 (95 → 68), 23.7 (68 → 40).

Anal. Calcd. for C$_6$H$_8$N$_6$: C, 43.90; H, 4.91; N, 51.19. Found: C, 43.70; H, 4.98; N, 51.29.

The Reaction of Chloropyrazine with Hydrazine.

A solution of chloropyrazine (11.5 g., 0.1 mole), 95+% hydrazine (16 ml., 0.5 mole) and absolute ethanol (50 ml.) was refluxed for 3 hours. Solvents were evaporated in vacuo, and the residue was extracted with benzene (3 x 200 ml.) to give hydrazinopyrazine (6.4 g., 58%), m.p. 110-112°, lit. (7) 112-113°.

The benzene-insoluble residue was dissolved in water (20 ml.) and the clear yellow solution (pH = 8) was stored at 25° for 24 hours to provide 3 (0.4 g., m.p. 335°, dec.). The mother liquor was then acidified with concentrated hydrochloric acid to pH 5 to yield 5 (1.0 g., m.p. 335°, dec.).

In another run, the benzene-insoluble residue was dissolved in deuterium oxide or DMSO-d$_6$ and the solution was studied by pmr. It was found that no resonance signals corresponding to 3 could be detected. Besides signals due to residual hydrazinopyrazine and hydrazine, a singlet corresponding to glyoxal bishydrazone, 4, (δ 7.58) was observed (this singlet was intensified when 4 was added to this nmr solution). When the deuterium oxide solution was kept at 25° for several hours, it was noted that a yellow precipitate of 3 was formed gradually in the expense of 4 and hydrazinopyrazine. Proof for the existence of 4 in this mixture was provided when this substance was actually isolated from a similar reaction mixture as described in the next experiment.

The Reaction of Hydrazinopyrazine with Hydrazine Hydrochloride.

A solution of hydrazinopyrazine (3 g.), hydrazine hydrochloride (3 g.) 95+% hydrazine (3 ml.) and absolute ethanol (15 ml.) was refluxed for 44 hours. The reaction mixture was monitored by

pmr (in deuterium oxide) at several hours interval. It was found that the signal intensity at δ 7.58 increased with reaction time and reached its maximum in about 44 hours reflux. At the end of this period, the mixture consisted of two phases and was cooled at 5° for several hours. The oily lower layer proved to be excess hydrazine hydrochloride since only exchangeable protons were visible in its pmr spectrum. This layer was discarded. The upper layer was separated and evaporated to dryness *in vacuo*. The yellow semisolid mixture was extracted with boiling chloroform (5 x 20 ml.). The combined chloroform extracts were concentrated to about 20 ml. to furnish **4** (0.9 g., 20%, m.p. 95-97°).

Fusion of Hydrazinopyrazine.

Hydrazinopyrazine (0.5 g.) was heated at 160° for 15 minutes in a 25 ml. Erlenmeyer flask. During this period, a basic gas ($pH = 9$ to moistened Hydrion paper) was evolved continuously, which clouded when hydrogen chloride vapors were brought near its vicinity. The cold residue was triturated with water (10 ml.) and filtered to give **5** (0.22 g., 85%, based on recovered starting material, m.p. 335°, dec.).

After the filtrate was evaporated to dryness and the residue extracted with benzene, hydrazinopyrazine (0.2 g., 20%, m.p. 108° was recovered.

Fusion of Hydrazinopyrazine with Urea.

When hydrazinopyrazine (0.5 g.) was fused with urea (0.5 g.) at 160° for 15 minutes, a slightly different workup was employed.

The crude mixture was purified by dissolving in 30 ml. warm (60°) 10% hydrochloric acid solution. The filtrate was neutralized with sodium carbonate to pH 6. The precipitate was washed first with water, and then with ethanol to yield **5** (0.2 g., 46%, m.p. 335°).

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(12) The same polymer was also obtained by heating an aqueous solution of glyoxal bishydrazine, see also Ref. 3.