A Mannich-Type Cyclisation to Thiazepines. Synthesis of Pyrimido[5,4-*f*]benzo[*b*]-1,4-thiazepines, a New Tricyclic System

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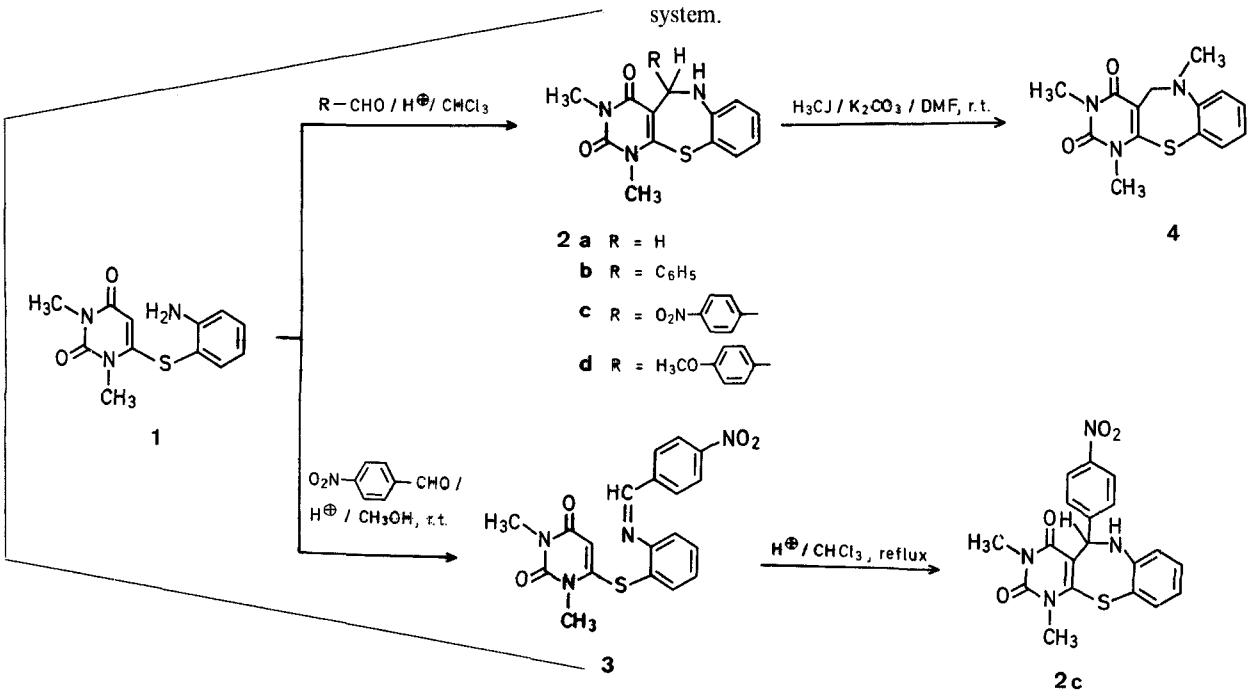
One of the convenient methods for the synthesis of dibenzo[*b,f*]1,4-thiazepines is a Bischler-Napieralski-type cyclisation of *o*-(phenylthio)-acylanilides[1]. A Mannich-type (Pictet-Spengler-type) cyclisation of *o*-(phenylthio)-anilines, however, has not been utilised advantageously as an alternative approach to the fused thiazepines[1].

In this paper, we wish to describe a novel example of the Mannich-type thiazepine cyclisation which could be extended to the synthesis of some fused[*f*]benzo[*b*]-1,4-thiazepines.

Previous reports of the Mannich reaction at the 5-position of uracil ring[2] prompted us to examine an intramolecular Mannich-type cyclisation of 1,3-dimethyl-6-(*o*-aminophenylthio)-uracil (**1**) leading to a new tricyclic system, the 1,2,3,4,5,6-hexahydropyrimido[5,4-*f*]benzo[*b*]-1,4-thiazepines (**2a–d**)[3]. The present successful results show that, in principle, the Mannich-type thiazepine cyclisation is applicable to molecules involving a 3-(*o*-aminophenylthio)-2-enone system.



Reaction of **1** with excess formaldehyde, benzaldehyde, or *p*-nitro (or methoxy)-benzaldehyde was conducted in chloroform in the presence of a catalytic amount of *p*-toluenesulfonic acid at room temperature or under reflux for 4–10 h (see Table). After the usual work-up, thiazepines (**2a–d**) were isolated in moderate to high yields.

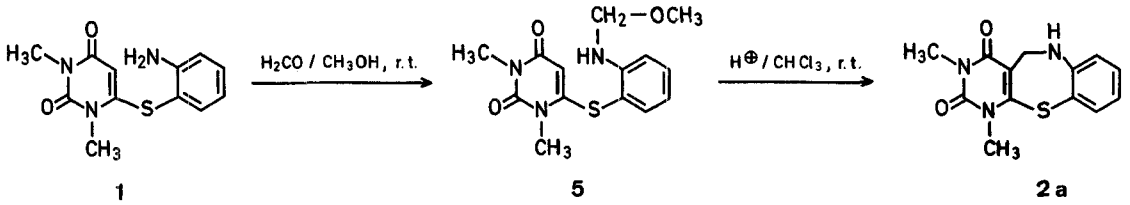
The thiazepine cyclisation using aliphatic aldehydes other than formaldehyde, i.e., acetaldehyde and propionaldehyde, did not give satisfactory results. In these cases, the reaction resulted in the formation of a dimeric product which probably arises from the reaction of an intermediary Schiff base with its tautomeric enamine.

Physicochemical data and microanalytical results fully support the structures of **2a–d**, e.g., the N.M.R. spectrum of **2a** showed a signal at 4.75 ppm (2H, broad singlet, coalesced to a sharp singlet by deuterium exchange) assignable to the methylene protons adjacent to an amino function. The *N*-methyl derivative **4**, m.p. 146°, was easily obtained in 60% yield upon treatment of **2a** with methyl iodide in dimethylformamide containing potassium carbonate.

An intermediary Schiff base **3**, m.p. 221°, was isolated when **1** was allowed to react with *p*-nitrobenzaldehyde in methanol in the presence of *p*-toluenesulfonic acid at room temperature for 1 h. The Schiff base thus obtained was converted into thiazepine **2c** by further heating in chloroform containing *p*-toluenesulfonic acid.

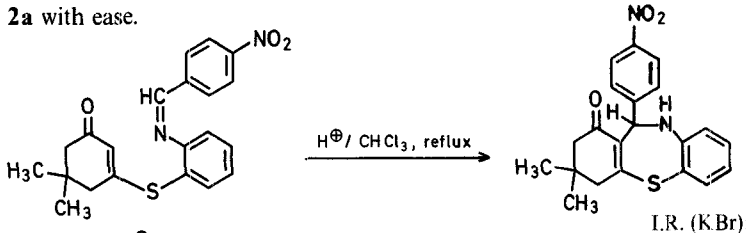
The Schiff base of 3-(*o*-aminophenylthio)-5,5-dimethylcyclohex-2-enone[4], which has structural similarity to **1** with respect to involvement of a 3-(*o*-aminophenylthio)-2-enone moiety, underwent the analogous acid-catalysed cyclisation to give the corresponding thiazepine **7**. In agreement with previous observation[1], however, the Mannich-type cyclisation of *o*-(phenylthio)-anilines, e.g., 3-(2′-p-nitrobenzylideneaminophenylthio)-toluene (**8**), was unsuccessful.

The synthesis of some other fused thiazepine systems by means of the Mannich-type cyclisation is now in progress.

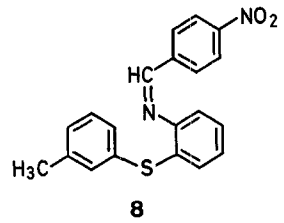


1 **5** **2a**

Reaction of **1** with formaldehyde in methanol at room temperature gave the methoxymethylamino derivative **5**, m.p. 178°; N.M.R. ($CDCl_3$) $\delta = 3.30$ (3H, singlet, OCH_3), 4.67 ppm (2H, doublet, $J = 7$ Hz, $-NHCH_2OCH_3$, coalesced to a singlet by deuterium exchange). Subsequent treatment of **5** with *p*-toluenesulfonic acid led to the formation of **2a** with ease.



6 **7**



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Preparation of 1,3-Dimethyl-6-(*o*-aminophenylthio)-uracil (1):
A solution of 6-chloro-1,3-dimethyluracil (1.75 g), *o*-aminothiophenol (1.25 g), and triethylamine (2.0 g) in chloroform (50 ml) was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was triturated with ether. The separated solid was collected, washed with water and recrystallised from ethanol to give **1**, as colourless prisms; yield: 2.5 g (93%); m.p. 185°.

$C_{12}H_{13}N_3O_2S$	calc.	C 54.75	H 4.98	N 15.96
(263.3)	found	54.65	4.88	15.75

I.R. (KBr): $\nu_{max} = 3450, 3350, 1690, 1620\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.30$ (s, 3H, NCH_3), 3.60 (s, 3H, NCH_3), 4.35 (s, 2H, NH_2), 5.10 (s, 1H, H—C-5), 6.65–7.60 ppm (m, 4H$_{arom}$).

Preparation of Thiazepines (2a–d) by Mannich-Type Cyclisation; Typical Procedure:
To a chloroform solution of **1** (0.52 g) was added 37% formalin (1.5 ml) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred at room temperature for 4 h. The reaction mixture was washed with 5% aqueous sodium hydrogen carbonate and the chloroform layer was dried over anhydrous sodium sulfate. After removal of the solvent, the residue was triturated with

Table. Preparation of Thiazepines (**2a–d** and **7**)

Thiazepine	Reaction Temp./Time	Yield[a] [%]	m.p. (solvent)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm] H—C-5	Molecular Formula[b]
2a	r.t/4 h	65	212° (CH_3OH)	4.75 (2H, broad singlet)	$C_{13}H_{13}N_3O_2S$ (275.4)
2b	reflux[c]/7 h	64	171° (C_2H_5OH)	6.10 (1H, doublet, $J = 8$ Hz)	$C_{19}H_{17}N_3O_2S$ (351.5)
2c	reflux/4 h	97	140° (C_2H_5OH)	6.17 (1H, doublet, $J = 8$ Hz)	$C_{19}H_{16}N_4O_4S$ (396.5)
2d	reflux/10 h	25	171° (C_2H_5OH)	6.03 (1H, broad singlet)	$C_{20}H_{19}N_3O_3S$ (381.5)
7[d]	reflux/10 h	23	192° ($C_2H_5OH/CHCl_3$)	6.05 (1H, broad singlet)	$C_{21}H_{20}N_2O_3S$ (380.5)

[a] Yield of isolated product.
[b] All products gave satisfactory microanalyses (C ± 0.30%, H ± 0.10%, N ± 0.30%).
[c] All reactions were carried out in chloroform.
[d] Reaction temp./time and yield in acid catalysed cyclisation of Schiff base **6**.

ethanol (20 ml). On standing for a few days, the separated solid was collected and recrystallised from methanol to give **2a**; yield: 0.35 g (65%).

1,3-Dimethyl-6-(*o*-methoxymethylaminophenylthio)-uracil (5):
A mixture of **1** (1.31 g) and 37% formalin (5 ml) in methanol (30 ml) was stirred at room temperature for 6 h. The separated solid was collected and recrystallised from methanol to give the methoxymethylamino derivative **5** as colourless needles; yield: 1.20 g, (80%); m.p. 178°.

$C_{14}H_{17}N_3O_3S$	calc.	C 54.72	H 5.58	N 13.68
(307.4)	found	54.61	5.54	13.83

I.R. (KBr): $\nu_{max} = 3400, 1695, 1640\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.30$ (s, 3H, NCH_3), 3.30 (s, 3H, OCH_3), 3.62 (s, 3H, NCH_3), 4.67 (d, 2H, $J = 7$ Hz, CH_2), 5.05 (s, 1H, H—C-5), 5.64 (t, 1H, $J = 7$ Hz, NH), 6.70–7.60 ppm (m, $4H_{arom}$).

Treatment of **5** with *p*-toluenesulfonic acid in chloroform at room temperature gave thiazepine **2a** in 63% yield.

***p*-Nitrobenzilideneamino Derivative (3):**
A solution of **1** (0.52 g), *p*-nitrobenzaldehyde (0.33 g) and a catalytic amount of *p*-toluenesulfonic acid in ethanol (30 ml) was stirred at room temperature for 2 h. The precipitated solid was collected and recrystallised from chloroform/ethanol to give the Schiff base **3** as yellow needles; yield: 0.50 g (73%); m.p. 221°.

$C_{19}H_{16}N_4O_4S$	calc.	C 57.57	H 4.07	N 14.14
(396.5)	found	57.67	3.99	14.19

I.R. (KBr): $\nu_{max} = 1695, 1640\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.28$ (s, 3H, NCH_3), 3.60 (s, 3H, NCH_3), 5.15 (s, 1H, H—C-5), 7.14–8.53 (m, $8H_{arom}$), 8.57 ppm (s, 1H, N=CH).

Treatment of **3** with *p*-toluenesulfonic acid in chloroform under reflux gave the thiazepine **2c** in 96% yield.

***N*-Methylthiazepine Derivative (4):**
A mixture of **2a** (0.55 g), anhydrous potassium carbonate (0.55 g) and methyl iodide (1 ml) in dimethylformamide (20 ml) was stirred for 10 h at room temperature. The reaction mixture was poured into ice/water. After stirring over night, the precipitated solid was collected and recrystallised from ethanol to give the *N*-methyl derivative **4** as pale yellow needles; yield: 0.35 g (61%); m.p. 146°.

$C_{14}H_{15}N_3O_2S$	calc.	C 58.12	H 5.23	N 14.53
(289.5)	found	58.06	5.30	14.48

I.R. (KBr): $\nu_{max} = 1690, 1640\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.02$ (s, 3H, NCH_3), 3.32 (s, 3H, NCH_3), 3.60 (s, 3H, NCH_3), 4.48 (s, 2H, CH_2), 6.60–7.30 ppm (m, $4H_{arom}$).

Acid-Catalysed Cyclisation of Schiff Base 6:
A solution of Schiff base **6**[4] (0.5 g) and *p*-toluenesulfonic acid (0.03 g) in chloroform (50 ml) was refluxed for 10 h. After removal of the solvent, the residue was purified by column chromatography (silica gel, chloroform as eluent) to give the thiazepine **7**; yield: 0.21 g; which was recrystallised from chloroform/ethanol to give yellow prisms.

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[1] For a leading reference, see: P. Catsoulacos, *J. Heterocycl. Chem.* **7**, 409 (1970).

[2] E. I. Budowsky, V. N. Shibaev, G. I. Eliseeva, *Synthetic Procedure in Nucleic Acid Chemistry*, W. W. Zorbach, R. S. Tipson, Ed., Vol. 1, p. 436, Interscience, New York, 1968.

[3] Isomeric 1,2,3,4,5,11-hexahydropyrimido[4,5-*e*]benzo[*b*]-1,4-thiazepines have been prepared by photolysis of the corresponding 1,2,3,4-tetrahydropyrimido[5,4-*b*]-1,4-benzothiazine sulfonium ylides (Y. Maki, T. Hiramitsu, submitted to *Chem. Pharm. Bull. (Tokyo)*; I. M. Goldman, *U.S. Patent* 3,483,198 (1969); *C.A.* **72**, 79078 (1970)).

[4] S. Miyano, N. Abe, K. Sumoto, K. Teramoto, *J. Chem. Soc. Perkin Trans. 1*, **1976**, 1146.