Pyridine Chemistry. II. Further Studies on the Smiles Rearrangement of the 3-Amino-2,2′-dipyridyl Sulfide System. The Synthesis of Some 1,6-Diazaphenothiazines[1]

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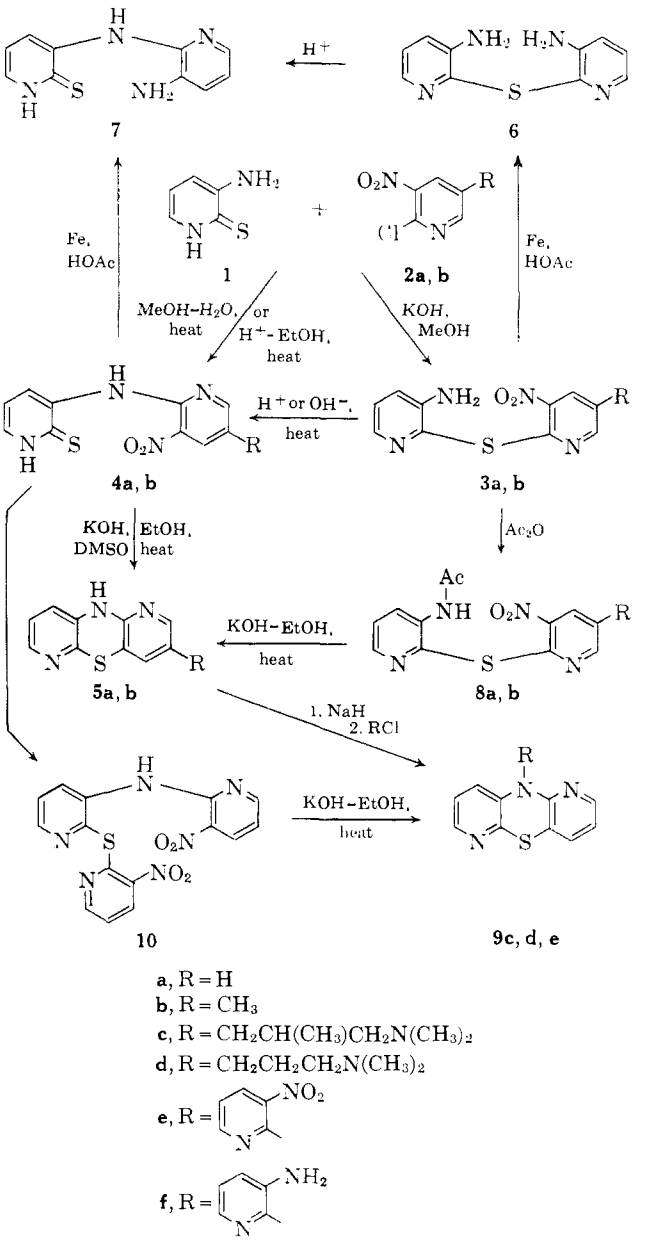
Additional studies on factors affecting the Smiles rearrangement of 3-amino-2,2′-dipyridyl sulfides are reported, along with a superior preparation of the thiolactams **4a** and **b**. The conversion of these thiolactams to 1,6-diazaphenothiazines of potential biological interest is discussed, including an unusual synthetic approach to the 10-aryl derivatives. The reactions of several of the thiazines in standard antiinflammatory and central nervous system tests are given.

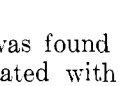
In a previous publication[2] we reported on the Smiles-type rearrangements which 3-amino-2,2′-dipyridyl sulfides (*e.g.*, **3a** and **b**) undergo in acidic, basic, and neutral media, investigations which yielded compounds of structure **4**. The continuing interest in the relationships between the chemical structure of phenothiazines and their actions upon specific physiological and psychophysiological functions[3] induced us to study the conversion of these substances to the corresponding 1,6-diazaphenothiazines (**5**).[4]

The heretofore preferred preparation for the thio amide[5] derivatives **4** involves the base-catalyzed condensations of 3-amino-1H-pyridinethione (**1**)[5] with the corresponding chloropyridine **2**, followed by the acid-catalyzed rearrangements of the ensuing dipyridyl sulfides (Chart I).[2] It has now been found that amines of type **4** can be prepared in good yield directly from the corresponding pyridinethiones and pyridyl chlorides by heating these reactants in alcohol with, or without, a small amount of added hydrochloric acid. Compounds **4a** and **b** were prepared by this method.

In the course of this work, it was of intrinsic interest to examine the rearrangement aptitude of the diamino-dipyridyl sulfide **6**, since the conversion of the nitro group to an amine function should disfavor the nucleophilic rearrangement.[6] The sulfide **6** was readily prepared by the iron–acetic acid reduction of the nitro group in **3a** and was found to rearrange to the thio amide **7** when treated with 10% hydrochloric acid, although at a considerably slower rate than did the corresponding nitro compound. The structure of the

CHART I



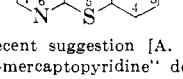
a, R = H
b, R = CH_3
c, R = $CH_2CH(CH_3)CH_2N(CH_3)_2$
d, R = $CH_2CH_2CH_2N(CH_3)_2$
e, R =
f, R = 

(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, and the Ph.D. Dissertation of R. K. Schlatzer, University of Virginia, 1966.

(2) Paper I: O. R. Rodig, R. E. Collier, and R. K. Schlatzer, *J. Org. Chem.*, **29**, 2652 (1964).

(3) For example, see M. Gordon, P. N. Craig, and C. L. Zirkle, Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p. 140, for a recent review.

(4) The numbering used is that recommended by L. T. Capell and D. F. Walker, Jr., "The Ring Index," American Chemical Society, Washington, D. C., 1st Supplement, 1963, namely



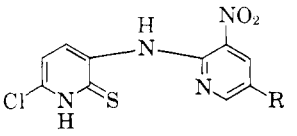
(5) In response to a recent suggestion [A. R. Katritzky, *Chem. Ind.* (London), 331 (1965)] "2-mercaptopyridine" derivatives reported in this communication are depicted and named to conform to the prevalent tautomeric form. In the present case, this is the thiolactam structure in each instance, as evidenced by the presence of a thiocarbonyl stretching band near 1140 cm.$^{-1}$ [E. Spinner, *J. Chem. Soc.*, 1237 (1960)], as well as the absence of –SH absorption in the infrared spectra of these compounds.

(6) At sufficiently high acid concentrations, the protonation of one of the primary amino groups might occur, which would negate its deactivating influence. Yet, from the known pK_a values for 3-aminopyridines [A. Albert, *ibid.*, 1020 (1960)], this should not happen to any extent until both ring nitrogen atoms have been protonated.

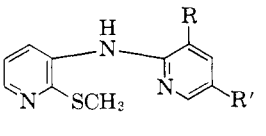
thiolactam **7** was confirmed by its preparation from the pyridinethione **4a** by the reduction of the nitro group with iron in acetic acid.

The diazaphenothiazines **5a** and **b** could be obtained from the N-acetyl-2,2′-dipyridyl sulfides **8a** and **b**[2] when these compounds were heated in ethanolic potassium hydroxide. Under these conditions, however, the sulfide **8a** yielded about 25% of the uncyclized product **4a** as well.

When the thiolactam **4a** was treated in like manner, no ring closure occurred, even when the reaction mixture was heated at reflux for an extended period of time.



12, R = H, NO_2



13a, R = NO_2; R′ = H
b, R = NO_2; R′ = CH_3
c, R = H; R′ = NO_2
d, R = CH_3; R′ = NO_2

A similar observation was reported by Maki[7] who tried to convert the chloro derivatives **12**[8] to the corresponding diazaphenothiazines by the same method. He attributed the failure of the cyclization to the presence of strong hydrogen bonding between the amino hydrogen atom and the *o*-nitro group in each case.[9] This argument is embraced by abundant evidence which supports the fact that nitro groups can hydrogen bond[10] and apparently do so quite strongly if a resonating system prevails, as is the case in the nitroamines **4a** and **b**.[11] Yet, it seemed to us remarkable that this bonding is indeed of such a magnitude as to preclude the formation of diazaphenothiazines under the conditions investigated.

In an effort to shed additional light on this question, the N–H stretching frequencies of the thiomethyl derivatives **13a–d**[2] were studied. The results observed in both the solid and the liquid phases are shown in Table I. The CCl_4 solution spectra distinctly show that the amino group is intramolecularly hydrogen bonded in compounds **13a** and **b**, while it is not so in dipyridylamines **13c** and **d**. These effects are also noted in the solid state spectra for compounds **13a**, **b**, and **d**, but **13c** gave a typical hydrogen-bonded spectrum, the bonding presumably occurring *via* an *inter*molecular process.

TABLE I

N–H STRETCHING FREQUENCIES[a] IN THE INFRARED SPECTRA OF SOME 3- AND 5-NITRO-2,3′-DIPYRIDYLAMINES

	Medium		
Compd.	KBr	CCl_4	CCl_4 + DMSO
13a	3306 (s)	3289 (b), 3340 (sh)	
13b	3295 (s)	3285 (b), 3350 (sh)	
13c	3155 (b), 3185 (sh)	3378 (s)	3180, 3231
13d	3380 (s)	3394 (s)	3200 (sh), 3240

[a] s = sharp, b = broad, sh = shoulder; values are in reciprocal centimeters.

In view of these findings, a reagent was sought which might compete successfully with the nitro group for the amino hydrogen atom when added to the reaction medium, thus sufficiently freeing the nitro group to assure success of the cyclization process. Dimethyl sulfoxide was studied as one such possibility,[12] and when a small amount of this reagent was added to the solution samples of **13c** and **d** used for infrared studies, a pronounced shift to lower frequency of the N–H stretching mode was observed (see Table I). Clearly, dimethyl sulfoxide hydrogen bonds with the amino groups, and possibly more strongly (absorption at lower frequency[13]) than does the nitro group. Indeed, when the reaction was carried out in the presence of this reagent, the diazaphenothiazines **5a** and **b** were obtained in good yield. The dimethyl sulfoxide may also serve to increase the nucleophilic character of the sulfide ion, since anions are at most only weakly solvated by this reagent.[14]

The dimethylaminopropyl and -butyl side chains were added by treating the diazaphenothiazine **5a** with the corresponding dimethylaminoalkyl chloride in the presence of sodium hydride. Under these conditions, alkylation occurs mainly at position 10, rather than at positions 1 or 6,[15] and infrared and ultraviolet absorption data supported this premise. The dimethylaminobutyl derivative **9c** was obtained as a well-defined solid, m.p. 99–101°, after purification as the dihydrochloride. On the other hand, the dimethylaminopropyl derivative **9d** was obtained as an oil which could not be crystallized. It yielded both a solid dihydrochloride and a solid picrate, however.

It was intriguing to attempt the synthesis of aryl side-chain derivatives of **9** (R = aryl) from the thio amide **4a** by a process involving a Smiles rearrangement. The method is exemplified by the following sequence and may at times prove to be the method of choice for preparing such thiazines. The thio amide **4a** was treated with 2-chloro-3-nitropyridine under basic conditions, whereby the condensation product **10** was obtained. More vigorous treatment of this product with base effected the rearrangement and ring closure, giving the diazaphenothiazine **9e** in good yield. The amine **9f** was readily prepared by the reduction of the

(7) Y. Maki, *J. Pharm. Soc. Japan*, **77**, 485 (1957).

(8) By analogy with our compounds, pyridinethione structures are assumed for these substances, rather than the mercaptodipyridylamine structures reported by Maki.[7]

(9) The possibility of such an effect has also been entertained by O. L. Brady and C. Waller [*J. Chem. Soc.*, 1218 (1930)] to explain the previously observed inability of certain *o*-(2-nitroanilino)phenols to cyclize in basic media to yield phenoxazines. However, in order to satisfy all of the known facts, they found it necessary to abandon this argument in favor of a purely steric one. In the case of phenoxazines, it now appears that *both* hydrogen bonding and steric effects play an important role in the cyclization process [*cf.* K. C. Roberts and H. B. Clark, *ibid.*, 1312 (1935)].

(10) For example, see W. F. Baitinger, P. von R. Schleyer, T. S. S. R Murty, and L. Robinson, *Tetrahedron*, **20**, 1635 (1964), and references cited therein.

(11) These compounds can be compared to the *o*-nitroanilines, the intramolecular hydrogen bonding of which has been extensively studied. See footnote 21 in ref. 10.

(12) The strong hydrogen-bonding properties of dimethyl sulfoxide are well known. For example, see D. Barnard, J. Fabian, and H. Koch, *J. Chem. Soc.*, 2442 (1949); O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964); A. Allerhand and P. von R. Schleyer, *ibid.*, **85**, 1715 (1963). For such bonding concerned specifically with amines, see W. K. Thompson, *J. Chem. Soc.*, 617 (1962).

(13) A number of investigators have recently questioned the general validity of the so-called Badger–Bauer rule, which supposes a correlation between the enthalpy of a hydrogen bond and the magnitude of the observed spectral shift. Although this rule apparently holds for a number of cases, it breaks down for others; see A. Allerhand and P. von R. Schleyer[12] for leading references.

(14) (a) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962); J. Miller, *J. Am. Chem. Soc.*, **85**, 1628 (1963); J. Miller and A. J. Parker, *ibid.*, **83**, 117 (1961). (b) In mixed systems containing dimethyl sulfoxide and a protic solvent, the mechanism of DMSO-induced nucleophilic catalysis apparently depends on the relative concentrations of the solvent components: C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).

(15) E. Kopp and M. Strell, *Arch. Pharm.*, **295**, 36, 99 (1962).

nitro group in **9e** using iron in dilute hydrochloric acid.

Pharmacology.—The diazaphenothiazines **9c** and **d** were tested for antiinflammatory activity[16] in the ultraviolet-induced erythema test with male guinea pigs. One-half of the total dosage was administered orally 1 hr. prior to exposure, and the remainder at irradiation. Both compounds were found to be inactive at a dose level of 80 mg./kg.

When diazaphenothiazine **9c** was administered orally to male rats at a dosage of 300 mg./kg., it produced central nervous system depression characterized by hypotonia, reduced spontaneous motor activity, and disorientation in one of three animals. In this animal it caused a stance, characterized by limb spreading, which is typical of phenothiazine drugs producing severe central nervous system depression. The thiazine **9d** at the same dosage produced salivation and a slight reduction in spontaneous motor activity, followed by death, in one of three animals.

Experimental Section[17]

3-[(3-Nitro-2-pyridyl)amino]-2(1H)-pyridinethione (4a).—A mixture of 620 mg. (4.92 mmoles) of 3-amino-2(1H)-pyridinethione (1),[2,5,18] 780 mg. (4.92 mmoles) of 2-chloro-3-nitropyridine (**2a**),[19] 10 ml. of methanol, and 30 ml. of water was heated on a steam bath. The solution turned dark, and after 20 min. a thick mass of dark red crystals had separated. The mixture was cooled, the solid was removed by filtration, washed with hot water (the washings were added to the original filtrate), and dried, yielding 1.03 g. (85%) of **4a**, m.p. 231–238° dec. One recrystallization from acetone raised the melting point to 240–242.5° dec.[20] (lit.[2] m.p. 242–244° dec.). This compound showed an infrared band at 1134 cm.$^{-1}$ attributed to the C=S stretching mode.

When $NaHCO_3$ was added to the mother liquor until pH 7, 0.171 g. (14%) of crude 3-amino-3′-nitro-2,2′-dipyridyl sulfide (**3a**) precipitated as an orange solid, m.p. 162.5–165° (lit.[2] m.p. 167–168°).

3-[(5-Methyl-3-nitro-2-pyridyl)amino]-2(1H)-pyridinethione (4b).—A mixture of 282 mg. (2.23 mmoles) of 1,[2,5] 383 mg. (2.22 mmoles) of 2-chloro-3-nitro-5-methylpyridine (**2b**),[21] 19 ml. of absolute ethanol, 10 ml. of water, and 1.0 ml. of concentrated HCl was heated to gentle boiling in an open flask on a steam bath, allowing some of the solvent to boil off. After 35 min., the solution had turned dark and a bright red solid had precipitated. The mixture was cooled in ice and the solid was removed by filtration, washed with water (wash added to the filtrate), and dried, yielding 505 mg. (87%) of **4b**, m.p. 246–255° dec. A recrystallization from acetone raised the melting point to 253–255° dec.[20] (lit.[2] m.p. 257–257.5° dec.); infrared band at 1136 cm.$^{-1}$ assigned to the C=S stretching mode.

On standing for 5 days, the filtrate yielded an additional 49 mg. (8%) of somewhat less pure **4b**, m.p. 230–234° dec.

3,3′-Diamino-2,2′-dipyridyl Sulfide (6).—A mixture of 529 mg. (2.13 mmoles) of 3-amino-3′-nitro-2,2′-dipyridyl sulfide (**3a**),[2] 1048 mg. of powdered iron (100 mesh), and 5.0 ml. of glacial acetic acid was gently warmed on a steam bath for 5 min. Water (5 ml.) was added and heating was continued for an additional 10 min. The hot mixture was filtered and the residue remaining on the filter was washed with hot water (washings added to the filtrate). The acidity of the filtrates was adjusted to approximately pH 5 by the addition of solid KOH (3 pellets), producing a colorless crystalline precipitate. The solid was separated by filtration, yielding 314 mg. (68%) of **6**, m.p. 205–211° with previous decomposition. One recrystallization from aqueous methanol gave fine colorless crystals, m.p. 213–214° with previous decomposition.

Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.03; H, 4.62; N, 25.67. Found: C, 55.21; H, 4.54; N, 25.83.

When the mother liquor was further treated with solid KOH (3 pellets) and cooled in ice, an additional 59 mg. (13%) of **6** was obtained, m.p. 205–209° with previous decomposition.

A dihydrochloride was prepared by adding several drops of concentrated HCl to **6** dissolved in hot absolute ethanol. On cooling to room temperature the product was obtained as a pale yellow solid which melted at approximately 185° but then resolidified to an orange-yellow solid which slowly decomposed at 220–235°. Recrystallization of the product from aqueous ethanol did not change its melting point.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_4S$: C, 41.25; H, 4.15. Found: C, 40.93; H, 4.24.

3-[(3-Amino-2-pyridyl)amino]-2(1H)-pyridinethione (7). A. From the Reduction of the Thiolactam 4a.—A mixture of 214 mg. (0.862 mmole) of **4a**, 368 mg. of powdered iron (100 mesh), 5.0 ml. of glacial acetic acid, and 5.0 ml. of water was heated on a steam bath for 5 min. The hot mixture was filtered and the residue on the filter was washed with hot water (washings added to the filtrate). Water (10 ml.) was added to the filtrate and the acidity was then adjusted to approximately pH 4 by the addition of solid KOH (8 pellets), whereby the product precipitated. The solid was collected by filtration, washed with water, and recrystallized from aqueous methanol (charcoal), yielding 45 mg. (24%) of **7** as pale yellow needles, m.p. 200–205° dec. When the acidity of the mother liquor was adjusted to approximately pH 6 with additional solid KOH, a precipitate was obtained which was treated in the same manner as that described above, yielding another 19 mg. (10%) of **7**, m.p. 203–206° dec. The combined crops were recrystallized twice from aqueous methanol, which raised the melting point to 204–208° dec. This compound showed an infrared band at 1134 cm.$^{-1}$ which is assigned to the C=S stretching mode.

Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.03; H, 4.62; N, 25.67. Found: C, 55.04; H, 4.56; N, 25.57.

Additional product was obtained when the mother liquor was made basic to approximately pH 8 by adding KOH and then $NaHCO_3$. The mixture was extracted with ether, the ether layers were combined and dried, and the solvent was removed. The pale yellow solid which remained was recrystallized from aqueous methanol to give a further 19 mg. (10%) of **7**, m.p. 198–205° dec.

B. From the Smiles Rearrangement of 3,3′-Diamino-2,2′-dipyridyl Sulfide (6).—A solution of 72.9 mg. (0.334 mmole) of **6** in 3.0 ml. of 10% HCl was heated at reflux for 1.25 hr. Acetone (20 ml.) was then added whereby a pale yellow solid precipitated. This was separated by filtration, washed with acetone, and dried, yielding 60.0 mg. of **6** dihydrochloride, which partially melted and resolidified to an orange-yellow solid at 190° followed by decomposition at 213–229°. When an aqueous solution of the dihydrochloride was neutralized with $NaHCO_3$, the free amine **6** was recovered.

The filtrate was concentrated on a steam bath to remove most of the acetone. A small amount of water was added, followed by the addition of $NaHCO_3$ until CO_2 evolution ceased. The pale yellow solid which had separated was collected by filtration, washed with water, and dried, yielding 22.6 mg. of crude thiolactam **7**, m.p. 192–196° dec. Recrystallization of this material

(16) For reported antiinflammatory characteristics of phenothiazine derivatives, see V. S. Mitrofanov, Z. A. Popenkova, N. S. Tolmacheva, and A. M. Chernukh, *Uch. Zap., Inst. Farmakol. i Khimioterap. Akad. Med. Nauk*, **1**, 167 (1958); *Biol. Abstr.*, **45**, 64654 (1964); J. C. Stucki and C. R. Thompson, *Am. J. Physiol.*, **193**, 275 (1958); L. Kato and B. Gozsy, *J. Pharmacol. Exptl. Therap.*, **129**, 231 (1960); G. Vogel, *Arzneimittel-Forsch.* **11**, 978 (1961).

(17) All melting points were taken in a heated oil bath and are corrected. Although not usually specified, infrared spectra were taken of all compounds, using a Perkin-Elmer Model 21, 137, or 337 instrument. The spectra were taken in a KBr matrix unless indicated otherwise and were used in conjunction with melting points to determine the structures of all products. In addition, the spectra reported in Table I and for compounds **5a**, **b**, and **9c–f** were determined on a Perkin-Elmer Model 521 instrument calibrated against a polystyrene standard (w = weak, m = medium, s = strong). The ultraviolet absorption spectra were determined in 95% ethanol with a Cary Model 11 spectrophotometer. Microanalyses were performed by Mrs. W. E. Coyne and Mrs. J. D. Reed of this laboratory, and by Galbraith Laboratories, Inc., Knoxville, Tenn.

(18) The solid state infrared spectrum of this compound showed a band at 1131 cm.$^{-1}$ attributed to the C=S stretching mode.

(19) Light and Co., Ltd., Colnbrook, Buckinghamshire, England.

(20) The melting point of this compound was found to be dependent on the rate of heating of the melting point bath. That reported was taken with a heating rate of 2–3°/min.

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

from aqueous methanol gave 13.1 mg. (47%)[22] of the desired product as yellow-tan needles, m.p. 203–205° dec. A second crop yielded an additional 3.1 mg. (11%)[22] of **7**, m.p. 193–204° dec. No attempt was made to obtain optimum yields in this case, but in view of the large amount of starting material recovered, it appears that a longer reaction time should prove beneficial to the yield of rearranged product.

10H-Dipyrido[2,3-*b*:2′,3′-*e*][1,4]thiazine (5a). A. From 3-Acetamido-3′-nitro-2,2′-dipyridyl Sulfide (8a).—A solution of 337 mg. (1.16 mmoles) of **8a** and 160 mg. of KOH in 15 ml. of ethanol was heated at reflux for 40 min. When the mixture was cooled in ice, dark crystals separated. These were collected by filtration and recrystallized from an ethanol–ether solvent pair, giving 82.9 mg. (25%) of the potassium salt of 3-[(3nitro-2-pyridyl)amino]-2(1H)-pyridinethione having an ill-defined melting point with decomposition occurring at 244°. When this material was treated with water, it gave back the thio amide **4a**.

Water was added to the mother liquor and the mixture was concentrated on a steam bath. Successive cooling in ice caused several crops of product to separate which were combined and recrystallized from aqueous ethanol, yielding 101 mg. (43%) of **5a**, m.p. 223–225°. An analytical sample was recrystallized from ethanol; m.p. 225°; λ_{max}^{EtOH} 239 mμ (log ε 4.42), 337.5 mμ (log ε 3.99); $(1/\lambda)_{max}^{KBr}$ (principal peaks, cm.$^{-1}$) 3196 (w), 3144 (w), 3082 (w), 3053 (w), 1599 (m), 1589 (m), 1555 (m), 1517 (m), 1433 (s), 1123 (m), 780 (m), 751 (m).

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88. Found: C, 59.80; H, 3.85; N, 20.39.

B. From 3-[(3-Nitro-2-pyridyl)amino]-2(1H)-pyridinethione (4a).—To 50 ml. of dimethyl sulfoxide was added 1.84 g. of KOH and enough absolute ethanol (approximately 50 ml.) to dissolve the base when the mixture was heated on a steam bath. This hot basic solution was then added to a stirred mixture of 7.83 g. (0.0315 mole) of **4a** in 20 ml. of dimethyl sulfoxide. The maroon mixture was heated at reflux for 7 hr. and the ethanol was then removed by distillation over a 0.5-hr. peroid. The greenish tan residue was allowed to cool and was poured into 150 ml. of water, whereby 5.81 g. (92%) of the thiazine **5a** separated, m.p. 222.5–224.5°.

A similar run, differing in that the reflux step was eliminated and the ethanol was distilled over a 20-min. period, gave an 87% yield of the thiazine, m.p. 220–224°.

An attempt to prepare **5a** by heating **4a** in ethanolic KOH solution for 4 hr. produced only the potassium salt of 2-mercapto-3′-nitro-3,2′-dipyridylamine as black crystals, m.p. 251–254° dec. This salt appeared to decompose partly in protic solvents and attempts to purify it for analysis (*e.g.*, by recrystallization from absolute ethanol) were unsuccessful.

3-Methyl-10H-dipyrido[2,3-*b*:2′,3′-*e*][1,4]thiazine (5b). A. From 3-Acetamido-3′-nitro-5′-methyl-2,2′-dipyridyl Sulfide (8b). A solution of 1.00 g. (0.00329 mole) of **8b** and 0.25 g. of KOH in ethanol was heated at reflux for 30 min. The solution was then taken to dryness under reduced pressure and the residue was treated with hot ethanol. The inorganic salts were removed by filtration and, on cooling, the filtrate yielded 0.51 g. (72%) of the thiazine **5b** as a tan crystalline solid, m.p. 205–208°. Recrystallization from ethanol raised the melting point to 217–218; λ_{max}^{EtOH} 239 mμ (log ε 4.41), 341 mμ (log ε 3.99); $(1/\lambda)_{max}^{KBr}$ (principal peaks, cm.$^{-1}$) 3224 (w), 3152 (w), 2979 (w), 1600 (m), 1434 (s), 790 (m), 692 (m).

Anal. Calcd. for $C_{11}H_9N_3S$: C, 61.37; H, 4.21; N, 19.52. Found: C, 61.04; H, 3.97; N, 19.29.

B. From the Pyridinethione 4b.—In a flask equipped with a distilling head were placed 437 mg. (1.67 mmoles) of **4b**, 5 ml. of dimethyl sulfoxide, and a solution of 90 mg. of KOH in 15 ml. of absolute ethanol. The deep purple mixture was heated at such a rate that the ethanol distilled over a 20-min. period. The brown solution was cooled and 20 ml. of water was added, causing a solid to precipitate. After cooling in an ice bath, the solid was collected by filtration, washed with water (washings added to filtrate), and recrystallized from aqueous ethanol (charcoal), yielding 260 mg. (72%) of the thiazine **5b** as a tan solid, m.p. 216–219°. On standing, the filtrate deposited an additional 25 mg. (7%) of less pure product, m.p. 207–216°.

10-(2-Methyl-3-dimethylamino-1-*n*-propyl)dipyrido[*2*,3-*b*:2′,3′-*e*][1,4]thiazine (9c).—A solution of 7.57 g. (0.0377 mole) of 10H-dipyrido[2,3-*b*:2′,3′-*e*][1,4]thiazine (**5a**) in 200 ml. of dry benzene was placed in a three-necked flask fitted with a stirrer, dropping funnel, dry-nitrogen inlet, and a reflux condenser. Two grams of 52.7% NaH in mineral oil[23] was added, the system was flushed with dry nitrogen, and the stirred mixture was heated at reflux for 3 hr. Heating was then discontinued and a benzene solution of 3-chloro-2-methyl-1-dimethylaminopropane was added to the reaction mixture. The chloramine solution was prepared by neutralizing 6.50 g. (0.0378 mole) of 3-chloro-2-methyl-1-dimethylaminopropane hydrochloride[24] with aqueous KOH solution extracting the free amine with three 50-ml. portions of benzene and drying the combined benzene extracts (Na_2SO_4).

The mixture was heated at reflux for an additional 16 hr., after which time a second portion of the chloramine in benzene was added without discontinuing the heating. This second portion was prepared as described above from 3.00 g. (0.0174 mole) of the hydrochloride, the free amine being extracted with 35 ml. of benzene. After heating at reflux for an additional 8 hr., the reaction mixture was cooled to room temperature, washed with water, and extracted with 10% HCl. The combined acid extracts were washed with benzene, filtered and made basic by adding (with cooling) solid KOH, and the acidity was then adjusted to approximately pH 4 with dilute HCl. The solid which precipitated was collected by filtration, yielding 2.89 g. (38%) of unreacted thiazine, m.p. 222–225°. The filtrate was made basic by adding additional KOH, followed by extraction with ether. Removal of the ether from the combined and dried (Na_2SO_4) extracts left an oily solid which was triturated with 50 ml. of absolute ethanol. The remaining solid was separated by filtration, and washed on the filter with 35 ml. of absolute ethanol, yielding an additional 0.28 g. (4%) of unreacted thiazine, m.p. 221–224°.

The filtrate was treated with charcoal, followed by the addition of 40 ml. of absolute ethanol, 10 ml. of concentrated HCl, 200 ml. of ether, and 100 ml. of acetone. The precipitated oil slowly solidified, was collected by filtration, and washed with acetone, yielding 5.03 g. (62%)[22] of **9c** dihydrochloride, m.p. 208–214°. The hygroscopic product was recrystallized for analysis from an absolute ethanol–ether mixture, giving yellow crystals, softening at 200°, m.p. 210–215°.

Anal. Calcd. for $C_{16}H_{22}Cl_2N_4S$: C, 51.47; H, 5.94; N, 15.01. Found: C, 51.83; H, 5.79; N, 15.99.

An aqueous solution containing 3.96 g. of the thiazine dihydrochloride was made basic by adding solid KOH. An oil separated which solidified on cooling. The solid was collected by filtration and recrystallized from aqueous ethanol (with charcoal treatment), giving 2.93 g. of the thiazine **9c** as a pale tan crystalline solid, m.p. 99–101°. When this product was recrystallized from aqueous methanol (charcoal), colorless crystals were recovered with no change in the melting point; λ_{max}^{EtOH} 243.5 mμ (log ε 4.32), 328.5 mμ (log ε 3.94); $(1/\lambda)_{max}^{KBr}$ (principal peaks, cm.$^{-1}$) 3050 (w), 2818 (m), 2761 (m), 1585 (m), 1434 (m), 1400 (s), 1210 (m), 1038 (m), 799 (m), 787 (m), 760 (m).

Anal. Calcd. for $C_{16}H_{20}N_4S$: C, 63.97; H, 6.71; N, 18.65. Found: C, 63.68; H, 6.54; N, 18.48.

10-(3-Dimethylamino-1-*n*-propyl)dipyrido[2,3-*b*:2′,3′-*e*][1,4]-thiazine (9d) Dihydrochloride.—The thiazine **9d** dihydrochloride was prepared in a manner similar to that described for **9c**, with the following major procedural differences. The quantities used were thiazine **5a**, 4.21 g. (0.0210 mole); dry benzene, 300 ml.; NaH, 1.00 g. (52.7% in mineral oil)[23]; first portion of 3-chloro-1-dimethylaminopropane hydrochloride,[24] 6.00 g. (0.0380 mole); 50 ml. of dry benzene; reflux period after addition of the first chloramine portion, 2.5 hr.; second portion of 3-chloro-1-dimethylaminopropane hydrochloride, 6.70 g. (0.0424 mole); 50 ml. of dry benzene; reflux period after second chloramine addition, 27 hr.

The reaction mixture was then allowed to cool, washed with water, and extracted with 5% HCl. The combined acid extracts were cooled in ice and made basic by adding solid KOH. The yellow-orange oil which separated was taken up in ether and the ether solution was dried (Na_2SO_4), followed by removal of the solvent under reduced pressure. The residual orange oil was dissolved in absolute ethanol, the solution was filtered and then acidified by adding 10 ml. of concentrated HCl. The mixture was cooled in ice and the yellow solid which had precipitated was collected by filtration, yielding 6.00 g. (80%) of **9d** dihydrochlo-

(22) Yield based on recovered starting material.

(23) Metal Hydrides, Inc., Beverly, Mass.

(24) We wish to thank Dr. James Kerwin of Smith Kline and French Laboratories, Philadelphia, Pa., for a generous supply of this compound.

ride, softening at 165°, m.p. 198–213°. Several recrystallizations from absolute ethanol gave bright yellow crystals: softening at 190°, m.p. 206–210°; λ_{max}^{EtOH} 242 mμ (log ε 3.94), 332 mμ (log ε 4.36), taken at pH 10; $(1/\lambda)_{max}^{KBr}$ (principal peaks, cm.$^{-1}$) 3462 (m), 3401 (m), 3034 (w), 2968 (w), 2675 (m), 2290 (m), 2001 (m), 1584 (m), 1537 (m), 1423 (s), 795 (m).

Anal. Calcd. for $C_{15}H_{20}Cl_2N_4S$: C, 50.14; H, 5.61; N, 15.59. Found: C, 49.94; H, 5.81; N, 15.82.

When 5.0 ml. of concentrated HCl and some acetone were added to the filtrate, an additional 0.20 g. of less pure product was obtained, m.p. 166–214°, the infrared spectrum of which was identical with that obtained above.

A picrate of **9d** was prepared by neutralizing an aqueous solution of the dihydrochloride with KOH solution. The oil which separated was extracted with ether and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residual oil was treated with an ethanolic solution of picric acid, whereby a crystalline picrate, m.p. 148.5–160°, was obtained. When this substance was recrystallized from absolute ethanol, golden-orange platelets were recovered, which melted at 145–147°, resolidified, and then remelted at 160–162°. A further recrystallization from methanol yielded orange-red crystals, m.p. 145–148°.

Anal. Calcd. for $C_{21}H_{21}N_7O_7S$: C, 48.92; H, 4.11; N, 19.02. Found: C, 48.81; H, 4.23; N, 19.19.

It appears that the picrate exists in two polymorphic forms, and the form which is obtained depends somewhat on the method of crystallization. Thus, when water was added to a solution of the picrate in absolute ethanol, it was possible to obtain a yellow form, softening at 158°, m.p. 160–162°. Likewise, when a hot methanolic solution of the picrate was quickly cooled in ice, the yellow form predominated in the precipitate; whereas, if the solution were allowed to cool slowly to room temperature, the orange-red form was favored.

2-(3-Nitropyridyl-2-thio)-3′-nitro-3,2′-dipyridylamine (10).—A mixture of 288 mg. (1.16 mmoles) of the thiolactam **4a**, 70.4 mg. of KOH, and 15 ml. of absolute ethanol was heated to dryness on a steam bath. Absolute ethanol (10 ml.) was added to the residue and the mixture was again heated to dryness. The deep purple residue, which consisted of the potassium salt of 3-[(3-nitro-2-pyridyl)amino]-2(1H)-pyridinethione, was treated with a solution of 184 mg. (1.16 mmoles) of 2-chloro-3-nitropyridine (**2a**) in 6 ml. of dimethyl sulfoxide. The resulting solution was manually agitated for 5 min. on a steam bath, removed from the heat, and swirled for an additional 5 min. During these manipulations the color of the solution turned from black to a deep orange. Water was added to the mixture, causing an orange solid to precipitate. This was collected by filtration and recrystallized from an acetone–methanol mixture, yielding 283 mg. (66%) of **10** as orange crystals, m.p. 212–212.5° dec. Two recrystallizations from $CHCl_3$ failed to raise the melting point.

Anal. Calcd. for $C_{15}H_{10}N_6O_4S$: C, 48.65; H, 2.72; N, 22.69. Found: C, 48.49; H, 2.49; N, 22.60.

By concentrating the acetone–methanol mother liquor an additional 43 mg. (10%) of **10** was obtained, m.p. 210–211° dec.

10-(3-Nitro-2-pyridyl)dipyrido[2,3-*b*:2′,3′-*e*][1,4]thiazine (9e).—A solution of 0.665 g. of KOH in 25 ml. of absolute ethanol was added to a solution of 4.39 g. (0.0119 mole) of 2-(3-nitropyridyl-2-thio)-3′-nitro-3,2′-dipyridylamine (**10**) in 20 ml. of dimethyl sulfoxide. The mixture was heated at such a rate so that all of the ethanol distilled over a 40-min. period. The residue was poured into 150 ml. of water and the mixture was extracted ($CHCl_3$). The combined extracts were washed with water and dried (Na_2SO_4), and the solvent was removed. The residual solid was recrystallized from ethanol, yielding 2.74 g. (72%) of **9e** as fine red crystals, m.p. 179–180°. For analysis, the product was recrystallized from acetone–methanol; m.p. 181–181.5°; $(1/\lambda)_{max}^{KBr}$ (principal peaks, cm.$^{-1}$) 3047 (w), 1595 (s), 1574 (s), 1533 (s), 1412 (s), 1362 (s), 1332 (s), 782 (m), 637 (m).

Anal. Calcd. for $C_{15}H_9N_5O_2S$: C, 55.72; H, 2.81; N, 21.66. Found: C, 55.75; H, 2.76; N, 21.84.

When the volume of the ethanol mother liquor was reduced, an additional 0.225 g. (6%) of **9e** was obtained, m.p. 177–179°.

10-(3-Amino-2-pyridyl)dipyrido[2,3-*b*:2′,3′-*e*][1,4]thiazine (9f).—A combination of 897.6 mg. (2.780 mmoles) of 10-(3-nitro-2-pyridyl)dipyrido[2,3-*b*:2′,3′-*e*][1,4]thiazine, 15 ml. of dilute HCl (5 ml. of concentrated HCl/45 ml. of water), and 10 ml. of methanol was warmed on a steam bath. To this warm mixture, 0.50 g. of iron powder (100 mesh) was added slowly with shaking. After 10 min. of warming on the steam bath, the hot mixture was filtered and the residue on the filter was washed with 5 ml. of hot methanol. A light cream-colored crystalline material precipitated from the filtrate. After cooling in an ice bath, this material was collected on a filter and washed with two 5-ml. portions of cold water. After drying, this material gradually darkened when heated and then melted at 180–186°. Recrystallization from ethanol–water produced 222.1 mg. (26%) of pale cream-colored solid, which darkened and decomposed when heated, melting at 203–205°.

The mother liquor was treated with $NaHCO_3$ until the pH was approximately 7. A gray-green inorganic solid precipitated which was separated by filtration and washed with two 10-ml. portions of hot methanol. The combined filtrate and washings were extracted ($CHCl_3$), the chloroform extracts were dried (Na_2SO_4), and the solvent was then evaporated on a steam bath. The tan residue was recrystallized from methanol–water (charcoal) yielding 107.6 mg. (12%) of a pale cream-colored solid which darkened when heated and then decomposed as it melted at 209–211°. The two crops of material (m.p. 203–205° dec. and 209–211° dec.) were combined and recrystallized from ethanol–water twice to give light tan crystals which decomposed at 214–215°. This material gave the correct analysis for **9f** with an added mole of water. The yields given were calculated on this basis.

Anal. Calcd. for $C_{15}H_{11}N_5S \cdot H_2O$: C, 57.86; H, 4.21; N, 22.49. Found: C, 57.70; H, 4.03; N, 22.42.

The thiazine **9f** was also prepared by an iron–acetic acid reduction of the nitro compound, and the product was recrystallized from absolute ethanol to yield pale yellow crystals, m.p. 228–231°. There was no water of crystallization in this case as shown by comparison of the infrared spectrum with that of the material mentioned above and as indicated by analysis: $(1/\lambda)_{max}^{KBr}$ (principal peaks, cm.$^{-1}$) 3412 (w), 3320 (w), 3260 (w), 3059 (w), 1634 (m), 1588 (m), 1569 (m), 1410 (s), 805 (s), 794 (s).

Anal. Calcd. for $C_{15}H_{11}N_5S$: C, 61.42; H, 3.78; N, 23.87. Found: C, 61.28; H, 3.75; N, 23.80.

Infrared Measurements.—The infrared measurements reported in Table I were carried out on a Perkin-Elmer Model 521 grating spectrophotometer. The CCl_4 used was of reagent grade and was dried (P_2O_5) until immediately before use. Sodium chloride cells of 5.00-mm. thickness were used and the concentrations of the dipyridylamines were 0.0005 *M* or less to avoid interference from intermolecular hydrogen bonding. The spectra on samples containing dimethyl sulfoxide (DMSO) were obtained using 10 μl./ml. of this reagent.[25] Since the DMSO gives slight absorption in the N–H stretching frequency region at this concentration, the values reported in Table I were determined by subtracting from the spectrum of the dipyridylamine + DMSO in CCl_4 the spectrum of the same concentration of DMSO alone in CCl_4.

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(25) The DMSO was reagent grade, J. T. Baker Chemical Company, Phillipsburg, N. J., and was used without further purification.