Tetrahedron, 1967, Vol. 23, pp. 891 to 896. Pergamon Press Ltd. Printed in Northern Ireland

HETEROCYCLIC SYNTHESES FROM *o*-AMINONITRILES—XXVII[1]

A ONE-STEP SYNTHESIS OF FUSED PYRIMIDINEDITHIONES[2]

E. C. TAYLOR, A. MCKILLOP and R. N. WARRENER
Department of Chemistry, Princeton University, Princeton, N.J.

(*Received* 12 *February* 1966)

Abstract—The reaction of aromatic and heterocyclic *o*-aminonitriles with carbon disulfide in pyridine solution constitutes a convenient, one-step synthesis of fused pyrimidinedithiones (fused 2,4-dimercaptopyrimidines). The reaction proceeds by the intermediate formation of a 4-imino-*m*-thiazine which rearranges rapidly and irreversibly by a base-catalysed (pyridine) ring-opening, ring-closure sequence to give the observed product.

[1] Over the past decade we have published a number of papers dealing with the utilization of *o*-aminonitriles in heterocyclic syntheses. We are planning extensive further exploitation of these intermediates, and in order to unify the past work, as well as to relate it to work in progress and projected, we believe it expedient to number these papers in a series to be titled "Heterocyclic Syntheses from *o*-Aminonitriles". Previous papers in this series are as follows:
Part XXVI. E. C. Taylor, A. McKillop and S. Vromen, *Tetrahedron* **23**, 885 (1967)
Part XXV. E. C. Taylor, S. Vromen, A. McKillop, and R. V. Ravindranathan, *Angew. Chem.* **78**, 332 (1966); Intern. Ed. **5**, 308 (1966).
Part XXIV. Z. C. Taylor, R. N. Warrener and A. McKillop, *Ibid.*, **78** 333 (1966); Intern. Ed., **5**, 309 (1966).
Part XXIII. E. C. Taylor and A. Abul-Husn, *J. Org. Chem.* **31**, 342 (1966).
Part XXII. E. C. Taylor and J. G. Berger, *Angew. Chem.* in press.
Part XXI. E. C. Taylor and R. W. Hendess, *J. Amer. Chem. Soc.* **87**, 1995 (1965).
Part XX. E. C. Taylor and R. W. Hendess, *Ibid.* **87**, 1980 (1965).
Part XIX. E. C. Taylor and R. W. Morrison, Jr., *Ibid.* **87**, 1976 (1965).
Part XVIII. E. C. Taylor and E. E. Garcia, *J. Org. Chem.* **29**, 2116 (1964).
Part XVII. E. C. Taylor and R. W. Hendess, *J. Amer. Chem. Soc.* **86**, 951 (1964).
Part XVI. E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.* **27**, 2622 (1962).
Part XV. E. C. Taylor and A. L. Borror, *Ibid.* **26**, 4967 (1961).
Part XIV. E. C. Taylor and J. A. Zoltewicz, *J. Amer. Chem. Soc.* **83**, 248 (1961).
Part XIII. E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton and W. Pfleiderer, *Ibid.* **82**, 6058 (1960).
Part XII. E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes and M. L. Hoefle, *Ibid.* **82**, 5711 (1960).
Part XI. E. C. Taylor, R. J. Knopf and A. L. Borror, *Ibid.* **82**, 3152 (1960).
Part X. E. C. Taylor and P. K. Loeffler, *Ibid.* **82**, 3147 (1960).
Part IX. E. C. Taylor and W. A. Ehrhart, *Ibid.* **82**, 3138 (1960).
Part VIII. E. C. Taylor and P. K. Loeffler, *J. Org. Chem.* **24**, 2035 (1959).
Part VII. E. C. Taylor and K. S. Hartke, *J. Amer. Chem. Soc.* **81**, 2456 (1959).
Part VI. E. C. Taylor and K. S. Hartke, *Ibid.* **81**, 2452 (1959).
Part V. E. C. Taylor, A. J. Crovetti and R. J. Knopf, *Ibid.* **80**, 427 (1958).
Part IV. E. C. Taylor and N. W. Kalenda, *Ibid.* **78**, 5108 (1956).
Part III. E. C. Taylor and W. W. Paudler, *Chem. and Ind.*, 1061 (1955).
Part II. E. C. Taylor and A. J. Crovetti, *J. Org. Chem.* **19**, 1633 (1954).
Part I. E. C. Taylor and N. W. Kalenda, *Ibid.* **18**, 1755 (1953).

[2] This work was supported in part by a generous grant to Princeton University from the Smith Kline and French Laboratories, Philadelphia, Pa.

IN VIEW of the ubiquitous utility of fused pyrimidinethiones as synthetic intermediates and as pharmacologically interesting purine analogs,[3] it is noteworthy that the corresponding dithiones have received relatively little attention. This presumably is a reflection of the circuity of synthetic routes leading to such intermediates, since the only previously available general synthesis has involved the treatment of a fused dichloropyrimidine with sodium hydrosulfide[4] or thiourea[5] or, in a few cases, the direct replacement of oxygen by sulfur by the use of phosphorus pentasulfide.[6-9]

We have found that the reaction of aromatic and heterocyclic *o*-aminonitriles with carbon disulfide in pyridine solution constitutes a facile one-step synthesis of fused pyrimidinedithiones. Thus, when a mixture of 2-aminobenzonitrile, carbon disulfide, and pyridine is heated for several hours under reflux, quinazoline-2,4(1H,3H)-dithione separates in 97% yield on dilution of the reaction mixture with ethanol. The product was identical with an authentic sample prepared by the reaction of thiourea with 2,4-dichloroquinazoline. The reaction was equally successful with a number of substituted 2-aminobenzonitriles and with a variety of heterocyclic *o*-aminonitriles, as illustrated in Table 1.

The course of this apparent one-step conversion was revealed in the study of the reaction of carbon disulfide with 3-amino-4-cyanopyrazole (I). The initial product which precipitated upon cooling of the reaction mixture was a yellow crystalline pyridine salt. This compound showed no nitrile band in its IR spectrum; treatment with cold, dilute hydrochloric acid gave a light yellow solid which could be recrystallized from concentrated sulfuric acid. We believe this compound to be the *m*-thiazine derivative III; it exhibits a strong imine NH band at 3510 cm^{-1} and its UV spectrum (see Experimental) indicates conclusively that the compound is neither a simple pyrazole nor a pyrazolo(3,4-d)pyrimidine. Treatment of III with cold, dilute sodium hydroxide solution resulted in instantaneous and quantitative rearrangement to IV; heating with acetic anhydride likewise resulted in rearrangement to give 1-acetyl-4,6(5H,7H)-pyrazolo(3,4-d)pyrimidinedithione (V).

The rearrangement of *m*-thiazines to pyrimidines is now a well-documented reaction of considerable synthetic utility. The apparent one-step conversion of *o*-aminonitriles to fused pyrimidinedithiones is another example of the intervention of *m*-thiazines in a pyrimidine synthesis; this conversion must involve the initial formation of a dithiocarbamate salt (e.g. II), cyclization to a *m*-thiazine (presumably as its pyridinium salt), followed by a ring-opening, ring-closure sequence (initiated by the solvent pyridine acting as the requisite base) leading rapidly and irreversibly to the observed pyrimidinedithione.[10]

Examination of a variety of substituted 2-aminobenzonitriles indicated that the above-described reaction is dependent both upon the basicity of the amino grouping

[3] For a general review see R. K. Robins, *J. Med. Chem.* **7**, 186 (1964).
[4] H. L. Yale, *J. Amer. Chem. Soc.* **75**, 675 (1953).
[5] Cf. H. C. Koppel and R. K. Robins, *J. Amer. Chem. Soc.* **80**, 2751 (1958).
[6] H. C. Koppel and R. K. Robins, *J. Org. Chem.* **23**, 1457 (1958).
[7] C. W. Noell and R. K. Robins, *J. Amer. Chem. Soc.* **81**, 5997 (1959).
[8] R. K. Robins, *J. Amer. Chem. Soc.* **78**, 784 (1956).
[9] G. B. Elion and G. H. Hitchings, *J. Amer. Chem. Soc.* **69**, 2138 (1947).
[10] This reaction sequence is analogous in principle to the conversion of aliphatic α-aminonitriles with carbon disulfide to 5-amino-4-substituted 2(3*H*)-thiazolethiones, which can be rearranged with strong base to imidazole-2,4(1*H*,3*H*)-dithiones [I. Heilbron, *J. Chem. Soc.* 2099 (1949)].

TABLE 1a

o-Aminonitrile	Solvent	Time, hr.	Temp	Product	Yield, %
2-Aminobenzonitrile	*a*	1	*d*	Quinazoline-2,4(1H,3H)-	67
	a	2	*d*	dithione	97
	b	3·5	*d*		43
2-Amino-5-methylbenzo-	*a*	36	*e*	6-Methylquinazoline-	51
nitrile	*a*	4	*d*	2,4(1H,3H)-dithione	98
	a	72	*e*		96
2-Amino-5-piperidino-	*a*	1	*d*	6-Piperidinoquinazoline-	95
benzonitrile				2,4(1H,3H)-dithione	
2-Amino-5-methoxy-	*a*	0·5	*d*	6-Methoxyquinazoline-	99
benzonitrile				2,4(1H,3H)-dithione	
2-Amino-5-bromobenzo-	*a*	12	*e*	6-Bromoquinazoline-	50
nitrile	*a*	70	*e*	2,4(1H,3H)-dithione	92
2-Amino-3-	*a*	14	*d*	2,4(1H,3H)-pyrimido(4,5-b)-	30
cyanoquinoline				quinolinedithione	
4-Amino-5-	*c*	10	*d*	2,4(1H,3H)-pyrimido(4,5-d)-	68
cyanopyrimidine				pyrimidinedithione	
1-Methyl-4-cyano-5-	*a*	6	*d*	1-Methyl-4,6(5H,7H)-pyrazolo-	67
aminopyrazole	*a*	52	*d*	(3,4-d)pyrimidinedithione	87
1-Phenyl-4-cyano-5-	*a*	115	*d*	1-Phenyl-4,6(5H,7H)-pyrazolo-	93
aminopyrazole	*c*	45	*d*	(3,4-d)pyrimidinedithione	97
3-Amino-4-cyanopyrazole	*a*	1	*d*	4,6(5H,7H)-Pyrazolo(3,4-d)-	81
				pyrimidinedithione	

[a] pyridine [b] dimethylformamide [c] dimethylformamide + sodium methoxide [d] reflux [e] room temp.

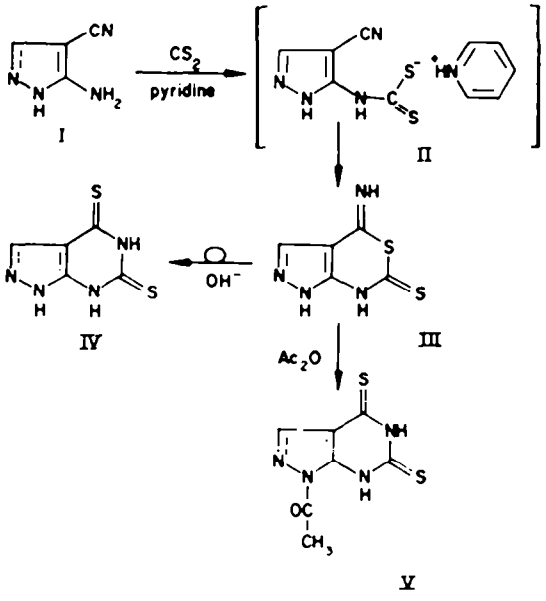
TABLE 1b

m.p., °C	Formula	Calcd.				Found			
		C	H	N	S	C	H	N	S
335–338 d.	$C_8H_4N_2S_2$	49·47	3·12	14·43	32·97	49·52	3·1	14·2	32·7
350–354 d.	$C_9H_6N_2S_2$	51·92	3·87	13·46	30·74	52·02	3·86	13·40	30·42
>360	$C_{13}H_{16}N_6S_2 \cdot H_2O$	52·87	5·80	14·23	21·68	52·59	5·52	13·99	21·53
350–352 d.	$C_9H_6N_4OS_2$	48·22	3·60	12·50	28·55	48·19	3·65	12·36	28·29
>360	$C_8H_5N_2S_2Br$	35·38	1·78	10·11	23·43	35·17	1·85	10·25	23·47
321–322 d.	$C_{11}H_7N_3S_2$	53·88	2·88	17·14	26·10	54·13	3·06	16·97	26·26
>360	$C_8H_4N_4S_2$	36·74	2·06	28·57	32·63	37·00	2·28	28·37	32·64
321–323 d.	$C_8H_6N_4S_2$	36·37	3·05	28·28	32·30	36·29	3·06	28·32	32·49
248–260 d.	$C_{11}H_6N_4S_2$	50·77	3·10	21·53	24·60	50·62	3·06	20·58	24·39
>360	$C_8H_4N_4S_2$	32·62	2·19	30·43	34·76	32·58	2·31	30·15	34·49

and upon the ability of the *o*-situated nitrile grouping to act as a site for nucleophilic addition. Thus, 2-amino-5-methoxybenzonitrile reacted rapidly with carbon disulfide in pyridine to give the corresponding quinazoline-2,4(1H,3H)-dithione in quantitative yield. On the other hand, 2-amino-5-nitrobenzonitrile was recovered unchanged even after prolonged heating with carbon disulfide in pyridine. Alicyclic *o*-aminonitriles such as 1-amino-2-cyano-1-cyclohexene also failed to react with carbon disulfide in pyridine; this failure can confidently be attributed to the lack of basicity of the amino group. The low yield obtained with 2-amino-3-cyanoquinoline is probably also due to its low basicity. 2-Phenyl-4-cyano-5-aminooxazole also failed to give a fused

pyrimidinedithione under the above conditions and in this instance it appears that the reaction failed at the final cyclization step involving nucleophilic addition of the dithiocarbamate anion to the nitrile grouping. A similar failure was observed with 3-methyl-4-cyano-5-aminoisoxazole. The failure of these latter compounds to undergo intramolecular nucleophilic addition to the nitrile grouping is parallelled by observations on the propensity for dimerization of *o*-aminonitriles.[11,12]

Fused pyrimidine-2,4-dithiones are thus readily accessible intermediates which should see considerable exploitation as synthetic intermediates in heterocyclic chemistry.



EXPERIMENTAL[13]

Quinazoline-2,4(1H,3H)-dithione

Method A: *from 2-aminobenzonitrile.* A solution of 3·0 g 2-aminobenzonitrile in a mixture of 10 ml anhydrous pyridine and 10 ml CS_2 was refluxed for 2 hr and allowed to stand overnight at room temp. The solution was filtered to remove traces of insoluble material and the filtrate diluted with 150 ml EtOH. The bright yellow precipitate of the dithione was filtered off, washed with ethanol, ether and dried, giving 4·82 g (97%) of product, m.p. 320–325° dec. Recrystallization from *n*-butanol gave long yellow needles, m.p. 335–338° dec.[14]

Method B: *from 2,4-dichloroquinazoline.* A mixture of 10·0 g 2,4-dichloroquinazoline[15] and 10·0 g thiourea in 150 ml abs EtOH was refluxed for 3 hr. The product separated on cooling and was collected and purified as described above, giving 7·5 g (77%) of product, m.p. 327–330° dec.

[11] E. C. Taylor, R. J. Knopf and A. L. Borrer, *J. Amer. Chem. Soc.* **82**, 3152 (1960).

[12] E. C. Taylor and A. L. Borror, *J. Org. Chem.* **26**, 4967 (1961).

[13] M.ps were determined on a Thomas-Hoover silicon bath apparatus and are uncorrected. Microanalyses were performed by the Robertson Microanalytical Laboratory, Florham Park, N.J., and by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Where appropriate, identity of compounds was confirmed by comparison of IR spectra determined by the normal Nujol mull technique on a Perkin-Elmer Model 237B Grating Infracord.

[14] This compound has previously been reported to melt with decomposition at 313° (Ref. 4), 308–309° (Ref. 9) and 260° [A. Kötz, *J. prakt. Chem.* [2] **47**, 303 (1893)].

[15] F. H. S. Curd, J. K. Landquist and F. L. Rose, *J. Chem. Soc.* 775 (1947).

6-Methylquinazoline-2,4(1H,3H)-dithione

A mixture of 1·0 g 2-amino-5-methylbenzonitrile, 10 ml of pyridine and 10 ml CS_2 was refluxed for 4 hr, allowed to stand at room temp for 30 hr and then the solvents were stripped off under red. press. The residual yellow solid was dissolved in dil. NaOH, the solution heated to boiling, treated with charcoal, filtered and the filtrate acidified with glacial AcOH. The bright yellow product was filtered off, washed with water, dried and crystallized from *n*-butanol, giving 1·54 g (98%) of bright yellow needles, m.p. 350–354° dec.

A 96% yield of product was obtained when the mixture, instead of being refluxed, was allowed to stand at room temp for 72 hr and then worked up as described above.

2-Amino-5-piperidinobenzonitrile

To a suspension of 2·80 g of 2-nitro-5-bromobenzonitrile[11] in 20 ml abs EtOH was added 2 ml piperidine and the mixture heated gently under reflux for 2 hr. The solution was allowed to cool slowly to room temp, during which time it set to a mass of fine yellow needles. The solid mass was diluted with 20 ml water, collected by suction filtration, and dried at 60° under red. press. to give 2·30 g (80%) of 2-nitro-5-piperidinobenzonitrile as fine yellow needles, m.p. 129–130°.

To a well-stirred suspension of 7·0 g of mossy Sn in 30 ml 18% HCl maintained at 45° in an oil bath, was added in several portions 2·20 g 2-nitro-5-piperidinobenzonitrile. The reduction of the nitro compd required about 45 min, after which the reaction mixture was filtered to remove unreacted Sn. The filtrate was rendered strongly alkaline by the addition of a large excess of 15% NaOH and then chilled in an ice bath. The pale yellow solid which separated was collected by filtration, washed with water and dried under red. press. at 60° to give 1·70 g (89%) of the crude amine, m.p. 85–95°. Crystallization from pet. ether (b.p. 60–70°) afforded greenish-yellow plates, m.p. 94–96°, which were strongly fluorescent in solution. (Found: C, 71·80; H, 7·55; N, 21·00. Calc. for $C_{12}H_{15}N_3$: C, 71·61; H, 7·51; N, 20·88.)

6-Piperidinoquinazoline-2,4(1H,3H)-dithione

It was prepared, isolated and purified exactly as described for the 6-methyl compound except that a 1 hr reflux was sufficient to achieve complete conversion of the aminonitrile. The product was purified by dissolving it in hot dil. NaOH, treating with charcoal, filtering and acidifying the filtrate with glacial AcOH.

6-Methoxyquinazoline-2,4(1H,3H)-dithione

A solution of 3·0 g freshly prepared 2-amino-5-methoxybenzonitrile in 30 ml of pyridine and 30 ml CS_2 was refluxed for 0·5 hr. Much of the product precipitated from the solution during this time and was obtained by filtration. The mother liquors were treated exactly as described for the 6-methyl compound to give a further crop of product. The total yield of yellow solid was 4·52 g (99%), which crystallized from *n*-butanol as fluffy yellow needles, m.p. 350–352° dec.

6-Bromoquinazoline-2,4(1H,3H)-dithione

A solution of 1·5 g 2-amino-5-bromobenzonitrile in 8·5 ml pyridine and 7·5 ml CS_2 was allowed to stand in a closed flask at room temp for 70 hr, after which time some yellow solid had separated. The mixture was poured into ice water, this solution made strongly basic with dil. NaOH, filtered, and the filtrate acidified with glacial AcOH. The resultant yellow solid was filtered off, washed with water, dried and recrystallized from aq. dimethylformamide giving 1·92 g (92%) of product as yellow needles, m.p. >360°.

2,4(1H,3H)-Pyrimido(4,5-b)quinolinedithione

A solution of 1·0 g of 2-amino-3-cyanoquinoline in 10 ml pyridine and 10 ml CS_2 was refluxed for 14 hr, the solvents removed by distillation under red. press. and the residue stirred with 50 ml dil. NaOH. Filtration removed 0·29 g unchanged starting material, and acidification of the filtrate with glacial AcOH gave 0·44 g (30%) of product as a yellow solid. Recrystallization from dimethylformamide gave yellow needles, m.p. 321–322° dec. This compound turned red when dried under red. press., and showed a series of color changes on being heated.

2,4(1H,3H)-*Pyrimido*(4,5-d)*pyrimidinedithione*

To a solution of 1·0 g 4-amino-5-cyanopyrimidine in 30 ml dimethylformamide were added 10 ml CS_2 and 0·5 g MeONa. The solution was refluxed for 10 hr, but at no time did the methoxide pass completely into solution. The solvents were removed by distillation under red. press., the residue dissolved in dil. NaOH, filtered, and the filtrate acidified with glacial AcOH. This gave 1·11 g (68%) of brown solid m.p. > 360°. This compound could be recrystallized from dimethylsulfoxide as light brown prisms which contained one molecule of dimethylsulfoxide of crystallization.

1-*Methyl*-4,6(5H,7H)-*pyrazolo*(3,4-d)*pyrimidinedithione*

It was prepared, isolated and purified exactly as described for 6-methylquinazoline-2,4(1H,3H)-dithione, except that a 52-hr reflux was necessary to effect complete reaction. The product crystallized from dimethylformamide as yellow needles.

1-*Phenyl*-4,6(5H,7H)-*pyrazolo*(3,4-d)*pyrimidinedithione*

Method A. The product was obtained exactly as described for 6-methylquinazoline-2,4(1H,3H)-dithione when the reaction mixture was refluxed for 115 hr. The product was purified by dissolving it in dil. NaOH and acidifying this solution with dil. HCl.

Method B. To a solution of 1·0 g 1-phenyl-4-amino-5-cyanopyrazole in 30 ml dimethylformamide were added 10 ml CS_2 and 0·5 g MeONa, and the mixture was refluxed for 45 hr. The solution was then evaporated under red. press. until the volume was approximately 2 ml, and 30 ml dil. NaOH was added. The resulting clear solution was filtered to remove traces of impurities and the filtrate acidified with dil. HCl to give 1·66 g (97%) of product.

4-*Imino*-6(7H)-*pyrazolo*(3,4-d)-m-*thiazinethione*

A mixture of 5·0 g 3-amino-4-cyanopyrazole, 50 ml pyridine and 50 ml CS_2 was heated under reflux for 1 hr, during which time a yellow solid precipitated from the solution. The solution was cooled, filtered and the filtrate washed with ether (3 × 150 ml.), giving 10·25 g (84%) of the pyridine salt of 4-imino-6(7H)-pyrazolo(3,4-d)-*m*-thiazinethione as a pale yellow solid, m.p. >360°. (Found: C, 45·88; H, 3·68; N, 26·89; S, 24·43. Calc. for $C_{16}H_6N_6S_2$: C, 45·63; H, 3·45; N, 26·61; S, 24·32.)

The above pyridine salt was ground in a mortar with 0·1N HCl, the resulting thiazine filtered, washed well with water and then with EtOH and dried. The pyridine salt could not be recrystallized at this stage without rearrangement occurring, but the following procedure was found to give the pure thiazine. The pyridine salt was carefully dissolved in conc. H_2SO_4, the solution allowed to stand at room temp for a few min and then stirred into ice water. The precipitated thiazine (93% yield) was filtered off, washed with water and EtOH and dried. The thiazine prepared by either of these procedures was a pale yellow solid, m.p. >360°, which showed no nitrile absorption in the IR spectrum, but did show a strong imine band at 3510 cm^{-1}. The UV spectrum (EtOH) showed λ_{max} at 237, 262, 311 and 382 mμ (ε = 11,160, 12,270, 11,340 and 2,950 respectively). (Found: C, 31·07; H, 2·61; N, 28·99; S, 33·18. Calc. for $C_6H_4N_4S_2 \cdot \frac{1}{2}H_2O$: C, 31·08; H, 2·61; N, 29·00; S, 33·18.)

4,6(5H,7H)-*Pyrazolo*(3,4-d)*pyrimidinedithione*

A solution of 5·0 g of the pyridine salt of the above-mentioned thiazine in 25 ml 1N NaOH was heated on the steam bath for 30 min. The cooled solution was acidified with glacial AcOH, the precipitate filtered, washed with water and dried. This gave 3·35 g (96%) of the dithione as a yellow solid, m.p. >360°, which was crystallized from aq. dimethylformamide.

The pyridine salt of the thiazine also rearranged to the dithione on being refluxed in dimethylformamide.

1-Acetyl-4,6(5H,7H)-*pyrazolo*(3,4-d)*pyrimidinedithione*

Method A. A solution of 1·0 g 4,6(5H,7H)-pyrazolo(3,4-d)pyrimidine in 25 ml acetic anhydride was refluxed for 2 hr. The mixture was filtered to remove a small amount of insoluble material, allowed to cool to room temp, the yellow needles filtered, washed with EtOH (2 × 5 ml) and ether (2 × 5 ml) and dried. This gave 0·65 g (49%) of the acetyl derivative which crystallized from acetic anhydride as yellow needles, m.p. 262°. (Found: C, 37·54; H, 2·67. Calc. for $C_7H_4N_4OS_2$: C, 37·17; H, 2·67.)

Method B. A solution of 1·0 g of the above thiazine was refluxed for 7 hr in 25 ml of acetic anhydride. Isolation of the product as described above gave 0·72 g (55%) of the acetyl derivative as yellow needles, m.p. 262°.