

Department of Chemistry, University of New Mexico

Dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiins

Raymond N. Castle (1), Kenji Kaji (2) and Dean Wise

The synthesis and cleavage of the novel ring system, dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin was reported from this laboratory as a communication to the editor (3). Dury has reported the synthesis of *N*-substituted dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-diones without experimental details (4).

4,5-Dichloro-6-pyridazone (I) (5) and sodium hydrosulfide were allowed to react in ethanol solution. The expected 4,5-dimercapto-6-pyridazone was not obtained, rather dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-dione (II) was obtained in 90% yield. Likewise when 4,5-dichloro-1-phenyl-6-pyridazone (VIII) (5) was treated with sodium hydrosulfide in ethanol solution, 2,7-diphenyldipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-dione (IX) (6) was obtained in 62% yield. Attempts to prepare dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-dithione (IV) by allowing II to react with phosphorus pentasulfide in boiling pyridine solution resulted in cleavage of II. The sole product was pyridazine-3,4,5-trithiol (V) (7) in 88% yield.

Therefore the synthesis of 1,6-dichlorodipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin (III) and 1,6-dibromodipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin (VI) was undertaken. The two compounds were obtained when II was treated with phosphorus oxychloride (IV, 24% yield), phosphorus oxybromide and bromine (VI, 13% yield), respectively. Compound III was then converted into IV by the standard thiourea method in 66% yield. The 1,6-bisalkylthio compounds (VIIa-f) were prepared from IV and the appropriate alkyl halide in alkaline solution.

These compounds have been prepared because of the mild antitumor activity of II.

## EXPERIMENTAL (8)

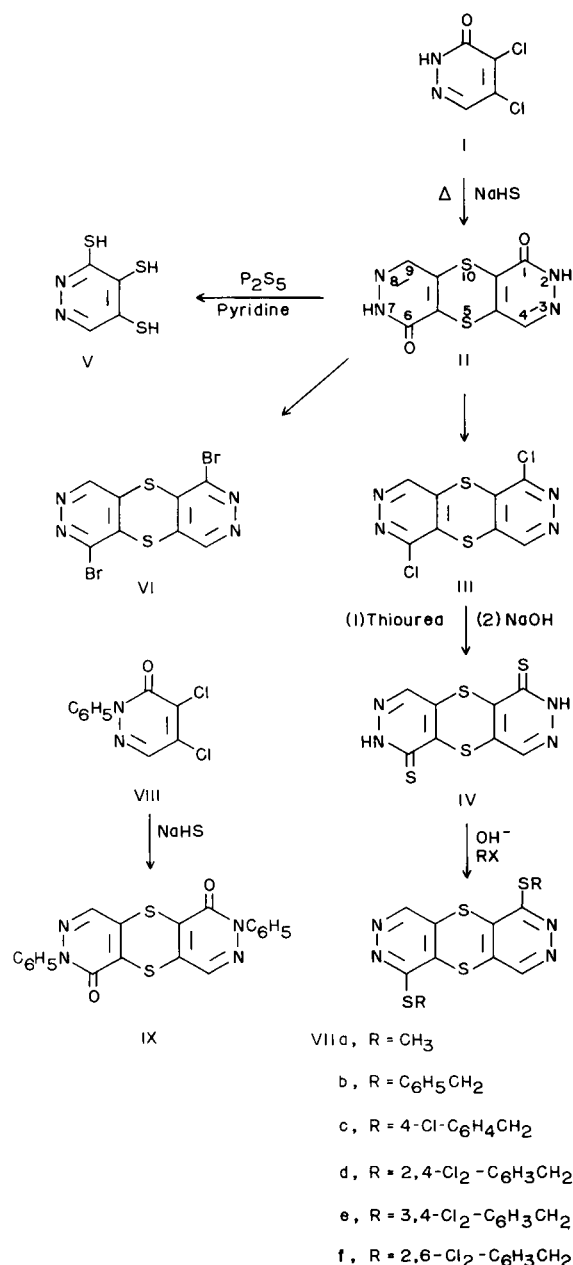
## 4,5-Dichloro-6-pyridazone (5).

Compound I was prepared from mucochloric acid by the method of Mowry (5).

Dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-dione (II).

4,5-Dichloro-6-pyridazone (33 g., 0.2 mole) was added to a solution containing 28 g. (0.48 mole) of purified sodium hydrosulfide in 1.5 l. of absolute ethanol. The mixture was heated under reflux for 3 hours. The orange precipitate which formed was collected after standing overnight at room temperature. The product was dissolved in about 2 l. of 0.5% aqueous sodium hydroxide, the solution was filtered and the filtrate was acidified to ~pH 1 with concentrated hydrochloric acid. The precipitated product was collected by filtration, washed with water, then with ethanol and finally with ether. There was obtained 19.54 g. of II (78% yield), m.p. 404° dec. In smaller scale experiments, yields up to 90% were obtained; infrared  $\text{cm}^{-1}$ , 3285(m), 3230(sh), 3190(s), 3135(s), 3075(s), 3040(s), 3010(s), 2950(sh), 2935(s), 2880(s), 2580(w), 1680(s), 1650(s), 1595(s), 1540(s), 1500(m), 1360(m),

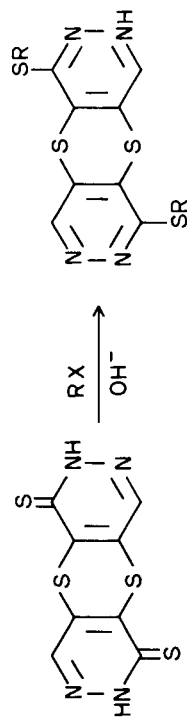
## Flow Sheet



1291(w), 1183(s), 1134(s), 1081(s), 943(s), 899(sh), 879(m), 775(sh), 761(s), 748(m), 619(s), 561(s), 500(w), 452(w); U. V.  $\lambda$  max (95% C<sub>2</sub>H<sub>5</sub>OH): 214 ( $\epsilon$ , 36,800); 294 m $\mu$  ( $\epsilon$ , 4,390).

Anal. Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>: C, 38.08; H, 1.59; N, 22.21; S, 25.42. Found: C, 38.01; H, 1.47; N, 21.86; S, 25.05.

TABLE I



IV

VII

R	X	m. p. °	Yield % (a)	Recrystallization Solvent	Formula	C		H		N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
Methyl	I	286-287	73	Acetic Acid	C <sub>10</sub> H <sub>8</sub> N <sub>4</sub> S <sub>4</sub>	38.43	38.85	2.58	2.87	17.93	17.50
Benzyl (b)	Br	176-178	86	Chloroform	C <sub>22</sub> H <sub>16</sub> N <sub>4</sub> S <sub>4</sub>	56.86	57.27	3.47	3.78	12.06	12.12
<i>p</i> -Chlorobenzyl	I	232-233	79	Chloroform	C <sub>22</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>4</sub> S <sub>4</sub>	49.51	49.87	2.64	2.64	10.50	10.36
2,4-Dichlorobenzyl	I	249-251	81	Benzene	C <sub>22</sub> H <sub>12</sub> Cl <sub>4</sub> N <sub>4</sub> S <sub>4</sub>	43.86	44.28	2.01	2.40	9.30	9.34
2,6-Dichlorobenzyl	I	296-298 dec.	71	Chloroform	C <sub>22</sub> H <sub>12</sub> Cl <sub>4</sub> N <sub>4</sub> S <sub>4</sub>	43.86	44.08	2.01	2.15	9.30	8.91
3,4-Dichlorobenzyl	I	237-238	76	Chloroform	C <sub>22</sub> H <sub>12</sub> Cl <sub>4</sub> N <sub>4</sub> S <sub>4</sub>	43.86	43.79	2.01	2.19	9.30	9.63

(a) Yields are recorded on material of high quality, but not necessarily of analytical quality. Usually there was not more than 1-2° difference in melting point of this product and that of the analytical specimen. (b) Two crystalline forms of this compound were isolated from the reaction mixture. Chromatography (Silica gel), with dichloromethane, of the crude product gave white needle crystals on crystallization from chloroform which had the physical properties and analysis given above in Table I. Further elution with chloroform and recrystallization of the product from chloroform gave yellow needle crystals (m.p. 168-170°; *Anal.* Calcd. for C<sub>22</sub>H<sub>16</sub>N<sub>4</sub>S<sub>4</sub>: C, 56.86; H, 3.47; N, 12.06. Found: C, 56.68; H, 3.42; N, 12.09). The mixed melting point was depressed to 151° and melted over a range. The infrared spectra in potassium bromide discs for the two forms were not superimposable. The ultraviolet spectra of these two forms were identical and are reported in Table II. Proof that *N*-alkylation had not occurred and that one of these crystalline isomers was not indeed the *N*-alkylated structural isomer was shown by the NMR data. NMR: δ 8.73, C-4H and C-9H, singlet; δ 7.18-7.52; phenyl protons, multiplet; δ 4.66, -CH<sub>2</sub>; singlet.

## 1,6-Dichlorodipyridazo[4,5-b:4,5-e]-1,4-dithiin (III).

Finely powdered II (23 g., 0.09 mole) was added to 500 ml. of phosphorus oxychloride while the mixture was magnetically stirred. The suspension was heated under reflux with magnetic stirring for 4 days. After about 3 days, solution was complete, however, at this point the product began to separate. The excess phosphorus oxychloride was removed by distillation under reduced pressure and the residue was poured on ice. The precipitate which separated upon hydrolysis of the residue was collected by filtration and recrystallized from ethanol, yield 6.45 g. (24%), m.p. 284-285° dec.; infrared  $\text{cm}^{-1}$ , 3055(m), 1510(m), 1480(s), 1340(w), 1298(m), 1280(s), 1263(s), 1183(w), 1102(m), 1029(sh), 1020(m), 938(w), 925(w), 828(s), 726(m), 573(w), 552(m), 518(w), 504(w), 472(w); U. V.  $\lambda$  max (95%  $\text{C}_2\text{H}_5\text{OH}$ ): 204 ( $\epsilon$ , 22,000); 229 ( $\epsilon$ , 16,600), 264 ( $\epsilon$ , 26,900); 296(sh)  $\mu\text{m}$  ( $\epsilon$ , 7,700).

Anal. Calcd. for  $\text{C}_8\text{H}_2\text{Cl}_2\text{N}_4\text{S}_2$ : C, 33.23; H, 0.70; N, 19.38; S, 22.19; Cl, 24.52. Found: C, 33.43; H, 0.96; N, 19.72; S, 21.77; Cl, 24.00.

## 1,6-Dibromodipyridazo[4,5-b:4,5-e]-1,4-dithiin (VI).

To 100 g. of phosphorus oxybromide at 120° was added 5.05 g. (0.02 mole) of finely powdered II with magnetic stirring. A 4.0 g. amount of bromine was then added dropwise to the mixture and heating at 120° was continued for 2 hours. During the heating period the mixture solidified. The excess of bromine was removed under reduced pressure and the residue was hydrolyzed by adding ice. The resulting suspension was made strongly basic with ammonium hydroxide and filtered. The solid was extracted with absolute ethanol in a Soxhlet extractor. There was obtained 1.6 g. of crude product from the ethanol. The ammonium hydroxide filtrate was continuously extracted with ether and from the ether solution an additional 0.1 g. of crude product was obtained. The combined crude products produced two spots on TLC (alumina), therefore the crude product was chromatographed on alumina (chloroform). A yield of 1 g. (13%) of pure product was obtained after recrystallization from a dimethyl formamide-water mixture, m.p. 227-228° dec.; infrared  $\text{cm}^{-1}$ , 1655(w), 1510(sh), 1500(s), 1490(s), 1480(s), 1415(w), 1375(m), 1285(s), 1265(s), 1250(s), 1240(s), 1200(w), 1185(m), 1105(w), 1030(m), 1010(w), 910(w), 900(w), 810(m), 795(m), 760(sh), 745(w), 570(w), 530(w), 505(w), 435(w); U. V.  $\lambda$  max (95%  $\text{C}_2\text{H}_5\text{OH}$ ): 208 ( $\epsilon$ , 33,800); 269 ( $\epsilon$ , 24,000); 300(sh)  $\mu\text{m}$  ( $\epsilon$ , 5,200).

Anal. Calcd. for  $\text{C}_8\text{H}_2\text{Br}_2\text{N}_4\text{S}_2$ : C, 25.41; H, 0.53; N, 14.82. Found: C, 25.71; H, 0.74; N, 14.60.

## Dipyridazo[4,5-b:4,5-e]-1,4-dithiin-1,6-dithione (IV).

Compound III (15 g., 0.053 mole) was suspended in 500 ml. of absolute methanol with heating and magnetic stirring. To the hot suspension was added 19.5 g. (0.25 mole) of thiourea and the mixture was heated under reflux for 3 hours. After cooling the red precipitate was collected by filtration, washed with methanol and heated with 100 ml. of 10% aqueous sodium hydroxide solution for 40 minutes.

The resulting solution was filtered and the filtrate acidified to  $\sim\text{pH}$  1 with concentrated hydrochloric acid. The product amounted to 9.95 g. (66% yield). An analytical sample was prepared by repeated precipitation from an alkaline solution by acidification and washing with water; infrared  $\text{cm}^{-1}$ , 3140(s), 3075(s), 3010(s), 2920(s), 2840(s), 1630(w), 1550(s), 1522(s), 1430(s), 1360(w), 1300(w), 1268(w), 1227(s), 1168(m), 1105(w), 1090(w), 1050(s), 845(m), 758(s), 710(w), 578(w), 560(w), 525(w), 490(w), 430(w), 410(w); U. V.  $\lambda$  max (5% NaOH, saturated solution) 218; 250; 276; 366  $\mu\text{m}$ .

Anal. Calcd. for  $\text{C}_8\text{H}_4\text{N}_4\text{S}_4$ : C, 33.78; H, 1.42; N, 19.70. Found: C, 33.73; H, 1.58; N, 19.32.

Attempts to prepare dipyridazo[4,5-b:4,5-e]-1,4-dithiin-1,6-dithione by the direct phosphorus pentasulfide-pyridine thiation was not successful resulting in ring cleavage as described below.

## 3,4,5-Pyridazinetrithiol (V).

Dipyridazo[4,5-b:4,5-e]-1,4-dithiin-1,4-dione (5.04 g., 0.02 mole) was mixed thoroughly with 53.4 g. (0.24 mole) of phosphorus pentasulfide and this mixture was added to 400 ml. of dry pyridine. The reaction mixture was heated under reflux for 16 hours after which the excess pyridine was removed under reduced pressure. The residue was poured onto crushed ice and the mixture was digested on the steam bath until the evolution of hydrogen sulfide had ceased. The mixture was filtered and the filtrate was acidified to  $\text{pH}$  1-1.5 with concentrated hydrochloric acid. The 3,4,5-pyridazinetrithiol was precipitated, 6.2 g. (88% yield), m.p. > 400° (6).

Typical Procedure, Table I, Compounds VIIa-f.

## 1,6-Bis(3,4-dichlorobenzylmercapto)dipyridazo[4,5-b:4,5-e]-1,4-dithiin.

3,4-Dichlorobenzyl iodide (2.1 g., 0.074 mole) in 10 ml. of ethanol was added portionwise to 1 g. (0.0035 mole) of dipyridazo[4,5-b:4,5-e]-1,4-dithiin-1,6-dithione (II) dissolved in a mixture of 20 ml. of 5% sodium hydroxide solution and 15 ml. of 28% aqueous ammonia. Yellow crystals of product began to separate during the addition. Stirring was continued for 24 hours at room temperature. The solid was collected, washed with 50 ml. of ethanol, and dried overnight. This crude product produced two spots on TLC (Silica gel), therefore the precipitate was chromatographed on Silica gel (chloroform). The chromatographed material was recrystallized from chloroform, m.p. 237-238°.

## 2,7-Diphenyldipyridazo[4,5-b:4,5-e]-1,4-dithiin-1,6-dione (IX).

4,5-Dichloro-1-phenyl-6-pyridazone (VIII) (9) (4.82 g., 0.02 mole) was added to 250 ml. of absolute ethanol containing 4.50 g. (0.08 mole) of sodium hydrosulfide and the mixture was heated under reflux for 2-5 hours. The yellow precipitate which formed was collected by filtration, washed with water and then ethanol. There was obtained 2.5 g. of IX (62% yield), m.p. > 365°; infrared  $\text{cm}^{-1}$ , 3060(m), 3040(w), 1630(s), 1600(m), 1570(s), 1500(s), 1460(m), 1370(w), 1325(w), 1300(w), 1265(m), 1180(w), 1170(w), 1145(s), 1075(w), 1070(w), 1030(w), 950(m), 905(w), 815(m), 755(s), 745(sh), 720(s), 655(s), 645(m), 620(m), 610(m), 540(w), 485(w); U. V.  $\lambda$  max (95%  $\text{C}_2\text{H}_5\text{OH}$ ; saturated solution): 208; 278  $\mu\text{m}$ ;  $\lambda$  max (5% NaOH, saturated solution): 224; 240; 288; 352  $\mu\text{m}$ .

Anal. Calcd. for  $\text{C}_{26}\text{H}_{12}\text{O}_2\text{N}_4\text{S}_2$ : C, 59.38; H, 2.99; N, 13.86; S, 15.86. Found: C, 59.68; H, 2.90; N, 13.93; S, 15.80.

TABLE II

## Ultraviolet Spectral Data

Compound Number	$\lambda$ max	$\epsilon$
VIIa	207; 241; 248; 330	29,700; 26,300; 27,100; 2,490. (a)
VIIb	206; 244; 264; 338	42,700; 31,100; 32,800; 3,640. (a)
VIIc	206; 241; 262; 320	51,400; 36,600; 35,300; 3,480. (a)
VIIId	206; 230; 260. (b)	
VIIe	206; 224; 262. (b)	
VIIIf	206; 222; 260. (b)	

(a) 95%  $\text{C}_2\text{H}_5\text{OH}$ . (b) 95%  $\text{C}_2\text{H}_5\text{OH}$ , saturated solution.

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- (1) To whom inquiries concerning this paper should be directed.
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- (8) All melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The infrared spectra were determined with a Perkin-Elmer 337 Spectrophotometer over the range 4000-400  $\text{cm}^{-1}$  in potassium bromide discs. The ultraviolet spectra were taken in the solvent indicated with a Baush and Lomb Spectronic 505 Spectrophotometer. NMR Spectra were taken on a Varian A-60 A spectrometer in deuteriochloroform.

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Albuquerque, New Mexico 87106