filter cake was extracted with boiling benzene and acetone (1 to 1 mixture). Concentration and cooling of the extracts gave 25.6 g. of crude 2'-amino-2-bromo-4'-dimethylsulfonamidodiphenyl ether (IXd). This compound was heated at 100° with 63 g. of 88% formic acid until the excess formic acid had evaporated.

The residue (Xd) was taken up in 30 ml. of xylene, and the xylene was removed by distillation at atmospheric pressure to remove traces of formic acid. The residual gum was stirred at reflux for 18 hr. with 8.6 g. of potassium carbonate, 1 g. of copper carbonate and 40 ml. of xylene. Excess water and benzene were added to the cooled mixture and the organic layer was evaporated to leave a gum. Crystallization from benzene-hexane (1 to 3) gave 8.2 g. of 2-dimethylsulfonamidophenoxazine (Id) (19% overall yield); m.p. 184–185°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.91; H, 4.86; N, 9.65; S, 11.04. Found: C, 58.18; H, 5.24; N, 9.44; S, 10.81.

Phenoxazine and 2-chlorophenoxazine by Scheme C: The condensation of 2-bromophenol with 2-chloronitrobenzene and with 2,5-dichloronitrobenzene, carried out as described for the preparation of VIIIc, afforded 2-bromo-2'-nitrodiphenyl ether (40% conversion) and 2-bromo-4'-chloro-2'-nitrodiphenyl ether (50% conversion), respectively. Since the analogous condensation to form the trifluoromethyl derivative, VIIIc, was accomplished with a 70% conversion, the presence of an electron-attracting group para to the reactive chlorine atom appears to aid the condensation reaction, as expected.[12] Reduction of nitrodiphenyl ethers with iron and acetic acid proceeded smoothly to give IXa and IXc in approximately 90% yields. Ring-closure of Xa and Xc by the method described for the preparation of Ic resulted in the preparation of phenoxazine (68% yield) and 2-chlorophenoxazine (62% yield).

2-Amino-2'-bromodiphenyl ether (IXa) was obtained as a yellow oil; b.p. 140–155° (0.2–0.4 mm.).

2-Bromo-4'-chloro-2'-nitrodiphenyl ether (VIIIb), b.p. 165° (0.2 mm.), solidified on long standing at room temperature; light yellow needles (from ethanol); m.p. 73.5–74°.

Anal. Calcd. for $C_{12}H_7BrClNO_3$: C, 43.86; H, 2.15. Found: C, 43.86; H, 2.28. Reduction of VIIIb to 2'-amino-2-bromo-4'-chloridiphenyl ether (IXb) by means of iron and acetic acid gave IXb as a pale yellow oil; b.p. 150–170°/0.2–1.0 mm.

Alkylation of phenoxazines and phenoselenazines. Sodamide in benzene or toluene was stirred at reflux with 0.9 molar ratio of the phenoxazine or phenoselenazine for 0.25–2 hr. After addition of 1.2 molar ratio of the dialkylaminoalkyl chloride, stirring at reflux was continued for 4 to 18 hr. Water was added, the layers were separated, and dilute hydrochloric acid was used to extract the organic layer. Neutralization with excess sodium hydroxide liberated the free base, which was taken up in benzene. Removal of the solvent was followed by distillation of the free base in a sausage flask. The free base was converted to the desired salt by standard techniques, and the salt was purified to a constant melting point by recrystallization from suitable solvents, such as ethanol-ether, methanol, acetone, etc.

The hydroxyethylpiperazinylpropyl analogs (compounds 12 and 14, Table II) were prepared by the method previously described.[13]

Acknowledgment. The elemental analyses were obtained by Mrs. Doris Rolston and co-workers, of the Analytical & Physical Chemistry Section. We also wish to acknowledge the help of Dr. Walter Thompson and co-workers, of the Analytical & Physical Chemistry Section, and Dr. Eugene DeWald and co-workers of the Analytical Control Laboratory, Smith Kline and French Laboratories, who obtained the spectral data.

PHILADELPHIA 1, PA.

(12) J. F. Bennett and R. E. Zahler, *Chem. Revs.*, 49, 273 (1951).

(13) P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, 25, 944 (1960).

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

The Synthesis and Properties of Iodopyrazines

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The lack of reactivity of chloro- and bromopyrazines towards the preparation of organometallic derivatives stressed the desirability of preparing iodopyrazines. Using a methyl ethyl ketone solution of sodium iodide and hydriodic acid, it was possible to prepare eight iodopyrazines, by displacement of the chlorine from variously substituted chloropyrazines, in 30–60% yield. Treatment of the isodiazotate salt of 2-amino-3,6-dimethylpyrazine (XI) with hydriodic acid, according to a procedure described by Chichibabin for the preparation of iodopyridine, afforded 2-amino-3,6-dimethyl-5-iodopyrazine (XIII). Similarly, the isodiazotate salt of 2-amino-3-methylpyrazine (X) afforded 2-amino-3-methyl-5-iodopyrazine (XVI). It could be demonstrated that the isodiazotate salts were reduced to the corresponding amines, which in the subsequent workup were iodinated. The isodiazotate salt of aminopyrazine (IX) afforded iodopyrazine, but in poor yield.

The convenient synthesis of 2-hydroxypyrazines published by Jones[3] and its subsequent modification by Karmas and Spoerri[4] led also to improved methods for the preparation of chloro- and bromopyrazines. Thus a variety of 2-chloropyrazines were synthesized by the reaction of hydroxypyra-

(1) (a) The work here reported is based on a dissertation by Albert Hirschberg in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn, June, 1960. (b) Du Pont Teaching Fellow, 1958–1959; Texaco Research Fellow, 1959–60.

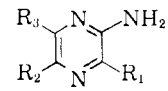
(2) To whom all inquiries should be addressed.

(3) R. G. Jones, *J. Am. Chem. Soc.*, 71, 78 (1949); R. G. Jones, U. S. Patent 2,520,088 (1950).

(4) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, 74, 1580 (1952).

TABLE I

AMINOPYRAZINES



I	R_1	R_2	R_3	Observed M.P.	Lit. M.P.	Yield, %	%, N Calcd.	%, N Found
I	H	H	H	117–118	118–120[a]	70		
II	CH_3	H	H	166–167		64	38.51	38.44
III	CH_3	H	CH_3	111–113	111–112[b]	68		
IV	C_2H_5	H	H	56–57		68	34.12	34.42
V	CH_3	CH_3	H	94–95	94–96[c]	17		
VI	H	CH_3	CH_3	146–148	140–144[d]	43		
VII	H	C_6H_5	C_6H_5	224–225	225–227[d]	61		
VIII	CH_3	C_6H_5	C_6H_5	150–151		79	16.08	15.75

[a] Reported by Erickson and Spoerri (ref. 11). [b] R. R. Joiner and P. E. Spoerri, *J. Am. Chem. Soc.*, *63*, 1929 (1941). [c] W. Sharp and F. S. Spring, *J. Chem. Soc.*, 932 (1951). [d] J. Weiljard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, *67*, 802 (1945).

zines with phosphorus oxychloride[4] while 2-bromopyrazines were prepared analogously using phosphorus tribromide or phosphorus oxybromide.[5] The limited reactivity of these halopyrazines in attempts at preparation of metallo pyrazine derivatives,[6,7,8] however, prompted a study of the preparation of iodopyrazines with the expectation of a greater reactivity for these compounds.

In analogy with the preparation of chloro- and bromopyrazines, a number of attempts were made to prepare iodopyrazines by treating hydroxypyrazines with phosphorus triiodide. Unfortunately, phosphorus triiodide is not very stable, and decomposed under the conditions of the reaction. Attempts to use mild conditions were unsuccessful.

A survey of the literature in connection with iodopyridine and iodoquinoline, revealed two rather likely approaches towards the synthesis of iodopyrazines. Thus, Chichibabin prepared 2-iodopyridine by treating the isodiazotate salt of 2-aminopyridine with hydriodic acid,[9] while Baker, Curtis, and Edwards[10] prepared 2-iodopyridine and 2-iodoquinoline by a displacement reaction.

In order to study the former procedure, a number of aminopyrazines were prepared. These compounds were obtained most conveniently from the corresponding chloropyrazines, by means of high temperature ammonolysis, according to a procedure described by Erickson and Spoerri.[11] This general synthesis is summarized in Table I.

(5) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **78**, 2141 (1956).

(6) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, **72**, 2949 (1951).

(7) B. Klein, Doctoral dissertation, Polytechnic Institute of Brooklyn, June, 1950.

(8) A. E. Erickson, Doctoral dissertation, Polytechnic Institute of Brooklyn, June, 1950.

(9) A. E. Chichibabin and M. J. Rjasancew, *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915).

(10) W. Baker, R. F. Curtis, and M. G. Edwards, *J. Chem. Soc.*, 83 (1951).

(11) A. E. Erickson and P. E. Spoerri, *J. Am. Chem. Soc.*, **68**, 400 (1946).

The conversion of several of these aminopyrazines to the corresponding isodiazotates was accomplished according to a procedure described by Chichibabin[9] by treating the amine with sodium amide in refluxing ethyl ether. The resulting sodium salt was then allowed to react with isoamyl nitrite and the isodiazotate salt isolated directly by filtration. The salts were then *exhaustively* extracted with ether to remove any traces of starting amine and then kept in a vacuum dessiccator until ready for use. The procedure is summarized in the accompanying equation and in Table II.

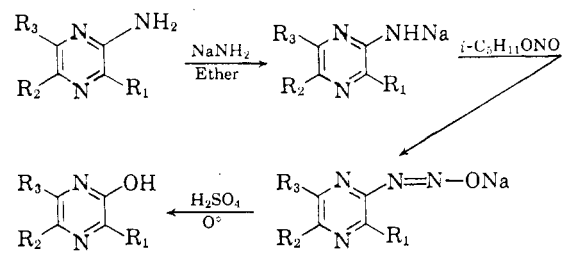
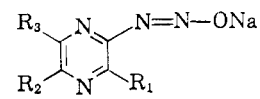


TABLE II

PYRAZINE ISODIAZOTATES



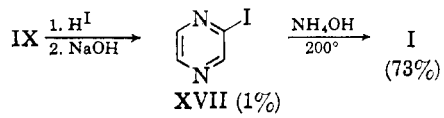
	R_1	R_2	R_3	Yield, %	% Yield of Derived Hydroxypyrazine
IX	H	H	H	51	42
X	CH_3	H	H	49	72
XI	CH_3	H	CH_3	67	66
XII	C_2H_5	H	H	30	69

The salts were assigned to the isodiazotate structure, on the basis of their inability to couple with β-naphthol in alkaline solution.[12] The salts

(12) K. H. Saunders, *The Aromatic Diazo Compounds and Their Technical Application*, p. 126, Longmans Green and Co. (1949).

possessed no definite melting point and indeed decomposed violently upon heating. Characterization of these salts was accomplished by hydrolysis to the known hydroxypyrazines[4] in cold 40% aqueous sulfuric acid.[11] The yields of derived hydroxypyrazines are also listed in Table II.

Treatment of the isodiazotate salt of aminopyrazine (IX) with cold 57% hydriodic acid, followed by the addition of strong base, and extraction afforded at best very small quantities of an oil, and only after many experiments was it possible to accumulate a sufficient amount of this material for characterization. This was accomplished by means of a sodium fusion which showed the presence of iodine and a quantitative elemental analysis which yielded values consistent for iodopyrazine proper. As proof of structure the iodinated oil was subjected to ammonolysis, affording aminopyrazine (I).

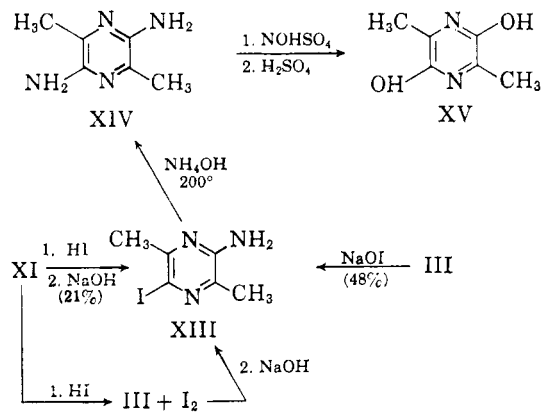


Repetition of this experiment using isodiazotate salt XI, afforded reasonably good yields of a solid iodinated material. Unexpectedly however, the product isolated, exhibited sharp peaks in the infrared at 3440 cm.$^{-1}$, 3333 cm.$^{-1}$, 3175 cm.$^{-1}$, and 1640 cm.$^{-1}$, all attributable to a primary amino group. In addition the analytical data indicated that the material was an aminoiodopyrazine, presumably 2-amino-3,6-dimethyl-5-iodopyrazine (XIII).

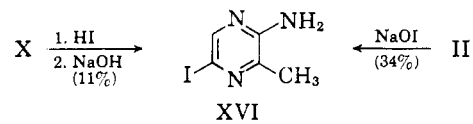
Repetition of this experiment with another carefully prepared and purified sample of isodiazotate salt XI revealed the formation of free iodine as the addition of XI to hydriodic acid progressed, indicating that the hydriodic acid was being oxidized. As a corresponding reduction it seemed likely that the isodiazotate salt XI was being reduced back to the starting amine. As the succeeding workup then involved the addition of base till a strongly alkaline solution was obtained, the free iodine present was converted to hypoiodite, which then presumably iodinated the regenerated aminopyrazine.

In order to test this conclusion, 2-amino-3,6-dimethylpyrazine (III) was treated with sodium hypoiodite directly. This procedure afforded a material which proved to be identical with the iodinated material obtained from the isodiazotate salt XI, as shown by comparison of the infrared curves and mixture melting point.

Proof of structure of the aminoiodo compound XIII was accomplished by ammonolysis which afforded 2,5-diamino-3,6-dimethylpyrazine (XIV). XIV was then treated with nitrosylsulfuric acid, afforded an intermediate diazonium solution which was then hydrolyzed with sulfuric acid to the corresponding dihydroxy compound XV.[11] Comparison of XV with a known sample of the dihydroxy compound[13] showed the two to be the same.



Similarly, treatment of isodiazotate salt X with 57% hydriodic acid afforded an aminoiodo derivative which was presumably 2-amino-3-methyliodopyrazine (XVI). This same compound was obtained by treating amine II directly with sodium hypoiodite. It therefore seems reasonable to assume that the same type of reaction course operated in this instance as that previously described for isodiazotate salt XI.



While the position of the iodine in XVI is not known with certainty, it seems reasonable to assume that the iodination goes *para* to the activating amino group.

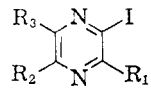
Examination of the oily product obtained from the treatment of isodiazotate salt XII with 57% hydriodic acid by means of a sodium fusion and infrared revealed the presence of both iodine and a primary amino group. Further examination of the spectrum revealed its close similarity to the curve of 2-amino-3-ethylpyrazine (IV) itself. This finding seemed to indicate that XII had been reduced, but that the regenerated amine reacted with sodium hypoiodite to only a small extent, thus affording a mixture containing mostly regenerated amine IV with some small amounts of iodinated material. As IV has a low melting point at 55°, it seems likely that even traces of an impurity would cause this material to become an oil.

Treatment of amine IV with sodium hypoiodite confirmed this lack of reactivity towards iodination, because only small quantities of an oil were obtained, which possessed all the characteristics of the oil previously secured from the treatment of isodiazotate salt XII with hydriodic acid. Attempts

(13) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, 79, 680 (1957).

TABLE III

IODOPYRAZINES



	R_1	R_2	R_3	Yield, %	B.P./Mm.	M.P.	n_D^t	t	I% Calcd.	I% Found	Yield of Derived Amine, %
XVII	H	H	H	40	109–110/34	—	1.6403	24	61.61	61.67	73
XVIII	CH_3	H	H	35	137–138/65	40–41	—	—	57.41	57.68	72
XIX	CH_3	CH_3	H	45	154–155/70	—	1.6042	27	54.22	54.53	23
XX	CH_3	H	CH_3	56	140–141/47	61–62	—	—	54.22	54.02	72
XXI	H	CH_3	CH_3	47	120–121/20	55–57	—	—	54.22	54.36	51
XXII	C_2H_5	H	H	46	152–153/72	—	1.6003	27	54.22	54.12	76
XXIII	H	C_6H_5	C_6H_5	33	—	141–142			51.16	50.84	69

at crystallizing this oil or its purification by chromatography were not successful.

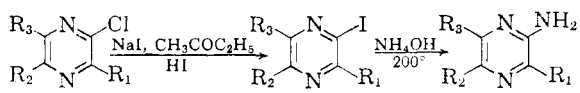
Although the reducing properties of hydriodic acid are well known, this work represents the first reported use of hydriodic acid as a reducing agent for isodiazotates. Indeed, there is only one reported reduction of an isodiazotate and that is the reduction of the sodium salt of benzene isodiazotate to aniline using sodium amalgam in aqueous acetic acid.[14]

Simultaneous with the above work, a number of attempts to prepare the desired iodo derivatives by displacement of chlorine in variously substituted chloropyrazines were undertaken. Attempts to prepare iodopyrazine using 57% hydriodic acid, duplicating a procedure outlined by Baker, Curtis, and Edwards[10] for 2-iodopyridine was not successful as only polymeric degradation products could be isolated.

These same authors also report the preparation of 2-iodoquinoline by means of halogen interchange using sodium iodide in methyl ethyl ketone containing a small amount of water and hydriodic acid. No displacement was reported to occur if a neutral solution of sodium iodide in methyl ethyl ketone were employed.

An experiment was therefore conducted wherein 2-chloropyrazine was treated with a saturated solution of sodium iodide in methyl ethyl ketone to which had been added a small quantity of 57% hydriodic acid. The mixture, upon refluxing, afforded a precipitate of sodium chloride, and yielded upon work-up an oil which proved to be identical with the sample of iodopyrazine previously prepared from the isodiazotate salt X.

The success of this reaction led to its general application and a series of iodinated pyrazines were thus prepared. This procedure is summarized in Table III.



(14) G. Walther, *J. prakt. chem.*, **53** ii, 467 (1895).

The iodopyrazines listed were converted by means of high temperature ammonolysis to the corresponding aminopyrazines, which, being known, constituted a convenient proof of structure. The yields of the amines derived from the iodo derivatives are also listed in Table III.

The chemical properties of these iodopyrazines, especially in regard to organometallic reactions is now being investigated, and will be reported on at a later date.

EXPERIMENTAL[15]

All necessary chloropyrazines were prepared according to a procedure described by Karmas and Spoerri.[4]

2-Aminopyrazines. A mixture of 0.02 mole of the appropriate halopyrazine and 80 ml. of 28% aqueous ammonia was heated in a stainless steel autoclave at 200° for 30 hr. The resulting solution was cooled to 0° and saturated with sodium hydroxide pellets, and then was extracted thoroughly with ether. The ether extracts were dried over sodium sulfate and then evaporated yielding solid residues. In the two cases (compounds IV and V) where the residues were oils, crystallization was induced by cooling. The residues were recrystallized from either a benzene–petroleum ether (b.p. 70–80°) mixture or ethanol, with the exception of aminopyrazine (compound I), which was recrystallized from ethyl acetate.

Pyrazine isodiazotates. A solution of 0.1 mole of the appropriate aminopyrazine in anhydrous ether was added, with stirring to a slurry of 0.39 g. (0.01 mole) of sodium amide in 50 ml. of anhydrous ether. The resulting mixture was allowed to reflux with continuous stirring for 15 hr. during which time a heavy precipitate formed. To this suspension was added 0.01 mole of freshly distilled isoamyl nitrite in 10 ml. of anhydrous ether. The resulting mixture was allowed to reflux with mechanical stirring for a further period of 8 hr. after which time it was filtered.

The residue was washed with fresh anhydrous ether and then *exhaustively* extracted in a Soxhlet apparatus until no further organic material was extracted by the ether. The residue was dried and stored in a dessicator until ready for use. The yields of isodiazotates prepared in this way are listed in Table II.

(15) All melting points are corrected. Infrared spectra were determined using potassium bromide disks on a Perkin-Elmer Model 21 recording infrared spectrophotometer. Microanalyses were performed by Schwarzkopf Laboratories in New York, or M. Manser, Basel, Switzerland.

Hydrolysis of isodiazotate salts. To 10 ml. of water was added 0.5–1.0 g. of the appropriate isodiazotate. The resulting solution was filtered to remove any small amounts of insoluble material, and then added slowly dropwise, with stirring, to 25 ml. of cold (0–5°) 40% sulfuric acid. After the addition was complete, the resulting solution was adjusted to *p*H 6 with 12.5*N* sodium hydroxide solution. The resulting inorganic salts were filtered off and washed with three 5-ml. portions of ice water. The filtrate and washings were combined and evaporated to dryness under reduced pressure at 50°.

The resulting residue was exhaustively extracted with acetone in a Soxhlet apparatus. The acetone extract was then evaporated to dryness under reduced pressure at 50° and the residue recrystallized from the appropriate solvent listed in Table IV. The yields of these derived hydroxypyrazines are listed in Table II.

TABLE IV

DERIVED HYDROXYPYRAZINES

	M.P., Observed	M.P., Lit.[4]	Recrystallization Solvent
Hydroxypyrazine	185–187	188–190	Ethanol
2-Hydroxy-3-methylpyrazine	148–150	151–152	Ethyl acetate
2-Hydroxy-3,6-dimethylpyrazine	210–211	210–211	Butyl acetate
2-Hydroxy-3-ethylpyrazine	102–103	96–97	Benzene + Pentane

2-Amino-3,6-dimethyl-5-iodopyrazine (XIII). *Procedure A.* To a solution of 1.20 g. (0.030 mole) of sodium hydroxide in 50 ml. of water was added 2.54 g. (0.010 mole) of iodine. To this solution was added 1.23 g. (0.010 mole) of 2-amino-3,6-dimethylpyrazine (III). The resulting solution was refluxed for 1 hr., cooled, and then extensively extracted with ether. The ether extracts were dried over magnesium sulfate and concentrated on a water bath leaving an oily residue, which solidified on cooling. The solid residue was then washed with water and recrystallized from isooctane affording 1.8 g. (40%) of white crystals, melting at 129–130°.

Anal. Calcd. for $C_6H_8N_3I$: C, 28.93; H, 3.24; N, 16.88; I, 50.96. Found: C, 29.03; H, 3.48; N, 16.87; I, 51.11.

Procedure B. A solution of 1.4 g. (0.0080 mole) of isodiazotate salt XI in 10 ml. of water was added slowly, with stirring, to 15 ml. of 57% hydriodic acid solution maintained at 0° in an ice salt bath. After the addition was complete, the mixture was stirred at 0–5° for 30 min. and then heated on a steam bath for another half hour. The mixture was then cooled and made basic (*p*H 10) with 12.5*N* sodium hydroxide solution. The resulting homogeneous solution was completely extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated, leaving an oily residue which solidified on cooling. The solid residue was washed with water and recrystallized from isooctane affording 0.430 g. (21%) of the aminoiodo compound melting at 129–130°.

2-Amino-3-methyl-5-iodopyrazine (XVI). *Procedure A.* To a solution of 1.09 g. (0.010 mole) of 2-amino-3-methylpyrazine (II), in 50 ml. of water containing 0.60 g. (0.015 mole) of sodium hydroxide was added 2.54 g. (0.010 mole) of iodine. The resulting mixture was heated on a steam bath for 2 hr., cooled to room temperature, and completely extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated on a water bath to yield an oily residue which solidified on cooling. The residue (1.10 g.) was washed with water and recrystallized from isooctane. Unchanged starting material, amounting to 0.40 g., insoluble in isooctane, was recovered. Cooling of the isooctane solution afforded 0.51 g. of aminoiodopyrazine melting at 95–96°. A 22% conversion was obtained while the yield was 34%.

Anal. Calcd. for $C_5H_6N_3I$: C, 22.56; H, 2.57; N, 17.87; I, 53.99. Found: C, 22.69; H, 2.79; N, 18.01; I, 53.94.

Procedure B. A solution of 0.73 g. (0.0045 mole) of isodiazotate salt X in 10 ml. of water was added slowly, with stirring, to 15 ml. of 57% hydriodic acid solution maintained at 0° in an ice salt bath. After the addition was complete, the mixture was stirred at 0–5° in an ice salt bath. After the addition was complete, the mixture was stirred at 0–5° for 30 min. and then heated on a steam bath for an additional half hour. The mixture was cooled and made alkaline (*p*H 10) with 12.5 *N* sodium hydroxide solution. The resulting homogeneous solution was completely extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated on a water bath leaving an oily residue which solidified on cooling. The residue was washed with water and recrystallized from isooctane affording 0.12 g. (11%) of the aminoiodo compound melting at 96–97°.

2,5-Diamino-3,6-dimethylpyrazine (XIV). A mixture of 25 ml. of 28% aqueous ammonia and 0.30 g. (0.0012 mole) of 2-amino-5-iodo-3,6-dimethylpyrazine (II) was heated in an autoclave at 200° for 15 hr. After cooling, the contents of the autoclave were made strongly basic with sodium hydroxide pellets and the basic mixture completely extracted with ether. The ether extract was dried over magnesium sulfate and concentrated on a water bath to yield a solid residue. The residue was recrystallized from benzene affording the diamino compound as prisms, melting at 210–211°. The yield was 0.13 g. (78%).

Anal. Calcd. for $C_6H_{10}N_4$: N, 40.55. Found: N, 40.47.

2,5-Dihydroxy-3,6-dimethylpyrazine (XV). Fifteen milliliters of concentrated sulfuric acid was cooled to 0° and 0.36 g. (0.0052 mole) of sodium nitrite was added slowly with stirring, so that the temperature of the resulting solution did not rise above 5°. After addition was complete, the mixture was allowed to come to room temperature, and then heated in an oil bath until a clear solution was obtained.

The solution of nitrosylsulfuric acid was cooled to 0° and to it a cold solution of 0.36 g. (0.0019 mole) of 2,5-diamino-3,6-dimethylpyrazine (XV) in 5 ml. of concd. sulfuric acid was added slowly dropwise, with cooling and stirring. The cold diazonium solution was then added slowly, with stirring to 100 g. of chopped ice. After the evolution of nitrogen had ceased, the cold acidic solution was carefully adjusted to *p*H 6 with sodium hydroxide pellets, with cooling.

The resulting cold solution was filtered and the precipitate of sodium sulfate washed with 50 ml. of ice water. The filtrate and washings were combined and concentrated to dryness under reduced pressure at 50°. The solid residue was dried and extracted in a Soxhlet apparatus with methanol. The methanol extracts were evaporated to dryness affording 0.32 g. (61%) of 2,5-dihydroxy-3,6-dimethylpyrazine as small yellow granules. The product did not melt below 320° and its infrared spectrum corresponded exactly with that of a known sample of product.[13]

2-Iodopyrazines. A mixture of 140 ml. of methyl ethyl ketone and 2 ml. of water was saturated at the boiling point with sodium iodide. The resulting hot saturated solution was added, with stirring, to 0.036 mole of the appropriately substituted chloropyrazine. A solution of 2 ml. of 57% hydriodic acid and 4 ml. of water was then added, and the mixture stirred and refluxed for 48 hr.

The precipitated sodium chloride was filtered off and washed with 25 ml. of methyl ethyl ketone. The filtrate and washings were combined and evaporated under reduced pressure at room temperature. The oily residue was treated with 75 ml. of water and 0.2 g. of sodium bisulfite. This was followed by the addition of sodium hydroxide pellets until

the resulting solution was strongly alkaline. This solution was then exhaustively extracted with ether, using a continuous liquid-liquid extraction apparatus.

The ether extract was dried over magnesium sulfate, treated with decolorizing carbon, and then filtered. The filtrate was carefully concentrated and the residual oil fractionated. Compound XXIII was isolated directly as a solid residue and recrystallized from methanol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF FLORIDA]

Pyrazolines. V. Application of Nuclear Magnetic Resonance Spectrometry to Structure Determinations[1]

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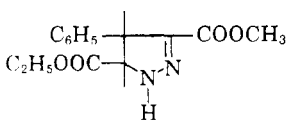
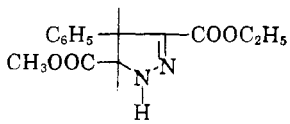
The structures of the two isomeric mixed methyl, ethyl esters of 4-phenyl-2-pyrazoline-3,5-dicarboxylic acid have been elucidated by comparison of their NMR spectra with appropriate model compounds. Interpretation of various features of the NMR spectra is discussed.

In the latter part of the nineteenth century, Buchner and his co-workers[2] made the interesting observation that the reactions of methyl diazoacetate with ethyl cinnamate and ethyl diazoacetate with methyl cinnamate led to two different isomeric 2-pyrazolines to which they assigned structures I and II, respectively. Although they did

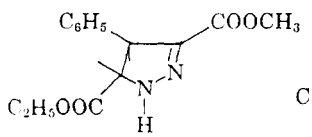


I

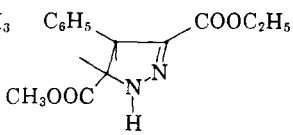


II

present compelling evidence for gross structures for these two isomers, they were not able to demonstrate conclusively the positions of the ester methyl and ethyl groups. In addition, no attempt was made to assign geometrical configurations to these two products.



I a



II-a

Geometrical configurations Ia and IIa have recently been assigned[1] as a result of an examination of the decomposition products of these two materials and the application of the rule[3] that "the geometrical configuration of the primary cyclopropane resulting from the decomposition of a 2-pyrazoline is determined by the relative thermodynamic stabilities of the intermediate 1-pyrazolines."

There still remained, however, the problem of distinguishing between the two isomers Ia and IIa. This distinction has been effected by comparing the proton magnetic resonance spectra of these two compounds with four model compounds.

EXPERIMENTAL

The mixed methyl, ethyl esters were synthesized by the method of Buchner and co-workers[2]; I, m.p. 106–106.5°, reported m.p. 107°; II, m.p. 75–76°, reported m.p. 76°. The methyl ester of 4-phenyl-2-pyrazoline-3-carboxylic acid (III) was prepared by the method of von Pechman and Burkhard[4]; m.p. 127–128°, reported m.p. 128°. The ethyl ester of 4-phenyl-2-pyrazoline-3-carboxylic acid (IV) was synthesized according to von Auwers and Cauer[5]; m.p. 99.5–100.5°, reported m.p. 100–100.5°. The dimethyl ester (V) of 4-phenyl-2-pyrazoline-3,5-dicarboxylic acid and the diethyl ester (VI) of this acid were prepared by the method of Buchner and co-workers;[2a,6] dimethyl ester, m.p. 103–104°, reported m.p. 105°; diethyl ester, m.p. 78–78.5°, reported m.p. 79°. Assignment of the *trans* configuration to both the dimethyl and the diethyl esters is based on the decomposition products of these two materials[3, 6, 7] and the recent demonstration that tautomeric equilibrium is not attained prior to nitrogen loss in the thermal decomposition of 3,5-dicarboalkoxy-2-pyrazolines.

NMR spectra were determined for the mixed esters and the model compounds in saturated solutions in carbon tetrachloride. A Varian 4300-2 high-resolution spectrometer, operating at 56.4 megacycles, was employed. Shifts were measured with respect to benzene as an internal reference, using sidebands applied by a calibrated audio oscillator. The amount of benzene added to the solutions was adjusted to give a peak of the same size as that of the phenyl group of the sample.

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(1) For the previous paper, see W. M. Jones, *J. Am. Chem. Soc.*, **82**, 3136 (1960).

(2)(a) E. Buchner and H. Dessauer, *Ber.*, **26**, 258 (1893); (b) E. Buchner and C. von der Heide, *Ber.*, **35**, 31 (1902).

(3) W. M. Jones, *J. Am. Chem. Soc.*, **80**, 6687 (1958); **81**, 5153 (1959).

(4) H. von Pechman and E. Burkhard, *Ber.*, **33**, 3595 (1900).

(5) K. von Auwers and E. Cauer, *Ann.*, **470**, 284 (1929).

(6) E. Buchner, *Ber.*, **21**, 2637 (1888).

(7) E. Buchner and H. Dessauer, *Ber.*, **25**, 1147 (1892).