Pyridine Chemistry. I. The Smiles Rearrangement of the 3-Amino-2,2′-dipyridyl Sulfide System[1]

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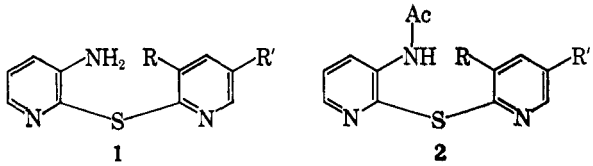
It is shown that the Smiles rearrangement of 3-amino-2,2′-dipyridyl sulfides and their N-acetyl derivatives can be acid, base, or heat catalyzed. In some cases solvent effects were observed, and examples are cited where the compounds underwent rearrangement in the solid state.

The Smiles rearrangement[2] is generally considered to be an intramolecular nucleophilic aromatic substitution reaction resulting in the migration of an aromatic ring from one hetero atom to another. The change which occurs can be generally represented by the scheme as shown in Fig. 1, where –YH may be –OH, –SH, –NHR, –CONHR, or $-SO_2NHR$, while Z may be O, S, SO, or SO_2.[3] The rearrangement has normally been considered to be base catalyzed and, because a rather intriguing interplay of electronic effects arises from ring substituents, some kinetic data also have been reported.[4]

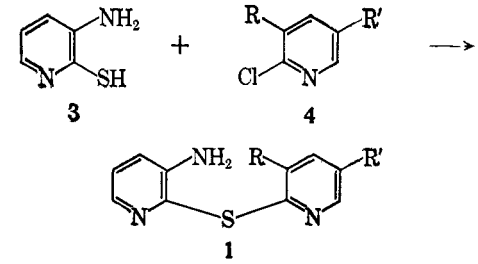
We became interested in this rearrangement in connection with studies on the transmission of substituent effects across the pyridine ring system. The 3-amino-2,2′-dipyridyl sulfides (**1**) appeared well suited for our purposes, especially since the Smiles rearrangement of this type of compounds has been reported.[5] However, our work clearly required a more concise definition of the conditions necessary for rearrangement and this communication describes some results observed in basic, acidic, and neutral media.



1 **2**

	R	R′
a	H	NO_2
b	NO_2	H
c	CH_3	NO_2
d	NO_2	CH_3
e	H	H (1 only)

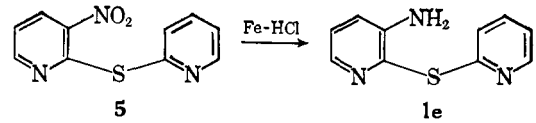
Preparation of the Dipyridyl Sulfides.—For our investigations, the 3-amino-2,2′-dipyridyl sulfides (**1**) and the N-acetyl derivatives (**2**) were employed, of which only **1a** and **2a** had been reported previously.[5c] Four of the dipyridyl sulfides (**1a–d**) were readily prepared at room temperature by the condensation of 2-mercapto-3-aminopyridine (**3**) with the appropriate 2-chloropyridines (**4a–d**) in the presence of methanolic potassium hydroxide. With an excess of potassium hydroxide, the condensation of the mercaptopyridine **3** with 2-chloro-3-methyl-5-nitropyridine (**4c**) gave some 2-methoxy-3-methyl-5-nitropyridine in addition to the expected dipyridyl sulfide **1c**. This by-product, obviously formed by the nucleophilic displacement of halide by methoxide ion, was avoided when stoichiometric amounts of base were used.[6]



3 **4** **1**

When the nitro group was absent, the condensation consistently failed, even if carried out in refluxing propylene glycol for prolonged periods of time. For example, the aminomercaptan **3** failed to condense with 2-bromopyridine or with 2-bromo-3-methylpyridine. The dipyridyl sulfide **1e** could likewise not be prepared by the condensation of 2-chloro-3-aminopyridine with 2-mercaptopyridine. The need for an electron-withdrawing group to provide the necessary activation of the halopyridine in these cases is thus apparent.

The dipyridyl sulfide **1e** was prepared successfully, however, by the reduction of the nitro group in the dipyridyl sulfide **5** with iron and hydrochloric acid. The sulfide **5** was, in turn, obtained by the condensation of 2-chloro-3-nitropyridine with 2-mercaptopyridine. The N-acetyl derivatives **2a–d** were obtained in good yield when the corresponding 3-aminodipyridyl



5 **1e**

(1) (a) Supported by research Grant NSF G-11388 of the National Science Foundation; (b) taken in part from the M. S. Thesis of R. E. Collier, University of Virginia, 1962.

(2) This rearrangement derives its name from Samuel Smiles who did much to develop its chemistry. A comprehensive coverage of much of the earlier work in this field may be found in (a) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 362 (1951); (b) J. F. Bunnett, *Quart. Rev.* (London), **12**, 12 (1958).

(3) Actually, there are some restrictions as to the allowable combinations of –YH and Z. Additional variations also have been observed and, in fact, the aromatic ring A is not a requirement (see ref. 2a for leading references).

(4) For example, see (a) K. C. Roberts, C. G. M. de Worms, and H. B. Clark, *J. Chem. Soc.*, 196 (1935); (b) C. S. McClement and S. Smiles, *ibid.*, 1016 (1937), and references cited therein; (c) J. F. Bunnett and T. Okamoto, *J. Am. Chem. Soc.*, **78**, 5363 (1956).

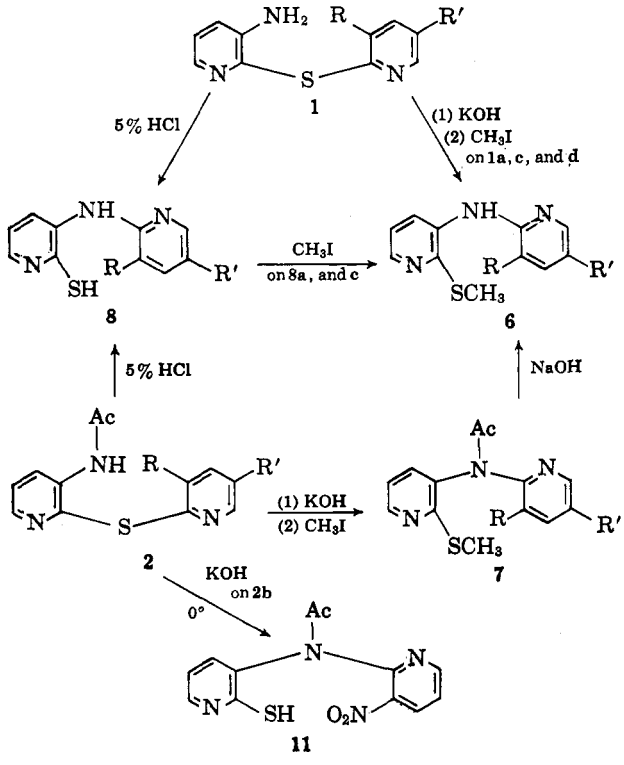
(5) (a) T. Takahashi and Y. Maki, *Pharm. Bull.* (Tokyo), **3**, 361 (1955); (b) Y. Maki, *J. Pharm. Soc. Japan*, **77**, 485, 862 (1957); (c) T. Takahashi and Y. Maki, *ibid.*, **78**, 417 (1958); (d) T. Takahashi and Y. Maki, *Chem. Pharm. Bull.* (Tokyo), **6**, 369 (1958).

(6) In the preparation of the dipyridyl sulfide **1c**, about 12% of the rearranged product **8c** was also isolated. On the other hand, Takahashi and Maki[5c] prepared the dipyridyl sulfide **1a** by virtually the same method and reported no rearranged product. Since our compound differed only by an additional methyl group, it was of interest that there should be so large a difference in the rearrangement abilities of these two substances. It was for this reason that the 3-amino-5′-nitro-2,2′-dipyridyl sulfide series reported by the Japanese workers was reinvestigated, and it was found that some of the rearranged product **16a** is formed here also, albeit in much smaller amount (see Experimental). This result might actually be predicted from the arguments of Bunnett and Okamoto that certain conformational requirements are necessary for the Smiles-type rearrangement (ref. 4c).

sulfides (**1a–d**) were treated with acetic anhydride at room temperature.

Rearrangement of the Dipyridyl Sulfides. A. Under Basic Conditions.—In almost all previously reported cases, the Smiles rearrangement has been carried out in basic media, and this has led to the postulation that the initial step of the reaction involves the removal of a proton from –YH (Fig. 1) to give $-Y^-$, which then acts as the attacking nucleophile.[7] In light of this mechanism, it is then not unexpected that the 3-amino-2,2′-dipyridyl sulfides reported in this paper undergo the rearrangement under similar circumstances.

The aminodipyridyl sulfides **1a, c,** and **d,** as well as the N-acetyl derivatives **2a–d,** readily rearranged in alcoholic potassium hydroxide, the products being isolated as their thiomethyl ether derivatives **6a, c,** and **d** and **7a–d**,[8] respectively. The structures were correlated by hydrolyzing dipyridylamines **7a, c,** and **d** to the deacetylated products **6a, c,** and **d** with sodium hydroxide in ethanol. With **2b** and **d,** some of the deacetylated products **6b** and **d** were also obtained directly from the rearrangement reactions.



In some instances, small amounts of other products were isolated as well. For example, the rearrangement of the dipyridyl sulfide **1c** also yielded considerable 2-methoxy-3-methyl-5-nitropyridine[9] and some of the free mercapto compound **8c**.

B. Under Acidic Conditions.—Since it is known that protonation of the ring nitrogen in pyridine derivatives increases the ease of nucleophilic substitution,[10] one might expect the Smiles rearrangement of 3-amino-2,2′-dipyridyl sulfides to be also acid catalyzed. Apparently, the only case where this has been observed

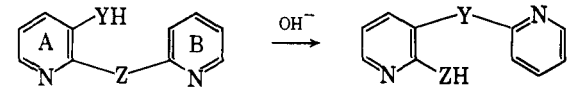


Figure 1.

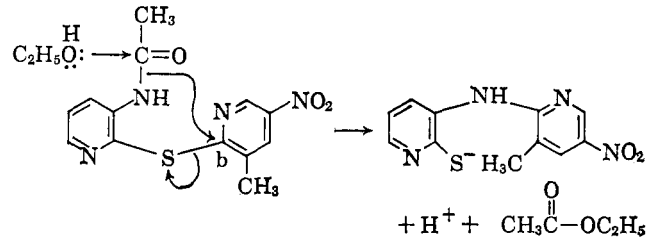
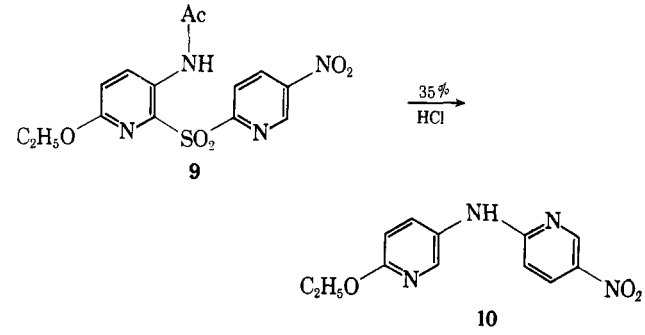


Figure 2.



was reported by Takahashi and Maki, who tried to remove the acetyl group of the dipyridyl sulfone **9**, by hydrolysis in 35% hydrochloric acid and obtained the dipyridylamine **10**.[5d]

We found that the dipyridyl sulfides **1a–e** rearranged smoothly when heated in 5% hydrochloric acid, the products **8a–d** being obtained as the free amines and, in the case of **8e**, as a hydrochloride which yielded the free amine when treated with base. The rearrangement occurs even more easily in concentrated hydrochloric acid. This was demonstrated with the dipyridyl sulfides **1a** and **b**, which rearranged in high yield within a few minutes when treated with this reagent at room temperature.

The corresponding N-acetyl derivatives **2a–d** also underwent rearrangement in 5% hydrochloric acid, however, at a slower rate than did the nonacetylated compounds. Furthermore, the products obtained were all deacetylated (**8a–d**), indicating that loss of the acetyl group may be necessary before rearrangement can occur. An alternative is that the amides rearrange more slowly than the amines, followed by rapid solvolysis of the products. The latter explanation finds support in the fact that the compound **11**, readily obtained when the rearrangement is conducted at lower temperature, undergoes rapid loss of the acetyl group when heated for several minutes in ethanol. A concerted process of the type discussed later (Fig. 2), perhaps

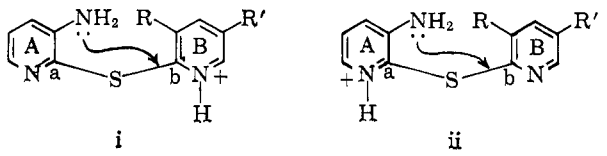
(7) A. A. Levy, H. C. Rains, and S. Smiles, *J. Chem. Soc.*, 3264 (1931), and subsequent papers; see also W. J. Evans and S. Smiles, *ibid.*, 181 (1935), for a slight variation of this mechanism.

(8) Previous workers found it easier to isolate the products as their thiomethyl ether derivatives, rather than as the free mercaptans or their salts. In the cases reported herewith, it was subsequently found that the free mercaptans could be isolated without undue difficulty, thus making the methyl iodide addition unnecessary.

(9) Similar cleavage products have been reported; *cf.* ref. 5b.

(10) (a) C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944); (b) N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1563 (1956); (c) J. D. Reinheimer, J. T. Gerig, R. Garst, and B. Schrier, *J. Am. Chem. Soc.*, **84**, 2770 (1962).

(11) It is interesting that the thiomethyl derivative **7b** does not undergo such solvolysis in ethanol, even when heated at reflux for 24 hr. The observed neighboring-group effect involving the free mercaptan is, of course, not entirely unpredicted.



i ii

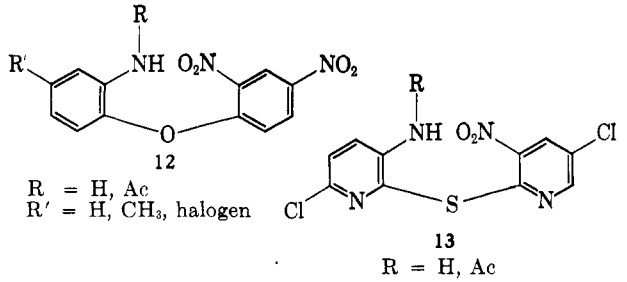
Figure 3.

involving initial protonation of the amide carbonyl group, is yet another possibility. At the present time there is insufficient evidence to allow a preference for one or the other of these mechanisms. The structures of the rearranged products were correlated with those obtained under basic conditions by converting **8a** and **c** to the thiomethyl ether derivatives **6a** and **c** with methyl iodide.

When treated with a mixture of hydrochloric acid in ethanol, both the 3-amino-3′-nitrodipyridyl sulfide (**1b**) and its acetyl derivative (**2b**) readily formed monohydrochlorides. When these hydrochlorides were heated in aqueous solution, both rearranged to the same mercaptodipyridylamine **8b**. It was qualitatively observed that the acetyl derivative underwent this conversion considerably more slowly than did the parent amine.

The catalyzing effect of acid can be explained by the protonation of either of the two ring nitrogen atoms (Fig. 3). If the nitrogen of ring B were protonated (i), it would increase the susceptibility of carbon "b" to nucleophilic attack by increasing its positive character.[10] If, on the other hand, the nitrogen in ring A were protonated (ii), a catalyzing effect on the rearrangement could be felt through the increased positive character of carbon "a" which should enhance the ability of the sulfur atom to accommodate a negative charge. Ring-A protonation would undoubtedly also affect the nucleophilic power of the amino group to some extent.

C. Under Thermal Conditions.—There are a few cases in the literature where the Smiles rearrangement has been initiated by heat alone. Roberts and de Worms[12] found that heat would rearrange aminodiphenyl ethers of type **12**, while Takahashi and Maki[6d] found that heating the dipyridyl sulfide **13** in a sealed tube with methyl iodide also gave a rearranged product.



12

R = H, Ac
R′ = H, CH_3, halogen

13

R = H, Ac

We observed such a heat-induced rearrangement during an attempted recrystallization of the N-acetyldipyridyl sulfide **2c** from ethanol. The yellow solution initially formed turned orange on heating and deposited the rearranged product **8c** when the mixture was allowed to cool. Furthermore, when the N-acetyldipyridyl sulfide was heated in benzene for 68 hr., no rearrangement occurred. The acetamidodipyridyl sulfide **2b** showed a similar behavior, undergoing rearrangement to the deacetylated product **8b** (79%) when heated in ethanol for 8 hr., or water for 45 hr., but again remaining unchanged when heated in benzene. An additional interesting observation was that the nonacetylated aminodipyridyl sulfides rearrange considerably more slowly in ethanolic solution than do their acetylated counterparts, in direct contrast to the results observed under acidic conditions.

These findings strongly suggest that the reaction involves solvent participation and two possible mechanisms are immediately apparent. Solvent can initiate the rearrangment by attack at the amide carbonyl group (Fig. 2), with simultaneous release of a pair of electrons for attack at carbon "b." Since initial attack is not possible in the absence of a Lewis base (benzene solvent) or with the nonacetylated compounds, the rearrangement is less favored in these cases.

Alternatively, the solvent may initiate ionization of the relatively acidic amide proton. The rearrangement could then proceed by attack of the resulting anion at carbon "b," followed by rapid solvolysis of the N-acetyldipyridylamine product. Support for this mechanism comes from the previously mentioned fact that compound **11** does indeed undergo rapid loss of the acetyl group when heated for several minutes in ethanol. The observation that the rate of rearrangement is considerably slower in water than in ethanol, however, argues against the ionization mechanism, since the ionizing power of water is normally considered to be the greater.[13]

To further clarify this point, the rearrangement of **2b** was attempted in an aprotic solvent of high ionizing ability. When the acetamidodipyridyl sulfide was heated at 80° for 11 hr. in dimethyl sulfoxide, virtually no rearrangement occurred and about 80% of the starting material was recovered unchanged. This then tends to rule out the ionization mechanism and favors the concerted process (Fig. 2).

Homogeneity of solution is not necessarily a requirement for the thermal rearrangement, since it was found possible to rearrange the dipyridyl sulfide **1b** by heating it with water in which it appears to be only slightly soluble. In fact, it was found that solvent was not even necessary. The rearrangements of **1a–c** went cleanly even when they were heated in the solid state in a drying oven at 110°.

Experimental[14]

2-Hydroxy-3-nitro-5-methylpyridine.—This compound was prepared using method A described by Hawkins and Roe[15] for the synthesis of 2-hydroxy-3-methyl-5-nitropyridine. 2-Amino-5-methylpyridine[16] (100 g., 0.926 mole) yielded 86.1 g. (60%) of product as orange-yellow crystals, m.p. 245–247° (lit.[17] m.p. 250–252°). This compound was carried through the next step without further purification.

(12) K. C. Roberts and C. G. M. de Worms, *J. Chem. Soc.*, 727 (1934); 1309 (1935).

(13) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948); S. G. Smith, A. H. Fainberg, and S. Winstein, *ibid.*, **83**, 618 (1961).

(14) All melting points were taken in a heated oil bath and are corrected. Although not usually specified, infrared spectra of all compounds were made, using either a Perkin Elmer Model 137 (Infracord) or a Model 21 instrument. These spectra were used in conjunction with melting points to determine the structures of all products. The authors are indebted to Mrs. William E. Coyne of this laboratory for performing the microanalyses.

(15) G. F. Hawkins and A. Roe, *J. Org. Chem.*, **14**, 328 (1949).

(16) Reilly Tar and Chemical Corp., Indianapolis, Ind.

(17) S. J. Childress and R. L. McKee, *J. Am. Chem. Soc.*, **73**, 3504 (1951).

2-Chloro-3-aminopyridine.—This compound is commercially available[18]; it was also prepared by the method of Ahmad and Hey.[19] *Note: During one preparation by the described procedure,[19] differing only in that double quantities were being used, a violent explosion occurred while the reaction mixture was being heated to 75°. The mixture suddenly turned dark at 65°, followed by the explosion. It is assumed that there was probably a buildup of perchlorate ions under the conditions of the reaction. When heat was applied, the concentration of these ions was sufficient to cause an explosion. It is strongly recommended that adequate precautions be taken when this reaction is carried out.*

2-Mercapto-3-aminopyridine (3).—This compound was prepared by the adaptation of the method reported by Thirtle[20] for the preparation of 2-mercaptopyridine. From 90.0 g. (0.701 mole) of 2-chloro-3-aminopyridine and 117.0 g. (3.04 moles) of sodium sulfhydrate in 350 ml. of propylene glycol, 57.9 g. (65%) of product was obtained. After one recrystallization from benzene, the product melted at 131–133°.[21]

Anal. Calcd. for $C_5H_6N_2S$: C, 47.59; H, 4.79; N, 22.20. Found: C, 47.70; H, 4.82; N, 22.06.

The hydrochloride was prepared in ethanol by the addition of several drops of concentrated hydrochloric acid, yellow needles, m.p. 227–228° dec. (lit.[5c] m.p. 225–228° dec.). Recrystallization from an absolute ethanol–ether mixture did not raise the melting point.

2-Methoxy-3-methyl-5-nitropyridine.—One gram (5.8 mmoles) of 2-chloro-3-methyl-5-nitropyridine (**4c**) was dissolved in a solution containing 650 mg. (11.6 mmoles) of potassium hydroxide in 10 ml. of methanol. After several minutes of stirring, a fluffy precipitate appeared which was separated by filtration and dissolved in ether. The ether solution was refiltered to remove the potassium chloride and dried over calcium sulfate; the solvent was removed, yielding 870 mg. (89%)of the 2-methoxy derivative, m.p. 86–89°. Further purification by sublimation gave long colorless needles, m.p. 91–92°.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.02; H, 4.76; N, 16.67. Found: C, 50.29; H, 5.03; N, 16.95.

2-Methoxy-3-nitro-5-methylpyridine.—This compound was prepared using the same procedure described above for 2-methoxy-3-methyl-5-nitropyridine. From 1.00 g. (5.8 mmoles) of 2-chloro-3-nitro-5-methylpyridine (**4d**) dissolved in a methanolic solution containing 650 mg. (11.6 mmoles) of potassium hydroxide, 890 mg. (91%) of crude product was obtained. Purification by sublimation gave 689 mg. (71%) of the 2-methoxy compound, m.p. 75–76°.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.02; H, 4.76; N, 16.67. Found: C, 49.74; H, 4.58; N, 16.75.

2,2′-Dipyridyl Sulfides 1a–d, 11.—These compounds were prepared by the method given below for 3-amino-3′-methyl-5′-nitro-2,2′-dipyridyl sulfide (**1c**). Pertinent information on experimental conditions, results, and physical constants of the products are summarized in Table I.

3-Amino-3′-methyl-5′-nitro-2,2′-dipyridyl Sulfide (1c).—Six grams (0.0476 mole) of 2-mercapto-3-aminopyridine was dissolved in a methanolic solution containing 2.68 g. of potassium hydroxide. To this mixture 8.23 g. (0.0476 mole) of 2-chloro-3-methyl-5-nitropyridine (**4c**) was added at room temperature with stirring. The orange solid which precipitated within a few minutes was filtered, dried, dissolved in chloroform, and refiltered to remove potassium chloride formed in the reaction. The filtrate was taken to dryness, and the residue was recrystallized from ethanol to give 9.50 g. (76%) of the desired product as a granular orange solid, m.p. 159–160°. Two recrystallizations from ethanol yielded yellow crystals, m.p. 161–161.5°.[22]

Concentration of the combined mother liquors gave 1.46 g. (12%) of a reddish orange solid, m.p. 279–280° dec.,[23] which was identified as 2-mercapto-3′-methyl-5′-nitro-3,2′-dipyridylamine (**8c**).[22]

3-Amino-2,2′-dipyridyl Sulfide (1e).—A mixture of 7.15 g. of iron powder (100 mesh), 5 ml. of water, 30 ml. of methanol, 5

TABLE I
PREPARATIONS OF THE 2,2′-DIPYRIDYL SULFIDES

Run	Starting materials: Mercaptopyridine Compd.	Mercaptopyridine g.	Mercaptopyridine Moles	Chloropyridine Compd.	Chloropyridine g.	Chloropyridine Moles	KOH, g.	Products[a] Compd.	g.	%	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
A	**3**	7.95	0.0631	**4a**[b]	10.0	0.0631	3.54	**1a**	11.33	72	176–177[c]	$C_{10}H_8N_4O_2S$	48.38	3.25	22.57	48.35	3.39	22.72
								8a[d]	0.047	0.3	258–261 dec.[e]	$C_{10}H_8N_4O_2S$	48.38	3.25	22.57	48.20	3.51	22.41
B	**3**	3.15	0.0250	**4b**[f]	3.96	0.0250	1.40	**1b**	4.34	70	167–168[g]	$C_{10}H_8N_4O_2S$	48.38	3.25	22.57	48.46	3.42	22.59
C	**3**	6.00	0.0476	**4c**[h]	8.23	0.0476	2.68	**1c**	9.50	76	159–160[i]	$C_{11}H_{10}N_4O_2S$	50.37	3.84	21.36	50.17	3.90	21.60
								8c	1.46	12	279–280 dec.[e]	$C_{11}H_{10}N_4O_2S$	50.37	3.84	21.36	50.07	3.87	21.12
D	**3**	6.00	0.0476	**4d**[j]	8.23	0.0476	2.68	**1d**	8.45	68	145–146	$C_{11}H_{10}N_4O_2S$	50.37	3.84	21.36	50.24	3.92	21.56
E	*k*	11.6	0.105	**4b**[f]	16.6	0.104	5.87[l]	**5**	18.1	75	138–139	$C_{10}H_7N_3O_2S$	51.49	3.03	18.02	51.31	2.82	18.13

[a] All products were recrystallized from ethanol. [b] M. A. Phillips, *J. Chem. Soc.*, 12 (1941). [c] Lit.[5c] m.p. 179–180°. [d] Isolated from the mother liquors by chromatography on alumina. [e] See ref. 23. [f] See ref. 18. [g] The monohydrochloride was prepared in absolute ethanol containing several drops of concentrated hydrochloric acid, recrystallized as pale yellow needles from aqueous ethanol, m.p. 211° (dec. with gas evolution). *Anal.* Calcd. for $C_{10}H_9ClN_4O_2S$: C, 42.18; H, 3.19; N, 19.68. Found: C, 42.00; H, 3.22; N, 19.90. [h] See ref. 15. [i] Analytical sample, m.p. 161–161.5°. [j] See ref. 17. [k] 2-Mercaptopyridine.[20] [l] Reaction run in ethanol and heated on a steam bath for 20 min.

(18) Light and Co., Ltd., Colnbrook, Bucks, England.

(19) Y. Ahmad and D. H. Hey, *J. Chem. Soc.*, 4516 (1954).

(20) J. R. Thirtle, *J. Am. Chem. Soc.*, **68**, 342 (1946).

(21) This compound is reported by T. Takahashi and Y. Yamoto [*J. Pharm. Soc. Japan*, **72**, 1491 (1952)] to decompose at 222°. It is our feeling that the Japanese workers may have had the disulfide.

(22) For analyses, see Table I, run C.

(23) The melting points of the mercapto dipyridylamines containing a nitro group were found to depend on the rate of heating of the melting point bath. Those reported were taken with a heating rate of 2–3°/min.

TABLE II

ACETYLATION OF THE 3-AMINO-2,2′-DIPYRIDYL SULFIDES

Starting material			Ac_2O,	Product					% carbon		% hydrogen		% nitrogen	
Compd.	g.	Moles	ml.	Compd.	g.	% yield[a]	M.p., °C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
1a	2.54	0.0102	50	2a	2.74	92	177–178	$C_{12}H_{10}N_4O_3S$	49.65	49.66	3.47	3.53	19.30	19.49
1b	2.00	0.0081	40	2b	1.79	76	171–172[b]	$C_{12}H_{10}N_4O_3S$	49.65	49.51	3.47	3.65	19.30	19.47
1c	1.00	0.0038	25	2c	1.08	93	151–152	$C_{13}H_{12}N_4O_3S$	51.30	51.03	3.97	3.90	18.41	18.53
1d	2.00	0.0076	40	2d	2.21	96	197–198	$C_{13}H_{12}N_4O_3S$	51.30	51.10	3.97	3.81	18.41	18.52

[a] Before recrystallization. [b] Lit.[5c] m.p. 171–172°.

TABLE III

REARRANGEMENT OF THE 2,2′-DIPYRIDYL SULFIDES IN BASIC MEDIA

Starting material			KOH,		CH_3I,	Reflux time,	Product(s)					
Compd.	mg.	mmoles	mg.	Solvent	ml.	min.	Compd.	mg.	%	M.p., °C.	Recrystn. solvent	Method[n]
1a	1000	4.00	248	C_2H_5OH	5	10	6a	504[a]	48	140–141	C_2H_5OH	C
1c	500	1.91	107	CH_3OH	1	45	8c	56[b]	11	262–268 dec.[c]		A
							6c	316	60	140–144[d]	C_2H_5OH	
1d	500	1.91	123	C_2H_5OH	2	10	6d	291[e]	55	145–146	C_2H_5OH	B
2b	1000	3.44	19.2	CH_3OH	3.3	*f*	6b	54.8	6	195–196[g]	C_2H_5OH	C
							7b	635	61	*h*	CH_3OH	
							8b	7[i]		195–220 dec.[c,j]	C_6H_6	
2c	712	2.34	131	CH_3OH	4	*f*	7c	454	61	148–149[k]	$C_2H_5OCOCH_3$	B
2d	2000	6.58	370	CH_3OH	5	*f*	6d[l]	184	10	145–147[m]	C_2H_5OH	A
							6d[l]	1140	54	121–126	$(C_2H_5)_2O$	

[a] An additional 329 mg. (31%) of less pure product, m.p. 130–136°, was obtained on concentration of the mother liquor. [b] 2-Methoxy-3-methyl-5-nitropyridine was also isolated, crude weight 115 mg., m.p. 65–66°. [c] See ref. 23. [d] *Anal.* Calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.15; H, 4.38; N, 20.28. Found: C, 52.23; H, 4.23; N, 20.22. [e] In addition, 101 mg. (20%) of starting material was recovered. [f] Not heated. [g] Analytical sample, m.p. 196–199°. *Anal.* Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.24; H, 3.86; N, 21.41. [h] Consists of two crops. See the detailed procedure for method C for the melting points. [i] In addition, 54 mg. (5%) of starting material was recovered. [j] One recrystallization from benzene gave raised m.p. 234–235° dec.[23] [k] *Anal.* Calcd. for $C_{14}H_{14}N_4O_3S$: C, 52.83; H, 4.40; N, 17.61. Found: C, 52.83; H, 4.57; N, 17.38. [l] Products separated by chromatography on alumina. [m] Analytical sample, m.p. 148–149°. *Anal.* Calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.15; H, 4.38; N, 20.28. Found: C, 52.38; H, 4.43; N, 20.35. [n] See Experimental section.

ml. of 3% hydrochloric acid, and 7.23 g. (0.031 mole) of 3-nitro-2,2′-dipyridyl sulfide (**5**) was heated on a steam bath for 5 min. with stirring. During this time, it was necessary to add an additional 20 ml. of methanol to dissolve the dipyridyl sulfide. The mixture was allowed to cool at room temperature for 10 min., decolorizing charcoal was added, and the mixture was filtered. The residue on the filter was washed with 20 ml. of methanol; the filtrate then was poured into 100 ml. of water and extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the solvent was evaporated. The remaining oil crystallized to a pale yellow solid when treated with water, yielding 3.33 g. (53%) of 3-amino-2,2′-dipyridyl sulfide, m.p. 105–108°. Several recrystallizations from aqueous methanol gave colorless needles with the same melting point.

Anal. Calcd. for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.29; H, 4.31; N, 20.82.

A picrate, prepared in absolute ethanol and recrystallized from the same solvent, had m.p. 159–160.5°.

Anal. Calcd. for $C_{16}H_{12}N_6O_7S$: C, 44.45; H, 2.80; N, 19.44. Found: C, 44.14; H, 2.63; N, 19.22.

3-Acetamido-2,2′-dipyridyl sulfides (2a–d) were prepared by suspending the 3-amino-2,2′-dipyridyl sulfides in acetic anhydride and allowing the mixture to stir at room temperature for 2 hr. during which time it became homogeneous. Ice was then added to precipitate the the product which was recrystallized for analysis from benzene. The results are shown in Table II.

Rearrangement of the 2,2′-Dipyridyl Sulfides 1a, c, and d and 2b, c, and d in Basic Media.—These reactions were carried out using one of the three procedures given below for the dipyridyl sulfides **1c**, **1d**, and **2b**. A summary of the conditions used and the results obtained are given in Table III.

Method A.—A solution of 500 mg. (1.91 mmoles) of the dipyridyl sulfide **1c** and 107 mg. of potassium hydroxide in methanol was refluxed for 45 min. on a water bath. The solution was allowed to cool and 1.0 ml. of iodomethane was added to the red solution. An additional hour of stirring at room temperature yielded a yellow solution which was taken to dryness. The residue was dissolved in chloroform and filtered, the solvent was removed from the filtrate, and the remaining solid was recrystallized from ethanol to give 56 mg. (11%) of impure 2-mercapto-3′-methyl-5′-nitro-3,2′-dipyridylamine (**8c**), m.p. 262–268° dec.[23] The filtrate from the recrystallization was taken to dryness and treated with petroleum ether (b.p. 30–60°), from which 115 mg. of crude 2-methoxy-3-methyl-5-nitropyridine, m.p. 65–66°, was obtained. The remaining residue was again recrystallized from ethanol to give 316 mg. (60%) of the methylated dipyridylamine **6c**, m.p. 140–144°.

Anal. Calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.15; H, 4.38; N, 20.28. Found: C, 52.23; H, 4.23; N, 20.22.

Method B.—The dipyridyl sulfide (**1d**) was rearranged by refluxing 500 mg. (1.91 mmoles) of the sulfide in a solution of 123 mg. of potassium hydroxide in 10 ml. of ethanol for 10 min. Addition of 2 ml. of methyl iodide produced a clear solution from which 291 mg. (55%) of the methylated product (**6d**) precipitated, m.p. 145–146°. A mixture melting point of the dipyridylamine **6d** with the same compound obtained by hydrolysis of the rearrangement product from the sulfide (**2d**) showed no depression. When concentrated further, the solution yielded 101 mg. (20%) of starting sulfide (**1d**).

Method C.—To a methanolic solution containing 19.2 mg. (3.43 mmoles) of potassium hydroxide was added 1.0 g. (3.44 mmoles) of the disulfide **2b**. After several minutes, the color of the solution turned from yellow to red. After 5 min., 3.3 ml. of methyl iodide was added, causing an orange solid to precipitate. The solution was cooled in an ice bath and the solid was collected by filtration. It was then dissolved in chloroform, the solution was filtered to remove inorganic salts, and the chloroform solution was evaporated. The residue was recrystallized from ethanol, yielding 54.8 mg. (6%) of 2-methylthio-3′-nitro-3,2′-dipyridylamine (**6b**) as orange needles, m.p. 195–196°. Several recrystallizations from absolute ethanol raised the melting point to 196–199°.

Anal. Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.24; H, 3.86; N, 21.41.

When the ethanol filtrate was concentrated, 393 mg. (38%) of the expected N-acetyldipyridylamine **7b** was obtained, m.p. 152–154°. An analytical sample was recrystallized from methanol, m.p. 153–154°.

TABLE IV

REARRANGEMENT OF 2,2′-DIPYRIDYL SULFIDES IN 5% HYDROCHLORIC ACID

Starting material			Amount of acid used,	Time of heating,	Product			
Compd.	mg.	mmoles	ml.	hr.	Compd.	mg.	% yield	M.p., °C., dec.[b]
1a	94.1	0.38	10	1	8a	89.5	95	262–263
2a	33.2	0.114	10	1	8a	22.9	81	255–260
1b	881.	3.55	15	1	8b	873.	99	235[c]
2b	60.9	0.209	5	0.25	8b	34.7	67[a]	237–238
1c	57.2	0.218	10	1	8c	52.5	92	274–277
2c	90.1	0.296	10	1	8c	73.9	95	280–282
1d	49.1	0.187	10	1	8d	40.3	82	255–257[d]
2d	76.3	0.250	10	1	8d	61.3	93	255–259

[a] A longer heating time would undoubtedly improve this yield. [b] See ref. 23. [c] Repeated recrystallization from benzene raised the melting point to 242–244° dec. *Anal.* Calcd. for $C_{10}H_8N_4O_2S$: C, 48.38; H, 3.25; N, 22.57. Found: C, 48.19; H, 3.22; N, 22.88. [d] Recrystallized from an acetone–water mixture, m.p. 257–257.5° dec. *Anal.* Calcd. for $C_{11}H_{10}N_2O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.56; H, 3.78; N, 21.42.

Anal. Calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.31; H, 3.97; N, 18.41. Found: C, 51.70; H, 3.65; N, 18.08.

The N-acetyldipyridylamine **7b** was converted to the dipyridylamine **6b** by heating it for 10 min. in dilute hydrochloric acid followed by treatment of this solution with potassium bicarbonate. The product was recrystallized once from ethanol, m.p. 196–199.5°.

When the original methanolic filtrate was worked up in a similar fashion, an additional 242 mg. (23%) of **7b** was obtained, m.p. 149–150°, along with 54 mg. of the starting material, m.p. 165–166°, and 7 mg. of crude 2-mercapto-3′-nitro-3,2′-dipyridylamine **8b**, m.p. 195–220° dec. A recrystallization of the latter from benzene raised the melting point to 234–235° dec.[23]

Rearrangement of 3-Acetamido-5′-nitro-2,2′-dipyridyl Sulfide (2a) in a Basic Medium.—One gram (3.4 mmoles) of the dipyridyl sulfide was dissolved with stirring in a solution of 193 mg. of potassium hydroxide in methanol. One milliliter of water was added to the blood red solution, causing a cloudiness. When 4 ml. of methyl iodide was added, the mixture became clear and a solid precipitated. Filtration yielded 581 mg. of product, m.p. 138–139°, and an additional 358 mg. was obtained by adding water to the filtrate, m.p. 129–130°. The infrared spectra of these two substances were identical. They were combined and recrystallized from a small volume of ether on a Soxhlet extractor to give 924 mg. (89%) of the expected product (**7a**) as yellow needles, m.p. 136–137°. Recrystallization from ethanol raised the melting point to 139–140°.

Anal. Calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.30; H, 3.98; N, 18.41. Found: C, 51.58; H, 4.12; N, 18.29.

When the mother liquor was taken to dryness, 9.5 mg. (1%) of 2-mercapto-5′-nitro-3,2′-diyridylamine (**8a**) was obtained, m.p. 258–259° dec.[23]

N-Acetyl-2-mercapto-3′-nitro-3,2′-dipyridylamine (11).—A solution of 72.0 mg. (1.27 mmoles) of potassium hydroxide in 10 ml. of absolute methanol was cooled to 0° and then added to 368 mg. (1.27 mmoles) of 3-acetamido-3′-nitro-2,2′-dipyridyl sulfide in a 125-ml. flask. An additional 5 ml. of methanol was used as a rinse and the mixture was then shaken for 20 min. at 0°, during which time the solid dissolved. After the addition of 50 ml. of water, the orange mixture was cooled in ice and carefully treated with dilute hydrochloric acid until the pH of the solution was approximately 2. Solid sodium bicarbonate was then added to adjust the pH to 7–8. Upon standing in an ice bath, the solution deposited a pale yellow solid which was collected by filtration, washed with cold water, and dried, yielding 262 mg. (71%) of the N-acetyldipyridylamine **11**. The product was best recrystallized from an acetone–ether mixture, m.p. 170–172° dec.[23]

Anal. Calcd. for $C_{12}H_{10}N_4O_3S$: C, 49.65; H, 3.47; N, 19.30. Found: C, 49.88; H, 3.69; N, 19.07.

The N-acetyldipyridylamine **11** underwent rapid solvolysis when heated for several minutes in ethanol, yielding 2-mercapto-3′-nitro-3,2′-dipyridylamine (**8b**). On the other hand, 83% of the thiomethyl derivative **7b** was recovered unchanged (m.p. 153–154.5°) when it was refluxed in absolute ethanol for 24 hr.

Rearrangement of the 3-Amino- and the 3-Acetamido-2,2′-dipyridyl Sulfides in 5% Hydrochloric Acid. General Procedure for 1a–d and 2a–d.—The compounds were heated in 5% aqueous hydrochloric acid on a steam bath, the mixtures were then cooled, and the products were obtained by filtration. It was qualitatively observed that under these conditions the acetylated compounds rearrange more slowly than do the parent amines. The results obtained are shown in Table IV.

Rearrangement of 3-Amino-2,2′-dipyridyl Sulfide (1e) in 5% Hydrochloric Acid.—A solution containing 392 mg. (1.93 mmoles) of 3-amino-2,2′-dipyridyl sulfide in 10 ml. of 5% hydrochloric acid was heated at reflux for 2.5 hr. The mixture was allowed to cool and the addition of ether caused a bright yellow precipitate. The ether was decanted and 344 mg. (74%) of a hydrochloride was collected by filtration of the aqueous layer, m.p. 235–240° (giving off a gas having a hydrogen sulfide odor). Prolonged cooling of the filtrate in ice yielded an additional 41.9 mg. of product, m.p. 230–237° dec. This material apparently decomposes when heated in ethanol, for its repeated recrystallization from this solvent gave continually lower melting points. This prevented the preparation of a satisfactory analytical sample.

When 41 mg. (0.17 mmole) of the hydrochloride was dissolved in water and a small amount of dilute potassium hydroxide (or aqueous sodium bicarbonate) was added, the mixture became cloudy and then cleared to give a colorless solution. Dilute hydrochloric acid was added to give a pH of approximately 6. On standing, 26 mg. (75%) of 2-mercapto-3,2′-dipyridylamine (**8e**) crystallized, m.p. 175–177°. Recrystallization from a water–methanol mixture did not raise the melting point.

Anal. Calcd. for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.00; H, 4.29; N, 20.62.

When the dipyridylamine was dissolved in ethanol containing a few drops of concentrated hydrochloric acid, it yielded a hydrochloride different (infrared spectrum) from the one described above. For analysis the product was recrystallized from methanol–ether, m.p. 227–228° dec.

Anal. Calcd. for $C_{10}H_{10}ClN_3S$: C, 50.10; H, 4.20; N, 17.53. Found: C, 50.32; H, 4.04; N, 17.32.

Rearrangement of 3-Amino-3′-nitro-2,2′-dipyridyl Sulfide (1b) and 3-Amino-5′-nitro-2,2′-dipyridyl Sulfide (1a) in Concentrated Hydrochloric Acid.—Dipyridyl sulfide **1b** (39 mg., 0.157 mole) was dissolved by shaking with 3 ml. of concentrated hydrochloric acid at room temperature. The solution was allowed to stand for 7 min. and poured onto crushed ice, whereby the red product precipitated. Filtration yielded 37.0 mg. (95%) of 2-mercapto-3′-nitro-3,2′-dipyridylamine (**8a**), m.p. 228–235° dec., the infrared spectrum of which showed that rearrangement was essentially complete. Recrystallization from an acetone–benzene mixture raised the melting point to 239–243° dec.[23]

By the same method, 40.6 mg. (0.163 mole) of the dipyridyl sulfide **1a** yielded 39.0 mg. (96%) of crude 2-mercapto-5′-nitro-3,2′-dipyridylamine (**8a**), m.p. 242–246° dec. The infrared spectrum again indicated that essentially complete rearrangement had occurred. Recrystallizations from acetone–water and acetone–benzene raised the melting point to 260–261.5° dec.[23]

Rearrangement of 3-Acetamido-3′-methyl-5′-nitro-2,2′-dipyridyl Sulfide (2c) in Ethanol.—A mixture of 19.8 mg. (0.0650 mmole) of the dipyridyl sulfide was dissolved in 10 ml. of absolute ethanol by gentle heating on a steam bath so that the solvent did not boil. Heating was continued for 4.5 hr., during which time the solution was reduced to about half volume and an orange precipitate had formed. The mixture was cooled in ice and filtered, yielding 9.7 mg. (57%) of the dipyridylamine **8c**, m.p. 266.5–273° dec., identified by comparison of its infrared spectrum with that of an authentic sample. A recrystallization from

ethanol raised the melting point to 271–274° dec.[23] Similar results were obtained with the dipyridyl sulfide **2b**. When this compound was heated at reflux in absolute ethanol for 8 hr., it was converted to the dipyridylamine **8b** in 79% yield. On the other hand, the nonacetylated derivative **1b** rearranged only to the extent of about 10% during a 21-hr. reflux period in the same solvent.

In another experiment, 23.9 mg. (0.0785 mmole) of the dipyridyl sulfide **2c** was heated at reflux for 68 hr. in 10 ml. of dry benzene. Under these conditions no rearrangement occurred, as evidenced by the lack of a color change during the heating period and the isolation of 17.6 mg. (74%) of starting material, m.p. 145–147°. A second crop yielded an additional 5.1 mg. (21%) of less pure starting material, m.p. 131–141°.

Attempted Rearrangement of 3-Acetamido-3′-nitro-2,2′-dipyridyl Sulfide (2b) in Dimethyl Sulfoxide.—A solution of 76.7 mg. of the dipyridyl sulfide **2b** in 1.0 ml. of distilled dimethyl sulfoxide was heated for 11 hr. in an oil bath at 80°. Water was added and the mixture extracted with chloroform. The organic solvent was removed in a dry air stream and the residual solid was recrystallized from benzene–petroleum ether, yielding 61.0 mg. (80%) of unchanged (infrared spectrum) 3-acetamido-3′-nitro-2,2′-dipyridyl sulfide as pale yellow crystals, m.p. 162–165° dec. One recrystallization raised the melting point to 169–170° dec. A mixture melting point with an authentic sample showed no depression.

Rearrangement of 3-Acetamido-3′-nitro-2,2′-dipyridyl Sulfide (2b) in Water.—A mixture of 15.0 mg. (0.0517 mmole) of the dipyridyl sulfide and 5 ml. of distilled water was heated at reflux for 45 hr. During this time, the starting material dissolved, followed by the appearance of a red solid which deposited on the sides of the reaction vessel. This solid was collected by filtration, yielding 10.1 mg. (79%) of crude 2-mercapto-3′-nitro-3,2′-dipyridylamine (**8b**), m.p. 228–232° dec., the structure of which was confirmed by comparison of its infrared spectrum with that of an authentic sample. A recrystallization from acetone–water raised the melting point to 235–236° dec.[23]

Rearrangement of 3-Amino-3′-nitro-2,2′-dipyridyl Sulfide (1b) in Water.—A mixture of 57.0 mg. of the sulfide **1b** and 10 ml. of water was heated on a steam bath. After a short time the water became slightly yellow, but for the most part the sulfide appeared to remain insoluble. The color of the water slowly changed to a red, and after 0.5 hr. of heating, dark red needles of 2-mercapto-3′-nitro-3,2′-dipyridylamine (**8b**) began to appear. Additional water was added from time to time to replace that lost by evaporation. After 8.5 hr., no more undissolved starting sulfide **1b** could be detected among the red crystals of product. After cooling, 50.2 mg. (88%) of the dipyridylamine **8b** was collected by filtration as dark red needles, m.p. 236–238° dec. One recrystallization from acetone raised the melting point to 238–241° dec.[23]

Rearrangement of 3-Amino-5′-nitro-2,2′-dipyridyl Sulfide (1a), 3-Amino-3′-nitro-2,2′-dipyridyl Sulfide (1b), and 3-Amino-3′-methyl-5′-nitro-2,2′-dipyridyl Sulfide (1c) in the Solid State.—The dipyridyl sulfides **1a–c** were heated in an oven at 110° for 9 days, after which time their infrared spectra indicated that complete rearrangement to the corresponding dipyridylamines (**8a–c**) had taken place. Recrystallization in each case yielded pure rearranged product.

Hydrolysis of N-Acetyl-2-methylthio-5′-nitro-3,2′-dipyridylamine (7a).—A mixture of 309 mg. (1.02 mmoles) of the dipyridyl amine, 5 ml. of ethanol, and 5 ml. of 5 *N* aqueous sodium hydroxide was heated at the boiling point for 10 min. The dark mixture was diluted with a large amount of water, whereby it turned orange. The solid which formed was collected by filtration, washed with water, and recrystallized from ethanol, yielding 203 mg. (76%) of 2-methylthio-5′-nitro-3,2′-dipyridylamine (**6a**) as yellow crystals, m.p. 142–143°.

Anal. Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.13; H, 3.87; N, 21.59.

Hydrolysis of N-Acetyl-2-methylthio-3′-methyl-5′-nitro-3,2′-dipyridylamine (7c).—By the same procedure described above, 198 mg. (0.62 mmole) of the N-acetyldipyridylamine (**7c**) yielded 131 mg. (77%) of product **6c**, m.p. 143–144°.

Hydrolysis of N-Acetyl-2-methylthio-3′-nitro-5′-methyl-3,2-dipyridylamine (7d).—By the procedure reported above, 214 mg. (0.67 mmole) of the N-acetyl derivative **7d** yielded 145 mg. (78%) of the deacetylated product **6d** as orange crystals, m.p. 149–150°.

Methylation of 2-Mercapto-3′-methyl-5′-nitro-3,2′-dipyridylamine (8c) and 2-Mercapto-5′-nitro-3,2′-dipyridylamine (8a).—Methyl iodide (1 ml.) was added to a hot solution of 169 mg. (0.64 mmole) of the dipyridylamine **8c** and 34 mg. of potassium hydroxide in methanol. The mixture was cooled and the yellow solid was collected by filtration, giving 124 mg. (70%) of the methylated derivative **6c** as yellow needles, m.p. 145–146°. Recrystallization from ethanol did not change the melting point.

By a similar procedure, the dipyridylamine **8a** gave the thiomethyl derivative **6a**, m.p. 139–140°, which showed no melting point depression on admixture with the thiomethyl product obtained by rearrangement of the dipyridyl sulfide **1a**.

The Synthesis of Polymers and Copolymers of β-(3-Pyridyl)-DL-alanine[1a,b]

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A reliable procedure for preparing β-(3-pyridyl)-DL-alanine in about 55% over-all yield, starting from 3-pyridylaldehyde, was developed. Methods for the preparation of synthetic polypeptides containing β-(3-pyridyl)-DL-alanine residues are described. These methods include the preparation of the carbobenzoxy derivative and the N-carboxy anhydride of pyridylalanine.

This paper describes the synthesis and polymerization of β-(3-pyridyl)alanine.[2] Polymers based on this amino acid are of interest because of their structural similarity to polypeptides of aromatic amino acids (phenylalanine, tyrosine, etc.) and because of the chemical similarity of pyridylalanine and histidine. The imidazole group of the latter amino acid is important for the catalytic activity of a number of enzymes.[6–9] In addition, both pyridyl and imidazole groups show interesting catalytic behavior.[10] Polypeptides described in this paper will subsequently be investigated as catalysts for ester hydrolysis and other reactions. Interesting catalytic behavior has already been reported for L-histidine containing polypeptides,[11–12] for poly(vinyl-

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