SYNTHESIS OF PYRAZOLO[3,4-d]PYRIDAZINE DERIVATIVES —— TWO COMPARABLE APPROACHES, RING CONTRACTION THROUGH EXTRUSION OF SULPHUR AND PHOTOCHEMICAL CYCLISATION

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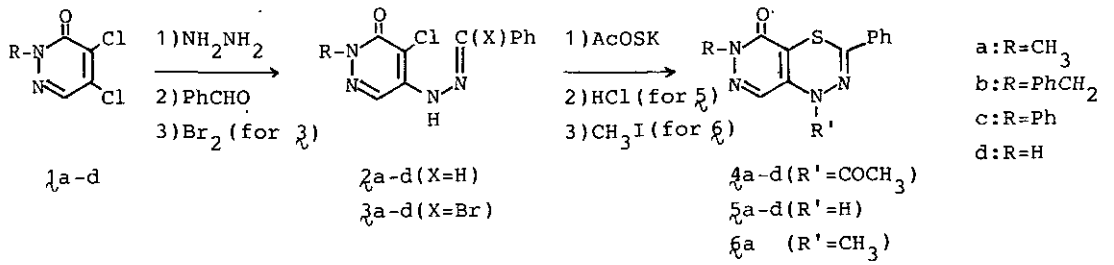
Abstract —— Ring contraction of 7-substituted 2-phenyl-4H-pyridazino[4,5-e][1,3,4]thiadiazin-8(7H)-ones (5a-d) to 5-substituted 3-phenyl-1H-pyrazolo[3,4-d]pyridazin-4(5H)-ones (7a-d), through base-induced extrusion of sulphur, is described. Similar reactions proceed, not only on the 4-acetyl derivatives (4a-d) in basic media, but on 5a and the 4-methyl derivative (6a) thermally. Probable mechanisms of these reactions are discussed. A comparable approach to the ring contraction, photochemical cyclisation of 2-substituted 5-(1-alkyl-2-benzylidenehydrazino)-4-chloro-3(2H)-pyridazinones (9a-e) to the corresponding 1-alkylpyrazolo[3,4-d]-pyridazinone derivatives (8a-e) is also performed.

Previous papers from our laboratory have dealt with the conversion of 2,7-disubstituted 10H-dipyridazino[4,5-b:4',5'-e][1,4]thiazine-1,6(2H,7H)-diones into 2,6-disubstituted 9H-dipyridazino[4,5-b:4',5'-d]pyrrole-1,5(2H,6H)-diones, by ring contraction through base-induced extrusion of sulphur.[1] Our observation and the attractive ring contraction in the anionic 8π-ring systems[2] have encouraged us to extend such analogous types of reactions to the synthesis of some novel condensed pyridazine rings. We wish to call further attention here to the synthesis of the pyrazolo[3,4-d]pyridazine derivatives performed by two comparable approaches, ring contraction of pyridazino[4,5-e][1,3,4]thiadiazines and photochemical cyclisation of 5-(1-alkyl-2-benzylidenehydrazino)-4-chloro-3(2H)-pyridazinones. 2-Substituted 5-[(α-bromo-benzylidene)hydrazino]-4-chloro-3(2H)-pyridazinones (3a-d), as promising intermediates to formation of the pyridazino[4,5-e][1,3,4]-

thiadiazine derivatives (4a-d, 5a-d and 6a), were readily derived from the corresponding 2-substituted 4,5-dichloro-3(2H)-pyridazinones (1a-d)[3] by successive hydrazination, hydrazone formation and bromination. Compound 3a was allowed to react with potassium thioacetate[4] in boiling acetonitrile for 4 h to give 4-acetyl-7-methyl-2-phenyl-4H-pyridazino[4,5-e][1,3,4]thiadiazin-8(7H)-one (4a) in 35% yield, as yellow needles (CH_3CN). Similar treatment of 3b-d afforded the homologous N[4]-acetyl derivatives (4b-d) (b: 38%, c: 39%, d: 82%). Removal of the acetyl group from 4a-d was effected by acidic treatment (HCl-EtOH) to yield 7-substituted 2-



1a-d

2a-d(X=H)
3a-d(X=Br)

4a-d(R'=$COCH_3$)
5a-d(R'=H)
6a (R'=CH_3)

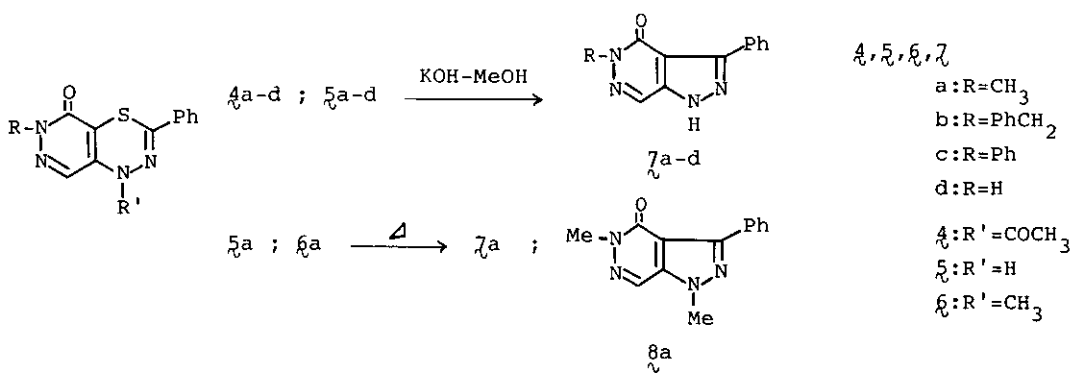
Table I. Pyridazino[4,5-e][1,3,4]thiadiazines

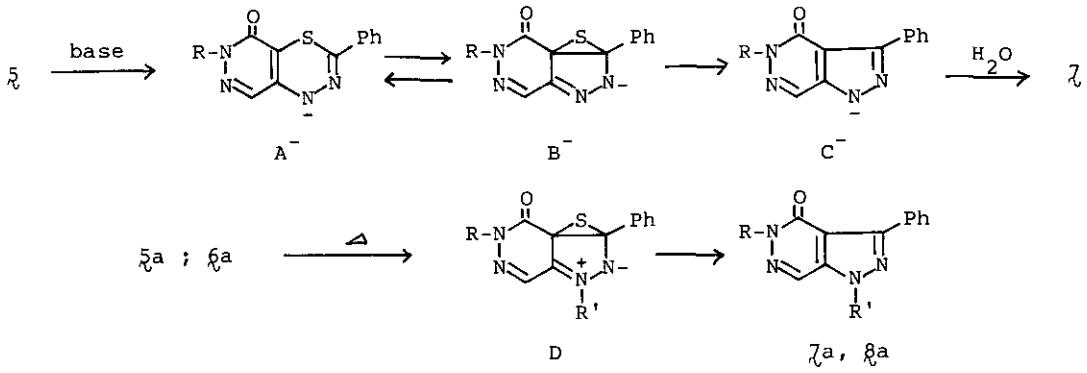
Compd.	R	R'	mp(°C)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR (δ in ppm)*)
4a	Me	COMe	213-215	1640 (CO) 1690 (CO)	2.47(3H,s,$COCH_3$), 3.74(3H,s,NCH_3), 7.33-7.95(5H,m,C_6H_5), 8.27(1H,s,C^5-H)
4b	$PhCH_2$	COMe	151-152	1640 (CO) 1695 (CO)	2.64(3H,s,$COCH_3$), 5.23(2H,s,NCH_2), 7.15-7.93(10H,m,C_6H_5×2), 8.28(1H,s, C^5-H)
4c	Ph	COMe	178-180	1645 (CO) 1700 (CO)	2.50(3H,s,$COCH_3$), 7.25-7.85(10H,m, C_6H_5×2),8.39(1H,s,C^5-H)
4d	H	COMe	248-251	1650 (CO) 1690 (CO) 3160 (NH)	2.50(3H,s,COMe), 7.51-8.08(5H,m,C_6H_5) 8.31(1H,s,C^5-H)
5a	Me	H	255-256	1620 (CO) 3300 (NH)	3.54(3H,s,NCH_3), 7.32-7.78(5H,m,C_6H_5) 7.36(1H,s,C^5-H), 10.20(1H,s,NH)
5b	$PhCH_2$	H	219-220	1625 (CO) 3260 (NH)	5.14(2H,s,NCH_2), 7.11-7.80(10H,m,C_6H_5× 2), 7.47(1H,s,C^5-H), 10.32(1H,s,NH)
5c	Ph	H	235-236	1605 (CO) 3270 (NH)	7.30-7.85(11H,m,C_6H_5×2 and C^5-H), 10.40 (1H,s,NH)
5d	H	H	>300	1610 (CO) 3220 (NH)	7.41-7.92(5H,m,C_6H_5), 8.12(1H,s,C^5-H), 10.18(1H,s,NH)
6a	Me	Me	96-99	1645 (CO)	3.42(3H,s,NCH_3), 3.75(3H,s,NCH_3), 7.25-7.50, 7.85-7.98(6H,m,C_6H_5 and C^5-H)

*) Solvent : 4a, 4b, 4c, 6a (in $CDCl_3$) ; 4d, 5a, 5b, 5c, 5d (in DMSO-d_6).

phenyl-4H-pyridazino[4,5-e][1,3,4]thiadiazin-8(7H)-ones (5a-d) (a: 97%, b: 85%, c: 94%, d: 86%). A methylation of 5a to 6a with methyl iodide was carried out under ice-cooling (77%). Assigned structures were supported by their spectral and elemental analysis data.[5]

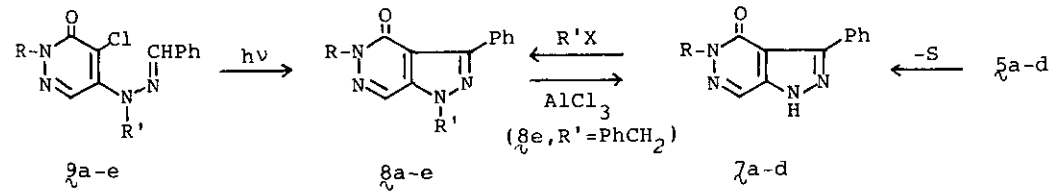
Conversion of the pyridazino[4,5-e][1,3,4]thiadiazine derivatives (5a-d) into the corresponding 5-substituted 3-phenyl-1H-pyrazolo[3,4-d]pyridazin-4(5H)-ones (7a-d), by ring contraction through extrusion of sulphur, was effectively performed either in basic media or thermally. The desulphurisation of the compounds (5a-d) in methanolic potassium hydroxide solution proceeded so rapidly as it reached almost to completeness within 1 h at room temperature or 10 min at refluxing. On acidification, high yields of the products (7a-d) (a: 88%, b: 83%, c: 83%, d: 81%, on refluxing condition) were obtained. N^4-Acetyl derivatives (4a-d) afforded the same products (7a-d) (a: 65%, b: 75%, c: 80%, d: 90%) by heating under reflux for 1 h in the similar basic medium. The ring contraction also took place thermally, e.g., heating 5a in boiling DMF for 4 h gave the product (7a) in 85% yield, while N^4-methyl compound (6a) also afforded the N^1-methyl product (8a) in 89% yield by refluxing for 2 h. These thermal desulphurisations seem to show that the conversion (5a→7a) proceeds without any deprotonation from the substrate, although the reaction is slower than that of the latter (6a→8a). Studies on the synthesis and reaction of 1,3,4-thiadiazine and its benzo-analogue derivatives have been recently increased[4,6] and the thermal or acid-catalysed ring contraction of the 1,3,4-thiadiazines into the pyrazoles has been also reported. However, to our knowledge, there has not yet been found any paper concerned with base-induced ring contraction, except some condensed 1,3,4-thiadiazines.[2] A probable pathway for the ring contraction of 5a-d to 7a-d, through base-induced extrusion of sulphur, may be depicted as a process in which an initially generated anion (A^-) is converted, via a reactive





intermediate containing a thiirane ring (B^-), into an anion (C^-).[1] Analogously another transient species, zwitter ionic ones, such as D's (R=Me, R'=H or Me) in the thermal condition, might be reasonably envisaged.

Assigned structures for the pyrazolo[3,4-d]pyridazines (7a-d, 8a) were supported by their spectral and elemental analysis data[5] and also confirmed by the independent synthesis using photochemical cyclisation. Recently photochemical procedure has been increasingly utilised for the synthesis of some condensed heterocycles.[8] The cyclisation of 2-substituted 5-(1-alkyl-2-benzylidenehydrazino)-4-chloro-3(2H)-pyridazinones (9a-e) into the pyrazolo[3,4-d]pyridazines (8a-e) was performed as follows: A solution of 9a (1 mmol) in benzene (200 ml) was irradiated with a 100 W high-pressure mercury lamp surrounded by a water-cooled Pyrex filter at room temperature for 4 h to afford 8a in 86% yield, as colourless needles (EtOH), which was identical in all respects (mp, TLC and spectral data) with the product derived from 7a by methylation. Of other benzylidenehydrazino derivatives (9b-e), the photochemical reaction proceeded smoothly to give the corresponding 1,5-disubstituted 3-phenyl-1H-pyrazolo[3,4-d]pyridazin-4(5H)-ones (8b-e) in good yield (b: 88%, c: 76%, e: 85%).[9] Furthermore, facile dealkylation of the N^1-benzyl derivative (8e, R=Me, R'=$PhCH_2$) on exposure to a Lewis acid ($AlCl_3$ in toluene)[3] leads to the N^1-H derivative (7a, R=Me, R'=H, 90%), which is identical with that obtained from 5a.



The majority of the current synthetic approaches to obtain pyrazolo[3,4-d]-pyridazines utilises pyrazoles or pyrazolones with appropriate o-functional groups, capable of forming the pyridazine ring, as starting material.[10-13] Thus, the two procedures herin presented, utilising the analogous 2-substituted 5-benzylidene-hydrazino-4-chloro-3(2H)-pyridazinones (3a-d, 5a-e), can be referred to as novel and comparable route for the synthesis of the pyrazolo[3,4-d]pyridazinones (7a-d, 8a-e).

Table II. Pyrazolo[3,4-d]pyridazines

Compd.	R	R'	mp(°C)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR (δ in ppm)**)
7a	Me	H	258	1630 (CO) 3170 (NH)	3.68(3H,s,NCH_3), 7.30-7.50, 8.20-8.40(5H m,C_6H_5), 8.30(1H,s,C^7-H)
7b	$PhCH_2$	H	199-200	1630 (CO) 3280 (NH)	5.27(2H,s,NCH_2), 7.24(5H,s,C_6H_5), 7.32-7.48, 8.17-8.37(5H,m,C_6H_5), 8.38(1H,s,C^7-H)
7c	Ph	H	276-278	1625 (CO) 3195 (NH)	7.25-7.53, 8.10-8.30(10H,m,C_6H_5x2), 8.48 (1H,s,C^7-H)
7d	H	H	>300	1640 (CO) 3170 (NH)	7.35-7.58, 8.30-8.45(5H,m,C_6H_5), 8.37 (1H,s,C^7-H)
8a	Me	Me	146	1645 (CO)	3.85, 4.00(each 3H,s,NCH_3), 7.40-7.65, 8.30-8.60(5H,s,C_6H_5), 8.50(1H,s,C^7-H)
8b	$PhCH_2$	Me	137-139	1650 (CO)	4.05(3H,s,NCH_3), 5.46(2H,s,NCH_2), 7.27-7.57, 8.28-8.50(10H,m,C_6H_5x2), 8.11(1H, s,C^7-H)
8c	Ph	Me	198-200	1675 (CO)	4.09(3H,s,NCH_3), 7.32-7.75, 8.30-8.55 (10H,m,C_6H_5x2), 8.22(1H,s,C^7-H)
8d	H	Me	285-286	1640 (CO) 3230 (NH)	4.42(3H,s,NCH_3), 7.60-8.10(5H,m,C_6H_5), 8.85(1H,s,C^7-H)
8e	Me	$PhCH_2$	135-137	1640 (CO)	3.87(3H,s,NCH_3), 5.60(2H,s,NCH_2), 7.30-7.80, 8.20-8.60(10H,m,C_6H_5x2), 8.00(1H, s,C^7-H)

**) Solvent : 3a, 3b, 3c (in DMSO-d_6) ; 8a, 8b, 8c, 8e (in $CDCl_3$) ; 7d, 8d (in CF_3CO_2H).

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5. All new compounds (3a-d, 4a-d, 5a-d, 6a, 7a-d, 8a-e and 9a-e) gave satisfactory elemental analysis data (C, H and N).

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9. Reaction solvents: b (1 mmol) in benzene (200 ml); c (0.5 mmol) in acetone (200 ml); d (2 mmol) in acetone (300 ml). A 400 W high-pressure mercury lamp was employed in the case of d.

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