several days. It softened between 60 and 85° and began to flow at 100°. At about 150° bubbles appeared.

Anal. Calcd. for $(C_6HOBr_2F)_2$: Br, 59.65, mol. wt., 536. Found: Br, 58.48, mol. wt., 584.

Spontaneous Decomposition of the Sodium Salt of 2,4,6-Tribromo-3-fluorophenol.—The first sample prepared was kept for several months without decomposition, but almost all subsequent preparations decomposed in from several days to several hours as indicated by a change from colorless to brownish red. The decomposed salt showed no change in composition.

Anal. Calcd. for C_6HOBr_3FNa: Br, 64.67, Found: Br, 64.87.

The decomposed salt, 3.28 g., was extracted with 30 ml. of dioxane and the insoluble residue was centrifuged and washed twice with dioxane. After drying the yield was 0.86 g. of an almost white solid, corresponding to 94.5% of the sodium bromide expected on the basis of the formation of one molecule of sodium bromide per molecule of the sodium salt. Analysis for bromine indicated that the sodium bromide was 98.5% pure.

The dioxane soluble material was precipitated by the addition of water. After drying it was a brownish-red amorphous powder that did not melt up to 215°.

Anal. Calcd. for C_6HOBr_2F: Br, 59.65. Found: Br, 56.32; mol. wt., 2185 (8.2 times the smallest unit).

When the sodium salt of this phenol was heated with sodium carbonate solution it decomposed to give the same kind of brown, amorphous polymer described above.

Spontaneous Decomposition of the Sodium Salt of Tribromophenol.—This salt decomposed on standing in the same way as that of its 3-fluoro derivative. The decomposition in sodium carbonate solution was also observed. A sample of tribromophenol was treated with hot saturated sodium carbonate solution to give the same kind of polymer, a reddish-brown amorphous powder. This substance was washed free of inorganic salts and dried.

Anal. Calcd. for $C_6H_2OBr_2$: Br, 63.94. Found: Br, 61.73.

This product was purified by solution in dioxane and precipitation by alcohol. After two such treatments the analysis was better.

Anal. Calcd. for $C_6H_2OBr_2$: Br, 63.94. Found: Br, 63.68.

The molecular weight determination (mol. wt., 8300) was not reliable since the solution showed a Tyndall effect.

Summary

Several types of polymers of the composition $(C_6HOBr_2F)_n$ have been obtained, either from 2,4,6-tribromo-3-fluorophenol bromide by loss of two bromine atoms or from the sodium salt of 2,4,6-tribromo-3-fluorophenol by the elimination of one molecule of sodium bromide. Tribromophenol bromide, 2,4,6-tribromo-3-chlorophenol bromide and the sodium salt of tribromophenol undergo the same kind of reaction.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Syntheses in the Pyrazine Series. The Preparation and Properties of the Pyrazyl Halides

BY A. E. ERICKSON AND PAUL E. SPOERRI

In comparison with benzene, pyridine, pyrimidine and other six-membered conjugated ring systems, the chemistry of pyrazine compounds has received little attention. On the basis of the available literature, it appears that the lack of information on simple functional derivatives and transformations is due mainly to the fact that pyrazine does not undergo with practical facility the orthodox substitution reactions of direct halogenation, nitration, sulfonation, etc., which serve quite well in the other cyclic series. The major portion of the work published thus far has dealt with the chemistry of the pyrazine carboxylic acids, their derivatives and degradation products. In order to prepare some of the synthetically more versatile derivatives, a new approach seemed necessary. The present investigation has been concerned mainly with the preparation of the simple halogen derivatives which have hitherto been so noticeably lacking in pyrazine syntheses.

In regard to the halogenation of pyrazine, it is reported[1] that pyrazine reacts with bromine to give an addition product which is too unstable for isolation and characterization. To effect substitution of bromine would probably require, as it does in the case of pyridine[2] a vapor-phase reaction at elevated temperatures. However, it is unlikely that the pyrazine ring would survive such conditions. As an alternative method of preparation, it was thought that the well defined aminopyrazine[3] might serve as a source of the desired pyrazyl halides via diazotization and application of the Sandmeyer reactions. Preliminary efforts to diazotize amino-pyrazine by the usual procedure in dilute aqueous media were unsuccessful. As in the case of other weakly basic amines, it was found that the diazotization can be satisfactorily accomplished by the use of nitrosylsulfuric acid in concentrated sulfuric acid solution.

By diazotization in this way followed by hydrolysis of the diazo compound, amino-pyrazine was converted in a yield of 65% to hydroxypyrazine.[4] This transformation might be applied as well to other substituted amino-pyrazines. For example, 2-amino-3-carboxypyrazine was converted in a yield of 85% to 2-hydroxy-3-carboxypyrazine.[4]

(1) Stoehr, *J. prakt. Chem.*, **51**, 456 (1895).

(2) Den Hertog and Wibaut, *Rec. trav. chim.*, **51**, 381 (1932).

(3) Gabriel and Sonn, *Ber.*, **40**, 4851 (1907).

(4) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 805 (1945), recently reported the preparation of these compounds by an alternative method.

Attempts to apply the Sandmeyer reaction to diazotized amino-pyrazine under conditions similar to those recommended by Craig[5] for the preparation of α-pyridyl bromide, gave insignificant yields of impure bromo-pyrazine. The rate of hydrolysis of the intermediate diazo compound is apparently greater than the velocity of the halogen replacement reaction.

Since hydroxy-pyrazine could be readily prepared by diazotization and hydrolysis of amino-pyrazine, attempts were made to convert the hydroxy compound to the desired pyrazyl halides by reaction with an appropriate phosphorus halide (PX_3, POX_3 or PX_5). Hydroxy-pyrazine when treated with one molar equivalent of phosphorus pentachloride in excess phosphorus oxychloride gave a 58% yield of chloro-pyrazine. The pyrazyl chloride was identified by hydrolysis to hydroxy-pyrazine, and a mixed melting point. By the same type of reaction, hydroxy-pyrazine was converted into a mixture of monobromo and di-bromo pyrazines which were separated by fractional distillation under reduced pressure. The determination of structure or orientation of the two bromine groups in the di-bromo compound is being investigated.

A preliminary study was made of the lability of the halogen group attached to the pyrazine nucleus by comparison in simple transformations (hydrolysis, amination, alcoholysis) with the halogen derivatives of the more common cyclic series. One would expect the mono-halogen derivatives to be reactive since in pyrazine (a symmetrical 1–4 diazine) the halogen group must be ortho to the negative nitrogen atom. They should thus resemble the α-pyridyl halides. Chloro-pyrazine was used as an example since it is more stable than bromo-pyrazine upon storage, and the reagents required for its preparation are more readily accessible. Bromo-pyrazine gives a positive test for "active" halogen with alcoholic silver nitrate whereas the test with chloro-pyrazine is negative. Pyrazyl bromide would therefore very likely undergo the same reactions as given for chloro-pyrazine but with greater speed and facility.

Chloro-pyrazine can be hydrolyzed by heating with dilute (5%) alkali at 150°. The halogen group is thus more reactive than in chlorobenzene which requires 15–20% alkali at 300°[6] while α-chloro-pyridine is hydrolyzed by heating at 175° with alkali or acid.[7] In respect to ease of hydrolysis, the pyrazyl halides are of approximately the same order of reactivity as the pyridyl halides.

Under anhydrous conditions amination of chloro-pyrazine was unsuccessful. For purposes of comparison with chloro-pyridine, chloro-pyrazine was treated with excess aqueous ammonia (28%) at 200°. Under these conditions, chloro-pyrazine was converted to amino-pyrazine in a yield of 80%. The corresponding pyridyl halides are less reactive, requiring aqueous ammonia at 250° in the presence of a catalyst.[7]

Chloro-pyrazine reacts quite readily with sodium ethylate at room temperature to give ethoxy-pyrazine.

The above reactions of chloro-pyrazine would indicate that the halogen group in the pyrazyl halides is sufficiently labile so that they may be of general application to the preparation of phenols, thiols, ethers, primary amines, hydrazides, etc., in the pyrazine series.

(5) Craig, THIS JOURNAL, **56**, 232 (1934).
(6) Meyer and Bergius, *Ber.*, **47**, 3156 (1914).
(7) O. Fischer, *ibid.*, **32**, 1297 (1899).

Experimental

(I) **Hydroxy-pyrazine.**—Seventy-five ml. of concd. sulfuric acid was cooled to −5° in a three-necked flask provided with mechanical stirrer and thermometer. Nine and one-half grams (0.15 mole) of sodium nitrite was added in small portions with stirring and cooling at such a rate that the temperature was maintained at −5 to 0°. After addition was complete, the mixture was allowed to gradually assume room temperature and then heated in an oil-bath to 60–65° until a clear solution was obtained. The solution of nitrosylsulfuric acid was then cooled to 0° and a cold solution of 12 g. (0.125 mole) of amino-pyrazine in 50 ml. concd. sulfuric acid added dropwise with stirring at 0–5° over a period of fifteen minutes. The cold diazonium solution was added dropwise with stirring to 300 g. of cracked ice and stirred until the evolution of nitrogen ceased. The cold acidic solution was adjusted to *p*H 6 with a 40% solution of sodium hydroxide. After cooling, the sodium sulfate was filtered off and washed once with 200 ml. of ice water. The combined filtrate and washings was concentrated *in vacuo* to dryness and the residue air-dried. The solid mixture was extracted in a Soxhlet apparatus with acetone, and the extract allowed to crystallize at room temperature overnight. The hydroxy-pyrazine was filtered off and dried *in vacuo*. The yield was 7.77 g. (65%); m. p. 187–188° (cor.).

Anal. Calcd. for $C_4H_4ON_2$: C, 50.00; H, 4.20. Found: C, 49.82; H, 4.27.

(II) **2-Hydroxy-3-carboxy-pyrazine.**—The 2-amino-3-carboxy-pyrazine used was prepared by the method of Gabriel and Sonn.[8]

Two and eight-tenths grams (0.02 mole) of 2-amino-3-carboxy pyrazine was added gradually with cooling and stirring to 12 ml. of concd. sulfuric acid. A solution of nitrosylsulfuric acid was prepared by cooling 15 ml. of concd. sulfuric acid to 0° and adding 1.4 g. (0.02 mole) sodium nitrite in small portions over a period of fifteen minutes with agitation at 0 to 2°. The cold solution of nitrosylsulfuric acid was added at 0° over a period of fifteen minutes with agitation to the cold solution of amino-carboxy-pyrazine. After addition, the mixture was stirred for fifteen minutes. The cold diazonium solution was added dropwise with stirring to 125 g. of cracked ice and the mixture stirred until there was no further evolution of nitrogen. The strongly acidic suspension was filtered and the solid washed free of acid and dried *in vacuo*. The yield was 2.39 g. (85%); m. p. 215–216° (dec.) (cor.).

Anal. Calcd. for $C_5H_4O_3N_2$: N, 20.00. Found: N, 19.90.

(III) **Chloro-pyrazine.**—Nineteen and two-tenths grams (0.2 mole) of hydroxy-pyrazine was suspended in 120 ml. of phosphorus oxychloride in a three-necked flask equipped with mechanical stirrer and reflux condenser. To this suspension, 43.7 g. (0.22 mole) of phosphorus pentachloride was added with stirring. The mixture was warmed gradually by heating in an oil-bath to 90° (bath temperature) and held at 90–95° for forty minutes. There was a vigorous evolution of hydrogen chloride as the solid gradually dissolved. The reaction mixture was cooled in

an ice-bath, added slowly with agitation to 800 g. of cracked ice and stirred until all of the phosphorus oxychloride had been hydrolyzed. The acidic solution was extracted completely with chloroform and the extract dried over anhydrous sodium sulfate. The chloroform was removed by distillation under reduced pressure (50 mm.) and the residual oil fractionated using a short (15 cm.) column packed with glass helices. The chloro-pyrazine distilled at 62–63° at 31 mm. The yield was 13.2 g. (58%); $n^{26}D$ 1.5346.

Anal.[8] Calcd. for $C_4H_3N_2Cl$: N, 24.45; Cl, 31.00. Found: N, 24.04; Cl, 31.67.

Chloro-pyrazine is a colorless oil practically insoluble in water, dilute acid and alkali. It is freely soluble in the more common organic solvents such as ethanol, ether, petroleum ether, benzene, acetone and chloroform. Chloropyrazine, in common with the other pyrazyl halides prepared, has a penetrating, mildly pungent odor and a rather high vapor pressure at room temperature.

(IV–V) **Mono- and Di-bromo-pyrazine.**—Phosphorus pentabromide (0.05 mole) was prepared by adding slowly with cooling 8.0 g. (0.05 mole) bromine to 13.6 g. (0.05 mole) of phosphorus tribromide. Four and eight-tenths grams (0.05 mole) of hydroxy-pyrazine and 15 g. of phosphorus oxybromide were added and mixed manually with a glass rod.

The flask was connected with a reflux condenser and gradually heated in an oil-bath to 105° (bath temp.) and held there for one hour. The evolution of hydrogen bromide became quite vigorous at about 100°. During the reaction, the mixture gradually darkened and formed a gel. The cooled reaction mixture was added in small portions to 300 g. of cracked ice and thoroughly disintegrated. The acidic aqueous solution was promptly extracted with ether and the ether extract dried over anhydrous sodium sulfate. The ether was removed by distillation and the residual clear brown oil (7.4 g.) fractionated. The mono-bromo-pyrazine was collected at 58° at 9 mm.; yield 1.5 g. The di-bromo-pyrazine distilled at 97° at 10 mm.; yield 1.7 g.

Mono-bromo-pyrazine is a colorless oil practically insoluble in water but freely soluble in ethanol, acetone, ether, petroleum ether, benzene and chloroform. It has a penetrating, pungent odor; $n^{26}D$ 1.5785.

Anal. Calcd. for $C_4H_3N_2Br$: N, 17.62; Br, 50.29. Found: N, 17.11; Br, 50.65.

Di-bromo-pyrazine is a white crystalline (needles) solid having an unusually high vapor pressure at room temperature and strongly pungent odor. It is practically insoluble in water but freely soluble in the more commonly used organic solvents; m. p. 52–52.5°.

Anal. Calcd. for $C_4H_2N_2Br_2$: N, 11.77; Br, 67.21. Found: N, 11.76; Br, 67.42.

(IV) **Ethoxy-pyrazine.**—One and six-tenths grams (0.07 mole) of sodium was dissolved in 32 ml. of absolute ethanol. A solution of 4 g. (0.035 mole) of chloro-pyrazine in 8 ml. absolute ethanol was added to the sodium ethylate solution. There was an immediate precipitation of sodium chloride. The solution was boiled under reflux for one hour and then distilled under reduced pressure (50 mm.) to remove most of the alcohol. The residual oil was treated with 25 ml. water and the oil extracted completely from the alkaline aqueous liquor with ether. The ether extract was dried over anhydrous sodium sulfate and the solvent removed by distillation. The crude product was fractionated through a short column packed with glass helices and the fraction distilling at 72–73° at 30 mm. collected. The yield was 2.45 g. (56%); $n^{26}D$ 1.4960.

Ethoxy-pyrazine is a colorless, basic oil having a pronounced ethereal or ester-like odor. It is insoluble in water and dilute alkali but soluble in dilute acid. It is also soluble in ethanol, ether, benzene, petroleum ether and chloroform.

Anal. Calcd. for $C_6H_8ON_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.26; H, 6.38; N, 22.24.

Hydrolysis of Chloro-pyrazine.—A mixture of 0.5 g. (0.0043 mole) chloro-pyrazine and a solution of 0.6 g. (0.015 mole) sodium hydroxide in 10 ml. water was heated in a sealed tube at 150° for seven hours. The cooled solution was neutralized (*p*H 6.5) with dilute sulfuric acid. A small amount of silica was filtered off and washed with 3 × 5 ml. of water. The combined filtrate was concentrated *in vacuo* at a bath temperature of 50°. The dry residue was extracted in a Soxhlet apparatus with ether and the ether extract evaporated to dryness. The yield was 0.290 g. (70%); m. p. 180–182°. A sample recrystallized from ethanol melted at 187–188° and gave no depression on a mixed melting point with an authentic sample of hydroxy-pyrazine.

Amination of Chloro-pyrazine.—A mixture of 0.5 g. (0.0043 mole) of chloropyrazine and 25 ml. of conc. ammonia (28% NH_3) was heated in a sealed tube at 200° for twenty hours. The resulting clear solution was cooled and 5 g. of solid sodium hydroxide dissolved therein. The strongly alkaline solution was extracted with ether and the extract dried over anhydrous sodium sulfate. The dried ether extract was evaporated to dryness. The yield was 0.330 g. (80%); m. p. 118–120°. A mixed melting point with an authentic sample of amino-pyrazine showed no depression.

Summary

A procedure has been described for the diazotization of amino-pyrazine.

Hydroxy-pyrazine and 2-hydroxy-3-carboxy-pyrazine have been prepared by diazotization and hydrolysis of amino-pyrazine and 2-amino-3-carboxy-pyrazine, respectively.

Hydroxy-pyrazine has been converted by reaction with the appropriate phosphorus halides to chloro-pyrazine, bromo-pyrazine and di-bromo-pyrazine. As these simple halogen derivatives have not previously been reported, they have been prepared in analytically pure form and characterized.

A preliminary study has been made of the reactivity of pyrazyl chloride in regard to ease of hydrolysis, amination and alcoholysis. The results indicate that the halogen group attached to the pyrazine nucleus is sufficiently labile so that as a class the pyrazyl halides should be of general utility in the synthesis of phenols, thiols, primary amines, hydrazides, etc., in the pyrazine series.

Ethoxy-pyrazine has been prepared by reaction of chloro-pyrazine with sodium ethylate and some of its physical properties described.

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(8) The micro-analyses on the halogen derivatives reported in this paper were performed by Dr. Carl Tiedcke of 366 Fifth Avenue, New York City.