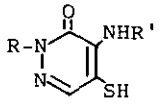
REGIOCONTROLLED CYCLISATION TO THE ISOMERIC DIPYRIDAZINO[4,5-b:4',5'-e][1,4]THIAZINES —— COMPETENCE AND PERFORMANCE OF BENZYLAMINO AND THIOETHER FUNCTIONS ON THE 3(2H)-PYRIDAZINONES AS REGIOCONTROLLING ELEMENTS

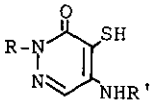
Kenji Kaji, Hiromu Nagashima and Hirohisa Oda *
Gifu College of Pharmacy, 5-6-1, Mitahora-higashi, Gifu 502, Japan

Abstract —— The 5,5'-thioethers (5a-c) perform a regiocontrolled cyclisation affording either the 10H-dipyridazino[1,4]thiazine-1,9-diones (1'a-c) (by Ullmann mode) or the 10-benzyl derivatives of 1,6-dione isomers (2a-c) (via Smiles rearrangement), only depending on the acidity of media employed. The 4,5'-thioethers (6a-c) exhibit also the regiospecific control to give exclusively the 10H-dipyridazino[1,4]thiazine-1,6-diones (2'a-c) in acidic conditions or the 10-benzyl-4,6-dione isomers (3a-c) in basic conditions, respectively. Some principal features of the regiocontrolled cyclisation are discussed.

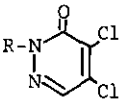
In the preceding paper[1] we have reported the synthesis of three types of dipyridazino[4,5-b:4',5'-e][1,4]thiazine derivatives (1a, 2a and 3a) by the condensation between the amino-mercaptopyridazinone (7'a or 8'a) and the dichloropyridazinone (9a) followed by benzylation. The following paper[2] describing the conversion of 2,7-disubstituted 10H-dipyridazino[4,5-b:4',5'-e][1,4]thiazine derivatives (2'a-c) into the corresponding 2,6-disubstituted 9H-dipyridazino[4,5-b:4',5'-d]pyrrole-1,5(2H,6H)-diones (4'a-c) by base-induced extrusion of sulphur, prompted us to exploit a regiocontrolled synthesis of all of the individual members belonging to the dipyridazino[4,5-b:4',5'-e][1,4]thiazines (1a-c, 2a-c and 3a-c).



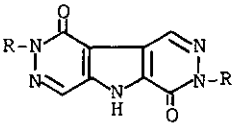
7a-c (R'=$PhCH_2$)
7'a (R'=H)



8a-c (R'=$PhCH_2$)
8'a (R'=H)



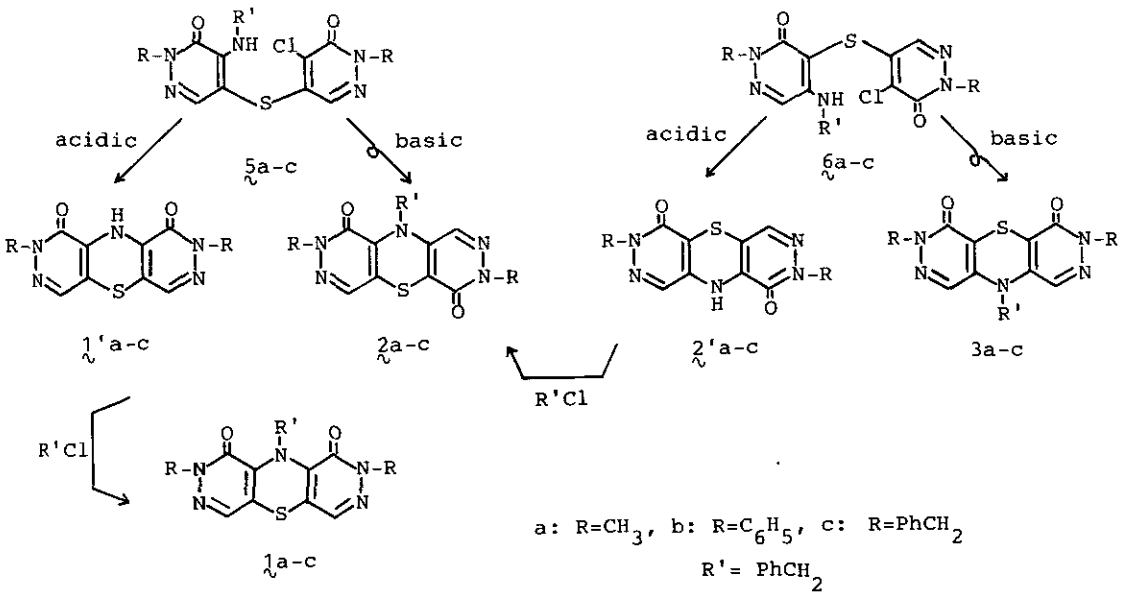
9a-c



4'a-c
a: R=CH_3, b: R=C_6H_5, c: R=$PhCH_2$

The present work deals with the exclusive synthesis of the individual dipyridazino-[4,5-b:4',5'-e][1,4]thiazine derivatives (1'a-c or 2a-c; 2'a-c or 3a-c) by regio-controlled cyclisations of the thioethers, 5-(2-substituted 4-benzylamino-2,3-dihydro-3-oxo-pyridazinyl)-5'-(2'-substituted 4'-chloro-2',3'-dihydro-3'-oxo-pyridazinyl)sulphides (5a-c) and the isomeric 4,5'-sulphides (6a-c), depending on the acidity of medium employed. The thioethers, 4-(2-substituted 5-benzylamino-2,3-dihydro-3-oxo-pyridazinyl)-5'-(2'-substituted 4'-chloro-2',3'-dihydro-3'-oxo-pyridazinyl)sulphides, 6a-c (a: mp 235-236°C, 63%; b: mp 244-246°C, 69%; c: mp 239-241°C, 71%) were easily prepared by the interaction of the 5-benzylamino-4-mercaptopyridazinones (8a-c) and the corresponding 4,5-dichloropyridazinones (9a-c) similarly as the formation of the thioethers (5a-c).[2]

Much attention has been long paid to the regiocontrolled synthesis of polyaza-phenothiazines, including pyridazine or pyridazinone rings,[3-6] however, any paper concerned with examination of benzylamino or thioether functions as regiocontrol-ling elements for the cyclisation, has not yet been found. Heating the thioethers (5a-c) with fortified acetic acid (with concd. HCl) under reflux for 4 h caused an Ullmann mode of cyclisation, attended with debenzylation, to afford 2,8-disubsti-tuted 10H-dipyridazino[4,5-b:4',5'-e][1,4]thiazine-1,9(2H,8H)-diones (1'a-c) in high yield (a: 92%, b: 90%, c: 93%). Contrary to this, the cyclisation of the thioethers (5a-c) in a sodium hydroxide solution, had proceeded via Smiles rear-rangement, to give the corresponding 2,7-disubstituted 10-benzyl-10H-dipyridazino-



[4,5-b:4',5'-e][1,4]thiazine-1,6(2H,7H)-diones (2a-c: a, 79%; b, 63%; c, 81%).[2] Similarly, another thioethers (6a-c) exhibited the alternative competence for the regiocontrolled cyclisation, performing the formation of 2,7-disubstituted 10H-pyridazino[4,5-b:4',5'-e][1,4]thiazine-1,6(2H,7H)-diones (2'a-c: a, 63%; b, 85%; c, 79%) in acidic conditions, and of 3,7-disubstituted 10-benzyl-10H-dipyridazino[4,5-b:4',5'-e][1,4]thiazine-4,6(3H,7H)-diones (3a-c: a, 76%; b, 64%; c, 81%) in bacic conditions. Assigned structures for the dipyridazino[1,4]thiazines, 1'a-c, 2'a-c, 2a-c and 3a-c, were supported by their spectral and microanalytical data, and also confirmed by the alkylation of 1'a-c and 2'a-c to the corresponding 10-benzyl derivatives 1a-c and 2a-c, respectively.

The principal features of the regiocontrolled cyclisation are assumed as follows:

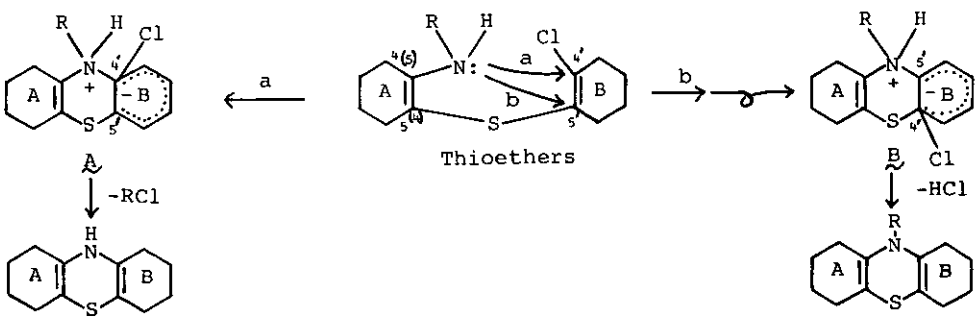
(1) Any of the thioethers (5a-c, 6a-c) bears a benzylamino function as an internal nucleophile which might attack exclusively either $C^{4'}$ atom (in an acidic medium) or $C^{5'}$ atom (in a basic medium) on the B ring.

(2) The thioether linkage, C^{5}–S–$C^{5'}$ or C^{4}–S–$C^{5'}$, joining together A and B rings, is also essential to the regiocontrolled cyclisation and exerts first a competence of a nucleofuge and then that of a nucleophile (Smiles rearrangement).

(3) On the transition state (A), leading to the product by Ullmann mode of cyclisation, elimination of the benzyl function from the quaternary nitrogen might be more favourable than deprotonation, due to the release from the steric crowding of the neighbourhood.

(4) On the transition state (B), leading to the product *via* Smiles rearrangement, the deprotonation might be more feasible than the elimination of the bulky group.

(5) The oxo and chloro functions, pertinently built in the B ring, might cooperate essentially the competence and performance of the benzylamino and thioether functions as the regiocontrolling elements.



Physical Properties*)

1'a) mp>300°C. IR ν_{max}^{KBr} cm^{-1}: 1640(CO), 3310(NH). ^{1}H-NMR(CF_3CO_2H) δ: 3.35(6H, s, N-CH_3×2), 7.00(2H, s, 4-H and 6-H).

1'b) mp>300°C. IR ν_{max}^{KBr} cm^{-1}: 1640(CO), 3340(NH). ^{1}H-NMR(CF_3CO_2H) δ: 7.14(10H, s, C_6H_5×2), 7.28(2H, s, 4-H and 6-H).

1'c) mp>300°C. IR ν_{max}^{KBr} cm^{-1}: 1645(CO), 3360(NH). ^{1}H-NMR(CF_3CO_2H) δ: 5.07(4H, s, N-CH_2×2), 7.05(10H, s, C_6H_5×2), 7.23(2H, s, 4-H and 6-H).

1a) mp 193-194°C. IR ν_{max}^{KBr} cm^{-1}: 1635(CO). UV λ_{max}^{EtOH} nm(log ε): 236(4.03), 272 (4.15), 315(4.10). ^{1}H-NMR($CDCl_3$) δ: 3.72(6H, s, N-CH_3×2), 5.63(2H, s, N-CH_2), 7.30(2H, s, 4-H and 6-H), 7.20-7.62(5H, m, C_6H_5).

1b) mp 224-225°C. IR ν_{max}^{KBr} cm^{-1}: 1640(CO). UV λ_{max}^{EtOH} nm(log ε): 228(4.13), 267 (4.08), 312(4.03). ^{1}H-NMR($CDCl_3$) δ: 5.62(2H, s, N-CH_2), 7.48(15H, s, C_6H_5×3), 7.58(2H, s, 4-H and 6-H).

1c) mp 178-179°C. IR ν_{max}^{KBr} cm^{-1}: 1640(CO). UV λ_{max}^{EtOH} nm(log ε): 226(4.18), 268 (4.17), 310(4.08). ^{1}H-NMR($CDCl_3$) δ: 5.23(4H, s, N-CH_2×2), 5.57(2H, s, N-CH_2), 7.31(5H, s, C_6H_5), 7.33(10H, s, C_6H_5×2), 7.40(2H, s, 4-H and 6-H).

3a) mp 275-276°C. IR ν_{max}^{KBr} cm^{-1}: 1640(CO). UV λ_{max}^{EtOH} nm(log ε): 234(4.42), 276 (4.47), 316(4.16). ^{1}H-NMR($CDCl_3$) δ: 3.62(6H, s, N-CH_3×2), 4.68(2H, s, N-CH_2), 6.69(2H, s, 1-H and 9-H), 7.30-7.50(5H, m, C_6H_5).

3b) mp>300°C. IR ν_{max}^{KBr} cm^{-1}: 1650(CO). UV λ_{max}^{EtOH} nm(log ε): 232(4.43), 271(4.49), 312(4.20). ^{1}H-NMR(DMSO-$\underline{d}_6$) δ: 4.83(2H, s, N-CH_2), 7.26-7.60(17H, m, C_6H_5×3, 1-H and 9-H).

3c) mp 272-274°C. IR ν_{max}^{KBr} cm^{-1}: 1640(CO). UV λ_{max}^{EtOH} nm(log ε): 233(4.48), 273 (4.49), 315(4.21). ^{1}H-NMR(DMSO-$\underline{d}_6$) δ: 5.20(2H, s, N-CH_2), 5.29(4H, s, N-CH_2×2), 7.15-7.51(17H, m, C_6H_5×3, 1-H and 9-H).

6a) mp 236°C. IR ν_{max}^{KBr} cm^{-1}: 1620, 1650(CO), 3290(NH). ^{1}H-NMR($CDCl_3$) δ: 3.61, 3.72 (each 3H, s, N-CH_3), 4,59(2H, d, $\underline{J}$=7Hz, NH-C$\underline{H}_2$), 7.30(5H, s, C_6H_5), 7.18, 7.68(each 1H, s, 6-H, 6'-H).

6b) mp 244-246°C. IR ν_{max}^{KBr} cm^{-1}: 1620, 1660(CO), 3310(NH). ^{1}H-NMR(DMSO-$\underline{d}_6$) δ: 4.63 (2H, d, $\underline{J}$=7Hz, NH-C$\underline{H}_2$), 7.21-7.50(10H, m, C_6H_5×2), 7.27(5H, s, C_6H_5), 7.35, 7.80(each 1H, s, 6-H, 6'-H).

6c) mp 239-241°C. IR ν_{max}^{KBr} cm^{-1}: 1620,1640(CO), 3280(NH). ^{1}H-NMR($CDCl_3$) δ: 4.62 (2H, d, $\underline{J}$=7Hz, NH-C$\underline{H}_2$), 5,27, 5.30(each 2H, s, N-CH_2), 7.20-7.49(15H, m, C_6H_5 ×3), 7.09, 7.63(each 1H, s, 6-H, 6'-H).

*) 1'a-c, 1a-c and 3a-c: see ref. 2.
All compounds gave satisfactory elemental analyses (C, H and N).

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