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Thienobenzothiopyranones III*
New 4*H*-thieno[2,3-*b*][1]benzothiopyran-4-ones Carrying Different Heterocyclic Moieties of Expected Pharmacological Interest

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Abstract □ Reaction of 2-formyl-4*H*-thieno[2,3-*b*][1]benzothiopyran-4-one (**1**) with different heterocyclic amines afforded the corresponding Schiff's bases (**2-4**). Diethyl malonate, ethyl cyanoacetate and malononitrile were reacted with **1** to afford compounds **5**, **7** and **8**, respectively. Compound **5** was cyclized to the pyrazolidin-3,4-dione (**6**) by the action of hydrazine hydrate, whereas compound **7** was utilized for the synthesis of the thiazolin-4-one derivatives (**9-13**).

Keywords □ Synthesis, 4*H*-thieno[2,3-*b*][1]benzothiopyran-4-ones, thiazolin-4-ones, pyrazolidin-3,5-dione.

The concept of isosteric replacement of benzene by thiophene in biologically active compounds may improve the biological properties of the parent drug, has recently received a continuous attention[1-3]. Thioxanthone derivatives were reported to possess marked schistosomicidal[4-6] and carcinostatic[7,8] activities. The thiophenic isosteres of thioxanthones, 4*H*-thieno[2,3-*b*][1]benzothiopyran-4-ones, were reported to possess significant antihistaminic and antipsychotic activities[9-12]. In continuation of our interest towards the synthesis and pharmacological properties of thioxanthones and thioxanthone-like derivatives[13-17], we wish to report herein the synthesis and characterization of some newer 4*H*-thieno[2,3-*b*][1]benzothiopyran-4-ones as potential chemotherapeutic agents.

RESULTS AND DISCUSSION

2-Formyl-4*H*-thieno[2,3-*b*][1]benzothiopyran-4-one (**1**)[15], was reacted with the heterocyclic primary amines, 1-aminohydantoin, 4-aminoantipyrine or 6-aminouracil in acetic acid to afford the corresponding Schiff's bases (**2-4**), in relatively low yields (45-57%), this may be attributed to the poor solubility of reactants in acetic acid and the reduced basicity of these amino compounds. Interaction of (**1**) with diethyl malonate in presence of sodium ethoxide yielded compound (**5**) which was subsequently cyclized with hydrazine to afford the pyrazolidin-3,5-dione derivative (**6**). (Scheme 1).

The reactivity of the carbonyl compounds towards compounds with active methylene group was utilized for the preparation of compounds (**7,8**), by condensation of compound (**1**) with ethyl cyanoacetate or malononitrile in presence of sodium acetate in dimethylformamide. Compounds with activated nitrile group were reported to yield thiazolin-4-ones by the action of mercaptoacetic acid in pyridine or acetic acid[18,19]. Accordingly, compound (**7**) was reacted with mercaptoacetic acid in acetic acid to yield the corresponding thiazolin-4-one derivative (**9**). Attempted reaction of compound (**8**) with mercaptoacetic acid failed to produce compound (**18**), this may be explained that the nitrile group in compound (**8**) is deactivated by the effect of the other nitrile group. Compound (**9**) was allowed to react with certain aliphatic amines in ethanol to yield the corresponding amides (**10-13**). An alternative pathway was also adopted for preparation of compounds (**10-13**) by interaction of compound (**7**) with the appropriate primary amine to yield the cyanoamides (**14-17**), which were subsequently cyclized to the thiazolin-4-ones (**10-13**) by the action of mercaptoacetic acid. The yields of compounds (**10-13**) obtained *via* the application of the second pathway were found to be higher than that of the first one (Scheme 2).

*Part II, see Lit. 17.
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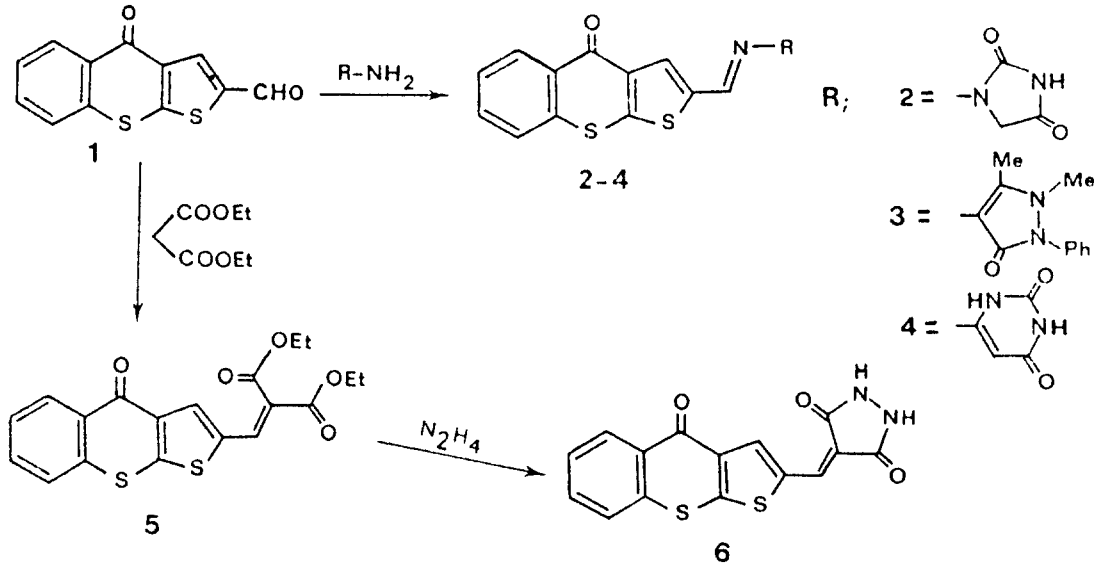
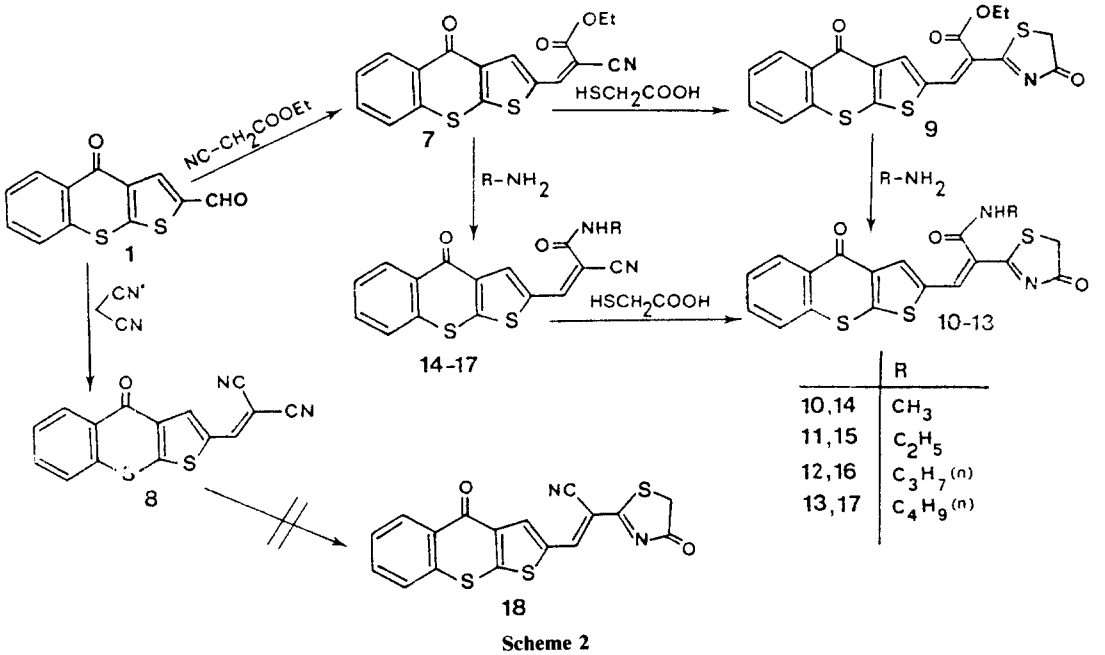


Scheme 1



Scheme 2

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded in KBr using a Pye-Unicam SP 1000 spectrophotometer (ν in cm^{-1}). ^1H-NMR spectra were obtained on a Varian EM 390 (90 MHz), using TMS as an internal standard and DMSO-d_6 as a solvent (Chemical shift in δ, ppm). Compound **1** was prepared from 5-bromo-2-thenaldehyde and thiosalicylic acid according to the method cited in Lit. 15. Characterization data of the newly prepared compounds are shown in Table I.

2-Heteroarylazomethine-4H-thieno[2,3-b][1]benzo-

Table I. Crystallization solvents, melting points, yield percentages and molecular formulae of the newly synthesized compounds

Comp. No.	Cryst. Solv.	Mp °C	Yield %	Molecular* Formulae
2	AcOH	256-8	57	$C_{15}H_9N_3O_3S_2$
3	AcOH	206-8	45	$C_{23}H_{17}N_3O_2S_2$
4	DMSO	>300	54	$C_{16}H_9N_3O_3S_2$
5	EtOAc	209-10	35	$C_{19}H_{16}O_5S_2$
6	EtOH	184-5	48	$C_{15}H_8N_2O_3S_2$
7	DMF	285-6	48	$C_{17}H_{11}NO_3S_2$
8	DMF	>300	62	$C_{15}H_6N_2OS_2$
9	AcOH	214-5	59	$C_{19}H_{13}NO_4S_3$
10	MeOH	180-2	38	$C_{18}H_{12}N_2O_3S_3$
11	MeOH	154-5	42	$C_{19}H_{14}N_2O_3S_3$
12	MeOH	138-9	53	$C_{20}H_{16}N_2O_3S_3$
13	MeOH	122-3	60	$C_{21}H_{18}N_2O_3S_3$
14	EtOH	320-1	72	$C_{16}H_{10}N_2O_2S_2$
15	EtOH	162-3	65	$C_{17}H_{12}N_2O_2S_2$
16	EtOH	140-2	72	$C_{18}H_{14}N_2O_2S_2$
17	EtOH	132-4	79	$C_{19}H_{16}N_2O_2S_2$

*Satisfactory elemental analysis for C, H & S within ±0.4% of the theoretical values was obtained for all compounds.

thiopyran-4-ones (2-4)

A mixture of compound **1** (0.25 g, 1.0 mmole) and the appropriate heterocyclic amine (1.0 mmole), in acetic acid (10 m*l*), was heated under reflux for 2 h. On cooling, the separated solid product was filtered, dried and crystallized.IR: (**2**) 3150 (NH), 1700, 1690 (C=O) and 1590 (CH=N); (**3**) 1700 (C=O) and 1580 (CH=*N*). ^{1}H-NMR: (**3**) 2.3 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), 7.2-8.0 (m, 8H, Ar-H), 8.3-8.5 (m, 2H, Ar-H) and 8.9 (s, 1H, CH=N).

2-[(3,5-Dioxopyrazolidin-4-yliden)methyl]-4H-thieno[2,3-b][1]benzothiopyran-4-one (6)

A solution of compound **1** (2.5 g, 0.01 mole) and sodium ethoxide (0.01 mole), in dimethylformamide (20 m*l*), was heated at 60 °C. Diethyl malonate (1.6 g, 0.01 mole), was then added dropwise with continuous stirring and the mixture was stirred at the same temperature for 6 h. On cooling, the separated solid (compound **5**) was filtered, washed with ethanol, dried and crystallized. IR: 1710 & 1690 (C=O). ^{1}H-NMR: 1.4-1.7 (t, 6H, $CH_2C\underline{H}_3$), 4.4-4.7 (m, 4H, $C\underline{H}_2CH_3$), 7.3-7.9 (m, 5H, Ar-H & olefinic-H) and 8.0-8.3 (m, 1H, Ar-H).

A mixture of compound **5** (3.9g, 0.01 mole) and hydrazine hydrate (98%, 0.5 m*l*), in ethanol (15 m*l*), was heated under reflux for 3 h. The solvent was then removed by distillation and the remaining residue was washed with water, dried and crystallized to afford compound **6**. ^{1}H-NMR: 4.1 (br. s, 2H, NH), 7.2-7.9 (m, 5H, Ar-H & olefinic-H) and 8.0-8.2 (m, 1H, Ar-H).

2-(2,2-Disubstituted-1-ethenyl)-4H-thieno[2,3-b]-[1]benzothiopyran-4-ones (7,8)

A mixture of compound **1** (2.5 g, 0.01 mole), ethyl cyanoacetate or malononitrile (0.01 mole) and fused sodium acetate (3.0 g), in dimethylformamide (20 m*l*), was heated under reflux for 2 h. On cooling, the precipitated solid was filtered, dried and crystallized. IR: (**7**) 1700, 1680 (C=O) and 2215 (CN); (**8**) 1710 (C=O) and 2220 (CN). ^{1}H-NMR: (**7**) 1.5-1.8 (m, 3H, $CH_2C\underline{H}_3$), 4.5-4.7 (m, 2H, CH_2CH_3), 7.3-7.9 (m, 5H, Ar-H & olefinic-H) and 8.0-8.3 (m, 1H, Ar-H).

2-[2-(4-Oxothiazolin-2-yl)-2-ethoxycarbonyl-1-ethenyl]-4H-thieno[2,3-b][1]benzothiopyran-4-one (9)

Mercaptoacetic acid (1.0 m*l*) was added to a solution of compound **7** (3.4g, 0.01 mole), in acetic acid (15 m*l*) and the mixture was heated under reflux for 6 h. The mixture was then evaporated *in vacuo* and the remaining residue was crystallized. ^{1}H-NMR: 1.6-1.8 (m, 3H, $CH_2C\underline{H}_3$), 4.6-4.8 (m, 2H, $C\underline{H}_2CH_3$), 5.8 (s, 2H, thiazoline-CH_2), 7.4-8.1 (m, 5H, Ar-H & olefinic-H) and 8.3-8.4 (m, 1H, Ar-H).

2-(2-Cyano-2-alkylamido-1-ethenyl)-4H-thieno[2,3-b][1]benzothiopyran-4-ones (14-17)

A mixture of compound **7** (3.4 g, 0.01 mole) and the appropriate alkylamine (0.01 mole), in ethanol (15 m*l*), was heated under reflux for 3 h. The solvent was then distilled off and the remaining crude product was crystallized. ^{1}H-NMR: (**14**) 2.9 (s, 3H, CH_3), 7.4-8.0 (m, 6H, Ar-H, olefinic-H &NH) and 8.1-8.3 (m, 1H, Ar-H).

2-[2-(4-Oxothiazolin-2-yl)-2-alkylamido-1-ethenyl]-4H-thieno[2,3-b][1]benzothiopyran-4-ones (10-13)
Method A (form compound 9):

A mixture of compound **9** (4.0 g, 0.01 mole) and the appropriate alkylamine (0.01 mole), in ethanol (15 m*l*), was heated under reflux for 3 h and continued as mentioned under compounds **14-17.** ^{1}H-NMR: (**13**) 0.6-0.9 (m, 3H, $(CH_2)_2C\underline{H}_3$), 1.0-1.6

(m, 4H, CH_2CH_2), 3.2-3.6 (m, 2H, CH_2), 5.6 (m, 2H, thiazoline-CH_2), 7.2-7.9 (m, 6H, Ar-H, olefinic-H & NH) and 8.1-8.3 (m, 1H, Ar-H).

Method B (form compounds 14-17):

Mercaptoacetic acid (1.0 m*l*), was added to a solution of compound **14-17** (0.01 mole), in acetic acid (15 m*l*), and the mixture was heated under reflux for 6 h and continued as mentioned under compound **9**.

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