Synthesis of 2,3-Dihydrothiazolo[3,2-*c*]pyrimidines

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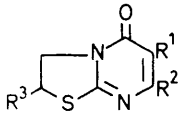
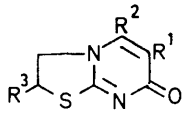
Hydrolysis of a 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one with 2N-hydrochloric acid gives first a 3-(2-mercaptoethyl)uracil, which then ring closes to a 2,3-dihydrothiazolo[3,2-*c*]pyrimidin-5-one.

FALCH and NATVIG [1] have described the hydrolysis of the 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-ones (1) and (2) with boiling N-hydrochloric acid during 20 h to the 3-(2-mercaptoethyl)uracils (12) and (13) and of the isomeric 7-ones (7) and (8) to the 1-(2-mercaptoethyl)-uracils (16) and (17). In contrast, hydrolysis of the ester (3) with formic acid and methanesulphonic acid proceeds without ring opening to give the acid (4).[2] Hydrolysis of the ester (3) with boiling 2N-hydrochloric acid during 1·5 h, however, led to both ester hydrolysis and ring opening to give a 48% yield of the uracil (14), confirming that the products obtained with mineral acid are different from those obtained with the formic acid reagent.[3] Diethyl 2-formylsuccinate reacted with 2-aminothiazoline at 100° to give the ester (9), the assignment of the 7-one structure being supported by a u.v. maximum at 232 and an inflection at 270 nm.[2] Hydrolysis of the ester (9) with the formic acid reagent again gave the corresponding acid (10).

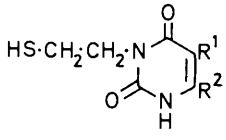
Hydrolysis of the ester (3) or the uracil (14) for longer periods gave mixtures, but after 72 h a single colourless solid was obtained. This material showed a strong carbonyl absorption at 1640—1655 cm^{-1} typical of an unsaturated urea, and no bands characteristic of hydroxy-, carboxy-, amino-, or mercapto-groups suggesting a cyclisation reaction had occurred. This was supported by the ^1H n.m.r. spectrum (solvent trifluoroacetic acid), which showed two olefinic doublets at chemical shifts characteristic of pyrimidine ring protons and two triplets suggesting two adjacent methylene groups (Table), and confirmed by the mass spectrum and elemental microanalysis. Cyclisation can only result in



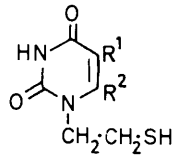
(1) R^1 = Ph, R^2 = R^3 = H
(2) R^2 = Ph, R^1 = R^3 = H
(3) R^1 = CO_2Et, R^2 = R^3 = H
(4) R^1 = CO_2H, R^2 = R^3 = H
(5) R^1 = R^2 = R^3 = H
(6) R^1 = R^2 = H, R^3 = Ph



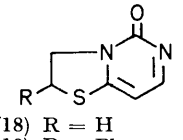
(7) R^1 = Ph, R^2 = R^3 = H
(8) R^2 = Ph, R^1 = R^3 = H
(9) R^1 = $CH_2{\cdot}CO_2Et$, R^2 = R^3 = H
(10) R^1 = $CH_2{\cdot}CO_2H$, R^2 = R^3 = H
(11) R^1 = R^2 = H, R^3 = Ph



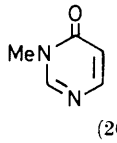
(12) R^1 = Ph, R^2 = H
(13) R^1 = H, R^2 = Ph
(14) R^1 = CO_2H, R^2 = H
(15) R^1 = R^2 = H



(16) R^1 = Ph, R^2 = H
(17) R^1 = H, R^2 = Ph



(18) R = H
(19) R = Ph



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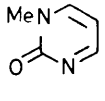

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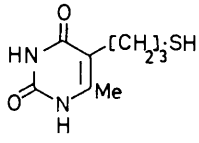

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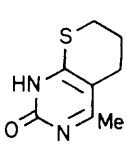


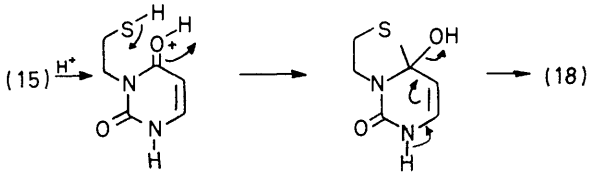
(23)

[1] E. Falch and T. Natvig, *Acta Chem. Scand.*, 1970, **24**, 1423.
[2] G. R. Brown and W. R. Dyson, *J. Chem. Soc.* (*C*), 1971, 1527.
[3] B. Loev, *Chem. and Ind.*, 1964, 193.

the formation of the known thiazolo[3,2-*a*]pyrimidine (5) or the isomeric thiazolo[3,2-*c*]pyrimidine (18). The maximum in the u.v. spectrum of (18) (322 nm) represents a shift to higher wavelength compared with the

Compound	$\nu_{max.}$/cm^{-1} amide I	$\lambda_{max.}$/nm (ε)	δ (60 MHz; $CF_3 \cdot CO_2H$)
(5)	1670	208 (10,190) 227 (7021) 289 (7473)	4·05, 4·95 (CH_2, t) 6·7, 8·0 (CH, d)
(18)	1640—1655	207 (6673) 225 (7186) 322 (11,290)	4·1, 5·1 (CH_2, t) 7·0, 8·25 (CH, d)

maximum (289 nm) for (5), in agreement with the different maxima (269 and 309 nm) reported [4] for the isomeric 3-methyl-4-oxo- and 1-methyl-2-oxo-pyrimidines (20) and (21). Thus (14) has undergone simultaneous decarboxylation and intramolecular condensation during the acidic treatment to give (18).



Hydrolysis of the thiazolo[3,2-*a*]pyrimidine (5) during 1·5 h with 2N-hydrochloric acid gave the 3-(2-mercaptoethyl)uracil (15) in 54% yield, and prolonged heating caused cyclisation to (18). Similarly, the phenyl derivative (6), which was separated from the 7-oxo-isomer (11) after reaction between 2-thiouracil and styrene dibromide, afforded after 72 h the thiazolo[3,2-*c*]pyrimidine (19).

A similar intramolecular condensation at the 4-oxo-group of a uracil (22) in polyphosphoric acid has been reported; [5] the product was the thiopyrano[2,3-*d*]-pyrimidine (23). The thiazolo[3,2-*c*]pyrimidine ring system has been described twice previously but with the ring junction nitrogen atom quaternary.[6]

EXPERIMENTAL

U.v. spectra were recorded for solutions in methanol on a Perkin-Elmer 137 recording spectrophotometer and the i.r. spectra on a Perkin-Elmer 437 spectrophotometer for Nujol mulls. N.m.r. spectra were recorded at 60 MHz on a Varian A60 instrument with tetramethylsilane as internal reference, and mass spectra on a Hitachi RMU-6E instrument at 80 eV.

Ethyl 2,3-*Dihydro*-7-*oxothiazolo*[3,2-a]*pyrimidine*-6-*acetate* (9).—Diethyl 2-formylsuccinate (9·9 g) and 2-aminothiazoline (5·0 g) were heated on a steam-bath for 1 h; the product crystallised from ethanol to give a yellow *solid* (2·2 g, 18%), m.p. 160—163° (Found: C, 49·5; H, 5·1; N, 11·5. $C_{10}H_{12}N_2O_3S$ requires C, 50·0; H, 5·0; N, 11·7%), $\lambda_{max.}$ 231 (ε 22,830) and 274 nm (7295).

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

2,3-*Dihydro*-7-*oxothiazolo*[3,2-a]*pyrimidine*-6-*acetic Acid* (10).—The ester (9) (2·0 g) was heated on a steam-bath for 5 h in 98% formic acid (10 ml) containing methanesulphonic acid (1·0 g). The acid was evaporated off and the residue shaken with water and chloroform. The aqueous phase was evaporated and the solid *product* (700 mg, 40%) was crystallised from ethanol; m.p. 265—267° (Found: C, 45·3; H, 4·0; N, 12·8. $C_8H_8N_2O_3S$ requires C, 45·3; H, 3·8; N, 13·2%).

5-*Carboxy*-3-(2-*mercaptoethyl*)*uracil* (14).—The ester (3) (3·0 g) was heated under reflux for 1·5 h with 2N-hydrochloric acid (20 ml). The cooled mixture was filtered to give the *uracil* (1·5 g, 48%), m.p. 220—221° (from 2-methoxyethanol) (Found: C, 39·0; H, 3·8; N, 12·9. $C_7H_8N_2O_4S$ requires C, 38·8; H, 3·7; N, 13·0%).

3-(2-*Mercaptoethyl*)*uracil* (15).—The thiazolopyrimidine (5) (5·0 g) was heated under reflux for 1·5 h in 2N-hydrochloric acid (50 ml). A *solid* (3·0 g, 54%) separated from the cooled mixture which crystallised from methanol; m.p. 197—198° (Found: C, 41·9; H, 5·1; N, 16·3. $C_6H_8N_2O_3S$ requires C, 41·9; H, 4·7; N, 16·3%).

2,3-*Dihydrothiazolo*[3,2-c]*pyrimidin*-5-*one* (18).—(*a*) The ester (3) was heated under reflux in 2N-hydrochloric acid (20 ml) for 72 h. The water was evaporated off and the residue dissolved in saturated sodium hydrogen carbonate solution. Extraction with chloroform and evaporation of the dried ($MgSO_4$) extract afforded a *solid* (1·5 g, 71%), m.p. 202—204° [from chloroform–light petroleum (b.p. 60—80°)] (Found: C, 46·5; H, 3·9; N, 18·1%; M^+, 154. $C_6H_6N_2OS$ requires C, 46·8; H, 3·9; N, 18·2%; *M*, 154).

(*b*) The uracil (15) (900 mg) was heated with 2N-hydrochloric acid (20 ml) as in (*a*) to give (18) (600 mg, 74%), m.p. 202—204°.

2,3-*Dihydro*-2-*phenylthiazolo*[3,2-a]*pyrimidine*-5- *and* -7-*one* (6) *and* (11)].—A solution of 2-thiouracil (9·6 g) and sodium hydroxide (3·0 g) in water (60 ml) was added dropwise during 1·5 h to a stirred mixture of styrene dibromide (75·0 g) and sodium hydrogen carbonate (28·0 g) in propan-2-ol (300 ml) heated under reflux. Heating was continued for 3 h and the solvents were evaporated off. The residue was shaken with chloroform (200 ml) and water (200 ml) and the chloroform phase was evaporated to a solid. The solid was shaken briefly with ligroin (250 ml) and insoluble material was collected. The solid was extracted with boiling benzene (150 ml) and the residue crystallised from ethanol to afford the 7-*one* (11) (3·2 g, 20%), m.p. 235—236° (Found: C, 62·4; H, 4·3; N, 11·9. $C_{10}H_{12}N_2OS$ requires C, 62·6; H, 4·4; N, 12·2%), $\lambda_{max.}$ 234 (ε 30,240) and 275infl nm (6390). The benzene solution was evaporated and the material obtained filtered through alumina (150 g; Spence type H) in chloroform. Evaporation of the eluates and crystallisation from benzene–light petroleum (b.p. 80—100°) afforded the 5-*one* (6) (4·8 g, 30%), m.p. 99—100° (Found: C, 62·4; H, 4·5; N, 12·1%), $\lambda_{max.}$ 213 (ε 19,930) and 293 nm (8440).

2,3-*Dihydro*-2-*phenylthiazolo*[3,2-c]*pyrimidin*-5-*one* (19).—The thiazolopyrimidine (6) (2·0 g) was heated under reflux in 2N-hydrochloric acid (20 ml) for 72 h and the water was evaporated off. The residue was shaken with chloroform and sodium hydrogen carbonate solution and the dried ($MgSO_4$) chloroform layer was evaporated. The *solid*

[5] H. Warnhoff and F. Korte, *Chem. Ber.*, 1966, **99**, 872.

[6] B. Roth, *J. Medicin. Chem.*, 1969, **12**, 227; K. Undheim and J. Roe, *Acta Chem. Scand.*, 1969, 2437.

(1·2 g, 60%) obtained had m.p. 168—169° (from ethanol) (Found: C, 62·3; H, 4·6; N, 12·6%; M^+, 230. $C_{12}H_{10}N_2OS$ requires C, 62·6; H, 4·4; N, 12·2%; M, 230), $\lambda_{max.}$ 212 (ε 13,590), and 323 nm (14,130), $\nu_{max.}$ 1640—1655 cm^{-1} (CO).

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