# Pyrimido[1,4]benzothiazines and Pyrimido[1,5]benzothiazepines. Part 3.[1] Novel Ring-contraction and Ring-opening of Pyrimido[1,5]benzothiazepines

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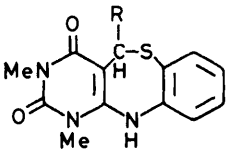
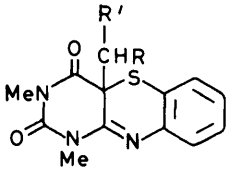
Pyrimido[1,5]benzothiazepine (1a) undergoes ready ring-contraction leading to 4a-alkoxymethylpyrimido[1,4]-benzothiazines (2a and b) upon treatment with iodine in alcohols. The reaction of (1a) with iodine in morpholine, however, results in the formation of pyrimido[1,4]benzothiazine (3) accompanied by loss of a methylene group. Ring-contraction of (1) to 4a-halogenoalkylpyrimido[1,4]benzothiazines (2c—f) is observed upon treatment with *N*-halogenosuccinimides or iodide in chloroform. When (1a—c) are allowed to react with alkyl halides in hot dimethylformamide, bispyrimidylmethane derivatives (4a—e) are obtained in moderate yields. Treatment of thiazepine *S*-oxide (10) with triethylamine in alcohols leads to the formation of the ring-contracted product, bis-(pyrimidobenzothiazinyl)methane (11). Additionally, pyrolysis of the bispyrimidylmethane derivative (4a) caused carbon–carbon bond cleavage to give the uracil derivatives (5) and (6) and the pyrimidoquinoline derivative (7). The mechanisms of the observed reactions are also discussed on the basis of available data.

ULTRAVIOLET irradiation of alkylsulphonium ylides of 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-10*H*-pyrimido-[5,4-*b*][1,4]benzothiazine (3) causes a ready ring-expansion leading to 1,3-dimethyl-2,4-dioxo-1,2,3,4,5,11-hexahydropyrimido[5,4-*c*][1,5]benzothiazepines (1a—c) in high yields.[1,2] The juxtaposition of the enamino and sulphide moieties in the pyrimidobenzothiazepine (1) prompted us to explore the chemistry of this heterocycle.



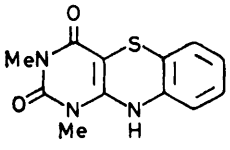
(1)

a; R = H
b; R = Me
c; R = Ph



(2)

a; R = H, R′ = OMe
b; R = H, R′ = OEt
c; R = H, R′ = Br
d; R = H, R′ = Cl
e; R = H, R′ = I
f; R = Ph, R′ = Br



(3)

This paper describes the novel ring-contraction and ring-opening of (1) and its *S*-oxide (10). Another intriguing fact is the loss of substituted methylene groups at position 5 of the 6-aminouracil moiety observed in some reactions.

When a mixture of the thiazepine (1a) and iodine in methanol or ethanol was stirred at room temperature for 5 h, 4a-methoxymethyl- or -ethoxymethyl-pyrimido[1,4]-benzothiazine (2a or b) was obtained in moderate yield. Addition of triethylamine to the above reaction mixture † resulted in the formation of some undetermined products which were difficult to separate. Reaction of the thiazepine (1a) with iodine in morpholine at room temperature without any other solvents, however, gave the thiazine (3) in 60% yield as a result of ring-contraction accompanied by loss of a methylene group from (1a).

Treatment of the thiazepine (1a) with iodine in chloroform instead of alcohols at room temperature allowed isolation of an unstable compound assigned the structure 4a-iodomethylpyrimido[1,4]benzothiazine (2e). Upon treatment of the thiazepines (1a and c) in chloroform or alcohols with an equimolar amount of *N*-bromo- or *N*-chloro-succinimide at room temperature, 4a-bromo- or -chloro-methyl derivative (2c, d, or f) was obtained in nearly quantitative yield.

The structures of the ring-contracted products (2a—f) were confirmed on the basis of their physicochemical data (see Experimental section), *e.g.*, the n.m.r. spectrum of the methoxymethyl derivative (2a) showed a singlet at δ 3.70 assignable to methylene protons and no NH signal. The u.v. spectrum of (2a) was superimposable on that of the 4a-methyl derivative which can be prepared by thermal rearrangement of the methylsulphonium ylide of the thiazine (3).[1] The bromomethyl derivative (2c) exhibited a clear AB-type quartet centred at δ 3.56 and 3.76 (*J* 10 Hz), which can be ascribed to methylene protons adjacent to an asymmetric 4a-carbon.

An episulphonium ion intermediate has been proposed

† Introduction of alkoxy groups at the 4a-position of pyrimido-[1,4]benzothiazine (3) has been achieved by oxidative coupling with alcohols in the presence of iodine and triethylamine [Y. Maki and T. Hiramitsu, *Chem. and Pharm. Bull* (*Japan*), 1976,, **24** 3135].

[1] Part 2, Y. Maki and T. Hiramitsu, *Chem. and Pharm. Bull.* (*Japan*), 1977, **25**, 292.

[2] J. M. Goldman, U.S.P. 3,483,198 (1969).

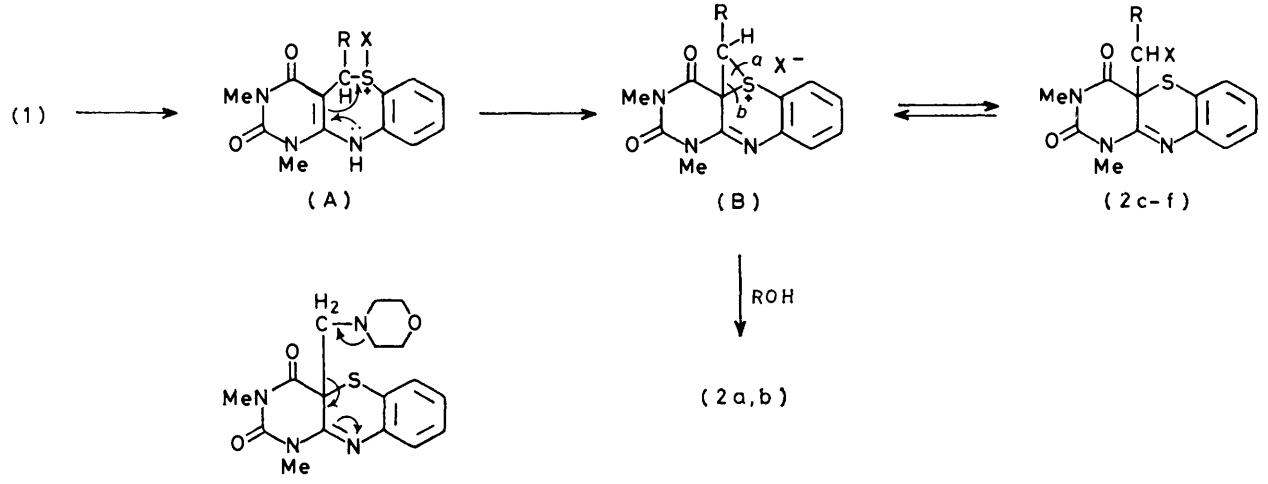
[3] H. C. Van der Plas, ' Ring Transformation of Heterocycles ', Academic Press, London and New York, 1973, vol. 2, p. 50.

[4] A. K. Mukerjee and A. K. Singh, *Synthesis*, 1975, 547.

[5] R. D. G. Cooper and D. O. Spry, in ' Cephalosporins and Penicillins, Chemistry and Biology ' ed. E. H. Flynn, Academic Press, New York, 1972, p. 203.

for a number of ring-contractions and -expansions of sulphur-containing heterocycles.[3-5]

The present ring-contraction of the thiazepine (1) to the thiazine (2) is also rationalized in terms of an episulphinium halide intermediate (B; X = Br, Cl, and I). The key intermediate (B) could be formed easily by an intramolecular nucleophilic attack of the appropriately positioned enamine carbon (at position 5 of the uracil ring) on the sulphur atom of the initially formed sulphonium halide (A). The distinct enamine character of 6-aminouracils containing a vinylogous amide has been well documented.[6] Subsequent ring-opening of the episulphide ring in (B) *via* cleavage *a* by attack of nucleophiles such as alcohols and halide ions could lead to the formation of the ring-contracted products (2a—f) (see Scheme 1).



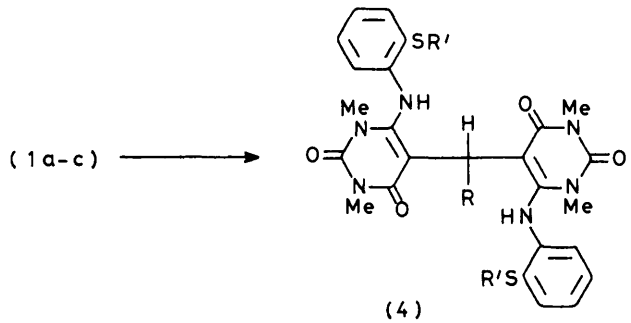

SCHEME 1

Although reaction of the 4a-iodomethyl derivative (2e) with alcohols at room temperature gave the 4a-alkoxymethyl derivatives (2a and b), the 4a-bromo- and -chloromethyl derivatives (2c and d) were stable even upon treatment with boiling alcohols. This can be explained by assuming that the 4a-iodomethyl derivative (2e) comes easily to equilibrium with the episulphonium ion (B; X = I) in solution in contrast with the 4a-bromo- and -chloro-methyl derivatives (2c and d). Thus, trapping of the intermediate (B; X = I) by alcohols could lead to the formation of the 4a-alkoxymethyl derivatives (2a and b).

Recently, a mechanism involving an episulphonium ion intermediate has been proposed for the ring-expansion of 2β-halogenomethylpenams to 3β-halogenocephams.[7] In connection with this, it should be noted that occurrence of the ring-expansion of the 4a-iodomethyl derivative (2e) to 4a-iodothiazepine derivative *via* cleavage *b* in (B) was not realized under our conditions.

The formation of the thiazine (3) accompanied by loss of a methylene group can be accounted for by a retro-Mannich type reaction of the 4a-morpholinomethyl derivative * initially formed in a manner similar to the 4a-alkoxymethyl derivatives (2a and b).

Ring-contraction of various types of 1,4-thiazepines into thiazoles, thiazolines, isothiazoles, pyrroles, and pyridines have been described.[3] To our knowledge, however, ring-contraction leading to 1,4-thiazines is unprecedented apart from a recently reported photo-induced ring-contraction.[8]




a; R = H, R′ = Me
b; R = H, R′ = Et
c; R = H, R′ = Bz
d; R = Me, R′ = Me
e; R = Ph, R′ = Me

SCHEME 2

A solution of the thiazepine (1a) in dimethylformamide containing a trace amount of water with excess of methyl

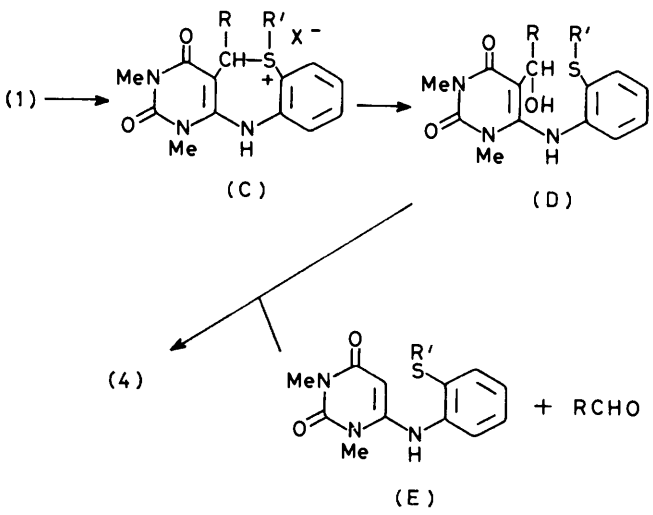
* Attempts to isolate this intermediate failed. Treatment of the bromomethyl derivative (2c) with morpholine in boiling methanol gave the thiazine (3).

[6] *E.g.*, see D. J. Brown, ' Heterocyclic Compounds, The Pyrimidines. Supplement 1,' eds. A. Weissberger and E. C. Taylor, Wiley, New York, 1970, p. 243.

[7] T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Letters*, 1973, 3001.

[8] M. F. Semmelhack, S. Kundes, and S. C. Lee, *Chem. Comm.*, 1971, 698.

iodide, ethyl iodide, or benzyl bromide was heated at 100° for 5 h. Work-up gave crystalline products in moderate yield, established as bis-[1,3-dimethyl-6-(2-methylthioanilino)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-methane derivatives (4a—c) on the basis of the n.m.r., i.r., and mass spectral data (see Experimental section) and a degradation study (*vide infra*). Analogously, the reaction of the 5-methyl- or 5-phenyl-thiazepines (1b or c) with methyl iodide led to the formation of derivatives (4d or e). The n.m.r. spectrum of the phenylmethane derivative (4e) at room temperature showed a broad SMe signal at δ 2.35, which changed to a sharp singlet at elevated temperatures. This observation suggests the presence of restricted rotation around the methine carbon of (4e) which is fairly crowded.




SCHEME 3

We propose the possible reaction sequence for the formation of the methane derivatives (4) shown in Scheme 3. The reaction appears to be initiated by nucleophilic attack of water contained in dimethylformamide on the substituted methylene carbon of the sulphonium ion (C), which can be produced by action of the thiazepines (1) with alkyl halides. 5-Hydroxymethyluracils (D) thus formed undergoes a retroaldol-type cleavage to give 6-(2-alkylthioanilino)uracils (E) and aldehydes. The lability of 5-hydroxy- and 5-aminomethyl groups in the uracil ring is well documented.[9] Subsequent condensation of (E) with the remaining 5-hydroxymethyluracil (D) could produce the methane derivatives (4).

It has been reported that the reaction of 6-aminouracils with aldehydes gives bis-(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methane derivatives.[10] Analogously, reaction of 6-(2-methylthioanilino)uracil (E; R′ = Me) with formaldehyde in ethanol at room temperature resulted in the formation of the methane derivative (4a) in high yield. This observation is relevant to the above reaction sequence involving the condensation of (E) with (D).

Pyrolysis of the methane derivative (4a) at 250 ± 5° in a sealed tube gave the 6-(2-methylthiophenylamino)-uracil derivatives (5) and (6), and the pyrimido[4,5-*b*]-quinoline derivative (7) in 41, 12, and 17% yields, respectively. The structures of these products were fully supported by physicochemical data and microanalyses. The uracil derivative (5) was identical in every respect with a sample prepared by the base-catalysed Smiles rearrangement of 6-(2-acetylaminophenylthio)-1,3-dimethyluracil (8) in the presence of excess of methyl iodide followed by treatment with sodium hydroxide.[11] Conversion of (5) into (6) was achieved upon treatment with methyl iodide in the presence of sodium hydroxide in methanol. The pyrimidoquinoline (7) was prepared independently by acid-catalysed cyclisation of 5-formyl-1,3-dimethyl-6-(2-methylthioanilino)uracil (9).

One conceivable mechanism for the formation of (5)—(7) from the methane derivative (4a) is outlined in Scheme 4.

The initial step of the reaction could involve a homolytic cleavage of the carbon–carbon bond probably *via* a tautomeric imine form of (4a). Both radicals (F) and (G) thus generated can be stabilized by conjugation with the aminouracil moiety. Steric interaction in (4a) or its tautomeric form appears to facilitate homolytic cleavage.[12] A space filling model of (4a) indicates that steric interaction around the methylene carbon is significant. Hydrogen transfer of radical (F) to (G) could give the uracil derivative (5) and an *exo*-methylene intermediate (H). However, an alternative mechanism involving heterolytic cleavage of the carbon–carbon bond of (4a) followed by proton transfer leading to (5) and (H) cannot be excluded. Cyclisation of the *exo*-methylene intermediate (H) presumably in an electrocyclic fashion would lead to the formation of dihydropyrimidoquinoline (I). Redox reaction between the dihydropyrimidoquinoline (I) and the remaining *exo*-methylene intermediate (H) could form concurrently the uracil derivative (6) and the pyrimidoquinoline (7). The product distribution, (5) : (6) : (7) = 2 : 1 : 1 (by n.m.r.), is explained by this reaction sequence.

When *S*-oxide (10) in methanol containing excess of triethylamine was heated under reflux for 5 h, an insoluble compound was obtained in 40% yield. In the absence of triethylamine, (10) was recovered unchanged. On the basis of its n.m.r. spectrum, δ 3.34 (6 H, NMe), 3.60 (6 H, NMe), and 2.53 (2 H, $CH_2$), mass spectrum, *m/e* 534($M^+$), 274 ($M^+$ — 260), and 260 ($M^+$ — 270), and microanalysis, the structure of the product was assigned as bis(pyrimidobenzothiazin-4a-yl)methane (11) (see Scheme 5). Although the detailed mechanism has not been elucidated at present, it is of interest that the

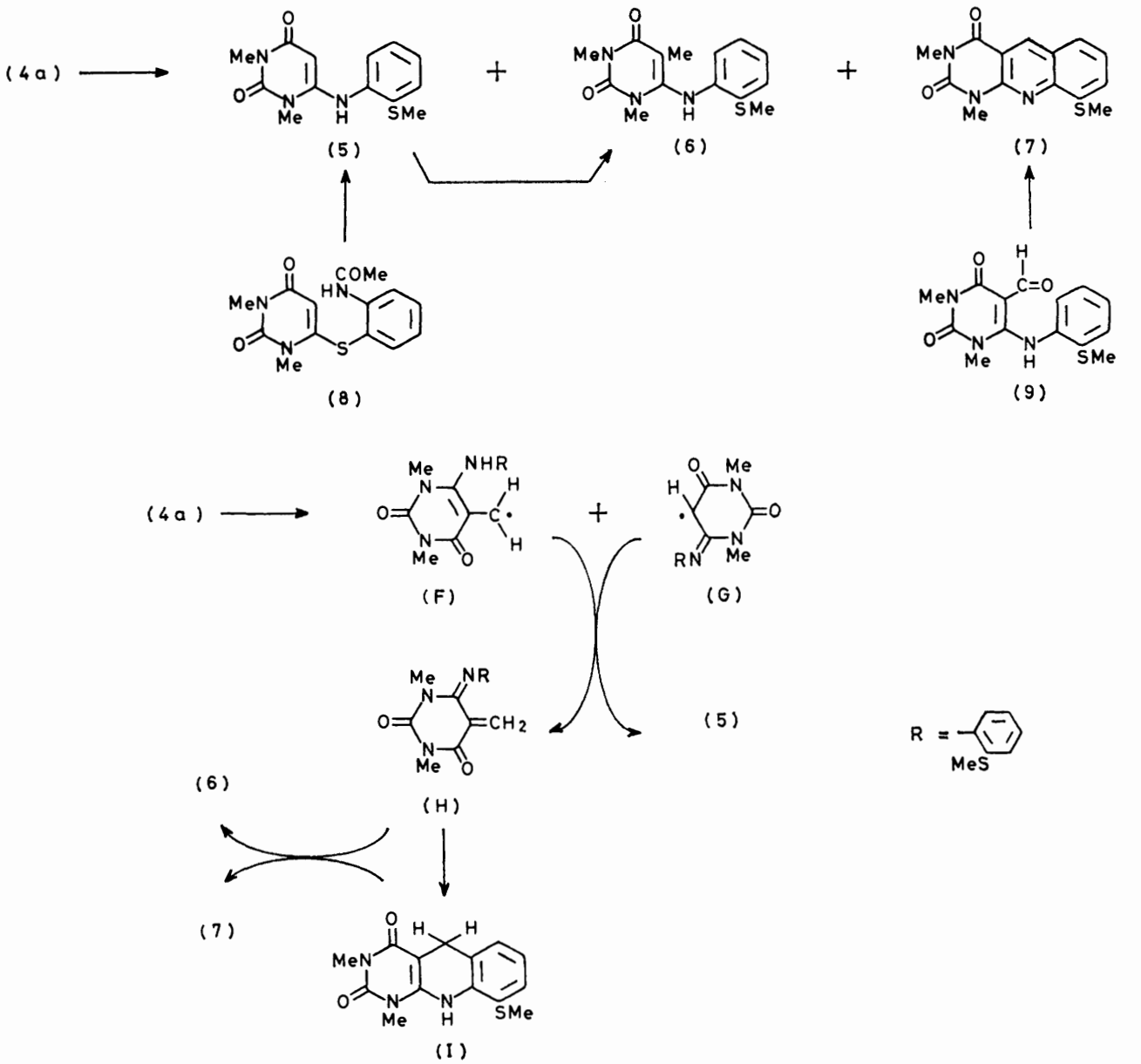
[9] A. N. Alegria, *Biochem. Biophys. Acta*, 1976, **149**, 317.
[10] W. Pfleiderer, F. Sagi, and L. Grozingen, *Chem. Ber.*, 1966, **99**, 3530.
[11] Y. Maki, M. Sato, and K. Yamane, *Yakugaku Zasshi*, 1965, **85**, 429.
[12] For a new example of ready carbon–carbon bond homolysis, see T. H. Koch, J. A. Olesen, and J. Denero, *J. Amer. Chem. Soc.*, 1975, **97**, 7285.

reaction involves the loss of a C-5 substituted methylene group in the 6-aminouracil moiety in analogy with formation of the methane derivatives (4).

## EXPERIMENTAL

I.r. spectra were recorded with a Hitachi 215 spectrometer for potassium bromide discs and $^1H$ n.m.r. spectra with a Hitachi R-20B 60 MHz spectrometer for solutions in deuteriochloroform containing tetramethylsilane as internal standard. Mass spectra were measured at 75 eV with a JEOL JMS-OISG spectrometer and u.v. spectra with a Shimazu MPS-50L spectrophotometer for solutions in ethanol. Column chromatography was performed on silica gel (Mallinckrodt; 100 mesh) using chloroform as eluant.

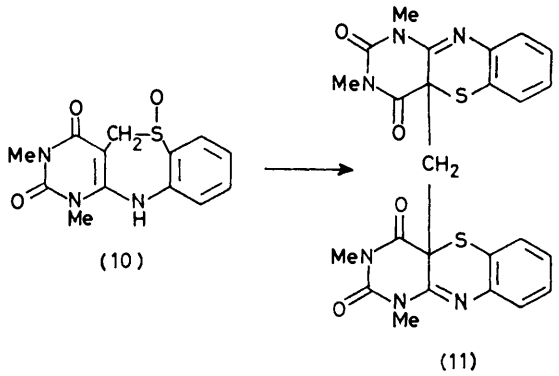
*4a-Methoxymethyl(and -Ethoxymethyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-4aH-pyrimido[5,4-b][1,4]benzothiazine* (2a *and* b).—A solution of thiazepine (1a) (0.55 g) and iodine (1.0 g) in methanol (50 ml) was stirred at room temperature for 4 h. After evaporation of the solvent, the residue was dissolved in chloroform (50 ml) and washed with 10% aqueous solution of sodium thiosulphate. The organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure at room temperature. The residue was purified by column chromatography and recrystallized from n-hexane to give the 4a-methoxymethyl derivative (2a) (0.31 g), as prisms, *m/e* 305 ($M^+$), 274, and 260, $\nu_{max.}$ 1 720 and 1 670 $cm^{-1}$ (CO), $\lambda_{max.}$ 227 (ε 46 100), 263 (32 600), and 291 nm (11 300), δ 3.30 (3 H, s, OMe), 3.40 (3 H, s, NMe), 3.61 (3 H,




SCHEME 4

s, NMe), 3.70 (2 H, s, $OCH_2$), and 7.04—7.52 (4 H, m, ArH).

Analogously, the reaction of (1a) (0.55 g) with ethanol in the presence of iodine gave the 4a-ethoxymethyl derivative



SCHEME 5

(2b) (0.26 g), as needles (from n-hexane), $\nu_{max.}$ 1 720 and 1 660 $cm^{-1}$ (CO).

4a-*Bromomethyl(and-Chloromethyl)*-1,3-*dimethyl*-2,4-*dioxo*-1,2,3,4-*tetrahydro*-4aH-*pyrimido*[5,4-b][1,4]*benzothiazine* (2c *and* d).—A solution of thiazepine (1a) (0.55 g) and *N*-bromosuccinimide (0.39 g) in chloroform (50 ml) was stirred at room temperature for 3 h. The solvent was evaporated at room temperature under reduced pressure and the residue was triturated with water (50 ml). The separated solid was collected and recrystallized from methanol to give the 4a-bromomethyl derivative (2c) (0.54 g) as needles, $\nu_{max.}$ 1 720 and 1 670 $cm^{-1}$ (CO), δ 3.44 (3 H, s, NMe), 3.63 (3 H, s, NMe), 3.57, 3.76 (2 H, AB q, *J* 10 Hz, $CH_2$), and 7.00—7.60 (4 H, m, ArH).

Analogously, the 4a-chloromethyl derivative (2d) was obtained by reaction of (1a) with *N*-chlorosuccinimide as prisms (from ethanol) in 81% yield.

4a-*Iodomethyl*-1,3-*dimethyl*-2,4-*dioxo*-1,2,3,4-*tetrahydro*-4aH-*pyrimido*[5,4-b][1,4]*benzothiazine* (2e).—A solution of thiazepine (1a) (0.55 g) and iodine (1.0 g) in chloroform (50 ml) was stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure at room temperature. The residue was purified by column chromatography and recrystallized carefully from n-hexane to give the 4a-iodomethyl derivative (2e) (0.20 g) as prisms, m.p. 80° (decomp.), $\nu_{max.}$ 1 720 and 1 670 $cm^{-1}$ (CO), δ 3.42 (3 H, s, NMe), 3.48 (2 H, s, $CH_2I$), 3.60 (3 H, s, NMe), and 7.08—7.58 (4 H, m, ArH).

4a-(α-*Bromobenzyl*)-1,3-*dimethyl*-2,4-*dioxo*-1,2,3,4-*tetrahydro*-4aH-*pyrimido*[5,4-b][1,4]*benzothiazine* (2f).—A solution of thiazepine (1c) (0.70 g) and *N*-bromosuccinimide (0.39 g) in chloroform (50 ml) was stirred at room temperature for 3 h. The solvent was removed under reduced pressure at room temperature, and the residue was triturated with water (50 ml). The separated solid was collected and recrystallized from ether to give the 4a-benzyl derivative (2f) as prisms, $\nu_{max.}$ 1 720 and 1 670 $cm^{-1}$ (CO), δ 3.43 (3 H, s, NMe), 3.63 (3 H, s, NMe), 5.00 (1 H, s, CH), and 7.00—7.60 (9 H, m, ArH).

1,3-*Dimethyl*-2,4-*dioxo*-1,2,3,4,5,11-*hexahydropyrimido*-[5,4-c][1,5]*benzothiazepine S-Oxide* (10).—To a stirred solution of thiazepine (1a) (0.55 g) in chloroform (50 ml) was added 85% *m*-chloroperbenzoic acid (0.41 g) at room temperature, and the mixture was further stirred for 3 h. The solvent was evaporated at room temperature to leave an oily residue, which was triturated with ether (50 ml). The solid mass which separated was collected and recrystallized from methanol to give needles (0.50 g), m.p. 230°, $\nu_{max.}$ 3 320 (NH), 1 690, 1 740 (CO), and 1 030 $cm^{-1}$ (SO), δ [$(CD_3)_2SO$] 3.25 (3 H, s, NMe), 3.55 (3 H, s, NMe), 3.66, 4.59 (2 H, AB q, *J* 12 Hz, $CH_2$), 7.10—8.00 (4 H, m, ArH), and 9.05br (1 H, NH).

*Bis*-(1,3-*dimethyl*-2,4-*dioxo*-1,2,3,4-*tetrahydro*-4aH-*pyrimido*[5,4-b][1,4]*benzothiazin*-4a-*yl*)*methane* (11).—A solution of *S*-oxide (10) (0.58 g) and triethylamine (2 ml) in methanol (50 ml) was refluxed for 10 h. After cooling, the precipitated solid was collected and recrystallized from acetone to give (11) (0.32 g) as *needles*, m.p. 277° (Found: C, 56.05; H, 4.2; N, 15.5. $C_{25}H_{22}O_4N_6S_2$ requires C, 56.2; H, 4.15; N, 15.75%), *m/e* 534 ($M^+$), 274, and 260, $\nu_{max.}$ 1 730 and 1 670 $cm^{-1}$ (CO), δ 2.53 (2 H, s, $CH_2$), 3.34 (6 H, s, 2 NMe), 3.60 (6 H, s, 2 NMe), and 6.90—7.40 (8 H, m, ArH).

*Conversion of Thiazepine* (1a) *into Thiazine* (3).—To a solution of thiazepine (1a) (0.55 g) in morpholine (30 ml) was added iodine (2 g) at room temperature, and the mixture was stirred for 2 h. The resulting solution was poured into ice–water containing 5% aqueous sodium thiosulphate. After stirring overnight, the separated solid (0.30 g) was collected and shown to be identical with authentic (3) [13] by i.r. and n.m.r. spectral comparisons.

*Bis*-[6-(2-*alkylthioanilino*)-1,3-*dimethyl*-2,4-*dioxo*-1,2,3,4-*tetrahydropyrimidin*-5-*yl*]*methane* (4a—c).—A solution of thiazepine (1a) (0.55 g) and methyl iodide (5 ml) in dimethylformamide (30 ml) was heated at 100° for 3 h. The solvent and excess of methyl iodide were removed under reduced pressure. The residue was purified by column chromatography and recrystallized from acetone to give (4a) (0.34 g) as prisms, *m/e* 566 ($M^+$), 289, and 277, $\nu_{max.}$ 3 175 (NH), 1 690, and 1 620 $cm^{-1}$ (CO), δ 2.57 (6 H, s, 2 SMe), 3.14 (6 H, s, 2 NMe), 3.47 (6 H, s, 2 NMe), 3.47 (2 H, s, $CH_2$), 6.45—7.45 (8 H, m, ArH), and 9.55 (2 H, s, 2 NH).

The ethylthio derivative (4b) was obtained by the reaction of thiazepine (1a) with ethyl iodide and purified according to the procedure given above for (4a), as prisms (from acetone), in 42% yield, $\nu_{max.}$ 3 175 (NH), 1 690, and 1 620 $cm^{-1}$ (CO).

The benzylthio derivative (4c) was also obtained by the reaction of (1a) with benzyl bromide under analogous conditions, as prisms (from chloroform–ethanol), in 45% yield, $\nu_{max.}$ 1 690 and 1 630 $cm^{-1}$ (CO).

1,1-*Bis*-[1,3-*dimethyl*-6-(2-*methylthioanilino*)-2,4-*dioxo*-1,2,3,4-*tetrahydropyrimidin*-5-*yl*]*ethane* (4d).—A solution of thiazepine (1b) (0.58 g) and methyl iodide (5 ml) in dimethylformamide (30 ml) was heated at 100° for 4 h. The solvent and excess of methyl iodide were evaporated under reduced pressure. The residue was purified by column chromatography and recrystallized from chloroform–ethanol to give (4d) (0.22 g), as a powder, $\nu_{max.}$ 3 170 (NH), 1 690, and 1 630 $cm^{-1}$ (CO), δ 1.30 (3 H, d, *J* 7 Hz, CMe), 2.52 (6 H, s, 2 SMe), 3.13 (6 H, s, 2 NMe), 3.42 (6 H, s, 2 NMe), 4.29 (1 H, q, *J* 7 Hz, CH), 6.40—7.40 (8 H, m, ArH), and 9.37br (2 H, 2 NH).

*Bis*-[1,3-*dimethyl*-6-(2-*methylthioanilino*)-2,4-*dioxo*-1,2,3,4-*tetrahydropyrimidin*-5-*yl*]*phenylmethane* (4e).—A solution of thiazepine (1c) (0.70 g) and methyl iodide (5 ml) in dimethylformamide (30 ml) was heated at 100° for 5 h. After evaporation of the solvent and excess of methyl iodide, the

[13] Y. Maki, T. Hiramitsu, and M. Suzuki, *Chem. and Pharm. Bull. (Japan)*, 1974, **22**, 1265.

residue was purified by column chromatography and recrystallized from benzene to give (4e) (0.23 g), as a powder, *m/e* 643 ($M^+$) and 365, $\nu_{max.}$ 3 200 (NH), 1 685, and 1 640 $cm^{-1}$ (CO), δ 2.35br (6 H, 2 SMe), 3.16 (6 H, s, 2 NMe), 3.50 (6 H, s, 2 NMe), 5.75 (1 H, s, CH), 6.30—7.35 (13 H, m, ArH), and 8.97br (2 H, 2 NH).

*Pyrolysis of Bispyrimidylmethane* (4a).—The bispyrimidylmethane derivative (4a) (0.28 g) was heated at 250 ± 5° in a sealed glass tube without solvent for 3 h. The mixture was subjected to preparative thick-layer chromatography (silica gel, chloroform) to separate 6-*anilinouracil* (5) (0.11 g), 5-*methyl*-6-*anilinouracil* (6) (0.04 g), and 1,3-*dimethyl*-9-*methylthio*-2,4-*dioxo*-1,2,3,4-*tetrahydropyrimido*[2,3-d]-*quinoline* (7) (0.05 g).

Recrystallization of (5) from acetone gave prisms, m.p. 226° (Found: C, 56.35; H, 5.45; N, 15.05. $C_{13}H_{15}O_2N_3S$ requires C, 56.3; H, 5.45; N, 15.15%), *m/e* 277 ($M^+$) and 262, $\nu_{max.}$ 3 275 (NH), 1 680, and 1 615 $cm^{-1}$ (CO), δ 2.43 (3 H, s, SMe), 3.32 (3 H, s, NMe), 3.60 (3 H, s, NMe), 5.00 (1 H, s, vinyl H), 6.57br (1 H, NH), and 7.20—7.50 (4 H, m, ArH). Compound (5) was obtained independently by the following procedure *via* Smiles rearrangement.[11] To a solution of 1,3-dimethyl-6-(2-acetylaminophenylthio)uracil (0.61 g) (8) and methyl iodide (1 ml) in methanol (50 ml), was added 5% aqueous sodium hydroxide (1.6 ml). After stirring for 1 h at room temperature, additional 5% aqueous sodium hydroxide (3.2 ml) was added with further stirring for 2 h. The mixture was evaporated at room temperature under reduced pressure. The residue was washed with water and recrystallized from methanol to give (5) (0.38 g) as needles.

Recrystallization of (6) from n-hexane gave needles, m.p. 115° (Found: C, 57.75; H, 5.85; N, 14.45. $C_{14}H_{17}O_2N_3S$ requires C, 57.7; H, 5.9; N, 14.45%), $\nu_{max.}$ 3 260 (NH), 1 680, and 1 630 $cm^{-1}$ (CO), δ 1.90 (3 H, s, CMe), 2.48 (3 H, s, SMe), 3.34 (3 H, s, NMe), 3.44 (3 H, s, NMe), 6.35br (1 H, NH), and 6.50—7.60 (4 H, m, ArH).

Recrystallization of (7) from acetone gave yellow needles, m.p. 250° (Found: C, 58.6; H, 4.35; N, 14.6. $C_{14}H_{13}O_2N_3S$ requires C, 58.55; H, 4.55; N, 14.65%), *m/e* 287 ($M^+$) and 254, $\nu_{max.}$ 1 700 and 1 650 $cm^{-1}$ (CO), δ 2.57 (3 H, s, SMe), 3.52 (3 H, s, NMe), 3.80 (3 H, s, NMe), 7.30—7.80 (3 H, m, ArH), and 8.95 (1 H, s, 5-H). The pyrimidoquinoline (7) thus obtained was identical in every respect with the sample prepared as follows. A solution of 6-chloro-5-formyl-1,3-dimethyluracil (1.0 g), 2-methylthioaniline (0.7 g), and triethylamine (2 ml) in chloroform (50 ml) was stirred at room temperature for 3 h. Solvent was removed at room temperature under reduced pressure. The residue was dissolved in methanol (30 ml) and allowed to stand for 5 h. The yellow powder deposited was collected and recrystallized from methanol to give (9) (0.8 g) as pale yellow needles, m.p. 207°, δ 2.50 (3 H, s, SMe), 2.97 (3 H, s, NMe), 3.40 (3 H, s, NMe), 6.90—7.45 (4 H, m, ArH), 10.05 (1 H, s, CHO), and 12.30br (1 H, NH). After heating (9) (0.8 g) at 100° in polyphosphoric acid (30 ml) for 5 h, the mixture was poured into ice–water and allowed to stand overnight. The separated solid was collected and recrystallized from acetone to give (7) (0.7 g) as yellow needles.

*Reaction of* 6-*Anilinouracil* (5) *with Formaldehyde*.—A solution of (5) (0.28 g), 37% formaldehyde (1 ml), and a catalytic amount of sulphuric acid in ethanol (20 ml) was stirred at room temperature for 3 h. The separated solid (0.20 g) was collected and identified with a sample of (4a) obtained by the reaction of (1a) with methyl iodide by i.r. and n.m.r. spectral comparisons.

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TABLE 1

4a-Substituted-pyrimido[5,4-*b*][1,4]benzothiazine (2a—d and f)

| Compound | M.p. (°C) | Found (%) C | H | N | Formula | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|
| (2a) | 143 | 54.95 | 4.95 | 13.8 | $C_{14}H_{15}O_3N_3S$ | 55.1 | 4.95 | 13.75 |
| (2b) | 93 | 56.25 | 5.4 | 13.1 | $C_{15}H_{17}O_3N_3S$ | 56.4 | 5.35 | 13.15 |
| (2c) | 153 | 44.35 | 3.55 | 12.15 | $C_{13}H_{12}O_2N_3SBr$ | 44.05 | 3.4 | 11.85 |
| (2d) | 136—137 | 50.4 | 3.9 | 13.4 | $C_{13}H_{12}O_2N_3SCl$ | 50.4 | 3.9 | 13.55 |
| (2f) | 164 | 53.3 | 3.75 | 9.7 | $C_{19}H_{16}O_2N_3SBr$ | 53.05 | 3.75 | 9.75 |

TABLE 2

Bis-[6-(2-alkylthioanilino)pyrimidin-5-yl]methane derivatives (4a—e)

| Compound | M.p (°C) | Found (%) C | H | N | Formula | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|
| (4a) | 245 | 57.3 | 5.3 | 14.85 | $C_{27}H_{30}O_4N_6S_2$ | 57.25 | 5.35 | 14.85 |
| (4b) | 249 | 58.35 | 5.5 | 14.0 | $C_{29}H_{34}O_4N_6S_2$ | 58.55 | 5.75 | 14.15 |
| (4c) | 182 | 65.15 | 5.4 | 11.5 | $C_{39}H_{38}O_4N_6S_2$ | 65.15 | 5.35 | 11.7 |
| (4d) | 213 | 57.95 | 5.55 | 14.45 | $C_{28}H_{32}O_4N_6S_2$ | 57.9 | 5.55 | 14.9 |
| (4e) | 235 | 61.65 | 5.25 | 12.95 | $C_{33}H_{34}O_4N_6S_2$ | 61.65 | 5.35 | 13.1 |