Synthesis and Reactions of Thiazolidino[3,2-*a*]pyrimidines

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A number of 5- and 7-oxothiazolidino[3,2-*a*]pyrimidines have been prepared from 1,2-dibromoethane and substituted 2-thiouracils. Compounds of the 5-oxo-series were also synthesised by reaction of 2-aminothiazoline and ethoxymethylenemalonic esters. Amongst reactions of the 5-oxo-series described bromination occurs under mild conditions. Reaction of the 6-bromo-5-oxo-compound with cyclic secondary amines lead to *cine*-substituted ‡ products.

THE recent report [1] of the synthesis of 7-methyl-5-oxo- and 5-methyl-7-oxo-thiazolidino[3,2-*a*]pyrimidines (1) and (16) from the sodium salt of 4-methylthiouracil and 1,2-dibromoethane in dimethylformamide prompts us to describe our investigation of this system. Employing an excess of sodium hydrogen carbonate as acid acceptor and isopropyl alcohol as solvent thiazolidinopyrimidines of the 5- and 7-oxo-series have been prepared (Tables 1 and 2). Low melting point and solubility in chloroform i.r. spectra. Although the carbonyl absorption of the 7-oxo-series occurs at 1640 cm.$^{-1}$ and is usually above 1670 cm.$^{-1}$ for the 5-oxo-series the tertiary amines (12)—(15) of the 5-oxo-series absorb at 1640 cm^{-1}. More reliable guides to structure are the u.v. spectra. The 5-oxo-series have maxima in the range 206—213 and 288—305 nm. and the 7-oxo-series have maxima at 229—234 nm. and an inflexion at 260—265 nm. The n.m.r. spectra of the isomers did not aid differentiation

TABLE 1

5-Oxothiazolidino[3,2-*a*]pyrimidines *

Compd.	Method	Yield (%)	M.p.	Found (%) C	H	N	Formula	Required (%) C	H	N	$\nu_{max.}$ Amide I cm.$^{-1}$	$\lambda_{max.}$ (log ε) nm.
(1)	B	40	127—138° [a]	49·6	4·8	16·6	$C_7H_8N_2OS$	50·0	4·8	16·7	1690	207 (4·02), 288 (3·86)
(2)	A	57	107—108	47·1	4·0	17·9	$C_6H_6N_2OS$	46·8	3·9	18·2	1670	207·5 (4·29), 290·5 (3·84)
(3)	C	35	94—95	55·2	6·3	14·3	$C_9H_{12}N_2OS$	55·1	6·2	14·3	1680	213 (3·91), 288 (3·91)
(4)	D	62	165—166	62·6	4·3	12·2	$C_{12}H_{10}N_2OS$	62·5	4·4	12·2	1680	211 (4·23), 305 (3·74) [b]
(5)	E	22	114—115	63·6	5·1	11·4	$C_{13}H_{12}N_2OS$	63·9	5·0	11·5	1670	206 (4·33), 288 (3·88)
(6)	B	33	123—124	50·4	4·9	16·7	$C_7H_8N_2OS$	50·0	4·8	16·7	1670	207·5 (3·99), 292 (3·92)
(22)											1690	204 (4·04), 291·5 (4·00)

* Compounds were crystallised from benzene–light petroleum.

[a] Lit. 1., m.p. 123—124°. [b] Recorded in 95% EtOH.

TABLE 2

7-Oxothiazolidino[3,2-*a*]pyrimidines *

Compd.	Method	Yield (%)	M.p.	Found (%) C	H	N	Formula	Required (%) C	H	N	$\nu_{max.}$ Amide I (cm.$^{-1}$)	$\lambda_{max.}$ (log ε) (nm.)
(16)	B	5	251—252° [a]	49·9	4·8	16·6	$C_7H_8N_2OS$	50·0	4·8	16·7	1640	230·5 (4·28), 260 (3·79) inf.
(17)	A	6	227—228 [b]	46·7	3·9	18·1	$C_6H_6N_2OS$	46·8	3·9	18·2	1640	232 (4·30), 260 (3·88)inf.
(18)	C	18	161—162	55·0	6·2	14·1	$C_9H_{12}N_2OS$	55·1	6·2	14·3	1640	232 (4·37), 260 (3·90) inf.
(19)	D	9	237—238	62·4	4·4	12·1	$C_{12}H_{10}N_2OS$	62·5	4·4	12·2	1640	236 (4·38), 265 (3·97) inf.[e]
(20)	E	11	215—216 [c]	63·6	5·1	11·4	$C_{13}H_{12}N_2OS$	63·9	5·0	1·15	1640	232 (4·27), 260 (3·81) inf.[e]
(21)	B	8	267—268 [d]	50·4	4·8	16·5	$C_7H_8N_2OS$	50·0	4·8	16·7	1640	229 (4·32), 260 (3·89) inf.[f]
(23)											1640	234 (4·35)

* Compounds crystallised from chlorobenzene unless indicated.

[a] Lit. 1, m.p. 229—230°. [b] Crystallised from ethanol. [c] Crystallised from water. [d] Lit. 3, m.p. 262°. [e] Recorded in 95% EtOH. [f] Lit. 3, 228 nm. (4·31) 260 nm. (3·83) inf.

was characteristic of compounds of the 5-oxo-series whereas the 7-oxo-compounds had high melting points and were soluble in water. This difference in solubility facilitated separation of the isomers; structures were assigned by comparison of the absorption spectra of the compounds with the known [2] and related pyrimidines (22) and (23). Pashkurov and Resnik [1] based structural assignment on the position of the amide I band in the between the series but were in support of the structures assigned. The 6-methyl-7-oxo-compound (21) has been synthesised by an unambiguous route.[3]

An alternative approach to the synthesis of the 5-oxo-compounds was the condensation of 2-aminothiazoline with diethyl ethoxymethylenemalonate and with ethyl ethoxymethylenecyanoacetate in boiling 1,2,4-trichlorobenzene which gave a high yield of the

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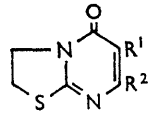
‡ *Cine*-substitution is substitution at a carbon atom adjacent to one carrying a leaving group (T. L. Gilchrist and C. W. Rees, 'Carbenes, Nitrenes, and Arynes,' Nelson, London, 1969, p. 46).

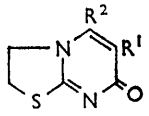
[1] H. C. Pashkurov and V. S. Resnik, *Chem. Heterocyclic Compounds*, 1968, **5**, 918.

[2] D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 1955, 211.

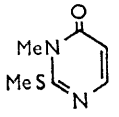
[3] G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1959, 50.



(1) R^1 = H, R^2 = Me
(2) R^1 = R^2 = H
(3) R^1 = H, R^2 = Pr^n
(4) R^1 = H, R^2 = Ph
(5) R^1 = H, R^2 = $PhCH_2$
(6) R^1 = Me, R^2 = H
(7) R^1 = CO_2Et, R^2 = H
(8) R^1 = CN, R^2 = H
(9) R^1 = CO_2H, R^2 = H
(10) R^1 = Br, R^2 = H
(11) R^1 = Cl, R^2 = H
(12) R^1 = H, R^2 = morpholino
(13) R^1 = H, R^2 = piperidino
(14) R^1 = H, R^2 = pyrrolidino
(15) R^1 = H, R^2 = *N*-methylpiperazino



(16) R^1 = H, R^2 = Me
(17) R^1 = R^2 = H
(18) R^1 = H, R^2 = Pr^n
(19) R^1 = H, R^2 = Ph
(20) R^1 = H, R^2 = $PhCH_2$
(21) R^1 = Me, R^2 = H



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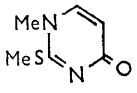

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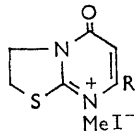
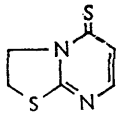


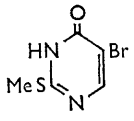
(24) R = H
(25) R = Me

ester (7) and the nitrile (8) respectively. Hydrolysis of the ester (7) with formic acid and methanesulphonic acid gave the acid (9) which, however, gave only traces of (2) on thermal or copper–quinoline decarboxylation.

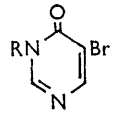
Reactions of 5-Oxothiazolidino[3,2-a]*pyrimidine* (2).—Excess of methyl iodide with (2) in nitromethane gave a methiodide (24) but with the 7-methyl homologue (1) reaction only proceeded if the mixture was heated to give the expected methiodide (25). Phosphorus pentasulphide and (2) in boiling pyridine gave a 59% yield of the thioxo-derivative (26). Attempts to prepare a



(26)



(27)



(28) R = H
(29) R = Me

sulphoxide or sulphone of (2) with hydrogen peroxide, potassium permanganate, sodium periodate, and *m*-chloroperbenzoic acid were unsuccessful. *N*-Halogenosuccinimides have recently [4] been reported to give high yields of sulphoxides from sulphides at 0—10° but with (2) no reaction occurred. At room temperature however a 64% yield of the 6-bromo-compound (10) was obtained using *N*-bromosuccinimide in anhydrous methanol. With *N*-chlorosuccinimide in methanol no reaction occurred but in glacial acetic acid at 100° the 6-chloro-compound (11) was obtained. The position of the halogen substituent was determined by comparing the n.m.r. spectrum of (10) with the spectra of thiazolidinopyrimidines prepared from known substituted 2-thiouracils and with 5-bromo-2-methylthiouracil (27) [5] (Table 3).

[4] R. Harville and S. F. Reed, *J. Org. Chem.*, 1968, **33**, 3976.
[5] H. W. Barrett, I. Goodman, and K. Dittmer, *J. Amer. Chem. Soc.*, 1948, **70**, 1753.

1-Chlorobenzotriazole has also been reported [6] to give high yields of sulphoxides from sulphides at −78° in methylene chloride or methanol but no reaction occurred with (2) in either solvent at 0°. At room temperature a 57% yield of the 6-chloro-compound (11) was obtained in methylene chloride. There was no reaction between (2) and fuming nitric acid even when the mixture was heated for a prolonged period at 100°.

Reactions of 6-Bromo-5-oxothiazolidino[3,2-a]*pyrimidine* (10).—The bromo-compound (10) failed both to form a Grignard reagent in tetrahydrofuran and to react with sodio-malonic ester. No reaction occurred between (10) and potassium phthalimide, potassium thiocyanate, sodium *p*-nitrophenoxide, or sodium fluoride in boiling dimethylformamide. No reaction occurred with boiling aniline but with an excess of morpholine piperidine, pyrrolidine, and *N*-methylpiperazine at 100° or in boiling 2-methoxyethanol good yields of the tertiary amines (12)—(15) were obtained. The n.m.r. spectra of these amines in deuteriochloroform (Table 3) showed

TABLE 3

N.m.r. spectra (τ values in $CDCl_3$ for aromatic protons)

Compd.	Substituent	6-H	7-H	Multiplicity
(1)	7-Me	4·05		s
(2)		3·9, 4·0	2·3, 2·4	d
(6)	6-Me		2·40	s
(10)	6-Br		1·95	s
(12)	7-Morpholino	4·80		s
(13)	7-Piperidino	4·80		s
(14)	7-Pyrrolidino	5·05		s
(15)	7-Methylpiperazino	4·90		s
(27)	5-Br [a]		1·70	s

[a] Pyrimidine numbering, recorded in $[^2H_6]$DMSO.

an aromatic singlet at τ 4·80—5·05 (6H) compared with τ 1·95 (7H) for (10) suggesting that the tertiary amino-groups were in the 7-position. A similar anomalous nucleophilic substitution has been reported [7] to occur when two 5-bromopyrimidines, (28) and (29), were allowed to react with piperidine when an elimination–addition mechanism was postulated involving a dehydropyrimidine intermediate.

EXPERIMENTAL

The u.v. spectra were recorded on a Hilger and Watts Ultrascan recording spectrophotometer and the $\lambda_{max.}$ values checked on a Hilger and Watts Uvispek manual instrument in water. I.r. spectra were recorded on a Perkin-Elmer model 237 spectrophotometer for Nujol mulls. M.p.s were measured on a Büchi apparatus. N.m.r. spectra were recorded on a Perkin-Elmer R10 60 MH2 instrument using tetramethylsilane as internal reference. Chromatographic separations were effected on grade H alumina (Peter Spence). Light petroleum was b.p. 60—80°.

5- and 7-Oxothiazolidino[3,2-a]*pyrimidines.*—The general method was followed for compounds in Tables 1 and 2, isomer separation procedures are indicated below (A—E).

[6] W. D. Kingsbury and C. R. Johnson, *Chem. Comm.*, 1969, 365.
[7] R. Promel, A. Cardon, M. Daniel, G. Jacques, and A. Vandermissen, *Tetrahedron Letters*, 1968, 3067.

General method. The 2-thiouracil (0·1 mole) and sodium hydroxide (0·1 mole) were dissolved in water (50 ml.) and isopropyl alcohol (50 ml.). The solution was added dropwise during 3 hr. to a stirred and boiling mixture of sodium hydrogen carbonate (0·25 mole), 1,2-dibromoethane (5 moles), and isopropyl alcohol (200 ml.) under reflux. Heating was continued for 2 hr.; the mixture was then evaporated to dryness under reduced pressure and the residue was shaken with chloroform (100 ml.) and water (100 ml.).

Method A. Evaporation of the chloroform gave the 5-oxo-isomer and crystallisation from ethanol of the residue from the aqueous phase the 7-oxo-isomer.

Method B. The residue from the chloroform phase was the 5-oxo-isomer and extraction of the residue from the aqueous phase with boiling chlorobenzene gave the 7-oxo-isomer.

Method C. Both isomers were in the chloroform phase. The 5-oxo-isomer was extracted from the residue with with boiling light petroleum.

Method D. The isomers were separated by filtration of the concentrated chloroform phase through alumina in chloroform which afforded the 5-oxo-isomer. The 7-oxo-isomer was obtained by further elution with ethanol–chloroform (1 : 3 to 3 : 1).

Method E. The 7-oxo-isomer was insoluble in water and chloroform and was filtered off; the 5-oxo-isomer was in the chloroform phase.

6-*Ethoxycarbonyl*-5-*oxothiazolidino*[3,2-a]*pyrimidine* (7).—Ethyl ethoxymethylenemalonate (10·8 g.) and 2-aminothiazoline (5·1 g.) were heated under reflux in boiling 1,2,4-trichlorobenzene (20 ml.) and ethanol was allowed to distil from the mixture. After 1 hr. the cooled mixture was filtered and the ester was crystallised from chloroform–light petroleum to give needles (10·9 g., 96%), m.p. 175—176° (Found: C, 47·4; H, 4·4; N, 12·2. $C_9H_{10}N_2O_3S$ requires C, 47·8; H, 4·5; N, 12·4%).

6-*Cyano*-5-*oxothiazolidino*[3,2-a]*pyrimidine* (8).—This compound was prepared as the ester above from ethyl ethoxymethylenecyanoacetate as yellow needles (45%), m.p. 180—181° from benzene–light petroleum (Found: C, 46·5; H, 2·8; N, 23·7. $C_7H_5N_3OS$ requires C, 46·9; H, 2·8; N, 23·5%).

6-*Carboxy*-5-*oxothiazolidino*[3,2-a]*pyramidine* (9).—The above ester (7) (1·1 g.) was heated on the steam-bath for 5 hr. with 98% formic acid (5 ml.) and methanesulphonic acid (500 mg.). *Needles* (570 mg., 57%), m.p. 238—239°, separated from the cooled mixture (Found: C, 42·1; H, 3·1; N, 14·0. $C_7H_6N_2O_3S$ requires C, 42·4; H, 3·0; N, 14·1%).

8-*Methyl*-5-*oxothiazolidino*[3,2-a]*pyrimidinium Iodide* (24).—The pyrimidine (2) (1·5 g.) and methyl iodide (3·0 g.) in nitromethane (5 ml.) were left at room temperature for 48 hr. The colourless crystals (2·0 g., 67%) which separated recrystallised from 2-methoxyethanol to afford the *methiodide*, m.p. 240—242° (Found: C, 28·3; H, 3·1; N, 9·9. $C_7H_9IN_2OS$ requires C, 28·4; H, 3·1; N, 9·5%).

7,8-*Dimethyl*-5-*oxothiazolidino*[3,2-a]*pyrimidinium Iodide* (25).—The *methiodide* was prepared as above at 37° in 46% yield, m.p. 286—288° (Found: C, 31·1; H, 3·6; N, 9·0. $C_8H_{11}IN_2OS$ requires C, 31·0; H, 3·6; N, 9·0%).

5-*Thioxothiazolidino*[3,2-a]*pyrimidine* (26).—The pyrimidine (2) (2·3 g.) and phosphorus pentasulphide (3·3 g.) were heated under reflux for 1·5 hr. in anhydrous pyridine (15 ml.); the cooled reaction mixture was poured into water (200 ml.) and the solid which separated was collected and extracted with boiling ethyl acetate. The product separated from the extract and crystallised as yellow *needles* (1·5 g., 59%), m.p. 197—198° (from toluene) (Found: C, 42·5; H, 3·6; N, 16·4; S, 38·1. $C_6H_6N_2S_2$ requires C, 42·4; H, 3·6; N, 16·5; S, 37·7%).

6-*Bromo*-5-*oxothiazolidino*[3,2-a]*pyrimidine* (10).—The pyrimidine (2) (6·1 g.) was dissolved in anhydrous methanol (30 ml.) and *N*-bromosuccinimide (7·2 g.) was added in portions with stirring during 10 min. After 1 hr. the methanol was evaporated off and the residue dissolved in chloroform was filtered through alumina (100 g.). Evaporation of the chloroform and crystallisation of the residue from benzene gave *needles* (5·9 g., 64%), m.p. 117—118° (Found: C, 30·9; H, 2·1; Br, 33·5; N, 12·0. $C_6H_5BrN_2OS$ requires C, 30·5; H, 2·1; Br, 33·8; N, 11·8%).

6-*Chloro*-5-*oxothiazolidino*[3,2-a]*pyrimidine* (11).—(*a*) The pyrimidine (2) (1·5 g.) and *N*-chlorosuccinimide (1·6 g.) were heated in glacial acetic acid (5 ml.) for 1 hr. at 100°. The acid was evaporated off under reduced pressure and the residue dissolved in chloroform was filtered through alumina (50 g.). Evaporation of the chloroform and crystallisation of the residue from benzene–light petroleum gave *needles* (1·3 g., 69%), m.p. 128—129° (Found: C, 38·1; H, 2·7; Cl, 18·7; N, 14·7. $C_6H_5ClN_2OS$ requires C, 38·2; H, 2·7; Cl, 18·8; N, 14·9%).

(*b*) The pyrimidine (2) (1·0 g.) and 1-chlorobenzotriazole (1·0 g.) were stirred in anhydrous methylene chloride (10 ml.) for 2·5 hr. The methylene chloride was evaporated off and the residue was shaken with 2N-sodium hydroxide solution (15 ml.) and chloroform (20 ml.). The chloroform solution was filtered through alumina (25 g.) in chloroform and the chloroform eluate was evaporated. Crystallisation of the residue from benzene–light petroleum gave needles (700 mg., 57%), m.p. 128—129°.

7-*Morpholino*-5-*oxothiazolidino*[3,2-a]*pyrimidine* (12).—The bromo-compound (10) (2·3 g.) and morpholine (8·7 g.) were heated on the steam-bath for 3 hr. The mixture was diluted with water and extracted with chloroform. Evaporation of the chloroform and crystallisation of the residue from benzene gave *needles* (1·7 g., 71%), m.p. 208—209° (Found: C, 50·2; H, 5·6; N, 17·6. $C_{10}H_{13}N_3O_2S$ requires C, 50·2; H, 5·5; N, 17·6%).

5-*Oxo*-7-*piperidinothiazolidino*[3,2-a]*pyrimidine* (13).—This compound was prepared as for the morpholine compound above in 56% yield as *needles*, m.p. 131—132° (from benzene–light petroleum (Found: C, 55·5; H, 6·7; N, 17·8. $C_{11}H_{15}N_3OS$ requires C, 55·7; H, 6·4; N, 17·7%).

5-*Oxo*-7-*pyrrolidinothiazolidino*[3,2-a]*pyrimidine* (14).—This compound was prepared as for the morpholino-compound above in 58% yield as *needles*, m.p. 197—198° (from benzene–light petroleum) (Found: C, 53·7; H, 5·9; N, 18·9. $C_{10}H_{13}N_3OS$ requires C, 53·8; H, 5·9; N, 18·8%).

7-*Methylpiperazino*-5-*oxothiazolidino*[3,2-a]*pyrimidine* (15).—This compound was prepared as for the morpholine compound above except that 2-methoxyethanol was employed as solvent. Crystallisation from benzene gave *needles* (65%), m.p. 186—187° (Found: C, 52·5; H, 6·5; N, 22·2. $C_{11}H_{16}N_4OS$ requires C, 52·4; H, 6·4; N, 22·2%).

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