Condensation Reactions of Chloroformylsulphur Chloride with 2- and 4-Aminopyrimidines, 2-Aminothiazole, and 2-Amino-Δ^2-thiazoline

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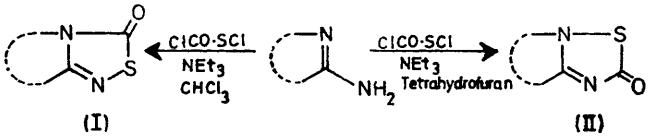
Treatment of 2- and 4-aminopyrimidines, 2-aminothiazole, and 2-amino-Δ^2-thiazoline with chloroformylsulphur chloride in ethanol-free chloroform and in the presence of an organic base leads to the formation of 3,4-fused 1,2,4-thiadiazolones. Spectral evidence for the structure of the products is presented.

The structure of 5,6-dihydrothiazolo[2,3-*c*][1,2,4]thiadiazol-3-one (VII) has been confirmed by *X*-ray analysis. A mechanism is suggested for the acid catalysed desulphurisation of 5,7-dimethyl[1,2,4]thiadiazolo[4,3-*c*]-pyrimidin-3-one (IX) to give ethyl 2,6-dimethylpyrimidin-4-ylcarbamate.

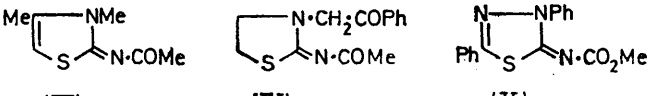
CONDENSATIONS of α-amino-*N*-heterocycles with chloroformylsulphur chloride [1] in the presence of an organic tertiary base can give rise to either a 3,4- or a 2,3-fused 1,2,4-thiadiazolone, (I) or (II), respectively, and the latter reaction has recently been reported [2] with tetrahydrofuran as solvent.

In the present work only the 3,4-fused isomers (I) have been isolated when 2- and 4-aminopyrimidines, 2-aminothiazole, and 2-amino-Δ^2-thiazoline were condensed with chloroformylsulphur chloride using ethanol-free chloroform as solvent.



(I) (II)

The evidence is based on differences in the i.r. spectra of the products obtained compared with those of *N*-(3,4-dimethyl-Δ^4-thiazolin-2-ylidene)acetamide (III), *N*-(3-phenacylthiazolidin-2-ylidene)acetamide (IV), and methyl 3,5-diphenyl-Δ^4-1,3,4-thiadiazolin-2-ylidenecarbamate (V), three examples which have the ·N·C:N·C:O system of the 2,3-fused 1,2,4-thiadiazolone ring (II).



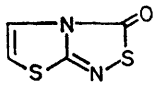
(III) (IV) (V)

Very different carbonyl (C=O) and imino (C=N) absorptions would be expected from the ring systems (I) and (II): in (I) the carbonyl group is isolated from the imino-function whereas in (II) the two functions are in conjugation.

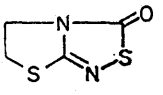
The i.r. spectra of the compounds (VI)—(IX), prepared from 2-aminothiazole, 2-amino-Δ^2-thiazoline, 2-aminopyrimidine, and 4-amino-2,6-dimethylpyrimidine, respectively, showed significant differences from those of the models (III)—(V), which could only be explained if the condensation products were related to the 3,4-fused 1,2,4-thiadiazolone system (I). The differences (Table 1) occur in the frequency shifts and, more significantly, in the reversal of the relative intensities of the $\nu_{C=O}$ and $\nu_{C=N}$ bands. The same intensity patterns

[1] E. Kuhle, *Synthesis*, 1970, 561.
[2] K. Pilgram and R. D. Skiles, *J. Org. Chem.*, 1973, **38**, 1575.

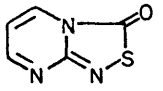
are found in the thiazolothiazoles and the thiazolopyrimidines.



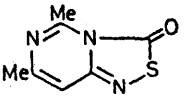
(VI)



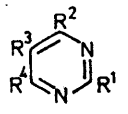
(VII)



(VIII)



(IX)



(X) R^1=NH_2, R^2=R^4=OMe, R^3=Cl

(XI) R^1=R^4=Me, R^2=NH·CO_2Et, R^3=H

Further support for the 3,4-fused system (I) is shown by the fact that $\nu_{C=O}$ of the model compound (V) is below that of the product (VI) despite the replacement of –S–CO by RO–CO (which normally shifts $\nu_{C=O}$ to a higher frequency), because the carbonyl and imino-functions are now in conjugation.

The 1,2,4-thiadiazolones had an absorption due to Fermi resonance at *ca.* 1730 cm^{-1}. In the thiazolothiadiazole (VI) this absorption occurred at 1728 cm^{-1} ($CHCl_3$) and did not move in a range of solvents, whereas the true carbonyl absorption showed significant shifts in a range of solvents.

TABLE 1

I.r. bands (cm^{-1})

Compound	$\nu_{C=O}$	$\nu_{C=N}$	Others
(VI)	1660s, br	1538w	1570 ($\nu_{C=C}$)
(VII)	1676vs, br	1555s	
(VIII)	1677s	1551m	1517ms ($\nu_{C=O}$ pyrimidine ring)
(IX)	1688s	1568m	1631s 1536ms
(III)	1590ms	1475vs	1570($CHCl_3$) ($\nu_{C=C}$)
(IV)	1638ms	1526vs	1692ms (Ph $\nu_{C=O}$)
(V)	1655s	1509	1556m (ring $\nu_{C=N}$)

The only significant peaks (>20% base peak) in the mass spectra of the thiadiazolones (VI)—(IX) are the molecular (M^+) and (M^+ — CO).

The structure of the thiazolothiadiazole (VII) was confirmed by *X*-ray analysis [3] (see Experimental section for brief details), full details of which will be reported elsewhere.

Thiazolo[2,3-*c*][1,2,4]thiadiazol-3-one (VI) and thiazolo[3,2-*b*][1,2,4]thiadiazol-2-one [2] have been prepared by the condensation of 2-aminothiazole with chloroformylsulphur chloride in different solvents, the latter being formed in a proton-acceptor solvent, tetrahydrofuran, which would solvate the exocyclic amino-group, whereas the former were produced in a proton-donor solvent, chloroform, which, if it were to solvate, would solvate the heterocyclic tertiary *N*-atom.

It is likely that the initial, kinetically controlled reaction between the amine and chloroformylsulphur chloride would be the attack of an amine function at the sulphur atom, the site of attack varying according to the nature of the solvent. It has been reported [4] that chloroformylsulphur chloride acylates amines to give carbamoylsulphur chlorides, but all examples quoted have been those where a kinetically controlled species has not been stabilised by rapid intramolecular cyclisation and hence the product obtained has been thermodynamically controlled. Further evidence supporting initial attack at the sulphur atom is provided by the fact that α-amino-*N*-heteroaromatic compounds always mono-acylate and -carbamoylate on the exocyclic amino-group.[5-9]

Since both the 3,4- and 2,3-fused 1,2,4-thiadiazolones are formed in different solvents, the initial attack must be at the sulphur atom with rapid intramolecular cyclisation preventing the labile intermediates being thermodynamically controlled.

2-Amino-4,6-dimethoxypyrimidine did not give the expected thiadiazolopyrimidine with chloroformylsulphur chloride, 2-amino-5-chloro-4,6-dimethoxypyrimidine (X) being the only product isolated.

The 4- and 6-methoxy-substituents have only a marginal effect on the pK_a of the base (Table 2) but they activate the 5-position of the pyrimidine ring such that electrophilic chlorination at C-5 becomes the favoured reaction. The chlorine electrophile can theoretically be generated by the base catalysed decomposition of chloroformylsulphur chloride to chlorine and carbonyl sulphide. By virtue of the 5-chloro-substituent, the product (X) is relatively non-basic (Table 2) and hence unable to react further with chloroformylsulphur chloride.

TABLE 2

pK_a Values

Compound	pK_a
2-Aminothiazole *	5·36
2-Amino-Δ^2-thiazoline	8·78
2-Aminopyrimidine *	3·45
4-Amino-2,6-dimethylpyrimidine	6·30 (in 50% Me_2CO)
2-Amino-4,6-dimethoxypyrimidine	3·36
2-Amino-5-chloro-4,6-dimethoxypyrimidine	0·60

* I.U.P.A.C., 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworth, London, 1965.

The reactions were carried out in ethanol-free chloroform, since reaction in technical grade chloroform (stabilised with 0·2% ethanol) gave the carbamate as a by-product. Thus under these conditions 4-amino-2,6-dimethylpyrimidine yielded ethyl 2,6-dimethylpyrimidin-4-ylcarbamate (XI) in 55% yield (calculated on the percentage of ethanol present).

[3] A. F. Cameron and F. D. Duncanson, in preparation.

[4] G. Zumach and E. Kuhle, *Angew. Chem.*, 1970, **82**, 63; *Angew. Chem. Internat. Edn.*, 1970, **9**, 54.

[5] F. Kröhnke, B. Kichhöfer, and C. Thoma, *Chem. Ber.*, 1955, **88**, 117.

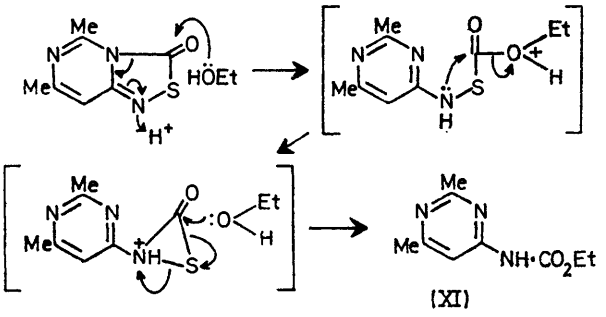
[6] A. H. Land, *Heterocyclic Compounds*, 1957, **5**, 595.

[7] F. Kurzer, *Adv. Heterocyclic Chem.*, 1965, **5**, 168.

[8] J. Sandstrom, *Adv. Heterocyclic Chem.*, 1968, **9**, 181.

[9] A. Schöberl and K. H. Magosch, *Annalen*, 1971, **742**, 74.

When an ethanolic solution of the dimethylthiadiazolopyrimidinone (IX) containing a few drops of dilute hydrochloric acid was refluxed for a few minutes, the same carbamate (XI) was obtained, possibly *via* a mechanism of the type indicated in the Scheme. Compound (IX) was completely stable to ethanol alone.



SCHEME

As would be expected, the extrusion of sulphur is more applicable to the 6,5-ring system (VIII) and (IX) than to the 5,5-ring system (VI) and (VII), and under the same conditions the latter two compounds are completely stable.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 457 double grating spectrophotometer in Nujol mulls. N.m.r. spectra were recorded on a Varian A60 instrument with tetramethylsilane as an internal standard or on a Varian HA100 instrument. Mass spectra were recorded on a Hitachi RMU-6E instrument at 80 eV. Column chromatography used Merck silica gel (0·05—0·2 mm mesh).

General Method.—Chloroformylsulphur chloride (27 g, 0·205 mol) in ethanol-free chloroform (50 ml) was slowly added to a solution of substrate (0·2 mol) in triethylamine (45 g, 0·45 mol) and ethanol-free chloroform (350 ml). The temperature was maintained below 5° throughout the addition. The mixture then was removed from the ice–salt bath and stirred for 2 h. The reaction mixture was washed with water (3 × 150 ml), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was dissolved in a minimum volume of eluant for purification on the column. The pure fractions were combined, evaporated to dryness, and recrystallised.

Thiazolo[2,3-c][1,2,4]*thiadiazol-3-one* (VI).—2-Aminothiazole (20·0 g, 0·2 mol) was treated by the general method. Chromatography (toluene–5% methanol) gave (VI) as *needles* (12·95 g, 41%), m.p. 136—138° (from ethanol) (Found: C, 30·4; H, 1·1; N, 17·6. $C_4H_2N_2OS_2$ requires C, 30·4; H, 1·25; N, 17·7%), *m/e* 158 (M^+, 76%) and 130 [$(M - CO)^+$, 100].

5,6-*Dihydrothiazolo*[2,3-c][1,2,4]*thiadiazol-3-one* (VII). 2-Amino-Δ^2-thiazoline (20·4 g, 0·2 mol) was treated as described in the general method. Chromatography (chloroform) gave (VII) as *needles*, m.p. 127—127·5° (from ethanol) (Found: C, 30·0; H, 2·7; N, 17·3; S, 39·8. $C_4H_4N_2OS_2$ requires C, 30·0; H, 2·5; N, 17·5; S, 40·0%), *m/e* 160 (M^+, 100%) and 132 [$(M - CO)^+$, 55].

[1,2,4]*Thiadiazolo*[4,3-a]*pyrimidin-3-one* (VIII). 2-Aminopyrimidine (19·0 g, 0·2 mol) was treated as in the general method. Chromatography (toluene–6% methanol) gave (VIII) as golden *needles* (10·4 g, 34%), m.p. 144·5—146° (from methanol) (Found: C, 39·5; H, 2·3; N, 27·4. $C_5H_3N_3OS$ requires C, 39·2; H, 2·0; N, 27·4%), *m/e* 153 (M^+, 48%) and 125 [$(M - CO)^+$, 100].

5,7-*Dimethyl*[1,2,4]*thiadiazolo*[4,3-c]*pyrimidin-3-one* (IX). 4-Amino-2,6-dimethylpyrimidine (24·6 g, 0·2 mol) was treated as in the general method. Chromatography (chloroform–10% cyclohexane) gave (IX) as pale yellow *prisms* (15·2 g, 39%), m.p. 68·5—70° (from ether) (Found: C, 46·6; H, 4·0; N, 23·0; S, 17·8. $C_7H_7N_3OS$ requires C, 46·4; H, 3·95; N, 23·2; S, 17·7%), *m/e* 181 (M^+, 100%) and 153 [$(M - CO)^+$, 67].

2-*Amino-5-chloro-4,6-dimethoxypyrimidine* (X). 2-Amino-4,6-dimethoxypyrimidine (31·0 g, 0·2 mol) was treated as described in the general method. Chromatography (chloroform) gave (X) as yellow needles (18·8 g, 53·5%), m.p. 176° (from ethanol) (Found: C, 37·9; H, 4·4; N, 22·3; Cl, 18·5. $C_6H_8ClN_3O_2$ requires C, 38·0; H, 4·25; N, 22·2; Cl, 18·7%), δ [60 MHz, $(CD_3)_2SO$] 3·88 (6H, s, 2-OMe) and 6·7 (2H, br, NH_2), *m/e* 189 (M^+, 100%) and 124 [$(160 - HCl)^+$, 57].

Ethyl 2,6-*dimethylpyrimidin-4-ylcarbamate* (XI). (i) A by-product of the reaction of 4-amino-2,6-dimethylpyrimidine in technical grade chloroform (stabilised with 0·2% ethanol) was the carbamate (XI). The compound was separated on a column (chloroform–10% cyclohexane) and crystallised from ether as pale yellow prisms (2·14 g, 55% calculated on the amount of ethanol present), m.p. 77—78° (lit.,[10] 79°) (Found: C, 55·4; H, 6·9; N, 21·8. Calc. for $C_9H_{13}N_3O_2$: C, 55·5; H, 6·7; N, 21·6%), δ (100 MHz, $CDCl_3$) 1·27 (3H, t, *J* 7 Hz, CH_2CH_3), 2·44 (3H, s, 6-Me), 2·55 (3H, s, 2-Me), 4·20 (2H, q, *J* 7 Hz, CH_2CH_3), 7·65 (1H, s, 5-H), and 9·20 (1H, s, NH).

(ii) The 5,7-dimethylthiadiazolopyrimidinone (IX) (250 mg) was dissolved in ethanol (5 ml) and 2N-hydrochloric acid (3 drops) added. The solution was refluxed for 5 min and evaporated to dryness under reduced pressure. The product was purified on a column (chloroform–10% cyclohexane) and crystallised from ether as pale yellow prisms (170 mg, 63%), m.p. 77—78°, and was identical with (XI) by mixed m.p. and t.l.c.

X-*Ray Analysis of Thiazolo*[2,3-c][1,2,4]*thiadiazol-3-one* (VII).—*Crystal data.* $C_4H_4NOS_2$, $M = 160·2$. Monoclinic, $a = 7·379$, $b = 14·587$, $c = 5·804$ Å, $\beta = 102·32°$, $U = 610·3$ Å^3, $D_m = 1·75$ (by flotation), $Z = 4$, $D_c = 1·74$, $F(000) = 328$. Space group $P2_1/c$ from systematic absences.

A small crystal was exposed to Mo-K_α radiation on a Hilger and Watts Y290 diffractometer and 959 ($I \geqslant 2\sigma_I$) intensities were measured. The structure was solved by application of centrosymmetric direct methods using programs incorporated in the X-RAY suite of programs and refinement of positional and anisotropic thermal parameters by least-squares calculations converged when *R* was 0·024.

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[10] E. Dyer and H. Richmond, *J. Medicin. Chem.*, 1965, **8**, 195.