the neutral fraction was tentatively identified by its glpc retention time.

Hydrolysis of *N*-Methyleneaniline.—A solution of 4.9 g of *N*-methyleneaniline in 200 ml of ether was extracted with three 300 ml-portions of 5% HCl. The acid extracts were combined and made alkaline by the addition of NaOH pellets. The basic solution was extracted with ether and the ether extract dried over Na_2SO_4. Removal of the ether produced 3.8 g (78%) of oil, identified as aniline by nmr spectroscopy.

Registry No.—Benzonitrile, 100-47-0; nitrobenzene, 98-95-3; nitrosobenzene, 586-96-9; *N*-methyleneaniline, 100-62-9; phenyl azide, 622-37-7; *N*-methylcarbazole, 1484-12-4; *o*-nitrotoluene, 88-72-2; *m*-nitrotoluene, 99-08-1; *p*-nitrotoluene, 99-99-0.

Acknowledgment.—This study was carried out under Contract No. 12-14-100-9575-(73) with the Agricultural Research Service, U. S. Department of Agriculture, administered by the Athens, Georgia Area, Richard B. Russell Agricultural Research Center, Athens, Georgia 30604.

Synthesis of [1]Benzothieno[3,2-*d*]pyrimidine Derivatives

JAMES R. BECK* AND JOSEPH A. YAHNER

Eli Lilly and Company, Greenfield Laboratories, Greenfield, Indiana 46140

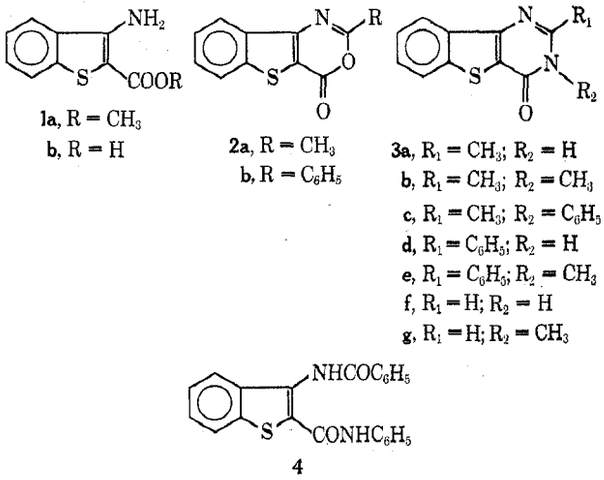
Received March 23, 1973

[1]Benzothieno[3,2-*d*]pyrimidine and several of its derivatives have been synthesized. Also described is the first reported example of the [1]benzothieno[3,2-*d*]-*v*-triazine ring system.

The literature contains only scattered reports concerning the synthesis of [1]benzothieno[3,2-*d*]pyrimidines. McClelland and Stammers[1] described the preparation of 2-methyl-4*H*-[1]benzothieno[3,2-*d*][1,3]oxazin-4-one (**2a**) from 3-acetamidobenzo[*b*]thiophene-2-carboxylic acid by treatment with acetic anhydride. The oxazinone was then converted to the corresponding pyrimidinone (**3a**) by reaction with ammonia. Travin and Magidson[2] later synthesized 4-chloro-2-methyl[1]-benzothieno[3,2-*d*]pyrimidine by treatment of **3a** with phosphorus oxychloride. Mamaev and Lyubimova[3] reported the synthesis of 3,4-dihydro-4-phenyl[1]benzothieno[3,2-*d*]pyrimidin-2(1*H*)-one 5,5-dioxide by the reaction of benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide with 1,1′-benzylidenediurea.

In a recent paper[4] we described a facile synthesis of methyl 3-aminobenzo[*b*]thiophene-2-carboxylate esters from *o*-nitrobenzonitriles. The synthesis involved nucleophilic displacement of an activated nitro function by methyl thioglycolate anion followed by base-catalyzed ring closure. Using these esters and their corresponding amides as starting materials, we set out to synthesize a variety of [1]benzothieno[3,2-*d*]-pyrimidine derivatives.

Saponification of the methyl ester **1a**[4] with potassium hydroxide in aqueous alcohol yielded 3-aminobenzo[*b*]-thiophene-2-carboxylic acid (**1b**),[5] characterized as its potassium salt (87% yield). Treatment of **1b** (potassium salt) with acetic anhydride in pyridine produced the previously described oxazinone **2a** (90%). Similar treatment with benzoyl chloride formed the oxazinone **2b** (46%). Reaction of **2a** with ammonia, methylamine, and aniline, respectively, produced **3a** (70%), **3b** (85%), and **3c** (28%). Condensation of **2b** with ammonia yielded **3d** (72%) and with methylamine gave **3e** (98%). Similar treatment with aniline, however, yielded the uncyclized product **4**. All attempts to cyclize **4** to the pyrimidinone were unsuccessful.



When the methyl ester **1a** was allowed to react with formamide at reflux temperature, the product formed was the pyrimidinone **3f** (59%).[6] Alkylation of **3f** with methyl iodide in base gave **3g** (75%). The position of methylation was ascertained by comparison of the nmr, ir, and uv spectra of **3g** and **3b**. They were nearly identical, thus ruling out methylation at the 1 position of **3f**. The chloropyrimidine **5a** (82%)[6a,b] was formed by treatment of **3f** with phosphorus oxychloride. Nucleophilic displacement of the active chlorine of **5a** gave the substituted pyrimidines **5b** (81%), **5c** (82%), and **5d** (92%).[6b] Catalytic hydrogenation of **5a** in the presence of sodium acetate yielded [1]benzothieno-[3,2-*d*]pyrimidine (**5e**, 94%).[6a]

For the preparation of other [1]benzothieno[3,2-*d*]-pyrimidines, it was necessary to synthesize carboxamide analogs of the methyl ester **1a**. Conditions could not be found for the direct conversion of **1a** to the amide **6a** by

(1) E. W. McClelland and D. W. Stammers, *J. Chem. Soc.*, 78 (1948).

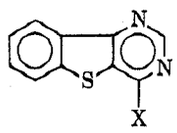
(2) A. I. Travin and O. Y. Magidson, *Khim. Geterotsikl. Soedin.* (Engl. trans.), **3**, 54 (1967).

(3) V. P. Mamaev and E. N. Lyubimova, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 96 (1969); *Chem. Abstr.*, **71**, 70566 (1969).

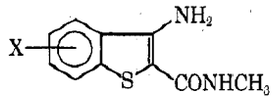
(4) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972).

(5) P. Friedlander and A. Laske, *Justus Liebigs Ann. Chem.*, **351**, 412 (1907).

(6) During the writing of this manuscript, two similar preparations of **3f** were reported: (a) M. Robba, P. Touzot, and R. M. Riquelme, *Tetrahedron Lett.*, 4549 (1972); (b) G. G. De Angelis and H. E. Hess, U. S. Patent 3,706,747 (1972).



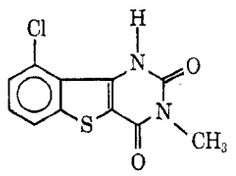
5a, X = Cl
b, X = OCH_3
c, X = SCH_3
d, X = $N(CH_3)_2$
e, X = H



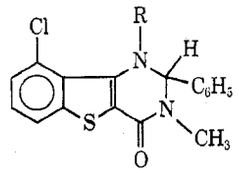
6a, X = H
b, X = 4-Cl
c, X = 6-Cl

reaction with methylamine. Reaction of *o*-nitrobenzonitrile with mercapto-*N*-methylacetamide[7] in the presence of base did produce **6a**, but only in 8% yield. However, similar treatment of 2-chloro-6-nitrobenzonitrile gave **6b** in 86% yield and 4-chloro-2-nitrobenzonitrile gave **6c** in 78% yield.

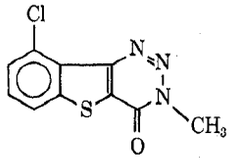
Reaction of **6b** with phosgene in refluxing chlorobenzene produced the pyrimidinedione **7** (90%). Condensation of **6b** with benzaldehyde formed the dihydropyrimidinone **8a** (76%), which was alkylated with methyl iodide to give **8b** (60%). The reaction of **6b** with nitrous acid resulted in the formation of 9-chloro-3-methyl[1]benzothieno[3,2-*d*]-*v*-triazin-4(3*H*)-one (**9**),



7



8a, R = H
b, R = CH_3



9

which represents the first reported example of this ring system.

Experimental Section[8]

3-Aminobenzo[*b*]thiophene-2-carboxylic Acid (1b) Potassium Salt.—A solution containing 5.0 g of **1a**[4] (24.2 mmol) and 3.0 g of potassium hydroxide in 75 ml of alcohol was refluxed for 0.5 hr. The mixture was cooled and filtered to yield 4.8 g (87%) of product, mp >300°.

Anal. Calcd for $C_9H_6KNO_2S$: C, 46.73; H, 2.61; N, 6.06. Found: C, 46.59; H, 2.63; N, 5.92.

2-Methyl-4*H*-[1]benzothieno[3,2-*d*][1,3]oxazin-4-one (2a).—A solution containing 5.0 g of **1b** (21.6 mmol) in 75 ml of pyridine and 25 ml of acetic anhydride was refluxed for 0.5 hr. The mixture was poured into ice–water and the solid was collected. Crystallization from absolute alcohol yielded 4.2 g (90%) of product, mp 179–181° (lit.[1] mp 179°).

Anal. Calcd for $C_{11}H_7NO_2S$: C, 60.82; H, 3.25; N, 6.45. Found: C, 60.61; H, 3.25; N, 6.67.

2-Phenyl-4*H*-[1]benzothieno[3,2-*d*][1,3]oxazin-4-one (2b).—A mixture of 20.0 g of **1b** (87 mmol) and 20 ml of benzoyl chloride in 200 ml of pyridine was refluxed for 20 hr and then poured into ice–water. The solid was collected and crystallized from methyl ethyl ketone to yield 11.0 g (46%) of product, mp 208–210°.

Anal. Calcd for $C_{16}H_9NO_2S$: C, 68.80; H, 3.25; N, 5.01. Found: C, 68.79; H, 3.17; N, 4.96.

2-Methyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3a).—A mixture of 4.5 g of **2a** (20.7 mmol) and 15 ml of concentrated ammonium hydroxide in 100 ml of alcohol was refluxed for 3.5 hr. The solution was cooled and filtered to yield 3.1 g (70%) of product, mp >350° (lit.[1] mp 340–345° dec).

Anal. Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95. Found: C, 60.84; H, 3.55; N, 13.10.

2,3-Dimethyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3b).—A solution containing 3.1 g of **2a** (14.3 mmol) and 15 ml of 40% aqueous methylamine solution in 100 ml of alcohol was refluxed for 3 hr. Water (10 ml) was added and the solution was cooled and filtered to yield 2.8 g (85%) of product, mp 177–179°.

Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.31; H, 4.24; N, 11.88.

2-Methyl-3-phenyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3c).—Aniline (18 ml) and 4.0 g of **2a** (18.4 mmol) were stirred and heated at 165° for 0.5 hr. The crude reaction mixture was crystallized from alcohol–water to yield 1.5 g (28%) of product, mp 239–241°.

Anal. Calcd for $C_{17}H_{12}N_2OS$: C, 69.84; H, 4.14; N, 9.58. Found: C, 69.57; H, 3.93; N, 9.32.

2-Phenyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3d).—Ammonia was slowly bubbled into a refluxing solution containing 3.5 g of **2b** (12.5 mmol) in 100 ml of absolute alcohol for 24 hr. The mixture was cooled and filtered and the crude product was crystallized from DMF–water to yield 2.5 g (72%) of product, mp 328–329°.

Anal. Calcd for $C_{16}H_{10}N_2OS$: C, 69.05; H, 3.62; N, 10.06. Found: C, 68.83; H, 3.82; N, 10.12.

3-Methyl-2-phenyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3e).—Methylamine (15 ml of 40% aqueous solution) and 3.3 g of **2b** (11.8 mmol) in 100 ml of absolute alcohol was heated at reflux temperature for 12 hr. Water (20 ml) was added and the solution was cooled and filtered to yield 3.4 g (98%) of product, mp 245–246°.

Anal. Calcd for $C_{17}H_{12}N_2OS$: C, 69.84; H, 4.14; N, 9.58. Found: C, 69.80; H, 4.37; N, 9.87.

3-Benzamidobenzo[*b*]thiophene-2-carboxanilide (4).—Aniline (8 ml) and 4.0 g of **2b** (14.3 mmol) were stirred and heated at 185° (oil bath) for 0.5 hr. The solution was cooled and triturated with hot acetone. The material crystallized and was collected to yield 3.2 g (60%) of product, mp 312–314°.

Anal. Calcd for $C_{22}H_{16}N_2O_2S$: C, 70.95; H, 4.33; N, 7.52. Found: C, 70.68; H, 4.50; N, 7.71.

[1]Benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3f).—A solution containing 18.0 g of **1a** (87 mmol) in 150 ml of formamide was refluxed for 6.5 hr. The mixture was cooled and the crude product was collected and washed with water. Crystallization from *n*-butyl acetate yielded 12.0 g (59%) of product, mp 308–309° (lit.[6a] mp 290°).

Anal. Calcd for $C_{10}H_6N_2OS$: C, 59.39; H, 2.99; N, 13.85; S, 15.85. Found: C, 59.14; H, 2.97; N, 13.79; S, 15.50.

3-Methyl[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (3g).—To a solution containing 5.0 g of **3f** (24.8 mmol) and 3.0 ml of methyl iodine in 100 ml of DMF was added slowly at room temperature a solution containing 1.6 g of potassium hydroxide in 30 ml of water. The mixture was stirred for 1 hr, cooled, and allowed to crystallize yielding 4.0 g (75%) of product, mp 195–196°.

Anal. Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.78; N, 12.95. Found: C, 60.86; H, 3.59; N, 13.23.

4-Chloro[1]benzothieno[3,2-*d*]pyrimidine (5a).—Phosphorus oxychloride (250 ml) and 15.0 g of **3f** (74 mmol) were heated at reflux temperature for 45 min. Excess phosphorus oxychloride was removed by vacuum distillation and the crude solid was crystallized from DMF–water to yield 13.4 g (82%) of product, mp 142–144° (lit.[6a] mp 138°).

Anal. Calcd for $C_{10}H_5ClN_2S$: C, 54.43; H, 2.28; N, 12.69; Cl, 16.07. Found: C, 54.62; H, 2.48; N, 12.92; Cl, 16.23.

4-Methoxy[1]benzothieno[3,2-*d*]pyrimidine (5b).—A mixture containing 4.4 g of **5a** (20 mmol) and 1.2 g of sodium methoxide (22 mmol) in 100 ml of methanol was refluxed for 6 hr and then poured into ice–water. The crude solid was collected and crystallized from alcohol–water to yield 3.5 g (81%) of product, mp 140–142°.

Anal. Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95. Found: C, 61.30; H, 3.66; N, 12.80.

(7) J. W. Haefele and R. W. Broge, *Proc. Sci. Sect. Toilet Goods Assoc.*, 52 (1959); *Chem. Abstr.*, **54**, 17233 (1960).

(8) Melting points were determined on a Mel-Temp apparatus and are uncorrected.

4-Methylthio[1]benzothieno[3,2-*d*]pyrimidine (5c).—To a solution containing 4.4 g of **5a** (20 mmol) and excess methanethiol in 150 ml of DMF was added slowly a solution of 2.0 g of potassium hydroxide in 20 ml of water, at a rate so as to maintain the temperature at 35–40°. The mixture was stirred at room temperature for 2 hr and poured into ice–water. The crude solid was collected and crystallized from alcohol–water to yield 3.8 g (82%) of product, mp 125–126°.

Anal. Calcd for $C_{11}H_8N_2S_2$: C, 56.87; H, 3.47; N, 12.06; S, 27.60. Found: C, 56.85; H, 3.63; N, 12.28; S, 27.33.

4-(Dimethylamino)[1]benzothieno[3,2-*d*]pyrimidine (5d).—Dimethylamine was bubbled slowly into a refluxing solution of 5.5 g of **5a** (24.9 mmol) in 70 ml of DMF for 2 hr. The mixture was cooled and poured into ice–water. Filtration yielded 5.1 g (91%) of product, mp 113–114°.

Anal. Calcd for $C_{12}H_{11}N_3S$: C, 62.86; H, 4.84; N, 18.30. Found: C, 62.87; H, 4.81; N, 18.20.

[1]Benzothieno[3,2-*d*]pyrimidine (5e).—A solution containing 2.2 g of **5a** (10 mmol), 0.85 g of anhydrous sodium acetate, and 0.5 g of 5% palladium on carbon in 100 ml of absolute alcohol was placed in a pressure bottle and hydrogenated for 2 hr using a Parr shaker at an initial hydrogen pressure of 45 psi. The solution was filtered and cooled to yield 1.15 g of product, mp 139–140° (lit.[6a] mp 144°). Concentration of the mother liquors yielded 0.6 g of product, mp 138–140°. The total yield was 1.75 g (94%).

Anal. Calcd for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.04. Found: C, 64.23; H, 3.35; N, 14.83.

General Procedure for Preparation of 6a, 6b, and 6c.—To a cold solution containing 30 mmol of the appropriate *o*-nitrobenzonitrile and 30 mmol of mercapto-*N*-methylacetamide[7] in 60 ml of DMF was added dropwise a solution containing 3.0 g of potassium hydroxide in 15 ml of water. The mixture was stirred in the cold for 1.5 hr and poured into ice–water. The product was collected and crystallized. The following were obtained (yield, melting point, and crystallization solvent): **6a** (8%, 163–164°, alcohol–water); **6b** (86%, 134–135°, alcohol–water); **6c** (78%, 156–157°, benzene–hexane).

Anal. Calcd for $C_{10}H_{10}N_2OS$ (**6a**): C, 58.23; H, 4.89; N, 13.58. Found: C, 58.26; H, 4.62; N, 13.44. Calcd for $C_{10}H_9ClN_2OS$ (**6b**): C, 49.91; H, 3.77; N, 11.64. Found: C, 49.71; H, 3.70; N, 11.90. Calcd for $C_{10}H_9ClN_2OS$ (**6c**): C, 49.91; H, 3.77; N, 11.64. Found: C, 50.03; H, 3.75; N, 11.64.

9-Chloro-3-methyl[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7).—Phosgene was bubbled slowly into a refluxing solution containing 6.5 g of **6b** (27 mmol) in 150 ml of chlorobenzene for 1 hr. The mixture was cooled to yield 6.45 g (90%) of product, mp 309–312°.

Anal. Calcd for $C_{11}H_7ClN_2O_2S$: C, 49.54; H, 2.65; N, 10.50; Cl, 13.29. Found: C, 49.32; H, 2.35; N, 10.69; Cl, 13.21.

9-Chloro-1,2-dihydro-3-methyl-2-phenyl[1]benzothieno[3,2-*d*]-pyrimidin-4(3*H*)-one (8a).—A mixture of 4.5 g of **6b** (18.7 mmol), 2.1 g of benzaldehyde (19.8 mmol), and 100 mg of *p*-toluenesulfonic acid in 100 ml of benzene was refluxed (water removed using a Dean-Stark trap) for 4 hr. The mixture was cooled and the product was collected and crystallized from DMF–water to yield 4.7 g (76%) of product, mp 245–247°.

Anal. Calcd for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.99; N, 8.52; Cl, 10.78. Found: C, 61.96; H, 4.04; N, 8.50; Cl, 10.56.

9-Chloro-1,2-dihydro-1,3-dimethyl-2-phenyl[1]benzothieno-[3,2-*d*]pyrimidin-4(3*H*)-one (8b).—To a solution containing 4.0 g of **8a** (12.2 mmol) and 4.0 ml of methyl iodide in 100 ml of DMF was added slowly a solution of 1.6 g of potassium hydroxide in 25 ml of water. The mixture was stirred at room temperature for 1 hr and poured into ice–water. Crystallization from DMF–water yielded 2.5 g (60%) of product, mp 188–192°. An analytical sample, mp 191–193°, was recrystallized from alcohol–water.

Anal. Calcd for $C_{18}H_{15}ClN_2OS$: C, 63.06; H, 4.41; N, 8.17; Cl, 10.34. Found: C, 62.82; H, 4.46; N, 8.04; Cl, 10.50.

9-Chloro 3-methyl[1]benzothieno[3,2-*d*]-*v*-triazin-4(3*H*)-one (9).—To a cold vigorously stirred mixture of 0.7 g of sodium nitrite (10 mmol) in 10 ml of concentrated sulfuric acid was added slowly a solution containing 2.4 g of **6b** (10 mmol) in 25 ml of acetic acid, while the reaction temperature was maintained at 20–25°. The mixture was stirred at room temperature for 0.5 hr and poured into ice–water. The crude solid was crystallized from acetic acid to yield 2.15 g (86%) of product, mp 269–271°.

Anal. Calcd for $C_{10}H_6ClN_3OS$: C, 47.72; H, 2.40; N, 16.70. Found: C, 47.59; H, 2.47; N, 16.93.

Registry No.—**1a,** 35212-85-2; **1b,** 40142-71-0; **1b** K salt, 40139-58-0; **2a,** 40139-59-1; **2b,** 40139-60-4; **3a,** 40139-61-5; **3b,** 40139-62-6; **3c,** 40139-63-7; **3d,** 40139-64-8; **3e,** 40139-65-9; **3f,** 40142-89-0; **3g,** 40139-67-1; **4,** 40139-68-2; **5a,** 36822-09-0; **5b,** 40139-70-6; **5c,** 40127-47-7; **5d,** 40127-48-8; **5e,** 245-16-9; **6a,** 40127-50-2; **6b,** 40127-51-3; **6c,** 40127-52-4; **7,** 40127-53-5; **8a,** 40127-54-6; **8b,** 40127-55-7; **9,** 40127-56-8; *o*-nitrobenzonitrile, 612-24-8; 2-chloro-6-nitrobenzonitrile, 6575-07-1; 4-chloro-6-nitrobenzonitrile, 34662-32-3; mercapto-*N*-methylacetamide, 20938-74-3.

Acknowledgments.—The authors wish to thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.