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 (I) and the 2,8-dimethyl-1,9-dione isomer (II). An analogous result leading to a mixture of products, (I) and the alternative 3,7-dimethyl-4,6-dione isomer (III), 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 (IV) to that of the mixtures of the respective dipyridazino[1,4]thiazine products (I+II or I+III).

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.[1-5] We would now like to report the concurrent formation of the two isomeric dipyridazino[4,5-b:4',5'-e][1,4]-thiazine derivatives (I+II or I+III) with subsequent occurrence of the unique dipyridazino[4,5-b:4',5'-d]pyrrole derivative (IV), observed during the course of our study on the synthesis of pyridazine derivatives.[6]

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

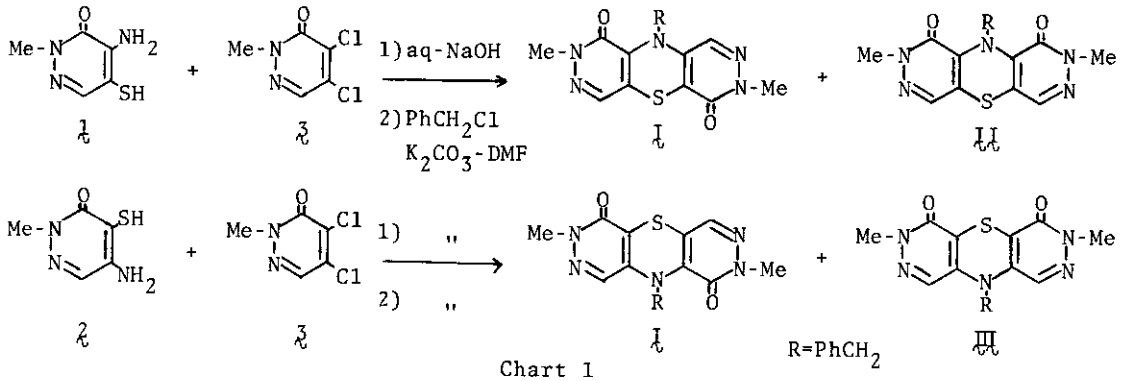

Chart 1

30 min with subsequent benzylation by heating at 80°C for 3 h with benzyl chloride and K_2CO_3 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) (41% yield) and the 2,8-dimethyl-1,9-dione isomer (II) (22% yield). An analogous result to yield simultaneously (I) (11% yield) and the alternative isomer, 3,7-dimethyl-4,6-dione derivatives (III) (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_o), the 2,8-dimethyl-1,9-dione isomer (II_o) and 3,7-dimethyl-4,6-dione isomer (III_o). Any of these products was feasibly derived from (I), (II) and (III) respectively, by debenzylation with $AlCl_3$ in toluene at 60°C for 5 h, in good yield (Chart 2).

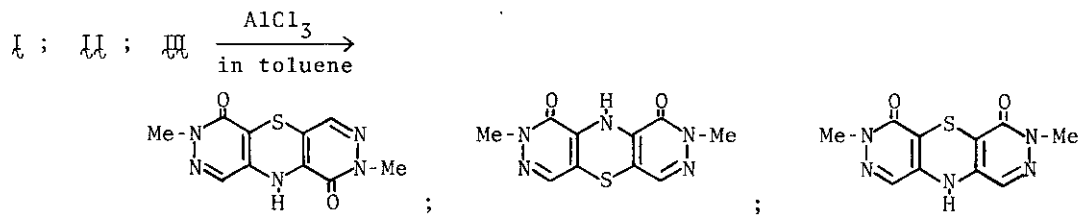

Chart 2

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+3 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) (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) 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),[7] 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).

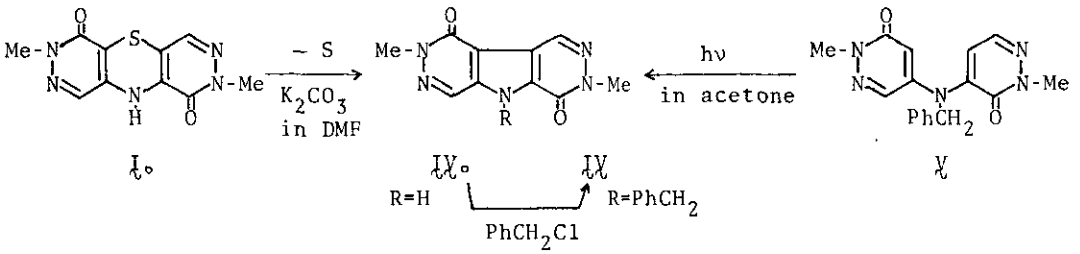

Chart 3

Table Melting Points and ^{1}H-NMR Data for Compounds (I-IV and I$_o$-IV$_o$)

Compd.[a]	mp(°C)	^{1}H-NMR[b] (δ in ppm)			
		N-CH_3	N-CH_2Ph	ring proton	C_6H_5
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 $CDCl_3$), I$_o$-IV$_o$ (in CF_3CO_2H)

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.[8] Examination of the crucial reaction conditions for the sulphur extrusion (Ⅰ$_o$→Ⅳ$_o$) 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.

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7. Ⅴ : colourless needles; mp 204-206°C; ^{1}H-NMR ($CDCl_3$) δ : 3.37, 3.87 (each 3H, s) 5.00 (2H, s), 6.19, 7.43 (each 1H, d, J=4Hz), 7.08, 7.78(each 1H, d, J=6Hz), 7.34 (5H, s); MS m/e 323 (M^+).
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