

Note

Novel synthesis of fused ring [1,4]benzothiazines/[1,4]benzoxazines and related heterocycles

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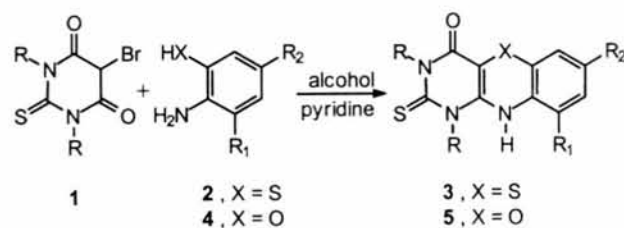
The interaction of 1,3-disubstituted-5-bromo-2-thioxo-barbituric acid with *o*-aminothiophenols and *o*-aminophenol affords 5, 7-disubstituted-8-oxo-6-thioxo-pyrimido[5, 4-*b*](1, 4) benzothiazines and 5,7-disubstituted-8-oxo-6-thioxo-pyrimido-[5,4-*b*](1,4)-benzoxazines, respectively. The reaction of 5, 5-dibromo-1, 3-disubstituted-2-thioxo-barbituric acid, with *o*-aminothiophenols and *o*-aminophenol is discussed. The compounds have been characterised by chemical reactions and spectral studies.

The 1,4-benzothiazine and 1,4-benzoxazine moiety in molecules have interesting analgesic, anti-microbial^{1,2} properties and anti-inflammatory activity³. Recently, the antiviral activity of benzothiazines against human immunodeficiency virus-1 and 2 (HIV-1 and HIV-2) has been reported^{4,5}. Similarly, thiobarbiturates are well-known for their narcotic⁶ and cardiovascular activity^{7,8}. In continuation of our work¹² on the synthesis of spiro compounds, we report herein the reactions of 5-bromo-1,3-disubstituted thiobarbituric acid **1** and 5,5-dibromo disubstituted thiobarbituric acid **6** with *o*-aminothiophenols **2**/*o*-aminophenol **4**.

On refluxing molar quantities of **1** and **2** in ethanol in the presence of pyridine, 5,7-disubstituted-8-oxo-6-thioxo-tetrahydropyrimido[5, 4-*b*](1,4)benzothiazine **3** was obtained. For **3a**, IR in KBr showed main bands at 3435.5 (–NH), 1608 (broad, >C=O), 1298 cm^{–1} (>C=S). ¹H NMR: δ 6.904-7.758 (m, 14H, Ar-H) and 8.821 (s, 1H, –NH).

Similarly, the reaction of **1** with **4** gave 5,7-disubstituted-8-oxo-6-thioxo-tetrahydropyrimido [5,4-*b*](1,4)benzoxazine **5** (Scheme I). For **5c**, IR (KBr): 3422.03 (–NH), 1633 (>C=O), 1282 cm^{–1} (>C=S). ¹H NMR: δ 3.182 (s, 6H, 2×–OCH₃), 6.728-7.813 (m, 12H, Ar-H), 9.8 (s, 1H, –NH).

A mixture of **2** (0.01 mole), **6** (0.01 mole) and



Compd	R	R ₁	R ₂
3a	C ₆ H ₅	H	H
3b	C ₆ H ₅	H	CH ₃
3c	C ₆ H ₅	H	OCH ₃
3d	C ₆ H ₅	Cl	H
3e	C ₆ H ₅	H	Cl
3f	<i>o</i> -CH ₃ -C ₆ H ₄	H	H
3g	<i>o</i> -CH ₃ -C ₆ H ₄	H	CH ₃
3h	<i>o</i> -CH ₃ -C ₆ H ₄	H	OCH ₃
3i	<i>o</i> -CH ₃ -C ₆ H ₄	H	Cl
3j	<i>o</i> -CH ₃ O-C ₆ H ₄	H	H
3k	<i>o</i> -CH ₃ O-C ₆ H ₄	H	CH ₃
3l	<i>o</i> -CH ₃ O-C ₆ H ₄	H	OCH ₃
3m	<i>o</i> -CH ₃ O-C ₆ H ₄	H	Cl
5a	C ₆ H ₅	H	H
5b	<i>o</i> -CH ₃ -C ₆ H ₄	H	H
5c	<i>o</i> -CH ₃ O-C ₆ H ₄	H	H

Scheme I

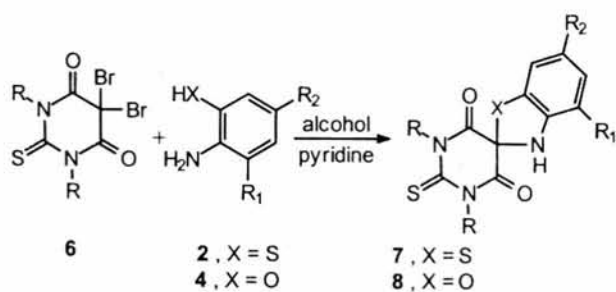
pyridine (0.01 mole) when heated under reflux for 4 hr afforded 4',5'-substituted-2, 3-benz-6,10-dioxo-7, 9-disubstituted-1-thia-4, 7, 9-triaza-8-thioxo-(4*H*)-spiro-[6.5] decane **7** (Scheme II). For **7b**; IR (KBr): 3422.03 (–NH), 1618 (>C=O), 1292 (>C=S). ¹H NMR: δ 2.416 (s, 3H, –CH₃), 7.081-7.611 (m, 13H, Ar-H) and 8.821 (s, 1H, –NH).

Similarly 2, 3-benz-6, 10-dioxo-7, 9-disubstituted-1-oxa-4, 7, 9-triaza-8-thioxo-(4*H*)-spiro [6.5] decanes **8** were obtained by the interaction of **6** and **4** in the presence of pyridine.

Experimental Section

Melting points were determined in an open glass capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 series. ¹H NMR and ¹³C NMR on 300 MHz VXR0 using DMSO-*d*₆ as solvent. TLC in various solvents showed the compounds to be homogeneous. Compounds **1**, **2** and **6** were prepared by adopting the literature methods⁹⁻¹¹.

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Compd	R	R ₁	R ₂
7a	C ₆ H ₅	H	H
7b	C ₆ H ₅	H	CH ₃
7c	C ₆ H ₅	H	OCH ₃
7d	C ₆ H ₅	H	Cl
7e	<i>o</i> -CH ₃ -C ₆ H ₄	H	H
7f	<i>o</i> -CH ₃ -C ₆ H ₄	H	CH ₃
7g	<i>o</i> -CH ₃ -C ₆ H ₄	H	OCH ₃
7h	<i>o</i> -CH ₃ -C ₆ H ₄	H	Cl
7i	<i>o</i> -CH ₃ O-C ₆ H ₄	H	H
7j	<i>o</i> -CH ₃ O-C ₆ H ₄	H	CH ₃
7k	<i>o</i> -CH ₃ O-C ₆ H ₄	H	OCH ₃
7l	<i>o</i> -CH ₃ O-C ₆ H ₄	H	Cl
8a	C ₆ H ₅	H	H
8b	<i>o</i> -CH ₃ -C ₆ H ₄	H	H
8c	<i>o</i> -CH ₃ O-C ₆ H ₄	H	H

Scheme II

5, 7-Disubstituted-8-oxo-6-thioxo-tetrahydropyrimido [5, 4-*b*] (1, 4)benzothiazine 3: General procedure. A mixture of **2** (0.01 mole), **1** (0.01 mole) and pyridine (0.01 mole) in ethanol (20 mL) were refluxed for 3 hr. The excess of the solvent was distilled off and the contents poured onto crushed ice to obtain a yellow coloured compound **3**. It was crystallised from glacial acetic acid.

The compounds **3a-m** were similarly synthesised.

3a: mp 240⁰(d), (78%); **3b:** mp 186⁰, (70%); **3c:** mp 125⁰ (68%); **3d:** mp 251⁰ (75%), ¹H NMR: δ 6.821-7.612 (m, 13H, Ar-H), 8.852 (s, 1H, -NH); **3e:** mp 123⁰ (72%); **3f:** mp 125⁰, (65%); **3g:** mp 200⁰, (78%), ¹H NMR: δ 2.158 (s, 3H, CH₃), 2.288 (s, 3H, CH₃), 2.352 (s, 3H, CH₃), 6.812-7.628 (m, 7H, Ar-H), 8.9 (s, 1H, -NH); **3h:** mp 156-80⁰, (73%); **3i:** mp 230⁰, (65%); ¹H NMR: δ 2.0613 (s, 3H, -CH₃), 2.135 (s, 3H, -CH₃), 6.812-7.601 (m, 11H, Ar-H), 8.92 (s, 1H, -NH), ¹³C NMR: 17.00 and 17.061 (2×-CH₃), 119 (>C=C<), 120-135.689 (18 aromatic carbons), 173 (>C=S), 178.28 ppm (>C=O); **3j:** mp 209⁰, (68%); **3k:** mp 141⁰, (68%); **3l:** mp 118⁰, (78%); **3m:** mp 275⁰, (72%), ¹H NMR: δ 3.902 (s, 6H, 2×-OCH₃), 6.802-7.612 (m, 11H, Ar-H), 8.812 (s, 1H, -NH).

5, 7-Disubstituted-8-oxo-6-thioxo-tetrahydropyrimido[5,4-*b*] (1,4)benzoxazine 5: General Procedure. A mixture of **1** (0.01 mole), **4** (0.01mole), pyridine (0.01 mole) and ethanol (20 mL) was refluxed for 3hr and then poured onto crushed ice when compound **5** was obtained. It was recrystallised from glacial acetic acid.

The compounds **5a-c** were prepared by the similar procedure.

5a: mp 256-58⁰ (75%); **5b:** mp 156⁰ (70%); **5c:** mp 188⁰ (78%).

2, 3-Benz-6, 10-dioxo-7, 9-disubstituted-3'/5'-substituted-1-thia-4,7, 9-triaza-8-thioxo-(4*H*)-spiro [6.5] decane 7: General procedure. A mixture of **6** (0.01 mole), **2** (0.01 mole) and pyridine (0.01 mole) in ethanol (20 mL) was refluxed for 4hr. The contents were then poured onto crushed ice when a yellow coloured compound was obtained. It was recrystallised from glacial acetic acid.

The compounds **7a-l** were synthesised in a similar way. **7a:** mp 131⁰, (75%); **7b:** mp >270⁰, (78%); **7c:** mp 246⁰, (76%); **7d:** mp 183⁰, (70%); **7e:** mp. 199⁰, (73%), ¹H NMR: δ 2.179 (s, 3H, -CH₃), 2.213 (s, 3H, CH₃), 2.292 (s, 3H, CH₃), 6.501-7.712 (m, 11H, Ar-H), 8.903 (s, 1H, -NH); **7f:** mp >275⁰ (68%), **7g:** mp 120⁰, (72%); **7h:** mp 109⁰, (69%); **7i:** mp 135⁰, (75%); **7j:** mp 239-41⁰, (70%); **7k:** mp 161⁰, (72%); **7l:** mp 190⁰, (70%).

2, 3-Benz-6, 10-dioxo-7, 9-disubstituted-1-oxa-4, 7, 9-triaza-8-thioxo-(4*H*)-spiro [6.5] decane 8: General procedure. A mixture of **6** (0.01 mole), **4** (0.01mole), pyridine (0.01 mole) and ethanol (20 mL) was refluxed for 4hr. The contents were then cooled and poured onto crushed ice, when a brown coloured compound was obtained. It was filtered and recrystallised from glacial acetic acid.

8a: mp 250⁰(d), (78%), ¹H NMR: δ 6.982-7.812 (m, 14H, Ar-H), 8.8 (s, 1H, -NH); **8b:** mp >275⁰, (68%), ¹H NMR: δ 2.121 and 2.182 (s, 2×-CH₃), 6.501-7.681 (m, 12H, Ar-H), 9.6 (s, 1H, -NH); **8c:** mp 231⁰, (72%).

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