Synthesis of [1]Benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines and Related Compounds

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The synthesis of several [1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines and other related heterocycles has been described. A study of the nmr spectra of these compounds was also reported.

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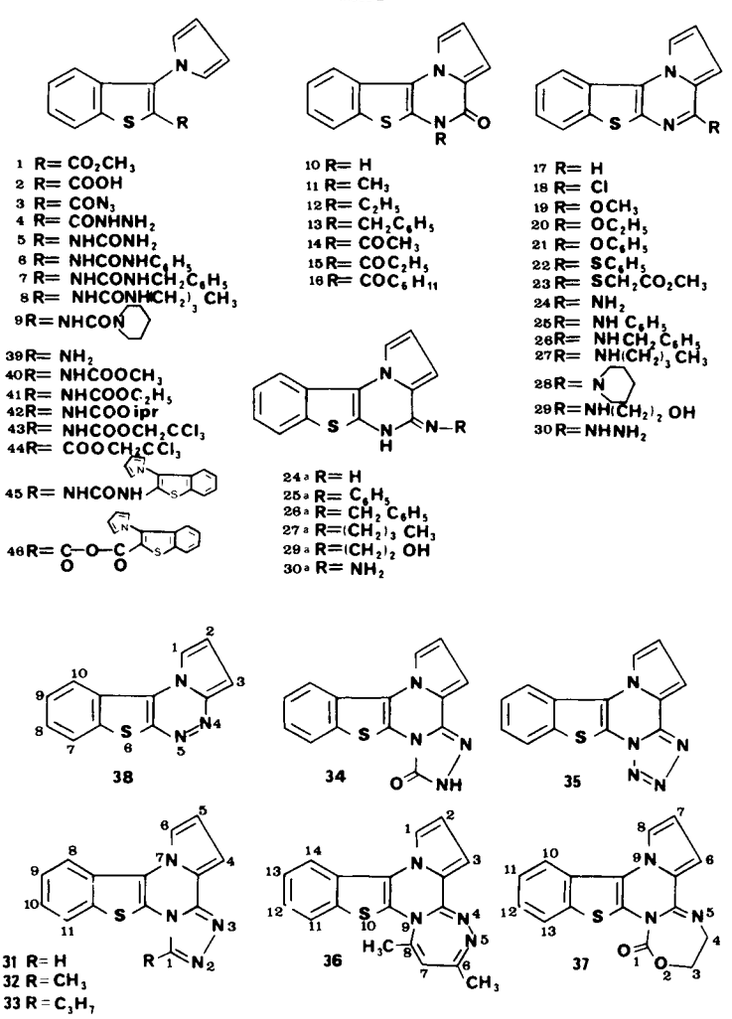
In continuation of our research program directed toward the synthesis of new polyheterocyclic compounds of biological importance [2], we have published a novel synthesis of 4-oxo-4,5-dihydro[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **10** [3]. This synthesis involved the direct conversion of the acid **2** into its azide **3** followed by Curtius rearrangement with subsequent ring closure by heating in orthodichlorobenzene.

In this paper, we wish to report the synthesis of several unknown polyfused heterocycles containing the pyrazine ring, and also to explore the utility of the oxopyrazine compound **10** in this synthesis.

It is worthy to note that the conversion of a carboxylic acid into its azide was reported by Weinstock [4] to proceed *via* the intermediacy of a mixed ester, however through the conversion of the acid **2** into the azide **3** we

TABLE I



could separate the intermediate compound and identified it as the anhydride **46**. The azide **3** was also obtained following another procedure, by converting the ester **1** into the corresponding hydrazide **4** followed by treatment with nitrous acid. The oxopyrazine [2] **10** was readily alkylated (dimethyl- and diethylsulfate) in alkaline medium giving the *N*-alkylated pyrazines **11** and **12** respectively, while with benzyl chloride it gave the *N*-benzyl derivative **13**. Also, when **10** was heated under reflux with acid anhydrides, the corresponding *N*-acyl derivatives **14-16** were resulted.

Heating **10** with phosphoryl chloride in a sealed tube overnight at 150° gave 4-chloro[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **18** which has served as a facile point of departure into the desired molecules. The chlorine atom of **18** showed the expected reactivity towards nucleophilic reagents such as alcoholate, phenolate, thiophenolate and methylthioglycolate anions giving the pyrazines **19-23** respectively, while with amines it gave the corresponding aminopyrazines **25-29** and with hydrazine hydrate gave the hydrazinopyrazine **30**. Alternatively, the aminopyrazines **25-28** could be also obtained *via* the interaction of **3** with the appropriate amines (aniline, benzylamine, butylamine and piperidine) followed by cyclodehydration of the resulting substituted ureas **6-9** in boiling phosphoryl chloride. Similarly, **3** was converted into the mono-substituted urea **5** by heating its solution in chloroform under reflux with ammonium hydroxide, followed by treatment with phosphoryl chloride to give the 4-aminopyrazine **24**.

The hydrazinopyrazine **30** proved to be a versatile molecule for synthetic realizations. Thus it was easily converted to the fused triazoles **31-33** by interacting with formic, acetic and butyric acids respectively (we have not considered the Dimroth rearrangement leading to 2-alkyl[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]-1,2,4-triazolo[3,2-*c*]pyrazine isomers). It is to be noted that the absence of the carbonyl absorption bands in the ir spectra of these compounds excluded at once the acylhydrazide structures.

Table 2

NMR Data of 3-(1-Pyrrolyl)[1]benzothiophene Derivatives

Compound No.	R	δ H4	δ H5, H6	δ H7	δ H2', H5'	δ H3', H4'	δ Other protons
39	NH_2	7.56	7.00	6.80	6.75	6.20	NH_2: 5.83
4	$CONHNH_2$	8.00	7.40	7.40	7.00	6.30	NH_2: 4.53, NH: 8.71
5	$NHCONH_2$	7.73	7.13	6.96	6.83	6.30	NH_2: 6.46, NH: 8.83
6	$NHCONHC_6H_5$	7.80	7.2 (m)	7.00	6.93	6.36	NH: 9.06 and 9.33, C_6H_5: 7.20 (m)
7	$NHCONHCH_2C_6H_5$	8.15	7.2 (m)	7.2 (m)	7.08	6.33	NH: 7.80, CH_2: 4.38, C_6H_5: 7.20 et 7.40 (m)
8	$NHCONH(CH_2)_3CH_3$	8.06	7.43	6.90	7.00	6.33	CH_2: 3.10 and 1.20, NH: 7.40, CH_2: 0.80
9	Piperidinocarbonylamino-	8.05	7.6 (m)	7.6 (m)	6.96	6.20	CH_2: 3.50, 3.06, 1.40 and 1.03
40	NHCOOMe	7.83	7.13	7.23	6.83	6.23	CH_3: 3.63, NH: 9.80
41	NHCOOEt	7.81	7.20	7.20	6.83	6.23	CH_2: 4.10, CH_3: 1.20, NH: 9.80
42	NH.COOipr	7.83	7.23	7.23	7.03	6.25	CH: 4.86, CH_3: 1.21, NH: 9.80
44	$COOCH_2CCl_3$	8.17	7.40	7.40	7.07	6.27	CH_2: 5.07
46	3-(1-Pyrrol)[1]benzothiophen-oxoacetyloxy-	8.06	7.46	7.46	6.96	6.20	—

Table 3

NMR Data of [1]Benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines

Compound No.	R	δ H1	δ H2	δ H3	δ H7	δ H8, H9	δ H10	δ Other protons
17	H	8.60	7.13	7.13	8.10	7.53	8.10	H4: 8.91 J^5H4/H1: 0.6 Hz
18	Cl	8.76	7.20	7.20	8.16	7.60	8.63	—
19	OCH_3	8.53	7.00	7.00	8.03	7.51	8.53	CH_3: 4.10
20	OC_2H_5	8.40	6.93	6.93	7.96	7.46	8.40	CH_2: 4.53
21	OC_6H_5	8.63	7.03	7.40 (m)	8.03	7.40 (m)	8.56	C_6H_5: 7.40 (m)
22	SC_6H_5	8.63	7.03	7.03	8.10	7.53	8.50	CH_2: 4.30, CH_3: 3.66
24	NH_2	8.33	6.80	7.13	7.90	7.40	8.26	NH_2: 7.10
25	NHC_6H_5	8.40	6.93	7.40 (m)	7.93	7.40 (m)	8.40	
26	$NHCHC_6H_5$	8.33	6.76	7.30 (m)	7.80	7.30 (m)	8.20	C_6H_5: 7.30 (m), NH: 7.30
27	$NH(CH_2)_3CH_3$	8.30	6.80	7.20	7.93	7.40	8.30	NH: 7.60
28	Piperidino-	8.38	6.86	6.96	7.96	7.40	8.38	CH_2: 3.26 and 1.66
29	$NH(CH_2)_2OH$	8.30	6.76	7.15	7.90	7.40	8.30	CH_2: 3.63, NH: 7.60, OH: 4.73
30	$NHNH_2$	8.30	6.76	7.15	7.91	7.40	8.30	NH: 8.93, NH_2: 4.50

When **30** was allowed to interact with phosgene in boiling toluene, the triazolinone **34** was obtained. The tetrazole **35** was easily obtained from **30** *via* the diazonium process involving sodium nitrite in acetic acid. The ir spectrum of **35** showed no bands near 2000 cm^{-1} which excludes the azidopyrazine structure in the solid state. Attempts to obtain this tetrazole by interacting **18** with sodium azide were unsuccessful.

The interaction of **30** with acetylacetone afforded a compound whose ir spectrum lacks of both ν C=O and ν N-H bands, indicating that both the two carbonyl groups of acetylacetone were condensed with the hydrazino group of **30** giving either 4-(3,4-dimethyl-1-pyrazolyl)[1]benzothieno[2,3-*d*]pyrrolo[1,2-*a*]pyrazine or 6,8-dimethyl[1]benzothieno[2',3':5,6]pyrrolo[1',2':1,2]pyrazino[3,4-*c*]-1,2,4-triazepine **36** depending whether **30** exists in the hydrazino form **30** or in the hydrazone form **30a**. This problem was solved by a careful nmr study. Thus nmr data of the pyrazines **17-23** showed an overlap of the signals corresponding to the two pyrrolic protons H2 and H3. However, in the case of oxopyrazines **10-16**, the H3 proton was deshielded due to the C=O anisotropy, and all the pyrrolic protons appeared separately. A similar spectral pattern was observed for the amino-**24, 27, 29** and the hydrazino-**30** derivatives.

This spectral analogy provided a strong evidence for the existence of **24, 27** and **30** in the imino and hydrazono form respectively. The deshielding of H3 of **24, 27, 29** and **30** could be due to an anisotropic effect of the exacylic C=N similar to that of C=O of **10-16**. Such a result is in favour of the structure **36**. Based upon the above discussion, the reaction product obtained from the interaction of **29** with phosgene was assigned to the oxadiazepinone structure **37**.

Deshydrazination of **30** afforded the parent benzothienopyrrolopyrazine **17**, which was also obtained, in a better yield, by the interaction of **39** with formic acid. Owing to the high reactivity of the α-position in pyrrole, the amine **39** gave directly the triazine under diazotization conditions.

On the other hand, several reactions were tried in order to prepare **39**. Thus, the carbamates **40-42** were prepared by heating **3** in the appropriate alcohol. Attempts to hydrolize any of these carbamates to **39** in acidic or alkaline medium were unsuccessful. Therefore, it seemed likely to prepare the rather hydrolizable trichloroethylcarbamate **43** however, unfortunately this was impossible since the acidity of the trichloroethanol catalizes the cyclization of isocyanate intermediate [3] giving the oxopyrazine **10** as the only product. However, when a suspension of **3** in ether was interacted with trichloroethanol, in the presence of triethanolamine, at the boiling point of ether the product was identified as 2-trichloroethyl-3-(1-pyrrolyl)[1]benzothiophene-2-carboxylate, which gave the acid **2** upon hydrolysis.

The only approach to the preparation of the amine **39** was concerned to involve the pyrolysis of the urea compound **45** [6] which was obtained, in turn, by heating the azide **3** in boiling water. The pyrolysis was affected by heating **45** either as a solid above its melting point or in an inert high boiling solvent as *o*-dichlorobenzene. The pyrolysis resulted in the formation of the amine **30** along with **10** which were easily separated from one another by virtue of their different solubility in ether.

EXPERIMENTAL

All melting points were determined on a Kofler block or on a Maquenne block apparatus and are uncorrected. The ir spectra were recorded (potassium bromide disk) on a Perkin Elmer model 157 G spectrometer. The nmr spectra were obtained with a Varian EM 390 using TMS (tetramethylsilane) as an internal standard and chemical shifts were expressed as δ, parts per million.

Materials.

Methyl-2-amino[1]benzothiophene-3-carboxylate **1** was prepared following the method of Beck [5]. The acid **2** and the pyrazine **10** were prepared by us in a previous publication [2].

3-(1-Pyrrolyl)-2-hydrazino[1]benzothiophene **4**.

To a solution of the ester **1** (5 g) in hot ethanol (40 ml) was added hydrazine hydrate (98%, 50 ml) and the reaction mixture was heated under reflux for 3 hours. This was then concentrated *in vacuo* and left to cool. The crystalline product was filtered, washed with water and crystallized

Table 4

NMR Data of 4-Oxo-4,5-dihydro[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine Derivatives

Compound No.	R	δ H1	δ H2	δ H3	δ H7	δ H8,H9	δ H10	δ Other protons
10	H	8.30	6.70	7.08	7.96	7.60, 7.30	8.30	NH: 3.00
11	CH_3	insoluble						
12	C_2H_5	8.30	6.83	7.10	8.03	7.40	8.30	CH_2: 4.08, CH_3: 1.37
13	$CH_2C_6H_5$	8.35	6.75	7.20	7.95	7.40	8.35	C_6H_5: 7.30, CH_2: 5.33
14	$COCH_3$	8.38	6.70	7.30	7.95	7.43	8.38	CH_3: 2.78
15	COC_2H_5	8.30	6.66	7.23	7.90	7.40	8.30	CH_2: 3.23
16	COC_5H_{11}	8.30	6.66	7.23	7.90	7.40	8.30	CH_2: 3.16, 1.66 and 1.33, CH_3: 0.86

from ethanol as yellow crystals, mp 133°, yield 4.2 g (82%); ir: ν cm^{-1} 3300, 3100, 3080, 1630, 1430, 700.

Anal. Calcd. for $C_{13}H_{11}N_3SO$: C, 60.69; H, 4.31; N, 16.34; S, 12.44. Found: C, 60.76; H, 4.38; N, 16.21; S, 12.22.

2-Azidocarbonyl-3-(1-pyrrolyl)[1]benzothiophene **3**.

To a solution of sodium nitrite (1.65 g, 0.024 mole) in acetic acid (100 ml, 10%), stirred for 10 minutes at ambient temperature, the hydrazide **4** (5.1 g, 0.02 mole) was added dropwise. Stirring was continued for 3 hours and the precipitate was then filtered, washed with cold water and air dried, yield 4.9 g (91%), mp 150° dec, that was not depressed when mixed with an authentic sample [3].

5-Alkyl and/or Aralkyl-4-oxo-4,5-dihydro[1]benzothieno[2,3-*e*]pyrrolo-[1,2-*a*]pyrazines **11-13**.

A suspension of **10** (0.6 g) in a mixture of sodium hydroxide solution (6*N*, 30 ml) and acetone (50 ml) was stirred at room temperature for 15 minutes. To this suspension an excess of dialkyl sulfate (alkyl = CH_3 and/or C_2H_5, 2.5 ml) and benzyl chloride (2 ml) was added and then the reaction mixture was heated under reflux on a water bath (0.5 hour for dialkyl sulfate and 2 hours for benzyl chloride). The acetone was removed *in vacuo* and the precipitate was filtered and washed wtih water and crystallized. Compound **11** was obtained as colorless crystals (acetone), mp 267°, yield 0.5 g (78%); ir: ν cm^{-1} 3160, 1650, 1580, 1470, 1350, 760, 740.

Anal. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.13; H, 3.96; N, 11.02; S, 12.60. Found: C, 66.31; H, 3.95; N, 10.99; S, 12.58.

Compound **12**.

This compound was obtained as colorless crystals (acetone), mp > 260°, yield 4.3 g (64%); ir: cm^{-1} 3000, 2980, 1680, 1580, 1460, 810, 740.

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.15; H, 4.50; N, 10.44; S, 11.95. Found: C, 67.35; H, 4.80; N, 10.21; S, 12.13.

Compound **13**.

This compound was obtained as colorless crystals (ethanol), mp 222°, yield 0.6 g (76%); ir: ν cm^{-1} 3120, 1630, 1580, 1435, 750.

Anal. Calcd. for $C_{20}H_{14}N_2OS$: C, 72.70; H, 4.27; N, 8.48; S, 9.70. Found: C, 72.71; H, 4.13; N, 8.42; S, 9.83.

5-Acyl-4-oxo-4,5-dihydro[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines **14-17**.

Oxopyrazine **10** (1.2 g) was heated under reflux with the appropriate acid anhydride (6 ml) for 2 hours. The solid product obtained after cooling was filtered and washed with petroleum ether (bp, 60-80°).

Compound **14**.

This compound was obtained as buff crystals (acetone), mp 204°, yield 80%; ir: ν cm^{-1} 3160, 2915, 1700, 1670, 1515, 1455, 1395, 720.

Anal. Calcd. for $C_{15}H_{10}N_2O_2S$: C, 63.82; H, 3.57; N, 9.92; S, 11.36. Found: C, 64.03; H, 3.34; N, 10.07; S, 11.09.

Compound **15**.

This compound was obtained as buff crystals (acetone), mp 166°, yield 80%; ir: ν cm^{-1} 3130, 2930, 2915, 1710, 1670, 1450, 1305, 750, 730.

Anal. Calcd. for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45; S, 10.81. Found: C, 64.96; H, 4.00; N, 9.40; S, 10.98.

Compound **16**.

This compound was obtained as fluffy buff crystals (acetone), mp 134°, yield 77%; ir: ν cm^{-1} 3130, 2830, 2825, 2810, 2020, 2010, 1695, 1665, 1515, 1425, 1395, 750, 650.

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47. Found: C, 67.58; H, 5.17; N, 8.57; S, 9.70.

4-Chloro[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **18**.

A suspension of **10** (5 g) in phosphoryl chloride (70 ml) was heated in a sealed tube overnight at 150°. After removing the excess phosphoryl chloride *in vacuo*, the residual solid product was worked up in an ammonium hydroxide-ice mixture, filtered, washed with water to give yellow crystals, mp 200°, yield, quantitative; ir: ν cm^{-1} 3170, 1575, 1440, 1420, 755, 650.

Anal. Calcd. for $C_{13}H_7ClN_2S$: C, 60.35; H, 2.72; N, 10.82; S, 12.39; Cl, 13.70. Found: C, 60.28; H, 2.62; N, 10.78; S, 12.19; Cl, 13.60.

4-Alkoxy[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines **19-20**.

A mixture of **18** (0.5 g) and sodium alcoholate (0.49 g of sodium) in alcohol (50 ml of methanol and/or ethanol) was heated under reflux for 3 hours. The solvent was then removed under reduced pressure and the residual solid was collected, washed with water and dried.

Compound **19**.

This compound was obtained as yellow crystals (ethanol), mp 150°, yield 0.4 g (83%); ir: ν cm^{-1} 2940, 1590, 1525, 1435, 1370, 1120, 750, 700.

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 66.13; H, 3.93; N, 11.01; S, 12.58. Found: C, 66.24; H, 4.20; N, 10.86; S, 12.78.

Compound **20**.

This compound was obtained as fluffy yellow needles (ethanol), mp 136°, yield 0.4 g (77%); ir: ν cm^{-1} 3130, 3000, 2990, 2890, 1590, 1520, 1430, 1200, 755, 725.

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.15; H, 4.50; N, 10.42; S, 11.95. Found: C, 66.94; H, 4.40; N, 10.36; S, 11.78.

4-Phenoxy[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **21**.

A mixture of **18** (0.5 g) and sodium phenolate (0.4 g of sodium) in phenol (25 g) was heated at 170-180° for 6 hours. After cooling the reaction mixture was worked up with cold diluted sodium hydroxide solution and the precipitate was filtered, washed with water and crystallized from ethanol as pale yellow crystals, mp 155°, yield 0.37 g (61%); ir: ν cm^{-1} 1580, 1500, 1475, 1405, 1220, 710, 685, 650.

Anal. Calcd. for $C_{19}H_{12}N_2OS$: C, 72.14; H, 3.82; N, 8.86; S, 10.14. Found: C, 72.38; H, 3.73; N, 8.57; S, 9.92.

4-Thiophenoxy[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **22**.

To a well stirred mixture of **18** (1.3 g, 0.005 mole) and thiophenol (1.7 g, 0.015 mole) in dimethylsulfoxide (7 ml) trimethylamine (2 ml) was added. The reaction mixture was then heated at 160° for 30 minutes. After cooling it was poured into crushed ice and the solid product was collected by filtration, washed with water and crystallized from ethanol as yellow crystals, mp 154°, yield 1.5 g (91%); ir: ν cm^{-1} 1565, 1500, 1430, 1330, 1315, 755, 690.

Anal. Calcd. for $C_{19}H_{12}N_2S_2$: C, 68.67; H, 3.64; N, 8.43; S, 19.26. Found: C, 68.50; H, 3.60; N, 8.55; S, 19.06.

Methyl [1]Benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazin-3-ylthioacetate **23**.

This compound was obtained following the above procedure using **19** (1.3 g, 0.005 mole) and methylthioglycolate (1.6 g, 0.015 mole). Crystallization from ethanol gave buff crystals, mp 150°, yield quantitative; ir: ν cm^{-1} 3140, 3100, 2990, 2970, 2820, 1730, 1425, 1305, 1165, 755, 720.

Anal. Calcd. for $C_{16}H_{12}N_2S_2O_2$: C, 58.52; H, 3.68; N, 8.53; S, 19.52. Found: C, 58.37; H, 3.61; N, 8.45; S, 19.65.

4-Hydrazino[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **30**.

To a suspension of **18** (3 g) in hydrazine hydrate (98%, 5 ml) ethanol (30 ml) was added. The reaction mixture was heated under reflux for 3 hours then it was concentrated under reduced pressure and left to cool. This was diluted with cold water and the resultant solid was filtered, washed with water and crystallized from ethanol as fluffy colorless needles, mp 225°, yield 2.7 g (93%); ir: ν cm^{-1} 3300, 3250, 1620, 1580, 1450, 1230, 750, 715.

Anal. Calcd. for $C_{13}H_{10}N_4S$: C, 61.41; H, 3.96; N, 22.04; S, 12.61. Found: C, 61.30; H, 3.87; N, 21.88; S, 12.65.

N-3-(1-Pyrrolyl)[1]benzothien-2-ylurea **5**.

To a solution of **3** (5 g) in chloroform (50 ml) ammonium hydroxide (20%, 40 ml) was added and the reaction mixture was heated under reflux with stirring for 2 hours. Chloroform was then evaporated under reduced pressure and the solid product was filtered, washed with water and crystallized from acetone as colorless crystals, mp >260°, yield 3.7 g (78%); ir: ν cm^{-1} 3410, 3315, 3110, 1680, 1660, 1595, 1490, 1460, 760, 750.

Anal. Calcd. for $C_{13}H_{11}N_3SO$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.67; H, 4.34; N, 16.32; S, 12.28.

N-Phenyl-*N'*-3-(1-pyrrolyl)[1]benzothien-2-ylurea **6**.

An equimolar mixture of the azide **3** (2.7 g) and aniline (0.93 g) in dry benzene (30 ml) was heated under reflux for 1 hour, concentrated and left to cool. The crystalline precipitate was filtered and recrystallized from benzene as cream crystals, mp 166°, yield 3.0 g (89%); ir: ν cm^{-1} 3310, 3020, 1660, 1610, 1600, 1550, 765, 730.

Anal. Calcd. for $C_{19}H_{15}N_3OS$: C, 68.46; H, 4.54; N, 12.61; S, 9.60. Found: C, 68.32; H, 4.54; N, 12.46; S, 9.55.

N-Benzyl-*N'*-3-(1-pyrrolyl)[1]benzothien-2-ylurea **7**.

This was prepared following a similar procedure to that of **6**, using **3** (2.7 g) and benzylamine (1.1 g). Crystallization from benzene gave light-cream crystals, mp 116°, yield 3.0 g (91%); ir: ν cm^{-1} 3380, 3340, 3120, 1640, 1525, 1250, 760, 735, 700.

Anal. Calcd. for $C_{20}H_{15}N_3S$: C, 72.93; H, 4.59; N, 12.76; S, 9.72. Found: C, 73.09; H, 4.71; N, 12.57; S, 9.62.

N-Butyl-*N'*-3-(1-pyrrolyl)[1]benzothien-2-ylurea **8**.

This was prepared following a similar procedure to that of **6** using **3** (2.7 g) and butylamine (0.73 g). Crystallization from diluted ethanol gave light cream crystals, mp 107°, yield 2.8 g (90%); ir: ν cm^{-1} 3395, 3120, 2960, 2880, 1640, 1100, 740.

Anal. Calcd. for $C_{17}H_{19}N_3OS$: C, 65.16; H, 6.11; N, 13.41; S, 10.21. Found: C, 65.20; H, 6.23; N, 13.50; S, 10.35.

2-Piperidinocarbonylamino-3-(1-pyrrolyl)[1]benzothiophene **9**.

This was prepared following a similar procedure to that of **6** using **3** (2.7 g) and piperidine (0.85 g). Crystallization from benzene gave cream crystals, mp 160°, yield 2.9 g (89%); ir: ν cm^{-1} 3100, 2980, 2880, 1620, 1485, 1265, 740.

Anal. Calcd. for $C_{18}H_{19}N_3OS$: C, 66.44; H, 5.89; N, 12.92; S, 9.84. Found: C, 66.57; H, 5.93 N, 13.01. S, 9.79.

4-Anilino[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **25**.

Method A.

A mixture of **18** (1 g) and excess aniline (6 ml) was heated under reflux for 2 hours. The reaction mixture was then evaporated to dryness *in vacuo* and the residual semi-solid was treated with ice-cold water (10 ml) and stirred for 10 minutes. The resulting solid was filtered and crystallized from ethanol as pale yellow crystals, mp 162°, yield 1 g (82%); ir: ν cm^{-1} 3300, 1595, 1440, 1230, 745, 715.

Anal. Calcd. for $C_{19}H_{13}N_3S$: C, 72.37; H, 4.16; N, 13.33; S, 10.15. Found: C, 72.33; H, 4.07; N, 13.22; S, 10.20.

Method B.

To compound **6** (1 g) phosphoryl chloride (25 ml) was added, and the reaction mixture was heated under reflux for 2 hours. The excess phosphoryl chloride was then eliminated *in vacuo* and the residual solid was stirred in diluted sodium hydroxide solution. This was filtered and the precipitate was washed with water and crystallized from ethanol, yield 0.7 g (66%), mp, ir and nmr spectra are identical with those of an authentic sample prepared by method A.

4-Benzylamino[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **26**.

This compound was prepared following a similar procedure to that of **25** (method A), using benzylamine, yield 89%; method B using **7**, yield (69%). Crystallization from ethanol gave yellow crystals, mp 212°; ir: ν cm^{-1} 3275, 3110, 2880, 1580, 1445, 750, 720.

Anal. Calcd. for $C_{20}H_{15}N_3S$: C, 72.93; H, 4.59; N, 12.76; S, 9.72. Found: C, 73.09; H, 4.71; N, 12.57; S, 9.65.

4-Butylamino[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **27**.

This was prepared following a similar procedure to that of **25**, method A, using butylamine, yield 81%, method B using **8**, yield 62%. Crystallization from ethanol gave colorless crystals, mp 150°; ir: ν cm^{-1} 3275, 2960, 2860, 1580, 1530, 1230, 750, 720.

Anal. Calcd. for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22; S, 10.85. Found: C, 69.20; H, 5.73; N, 14.22; S, 10.78.

4-(1-Piperidyl)[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **28**.

This was prepared using a similar procedure to that of **25**. Method A, using butylamine gave a yield 90%, method B using **9**, yield 66%. Crystallization from ethanol gave colorless crystals, mp 124°; ir: ν cm^{-1} 2920, 2820, 1570, 1505, 1450, 750, 720.

Anal. Calcd. for $C_{18}H_{17}N_3S$: C, 70.34; H, 5.58; N, 13.67; S, 10.71. Found: C, 70.12; H, 5.67; N, 13.52; S, 10.49.

4-(2-Hydroxyethylamino)[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **29**.

A mixture of **18** (1 g) and excess of 2-hydroxylamine (10 ml) was heated under reflux for 2 hours. The reaction mixture was then worked up as described for **25** (method A). Crystallization from ethanol gave yellow crystals, mp 168°, yield 0.98 g (83%).

Anal. Calcd. for $C_{15}H_{13}N_3OS$: C, 63.59; H, 4.63; N, 14.83; S, 11.29. Found: C, 63.65; H, 4.79; N, 14.88; S, 11.31.

4-Amino[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **24**.

A mixture of **5** (1 g) and phosphoryl chloride (20 ml) was heated under reflux for 2 hours. The reaction mixture was then worked up as described for **25** (method B). Crystallization from ether gave orange-yellow crystals, mp 246°, yield 0.5 g (54%).

Anal. Calcd. for $C_{13}H_9N_3S$: C, 65.27; H, 3.76; N, 17.57; S, 13.38. Found: C, 65.13; H, 3.63; N, 17.45; S, 13.56.

[1]Benzothieno[2,3-*e*]pyrrolo[1,2-*a*]-1,2,4-triazolo[3,4-*c*]pyrazine **31**.

A solution of **30** (1 g) in formic acid (30 ml) was heated under reflux for 2 hours. The reaction mixture was then evaporated *in vacuo* to dryness and the solid product was collected, washed with water and crystallized from ethanol as pale yellow crystals, mp 285°, yield 0.9 g (87%); ir: ν cm^{-1} 3160, 3080, 1620, 1500, 1460, 1370, 1255, 750, 720; nmr: ppm 9.43 (H1), 7.20 (H4), 6.81 (H5), 8.40 (H6, H8), 7.40 (H8, H9), 8.13 (H10).

Anal. Calcd. for $C_{14}H_8N_4S$: C, 63.63; H, 3.05; N, 21.20; S, 12.13. Found: C, 63.48; H, 2.95; N, 21.16; S, 12.07.

1-Methyl[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]-1,2,4-triazolo[3,4-*e*]pyrazine **32**.

This was prepared using a similar procedure to that of **31**, using glacial acetic acid. Crystallization from ethanol as light cream crystals, mp 328°, yield 88%; ir: ν cm^{-1} 3180, 1625, 1520, 1510, 1390, 1230, 725.

Anal. Calcd. for $C_{15}H_{10}N_4S$: C, 64.74; H, 3.62; N, 20.14; S, 11.52. Found: C, 64.52; H, 3.53; N, 20.04; S, 11.39.

1-Propyl[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]-1,2,4-triazolo[3,4-*c*]pyrazine **33**.

This was prepared following a similar procedure to that of **31** using butyric acid. Crystallization from benzene gave greenish crystals, mp 220°, yield 86%; ir: ν cm^{-1} 3150, 2995, 2940, 1625, 1505, 1435, 1225, 755, 730; nmr: δ ppm 1.46 (CH_3), 3.20 (CH_2-CH_2), 7.08 (H4), 6.71 (H5), 8.33 (H6, H8), 7.48 (H9, H10), 8.03 (H11).

Anal. Calcd. for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.60; N, 18.29; S, 10.46. Found: C, 65.79; H, 4.33; N, 18.16; S, 10.71.

[1]Benzothieno[2,3-*e*]pyrrolo[1,2-*a*]tetrazolo[5,1-*c*]pyrazine **35**.

To a solution of **30** (1.3 g) in glacial acetic acid (30 ml) was added at room temperature with stirring a solution of sodium nitrite (0.38 g in 7

ml of water). Stirring was continued for 15 minutes and the precipitate was filtered and washed with water. Crystallization from ethanol gave colorless crystals, mp 228°, yield 1 g (74%); ir: ν cm^{-1} 3165, 1630, 1490, 1390, 1260, 765, 730; nmr: δ ppm 7.40 (H4), 6.93 (H5), 8.50 (H6), 8.46 (H8), 7.50 (H9, H10), 8.10 (H11).

Anal. Calcd. for $C_{13}H_7N_3S$: C, 58.86; H, 2.66; N, 26.40; S, 12.05. Found: C, 58.77; H, 2.80; N, 26.23; S, 11.93.

1,2-Dihydro-1-oxo[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]triazolo[3,4-*c*]pyrazine **34**.

To a solution of **31** (1 g) in toluene (90 ml) phosgene (10 ml, 20% in toluene) was added, and the reaction mixture was heated under reflux for 1 hour. The product which precipitated hot was filtered after eliminating the excess phosgene by bubbling a current of nitrogen gas into the reaction mixture. Crystallization from acetone followed by sublimation *in vacuo* (160°, 0.05 mm Hg) gave colorless crystals, mp >260°, yield 0.6 g (58%); ir: ν cm^{-1} 3170, 3060, 1710, 1630, 1530, 750, 720; nmr: δ ppm 12.4 (NH), 7.03 (H4), 6.71 (H5), 8.40 (H6), 8.56 (H8), 7.53 (H9, H10), 8.16 (H11).

Anal. Calcd. for $C_{14}H_8N_4OS$: C, 60.00; H, 2.88; N, 19.99; S, 11.44. Found: C, 60.02; H, 2.70; N, 19.89; S, 11.59.

[1]Benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **17**.

Method A.

Compound **30** (0.5 g) was dissolved in a solution of sodium ethoxide (0.7 g of sodium) in ethanol (100 ml). Oxygen gas was then allowed to bubble in this solution for 20 minutes, followed by filtration, and the filtrate ws evaporated to dryness. The solid product was washed with water, crystallized from ethanol and sublimed *in vacuo* at 120°; 0.05 mm Hg giving colorless crystals, mp 161°, yield 0.27 g (61%); ir: ν cm^{-1} 3160, 1580, 1440, 1320, 760, 720.

Anal. Calcd. for $C_{13}H_8N_2S$: C, 69.62; H, 3.59; N, 12.49; S, 14.29. Found: C, 69.57; H, 3.57; N, 12.44; S, 14.23.

Method B.

A mixture of **42** (0.2 g) formic acid (20 ml) and a trace of fused sodium acetate was heated under reflux for 1 hour. The reaction mixture was evaporated under reduced pressure and the solid product was collected and washed with water. This was worked up as in method A. The mp was not depressed when mixed with authentic sample prepared by method A, yield 79%.

[1]Benzothieno[2,3-*d*]pyrrolo[2,1-*c*]-1,2,4-triazine **38**.

To a stirred solution of **39** (0.7 g) in acetic acid (20 ml) a solution of sodium nitrite (0.27 g/8 ml) was added dropwise at room temperature. Stirring was continued for 10 minutes and the precipitate was filtered, washed with water and crystallized from ether as reddish brown crystals, mp 225°, yield 0.6 g (82%); ir: ν cm^{-1} 3120, 1580, 1500, 1410, 1210, 1030, 750, 730; nmr: δ ppm 8.73 (H1), 7.53 (H2), 7.53 (H3), 8.30 (H7), 7.71 (H8, H9), 8.80 (H10).

Anal. Calcd. for $C_{12}H_7N_3S$: C, 64.00; H, 3.13; N, 18.66; S, 14.21. Found: C, 64.30; H, 3.40; N, 18.96; S, 13.90.

1,3-Dimethyl[1]benzothieno[2',3':5,6]pyrrolo[1',2':1,2]pyrazino[3,4-*c*]-1,2,4-triazepine **36**.

A mixture of hydrazinopyrazine **30** (0.5 g) and acetylacetone (10 ml) was heated under reflux for 2 hours. The excess acetylacetone was eliminated *in vacuo* and the solid product was collected and crystallized from methanol as yellow crystals, mp 178°, yield 0.5 g (80%); ir: ν cm^{-1} 2920, 1580, 1510, 1440, 1180, 760, 720, 700; nmr: δ ppm 2.90 (CH_3-C_1), 6.16 (H2), 2.30 (CH_3-C_3), 7.53 (H6), 7.06 (H7), 8.66 (H9), 8.60 (H10), 7.53 (H11, H12), 8.10 (H13).

Anal. Calcd. for $C_{18}H_{14}N_4S$: C, 67.91; H, 4.43; N, 17.60; S, 10.05. Found: C, 67.87; H, 4.55; N, 17.39; S, 10.21.

[1]Benzothieno[2',3':5,6]pyrrolo[1',2':1,2]pyrazine[3,4-*c*]-1,3,5-oxadiazepine **37**.

A mixture of **29** (0.5 g) and phosgene (15 ml, 20% in toluene) was heated under reflux in toluene for 1 hour. The reaction was then worked up as that described for **34**. Crystallization from acetone, sublimation *in vacuo* at 140°, 0.05 mm Hg gave yellow crystals, mp 235°, yield 0.3 g (55%); ir: ν cm^{-1} 3180, 3100, 2995, 2900, 1760, 1570, 1470, 1195, 760, 730; nmr: δ ppm 4.53 (H3), 4.30 (H4), 7.25 (H6), 7.08 (H7), 8.63 (H8), 8.60 (H10), 7.56 (H11, H12), 8.10 (H13).

Anal. Calcd. for $C_{16}H_{11}N_3O_2S$: C, 62.13; H, 3.59; N, 13.59; S, 10.34. Found: C, 62.22; H, 3.66; N, 13.38; S, 10.35.

Methyl *N*-(3-(1-Pyrrolyl)[1]benzothien-1-yl)carbamate **40**.

Compound **3** (1 g) was heated under reflux in methanol (50 ml) for 45 minutes. The reaction mixture was then concentrated and left to cool. The solid crystals were filtered and recrystallized from the same alcohol as colorless crystals, mp 126°, yield quantitative; ir: ν cm^{-1} 3300, 1710, 1610, 1500, 1265, 760, 740, 730.

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.76; H, 4.44; N, 10.29; S, 11.29. Found: C, 61.75; H, 4.39; N, 10.18; S, 11.68.

Ethyl *N*-(3-(1-Pyrrolyl)[1]benzothien-2-yl)carbamate **41**.

This was obtained by following the procedure described for **40** using ethanol instead of methanol. Crystallization from ethanol gave colorless crystals, mp 102°, yield quantitative; ir: ν cm^{-1} 3410, 3120, 3000, 1730, 1610, 1450, 1390, 1100, 770, 760, 700.

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78; S, 11.20. Found: C, 62.91; H, 4.83; N, 9.71; S, 11.23.

Isopropyl *N*-(3-(1-Pyrrolyl)[1]benzothien-2-yl)carbamate **42**.

This was obtained by following the procedure described for **40** using 2-propanol instead of methanol. Crystallization from 2-propanol gave colorless crystals, mp 94°, yield quantitative; ir: ν cm^{-1} 3290, 2990, 1700, 1610, 1500, 1260, 760. 740.

Anal. Calcd. for $C_{16}H_{16}N_2SO_2$: C, 63.99; H, 5.37; N, 9.33; S, 10.21. Found: C, 64.12; H, 5.28; N, 9.24; S, 10.47.

2-Trichloroethyl (3-(1-Pyrrolyl)[1]benzothien-2-yl)carboxylate **44**.

An equimolar mixture of **3** (1.3 g) and trichloroethanol (0.8 g, 0.52 ml) in ether (4 ml) was heated at 37° for 0.5 hour in the presence of triethylamine (0.5 ml). The reaction mixture was triturated with diluted acetic acid and the solid product was filtered, washed with water and crystallized from ether as yellow crystals, mp 134°, yield 1.41 g (77%); ir: ν cm^{-1} 3000, 2940, 1720, 1560, 1530, 1370, 1185, 1105, 800, 730.

Anal. Calcd. for $C_{15}H_{11}Cl_3N_2OS$: C, 48.21; H, 2.97; N, 7.50; S, 8.59; Cl, 28.46. Found: C, 48.24; H, 2.70; N, 7.76; S, 8.43; Cl, 28.30.

N,N'-Di-(3-pyrrolyl[1]benzothien-2-yl)urea **45**.

A suspension of **3** (5 g) in water (250 ml) and acetone (10 ml) was heated under reflux for 1 hour. The solid precipitate was filtered and crystallized from acetone as colorless crystals, mp >260°, yield 4.7 g (55%); ir: ν cm^{-1} 3290, 1660, 1610, 1525, 1395, 745, 730; rmn: insoluble.

Anal. Calcd. for $C_{25}H_{18}N_4OS_2$: C, 66.07; H, 3.99; N, 12.33; S, 10.56. Found: C, 66.31; H, 4.01; N, 12.55; S, 10.60.

2-Amino-3-(1-pyrrolyl)[1]benzothiophene **39**.

Method A.

Compound **45** (4 g) was heated at 270-280° for 10 minutes in a long glass tube. After cooling, the solid was treated with ether; the insoluble portion consisted of the oxopyrazine **10** (2.7 g). The ethereal solution was decolorized with charcoal, filtered, dried over magnesium sulfate and evaporated *in vacuo*. The solid product was crystallized from petroleum ether as pale yellow crystals, mp 118°, yield 0.3 g (16%); ir: ν cm^{-1} 3405, 3310, 3120, 1610, 1440, 1070, 765, 755, 745.

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.28; H, 4.71; N, 13.08; S, 14.94. Found: C, 67.38; H, 4.72; N, 13.11; S, 14.88.

Method B.

A suspension of **45** (4 g) in *o*-dichlorobenzene was heated under reflux for 3 hours. This was then cooled and the oxopyrazine (**10**) precipitate was filtered (3.1 g) and filtrate was evaporated *in vacuo* and the residual solid was dissolved in ether, decolorized with charcoal and filtered. The filtrate was then worked up as described in method A, yield 0.4 g (22%). The mp and ir spectra are identical with those of a sample prepared by method A.

3-(1-Pyrrolyl)-2[1]benzothenoic Anhydride **46**.

To a stirred, cold (0°) solution of **1** (2.4 g, 0.01 mole) in acetone (50 ml) and water (5 ml) was added a solution of triethylamine (1.2 g, 0.12 mole) in acetone (20 ml) followed after 30 minutes by a solution of ethyl chloroformate (1.3 g, 0.012 mole) in acetone (20 ml). Stirring was continued for 1 hour. The reaction mixture was then evaporated *in vacuo*. The semi-solid residue was triturated with ether, filtered and washed with ether. Crystallization from chloroform/ether gave yellow crystals, mp 136°, yield 3.5 g (76%); ir: ν cm^{-1} 1780, 1720, 1520, 1480, 1160, 720.

Anal. Calcd. for $C_{26}H_{16}N_2O_3S_2$: C, 66.65; H, 3.44; N, 5.98; S, 13.68. Found: C, 66.69; H, 3.31; N, 5.94; S, 13.60.

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