Pyrimidines. 65 [1].
Synthesis of 6-Substituted Thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones

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Several 6-substituted thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives were synthesized. 6-Ethoxycarbonyl derivatives **3** and **7** were prepared by treatment of 6-chloro-5-formyluracil **1** and 6-chloro-5-cyanouracil **6** with ethyl 2-mercaptoacetate in the presence of a base. Electrophilic substitution reactions (Vilsmeier-Haack reaction, bromination, and nitration) of 5,6-unsubstituted thieno[2,3-*d*]pyrimidine **9**, prepared by condensation of 6-mercaptouracil **8** with chloroacetaldehyde, afforded the corresponding 6-formyl-, 6-bromo-, and 6-nitrothieno[2,3-*d*]pyrimidines **10**, **15** and **16**, respectively.

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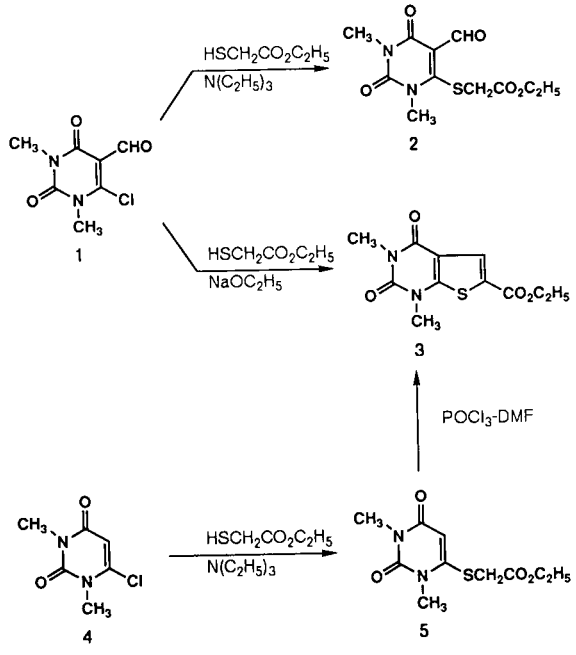
A number of thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives have been synthesized for the biological activities such as antihypertensive action [2,3], platelet aggregation inhibition [4-6], and antitumor [7] and antihistamine [8-10] activities. Most of the methods for the preparation of this ring system have been achieved by ring closure of 2-amino-3-ethoxycarbonylthiophene derivatives [3,11-20]. Few synthetic methods using pyrimidine derivatives as a starting material, however, have been reported [21]. Therefore, synthesis of the thieno[2,3-*d*]pyrimidine derivatives possessing various functional groups except alkyl and phenyl groups on the thiophene ring (at the 5- and/or 6-positions) seems to be difficult by conventional means. This paper describes the synthesis of 6-substituted thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones by cyclization of uracil derivatives or electrophilic substitutions of 6-unsubstituted thieno[2,3-*d*]pyrimidine **9**.

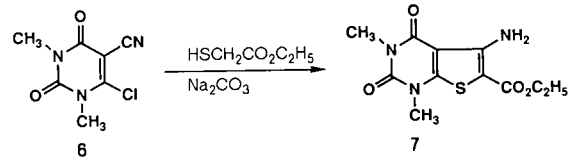
Scheme 1



6-Chloro-5-formyluracil derivatives are excellent intermediates for the synthesis of heterocycle-fused pyrimidines [22-31]. A new synthetic route to thieno[2,3-*d*]pyrimidine-6-carboxylate derivative involving construction of a thiophene ring has been studied by using 6-chloro-5-formyl-1,3-dimethyluracil (**1**) [32]. Thus, treatment of **1** with ethyl 2-mercaptoacetate in the presence of triethylamine under reflux gave 6-ethoxycarbonylmethylthiouracil derivative **2**. On the other hand, employment of sodium ethoxide instead of triethylamine as a base led to the formation of the expected cyclization product, 6-ethoxycarbonylthieno[2,3-*d*]pyrimidine-2,4-dione **3**, in 51% yield. Compound **3** was also obtained by the Vilsmeier-Haack reaction of 6-ethoxycarbonylmethylthiouracil **5** prepared with ease by the reaction of 6-chloro-1,3-dimethyluracil (**4**) [33] with ethyl 2-mercaptoacetate.

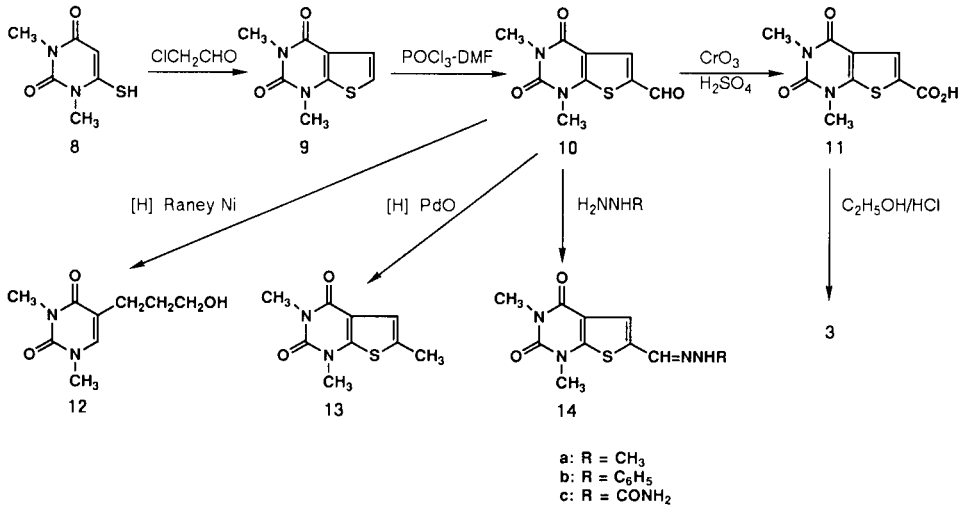
6-Chloro-5-cyano-1,3-dimethyluracil (**6**), prepared from the 5-formyluracil **1** in two steps [34], was cyclized to 5-aminothieno[2,3-*d*]pyrimidine **7** on heating with ethyl 2-mercaptoacetate in the presence of sodium carbonate.

Scheme 2



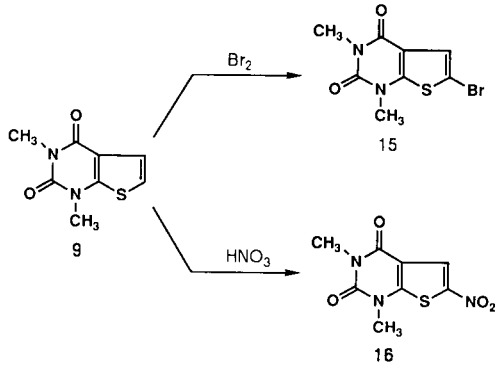
Previously, we reported the synthesis of pyrrolo[2,3-*d*]-pyrimidines by condensation of 6-aminouracils with chloroacetaldehyde [35]. This method was applied to the synthesis of 5,6-unsubstituted thieno[2,3-*d*]pyrimidine **9**. The

Scheme 3



6-mercaptouracil **8** [21] was allowed to react with chloroacetaldehyde in the presence of sodium acetate at room temperature to give the thieno[2,3-*d*]pyrimidine **9** in 66% yield. Electrophilic substitutions of **9** have been investigated to prepare 5- or 6-substituted thieno[2,3-*d*]pyrimidines. The Vilsmeier-Haack reaction of **9** using phosphorus oxychloride and dimethylformamide (DMF) resulted in the formation of the 6-formylated product **10** exclusively and none of the 5-formylated one. The structure of **10** was determined by the conversion of **10** into the thieno[2,3-*d*]pyrimidine-6-carboxylate **3** prepared above: oxidation of **10** with the Jones reagent followed by esterification afforded the ethyl ester **3**.

Scheme 4



Hydrogenation of **10** using Raney nickel under 50 atmospheres induced desulfurization to give 5-(3-hydroxypropyl)-1,3-dimethyluracil (**12**). When palladium(II) oxide was used as a catalyst for the hydrogenation of **10**, 6-methylthieno[2,3-*d*]pyrimidine **13** was obtained in 64% yield. The 6-formyl compound **10** reacted with carbonyl reagents, such as methylhydrazine, phenylhydrazine, and semicarbazide, to give the corresponding hydrazones **14a,b** and semicarbazone **14c**, respectively.

Bromination and nitration of **9** also occurred at the 6-position as in the Vilsmeier-Haack reaction to give the corresponding 6-bromo- and 6-nitrothieno[2,3-*d*]pyrimidines **15** and **16**, respectively. The substitution position of the bromo and the nitro group was determined by comparison of their ^{1}H nmr spectral data with those of other thieno[2,3-*d*]pyrimidines (see Table 1) and by consideration of the substituent effects on the chemical shifts in the ^{1}H nmr spectra of thiophene derivatives [36]. In compound **9**, the 6-H signal appears at higher field than the 5-H signal, which indicates that the 6-position is more reactive toward electrophiles than the 5-position. This fact fully accommodates the results obtained above for the electrophilic substitution reactions of **10**.

Table 1

^{1}H NMR Spectra of Thieno[2,3-*d*]pyrimidine-2,4-diones [a]

No.	H-5	No.	H-5	H-6
3	8.00	**9**	7.39	6.87
10	8.07	**13**	7.03	----
11	7.76	**17** [b]	----	6.48 [c]
15	7.35			
16	8.26			

[a] Measured in deuteriochloroform. [b] Compound **17** is 1,3,5-trimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione [c] Obtained from ref 21.

None of the 6-substituted thieno[2,3-*d*]pyrimidine-2,4-diones prepared here demonstrated any appreciable activity against antibacterial, antiviral, coccidiostatic, and antimycoplasmic activities.

EXPERIMENTAL

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. The ^{1}H nmr spectra were determined with a Hitachi Perkin-Elmer R-20B (60-MHz) instrument or a JEOL JNM-FX-100 (100-MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) and signals are quoted as a s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); and J values are first order.

6-Ethoxycarbonylmethylthio-5-formyl-1,3-dimethyluracil (**2**).

A mixture of 6-chloro-5-formyl-1,3-dimethyluracil (**1**) [32] (8.0 g, 0.039 mole), ethyl 2-mercaptoacetate (4.8 g, 0.04 mole), and triethylamine (5 ml) in pyridine (80 ml) was heated at 95-100° for 15 minutes. The solvent was removed under reduced pressure and water (80 ml) was added to the residue. The resulting precipitate was collected by filtration, washed with water, and recrystallized from ethanol to give 7.0 g (62%) of **2**, mp 110°; ^{1}H nmr (deuteriochloroform): δ 1.31 (3H, t, J = 7 Hz, CH_3), 3.38 (6H, s, CH_3 x 2), 3.69 (2H, s, CH_2), 4.25 (2H, q, J = 7 Hz, CH_2), 9.00 (1H, s, CHO).

Anal. Calcd. for $C_{11}H_{14}N_2O_5S$: C, 46.15; H, 4.93; N, 9.79. Found: C, 46.48; H, 4.97; N, 9.68.

6-Ethoxycarbonyl-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3**).

(a) A mixture of 6-chloro-5-formyl-1,3-dimethyluracil (**1**) [32] (8.0 g, 0.039 mole) and ethyl 2-mercaptoacetate (6.6 g, 0.055 mole) in ethanolic sodium ethoxide [prepared from sodium (1.0 g, 0.044 atom) in absolute ethanol (60 ml)] was refluxed for 2 hours. The reaction solution was evaporated to dryness under reduced pressure. The residue was triturated with water (60 ml) to give 8.0 g (80%) of the crude product. Recrystallization from ethanol gave 5.3 g (51%) of **3**, mp 189-190°; ^{1}H nmr (deuteriochloroform): δ 1.37 (3H, t, J = 7 Hz, CH_3), 3.41 (3H, s, CH_3), 3.56 (3H, s, CH_3), 4.34 (2H, q, J = 7 Hz, CH_2), 8.00 (1H, s, thiophene-H).

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44. Found: C, 49.37; H, 4.51; N, 10.59.

(b) A mixture of the 6-ethoxycarbonylmethylthiouracil **5** (1.0 g, 0.004 mole), phosphorus oxychloride (0.6 g), and DMF (10 ml) was refluxed for 30 minutes. The reaction mixture was evaporated under reduced pressure and water (30 ml) was added to the residue. The resulting precipitate was collected by filtration and washed with water to give 0.7 g (67%) of the crude product. Recrystallization from ethanol gave 0.4 g (38%) of **3**, mp 189-190°, which was identical with the product obtained above.

(c) Dry hydrogen chloride gas was bubbled into a solution of 6-carboxy-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**11**) (0.9 g, 0.004 mole) in absolute ethanol (150 ml) under reflux with stirring for 1 hour and the mixture was refluxed for another 1 hour. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give 0.4 g (38%) of **3**, mp 188-189°, which was identical with the product obtained above.

6-Ethoxycarbonylmethylthio-1,3-dimethyluracil (**5**).

A mixture of 6-chloro-1,3-dimethyluracil (**4**) [33] (8.7 g, 0.05 mole), ethyl 2-mercaptoacetate (6.6 g, 0.055 mole), and triethylamine (6 ml) in pyridine (10 ml) was heated at 95-100° for 1 hour. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give 6.7 g (52%) of **5**, mp 149° (lit [21] 149°).

Anal. Calcd. for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.70; H, 5.60; N, 10.76.

5-Amino-6-ethoxycarbonyl-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**7**).

A mixture of 6-chloro-5-cyano-1,3-dimethyluracil (**6**) [34] (7.5 g, 0.04 mole), ethyl 2-mercaptoacetate (5.3 g, 0.044 mole), and anhydrous sodium carbonate (4.3 g, 0.04 mole) in ethanol (200 ml) was refluxed with stirring for 3 hours. The reaction mixture was cooled. The resulting precipitate was collected by filtration, washed with water, and recrystallized from ethanol to give 4.5 g (40%) of **7**, mp 225-226°; ^{1}H nmr (deuteriochloroform): δ 1.35 (3H, t, J = 7 Hz, CH_3), 3.39 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.29 (2H, q, J = 7 Hz, CH_2), 6.77 (2H, br, deuterium exchangeable NH_2).

Anal. Calcd. for $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.63; N, 14.83. Found: C, 46.89; H, 4.82; N, 15.09.

1,3-Dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9**).

To a mixture of 6-mercapto-1,3-dimethyluracil (**8**) [21] (5.2 g, 0.03 mole) and sodium acetate (1.2 g, 0.015 mole) in water (50 ml) was added a solution of 30% aqueous chloroacetaldehyde (10 ml, 0.038 mole) and sodium acetate (1.2 g, 0.015 mole) in water (20 ml) dropwise at room temperature. The mixture was stirred overnight at room temperature. The resulting precipitate was collected by filtration to give 3.9 g (66%) of **9**, mp 161-163°. Recrystallization from ethanol gave the pure product, mp 168°; ^{1}H nmr (deuteriochloroform): δ 3.45 (3H, s, CH_3), 3.58 (3H, s, CH_3), 6.87 (1H, d, J = 6 Hz, thiophene-H), 7.39 (1H, d, J = 6 Hz, thiophene-H).

Anal. Calcd. for $C_8H_8N_2O_2S$: C, 48.97; H, 4.11; N, 14.28. Found: C, 49.12; H, 4.21; N, 14.11.

6-Formyl-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**10**).

A mixture of 1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9**) (10 g, 0.051 mole) and DMF (25 ml) in phosphorus oxychloride (50 ml) was heated at 95-100° with stirring for 1 hour. The excess phosphorus oxychloride was removed by evaporation under reduced pressure and the residue was poured into ice-water to give 10.5 g (92%) of the crude product. Recrystallization from methanol gave the pure **10**, mp 225°; ^{1}H nmr (deuteriochloroform): δ 3.46 (3H, s, CH_3), 3.63 (3H, s, CH_3), 8.07 (1H, s, thiophene-H), 9.87 (1H, s, CHO).

Anal. Calcd. for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49. Found: C, 48.41; H, 3.73; N, 12.60.

6-Carboxy-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**11**).

To a stirred solution of the 6-formylthieno[2,3-*d*]pyrimidine **10** (110 mg, 0.5 mmole) in DMF (20 ml) was added the Jones reagent [prepared by dissolving chromium(VI) oxide (2.67 g) in water (4 ml) followed by addition of concentrated sulfuric acid (2.3 ml) and dilution of the resulting mixture to 10 ml with water] (4 ml) with cooling in an ice bath. After being stirred for 5 hours at room temperature, the reaction mixture was poured into ice-water. The mixture was allowed to stand overnight at room temperature. The resulting precipitate was collected by filtration, washed with water, and dissolved in diluted aqueous solution of sodium carbonate. After addition of active carbon the solution was filtered and acidified with hydrochloric acid. The resulting precipitate was collected by filtration and washed with water to

give 100 mg (83%) of the crude product. Recrystallization from DMF gave the pure **11**, mp >300°; ^{1}H nmr (DMSO-d_6): δ 3.24 (3H, s, CH_3), 3.48 (3H, s, CH_3), 7.76 (1H, s, thiophene-H).

Anal. Calcd. for $C_9H_8N_2O_4S$: C, 45.00; H, 3.36; N, 11.66. Found: C, 45.24; H, 3.55; N, 11.57.

5-(3-Hydroxypropyl)-1,3-dimethyluracil (**12**).

A mixture of the 6-formylthieno[2,3-*d*]pyrimidine **10** (3.0 g, 0.0134 mole) and active Raney-Ni (15 g) in ethanol (100 ml) was heated at 100° under hydrogen (50 atmospheres) with stirring in an autoclave for 7 hours. After addition of active carbon the hot reaction mixture was filtered off and the filtrate was concentrated under reduced pressure. The residue was recrystallized from ether to give 0.9 g (34%) of **12**, mp 102-103°; ^{1}H nmr (deuteriochloroform): δ 1.77 (2H, quintet, J = 6 Hz, CH_2), 2.50 (2H, t, J = 6 Hz, CH_2), 2.55 (1H, s, deuterium exchangeable OH), 3.39 (3H, s, CH_3), 3.42 (3H, s, CH_3), 3.63 (2H, t, J = 6 Hz, CH_2), 7.09 (1H, s, pyrimidine-H).

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.60; H, 7.05; N, 14.02.

1,3,6-Trimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**13**).

A mixture of the 6-formylthieno[2,3-*d*]pyrimidine **10** (15 g, 0.067 mole) and palladium(II) oxide (2.0 g) in ethanol (650 ml) was heated at 100° under hydrogen (35 atmospheres) with stirring in an autoclave for 10 hours. After addition of active carbon the hot reaction mixture was filtered off and the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethanol to give 8.5 g (61%) of **13**, mp 151°; ^{1}H nmr (deuteriochloroform): δ 2.48 (3H, d, J = 1 Hz, CH_3), 3.44 (3H, s, CH_3), 3.55 (3H, s, CH_3), 7.03 (1H, q, J = 1 Hz, thiophene-H).

Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32. Found: C, 51.64; H, 4.97; N, 13.16.

1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxothieno[2,3-*d*]pyrimidine-6-carboxaldehyde Methylhydrazone (**14a**).

To a solution of the 6-formylthieno[2,3-*d*]pyrimidine **10** (1.0 g, 0.0045 mole) in chloroform (20 ml) was added methylhydrazine (1 ml) by portions. The mixture was stirred for 5 minutes at room temperature. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to give 0.8 g (71%) of **14a**, mp 223-225°; ^{1}H nmr (deuteriochloroform): δ 2.96 (3H, s, CH_3), 3.42 (3H, s, CH_3), 3.56 (3H, s, CH_3), 5.65 (1H, br, deuterium exchangeable NH), 7.18 and 7.53 (each 1H, each s, each thiophene-H or CH=N).

Anal. Calcd. for $C_{10}H_{12}N_4O_2S$: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.80; H, 5.02; N, 22.44.

1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxothieno[2,3-*d*]pyrimidine-6-carboxaldehyde Phenylhydrazone (**14b**).

A solution of the 6-formylthieno[2,3-*d*]pyrimidine **10** (1.0 g, 0.0045 mole) and phenylhydrazine (1 ml) in methanol (25 ml) was refluxed for 15 minutes. The reaction mixture was cooled and the resulting precipitate was collected by filtration. Recrystallization from methanol gave 0.6 g (43%) of **14b**, mp 280-284°.

Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82. Found: C, 57.22; H, 4.56; N, 17.61.

1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxothieno[2,3-*d*]pyrimidine-6-carboxaldehyde Semicarbazone (**14c**).

A solution of semicarbazide hydrochloride (1.0 g) and sodium acetate (1.5 g) in water (10 ml) was added to a solution of the 6-formylthieno[2,3-*d*]pyrimidine **10** (2.0 g, 0.009 mole) in methanol (25 ml). The mixture was heated on a water bath for 15 minutes. The reaction mixture was cooled. The resulting precipitate was collected by filtration and washed with water. Recrystallization from DMF gave 0.9 g (36%) of **14c**, mp >300°; ^{1}H nmr (DMSO-d_6): δ 3.24 (3H, s, CH_3), 3.47 (3H, s, CH_3), 6.34 (2H, br, deuterium exchangeable NH_2), 7.50 and 8.00 (each 1H, each s, each thiophene-H or CH=N), 10.35 (1H, br, deuterium exchangeable NH).

Anal. Calcd. for $C_{10}H_{11}N_5O_3S$: C, 42.70; H, 3.94; N, 24.90. Found: C, 42.95; H, 3.96; N, 24.84.

6-Bromo-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**15**).

A solution of bromine (8.8 g, 0.055 mole) in acetic acid (50 ml) was added dropwise to a mixture of the thieno[2,3-*d*]pyrimidine **9** (10 g, 0.051 mole) in acetic acid (50 ml). The mixture was stirred at room temperature for 1 hour. Water (150 ml) was added to the reaction mixture and the resulting precipitate was collected by filtration to give the crude product (12.9 g, 92%). Recrystallization from methanol gave the analytically pure **15**, mp 204°; ^{1}H nmr (deuteriochloroform): δ 3.43 (3H, s, CH_3), 3.54 (3H, s, CH_3), 7.35 (1H, s, thiophene-H).

Anal. Calcd. for $C_8H_7BrN_2O_2S$: C, 34.92; H, 2.56; N, 10.18. Found: C, 34.98; H, 2.58; N, 10.08.

6-Nitro-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**16**).

The thieno[2,3-*d*]pyrimidine **9** (2.0 g, 0.01 mole) was added by portions to a solution of fuming nitric acid (0.7 ml) in concentrated sulfuric acid (10 ml) at 0°. The mixture was stirred at 0° for 1 hour and stirring was continued at room temperature for 1 hour. Water (50 ml) was added into the reaction solution by portions with care. The aqueous solution was extracted with chloroform (10 ml x 4). The extract was dried, evaporated to dryness under reduced pressure, and purified by chromatography (chloroform). Recrystallization from ethanol gave 0.6 g (25%) of **16**, mp 209°; ^{1}H nmr (deuteriochloroform): δ 3.46 (3H, s, CH_3), 3.62 (3H, s, CH_3), 8.26 (1H, s, thiophene-H).

Anal. Calcd. for $C_8H_7N_3O_4S$: C, 39.83; H, 2.92; N, 17.42. Found: C, 40.08; H, 3.01; N, 17.31.

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