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Photochemical Synthesis of Fused Tricyclic Compounds from Bis-6,6′-(1,3-dialkyluracilyl)sulfides[1-3]

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Bis-6,6′-(1,3-dialkyluracilyl)sulfides (**3**) were synthesized by coupling of 6-chloro-1,3-dialkyluracil (**1**) and 1,3-dialkyluracil-6-mercaptide (**2**). Compounds (**3**) were found to undergo photochemical cyclization, giving rise to three types of isolable products with novel ring systems, namely, 1,3,6,8-tetraalkyl[1,4]dithiino[2,3-*d*; 5,6-*d*′]dipyrimidines (**4**), 1,3,6,8-tetraalkylthiopheno[2,3-*d*; 4,5-*d*′]dipyrimidines (**6**) and the dihydro derivatives (**8**) of the latter. These compounds were fully characterized by ′H-NMR, mass spectral and elemental analyses. A plausible mechanism for this photocyclization of **3** to **6** and to **8** has been proposed.

Keywords——photochemical ring construction; photochemical rearrangement; ′H-NMR; electrocyclic reaction; sulfur-containing pyrimidine and fused pyrimidine

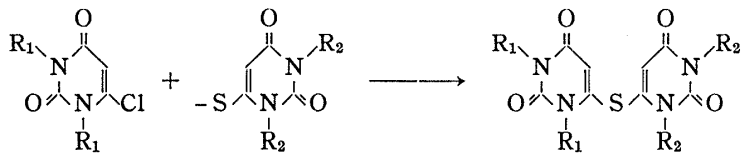
We recently reported that bis-6,6′-(1,3-dialkyluracilyl)sulfides undergo a photocyclization rearrangement to give heterocycles with a new ring system.[1] Herein, we present additional information and complete experimental details of our work.

Prior to this investigation, little was known about the photochemistry of thiophenes fused with a carbocyclic ring, (such as benzothiophenes and naphthothiophenes), obtained from unsaturated organic sulfides,[5,6] though Senda *et al.*[7] recently reported the photocyclization of phenylthiouracils into benzothienopyrimdines.

During the course of our work on heterocyclic compounds we became interested in the photocyclization of bis-6,6′-(1,3-dialkyluracilyl)sulfides (**3**). We found that the photocyclization of **3** cannot be formulated in terms of a simple mechanism, but involves rather complicated processes.

In this report we describe the synthesis and photoreaction of **3**, and also discuss plausible mechanisms for the reaction. Bis-6,6′-(1,3-dialkyluracilyl)sulfides (**3a**, **b**) were synthesized by coupling of 1,3-dimethyluracil-6-sodium mercaptide (**2**) with 6-chloro-1,3-dimethyl (or diethyl)uracil (**1a**, **b**), and bis-6,6′-(1,3-diethyluracilyl)sulfide (**3c**) was prepared by condensation of 1,3-diethyluracil-6-sodium mercaptide (**2**) with 6-chloro-1,3-diethyluracil (**1b**).

Moreover, bis-6,6′-(1,3-dimethyluracilyl)sulfide (**3a**) was prepared by addition of triethylamine to 6-mercapto-1,3-dimethyluracil and 6-chloro-1,3-dimethyluracil (**1a**).



1a: R_1=Me
1b: R_1=Et

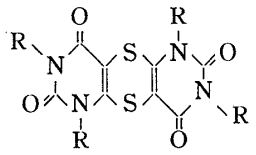
2

3a: R_1=R_2=Me
3b: R_1=Me, R_2=Et
3c: R_1=R_2=Et

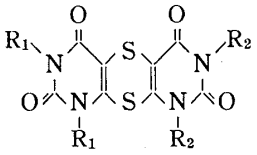
Chart 1

Irradiation of the sulfide (**3a**) in tetrahydrofuran gave three UV-absorbing products **4a** (mp 300°, 18%), **6a** (mp 266—269°, 18.2%) and **8a** (mp 196°, 9%), after chromatography on silica gel. The mass spectral (M^+) and microanalytical data were consistent with the indicated structures. The PMR spectrum of **4a** showed only two singlets.

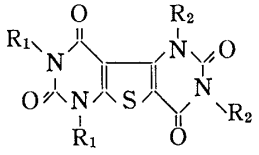
The formation of the [1,4]dithiino[2,3-*d*; 5,6-*d'*]dipyrimidine structure (**4a**) can readily be explained by dimerization of two uracil-6-thiol radicals followed by oxidation. The isomeric structure (**5a**) for this compound is eliminated because of the unusually low chemical shifts of the N-methyl signals (δ 4.12). Studies with molecular models show that **4a** takes a folded conformation and all the methyl groups come very close to carbonyls, whereas the structure **5a** does not bring about this close proximity of methyl and carbonyl groups.



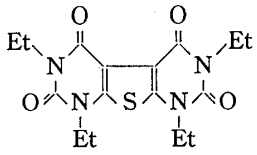
4a: R=Me
4b: R=Et



5a: $R_1=R_2=Me$



6a: $R_1=R_2=Me$
6b: $R_1=Et$, $R_2=Me$
6c: $R_1=Me$, $R_2=Et$



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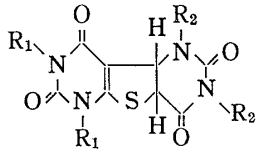

8a: $R_1=R_2=Me$
8b: $R_1=Et$, $R_2=Me$

Chart 2

The PMR spectrum of the second product showed the presence of four non-equivalent N-methyl groups in the molecule, thus establishing the structure **6** for this compound. The formation of the thiopheno[2,3-*d*; 4,5-*d'*]dipyrimidine system (**6a**) can be formulated as an electrocyclic reaction involving an unusual rearrangement, as shown below.

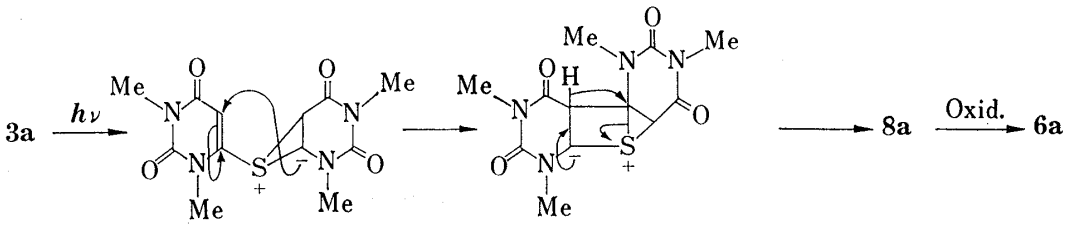

Chart 3

A similar mechanism was first proposed by Green *et al.*[5] for the rearrangement of 1-phenyl-1-phenylthioethene into 3-phenylbenzo(*b*)thiophene by photocyclization. Schultz and DeTar[6] later invoked this mechanism to explain the conversion of 1-(2-naphthylthio)-1-phenyl-1-propene into 2-methyl-3-phenylnaphtho[2,1-*b*]thiophene.

The third product of the photolysis of **3a** showed a pair of geminal proton doublets in addition to singlets for the four N-methyl groups in the PMR spectrum. The structure of this compound is assigned as **8a**, which is an intermediate in the reaction (from **3a** to **6a**). It should be noted that irradiation of **4a** did not give **5a** but resulted in a total recovery of the starting material. Thus, the intermediacy of **4a** in the formation of **6a** is ruled out.

Photocyclization of bis-6,6'-(1,3-diethyluracilyl)sulfide (**3c**) under similar conditions, however, gave only two products, 1,3,6,8-tetraethyl[1,4]dithiino[2,3-*d*; 5,6-*d'*]dipyrimidine-

2,3,4,9(1H, 3H, 6H, 8H)tetraone (**4b**) (mp 160—162°; 11%) and the normal cyclization product, 2,4,6,8-tetraethylthiopheno[2,3-*d*; 5,4-*d'*]dipyrimidin-1,3,7,9(2H, 4H, 6H, 8H) tetraone (**7**) (mp 204—206°, 13%).

The structure of the dithiine (**4b**) was assigned from the PMR spectrum.

In order to study the effects of N-substituents on the photocyclization, unsymmetrical 6-(1,3-diethyluracilyl)-6'-(1',3'-dimethyluracilyl)sulfide (**3b**) was photolyzed under the same conditions. The major products were **6b** (mp 204—205°, 12%) and **8b** (mp 170—173°, 6.5%) together with traces of **6a** and **6c** (mp 209—211°). No dithiine of type **4** or normal photocyclization product of type **7** was detected in the mixture.

The **6b** structure was confirmed by the unusually low field shift of the N-1 methyl signal in the PMR spectrum. This paramagnetic shift is caused by the close proximity of the N-1 methyl and C-9 carbonyl groups.

Similarly, the methylene quartet of the N-1 ethyl group in **6c** is observed at very low field (δ 4.74). The structure of the dihyrdo compound is assigned as **8b**, which is a precursor of **6b**. Compound **8b** appeared to be oxidized slowly to **6b** (mp 205—206°) by atmospheric oxygen on standing. Compound **6a** obtained from this reaction probably arose from **3a** which was formed by recombination of a dimethyluracil-6-thiol radical and a dimethyluracil radical.

It may be concluded from the above results that N-methyl substitution of **3** favors rearrangement during photocyclization whereas the N-ethyl derivative of **3** gives the normal photocyclization product **7**.

Experimental

NMR spectra were measured on a Varian T-60 instrument with tetramethylsilane as an internal standard. For spectroscopic data, the following abbreviations are used: d=doublet, m=multiplet, s=singlet, t=triplet. Mass spectra were obtained on a JEOL 01S spectrometer equipped with a direct inlet system at 75 eV. IR spectra were taken on a Shimadzu IR-27G spectrometer. Melting points are uncorrected. The ultraviolet spectra were taken with a Hitachi EPS-3T recording spectrophotometer. Photolyses were carried out in a quartz inmmersion apparatus equipped with a 400W high pressure mercury lamp without the filter and cooled internally with running water. Irradiation was carried out under nitrogen with stirring.

6-Mercapto-1,3-dimethyluracil[8]——A solution of $NaSH \times H_2O$ (abs. 70% pure, 30 g) in H_2O (50 ml) was added dropwise to a stirred solution of 6-chloro-1,3-dimethyluracil (**1a**: 20 g, 0.115 mol) in $CHCl_3$ (100 ml) and EtOH (250 ml) in an ice-water bath, and the mixture was stirred at room temperature overnight.

The reaction mixture was evaporated to dryness *in vacuo* at room temperature. The residual solid was dissolved in H_2O (100 ml) and extracted with CH_2Cl_2. The dried CH_2Cl_2 solution was concentrated and a white solid in the oily residue was filtered off. An alkaline aqueous solution of the residue was acidified with dil.HCl and then extracted with CH_2Cl_2 (the H_2O layer was kept at pH 1.0—2.0). The dried CH_2Cl_2 solution was evaporated to dryness, and the crude product was purified by crystallization from $CHCl_3$ to give 6-mercapto-1,3-dimethyluracil, 15.7 g, 79.6% yield of pale yellow crystals, mp 135—136°. NMR ($CDCl_3$), δ: 3.32 (3H, s, N–Me), 3.74 (3H, s, N–Me), 4.16 (2H, s, >$COCH_2CS$–). IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O).

Bis-6,6'-(1,3-dimethyluracilyl)sulfide (**3a**)——Method A: A solution of 6-chloro-1,3-dimethyluracil (**1a**: 2.61 g, 15 mmol) in EtOH (25 ml) was added dropwise to a stirred solution of 1,3-dimethyl-6-mercaptouracil (2.58 g, 15 mmol) and triethylamine (1.72 g, 17 mmol) in EtOH (30 ml). The mixture was stirred for 12 hr at room temperature.

The reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 ml) and the solution was washed with 10% HCl and H_2O solution then dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography with $CHCl_3$ as an eluent to give bis-6,6'-(1,3-dimethyluracilyl)sulfide (**3a**) 2.0 g, 43.0% yield, mp 248° (recrystallized from EtOH). *Anal.* Calcd for $C_{12}H_{14}N_4O_4S$ (310.328): C, 46.45; H, 4.55; N, 18.05. Found: C, 46.63; H, 4.53; N, 18.11. MS *m/e*: 310 (M^+) NMR ($CDCl_3$) δ: 3.36 (6H, s, 2×CH_3), 3.58 (6H, s, 2×CH_3), 5.88 (2H, s, 2×–CH=C—). UV λ_{max}^{EtOH} (log ε): 246 (3.70), 280 (4.14).

Method B: A solution of $NaSH. \times H_2O$ (abs. 70% pure, 1.5 g) in H_2O (3 ml) and EtOH (25 ml) was added dropwise to a solution of 6-chloro-1,3-dimethyluracil (**1a**: 2.61 g, 15 mmol) in $CHCl_3$ (30 ml) with ice cooling for 45 min. The solvents were evaporated off *in vacuo*. A solution of 6-chloro-1,3-dimethyluracil (**1a**: 2.61 g, 15 mmol) in $CHCl_3$ (20 ml) was added dropwise to a filtered solution of the residue in EtOH (30 ml) with stirring at room temperature. After 12 hr, the mixture was worked up in the manner described for **3a** to afford bis-6,6'-(1,3-dimethyluracilyl)sulfide (**3a**) 3.30 g, 71.6% yield, mp 248° (recrystallized from EtOH). The spectral and physical data of this compound were identical with those of **3a**.

Bis-6,6′-(1,3-diethyluracilyl)sulfide (3c)——A solution of NaSH.×H_2O (abs. 70% pure, 1.5 g) in H_2O (1 ml) and EtOH (30 ml) was added dropwise to a solution of 6-chloro-1,3-diethyluracil[9] (**1b**: 3.03 g, 15 mmol) in $CHCl_3$ (5 ml) and EtOH (25 ml) with stirring at 0—5° for 45 min. The solution was concentrated *in vacuo* to provide an oily residue. A solution of 6-chloro-1,3-diethyluracil (**1b**: 3.03 g, 15 mmol) in $CHCl_3$ (20 ml) was added dropwise to a filtered solution of the residue in EtOH (30 ml) at room temperature. After 12 hr, the reaction mixture was treated as described above for **3a** to give bis-6,6′-(1,3-diethyluracilyl)sulfide (**3c**) 0.66 g, 12% yield, mp 125° (recrystallized from MeOH). *Anal.* Calcd for $C_{16}H_{22}N_4O_4S$ (366.436): C, 52.44; H, 6.05; N, 15.29. Found: C, 52.22; H, 5.96; N, 15.62. MS *m/e*: 366 (M^+) NMR ($CDCl_3$) δ: 1.22 (3H, t, $-CH_3$), 1.23 (3H, t, $-CH_3$), 3.93 (2H, q, $-C\underline{H}_2CH_3$), 4.00 (2H, q, $-C\underline{H}_2CH_3$), 5.86 (2×H, s, $-CH=C<$). UV λ_{max}^{EtOH} nm (log ε): 248 (3.93), 279 (4.26).

6-(1,3-diethyluracilyl)-6′-(1′,3′-dimethyluracilyl)sulfide (3b)——A solution of NaSH.×H_2O (abs. 70% pure, 1.50 g) in H_2O (3 ml) was added dropwise to a solution of 6-chloro-1,3-dimethyluracil (**1a**: 2.61 g, 15 mmol) in $CHCl_3$ (15 ml) with stirring at 0—5° for 45 min. The solvents were evaporated off *in vacuo* to leave an oily residue. A solution of 6-chloro-1,3-diethyluracil (**1b**: 3.04 g, 15 mmol) in $CHCl_3$ (20 ml) was added dropwise to a filtered solution of the residue in EtOH (30 ml) with stirring at room temperature. After 12 hr, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 ml), and the solution was washed with 10% HCl and H_2O solution then dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography with $CHCl_3$ as an eluent to give 6-(1,3-diethyluracilyl)-6′-(1′,3′-dimethyluracilyl)sulfide (**3b**) as a colorless powder 1.27 g, 25.3% yield, mp 153—154° (recrystallized from MeOH). *Anal.* Calcd for $C_{14}H_{18}N_4O_4S$ (338.382): C, 49.69; H, 5.36; N, 16.56. Found: C, 49.38; H, 5.12; N, 16.35. MS *m/e*: 338 (M^+). NMR ($CDCl_3$) δ: 1.21 (3H, t, $-CH_3$), 1.40 (3H, t, $-CH_3$), 3.40 (3H, s, $-CH_3$), 3.60 (3H, s, $-CH_3$), 4.00 (2H, q, $-C\underline{H}_2CH_3$), 4.01 (2H, q, $-C\underline{H}_2-CH_3$), 5.78 (1H, s, $-C\underline{H}=C<$), 6.00 (1H, s, $-C\underline{H}=C<$).

Irradiation of Bis-6,6′-(1,3-dimethyluracilyl)sulfide (3a)——A solution of di-6,6′-(1,3-dimethyluracilyl)-sulfide (**3a**: 1.55 g, 5 mmol) in dry THF (600 ml) was irradiated for 12 hr. The residue obtained upon removal of the solvent was chromatographed on silica gel. Elution with $CHCl_3$ afforded the following products (**4a**, **6a** and **8a**).

1,3,6,8-Tetramethyl[1,4]dithiino[2,3-*d*; 5,6-*d*′]dipyrimidin-2,4,7,9-(1H,3H,6H,8H)tetraone (**4a**). 153 mg, 18% yield, mp>300°. *Anal.* Calcd for $C_{12}H_{12}N_4O_4S_2$ (340.372): C, 42.35; H, 3.55; N, 16.46. Found: C, 42.75; H, 3.68; N, 16.63. MS *m/e*: 340 (M^+), NMR (DMSO-d_6) δ: 4.03 (6H, s, 2×CH_3), 4.12 (6H, s, 2×CH_3).

1,3,6,8-Tetramethylthiopheno[2,3-*d*; 4,5-*d*′]dipyrimidin-2,4,7,9(1H,3H,6H,8H)tetraone (**6a**). 123 mg, 8.2% yield, mp 266—269° (recrystallized from MeOH). *Anal.* Calcd for $C_{12}H_{12}N_4O_4S$ (308.312) C, 46.75; H, 3.92; N, 18.17. Found: C, 46.60; H, 3.93; N, 17.97. MS *m/e*: 308 (M^+). NMR ($CDCl_3$) δ: 3.40 (3H, s, $-CH_3$), 3.42 (3H, s, $-CH_3$), 3.60 (3H, s, $-CH_3$), 3.92 (3H, s, $-CH_3$). UV λ_{max}^{EtOH} (log ε): 224 (4.15), 243 (4.29), 253 (4.12), 265 (4.20), 280 (3.71), 310 (4.08).

1,3,6,8-Tetramethylthiopheno[2,3-*d*; 4,5-*d*′]dipyrimidin-2,4,7,9-(1H,1′H,3H,4′H,6H,8H)tetraone (**8a**). 140 mg, 9% yield, mp 196° (recrystallized from MeOH). *Anal.* Calcd for $C_{12}H_{14}N_4O_4S$ (310.328): C, 46.45; H, 4.55; N, 18.05. Found: C, 46.73; H, 4.56; N, 18.12. MS *m/e*: 310 (M^+). NMR ($CDCl_3$) δ: 3.14 (3H, s, $-CH_3$), 3.26 (3H, s, $-CH_3$), 3.32 (6H, s, 2×CH_3), 4.40 (1H, d, J=8, >CH–CH<), 5.96 (1H, d, J=8, >CH–CH<). UV λ_{max}^{EtOH} (log ε); 232 (4.03).

Irradiation of Bis-6,6′-(1,3-diethyluracilyl)sulfide (3c)——A solution of bis-6,6′-(1,3-diethyluracilyl)sulfide (**3c**: 1.46 g, 4 mmol) in dry THF (600 ml) was irradiated for 12 hr. The residue obtained upon removal of the solvent was chromatographed on silica gel. Elution with $CHCl_3$ afforded first **4b** and then **7**.

1,3,6,8-Tetraethyl[1,4]dithiino[2,3-*d*; 5,6-*d*′]dipyrimidin-2,4,7,9(1H,3H,6H,8H)tetraone (**4b**), 87 mg, 11% yield, mp 160—162° (recrystallized from MeOH). *Anal.* Calcd for $C_{16}H_{10}N_4O_4S_2$ (396.480): C, 48.48; H, 5.08; N, 14.13. Found: C, 48.32; H, 4.86; N, 14.02. MS *m/e*: 396 (M^+). NMR ($CDCl_3$) δ: 1.28 (6H, t, 2×CH_3), 4.10 (4H, q, 2×$-C\underline{H}_2CH_3$), 4.75 (4H, q, 2×$C\underline{H}_2CH_3$). UV λ_{max}^{EtOH} (log ε): 229 (4.31), 242 (4.38), 255 (4.22), 265 (4.26), 285 (3.82), 318 (4.09).

2,4,6,8-Tetraethylthiopheno[2,3-*d*; 5,4-*d*′]dipyrimidin-1,3,7,9(2H,4H,6H,8H)tetraone (**7**). 189 mg, 13% yield, mp 204—206° (recrystallized from MeOH). *Anal.* Calcd for $C_{16}H_{10}N_4O_4S$ (364.42): C, 52.72; H, 5.53; N, 15.37. Found: C, 52.94; H, 5.61; N, 15.41. MS *m/e*: 364 (M^+). NMR ($CDCl_3$) δ: 1.25 (3H, t, $-CH_3$), 1.40 (3H, t, $-CH_3$), 4.03 (2H, q, $-C\underline{H}_2CH_3$), 4.08 (2H, q, $-C\underline{H}_2CH_3$). UV λ_{max}^{EtOH} (log ε): 222 (4.17), 250.

Irradiation of 6-(1,3-Diethyluracilyl)-6′-(1′,3′-dimethyluracilyl)sulfide (3b)——A solution of 6-(1,3-dimethyluracilyl)-6′-(1′,3′-dimethyluracilyl)sulfide (**3b**: 1.35 g, 4 mmol) in dry THF (600 ml) was irradiated for 24 hr. The residue obtained upon removal of the solvent was chromatographed on silica gel. Elution with $CHCl_3$ gave first **6b**, together with traces of **6a** (20 mg) and **6c**, and then **8a**.

1,3-Dimethyl-6,8-diethylthiopheno[2,3-*d*; 4,5-*d*′]dipyrimidin-2,4,7,9-(1H,3H,6H,8H)tetraone (**6b**). 160 mg, 12% yield, mp 209—211° (recrystallized from MeOH). *Anal.* Calcd for $C_{14}H_{16}N_4O_4S$ (336.366): c, 49.99; H, 4.79; N, 16.65. Found: C, 50.07; H, 4.82; N, 16.71. MS *m/e*: 336 (M^+). NMR ($CDCl_3$) δ: 1.26 (3H, t, $-CH_2C\underline{H}_3$), 1.40 (3H, t, $-CH_2C\underline{H}_3$), 3.42 (3H, s, $-CH_3$), 3.92 (3H, s, $-CH_3$), 4.08 (4H, q, 2×$C\underline{H}_2CH_3$). UV λ_{max}^{EtOH} (log ε): 225 (4.37), 244 (4.49), 253 (4.29), 266 (4.42), 283 (3.93), 314 (4.27).

1,3-Diethyl-6,8-dimethylthiopheno[2,3-*d*; 4,5-*d*′]dipyrimidin-2,4,7,9(1H,3H,6H,8H)tetraone (**6c**). 94 mg, 7% yield, mp 204—205° (recrystallized from MeOH). *Anal.* Calcd for $C_{14}H_{16}N_4O_4S$ (336.366): C, 49.99;

H, 4.79; N, 16.65. Found: C, 49.84; H, 4.72; N, 16.37. MS *m/e*: 336 (M^+). NMR ($CDCl_3$) δ: 1.29 (3H, t, $-CH_2C\underline{H}_3$) 3.62 (3H, s, $N-CH_3$), 4.10 (2H, q, $-C\underline{H}_2CH_3$), 4.74 (2H, q, $-C\underline{H}_2CH_3$). UV λ_{max}^{EtOH} (log ε): 225 (4.02), 244 (4.16), 253 (3.93), 266 (4.05), 283 (3.59), 317 (3.51).

1,3-Dimethyl-6,8-diethylthiopheno[2,3-*d*; 4,5-*d'*]dipyrimidin-2,4,7,9-(1H,1'H,3H,4'H,6H,8H)tetraone (**8b**). 88 mg, 6.5% yield, mp 170—173° (recrystallized from MeOH). *Anal.* Calcd for $C_{14}H_{18}N_4O_4S$ (338.38): C, 49.69; H, 5.36; N, 16.56. Found: C, 49.58; H, 5.24; N, 16.36. MS *m/e*: 338 (M^+). NMR ($CDCl_3$) δ: 1.20 (3H, t, $-CH_2C\underline{H}_3$), 1.28 (3H, t, $-CH_2C\underline{H}_3$), 3.34 (6H, s, $2\times NCH_3$), 3.60 (2H, q, $-C\underline{H}_2CH_3$), 3.90 (2H, q, $-C\underline{H}_2CH_3$), 4.32 (1H, d, J=8.0, >CH–CH<), 5.96 (1H, d, J=8.0, >CH–CH<). UV λ_{max}^{EtOH} (log ε): 227 (4.17), 235 (4.18), 254 (3.98), 265 (4.02), 278 (3.78), 311 (4.01).

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