The Synthesis of Novel Dipyridazinothiazine Ring Systems (1)

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The synthesis of several dipyridazinothiazines have been accomplished by: (a) cyclization in concentrated hydrochloric acid solution of the appropriate intermediates; and (b) *via* the Smiles rearrangement in either basic or glacial acetic acid solution of the appropriate intermediates. The following ring systems have been prepared and characterized: 10*H*-dipyridazino[4,3-*b*:4′,5′-*e*]-1,4-thiazine, 5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine, 10*H*-dipyridazino[4,5-*b*:-4′,5′-*e*]-1,4-thiazine, 5*H*dipyridazino[5,4-*b*:4′,3′-*e*]-1,4-thiazine, and 10*H*-dipyridazino[3,4-*b*:-3′,4′-*e*]-1,4-thiazine.

In 1958 Druey (4) reported the synthesis without experimental details of the first diazaphenothiazine wherein the two ring nitrogen atoms were adjacent in one of the six-membered rings (a pyridazine). In 1963 Yoneda, *et al*, (5) began a series of papers on this type of diazaphenothiazine and reported the synthesis of derivatives of 10*H*-benzo[*b*]pyridazino[3,4-*e*]-1,4-thiazine and 5*H*-benzo[*b*]-pyridazino[4,3-*e*]-1,4-thiazine. Yoneda, *et al*, (6) also reported the synthesis of derivatives of 10*H*-benzo[*b*]-pyridazino[4,5-*e*]-1,4-thiazine and later (7, 8) extended this work. More recently Maki, *et al*, (9, 10) have reported studies on the Smiles rearrangement of 10*H*-benzo[*b*]-pyridazino[4,5-*e*]-1,4-thiazines. Synthesis in which both benzenoid rings of the parent phenothiazine contain ring nitrogen atoms have been limited to several dipyridothiazines and more recently to the synthesis of the 1,3,6-triazaphenothiazine (10*H*-pyrido[3,2-*e*]pyrimidino[5,4-*b*]-1,4-thiazine) (11). We would now like to report the synthesis of several tetraazaphenothiazines in which both benzenoid rings of the parent phenothiazine were replaced by pyridazine rings.

The syntheses were approached by preparation of a diaryl sulfide and subsequent cyclization of this intermediate to the dipyridazinothiazines. By modification of the reaction conditions, the cyclization of the diaryl sulfide could be directed to yield one of two possible isomeric dipyridazinothiazines. Under strong acidic conditions direct cyclization was observed yielding an unrearranged dipyridazinothiazine. Under basic or mildly acidic conditions annulution proceeded in each case with rearrangement, presumably *via* a Smiles rearrangement (12) to the isomeric dipyridazinothiazine. This approach further exhibits the versatility of utilizing this route in the preparation of azaphenothiazines.

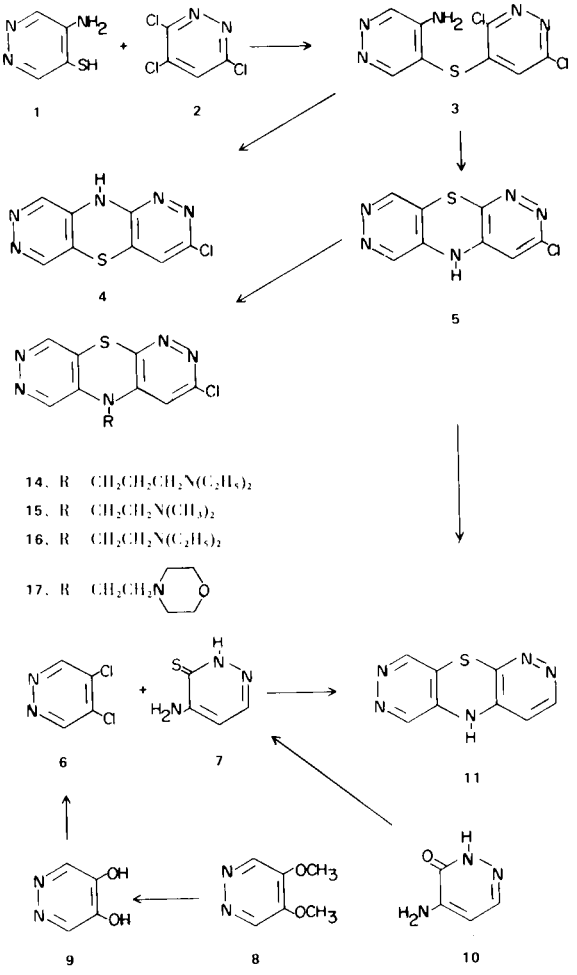
For the synthesis of 5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazines and the isomeric 10*H*-dipyridazino[4,3-*b*:-4′,5′-*e*]-1,4-thiazines, 4-aminopyridazine-5-thiol (**1**) was required. Compound **1** was prepared in 58% yield from 4-amino-5-chloropyridazine (13) and sodium hydrosulfide by heating under pressure. When **1** was allowed to react with 3,4,6-trichloropyridazine (**2**) (14) at -10 to -5° in ethanolic potassium hydroxide solution, 4-(5′-aminopyridazinyl-4′-thio)-3,6-dichloropyridazine (**3**) was obtained in 76% yield. When **3** was heated with concentrated hydrochloric acid, cyclization occurred and 3-chloro-10*H*-dipyridazino[4,3-*b*:4′,5′-*e*]-1,4-thiazine (**4**) was obtained in 63% yield. When **3** was heated with glacial acetic acid 3-chloro-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**5**) was obtained in 81% yield by the Smiles rearrangement. Compound **5** could also be obtained directly by heating 4-aminopyridazine-5-thiol (**1**) and 3,4,6-trichloropyridazine (2) in ethanolic potassium hydroxide at 50° for 3 hours. In order to establish the constitution of **4** and **5**, 4,5-dichloropyridazine (**6**) and 5-aminopyridazine-6(1*H*)-thione (**7**) were required. Treatment of 4,5-dimethoxypyridazine (**8**) (15) with refluxing 48% hydrobromic acid gave pyridazine-4,5-diol (**9**) in 89% yield. When **9** was allowed to reflux with excess phosphorus oxychloride, 4,5-dichloropyridazine (**6**) was obtained in 61% yield. 5-Aminopyridazine-6(1*H*)thione (**7**) was prepared in 62% yield by allowing 5-aminopyridazin-6(1*H*)one (**10**) (16) to react with phosphorus pentasulfide in pyridine solution. When 5-aminopyridazine-6(1*H*)thione (**7**) was allowed to react with 4,5-dichloropyridazine (**6**) in ethanolic potassium hydroxide at room temperature, the unsubstituted 5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**11**), the only azaphenothiazine which could be produced in the reaction, was obtained in 57% yield. By treatment with palladium

on charcoal compound **5** was also converted into **11** in 55% yield by catalytic dechlorination. Since compound **11** has been prepared by two routes the constitution of **5** has been established and **4** must be the alternate ring system.

In order to examine the reactivity of the two chlorine atoms toward nucleophilic displacement, compounds **4** and **5** were allowed to react with sodium methoxide. Under reflux conditions the reaction was incomplete, however, when compound **4** was allowed to heat with sodium methoxide in methanol under pressure, 3-methoxy-10*H*-dipyridazino[4,3-*b*:4′,5′-*e*]-1,4-thiazine (**12**) was prepared in 64% yield. Likewise **5** gave 3-methoxy-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**13**) in 53% yield under similar conditions.

3-Chloro-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**5**) was converted into the dialkylaminoalkyl derivatives as direct analogs of the neuropharmacologically active phenothiazines. Treatment of **5** with sodium amide and *N,N*-diethyl-3-chloropropylamine furnished 3-chloro-5-(3-diethylaminopropyl)-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**14**). In a similar fashion 3-chloro-5-(2-dimethylaminoethyl)-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**15**), 3-chloro-5-(2-diethylaminoethyl)-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**16**) and 3-chloro-5-(2-morpholinoethyl)-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**17**) were prepared.

Flow Sheet I



Another example of condensation and subsequent ring rearrangement was observed in the reaction of **1** with 4,5-dichloropyridazin-6(1*H*)one (**18**) in ethanolic potassium hydroxide solution kept at 0° for 24 hours. During the course of the reaction a white precipitate which initially formed turned orange as the reaction proceeded. Isolation of this orange precipitate and purification by repeated acid-base precipitation yielded a product for which a molecular formula of $C_8H_5N_5OS$ was assigned based upon elemental analysis. By repeating the reaction at -10° and reducing the reaction period to one hour it was possible to isolate the white intermediate from the above reaction. However, upon attempting recrystallization of this product from boiling ethanol a color change to orange occurred. The material proved to be identical with the product from the initial reaction for which two isomeric structures may be formulated; 10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-1(2*H*)one (**24**) or 10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)one (**20**). In order to assign the structure of the product obtained from the above reactions, these two compounds were synthesized by an unequivocal method.

Treatment of 5-amino-4-chloropyridazin-6(1*H*)one (**17**) with sodium hydrosulfide in ethanol under pressure at 160° furnished 5-amino-4-thiopyridazin-6(1*H*)one (**23**). Similarly 4-amino-5-thiopyridazin-(1*H*)one (**21**) was synthesized from 4-amino-5-chloropyridazin-6(1*H*)one (**22**).

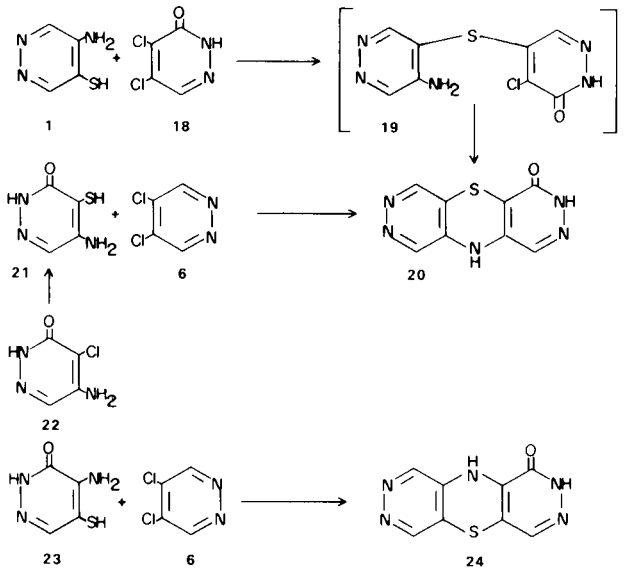
Condensation of **23** with **6** in ethanolic potassium hydroxide solution at room temperature afforded the the tetraazaphenothiazine, 10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-1(2*H*)one (**24**) which proved to possess different physical properties from **20**. 10*H*-Dipyridazino-[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)one (**20**) was synthesized similarly by treatment of **21** with **6** in the presence of base. This compound was shown to be identical with the product obtained by condensing **18** with **1** by comparison of their uv, ir and pmr spectra.

The formation of 10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)one (**20**) from the condensation of 4-amino-5-thiopyridazine and 4,5-dichloropyridazin-6(1*H*)one may be explained as initial formation of 4-(4′-aminopyridazinyl-5′-thio)-5-chloropyridazin-6(1*H*)one (**19**) followed by a Smiles rearrangement and ring closure to the tricyclic system.

The structural assignment of the intermediate as 4-(4′-aminopyridazinyl-5′-thio)-5-chloropyridazin-6(1*H*)one (**19**)

is made on the basis of analogy since it has been found that the halogen atom in the 4-position of 4,5-dichloropyridaz-6(1*H*)one is more susceptible to nucleophilic displacement than that in the more hindered 5-position (**18**). These observations are in harmony with those of Dury (19). The exceptional reactivity of the 4-halogen atom can also be explained if one considers it to be an activated vinylogous chloride such as those described by Benson and Pohland (20).

Flow Sheet 2

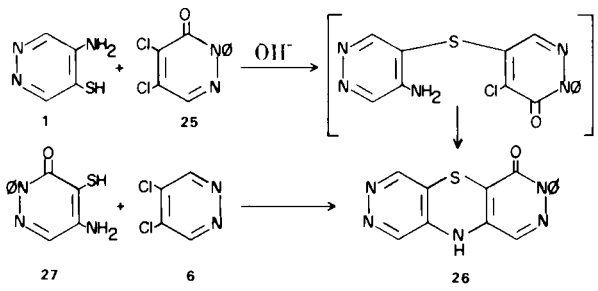


If ring closure of this intermediate occurred by direct cyclization the expected product would be **24**. However, this was not observed. Thus, the reaction is interpreted as proceeding *via* a Smiles-type rearrangement of the dipyridazinyl sulfide and subsequent annulation to **20**. There are a few cases in the literature (21) where the Smiles rearrangement has been initiated by heat alone, therefore, it is not unexpected that **19** rearranged and cyclized by heating in ethanol.

A similar isolation of a rearranged product was observed when 5-amino-4-thiopyridazine (**1**) was allowed to react with 4,5-dichloro-1-phenylpyridazin-6(1*H*)one (**25**) (22) in the presence of ethanolic potassium hydroxide solution. The product obtained was shown to be 3-phenyl-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)one (**26**) by the unequivocal synthesis of this compound by the condensation of 4-amino-1-phenyl-5-thiopyridazin-6(1*H*)one (**27**) with **6** in the presence of base.

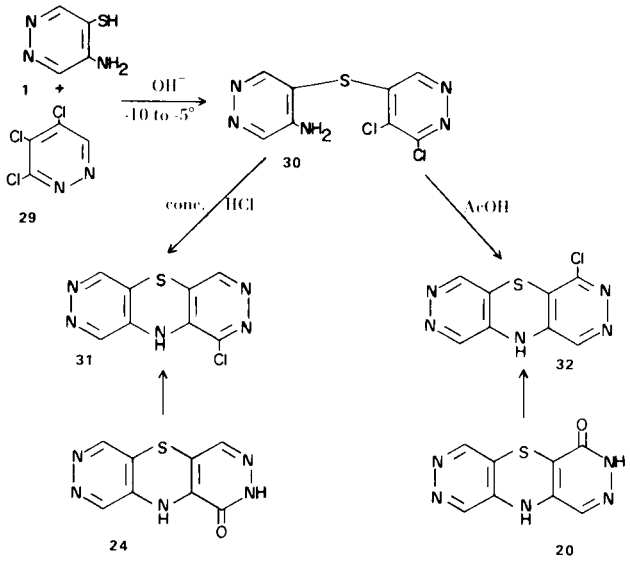
3,4,5-Trichloropyridazine (**29**) (22) upon treatment with **1** at -10° in ethanolic potassium hydroxide for 24 hours afforded 5-(5′-aminopyridazinyl-4′-thio)-3,4-dichloropyridazine (**30**) in 60% yield. It was expected that possibly

Flow Sheet 3

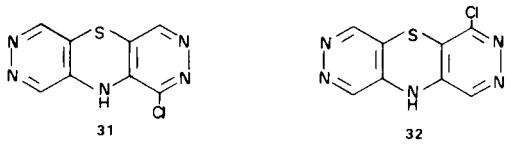


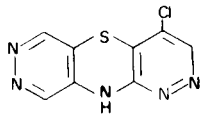
two isomeric products would be isolated from the reaction mixture, the observed product and 4-(5′-aminopyridazinyl-4′-thio)-3,5-dichloropyridazine, since the reactivity of both the 4- and 5-halogens are shown by molecualr orbital calculations to be approximately equal (6). In the literature, however, it has been reported that with equimolar amounts of sodium methoxide and 3,4,5-trichloropyridazine only the 5-chlorine atom is displaced (23). Proof that **30** was the 5-thioether was substantiated by examining the products of cyclization of this dipyridazinyl sulfide to tetraazaphenothiazines.

Flow Sheet 4



If the dipyridazinyl sulfide obtained in the above reaction was a mixture of the 4-dipyridazinyl sulfide and 5-dipyridazinyl sulfide subsequent ring closures with both weak and strong acid could yield up to four products **31**, **32**, **33**, and **34**.





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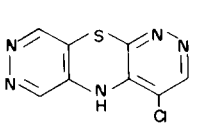

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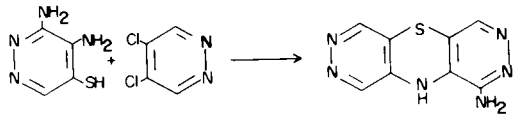
If the product obtained from the reaction was the 4-dipyridazinyl sulfide one would expect to obtain, upon cyclization in strong acid, a mixture of **33** and **32**. Ring closure under weak acid conditions would proceed through a Smiles rearrangement, followed by cyclization, to further furnish two additional products **31** and **34**; the 5-dipyridazinyl sulfide, on the other hand, could yield only **31** on treatment with strong acid, and only **32** on reaction with weak acid.

Treatment of **30** with concentrated hydrochloric acid at 90° for three hours followed by neutralization furnished 1-chloro-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**31**). The structure of **31** was substantiated by chlorination of **24** with phosphorus oxychloride in the presence of dimethylaniline.

Treatment of **30** with acetic acid for three hours at 90° furnished 4-chloro-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**32**) in 57% yield. Product **32** was also synthesized in an unequivocal manner by the chlorination of **20** with phosphorus oxychloride. A comparison of the uv spectra of **31** and **32** exhibits strong similarities to that of the unsubstituted ring **28**. This evidence supports the assignment of 5-(4′-aminopyridazinylthio)-3,4-dichloropyridazine for **30**.

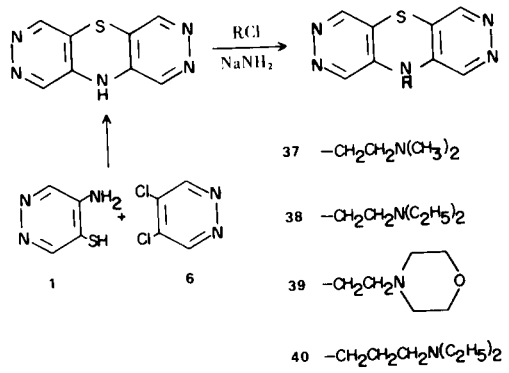
1-Amino-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**36**) was synthesized in 74% yield by the condensation of 3,4-diamino-5-thiopyridazine (**35**) (24) with **6** in ethanolic potassium hydroxide at room temperature for 24 hours.



35 6 36

The unsubstituted ring system 10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**28**) was prepared by treatment of **6** with **1** in the presence of ethanolic potassium hydroxide solution at room temperature. Several 10-substituted 10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazines were prepared by treatment of **28** with various dialkylaminoalkyl halides in the presence of sodium amide. By this procedure 10-(2-dimethylaminoethyl)-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**37**), 10-(2-diethylaminoethyl)-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**38**), 10-(2-morpholinoethyl)-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**39**), and 10-(3-diethylaminopropyl)-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**40**) were synthesized.

Treatment of 5-aminopyridazine-6(1*H*)thione (**41**) with



1 6

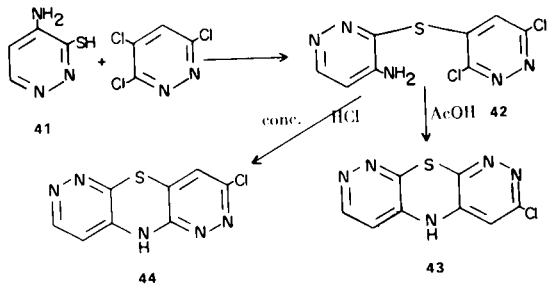
37 $-CH_2CH_2N(CH_3)_2$

38 $-CH_2CH_2N(C_2H_5)_2$

39 $-CH_2CH_2N$ O

40 $-CH_2CH_2CH_2N(C_2H_5)_2$

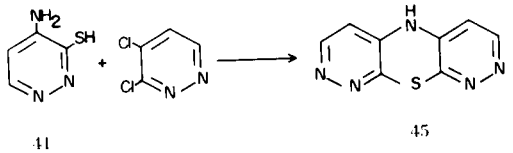
3,4,6-trichloropyridazine at -10° for 24 hours furnished, after recrystallization, a 31% yield of 4-(4′-aminopyridazinyl-3′-thio)-3,6-dichloropyridazine (**42**). Upon reaction of **42** with acetic acid at 90° for 3 1/2 hours, a 47% yield of the rearranged product 3-chloro-5*H*-dipyridazino-[3,4-*b*:4′,3′-*e*]-1,4-thiazine (**43**) was isolated.



41 44 43

Treatment of **42** with concentrated hydrochloric acid at reflux temperature for four hours gave 3-chloro-10*H*-dipyridazino[3,4-*b*:3′,4′-*e*]-1,4-thiazine (**44**).

The unsubstituted ring system, 5*H*-dipyridazino[3,4-*b*:-4′,3′-*e*]-1,4-thiazine (**45**) was prepared by condensation of **41** with 3,4-dichloropyridazine (25) in ethanolic potassium hydroxide solution at room temperature for 24 hours. Assignment of this structure to the product was based on comparison of the uv spectra. Its similarities to **43** and dissimilarity to **44** was considered conclusive.



41 45

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected. Ir, uv and pmr spectra were recorded on Perkin-Elmer 337, Bausch and Lomb Spectronic 505 and Varian A-60 spectrometers, respectively. The pmr spectra

were compared to TMS as an internal standard. The ir spectra were determined in potassium bromide discs and the uv spectra were determined in the solvent indicated. The elemental analyses and the ultraviolet spectra were preformed by Mrs. Ruby Ju and Mrs. Shigeko Nakogome.

4-Aminopyridazine-5-thiol (**1**).

A solution of sodium hydrosulfide (0.336 g., 6 mmoles) in 2 ml. of 50% ethanol was added to 5-amino-4-chloropyridazine (**13**) in a pressure bottle. The reaction mixture was heated at 140° with stirring for 14 hours and upon cooling a yellow precipitate separated from the solution. The reaction mixture was cooled in an ice bath, filtered, washed with cold water (20 ml.) and air dried to give 0.2 g. (58% yield) of product. Purification was by recrystallization from methanol, m.p. 230-231° dec.; ir cm^{-1}: 3480-3405 (>NH); 1565 (C=S); uv λ max (95% ethanol): 245 (ε, 16,500); 279 nm (ε, 15,200); nmr (DMSO-d_6): δ 8.45 (singlet, C_6H); δ 8.02 (singlet, C_3H); δ 7.11 (broad singlet, $-NH_2$, -5H).

Anal. Calcd. for $C_4H_5N_3S$: C, 37.8; H, 4.0; N, 33.1. Found: C, 38.0; H, 4.1; N, 32.9.

4-(5′-Aminopyridazinyl-4′-thio)-3,6-dichloropyridazine (**3**).

To a stirred solution of 3,4,6-trichloropyridazine (**14**) (0.86 g., 5 mmoles) in 15 ml. of ethanol at -10 to -5° was added slowly a cooled solution of **1** (0.64 g., 5 mmoles) and potassium hydroxide (0.5 g.) in 30 ml. of ethanol. The reaction was stirred and maintained at -10 to -5° for 24 hours. During the reaction period a precipitate formed. The crude product was collected by filtration, washed with water, and air dried. Recrystallization from ethanol yielded 1.04 g. (76%) of cream colored crystals, m.p. 155-157° dec.; ir cm^{-1}: 3410-3340 (broad, $-NH_2$); uv λ max (95% ethanol): 243 (ε, 18,700); 273 nm (ε, 17,800); nmr (DMSO-d_6): δ 9.15 (singlet, C_6H); δ 9.01 (singlet, C_3H); δ 8.55 (broad singlet, $-NH_2$); δ 7.47 (singlet, $-C_5$).

Anal. Calcd. for $C_8H_5Cl_2N_5S$: C, 35.1; H, 1.8; N, 25.6. Found: C, 35.3; H, 2.0; N, 25.5.

3-Chloro-10*H*-dipyridazino[4,3-*b*:4′,5′-*e*]-1,4-thiazine (**4**).

A solution of 4-(5′-aminopyridazinyl-4′-thio)-3,6-chloropyridazine (**3**) (0.64 g., 25 mmoles) and 30 ml. of concentrated hydrochloric acid was heated on a water bath at 90° for 3 hours. The mixture was made basic with 28% aqueous ammonia and the solution evaporated to dryness *in vacuo*. The tan residue was triturated with ethanol and filtered. The filtrate was then reduced to dryness. The resulting residue was recrystallized from ethanol to yield 0.37 g. (63%) of **4**, m.p. 256-257°; ir cm^{-1}: 3415-3310 (>NH); uv λ max (95% ethanol): 242 (ε, 21,100); 276 nm (ε, 16,400); nmr (DMSO-d_6): δ 9.6-9.1 (broad, singlet, >NH); δ 9.43 (singlet, C_9H); δ 9.17 (singlet, C_6H); δ 6.94 (singlet, C_4H).

Anal. Calcd. for $C_8H_4ClN_5S$: C, 40.4; H, 1.7; N, 29.5. Found: C, 40.4; H, 1.7; N, 29.6.

3-Chloro-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**5**).

Method A.

A mixture of 4-(5′-aminopyridazinyl-4′-thio)-3,6-dichloropyridazine (**3**) (0.64 g., 2.5 mmoles) in 20 ml. of acetic acid was heated on a steam bath at 95° for 3 hours. During this time the starting material dissolved. The solution was cooled and the solvent removed by evaporation under reduced pressure. Recrystallization of the residue from ethanol gave needle crystals (0.48 g., 81%), m.p. 234-235°; ir cm^{-1}: 3350-3210 (>NH); uv λ max (95% ethanol): 248 (ε, 16,300); 374 nm (ε, 17,500); nmr DMSO-d_6): δ 9.01 (singlet, C_6H); δ 9.3-8.6 (broad singlet, >NH); δ 8.73 (singlet, C_9H); δ 6.92 (singlet, C_4H).

Anal. Calcd. for $C_8H_4ClN_5S$: C, 40.4; H, 1.7; N, 29.5. Found: C, 40.3; H, 1.9; N, 29.5.

Method B.

To a stirred solution of 2,4,6-trichloropyridazine (1.72 g., 10 mmoles) in 30 ml. of ethanol was added slowly a solution of 5-aminopyridazine-4-thiol (1.28 g., 10 mmoles) and potassium hydroxide (1.0 g.) in 50 ml. of ethanol. After the addition was complete the reaction was heated to 50°. This temperature was maintained with stirring for 3 hours. The precipitate which formed was collected, washed with water and air dried. Recrystallization from ethanol gave 2.1 g. of pure product. This product was identical in all respects to that in Method A.

5-Aminopyridazine-6(1*H*)thione (**7**).

5-Aminopyridazin-6(1*H*)one (**10**) (1.1 g., 10 mmoles), phosphorus pentasulfide (4.3 g., 28 mmoles) and 50 ml. of pyridine (dried over potassium hydroxide) was heated at reflux temperature for 14 hours. The pyridine was removed by evaporation under reduced pressure and the residue hydrolyzed by the addition of 50 g. of ice followed by heating the mixture on a steam bath in a hood until the evolution of hydrogen sulfide had ceased. The solution was treated with Norite and filtered. The hot filtrate was adjusted to *p*H 1 with concentrated hydrochloric acid and allowed to cool to room temperature. The solution was then cooled at 14° for 14 hours. The yellow precipitate was collected and air dried. Recrystallization from methanol furnished yellow prisms, 0.79 g., (62%), m.p. 218-219° dec.; ir cm^{-1}: 3415-3240 (broad, -NH); 1570 (>C=S); uv λ max (95% ethanol): 324 (ε, 16,700), 304 (ε, 9,630); 276 nm (ε, 8,370); nmr (DMSO-d_6): δ 8.05 (doublet, C_3H); δ 7.11 (doublet, C_4H).

Anal. Calcd. for $C_4H_5N_3S$: C, 37.8; H, 4.0; N, 33.1. Found: C, 37.6; H, 3.9; N, 33.2.

Pyridazine-4,5-diol (**9**).

4,5-Dimethoxypyridazine (**8**) (15) (2.8 g., 20 mmoles) was added to 25 ml. of 48% hydrobromic acid and the mixture heated under reflux for 3 hours. During this period the starting material dissolved. Upon cooling prismatic crystals appeared which were collected. Recrystallization was from methanol to yield 2.0 g. (89%) of colorless prisms m.p. 178-179°; ir cm^{-1}: 3220-3090 (-OH); uv λ max (95% ethanol): 278 nm (ε, 16,400); nmr (DMSO-d_6): δ 9.01 (singlet, C_3 and C_6H); δ 8.29 (broad singlet, -OH).

Anal. Calcd. for $C_4H_4N_2O_2$: C, 42.9; H, 3.6; N, 25.0. Found: C, 42.7; H, 3.7; N, 25.2.

4,5-Dichloropyridazine (**6**).

A mixture of pyridazine-4,5-diol (**9**) (1.12 g., 10 mmoles), and 25 ml. of phosphorus oxychloride was heated under reflux for 2.5 hours. The solvent was removed under reduced pressure and the residue treated with ice and made alkaline with sodium carbonate. The aqueous alkaline solution was extracted with 3 x 50 ml. of chloroform and the combined chloroform extracts were dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the chloroform filtrate evaporated to dryness, to yield 1.18 g. of crude 4,5-dichloropyridazine (**6**). This was purified by passing it through a column containing 15 g. of silica gel using benzene as the eluent to furnish 0.94 g. of pure white compound. An analytical sample was prepared by sublimation; m.p. 67-68°; uv λ max (95% ethanol): 243 (ε, 22,300);

274 (ε, 26,400); 384 nm (ε, 27,300); nmr (deuteriochloroform): δ 9.16 (singlet, C_3 and C_6H).

Anal. Calcd. for $C_4H_2Cl_2N_2$: C, 32.2; H, 1.3; N, 18.8. Found: C, 32.2; H, 1.4; N, 18.9.

5*H*-Dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**11**).

Method A.

To a solution of 50 ml. of methanol was added 0.118 g. (0.5 mmole) of 3-chloro-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine, 0.2 ml. of 28% aqueous ammonia and 0.3 g. of 10% palladium-on-charcoal. The solution was hydrogenated at room temperature under atmospheric pressure for 8 hours. The solution was filtered through a celite pad and the filtrate evaporated to dryness. The yellow solid was boiled in ethanol, filtered and evaporated. The white product (0.056 g., 55%) was recrystallized twice from ethanol-ethyl acetate to give 0.037 g. of **11**, m.p. 184-185°; ir cm^{-1}: 3380-3335 (>NH); uv λ max (95% ethanol): 251 (ε, 15,800); 276 nm (ε, 18,000); nmr (DMSO-d_6): δ 9.04 (singlet, C_6H); δ 9.0 (broad singlet, >NH); δ 8.75 (singlet, C_9H); δ 8.17 (doublet, C_3H); δ 7.24 (doublet, C_4H).

Anal. Calcd. for $C_8H_5N_5O_2$: C, 47.3; H, 2.5; N, 34.5. Found: C, 47.0; H, 2.6; N, 34.3.

Method B.

To a stirred solution of **6** (0.150 g., 1 mmole) in 15 ml. of ethanol at 0° was added slowly a solution of **7** (0.127 g., 1.0 mmole) and potassium hydroxide (0.25 g.) in 25 ml. of ethanol. The reaction was allowed to come to room temperature after the addition was complete. Stirring was continued for 24 hours. The crude product was collected by filtration and recrystallized from ethanol-ethyl acetate. There was obtained 0.11 g., (57%) of material which was identical in all respects to that in Method A.

3-Methoxy-10*H*-dipyridazino[4,3-*b*:4′,5′-*e*]-1,4-thiazine (**12**).

A solution containing 3-chloro-10*H*-dipyridazino[4,3-*b*:4′,5′-*e*]-1,4-thiazine (**4**) (0.12 g., 0.5 mmole) and 20 ml. of methanol containing 0.1 g. of sodium was heated in a pressure bottle for 5 hours at 155-160°. After cooling and removal of sodium chloride by filtration, the filtrate was concentrated *in vacuo* and diluted with 10 ml. of water. The solid which separated was filtered, washed with water and air dried. Recrystallization from ethanol gave pure product, 0.062 g. (64%), m.p. >300°; ir cm^{-1}: 3440-3375 (broad, >NH); uv λ max (95% ethanol): 245 (ε, 19,800); 271 nm (ε, 15,900); nmr (DMSO-d_6): δ 9.2 (broad singlet, >NH); δ 9.32 (singlet, C_9H); δ 9.10 (singlet, C_6H); δ 7.18 (singlet, C_4H); δ 4.01 (singlet, OCH_3).

Anal. Calcd. for $C_9H_7N_5OS$: C, 46.4; H, 3.0; N, 30.0. Found: C, 46.2; H, 2.9; N, 29.8.

3-Methoxy-5*H*-dipyridazino[3,4-*b*:4′5′-*e*]-1,4-thiazine (**13**).

To a solution of 0.1 g. of sodium in 20 ml. of methanol in a pressure bottle was added 3-chloro-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**5**) (0.12 g., 0.5 mmole). The pressure bottle was heated for 5 hours at 150-160°. After cooling and removal of the sodium chloride by filtration, the filtrate was concentrated *in vacuo* and diluted with 20 ml. of water. The precipitated product was collected, washed with water, and dried, 0.047 g. (53%), m.p. >300°. An analytical sample was prepared by recrystallization from ethanol; ir cm^{-1}: 3380-3325 (>NH); uv λ max (95% ethanol): 253 (ε, 16,400); 279 nm (ε, 18,000); nmr (DMSO-d_6): δ 9.12 (singlet, C_6H); δ 9.0 (broad singlet, >NH); δ 8.81 (singlet, C_9H); δ 7.63 (singlet, C_4H); δ 3.93 (singlet, OCH_3).

Anal. Calcd. for $C_9H_7N_5OS$: C, 46.4; H, 3.0; N, 30.0. Found: C, 46.3; H, 3.2; N, 30.4.

3-Chloro-5-(3-diethylaminopropyl)-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**14**).

Compound **5** (0.237 g., 1 mmole) was added to a sodium amide solution prepared by dissolving 0.5 g. of sodium in 25 ml. of liquid ammonia. The mixture was stirred for 4 hours. The ammonia was evaporated in a nitrogen atmosphere and the residue was heated in 20 ml. of dioxane until the presence of ammonia could no longer be detected. The dioxane solution was then treated with 0.2 g. (1.3 mmoles) of 3-diethylaminopropyl chloride at 90°. The addition was made dropwise and the mixture stirred 3 hours at 90°. Methanol was added to decompose the excess sodium amide and the solution was cooled and filtered. The filtrate was evaporated to dryness under pressure, and the resulting residue heated in 25 ml. of ethanol, filtered and the filtrate cooled overnight to precipitate 0.17 g. (55%) of product, m.p. 142°; uv λ max (95% ethanol): 251 (ε, 16,600); 276 nm (ε, 17,300);

Method B.

Procedure A was followed except the reaction temperature was kept at -10° and the reaction was allowed to proceed for 1 hour. The white precipitate was collected and washed with ethanol. Heating the crude intermediate, 4-(4′-aminopyridazinyl-5′-thio)-5-chloropyridazin-6(1*H*)one (**19**) in ethanol in attempts to recrystallize the product resulted in the solid turning orange and isolation of 10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)-one (**20**) (0.098 g.). This product was identical in all respects to that isolated from Method A.

Method C.

To a solution of 4-amino-5-thiopyridazin-6(1*H*)one (**21**) (0.143 g., 1 mmole) and potassium hydroxide (0.5 g.) in 70 ml. of 50% ethanol was added 4,5-dichloropyridazine (**16**) (0.149 g., 1 mmole) in 10 ml. of ethanol at room temperature. The mixture was allowed to stir for 24 hours. The orange precipitate was collected, washed with water and air dried, 0.140 g. (64%). This product was identical in all respects to those obtained from Methods A and B.

5-Amino-4-thiopyridazin-6(1*H*)one (**23**).

5-Amino-4-chloropyridazin-6(1*H*)one (1.65 g., 10 mmoles) and sodium hydrosulfide (1.12 g., 20 mmoles) in 50 ml. of 50% ethanol was heated at 150-160° in a pressure bottle for 5 hours. The yellow solid which formed during the course of the reaction was filtered, washed with water and air dried, 0.83 g. (58%). An analytical sample was prepared by recrystallization from water-ethanol, m.p. >300°; ir cm^{-1}: 3440-3375 (-NH); 2560 (-SH); 1670 (>CON<); uv λ max (95% ethanol, saturated solution): 273; 308 nm.

Anal. Calcd. for $C_4H_5N_3OS$: C, 33.6; H, 3.5; N, 29.4. Found: C, 33.5; H, 3.7; N, 29.6.

4-Amino-5-thiopyridazin-6(1*H*)one (**21**).

4-Amino-5-chloropyridazin-6(1*H*)one (**22**) (17) (1.65 g., 10 mmoles) and sodium hydrosulfide (1.12 g., 20 mmoles) in 50 ml. of 50% ethanol was heated at 150-160° in a pressure bottle for 5 hours. The yellow precipitate which formed was filtered, washed with water and air dried, 1.01 g. (71%). An analytical sample was prepared by recrystallization from ethanol, m.p. >300°; ir cm^{-1}: 3415-3380 (-NH); 2590 (-SH); 1690 (>CONC<); uv λ max (95% ethanol): 283 (ε, 16,300); 303 nm (ε, 9,420).

Anal. Calcd. for $C_4H_5N_3OS$: C, 33.6; H, 3.5; N, 29.4. Found: C, 33.2; H, 3.7; N, 29.2.

3-Phenyl-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)one (**26**).

Method A.

To a solution of 4,5-dichloro-1-phenylpyridazin-6(1*H*)one (**25**) (28) (0.241 g., 1 mmole) in 75 ml. of ethanol was added a mixture of 4-aminopyridazine-5-thiol (**1**) (0.127 g., 1 mmole) and potassium hydroxide (0.4 g.) in 25 ml. of ethanol. An orange precipitate formed during the addition. The reaction was stirred at room temperature for 8 hours. The precipitate was collected and recrystallized from ethanol to yield 0.107 g. (47%). m.p. 300°; ir cm^{-1}: 3410-3385 (>NH); 1640 (CON<); uv λ max (saturated solution): 287 nm; nmr (DMSO-d_6): δ 8.9-8.6 (broad singlet, >NH); δ 9.04 (singlet, C_9H); δ 8.69 (singlet, C_6H); δ 8.34 (singlet, C_1H); δ 7.56 (singlet, phenyl-).

Anal. Calcd. for $C_8H_9N_5OS$: C, 43.1; H, 4.1; N, 31.4. Found: C, 42.9; H, 4.2; N, 31.7.

Method B.

To a solution of 4-amino-1-phenyl-5-thiopyridazin-6(1*H*)one (**27**) (0.143 g., 1 mmole) and potassium hydroxide (0.3 g.) in 50 ml. of 50% ethanol was added 4,5-dichloropyridazine (**6**) (0.149 g., 1 mmole) in 15 ml. of ethanol at room temperature. The mixture was stirred at room temperature for 24 hours. The precipitate was collected, washed with water, air dried and finally recrystallized from ethanol to furnish 0.13 g. (54% yield) of 3-phenyl-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)one (**26**). This product was identical in all respects with that obtained by Method A.

4-Amino-1-phenyl-5-thiopyridazin-6(1*H*)one (**27**).

A mixture of 4-amino-5-chloro-1-phenylpyridazin-6(1*H*)one (19) (0.222 g., 1 mmole) and sodium hydrosulfide (0.112 g., 2 mmoles) in 30 ml. of 50% ethanol was heated at 150-160° in a pressure bottle for 5 hours. The yellow precipitate which formed was filtered, washed with water and air dried. Recrystallization was from a water-ethanol (1:10) mixture, m.p. >300°; ir cm^{-1}: 3380-3210 (>NH); 2570 (-SH); 1685 (>CON<); uv λ max (95% ethanol): 323 (ε, 26,700); 308 nm (ε, 8,790); nmr (DMSO-d_6): δ 8.27 (singlet, C_3H); δ 7.53 (multiplet, -phenyl).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.8; H, 4.1; N, 19.2. Found: C, 54.4; H, 3.9; N, 19.3.

10*H*-Dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**28**).

To a stirred solution of 4,5-dichloropyridazine (**6**) (0.150 g., 1 mmole) in 10 ml. of ethanol at 0° was added slowly a solution of 5-aminopyridazine-4-thiol (0.127 g., 1 mmole) and potassium hydroxide (0.25 g.) in 25 ml. of ethanol. The reaction mixture was stirred and maintained at 0° for 24 hours. During this time a precipitate formed. The crude product was collected, washed with water, and dried. Recrystallization from ethanol gave colorless prisms (0.13 g., 66%), m.p. 167-168°; ir cm^{-1}: 3380-3350 (>NH); uv λ max (95% ethanol): 283 nm (ε, 14,600); nmr: 9.2 (broad singlet, >NH); δ 9.26 (singlet, C_1 and C_9H); δ 9.03 (singlet, C_4 and C_6H).

Anal. Calcd. for $C_8H_5N_5O_2$: C, 47.3; H, 2.5; N, 34.5. Found: C, 47.1; H, 2.7; N, 34.2.

5-(5′-Aminopyridazinyl-4′-thio)-3,4-dichloropyridazine (**30**).

A cooled solution of 5-aminopyridazine-4-thiol (**1**) (0.32 g., 2.5 mmoles) and potassium hydroxide (0.25 g.) in 30 ml. of 95% ethanol was added dropwise to a stirred solution of 3,4,5-trichloropyridazine (**29**) (21) (0.43 g., 2.5 mmoles) in 10 ml. of ethanol at -10 to -5°. The reaction was stirred and maintained at -10 to -5° for 24 hours. During the reaction period a white precipitate formed. The crude product was collected by filtration, washed with cold water and air dried. Recrystallization was from ethanol to yield 0.41 g. (60%), m.p. 268-270°; ir cm^{-1}: 3360-3320 (-NH_2); uv λ max (95% ethanol): 246 (ε, 14,200); 286 nm (ε, 12,500); nmr (DMSO-d_6): δ 9.18 (singlet, $C_6'H$); δ 8.99 (singlet, $C_3'H$); δ 9.3 (broad singlet, >NH); δ 7.96 (singlet, C_6H).

Anal. Calcd. for $C_8H_5Cl_2N_5S$: C, 35.1; H, 1.8; H, 25.6. Found: C, 34.9; H, 1.6; N, 25.7.

4-Chloro-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**32**).

Method A.

A solution of 5-(5′-aminopyridazinyl-4′-thio)-3,4-dichloropyridazine (**30**) (1.0 g., 3.9 mmoles) and 25 ml. of glacial acetic acid was heated on a water bath at 90° for 3 hours. The solution was cooled and the solvent removed by evaporation *in vacuo*. The residue was treated with 10 ml. of 28% aqueous ammonia and the volume reduced to dryness *in vacuo*. Recrystallization of the residue from ethanol furnished 0.52 g. (57%), m.p. 284-285° dec.; ir cm^{-1}: 3385-3350 (>NH); uv λ max (95% ethanol): 278 nm (ε, 14,600); nmr (DMSO-d_6): δ 9.5-8.9 (broad singlet, >NH); δ 9.34 (singlet, C_6H); δ 9.01 (singlet, C_9H); δ 8.44 (singlet, C_1H).

Anal. Calcd. for $C_8H_4ClN_5S$: C, 40.4; H, 1.7; N, 29.5. Found: C, 40.4; H, 1.6; N, 29.7.

Method B.

10*H*-Dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)one (**20**) (0.108 g., 0.5 mmole) in 5 ml. of phosphorus oxychloride and 1 ml. of *N,N*-dimethylaniline was heated under reflux for 1 hour. On cooling the excess phosphorus oxychloride was evaporated *in vacuo* to a brown syrup. The syrup was poured into ice water and the precipitated solid collected by filtration, 0.047 g. (40% yield) of **32**. This compound was identical in all respects to that obtained in Method A.

1-Chloro-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**31**).

Method A.

A solution of 5-(5′-aminopyridazinyl-4′-thio)-3,4-dichloropyridazine (**30**) (1.28 g., 5 mmoles) and 50 ml. of concentrated hydrochloric acid was heated on a water bath at 90° for 3 hours. The mixture was made basic with 28% aqueous ammonia and the solution evaporated to dryness *in vacuo*. The residue was triturated with ethanol and filtered. The filtrate was then reduced to dryness. The resulting residue was recrystallized from ethanol to yield 0.68 g. (58%), m.p. 247-249°; ir cm^{-1}: 3380-3345 (>NH); uv λ max (95% ethanol): 282 nm (ε, 13,400); nmr (DMSO-d_6): δ 9.3-9.1 (broad singlet, -NH); δ 9.23 (singlet, C_9H); δ 9.07 (singlet, C_6H); δ 8.16 (singlet, C_4H).

Anal. Calcd. for $C_8H_4ClN_5S$: C, 40.4; H, 2.7; N, 29.5. Found: C, 40.3; H, 2.0; N, 29.4.

Method B.

10*H*-Dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-1(2*H*)one (**24**) (0.108 g., 0.5 mmole) was warmed with phosphorus oxychloride (5 ml.) and *N,N*-dimethylaniline (0.5 ml.) for 30 minutes at 75°. The reaction mixture was poured onto ice. The resulting solution was extracted with chloroform (3 x 25 ml.). The extracts were combined, dried over anhydrous sodium sulfate, and filtered to remove the drying agent. The filtrate was reduced to dryness and the residue triturated with ethanol to furnish 0.032 g. (27%) of **32**. This compound was identical in all respects to that obtained in Method A.

1-Amino-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**36**).

To a solution of 3,4-diamino-5-thiopyridazine (**35**) (24) (0.142 g., 1 mmole) and 0.3 g. of potassium hydroxide in 25 ml. of ethanol was added 4,5-dichloropyridazine (**6**) (0.149 g., 1 mmole) in 15 ml. of ethanol at room temperature. The mixture was stirred for 24 hours. The precipitate was collected, washed with cold water and air dried. Recrystallization from ethanol-water furnished 0.154 g. (72%) of **36**, m.p. 217-218°; ir cm^{-1}: 3380-3250 (>NH); uv λ max (95% ethanol): 284 nm (ε, 14,800); nmr (DMSO-d_6): δ 9.28 (singlet, C_6H); δ 9.10 (singlet, C_9H); δ 8.34 (singlet, C_4H); δ 5.7 (broad singlet, $-NH_2$).

Anal. Calcd. for $C_8H_6N_6S$: C, 44.0; H, 2.8; N, 38.5. Found: C, 43.9; H, 2.8; N, 38.7.

4-(4′-Aminopyridazinyl-3′-thio)-3,6-dichloropyridazine (**42**).

A cooled solution of 5-aminopyridazine-6(1*H*)thione (**41**) (0.32 g., 2.5 mmoles) and potassium hydroxide (0.5 g.) in 20 ml. of ethanol was added dropwise to a stirred solution of 3,4,6-trichloropyridazine (0.43 g., 2.5 mmoles) in 15 ml. of ethanol at -10 to -5°. The reaction was stirred and maintained at -10 to -5° for 6 hours. During the reaction period a precipitate formed. The crude product was collected by filtration, washed with water and air dried. Recrystallization from ethanol yielded 0.21 g. (31%) of white needle crystals m.p. 176-178° dec.; ir cm^{-1}: 3280-3255 ($-NH_2$); uv λ max (95% ethanol): 248 (ε, 21,300); 279 nm (ε, 13,600); nmr (DMSO-d_6): δ 8.17 (doublet, $C_6'H$); δ 7.31 (doublet, $C_5'H$); δ 7.36 (singlet, C_5H).

Anal. Calcd. for $C_8H_5Cl_2N_5S$: C, 35.1; H, 1.8; N, 25.6. Found: C, 35.0; H, 1.5; N, 25.2.

3-Chloro-5*H*-dipyridazino[3,4-*b*:4′,3′-*e*]-1,4-thiazine (**43**).

4-(4′-Aminopyridazinyl-3′-thio)-3,6-dichloropyridazine (**42**) (0.32 g., 1.2 mmoles) in 15 ml. of acetic acid was heated on a steam bath at 90° for 3 1/2 hours. The solution was cooled and the solvent removed *in vacuo*. The residue was treated with 30 ml. of boiling ethanol and the solution filtered. Cooling overnight produced prism crystals (0.13 g., 47%), m.p. 183-184°; ir cm^{-1}: 3365 (>NH); uv λ max (95% ethanol): 277 (ε, 16,400); 304 nm (ε, 7,420); nmr (DMSO-d_6): δ 8.24 (doublet, C_7H); δ 7.28 (doublet, C_6H); δ 6.48 (singlet, C_4H).

Anal. Calcd. for $C_8H_4ClN_5S$: C, 40.4; H, 1.7; N, 29.5. Found: C, 40.2; H, 2.1; N, 29.3.

3-Chloro-10*H*-dipyridazino[3,4-*b*:3′,4′-*e*]-1,4-thiazine (**44**).

A solution of 4-(4′-aminopyridazinyl-3′-thio)-3,6-dichloropyridazine (**42**) (0.160 g., 0.5 mmole) and 20 ml. of concentrated hydrochloric acid was heated on a water bath at 90° for 4 hours. The solution was made basic with 28% aqueous ammonia and evaporated to dryness *in vacuo*. The resulting residue was treated with 20 ml. of boiling ethanol and filtered. The filtrate was cooled overnight resulting in the formation of needle crystals of **44** (45 mg., 61%), m.p. 256-258°; ir cm^{-1}: 3345-3285 (>NH); uv λ max (95% ethanol): 275 nm (ε, 14,800); nmr (DMSO-d_6): δ 8.26 (doublet, C_7H); δ 7.26 (doublet, C_6H); δ 7.18 (singlet, C_4H).

Anal. Calcd. for $C_8H_4ClN_5S$: C, 40.4; H, 1.7; N, 29.5. Found: C, 40.5; H, 1.9; N, 29.3.

5*H*-Dipyridazino[3,4-*b*:4′,3′-*e*]-1,4-thiazine (**45**).

To a stirred solution of 3,4-dichloropyridazine (0.15 g., 1 mmole) in 15 ml. of ethanol at room temperature was added slowly 5-aminopyridazine-6(1*H*)thione (**41**) (0.127 g., 1 mmole) and potassium hydroxide (0.25 g.) in 25 ml. of 50% ethanol. The reaction was stirred at room temperature for 24 hours. The crude product was collected by filtration, washed with water, and air dried. Recrystallization from ethanol furnished 0.11 g. (60%), m.p. 179-180°; ir cm^{-1}: 3380-3340 (>NH); uv λ max (95% ethanol): 277 (ε, 16,300); 305 nm (ε, 7,600); nmr (DMSO-d_6): δ 9.66 (doublet, C_3 and C_7H); δ 8.12 (doublet, C_4 and C_6H); δ 9.1 (broad singlet, >NH).

Anal. Calcd. for $C_8H_5N_5S$: C, 47.3; H, 2.5; N, 34.5. Found: C, 47.1; H, 2.7; N, 34.3.

nmr δ 9.04 (singlet, C_6H); δ 8.75 (singlet, C_9H); δ 6.95 (singlet, C_4H); δ 3.90 (triplet, $-N-CH_2$); δ 3.45 (multiplet, $-CH_2-N-(CH_2)_2-$); δ 2.46 (multiplet, $-C-CH_2-C$); δ 1.51 (multiplet, $-C-CH_3$).

Anal. Calcd. for $C_{15}H_{19}ClN_6S$: C, 51.4; H, 5.4; N, 23.9. Found: C, 51.5; H, 5.6; N, 24.1.

In a similar manner the following dialkylaminoalkyldipyridazinothiazines were prepared:

3-Chloro-5-(3-dimethylaminoethyl)-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**15**).

This compound was obtained in 46% yield, m.p. 162-164°.

Anal. Calcd. for $C_{12}H_{13}ClN_6S$: C, 46.7; H, 4.2; N, 27.3. Found: C, 47.1; H, 4.4; N, 27.6.

3-Chloro-5-(2-diethylaminoethyl)-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**16**).

This compound was obtained in 43% yield, m.p. 176-177°.

Anal. Calcd. for $C_{14}H_{18}ClN_6S$: C, 49.7; H, 5.4; N, 24.9. Found: C, 50.1; H, 5.2; N, 25.1.

3-Chloro-5-(2-morpholinoethyl)-5*H*-dipyridazino[3,4-*b*:4′,5′-*e*]-1,4-thiazine (**17**).

This compound was obtained in 48% yield, m.p. 136-137°.

Anal. Calcd. for $C_{14}H_{15}ClN_6OS$: C, 47.9; H, 4.3; N, 23.9. Found: C, 48.1; H, 4.6; N, 23.7.

10-(2-Dimethylaminoethyl)-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**37**).

This compound was obtained in 39% yield, m.p. 138-140°.

Anal. Calcd. for $C_{12}H_{15}N_6S$: C, 52.4; H, 5.5; N, 30.4. Found: C, 52.6; H, 5.5; N, 30.7.

10-(3-Diethylaminoethyl)-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**38**).

This compound was obtained in 51% yield, m.p. 172-173°.

Anal. Calcd. for $C_{14}H_{18}N_6S$: C, 55.6; H, 6.0; N, 27.8. Found: C, 55.7; H, 5.8; N, 28.1.

10-(2-Morpholinoethyl)-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**39**).

This compound was obtained in 42% yield, m.p. 166-167°.

Anal. Calcd. for $C_{14}H_{16}N_6OS$: C, 53.1; H, 5.1; N, 26.6. Found: C, 53.5; H, 5.1; N, 26.4.

10-(3-Diethylaminopropyl)-10*H*-dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazine (**40**).

This compound was obtained in 48% yield, m.p. 163-164°.

Anal. Calcd. for $C_{15}H_{20}N_6S$: C, 56.9; H, 6.4; N, 26.6. Found: C, 57.3; H, 6.0; N, 26.7.

10*H*-Dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-1(2*H*)one (**24**).

To a solution of 5-amino-4-thiopyridazin-6(1*H*)one (**23**) (0.143 g., 1 mmole) and potassium hydroxide (0.01 g.) in 10 ml.

of ethanol was added 4,5-dichloropyridazine (**6**) (0.149 g., 1 mmole) in 5 ml. of ethanol dropwise by use of a pressure equalizing dropping funnel. The funnel was washed with an additional 2.5 ml. of ethanol and this added to the reaction flask. The reaction was stirred at room temperature for 24 hours. An orange precipitate formed which was collected by filtration and washed with water. Recrystallization from *N,N*-dimethylformamide yielded orange needles (0.16 g., 73%), m.p. 360°; ir cm^{-1}: 3410-3280 (>NH), 1680 (>CON<); uv λ max (saturated solution): 288 nm; nmr (DMSO-d_6): δ10.2-9.2 (broad singlet, >NH); δ 9.12 (singlet, C_9H); δ 8.72 (singlet, C_6H); δ 8.29 (singlet, C_4H).

Anal. Calcd. for $C_8H_5N_5OS$: C, 43.8; H, 2.3; N, 32.0. Found: C, 44.1; H, 2.0; N, 32.2.

10*H*-Dipyridazino[4,5-*b*:4′,5′-*e*]-1,4-thiazin-4(3*H*)one (**20**).

Method A.

To a solution of 4,5-dichloropyridazin-6(1*H*)one (**18**) (0.165 g., 1 mmole) and potassium hydroxide (0.15 g.) in 30 ml. of 50% ethanol was added dropwise at 0° a mixture of 0.127 g. (1 mmole) of 4-aminopyridazine-5-thiol (**1**) and potassium hydroxide (0.25 g.) in 24 ml. of 50% ethanol. A white precipitate formed during addition which turned orange as the reaction proceeded. The mixture was stirred at 0° for 24 hours. The orange precipitate was collected (0.178 g., 56%), washed with water and air dried. Purification was by repeated acid-base precipitation, m.p. 360°; ir cm^{-1}: 3405-3310 (>NH); 1675 (>CON); uv λ max (saturated solution): 284 nm; nmr (DMSO-d_6): δ 9.06 (singlet, C_9H); δ 8.72 (singlet, C_6H); δ 8.42 (singlet, C_1H).

Anal. Calcd. for $C_8H_5N_5OS$: C, 43.8; H, 2.3; N, 32.0. Found: C, 44.2; H, 2.5; N, 32.2.

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