

CONCURRENT FORMATION OF TWO ISOMERIC DIPYRIDAZINO[4,5-b:4',5'-e]-  
[1,4]THIAZINES ATTENDED WITH OCCURRENCE OF A UNIQUE DIPYRIDAZINO-  
[4,5-b:4',5'-d]PYRROLE

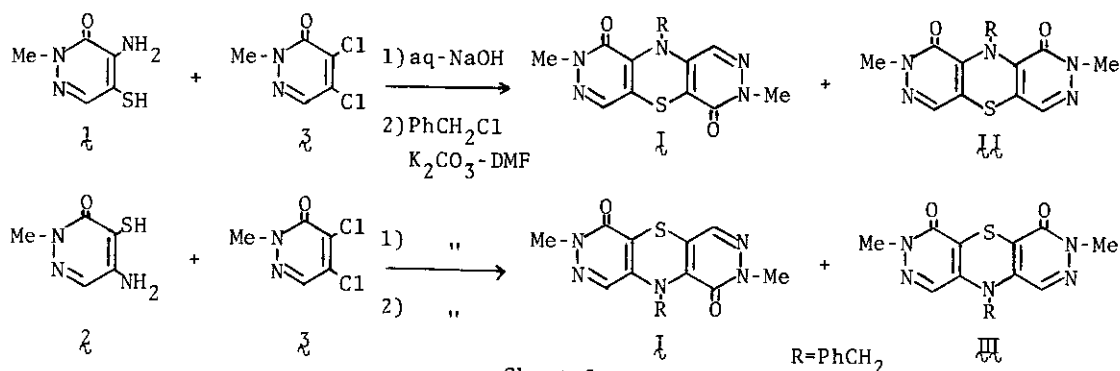
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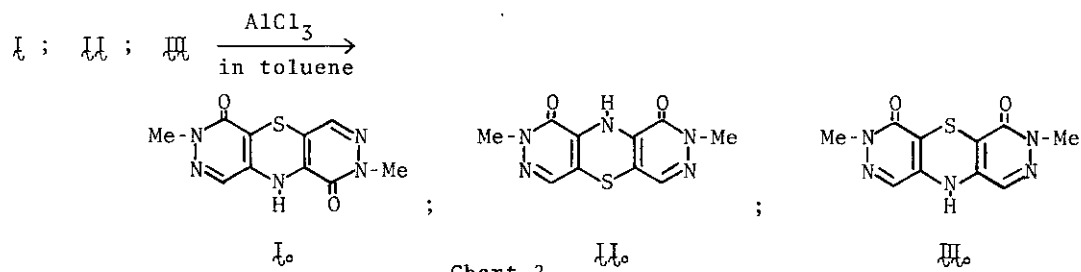
**Abstract** — Interaction of 4-amino-5-mercapto-2-methyl-3(2H)-pyridazinone (1) and 4,5-dichloro-2-methyl-3(2H)-pyridazinone (3) in a basic medium, followed by benzylation, yielded concurrently 10-benzyl-2,7-dimethyl-dipyridazino[4,5-b:4',5'-e][1,4]thiazine-1,6(2H,7H)-dione (1) and the 2,8-dimethyl-1,9-dione isomer (1). An analogous result leading to a mixture of products, (1) and the alternative 3,7-dimethyl-4,6-dione isomer (1), was also observed in the case of reaction between the 4,5-substituents of counterpart of 1, (2) and (3). Under somewhat more vigorous condition, the condensation reaction of either combination of the reactants added a consecutive formation of a unique 9-benzyl-2,6-dimethyl-dipyridazino[4,5-b:4',5'-d]pyrrole-1,5(2H,6H)-dione (1) to that of the mixtures of the respective dipyridazino[1,4]thiazine products (1+1 or 1+1).

Two modes of ring closure to the polyazaphenothiazines, including Ullmann type of direct cyclisation and indirect one through Smiles rearrangement, have been increasingly developed by several groups of investigators.<sup>1-5</sup> We would now like to report the concurrent formation of the two isomeric dipyridazino[4,5-b:4',5'-e][1,4]-thiazine derivatives (1+1 or 1+1) with subsequent occurrence of the unique dipyridazino[4,5-b:4',5'-d]pyrrole derivative (1), observed during the course of our study on the synthesis of pyridazine derivatives.<sup>6</sup>

Condensation of 4-amino-5-mercapto-2-methyl-3(2H)-pyridazinone (1) and 4,5-dichloro-2-methyl-3(2H)-pyridazinone (3) by refluxing in dilute sodium hydroxide solution for



30 min with subsequent benzylation by heating at 80°C for 3 h with benzyl chloride and K<sub>2</sub>CO<sub>3</sub> in DMF and chromatographic separation, afforded concurrently 10-benzyl-2,7-dimethyl-dipyridazino[4,5-b:4',5'-e][1,4]thiazine-1,6(2H,7H)-dione (I<sub>b</sub>) (41% yield) and the 2,8-dimethyl-1,9-dione isomer (II<sub>b</sub>) (22% yield). An analogous result to yield simultaneously (I<sub>b</sub>) (11% yield) and the alternative isomer, 3,7-dimethyl-4,6-dione derivatives (III<sub>b</sub>) (42% yield) was found in the similar reaction between 5-amino-4-mercapto-2-methyl-3(2H)-pyridazinone (2) and (3) (Chart 1). The subsequent benzylation in these reaction was performed for the separation of the condensation products; 2,7-dimethyl-10H-dipyridazino[4,5-b:4',5'-e][1,4]thiazine-1,6(2H,7H)-dione (I<sub>o</sub>), the 2,8-dimethyl-1,9-dione isomer (II<sub>o</sub>) and 3,7-dimethyl-4,6-dione isomer (III<sub>o</sub>). Any of these products was feasibly derived from (I<sub>b</sub>), (II<sub>b</sub>) and (III<sub>b</sub>) respectively, by debenylation with AlCl<sub>3</sub> in toluene at 60°C for 5 h, in good yield (Chart 2).



Under somewhat more vigorous conditions, e.g. prolonged reaction time (over 3 h) at elevated temperature (exceeded ca. 110°C), the condensation reaction of either combination of the reactants (1+2 or 2+3) added a consecutive formation of a unique 9-benzyl-2,6-dimethyl-dipyridazino[4,5-b:4',5'-d]pyrrole-1,5(2H,6H)-dione (IV<sub>b</sub>) (5-7 % yield) without contamination of any other isomer, to the production of mixtures of the respective dipyridazino[4,5-b:4',5'-e][1,4]thiazine derivatives (I+II or I+III). The formation of the compound (IV<sub>b</sub>) might be reasonably ascribed to the sulphur

extrusion from 2,7-dimethyl-10H-dipyridazino[4,5-b:4',5'-e][1,4]thiazine-1,6(2H, 7H)-dione ( $I_o$ ), but not from the isomer ( $II_o$ ) or ( $III_o$ ), and was indeed ascertained by desulphurisation of ( $I_o$ ) in a basic condition, followed by benzylation. The desulphurisation proceeded by heating at 140°C in DMF for 3 h in the presence of potassium carbonate to give the ring contraction product ( $IV_o$ ) in 71% yield, although it scarcely went forward in the absence of the base. The structure of ( $IV$ ) was further established by an unambiguous synthesis by photo-cyclisation of the dipyridazinyl-benzylamine ( $V$ ),<sup>7</sup> derived from ( $I$ ) by desulphurisation with Raney nickel in 74% yield. Irradiation was carried out in acetone with a 100 W high-pressure mercury lamp at room temperature for 1 h to afford ( $IV$ ) in 86% yield (Chart 3).

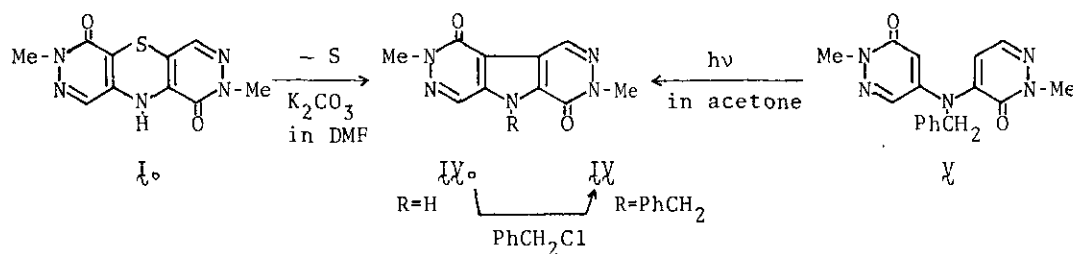


Table Melting Points and  $^1\text{H-NMR}$  Data for Compounds ( $I$ - $IV$  and  $I_o$ - $IV_o$ )

Compd. <sup>a)</sup>	mp(°C)	$^1\text{H-NMR}^b)$ ( $\delta$ in ppm)			
		N-CH <sub>3</sub>	N-CH <sub>2</sub> Ph	ring proton	C <sub>6</sub> H <sub>5</sub>
$I$	172-173	3.76(3H, s) 3.70(3H, s)	5.27(2H, s)	7.30(1H, s) 7.41(1H, s)	7.30-7.60(5H, m)
$II$	202-203	3.27(3H×2, s)	5.63(2H, s)	7.30(1H×2, s)	7.20-7.62(5H, m)
$III$	274-276	3.62(3H×2, s)	4.68(2H, s)	6.96(1H×2, s)	7.30-7.50(5H, m)
$IV$	215-216	3.89(3H, s) 3.94(3H, s)	6.09(2H, s)	8.15(1H, s) 8.79(1H, s)	7.31(5H, s)
$I_o$	>300	3.78(3H×2, s)		7.35(1H, s) 7.55(1H, s)	
$II_o$	>300	3.35(3H×2, s)		7.00(1H×2, s)	
$III_o$	>300	3.79(3H×2, s)		7.58(1H×2, s)	
$IV_o$	>300	3.70(3H×2, s)		8.43(1H, s) 8.75(1H, s)	

a) All compounds gave satisfactory microanalytical data (C, H and N).

b) Solvent:  $I$ - $IV$  (in CDCl<sub>3</sub>),  $I_o$ - $IV_o$  (in CF<sub>3</sub>CO<sub>2</sub>H)

To our knowledge, there has not yet been found such a desulphurisation reaction of the 1,4-thiazines to the pyrrole derivatives in a basic condition, but one report concerned with the thermal sulphur extrusion from the pyrimido[4,5-b][1,4]thiazines to the corresponding pyrrolo[3,2-d]pyrimidines.<sup>8</sup> Examination of the crucial reaction conditions for the sulphur extrusion ( $I_o \rightarrow N_o$ ) and the exclusive synthesis of the individual dipyridazino[4,5-b:4',5'-e][1,4]thiazine derivatives ( $I$ ,  $II$  and  $III$ ) are now in progress and will be reported at a later date.

#### REFERENCES AND NOTES

1. J. Druey, Angew. Chem., 1958, 70, 5.
2. a) F. Yoneda, T. Ohtaka and Y. Nitta, Chem. Pharm. Bull., 1963, 11, 954;  
b) Idem, ibid., 1965, 13, 580; c) Idem, ibid., 1966, 14, 698; d) F. Yoneda and T. Ohtaka, Yakugaku Zasshi, 1968, 88, 1638.
3. a) Y. Maki, M. Suzuki, O. Toyota and M. Takaya, Chem. Pharm. Bull., 1973, 21, 241; b) Y. Maki and M. Suzuki, Yakugaku Zasshi, 1973, 93, 171.
4. D. S. Wise, Jr., and R. N. Castle, J. Heterocyclic Chem., 1974, 11, 1001.
5. F. Duro, F. Vittorio, F. Pappalardo and G. Ronsisvalle, Farm. Ed. Sci., 1977, 32, 106.
6. a) K. Kaji, M. Kuzuya and R. N. Castle, Chem. Pharm. Bull., 1970, 18, 174; b) K. Kaji and M. Kuzuya, ibid., 1970, 18, 970; c) M. Kuzuya and K. Kaji, ibid., 1970, 18, 2420.
7.  $\bar{Y}$ : colourless needles; mp 204-206°C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  : 3.37, 3.87 (each 3H, s) 5.00 (2H, s), 6.19, 7.43 (each 1H, d,  $J=4\text{Hz}$ ), 7.08, 7.78 (each 1H, d,  $J=6\text{Hz}$ ), 7.34 (5H, s); MS  $m/e$  323 ( $M^+$ ).
8. a) H. Fenner and H. Motschall, Tetrahedron Lett., 1971, 4185; b) H. Fenner and A. Motschall, Arch. Pharm., 1978, 311, 153.

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