4. It is found that the force of contraction due to the internal energy is, in general, very much larger than that due to the entropy change. It is therefore concluded that the elastic element of hair involves principally the internal energy. In this respect the elasticity of hair is in sharp contrast with that of rubber.

CHICAGO, ILL. RECEIVED DECEMBER 26, 1944

[CONTRIBUTION FROM AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA],

The Synthesis of Arsenicals Containing Certain Heterocyclic Nuclei

BY E. J. CRAGOE, JR., AND CLIFF S. HAMILTON

Within the past few years organo-arsenic compounds which contain a heterocyclic nucleus have gained considerable interest as therapeutic agents.[1,2,3] Particular interest has been attached to those derivatives in which the heterocyclic nucleus is linked through an amino group to an aromatic ring bearing an arsenic atom. Since only a few heterocyclic types had been studied, it was the purpose of this investigation to extend the study to other heterocyclic nuclei. Hatlelid[2] had previously prepared 2-(*p*-arsonoanilino)-5-nitropyridine (I) and the corresponding *m*-derivative (II) by condensing *p*- or *m*-phenylenediamine with 2-chloro-5-nitropyridine (III) followed by the Bart[4] reaction on the resulting aminoanilino-5-nitropyridine.

In this investigation these compounds, (I) and (II), have been produced by the condensation of *p*- or *m*-arsanilic acid with 2-chloro-5-nitropyridine, (III), using aqueous media containing one equivalent of acid.[5] Reaction has also been successful between *o*-arsanilic acid and (III) to produce 2-(*o*-arsonoanilino)-5-nitropyridine (IV), which could not be prepared by the method used by Hatlelid to synthesize the *p*- and *m*-isomers.

Similar condensations occur when (III) is allowed to react with 3-amino-4-hydroxyphenylarsonic acid or 2-hydroxy-4-aminophenylarsonic acid. Like reactions have been observed between *m*-arsanilic acid and 2-bromopyridine, 2-bromothiazole, or 2-chloro-4-methylthiazole. *p*-Arsanilic acid reacts with these same haloheterocycles and also with 2-chlorobenzothiazole.

The reaction also has been extended to include haloheterocycles with a halogen atom *gamma* to the ring nitrogen. 4-Chlorobenzo(h)quinoline reacts with *m*- or *p*-arsanilic acid and 1-chlorobenzo(f)quinoline reacts with these same amines and also 3-amino-4-hydroxyphenylarsonic acid. With 3-bromopyridine, where the halogen atom is *beta* to the ring nitrogen, no reaction occurs with *p*- or *m*-arsanilic acid.

Binz and co-workers[6] reported the preparation of a few N-substituted derivatives of 2-amino-5-arsonopyridine and indicated these compounds to be of therapeutic value. However, derivatives in which an aromatic or heterocyclic residue was substituted on the amino nitrogen had received little or no attention. 2-(Arylamino)-5-arsonopyridines are produced readily by the action of 2-chloro-5-arsonopyridine (V) upon aromatic amines using aqueous media under acidic conditions. Reaction is also successful when (V) is condensed with γ-aminopyridines such as 2-N-morpholino-5-aminopyridine (VI) or 2-N-thiomorpholino-5-aminopyridine (VII); however, with heterocycles containing an amino group in the position *alpha* to the ring nitrogen, such as 2-aminopyridine and 2-aminothiazole no condensation product is isolated. Since all of these reactions belong to the same general type described by Banks,[5] the results obtained serve further to verify and extend the application of this acid catalyzed reaction.

A review of earlier work[7] reveals that a labile halogen atom such as that in 3-nitro-4-bromophenylarsonic acid (VIII) will condense with strong amines in aqueous solution containing alkali. Although this reaction had previously been applied to only two heterocyclic amines, piperidine and piperazine, it is readily extended to include both morpholine and thiomorpholine.

The catalytic method, using molecular hydrogen and Raney nickel, has been applied successfully to the preparation of 2-(*o*-arsonoanilino)-5-aminopyridine (IX) from the corresponding 5-nitro- derivative, (IV); however, this method is found unsatisfactory for the reduction of 4-N-morpholino- (X) and 4-N-thiomorpholino-3-nitrophenylarsonic acid (XI). Likewise, reduced iron powder and water give unsatisfactory results, but by using ferrous hydroxide, the corresponding 3-amino- derivatives, (XII) and (XIII), are obtained in low yields.

N-(*p*-Arsonobenzenesulfonyl)-thiomorpholine (XIV) is prepared by conventional methods.

Experimental[8]

The preparation of *o*-arsanilic acid[9] (70%), 2-bromopyridine[10] (b. p. 97–99° (35 mm.), 52%), 2-chloro-5-

(1) Friedheim, *Schweiz. med. Wochschr.*, **71**, 116 (1941); *C. A.*, **36**, 1676 (1942).

(2) Hatlelid, Doctor's thesis, University of Nebraska, 1942.

(3) Banks, Gruhzit, Tillitson and Controulis, THIS JOURNAL, **66**, 1771 (1944).

(4) Bart, *Ann.*, **429**, 55 (1922).

(5) Banks, THIS JOURNAL, **66**, 1127, 1131 (1944).

(6) Binz and Rath, *Ann.*, **455**, 127 (1927); Binz and Maier-Bode *Angew. Chem.*, **49**, 486 (1936).

(7) Maclay and Hamilton, THIS JOURNAL, **54**, 3310 (1932).

(8) The melting points of all arsenicals were taken by the method of Morgan and Hamilton, THIS JOURNAL, **66**, 874 (1944).

(9) Kalb, *Ann.*, **423**, 39 (1921).

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

TABLE I

ARSONOARYLAMINOHETEROCYCLES

Name	Yield, %	M. p., °C.	Formula	As analyses, %[17] Calcd.	Found
2-(*p*-Arsonoanilino)-pyridine[a]	71	220–221	$C_{11}H_{11}AsN_2O_3$	25.47	25.62
2-(*p*-Arsonoanilino)-5-nitropyridine[b] (I)	55	>250	$C_{11}H_{10}AsN_3O_5$	22.09	22.08
2-(*p*-Arsonoanilino)-thiazole[c]	30	238–240	$C_9H_9AsN_2O_3S$	24.96	24.82
2-(*p*-Arsonoanilino)-4-methylthiazole[d]	21	>250	$C_{10}H_{11}AsN_2O_3S$	23.84	23.85
4-(*p*-Arsonoanilino)-benzo(h)quinoline[d]	41	>250	$C_{19}H_{15}AsN_2O_3$	19.00	18.90
1-(*p*-Arsonoanilino)-benzo(f)quinoline[d]	60	>250	$C_{19}H_{15}AsN_2O_3$	19.00	18.87
2-(*p*-Arsonoanilino)-benzothiazole[d]	87	>250	$C_{13}H_{11}AsN_2O_3S$	21.39	21.33
2-(*m*-Arsonoanilino)-pyridine[c]	21	124.5–125.5	$C_{11}H_{11}AsN_2O_3$	25.47	25.48
2-(*m*-Arsonoanilino)-5-nitropyridine[a] (II)	73	>250	$C_{11}H_{10}AsN_3O_5$	22.09	22.09
2-(*m*-Arsonoanilino)-thiazole[c]	13	204–206	$C_9H_9AsN_2O_3S$	24.96	24.98
2-(*m*-Arsonoanilino)-4-methylthiazole[d]	65	>250	$C_{10}H_{11}AsN_2O_3S$	23.84	23.84
4-(*m*-Arsonoanilino)-benzo(h)quinoline[d]	37	>250	$C_{19}H_{15}AsN_2O_3$	19.00	18.94
1-(*m*-Arsonoanilino)-benzo(f)quinoline[d]	86	>250	$C_{19}H_{15}AsN_2O_3$	19.00	18.90
2-(*o*-Arsonoanilino)-5-nitropyridine[a] (IV)	52	236–237	$C_{11}H_{10}AsN_3O_5$	22.09	21.98
2-(*o*-Arsonoanilino)-5-aminopyridine[e] (IX)	29	230–231 (dec.)	$C_{11}H_{12}AsN_3O_3$	24.23	23.95
2-(2′-Hydroxy-5′-arsonoanilino)-5-nitropyridine[d]	51	>250	$C_{11}H_{10}AsN_3O_6$	21.09	21.03
1-(2′-Hydroxy-5′-arsonoanilino)-benzo(f)quinoline[d]	41	>250	$C_{19}H_{15}AsN_2O_4$	18.26	18.15
2-(3′-Hydroxy-4′-arsonoanilino)-5-nitropyridine[d]	70	176–178	$C_{11}H_{10}AsN_3O_6$	21.09	21.13

[a] Purified by dissolving in dilute sodium bicarbonate and precipitating with dilute hydrochloric acid. [b] Purified by crystallization from 90% acetic acid. [c] Purified by crystallization from 50% ethanol. [d] Purified by dissolving in dilute alkali and precipitating with dilute acetic acid. [e] Prepared by dissolving (IV) in water (60 ml.) and sufficient sodium hydroxide to give the solution an alkaline reaction with litmus then reducing with molecular hydrogen at 50 lb. using Raney nickel as a catalyst. (IX) was purified by dissolving in dilute hydrochloric acid and precipitating with dilute sodium hydroxide.

nitropyridine[11] (III) (m. p. 106°, 85%), 2-chloro-4-methylthiazole[12] (b. p. 161–161.5° (730 mm.), 31%), 2-chlorobenzothiazole[13] (b. p. 246–247° (735 mm.), 13%), thiomorpholine[14] (XV) (b. p. 100–105° (60 mm.), 30%), 2-chloro-5-arsonopyridine[15] (V) (m. p. 178–179°, 34%) and 3-nitro-4-bromophenylarsonic acid[7] (VIII) (59%) is adequately described in the literature. 1-Chlorobenzo(f)-quinoline, 4-chlorobenzo(h)quinoline, 2-hydroxy-4-aminophenylarsonic acid, 3-amino-4-hydroxyphenylarsonic acid and a procedure for the preparation of 2-bromothiazole (b. p. 70–71° (21 mm.), 45%) were supplied by Parke, Davis and Co.

***m*-Arsanilic acid** was prepared by the reduction of an aqueous solution of sodium *m*-nitrophenylarsonate, using molecular hydrogen at 50 lb. and Raney nickel catalyst; yield, 96%.

2-Chloro-5-aminopyridine (XVI).—To a rapidly stirring mixture of iron powder (reduced by hydrogen) (200 g., 3.58 moles) and water (300 ml.), (III) (70.3 g., 0.5 moles) was added portionwise, over two hours while the temperature was kept at 88–93°. After stirring at the same temperature for two more hours, the mixture was filtered and the iron residues twice extracted with 100-ml. portions of boiling water. After concentrating the combined filtrates at reduced pressure to a volume of 100 ml. and cooling (XVI) separated in white crystals. Further concentration and cooling brought the total to 60 g. (93%); m. p. 83–83.5°.[16]

Arsonoarylaminoheterocycles.—The appropriate aminophenylarsonic acid (0.1 mole) and haloheterocycle (0.12 mole) were dissolved or suspended in water (1 liter) containing hydrochloric acid (0.1 mole) and the mixture heated at reflux for five to one hundred hours, depending on the reactivity and solubility of the haloheterocycle. With highly insoluble haloheterocycles, 100–200 ml. of the water was replaced by ethanol. After concentrating the solution to 250–500 ml. and cooling, the product was precipitated by careful neutralization with alkali. Purification was carried out by dissolving the arsonic acid in dilute alkali and precipitating it with dilute acetic acid. The compounds were crystallized whenever a suitable solvent could be found. A summary of the results of the condensations carried out appears in Table I.

2-N-Morpholino-5-nitropyridine (XVII).—A solution of (III) (15.9 g., 0.1 mole) in carbon tetrachloride (250 ml.) was treated with morpholine (17.4 g., 0.2 mole) and the solution heated at reflux for ten hours. The solid which separated was filtered off and extracted for four hours by means of a Soxhlet extractor, using the filtrate as the solvent. Cooling the solvent gave 19 g. (92%) of crude product; after two recrystallizations from 95% ethanol 15 g. (72%) of long yellow needles remained; m. p. 142.3–143.3°.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30. Found: C, 51.60, 51.89; H, 5.53, 5.58.

2-N-Thiomorpholino-5-nitropyridine (XVIII).—A solution of (III) (15.9 g., 0.1 mole) in carbon tetrachloride (125 ml.) was treated with (XV) (20.6 g., 0.2 mole) and the solution heated at reflux for twelve hours. The product (XVIII) was isolated in 88% yield by the method employed for (XVII). After three recrystallizations from 95% ethanol, (XVIII) was obtained in dark yellow crystals; m. p. 132.1–132.6°.

Anal. Calcd. for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92. Found: C, 47.82, 47.99; H, 5.05, 5.12.

2-N-Morpholino-5-aminopyridine Dihydrochloride (VI).—A solution of (XVII) (15 g., 0.072 mole) in acetone (250 ml.) was reduced with molecular hydrogen at 50 lb. pressure using Raney nickel catalyst. After filtering off the catalyst, the filtrate was saturated with dry hydrogen chloride gas. The light brown precipitate was purified by suspending in boiling absolute ethanol, dissolving by the dropwise addition of water and precipitating by cooling and adding dry acetone. After repeating this process several times, 12.3 g. (80%) of (VI) remained; the white powder melts at 285–286° (dec.).

Anal. Calcd. for $C_9H_{16}Cl_2N_3O$: C, 42.87; H, 6.00;

(11) Phillips, *J. Chem. Soc.*, 9 (1941).

(12) Tcherniac, *ibid.*, **115**, 1071 (1919).

(13) Hofmann, *Ber.*, **12**, 1126 (1879).

(14) Davies, *J. Chem. Soc.*, **117**, 297 (1920).

(15) Binz and Schickh, *Ber.*, **68B**, 315 (1935).

(16) Mills and Widdows, *J. Chem. Soc.*, **93**, 1372 (1908), report m. p. 82–83.5°.

(17) Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

TABLE II

5-ARSONOPYRIDINES

Name	Yield, %	M. p., °C.	Formula	As analyses, % Calcd.	Found
2-(*p*-Carboxyanilino)-5-arsonopyridine[a]	80	247–248	$C_{12}H_{11}AsN_2O_5$	22.15	22.14
2-(*p*-Arsonoanilino)-5-arsonopyridine[b]	90	>250	$C_{11}H_{12}As_2N_2O_6$	35.84	35.73
2-(*p*-Sulfamylanilino)-5-arsonopyridine[b]	50	>250	$C_{11}H_{12}AsN_3O_5S$	20.07	19.84
2-[5′-(2′-N-Morpholinopyridylamino)]-5-arsonopyridine[c]	96	128–129	$C_{14}H_{17}AsN_4O_4$	19.70	19.47
2-[5′-(2′-N-Thiomorpholinopyridylamino)]-5-arsonopyridine[d]	80	174–175	$C_{14}H_{17}AsN_4O_3S$	18.90	19.00
2-(*p*-Ethoxyanilino)-5-arsonopyridine[a]	77	216–218	$C_{13}H_{15}AsN_2O_4$	22.15	22.13

[a] Purified by dissolving in dilute alkali and precipitating with dilute hydrochloric acid. [b] Purified by dissolving in dilute alkali and precipitating with dilute acetic acid. [c] Recrystallized from absolute ethanol. [d] Recrystallized from water.

TABLE III

BIS-(CARBOXYMETHYLTHIO)-ARSINO DERIVATIVES

Name	Yield, %	M. p., °C.	Formula	As analyses, % Calcd.	Found
1-[*p*-Bis-(carboxymethylthio)-arsinoanilino]-benzo(f)quinoline[a]	70	237–238	$C_{23}H_{19}AsN_2O_4S_2$	14.23	14.09
2-[*p*-Bis-(carboxymethylthio)-arsinoanilino]-benzothiazole[b]	56	196.5–197.5	$C_{17}H_{15}AsN_2O_4S_3$	15.53	15.48
2-[*m*-Bis-(carboxymethylthio)-arsinoanilino]-4-methylthiazole[c]	60	205–206	$C_{14}H_{15}AsN_2O_4S_3$	16.78	16.57
1-[*m*-Bis-(carboxymethylthio)-arsinoanilino]-benzo(f)quinoline[a]	85	>250	$C_{23}H_{19}AsN_2O_4S_2$	14.23	14.11
2-(*p*-Ethoxyanilino)-5-bis-(carboxymethylthio)-arsinopyridine[b]	85	200–201	$C_{17}H_{19}AsN_2O_5S_2$	15.93	15.86

[a] Recrystallized from 50% acetic acid. [b] Recrystallized from glacial acetic acid. [c] Recrystallized from 90% acetic acid.

Cl, 28.12. Found: C, 43.03, 43.11; H, 6.24, 6.27; Cl, 27.96, 27.84.

2-N-Thiomorpholino-5-aminopyridine Dihydrochloride (VII).—A solution of (XVIII) (14.0 g., 0.062 mole) in acetone (250 ml.) was prepared, and reduction and purification were carried out as for (VI). A yield of 16 g. (97%) of (VII) was obtained as a white powder; m. p. 264–265° (dec.).

Anal. Calcd. for $C_9H_{15}Cl_2N_3S$: C, 40.30; H, 5.64; Cl, 26.44. Found: C, 40.02, 40.05; H, 5.83, 5.89; Cl, 26.60, 26.69.

2-Heterocyclicamino- and 2-Arylamino-5-arsonopyridines.—2-Chloro-5-arsonopyridine (V) (4.75 g., 0.02 mole) was dissolved in water (100–200 ml.) containing hydrochloric acid (0.02 mole). The appropriate amine (0.02–0.025 mole) was added and the mixture heated at reflux for ten to twelve hours. If the product separated on cooling, it was removed by filtration. If no separation occurred on cooling, the solution was treated with dilute alkali until precipitation was complete. After filtering and washing, the crude product was purified by repeatedly dissolving in dilute alkali and precipitating with dilute acetic acid. The compounds were crystallized whenever a suitable solvent could be found. The results of these condensations are summarized in Table II.

Bis-(carboxymethylthio)-arsino Derivatives. The appropriate arsonic acid (0.02 mole) was suspended in water (40–50 ml.) and dissolved by the addition of a minimum quantity of sodium hydroxide solution. A solution of sodium thioglycolate was prepared from thioglycolic acid (8.3 g., 0.09 mole), sodium hydroxide (3.6 g., 0.09 mole) and water (20–40 ml.). The two solutions were then united and heated at 90° for one hour. Acidification of the reaction mixture with acetic acid precipitated the product. The crude material was filtered off and purified by dissolving in dilute alkali and precipitating with dilute acetic acid. Whenever possible the product was crystallized from glacial acetic acid or an acetic acid-water mixture. Data concerning these preparations appear in Table III.

3-Nitro-4-N-morpholinophenylarsonic Acid (X).—A mixture of (VIII) (54 g., 0.166 mole) and potassium carbonate (48.5 g., 0.35 mole) was dissolved in water (250 ml.). The solution was treated with morpholine (15.7 g., 0.186 mole) and then heated at reflux for five hours. After making the solution just acid to litmus with hydrochloric acid, it was boiled for ten minutes, filtered and cooled. The dark red filtrate was made acid to congo red paper with hydrochloric acid. The precipitate which separated was recrystallized from 95% ethanol to give 50 g. (91%) of bright yellow product (X); m. p. 203–204°.

Anal. Calcd. for $C_{10}H_{13}AsN_2O_6$: As, 22.55. Found: As, 22.45, 22.50.

3-Nitro-4-N-thiomorpholinophenylarsonic Acid (XI).—A mixture of (VIII) (58.7 g., 0.18 mole) and potassium carbonate (60 g., 0.44 mole) was dissolved in water (250 ml.). The solution was treated with (XV) (20 g., 0.193 mole) and heated at reflux for five hours. The product was isolated as was (X) and then recrystallized from dilute acetic acid to obtain 60 g. (96%) of (XI) as a bright yellow powder; m. p. 187–189° (instantly resolidifying to the anhydride).

Anal. Calcd. for $C_{10}H_{13}AsN_2O_5S$: As, 21.51. Found: As, 21.49, 21.51.

3-Amino-4-N-morpholinophenylarsonic Acid (XII).—A paste of ferrous hydroxide was prepared by dissolving ferrous sulfate pentahydrate (145.2 g., 0.6 mole) in water (470 ml.) and adding 6 *N* sodium hydroxide (200 ml.). A solution of (X) (33.2 g., 0.1 mole) in 2 *N* sodium hydroxide was added portionwise with shaking to the tightly stoppered ferrous hydroxide. The mixture was filtered, washed with water and concentrated at reduced pressure. Upon cooling and making the solution acid to congo red paper with hydrochloric acid the product (XII) separated After recrystallization from a 50–50 mixture of methanol and water, the pink product weighed 10 g. (33%); m. p. 256–258° (dec.).

Anal. Calcd. for $C_{10}H_{15}AsN_2O_4$: As, 24.79. Found: 24.71, 24.74.

3-Amino-4-N-thiomorpholinophenylarsonic Acid (XIII).—By using the method outlined for (XII) compound (XIII) was obtained in a 22% yield; m. p. 172° (dec.).

Anal. Calcd. for $C_{10}H_{15}AsN_2O_3S$: As, 23.54. Found: As, 23.34, 23.28.

N-(*p*-Acetylaminobenzenesulfonyl)-thiomorpholine (XIX).—After dissolving (XV) (30 g., 0.3 mole) in pyridine (180 ml.), *p*-acetylaminobenzenesulfonyl chloride (81 g., 0.35 mole) was added portionwise over thirty minutes. The solution was shaken at intervals, allowed to stand at room temperature overnight, and then heated on a steam-bath for thirty minutes. The cooled solution was added slowly, with stirring, to distilled water (1.8 liter). The oil which formed solidified on stirring. The solid was filtered off, washed with water and recrystallized from 20%

ethanol to give 83 g. (92%) of (XIX) as white crystals; m. p. 208°.

Anal. Calcd. for $C_{12}H_{16}N_2O_3S_2$: C, 47.98; H, 5.37. Found: C, 48.20, 48.24; H, 5.48, 5.51.

N-Sulfanilylthiomorpholine (XX).—A mixture of (XIX) (75 g., 0.25 mole) and 4 *N* hydrochloric acid (300 ml., 1.2 mole) was heated on a steam-bath for four hours. The cooled mixture was made alkaline with solid sodium carbonate and the precipitate which separated, filtered and washed with water. The crude product which weighed 61 g. (94%), when recrystallized from 50% ethanol gave pure (XX) as white plates; m. p. 181°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2S_2$: C, 46.49; H, 5.46. Found: C, 46.59, 46.38; H, 5.36, 5.30.

N-(*p*-Arsonobenzenesulfonyl)-thiomorpholine (XIV).—A solution of (XX) (28 g., 0.109 mole), absolute ethanol (260 ml.) concd. sulfuric acid (10.2 g., 0.222 equiv. wt.) and arsenic trichloride (29 g., 0.166 mole) was diazotized at 0° with a saturated aqueous solution of sodium nitrite (7.5 g., 0.109 mole). After adding cuprous bromide (1 g.) and heating at 60° until all the nitrogen was evolved, the solution was steam distilled. The residue was filtered off, suspended in water (300 ml.), treated with sodium bicarbonate (30 g.) and filtered. The two filtrates were united and made acid to congo red paper with hydrochloric acid. The precipitate which formed was filtered off, dissolved in dilute alkali and precipitated with dilute hydrochloric acid; yield, 23.5 g. (59%). By repeatedly dissolving the crude product in dilute alkali and precipitating with dilute acetic acid analytically pure (XIV) resulted, which did not melt below 250°.

Anal. Calcd. for $C_{10}H_{14}AsNO_5S_2$: As, 20.40. Found: As, 20.50, 20.50.

Summary

1. A number of new arsonoarylaminoheterocycles were prepared by condensing certain haloheterocycles with aminophenylarsonic acids in aqueous acid media.

2. 2-Chloro-5-arsonopyridine was condensed with several aryl and heterocyclic amines, under the same conditions, to obtain the corresponding 2-heterocyclicamino- and 2-arylamino-5-arsonopyridines.

3. Five of the arsonic acids prepared were converted to the corresponding bis-(carboxymethylthio)-arsino derivatives.

4. Morpholine and thiomorpholine were allowed to react with 3-nitro-4-bromophenylarsonic acid to produce 4-morpholino- and 4-thiomorpholino-3-nitrophenylarsonic acids; the corresponding 3-amino- derivatives were obtained by ferrous hydroxide reduction.

5. N-(*p*-Arsonobenzenesulfonyl)-thiomorpholine was prepared by conventional methods.

LINCOLN, NEBRASKA RECEIVED NOVEMBER 28, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Synthesis of Certain N,N-Dialkylethylenediamines[1]

BY MELVIN S. BLOOM, DAVID S. BRESLOW AND CHARLES R. HAUSER

N,N-Dialkylethylenediamines have been prepared by the Gabriel synthesis using ethylene bromide and a secondary amine,[2] by the amination of a dialkylaminoethyl bromide hydrobromide[3] and by the reduction of dialkylaminoacetonitriles.[4,5] The last method appears to be the best, since the nitriles are readily prepared in good yields by the following method.[6] Although several steps are involved, the reaction is readily carried out and requires only one distillation.

The dialkylaminoacetonitriles were reduced using sodium in ethanol or, preferably, in butanol, to form the corresponding diamines in yields of approximately 50%. The catalytic reduction of N,N-diethylaminoacetonitrile in 37% yield previously has been accomplished.[4] The reduction of the dibutyl derivative has been reported,[5] but no details were given. Although other N,N-dialkylethylenediamines could probably be prepared satisfactorily by the method here described, a monoalkylethylenediamine has been obtained in only 20% yield, while the monophenyl derivative failed to be produced in an appreciable yield. The results are summarized in Table I.

TABLE I

Nitriles, $RR'NCH_2CN$					Diamines, $RR'NCH_2CH_2NH_2$			
R	R′	B. p., °C.	Mm.	Yield,[a] %	Solvent	B. p., °C.	Mm.	Yield, %
C_2H_5	C_2H_5	60–60.5	14	81	Ethanol	144–145	760	53[b]
n-C_4H_9	*n*-C_4H_9	100–102	8	76	Butanol	98–99	13	50[c]
					Ethanol			46
i-C_5H_{11}	H	91–93	10	61	Butanol	92–92.5	30	20[d]
C_6H_5	H	47 (m. p.)		35	Butanol	.....	...	...

[a] Based on the amine. [b] Picrate, m. p. 207°.[2] [c] α-Naphthylurea, m. p. 102.5–103.5°.[3] [d] Picrate, m. p. 191.5°. Calcd. for $C_{13}H_{21}N_5O_7$: N, 19.5. Found: N, 20.0.

$$H_2CO \xrightarrow{NaHSO_3} H_2C(OH)SO_3Na \xrightarrow{R_2NH} H_2C(NR_2)SO_3Na \xrightarrow{KCN} R_2NCH_2CN$$

Experimental

Reduction of Aminoacetonitriles.—In a 500-ml. three-necked flask equipped with a mercury-sealed Hershberg

(1) This work was supported in part by a grant from the Duke University Research Council.

(2) Ristenpart, *Ber.*, **29**, 2526 (1896).

(3) Amundsen and Krantz, THIS JOURNAL, **63**, 305 (1941).

(4) Winans and Adkins, *ibid.*, **55**, 4167 (1933).

(5) *Chem. Zentr.*, **101**, II, 3083 (1930).

(6) Knoevenagel, *Ber.*, **37**, 4073 (1904); Knoevenagel and Merklin, *ibid.*, **37**, 4081 (1904).