# Heterocyclic Compounds. V. 2,4-Disubstituted Thienopyrimidones (1)

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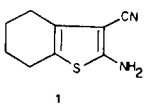
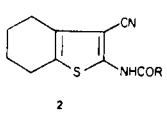
Thienopyrimidine derivatives have been synthesized by several workers because of their potential biological activity. Some of these compounds have shown antimalarial (2,3), CNS (4), and thrombocyte aggregation inhibition effect (5). In one of our earlier communications we reported the synthesis of 2,3-disubstituted thienopyrimidones and their antiinflammatory activity (6). In this communication we wish to report the synthesis of several 2,4-disubstituted thienopyrimidines and their biological evaluation.

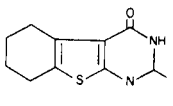
2-Amino-3-cyano-4,5-tetramethylenethiophene (**1**), prepared by the method of Gewald (7), was acylated with various acid chlorides to obtain the corresponding 2-amido derivatives (**2**). The cyclization of **2** to the thienoprimidones **3** could be carried out under acidic conditions. We have found that the overall yield of the thienopyrimidones (**3**) by this sequence of reactions was not very satisfactory. A more convenient synthesis of **3** consisted in the condensation of 2-amino-3-carboxamido-4,5-tetramethylene thiophene (**4**) (7) with appropriate aldehydes (8) in the presence of a catalytic amount of hydrochloric acid. An oxidation step must be involved besides condensation to obtain **3** from this reaction. Mass spectral analysis gave definitive evidence for **3**. In all the cases that we have studied, the formation of the corresponding 1,2-dihydro derivatives could not be detected spectroscopically even in the crude reaction product.



1

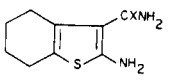


2



3

a. R = Ph
b. R = *o*-$C_6H_4CH_3$
c. R = *p*-$C_6H_4CH_3$
d. R = *p*-$C_6H_4OCH_3$

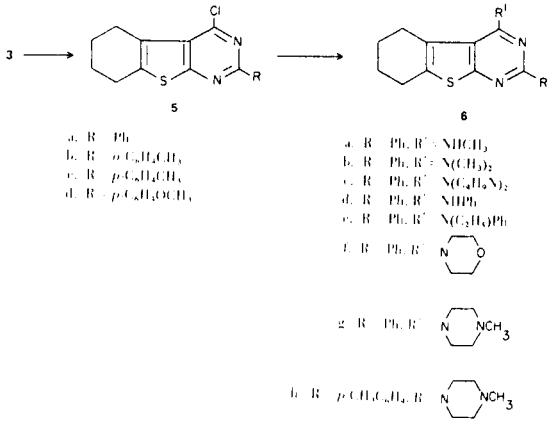


4 X = O
7 X = S

2

The thienopyrimidones **3** were converted to the 4-chloro derivatives **5** (9) by refluxing with phosphorus oxychloride. The 4-aminothienopyrimidines (**6c-h**) were synthesized by heating **5** under reflux with primary or secondary amines.

It has been reported by Heindel and coworkers (10) that the nuclear chlorine in quinoline and pyridine can be replaced by monoalkylamino- and dialkylamino functions by refluxing them with suitably substituted formamides. Bose and coworkers (11) have extended this reaction to the synthesis of amino substituted phenanthridines. We have noticed that the chlorine atom at $C_4$ in the thienopyrimidines is reactive enough to undergo a replacement reaction under these conditions to afford 4-alkylamino derivatives. Thus, the reaction of **5** with *N*-methylformamide and *N*,*N*-dimethylformamide gave **6a** and **6b** respectively.



5

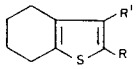
a. R = Ph
b. R = *o*-$C_6H_4CH_3$
c. R = *p*-$C_6H_4CH_3$
d. R = *p*-$C_6H_4OCH_3$

6

a. R = Ph, R' = $NHCH_3$
b. R = Ph, R' = $N(CH_3)_2$
c. R = Ph, R' = $N(C_6H_5N)_2$
d. R = Ph, R' = $NHPh$
e. R = Ph, R' = $N(C_2H_5)Ph$
f. R = Ph, R' = morpholino
g. R = Ph, R' = 4-methylpiperazino
h. R = *p*-$CH_3OC_6H_4$, R' = 4-methylpiperazino

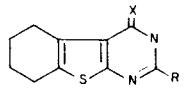
The conversion of **1** to the thiocarboxamide **7** by treating with hydrogen sulfide (12) did not give satisfactory yield of the product. However, **7** was obtained in about 80% yield from **4** by refluxing it with phosphorus pentasulfide in pyridine. The treatment of **7** with benzaldehyde and *p*-anisaldehyde afforded the 4-thiopyrimidones **8a** (9) and **8b**. The corresponding 4-thio-1,2-dihydropyrimidones could not be detected in this reaction even when the crude product was examined spectroscopically. As in the case

Table I



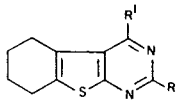
| No. | R | R′ | M.p. °C | Yield, % | Formula | Analysis C | Analysis H | Analysis N | Spectral Data |
|---|---|---|---|---|---|---|---|---|---|
| **2b** | $NHCOC_6H_4CH_3$ *(o)* | CN | 146-148 | 80 | $C_{17}H_{16}N_2O_2$ | 69.05 (68.90) | 5.35 (5.44) | 9.83 (9.44) | ir: 3450, 2210, 1645 $cm^{-1}$. |
| **2c** | $NHCOC_6H_4CH_3$ *(p)* | CN | 156-158 | 85 | $C_{17}H_{16}N_2OS$ | | | | ir: 3450, 2210, 1645 $cm^{-1}$, $m^+$ at m/e 296. |
| **2d** | $NHCOC_6H_4OCH_3$ *(p)* | CN | 194-195 | 80 | $C_9H_{12}N_2S_2$ | 65.67 (65.37) | 5.46 (5.60) | 8.62 (8.97) | ir: 3451. 2210, 1647 $cm^{-1}$. |
| **7** | $NH_2$ | $CSNH_2$ | 256-257 | 60 | $C_9H_{12}N_2S_2$ | | | | ir: 3300 $cm^{-1}$, $m^+$ at m/e 212. |
| **2a** (8) | NHCOPh | CN | 237-238 | 85 | $C_{16}H_{14}N_2OS$ | | | | |

Table II



| No. | R | X | M.p. °C | Yield, % | Formula | Analysis C | Analysis H | Analysis N | Spectral Data |
|---|---|---|---|---|---|---|---|---|---|
| **3a** (8) | Ph | O | 287-288 | 70 | $C_{16}H_{14}N_2OS$ | | | | |
| **3b** | $o$-$C_6H_4CH_3$ | O | 290-291 | 60 | $C_{17}H_{16}N_2OS$ | | | | ir: 1660 $cm^{-1}$, nmr δ 1.75-2.05 (b, 4H), 2.52 (S, 3H), 2.78-3.1 (b, 4H), 7.35-7.95 (b, 4H), $m^+$ at m/e 296. |
| **3c** | $p$-$C_6H_4CH_3$ | O | 307-308 | 65 | $C_{17}H_{16}N_2OS$ | 68.90 (68.91) | 5.76 (5.44) | 9.70 (9.46) | ir: 1660 $cm^{-1}$, nmr δ 1.82-2.0 (b, 4H), 2.45 (S, 3H), 2.7-3.15 (b, 4H). |
| **3d** | $p$-$C_6H_4OCH_3$ | O | 275-276 | 70 | $C_{17}H_{16}N_2O_2S$ | 65.46 (65.32) | 5.46 (5.16) | 9.18 (8.97) | 7.8 (q, 4H, J = 8 Hz). ir: 1658 $cm^{-1}$, $m^+$ at m/e 280. |
| **8a** (8) | Ph | S | 314-318 | 70 | $C_{16}H_{14}N_2OS_2$ | | | | |
| **8b** | $p$-$C_6H_4OCH_3$ | S | 217-219 | 80 | $C_{17}H_{16}N_2OS_2$ | 62.17 (62.19) | 4.62 (4.91) | 9.06 (8.53) | $m^+$ at m/e 328. |

Table III



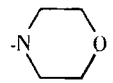
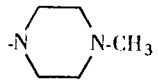
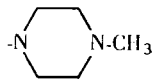
| No. | R | R′ | M.p. °C | Yield, % | Formula | Analysis C | Analysis H | Analysis N | Spectral Data |
|---|---|---|---|---|---|---|---|---|---|
| 6a | Ph | $NHCH_3$ | 189-190 | 90 | $C_{17}H_{17}N_3S$ | 69.10 (69.13) | 5.89 (5.80) | 14.06 (14.23) | ir: 1600 $cm^{-1}$, nmr δ 1.75-2.0 (b, 4H), 2.75-3.0 (b, 4H), 3.15 (d, 3H), 5.0-5.2 (b, 1H), 7.3-7.5 (b, 3H), 8.4-8.6 (b, 2H), $m^+$ at m/e 295. |
| 6b | Ph | $N(CH_3)_2$ | 124-125 | 89 | $C_{18}H_{19}N_3S$ | 69.44 (69.90) | 6.11 (6.15) | 14.02 (13.59) | ir: 1580 $cm^{-1}$, nmr δ 1.75-1.95 (b, 4H), 2.75-2.9 (b, 4H), 3.0 (S, 6H), 7.2-7.4 (t, 3H), 8.35-8.6 (t, 2H). |
| 6c | Ph | $N(C_4H_9)_2$ | 86-87 | 80 | $C_{24}H_{31}N_3S$ | 73.04 (73.25) | 7.81 (7.94) | 10.48 (10.68) | ir: 1580 $cm^{-1}$, nmr δ 1.75-1.95 (b, 4H), 2.75-2.9 (b, 4H), 3.0 (S, 6H), 7.2-7.4 (b, 3H), 8.35-8.65 (b, 2H). |
| 6d | Ph | NHPh | 259-261 | 90 | $C_{22}H_{19}N_3S$ | 74.25 (73.93) | 5.70 (5.36) | 11.52 (11.76) | ir: 1600, 1580 $cm^{-1}$, nmr δ 1.75-2.01 (b, 4H), 2.8-3.2 (b, 4H), 7.35-7.61 (b, 9H), 8.0-8.2 (b, 2H), $m^+$ at m/e 357. |
| 6e | Ph | $N(C_2H_5)Ph$ | 145-146 | 70 | $C_{24}H_{23}N_3S$ | 74.68 (74.80) | 6.08 (5.77) | 10.99 (10.90) | ir: 1600, 1580 $cm^{-1}$, nmr δ 1.41 (t, 3H) 1.72-2.0 (b, 4H), 2.62-2.85 (b, 4H), 4.35 (q, 2H), 6.9-7.5 (b, 8H), 8.5-8.7 (b, 2H). |
| 6f | Ph |  | 145-149 | 90 | $C_{20}H_{21}N_3OS$ | 68.20 (68.36) | 6.11 (6.02) | 11.96 (11.96) | ir: 1580 $cm^{-1}$, nmr δ 1.75-2.0 (b, 4H), 2.75-3.0 (b, 4H), 3.35-3.65 (b, 4H), 3.75-4.0 (b, 4H), 7.3-7.55 (b, 3H), 8.4-8.6 (b, 2H). |
| 6g | Ph |  | 189-191 | 90 | $C_{21}H_{24}N_4S$ | 69.00 (69.21) | 6.72 (6.64) | 15.03 (15.38) | ir: 1580 $cm^{-1}$, nmr δ 1.75-2.0 (b, 4H), 2.38 (S, 3H), 2.52-3.0 (b, 8H), 3.4-3.65 (b, 4H), 7.35-7.5 (b, 3H), 8.4-8.65 (b, 2H). |
| 6h | *p*-$CH_3C_6H_4$ |  | 190-192 | 92 | $C_{22}H_{26}N_4S$ | 69.97 (69.82) | 7.20 (6.92) | 14.52 (14.80) | ir: 1585 $cm^{-1}$, nmr δ 1.71-2.0 (b, 4H), 2.4 (S, 3H), 2.51-2.7 (b, 4H), 2.8-3.0 (b, 4H), 3.5-3.7 (b, 4H), 7.2-7.4 (d, 2H), 8.4-8.6 (d, 2H), $m^+$ at m/e 378. |
| 9b | *p*-$CH_3OC_6H_4$ | $SCH_3$ | 230-233 | 70 | $C_{18}H_{18}N_2OS_2$ | 63.04 (63.15 | 5.06 (5.30) | 8.29 (8.18) | ir: 1600 $cm^{-1}$, nmr δ 1.75-2.0 (b, 4H), 2.75-3.0 (b, 4H), 2.75 (S, 3H), 3.82 (S, 3H), 8.8 (d, 4H, J = 8 Hz). |

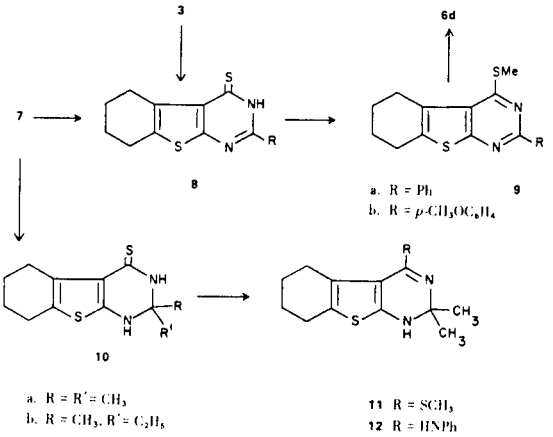
Table III (continued)

| No. | R | R' | M.p. °C | Yield, % | Formula | Analysis C | Analysis H | Analysis N | Spectral Data |
|---|---|---|---|---|---|---|---|---|---|
| 5a | Ph | Cl | 171-172 | 70 | $C_{16}H_{15}ClN_2S$ | | | | |
| 5b | *o*-$CH_3C_6H_4$ | Cl | 103-104 | 60 | $C_{17}H_{15}ClN_2S$ | 64.90 (64.86) | 4.94 (4.77) | 8.81 (8.90) | ir: 1600 $cm^{-1}$, nmr δ 1.8-2.02 (b, 4H), 2.5 (S, 3H), 2.75-3.2 (b, 4H), 7.15-7.35 (b, 4H). |
| 5c | *p*-$CH_3C_6H_4$ | Cl | 219-220 | 72 | $C_{17}H_{15}ClN_2S$ | 65.12 (64.86) | 5.03 (4.77) | 8.45 (8.90) | ir: 1600 $cm^{-1}$, nmr δ 1.7-2.0 (b, 4H), 2.4 (S, 3H), 2.8-3.2 (b, 4H), 7.2-7.4 (d, 2H, J = 8 Hz), 8.1-8.3 (d, 2H, J = 8 Hz). |
| 5d | *p*-$CH_3OC_6H_4$ | Cl | 168-170 | 70 | $C_{17}H_{15}ClN_2O_2$ | | | | ir: 1600 $cm^{-1}$, nmr δ 1.7-2.0 (b, 4H), 2.8-3.1 (b, 4H), 3.85 (S, 3H), 7.65 (d, 4H, J = 8 Hz). |

of the synthesis of **3**, an oxidation step must be involved here, too.

Refluxing the 4-pyrimidones **3a** and **3d** with phosphorus pentasulfide resulted in the formation of **8a** and **8b**, respectively, in almost quantitative yield.

4-Methylthiothienopyrimidines **9a** and **9b** were synthesized by the reaction of the thio compounds **8a** and **8b** with methyl iodide in tetrahydrofuran. The methylthio group in **9a** and **9b** did not lend itself to replacement by an *N*-alkylamino group on treatment with *N*,*N*-dimethylformamide. However, refluxing **9a** with aniline afforded **6d** in good yield. The reaction of **7** with acetone and methyl ethyl ketone gave 1,2-dihydrothienopyrimidones **10a** and **10b**, respectively. When **10a** was treated with methyl iodide in tetrahydrofuran, the hydroiodide of **11** was obtained. Refluxing **11** with aniline gave **12**.




Compounds **2b**, **3a**, **3c**, **6a**, **5b**, **5c**, **6b**, **6c**, and **6d** were tested for their antiviral, antibacterial, antifungal, complement inhibition, interferon release and antiinflammatory activity (14). None of these compounds were found to be active. It was, however, found that compound **6f** was slightly active (34%) in the inhibition of carrageenin induced edema in mice, **6c**, **6f**, and **6g** showed weak anorexogenic acitivity (24, 14 and 24%, respectively).

Acknowledgment.

The authors wish to thank the Central Drug Research Institute, Lucknow (India) and Lederle Laboratories for biological testing of the compounds.

## EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer Infracord. Nmr spectra were recorded with a Varian A60A spectrometer and mass spectra with a 21-103C CEC mass spectrometer. Microanalyses were performed by MHW Laboratories, Garden City, Michigan, and A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mülheim (Ruhr), West Germany.

2-Amino-3-cyano-4,5-tetramethylenethiophene (**1**) and 2-Amino-3-carboxamido-4,5-tetramethylenethiophene (**4**).

Table IV

| No. | M.p. °C | Yield, % | Formula | Analysis C | H | N | Spectral Data |
|---|---|---|---|---|---|---|---|
| **10a** | 250-251 | 70 | $C_{12}H_{16}N_2S_2$ | 55.07 (55.63) | 6.62 (6.81) | 10.84 (10.84) | ir: 3350 $cm^{-1}$; nmr δ 1.45 (S, 6H), 1.75 (b, 4H), 2.8 (b, 4H), 3.7 (b, 1H), 10.8 (b, 1H); $m^+$ at m/e 252. |
| **10b** | 239-240 | 75 | $C_{13}H_{18}N_2S_2$ | 59.05 (58.63) | 6.63 (6.03) | 10.50 (10.50) | ir: 3360 $cm^{-1}$; nmr δ 1.95 (t, 3H, J = 7 Hz), 1.4 (S, 3H), 1.7 (b, 4H) 2.8 (b, 4H). |
| **11** | 231-232 | 60 | $C_{13}H_{17}N_2S_2$ | 39.41 (39.50) | 4.76 (4.81) | 7.19 (7.09) | ir: 3350 $cm^{-1}$; nmr δ 1.65 (S, 6H), 1.8 (b, 4H), 2.6 (b, 4H), 2.85 (S, 3H), 10.4 (b, 1H). |
| **12** | 265-267 | 50 | $C_{18}H_{21}N_3S$ | 69.71 | 6.52 | 13.38 | ir: 3350 $cm^{-1}$; $m^+$ at m/e 311. |

These compounds were prepared by the method of Gewald and coworkers (7).

2-Amino-3-thiocarboxamido-4,5-tetramethylenethiophene (**7**).

A suspension of **4** (1.96 g., 0.01 mole), phosphorus pentasulfide (2.2 g., 0.01 mole) in pyridine (20 ml.) was heated under reflux for 1 hour. The reactants are filtered hot into 40 ml. of warm (50°) water. On cooling the thiocarboxamide (**7**) separated out as yellow needles which were collected by filtration (1.7 g., 80%), m.p. 256-257° (dimethylformamide). The analytical and spectral data are given in Table I.

Compounds **3a** and **3d** were also converted to the 4-thio derivatives, **8a** and **8b**, respectively, by refluxing with phosphorus pentasulfide in pyridine. (For analytical and spectral data, see Table II).

2-Benzoylamido-3-cyano-4,5-tetramethylenethiophene (**2a**).

This compound was prepared as described by Manhas, *et al.* (9).

Using the same general procedure, **2b, 2c** and **2d** also synthesized.

The spectral and analytical data on **2b, 2c, 2d** and **7** are given in Table I.

2-Phenyl-4-oxo-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidone (**3a**).

This compound was synthesized from **2a** as described in the literature (9).

Using the literature method **3b, 3c, 3d** and **8** were prepared from **2b, 2c, 2d** and **7**, respectively. Their analytical and spectral data are given in Table II.

2-(*p*-Methoxyphenyl)-4-oxo-5,6,7,8-tetrahydro[1]benzothieno-[1,3-*d*]pyrimidine (**3d**).

A mixture of the aminoamide (**2**, 1.96 g., 0.01 mole) and *p*-anisaldehyde (1.38 g., 0.01 mole) in 20 ml. of ethanol containing 2 drops of concentrated hydrochloric acid was refluxed for 2 hours. On cooling, the product separated as a light yellow solid and was filtered to give 2 g. (80%) of essentially pure material, m.p. 307-308° (dimethylformamide).

The thienopyrimidones **3a, 3b** and **3c** were also prepared by this method using the appropriate aldehydes.

The reaction of *o*-aminothiocarboxamide (**7**) with *p*-anisaldehyde, acetone and methylethylketone under these conditions resulted in the formation of **8b, 10a**, and **10b**, respectively. The analytical and spectral data on **10a** and **10b** are given in Table IV.

4-Chloro-2-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**5a**).

This compound was synthesized by the method described in reference 12.

Compounds **5b, 5c** and **5d** were similarly prepared by treatment of **3b, 3c** and **3d** with phosphorus oxychloride. Analytical data on these compounds is given in Table III.

General Method for the Synthesis of 4-Aminothienopyrimidine.

2-Phenyl-4-*N*-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]-pyrimidine (**6a**).

A mixture of **5a** (3 g.) and 30 ml. of *N*-methylformamide was refluxed for 6 hours. Excess *N*-methylformamide was removed under reduced pressure. The residue was extracted with methylene chloride, washed with water and dried (anhydrous magnesium sulfate). Removal of the solvent afforded **6a** (90% yield), m.p. 187-188° (methylene chloride).

Compound **6b** was similarly obtained from **5a** and dimethylformamide.

Compounds **6c-h** were formed by treating the 4-chlorothienopyrimidines (**5**) with the corresponding primary or secondary amines. In a similar manner, **11** was converted to **12**.

The analytical data and physical constants for **6a-6h** are given in Table III and for **11** and **12** in Table IV.

2-*p*-Methoxyphenyl-4-thiomethyl-5,6,7,8-tetrahydro[1]benzothieno[1,3-*d*]pyrimidine (**9b**).

A solution of **8b** (6.7 g., 0.02 mole), methyl iodide (2.82 g., 0.02 mole) in tetrahydrofuran (100 ml.) was refluxed for 3 hours. On cooling, the hydroiodide of **9b** crystallized out and was then separated by filtration. It was then suspended in methylene chloride and neutralized with an aqueous solution of triethylamine. The organic layer was washed with water, dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue after recrystallization from ethyl acetate gave **9b**.

Using the same reaction conditions, **9a** was obtained from **8a** and **11** from **10a**. The physical constants and analytical data on **9a** and **9b** are given in Table III.

## REFERENCES AND NOTES

(1) For part 4 in this series, see M. S. Manhas, S. D. Sharma, and S. G. Amin, *J. Med. Chem.*, 15, 106 (1972).

(2) A. Rosowsky, M. Chaykovsky, K. K. N. Chen, M. Lin, and E. J. Modest, *ibid.*, **16**, 185 (1973).

(3a) M. Chaykovsky, M. Lin, A. Rosowsky, and E. J. Modest, *ibid.*, **16**, 188 (1973); (b) A. Rosowsky, K. K. N. Chen, and M. Lin, *ibid.*, **16**, 191 (1973).

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