ethanol containing hydrogen chloride, dissolving the separated hydrochloride (m. p. 163–165°) in warm 95% ethanol and pouring the solution slowly into cold water, yielded the pure base of m. p. 72–73°.

Ultraviolet Spectra.—The apparatus used was a Beckman Model DU Quartz Spectrophotometer. The solvents were: for I, 95% ethanol; for II purified dioxane[22] finally redistilled through a 15-ball Snyder column with rejection of the fore-run; for III, pyridine dried over solid potassium hydroxide and distilled, only the middle fraction being used. The samples were purified as follows. Compound I was obtained from the hydrochloride (crystallized from 1 *N* hydrochloric acid) by action of warm aqueous ammonium hydroxide, and was then crystallized from 50% ethanol. Compound II was obtained pure from I by twice crystallizing from anhydrous dioxane. Compound III was obtained from I by two crystallizations from pyridine, and was freed of adhering solvent as described above. The ultraviolet spectra are shown in Fig. 1.

Infrared Spectra.—Samples of I, II and III, purified as outlined, were suspended in "Nujol" and examined in a double-beam infrared spectrophotometer.[23] The plotted results appear in Figs. 2 and 3.

Molecular Weight Determinations.—The Cottrell ebulliometer,[24] enclosed to exclude drafts, was swept out with dry nitrogen before each determination. About 65 ml. of solvent (dried and fractionally distilled) was used, and in each case several values were obtained at increasing concentrations. At higher concentrations some difficulty was encountered owing to irregular splashing and foaming. The results, calculated in terms of extents of association, are shown graphically in Fig. 4.

(22) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., N. Y., 2nd ed., 1941, p. 369.

(23) The spectra were determined by Samuel Sadtler and Son, Analytic and Consulting Chemists, Philadelphia, using an instrument made by Baird Associates, Inc.

(24) The low solubilities of the compounds in permissible solvents near their freezing points made the freezing point method inapplicable.

Acknowledgment is made to Dr. John G. Miller for helpful discussions, and to Sarah M. Woods who performed the analyses.

Summary

Study of the two previously known forms of 2,4(5)-diphenylimidazole and of a third form discovered during the work showed that each is obtained by bringing any one of the three into equilibrium with certain solvents, and that by proper choice of solvents the compounds are freely interconvertible. They are chemical individuals with respect to melting points, and are not interconvertible by seeding, either in solution or in the fused state, but the two higher-melting forms are slowly convertible to the stable low-melting form by heat. The three compounds are identical with respect to certain chemical reactions which might disclose structural differences, and they yielded ultraviolet and infrared spectra which showed no sharply distinctive characteristics for any one form. Determination of molecular weights at several concentrations disclosed that in appropriate solvents one form is monomeric, one form is dimeric, and the stable form is increasingly aggregated as concentration increases. It is concluded that the three diphenylimidazoles are not desmotropes, but that they represent three distinct and relatively permanent states of molecular aggregation responsive to the influence of solvent environment. States above the monomeric are attributed to hydrogen bonding.

RECEIVED JANUARY 26, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORY, MEAD JOHNSON AND COMPANY]

Pyrazine Chemistry. IV. Bromination of 2-Amino-3-carbomethoxypyrazine[1]

BY R. C. ELLINGSON AND R. L. HENRY

In search of methods for the preparation of brominated aminopyrazine derivatives the method used for the bromination of α-aminopyridine[2] was tried. Bromination of aminopyrazine by this method was unsuccessful. However, the bromination of 2-amino-3-carbomethoxypyrazine proceeds readily and forms a single monobrominated pyrazine derivative in 90% yield.

Since this compound was used in the synthesis of several pyrazine derivatives, its structure was studied. According to the rules of substitution in the benzene series one might expect substitution in position 5.

The determination of the position of the bromine atom proved to be more difficult than was anticipated. The first two methods we attempted failed. Since they are the obvious procedures, we shall briefly describe them and point out where they failed.

The first method is based on well established reactions in the pyrazine series, namely, the hydrolysis and decarboxylation of pyrazine esters, the replacement of pyrazine-ring halogen atoms by the NH_2 group,[3] and the conversion of the pyrazine carboxyl group to NH_2 by way of the amide and the Hofmann reaction.[4] Thereby we had hoped to convert the compound into a diaminopyrazine in which the amino groups would be in the 2,5- or 2,6-positions depending on the location of the bromine atom. We also proposed to degrade the known 2,5-dicarboxypyrazine[5] into 2,5-diaminopyrazine and to compare the latter with the diaminopyrazine obtained from the bromopyrazine.

The brominated ester readily underwent hydrolysis and decarboxylation, but attempts to

(1) Presented before the Organic Division of The American Chemical Society at its 109th meeting held at Atlantic City, N. J., April 1946.

(2) Chichibabin and Tyazhelova, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1918).

(3) Ellingson and Henry, THIS JOURNAL, **70**, 1257 (1948).

(4) Hall and Spoerri, *ibid.*, **62**, 664 (1940).

(5) Stoehr, *J. prakt. Chem.*, [2] **47**, 487 (1893).

replace the bromine atom by the amino group were unsuccessful. A substance of unknown structure was obtained. In addition, the Hofmann reaction failed to degrade 2,5-dicarbamylpyrazine to 2,5-diaminopyrazine.

In the second scheme we converted our brominated ester to an aminopyrazinoic acid by hydrolysis and decarboxylation of the former followed by replacement of the bromine with carboxyl. Attempts to prepare 5-aminopyrazinoic acid for comparison with our aminopyrazinoic acid by partial Hofmann degradation of 2,5-dicarbamylpyrazine were unsuccessful.

Craig's method[6] of converting α-aminopyridine into α-bromopyridine forms the basis of our successful scheme for establishing the structure of the brominated ester. Craig diazotized α-aminopyridine in an aqueous hydrobromic acid solution containing free bromine. To learn whether Craig's reaction would work on aminopyrazines we applied it to 2-amino-3-carbomethoxypyrazine.

2-Amino-3-carbomethoxypyrazine was converted into 2-bromo-3-carbomethoxypyrazine. To show that the bromine atom displaced the amino group and occupied its position the bromocarbomethoxypyrazine was converted into the dimethyl ester of 2,3-dicarboxypyrazine. A mixture of this ester with an authentic sample of 2,3-dicarbomethoxypyrazine prepared from quinoxaline[7] caused no depression of the melting point.

The following series of reactions was then carried out: hydrolysis and decarboxylation of the brominated 2-amino-3-carbomethoxypyrazine, replacement of the amino group by bromine, replacement of the two bromine atoms by carboxyl groups, and esterification of the carboxyl groups with methanol. If the bromine atom of the brominated 2-amino-3-carbomethoxypyrazine is at position 5, the ester obtained would be 2,5-dicarbomethoxypyrazine; if at 6, it would be 2,6-dicarbomethoxypyrazine.

Actually we obtained a dicarbomethoxypyrazine which melted at 169–170° and caused no depression of the melting point when mixed with an authentic sample of 2,5-dicarbomethoxypyrazine prepared from 2,5-dicarboxypyrazine.[5] Evidently the structure of the ester is 2-amino-3-carbomethoxy-5-bromopyrazine.

Experimental

Bromination of 2-Amino-3-carbomethoxypyrazine.—To a solution of 15.3 g. (0.1 mole) of 2-amino-3-carbomethoxypyrazine in 60 cc. of warm glacial acetic acid, was added dropwise over a period of twenty minutes 5.4 cc. of bromine. After the reaction mixture had been allowed to stand ten minutes longer, 450 cc. of water was added and the light yellow solid which separated was collected and dried. It weighed 21 g. (90.5%); m. p. 174°. For analysis[8] the compound was crystallized from water and came out as light yellow needles; m. p. 175.3–175.9° (cor.).

Anal. Calcd. for $C_6H_6BrN_3O_2$: Br, 34.44; N, 18.11. Found: Br, 34.60, 34.33; N, 17.71, 17.80.

Bromination of 2-Amino-3-carbomethoxypyrazine and Hydrolysis to 2-Amino-5-bromopyrazinoic Acid.—To a solution of 61.2 g. (0.40 mole) of crude 2-amino-3-carbomethoxypyrazine in 330 cc. of warm glacial acetic acid, was added dropwise over a period of thirty minutes 21.6 cc. of bromine. After the reaction mixture had been allowed to stand for thirty minutes, 2000 cc. of water and a solution of 210 g. of sodium hydroxide in 400 cc. of water were added. The solution was boiled for fifteen minutes, treated with Darco G60, filtered and cooled. The brown crystals which separated were collected and air-dried. This product, sodium 2-amino-5-bromopyrazinoate, weighed 90.5 g.

This sodium salt was dissolved in 2400 cc. of warm water, and the solution was strongly acidified by the addition of 60 cc. of 40% hydrobromic acid. After thorough cooling the light brown crystals were collected and dried. They weighed 64 g. (78.0%); m. p. 184–186° (dec.). Two crystallizations from water gave long straw-yellow needles; m. p. 185–186° (dec.).

Anal. Calcd. for $C_5H_4BrN_3O_2$: Br, 36.65; N, 19.27. Found: Br, 36.95, 36.99; N, 19.11, 19.04.

Decarboxylation of 2-Amino-5-bromopyrazinoic Acid to 2-Amino-5-bromopyrazine.—A suspension of 59.6 g. (0.274 mole) of crude 2-amino-5-bromopyrazinoic acid in 600 cc. of dry tetralin was boiled under reflux for thirty minutes. While still hot the solution was decolorized with Darco G60. The filtrate was thoroughly chilled, and the yellow crystals which separated were collected, washed by suspension in petroleum ether and air-dried. The yield was 38.4 g. (80.5%); m. p. 105–110°. This crude product was crystallized from a mixture of 400 cc. of water and 60 cc. of ethanol and came out as long yellow needles which melted at 113°. For analysis a sample was given a final crystallization from water; the compound melted at 113.6° (cor.).

Anal. Calcd. for $C_4H_4BrN_3$: C, 27.61; H, 2.32; Br, 45.92; N, 24.15. Found: C, 27.46, 27.20; H, 2.30, 2.12; Br, 45.43, 45.85; N, 24.20, 24.07.

Conversion of 2-Amino-5-bromopyrazine into 5-Aminopyrazinoic Acid.—In a Carius tube were placed 4.0 g. (0.023 mole) of 2-amino-5-bromopyrazine, 2.0 g. of cuprous cyanide, 3.0 g. of potassium cyanide, 14.0 cc. of water and 6.0 cc. of 95% ethanol and the mixture was heated at 170° for sixteen hours. The tube was opened and rinsed out with 400 cc. of water. The suspension was heated to boiling, acidified with hydrochloric acid and boiled for a few minutes to remove the hydrogen cyanide. Hydrogen sulfide was then passed into the solution, and the precipitated cupric sulfide was removed by filtration. The filtrate on cooling deposited a yellow-brown solid, which weighed 1.55 g. and melted at 261–263° (dec.). Analysis of this product indicated that it was a mixture of the amide and the acid.

Consequently, the mixture was suspended in 50 cc. of a 2% sodium hydroxide solution. The insoluble fraction was collected and dried; it weighed 0.7 g. and melted at 275–276°. Before analysis this fraction, 2-amino-5-carbamylpyrazine, was crystallized twice from water. It came out as light yellow needles; m. p. 277–279°.

Anal. Calcd. for $C_5H_6N_4O$: C, 43.47; H, 4.38; N, 40.56. Found: C, 43.60, 43.37; H, 3.76, 3.83; N, 40.27, 40.06.

The alkaline filtrate on acidification with hydrochloric acid yielded 0.55 g. of a yellow solid which melted at 270–272° with decomposition. This acid, 5-aminopyrazinoic acid, was crystallized from 50 cc. of water. Small light yellow crystals were obtained; m. p. 278° (dec.).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.16; H, 3.62; N, 30.21. Found: C, 42.72, 42.96; H, 3.70, 3.83; N, 29.57, 29.74.

Conversion of 2-Amino-3-carbomethoxypyrazine into 2-Bromo-3-carbomethoxypyrazine.—This procedure is es-

(6) Craig, THIS JOURNAL, **56**, 231 (1934).

(7) Gabriel and Sonn, *Ber.*, **40**, 4850 (1907).

(8) Dr. Carl Tiedcke, Laboratory of Microchemistry, 705 George St., Teaneck, N. J., performed the analyses.

sentially that of Craig[6] applied to an aminopyrazine instead of an aminopyridine. To 57 cc. of a 48% hydrobromic acid solution was added 15.3 g. (0.10 mole) of 2-amino-3-carbomethoxypyrazine and the solution was cooled in an ice-salt-bath. To the cold stirred solution, 15.2 cc. of bromine was added dropwise at such a rate that the reaction temperature remained below 0°. Then a solution of 17.4 g. of sodium nitrite in 30 cc. of water was added while the temperature was kept below 0°. The reaction mixture was next made slightly alkaline by the addition of a solution of 38 g. of sodium hydroxide in 100 cc. of water. The next day the light brown solid was collected and air-dried; it weighed 5.6 g. and melted at 40–45°. An additional 3.8 g. was obtained by extraction of the aqueous solution with ethyl acetate. The total yield was 9.4 g. (43.3%). On crystallization from a mixture of 100 cc. of water and 32 cc. of ethanol this gave 7.4 g. of colorless needles; m. p. 44° (cor.).

Anal. Calcd. for $C_6H_5BrN_2O_2$: C, 33.20; H, 2.32; Br, 36.82; N, 12.91. Found: C, 33.28, 33.16; H, 2.69, 2.58; Br, 37.13, 37.07; N, 12.96, 12.99.

Conversion of 2-Bromo-3-carbomethoxypyrazine into 2,3-Dicarbomethoxypyrazine.—In a Carius tube were placed 3.0 g. (0.014 mole) of 2-bromo-3-carbomethoxypyrazine, 2.5 g. of cuprous cyanide, 1.0 g. of potassium cyanide, 7 cc. of ethanol and 12 cc. of water and the mixture was heated at 125° for sixteen hours. The tube was opened and rinsed out with 100 cc. of water. The resulting suspension was filtered, and the filtrate was made alkaline and boiled for one hour. Ten cc. of a 25% barium chloride solution was added and, after digestion on the steam cone for an hour, the solid was collected and dried. This barium salt (1.0 g.) was suspended in 50 cc. of water and 0.25 cc. of concd. sulfuric acid added. After thorough agitation the barium sulfate was removed, and the clear filtrate was concentrated to about 5 cc. The tan crystals, which separated on thorough cooling, were collected and dried; 0.25 g., m. p. 171–175° (dec.).

A solution of 5 cc. of methanol, 0.5 cc. of concd. sulfuric acid and 0.55 g. of acid, prepared as described above, was boiled under reflux for fifteen hours. The reaction solution was diluted with water, made weakly alkaline by the addition of sodium carbonate and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, then filtered and evaporated to dryness. It left 0.4 g. of yellow solid which melted at 52–55°. On crystallization from a mixture of benzene and petroleum ether colorless crystals were obtained; m. p. 55–56°. There was no depression of the melting point when this compound was mixed with an authentic sample of 2,3-dicarbomethoxypyrazine prepared from quinoxaline.[7]

2,5-Dibromopyrazine.—To 29 cc. of 48% hydrobromic acid cooled in an ice-salt-bath were added consecutively 8.7 g. (0.05 mole) of 2-amino-5-bromopyrazine, 7.6 cc. of bromine and finally a solution of 8.7 g. of sodium nitrite in 15 cc. of water. During these additions the reaction temperature was held below 5°. The reaction mixture was made weakly alkaline by the addition of a solution of 19 g. of sodium hydroxide in 50 cc. of water. The yellow solid which separated was collected, washed with water and air-dried; it weighed 7.8 g. (66%) and melted at 38–44°. On two crystallizations from a 2:1 water-ethanol (v./v.) mixture colorless waxy plates were obtained; m. p. 47–48° (cor.). The crystals are rather volatile and sublime on exposure to air. In that property they behave like pyrazine itself.

Anal. Calcd. for $C_4H_2Br_2N_2$: C, 20.19; H, 0.85; Br, 67.18; N, 11.78. Found: C, 20.00, 20.10; H, 0.80, 0.91; Br, 67.53, 67.27; N, 11.36, 11.65.

2,5-Dicarbomethoxypyrazine.—In a Carius tube were placed 3.0 g. (0.0126 mole) of 2,5-dibromopyrazine, 2.3 g. of cuprous cyanide, 1.0 g. of potassium cyanide, 7.0 cc. of ethanol and 12 cc. of water and the mixture was heated at 125° for sixteen hours. The contents of the tube were rinsed out with 100 cc. of water and the suspension filtered. The black solid weighed 3.0 g.; it was suspended in 30 cc. of anhydrous methanol to which 4.0 cc. of concd. sulfuric acid had been added. The suspension was boiled under reflux for fifteen hours. The resulting dark brown solution was filtered while hot. As the filtrate cooled, it deposited brown crystals. These, after being collected and air-dried, weighed 0.25 g. and melted at 140–148°. On repeated crystallization from methanol, colorless needles which melted at 169.5–170.1° (cor.) were obtained. The compound did not depress the melting point when mixed with an authentic sample of 2,5-dicarbomethoxypyrazine. The authentic sample of 2,5-dicarbomethoxypyrazine was prepared from 2,5-dicarboxypyrazine.[5] Since 2,5-dicarbomethoxypyrazine is not in the chemical literature, we are recording our analytical data on it.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.17, 49.09; H, 4.11, 4.03; N, 14.05, 13.98.

Summary

The structure of the product obtained on bromination of 2-amino-3-carbomethoxypyrazine has been established as 2-amino-3-carbomethoxy-5-bromopyrazine. During the course of this work six new pyrazine compounds, namely, 2-amino-5-bromopyrazinoic acid, 2-amino-5-bromopyrazine, 2,5-dibromopyrazine, 2-bromo-3-carbomethoxypyrazine, 5-aminopyrazinoic acid and 2-amino-5-carbamylpyrazine have been prepared and their structures established.

EVANSVILLE 21, INDIANA RECEIVED FEBRUARY 19, 1949