[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL ENGINEERING, PURDUE UNIVERSITY]

The Amination of Pyrazine with Sodium Amide[1]

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The search for sulfanilamide derivatives having valuable therapeutic properties led to the substitution of pyrazine (1,4-diazine) for one of the amide hydrogens.[3] Since sulfapyrazine is prepared by the condensation of acetylsulfanilyl chloride with aminopyrazine, it was the purpose of this investigation to determine whether the aminopyrazine might be synthesized by the direct amination of pyrazine with sodium amide similar to that of heterocyclic compounds such as pyridine and quinoline.[4]

The pyrazine was supplied by Mead Johnson and Company.

Aminopyrazine has been obtained by the Hofmann degradation of the monocarboxylic acid,[5] and substituted aminopyrazines as well as the parent compound by heating the corresponding lumazines with sulfuric acid.[6]

Attempts to prepare aminopyrazine by direct amination with sodium amide fell into four general classifications: low temperature reaction in liquid ammonia; room temperature reaction in various solvents; reaction at elevated temperature in various solvents at their reflux temperature; and reaction in the absence of any solvent. Amination in the absence of a solvent appeared to be the most favorable.

Experimental

Sodium amide was prepared by reaction of sodium metal with liquid ammonia at −33°. Ferric nitrate seems to be the most efficient catalyst,[7] and about 0.15 g. was used per 2 g. of sodium in the early runs. Since this catalyst was found to decompose pyrazine acids,[8] it was abandoned in favor of sodium hydroxide.[9]

Reaction of pyrazine with sodium amide in liquid ammonia at −33° failed to yield any aminopyrazine.[10]

Reactions at Elevated Temperature.—Reagents, amounts and conditions for the amination of pyrazine at elevated temperatures are listed in Table I. After refluxing for the length of time indicated in Table I, the mixture was cooled to room temperature, ammonium iodide added and refluxing commenced. Approximately 50 ml. of water was then added to the refluxing mixture for the hydrolysis step. Aminopyrazine was recovered by vacuum sublimation of the dried residue.

TABLE I

AMINATION AT ELEVATED TEMPERATURE

Run	$NaNH_2$, g.	Pyrazine, g.	Solvent	Reflux temp., °C.	Reflux time, hr.	Complex treated with NH_4I, g.	Hydrolysis time, hr.	Method of separation	M. p. of product	Conversion, %
1	3.5	9	Dioxane	101	12	..	0.25	B	114	1.2
2	3.3	7	Chloroform	61	7	14	1.5	A	112	16
3	3	4	Dioxane	101	1–57[a]	10	50	D	106	6
4	3	4	Dioxane	101	1–57	..	40	D	105	3
5	4.5	5	Pyridine	115	1–90	..	75	C	110	12

[a] Shaken at room temperature for fifty-seven hours after one hour refluxing.

Methods of Separation: A.—The reaction mixture was evaporated to dryness in an 80° oven, powdered and vacuum sublimed in an apparatus similar to that described by Nelson.[11] B. The reaction mixture was salted with potassium carbonate into two layers. Each layer was evaporated separately under vacuum, and vacuum sublimed. C. Same as A except that evaporation was done on a steam-bath. D. The reaction mixture was made basic with potassium carbonate, then extracted continuously with acetone for twenty-four hours. The acetone extract was evaporated on a steam-bath and then vacuum sublimed.

Reactions at Room Temperature.—The amination of pyrazine with sodium amide was carried out at room temperature in rotating bottles in various solvent mediums. Reaction times and conditions are given in Table II.

Methods of Separation:—E. Acetone was added to the reaction mixture and then potassium carbonate added until two layers formed. Addition of potassium carbonate was continued until the lower, aqueous layer became almost saturated. The upper, acetone layer was separated and evaporated to dryness on a steam-bath. The lower layer was extracted continuously with acetone for twenty-four hours, and the extract then evaporated to dryness on a steam-bath. Both residues were vacuum sublimed. F. Same as E except that the reaction mixture was first steam distilled for thirty minutes.

In Run 12, approximately 2 g. of unreacted pyrazine was recovered by subjecting the reaction mixture to steam distillation for thirty minutes subsequent to hydrolysis. The residue from the steam distillation was treated by acetone extraction of Method E to get the aminopyrazine. The distillate from the steam distillation was saturated with sodium hydroxide. After most of the ammonia had bubbled off, three layers separated out. They were from top to bottom, dioxane, pyrazine as an oil, and aqueous caustic solution. The pyrazine layer was separated and poured on a porous plate where it crystallized.

(1) Abstracted from a thesis by Lloyd Berg submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) R. C. Ellingson, THIS JOURNAL, **63**, 2524 (1941).

(4) R. Norris Shreve, E. H. Riechers, H. Rubenkoenig and A. H. Goodman, *Ind. Eng. Chem.*, **32**, 173 (1940).

(5) S. A. Hall and P. E. Spoerri, THIS JOURNAL, **62**, 664 (1940).

(6) J. Weijlard, M. Tishler and A. E. Erickson, *ibid.*, **67**, 802 (1945).

(7) T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, *ibid.*, **56**, 2122 (1934).

(8) R. C. Ellingson, private communication.

(9) O. Liebknecht, U. S. Patent 1,359,080 (Nov. 16, 1920).

(10) Recently reported work: M. L. Crossley and J. P. English, U. S. Patent 2,394,963, Feb. 12, 1946, indicated that at higher temperature and pressure this reaction is successful.

(11) O. A. Nelson, *Ind. Eng. Chem., Anal. Ed.*, **14**, 153 (1942).

TABLE II

AMINATION AT ROOM TEMPERATURE

Run	$NaNH_2$, g.	Pyrazine, g.	Solvent	Shaking time, hr.	Complex treated with	Shaking time, hr.	Hydrolyzed with	Hydrolysis time, hr.	Method of sepn.	M. p. of product, °C.	Conversion, %
6	3	5.4	CCl_4	47	NH_4I	24	NaOH	25	A	112	0.5
7	4.5	6	Dioxane	48	NH_4I	23	H_2O	27	D	113	2.5
8	4.5	6	Pyridine	65		..	H_2O	48	C	115	8
9	5	3	Dioxane	40	NH_4I	34	H_2O	13	E	112	16
10	3	5	Dioxane	43	NH_4I	24	H_2O	24	E	114	17
11	3	5	Dioxane	43	NH_4I	24	H_2O	24	E	113	16
12	5	3	Dioxane	96	...	..	H_2O	22	F	114	12[a]

[a] Pyrazine recovered by steam distillation. Recycle yield = 36%.

Reactions in the Absence of Solvent.—The amination of pyrazine with sodium amide in the absence of any solvent medium was carried out in a ball mill at 50–55°. After grinding the melted pyrazine and sodium amide for three to four hours, water was added and grinding continued. Recovery of pyrazine and aminopyrazine was accomplished by Method E or F.. The results are summarized in Table III.

TABLE III

AMINATION IN THE ABSENCE OF SOLVENT

Run	$NaNH_2$, g.	Pyrazine, g.	Grinding temp.	Grinding time, hr.	Hydrolysis time, hr.	Method of sepn.	M. p. of product	Conversion, %	Recycle yield, %
13	1.6	3	60	0.25	0.16	E	110	11	..
14	6.6	15	50–55	2	.5	E	116	8	..
						½-E			
15	9	14.5	50–55	4	3	½-F	110	7.5	60

Discussion

Amination of pyrazine at room temperature gave, in general, higher yields per pass (conversion) of aminopyrazine than did the runs at elevated temperature. The solvents tried included dioxane, pyridine, *n*-hexane, *m*-xylene, petroleum ether (b. p., 47°), ethyl acetate, benzene, *n*-heptane, toluene, methylene chloride, chloroform, carbon tetrachloride, ethyl ether, carbon disulfide and acetone. Dioxane and pyridine seem to be the best solvent mediums in which to carry out the reaction. The yields under optimum conditions at room temperature were as high as 17% per pass. The recovery of pyrazine indicated that a recycle yield of 36% or better might be achieved. When the pyrazine was recovered by steam distillation, the amount of aminopyrazine was always less, sometimes even zero. This seems to be due to decomposition of aminopyrazine caused by a strong base.

In the reaction of pyrazine with sodium amide at room temperature, the amination takes place very slowly. Little pyrazine is lost, however, to decomposition or formation of other compounds. At temperatures considerably above room, the recovery of unreacted pyrazine was always low or zero indicating decomposition or side reactions.

No decided advantage of using ammonium iodide before hydrolysis was indicated. Enough aminopyrazine was obtained from runs containing no ammonium iodide to cast doubt on its value.

The most consistent results were obtained when the amination was carried out in the absence of any solvent. Here again, the adverse effect of steam distillation of the basic solution following hydrolysis was noted. For example, when the aminopyrazine was recovered by Method E (no steam distillation), conversion and yield were 7.5 and 60%, respectively. Yield is based on the amount of pyrazine recovered from the other half of the reaction mixture by steam distillation. The half of the mixture which was first steam distilled to recover unreacted pyrazine (Method F) gave a conversion and yield of only 5.1 and 41%, respectively.

Acknowledgment.—The authors are indebted to Drs. C. E. Bills and R. C. Ellingson of Mead Johnson and Co. for their advice and encouragement, and to that company for its financial support of this work.

Summary

Amination of pyrazine with sodium amide at room temperature or above in certain solvents, such as dioxane or pyridine, takes place to give aminopyrazine in yields up to 16%.

The most consistent conversions and yields of aminopyrazine, 8–17 and 36–60%, respectively, are obtained when melted pyrazine at 50–55° is treated with sodium amide in a ball mill in the absence of any solvent.

WEST LAFAYETTE, INDIANA RECEIVED[12] MAY 17, 1947

(12) Original manuscript received October 16, 1945.