Synthesis of Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine Derivatives (1)

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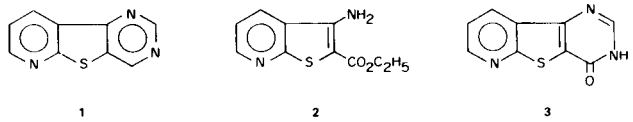
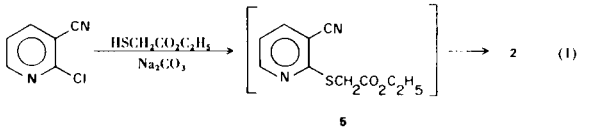
Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine and several of its derivatives have been synthesized.

The pyrimidine ring is a frequent partner in polycyclic heterocyclic systems of biological significance. Up to now no attention has been devoted to molecules of this type which contain a thienopyridine moiety. Thus, this study begins with an investigation of a variety of simple derivatives of pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**1**).



1 **2** **3**

The most direct route into this ring system proved to be *via* the reaction of ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate (**2**) with formamide to yield the pyrimidinone (**3**). Treatment of **3** with phosphorus oxychloride readily yielded 4-chloropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**4**; see Scheme) which has served as a facile point of departure into the desired molecules. The preparation of the required aminoester (**2**) was accomplished using the procedure in equation (1) and employed nucleophilic substitution by ethyl mercaptoacetate at the 2-position of 2-chloro-3-cyanopyridine (2) with subsequent base promoted (3,4) intramolecular ring formation (5).

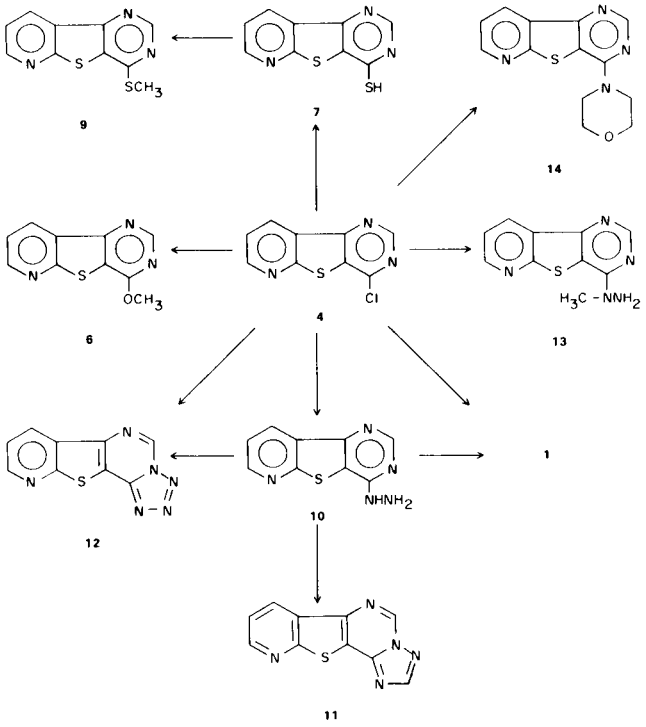


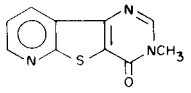
5 (1)

The Scheme summarizes the synthetic conversions accomplished in the direction of the stated goals. Treatment of **4** with sodium methoxide in methanol yielded the 4-methoxy derivative (**6**) while reaction with thiourea provided the 4-mercapto system (**7**). The infrared spectrum of **7** indicated bands at 3.65-4.00 μ and 6.92 μ suggesting that it existed as a tautomeric mixture of **7** and the corresponding thioamide. On the other hand the infrared spectrum of **3** contained only a strong band at 5.95 μ pointing to a predominance of the keto form for **3**. Both **3** and **7** were readily alkylated. The former yielded only the *N*-methyl derivative (**8**) while the latter produced only the *S*-methyl analog (**9**). An alternative preparation of **8** was achieved by treating **2** with *N*-methylformamide. This conversion also verifies the site of alkylation of **3**.

The 4-hydrazino derivative (**10**) also proved to be a versatile molecule for synthetic realizations. Reaction of **4** with hydrazine hydrate resulted in **10** which was easily converted to the fused *s*-triazole (**11**) with formic acid (6) and to the fused tetrazole (**12**) *via* a diazonium process involving sodium nitrite and acetic acid. Compound **12** was also available from the reaction of **4** with sodium azide. The parent ring, pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine

SCHEME





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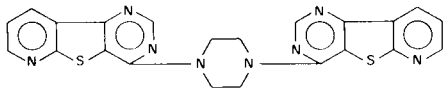

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(**1**), was prepared either from bubbling oxygen through a sodium ethoxide/ethanol solution of **10** or *via* direct catalytic hydrogenation of **4**. As suspected **1** has a remarkably simple nmr (see Experimental) and yields a mass spectrum with principal peaks at m/e 187 (100%, molecular ion) and m/e 160 (35%, $[M\text{-}HCN]^+$). In view of the fact that simple pyridines, pyrimidines and thienopyridines (7,8,9) readily extrude HCN upon mass spectral electron impact it is difficult to determine if the HCN is lost from the pyridine or the pyrimidine mocity of the tricyclic ring system (**1**). Finally, compound **4** is transformed back to **3** in refluxing dilute hydrochloric acid.

By analogy with hydrazine **4** also reacts with various representative amines to form **13** (methylhydrazine), **14** (morpholine) and **15** (piperazine). Structural assignment of **13** (as opposed to the isomer with an *N'*-methyl) was established by the nmr *N*-methyl singlet observed for **13**.

EXPERIMENTAL (10)

Ethyl 3-Aminothieno[2,3-*b*]pyridine-2-carboxylate (**2**).

To a mixture of 3.4 g. (24.0 mmoles) of 2-chloro-3-cyanopyridine (2) and 2.65 g. (25.0 mmoles) of anhydrous sodium carbonate in 25 ml. of absolute ethanol was added 3.0 g. (25.0 mmoles) of ethyl mercaptoacetate and the resulting mixture was refluxed for 6 hours with an accompanying color change of light brown to deep red. The reaction solution was cooled, evaporated to dryness on a rotovap, and the residue taken up in a small amount of water. The insoluble portion was filtered and the brownish yellow material recrystallized from boiling methanol as yellow crystals (23%), m.p. 181-182.5°; ir (potassium bromide): 2.92 μ (NH), 5.95 μ (C=O); ^{1}H nmr (deuteriochloroform): δ 1.15 (t, CH_3), δ 4.55 (q, CH_2), δ 7.55 (q, H-5), δ 8.12 (d, H-4), δ 8.27 (d, H-6), δ 8.95 (bs, NH_2).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.03; H, 4.53. Found: C, 54.15; H, 4.60.

Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)one (**3**).

A solution of 2 g. (9.0 mmoles) of **2** in 25 ml. of formamide was refluxed for 6.5 hours. Upon cooling a brown-green material precipitated which was filtered, dried and washed with warm ethyl acetate to leave a product which was recrystallized from 1-butanol/-ethyl acetate as white crystals (89%), m.p. 340-342° dec., ir (potassium bromide): 2.90 μ (NH), 5.95 μ (C=O); mass spectrum m/e (relative abundance): 203(100, M^+), 176 (23), 148 (20), 147 (12), 104 (25), 103 (16), 77 (15), 76 (15), 45 (18), 28 (60).

Anal. Calcd. for $C_9H_5N_3OS$: C, 53.19; H, 2.47. Found: C, 52.95; H, 2.60.

4-Chloropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**4**).

To a mixture of 10 ml. of pyridine and 20 ml. of phosphorus oxychloride was added 2 g. (9.9 mmoles) of **3**. The resulting solution was refluxed for 4 hours and after cooling was poured with vigorous stirring into ice water. The reddish-white crystals which formed after neutralization with sodium bicarbonate were filtered and recrystallized from 95% ethanol as colorless crystals (76%), m.p. 218-220°; ir (potassium bromide): 6.30 μ (C=N).

Anal. Calcd. for $C_9H_4ClN_3S$: C, 48.76; H, 1.82. Found: C, 48.61; H, 1.96.

4-Methoxypyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**6**).

A solution of 1 g. (4.54 mmoles) of **4** in 5 ml. of methanol and 20 ml. of tetrahydrofuran containing 0.21 g. (9.08 mmoles) of sodium was refluxed for 3 hours. Following cooling of the solution the methanol was removed on the rotovap and the residue treated with water. The aqueous solution was extracted with chloroform (4 x 25 ml.) and the combined chloroform extracts were dried over anhydrous magnesium sulfate. Evaporation of the chloroform yielded a solid residue which upon recrystallization from hexane was obtained as yellow crystals (97%), m.p. 194-195°; ir (potassium bromide): 6.30 μ (C=N).

Anal. Calcd. for $C_{10}H_7N_3OS$: C, 55.28; H, 3.24. Found: C, 55.42; H, 3.31.

4-Mercaptopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**7**).

A solution of 2 g. (9.0 mmoles) of **4** and 1.0 g. (13.0 mmoles) of thiourea in 60 ml. of 95% ethanol was refluxed 2.5 hours. Upon cooling, the product precipitated and was filtered and recrystallized from 95% ethanol as light yellow crystals (95%), m.p. 352-356°; ir (potassium bromide): 6.30 μ (C=N).

Anal. Calcd. for $C_9H_5N_3S_2$: C, 49.29; H, 2.30. Found: C, 49.21; H, 2.45.

4-Methylthiopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**9**).

To a solution containing 0.15 g. (0.0065 g.-atom) of sodium in 100 ml. of absolute ethanol was added 1 g. (4.58 mmoles) of **7**. The solution was refluxed for 1 hour and then 2 ml. of dimethyl sulfate was added slowly and the reflux resumed for an additional 4 hours. Upon cooling the solution was evaporated and the residue treated with water and the insoluble portion filtered, washed with water and recrystallized from hexane as white crystals (94%), m.p. 154-155°; ir (potassium bromide): 6.30 μ (C=N).

Anal. Calcd. for $C_{10}H_7N_3S_2$: C, 51.48; H, 3.02. Found: C, 51.51; H, 3.24.

4-Hydrazinopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**10**).

A solution consisting of 1 g. (4.5 mmoles) of **4** and 3 ml. of 64% hydrazine hydrate in 30 ml. of absolute ethanol was refluxed for 10 hours. Upon cooling the product precipitated and was filtered and recrystallized from absolute ethanol as white crystals (42%), m.p. 278-280°; ir (potassium bromide): 3.05 μ (NH), 3.19 μ (NH_2), 6.31 μ (C=N).

Anal. Calcd. for $C_9H_7N_5S$: C, 49.76; H, 3.25. Found: C, 49.98; H, 3.28.

Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**1**).

Method A.

Oxygen was bubbled through a 70 ml. of absolute ethanolic solution of 0.3 g. of sodium (0.013 g.-atom) and 0.4 g. (1.85 mmoles) of **10** for 1.5 hours. Following a multitude of color changes and when the solution became deep purple dilute hydrochloric acid was added until the solution became slightly acidic at

which time sodium bicarbonate was carefully added to achieve neutrality. The resulting orange solution was extracted with ether and the ether extracts combined and dried over anhydrous sodium sulfate. Removal of the ether resulted in a residue which was recrystallized from ether to yield 0.28 g. of white crystals (80%), m.p. 160-162°; ir (potassium bromide): 6.30 μ (C=N); ^{1}H nmr (DMSO-d_6) δ 8.69 (q, H-8), δ 9.81 (d, H-9), δ 9.98 (d, H-7), δ 10.46 (s, H-4), δ 10.71 (s, H-2); mass spectrum m/e (relative intensity): 187 (100, M^+), 160 (36), 57 (10).

Anal. Calcd. for $C_9H_5N_3S$: C, 57.73; H, 2.69. Found: C, 57.61; H, 2.80.

Method B.

Evaporation of a 35 ml. ethanolic solution of 0.6 g. (2.72 mmoles) of **4** and 50 mg. of palladium on charcoal which had been treated with an atmospheric pressure of hydrogen for two days yielded a residue which following recrystallization from ether was identical in all aspects to that described in method A.

s-Triazolo[4,3-*c*]pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**11**).

A solution of 0.75 g. (3.4 mmoles) of **10** in 15 ml. of 95% formic acid was refluxed for 2 hours. Upon cooling the formic acid was removed *in vacuuo*. The residue was dissolved in benzene:methanol (80:20) and filtered to remove a material which melted >370°. Evaporation of the benzene:methanol yielded a pale yellow residue which was purified by sublimation *in vacuuo* (220°/1.5mm) to yield a white product (46%), m.p. 228-232°; ir (potassium bromide): 5.95 μ (C=N).

Anal. Calcd. for $C_{10}H_5N_5S$: C, 52.85; H, 2.22. Found: C, 52.77; H, 2.30.

Tetrazolo[1,5-*c*]pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**12**).

Method A.

To a suspension of 0.8 g. (3.7 mmoles) of **10** in 25 ml. of *N* acetic acid at 45° was added 0.3 g. (4.0 mmoles) of sodium nitrite. Effervescence occurred immediately. After 1.5 hours the solution was cooled and the product filtered and recrystallized from aqueous acetone as cream crystals (47%), m.p. 214-216°; ir (potassium bromide): 5.95 μ (C=N).

Anal. Calcd. for $C_9H_4N_6S$: C, 47.36; H, 1.77. Found: C, 47.61; H, 1.84.

Method B.

A solution of 1 g. (4.54 mmoles) of **4** and 0.6 g. (9.0 mmoles) of sodium azide in 25 ml. of 95% ethanol was refluxed for 5 hours. Cooling yielded a cream colored product (40%) which upon recrystallization was identical to that described in method A.

General Procedure for 4-Substituted Aminopyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidines (**13**, **14**, **15**).

An equimolar amount of the amine with 1 g. (4.54 mmoles) of **4** in 30 ml. of absolute ethanol was refluxed for 5-48 hours. The solution was cooled and the product precipated and purified as indicated below.

4-(*N*-Methylhydrazino)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**13**).

This compound was obtained in 58% yield after refluxing 48 hours and was recrystallized from 95% ethanol as white crystals, m.p. 279-280°; ir (potassium bromide): 2.90 μ and 3.03 μ (NH_2); ^{1}H nmr (DMSO-d_6): δ 5.58 (s, CH_3), δ 8.33 (q, H-8), δ 9.48 (s, NH_2), δ 9.63 (d, H-9), δ 9.73 (d, H-7), δ 9.85 (s, H-2).

Anal. Calcd. for $C_{10}H_9N_5S$: C, 51.93; H, 3.92. Found: C, 51.99; H, 4.10.

4-(*N*-Morpholino)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**14**).

This compound was obtained in 80% yield after refluxing 10 hours and was recrystallized from ethanol as white crystals, m.p. 160-162°.

Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44. Found: C, 57.29; H, 4.47.

N,N′-Bis(pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)piperazine (**15**).

This compound was obtained in 90% yield after 5 hours refluxing and was recrystallized from dimethylformamide as white crystals, m.p. >270° dec.

Anal. Calcd. for $C_{22}H_{16}N_8S_2$: C, 57.88; H, 3.53. Found: C, 57.98; H, 4.03.

3-Methylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)one (**8**).

Method A.

A solution of 2 g. (9.0 mmoles) of **2** in 25 ml. of *N*-methylformamide was refluxed for 72 hours. Upon cooling to room temperature the product precipitated and was filtered and recrystallized from ethyl acetate as colorless crystals (54%), m.p. 230-232°; ir (potassium bromide); 5.95 μ (C=O); ^{1}H nmr (DMSO-d_6): δ 3.65 (s, CH_3), δ 7.70 (q, H-8), δ 8.72 (s, H-2), δ 8.72 (d of d, H-9), δ 8.99 (d of d, H-7).

Anal. Calcd. for $C_{10}H_7N_3OS$-½H_2O: C, 53.08; H, 3.56. Found: C, 53.29; H, 3.63.

Method B.

Methyl iodide (1 ml.) was added dropwise with stirring to 0.2 g. (1.0 mmole) of **3** dissolved in 2 ml. of 1 *M* potassium hydroxide and 2 ml. of dimethyl formamide. After 10 minutes, the product precipitated which, after filtering and recrystallization, was identical to the material described in method A.

Acknowledgements.

The assistance of Mr. Omar Richany in the preparation of **2** and Professor E. E. Campaigne of Indiana University for obtaining the mass spectra of **1** and **3** is gratefully appreciated.

REFERENCES

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(5) Although **5** is not isolated in the process presented here, evidence in our laboratory indicates **5** is initially formed in this process and the sodium carbonate promotes its ring cyclization.

(6) Use of triethylorthoformate produced only a very high melting material (m.p. >390°) which was not characterized.

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(10) Melting points were taken on a Mel-Temp Capillary melting point apparatus and are uncorrected. The nmr spectra were obtained on a Varian A-60 spectrometer using TMS as an internal standard. Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. The mass spectra were determined on a Varian MAT CH-7 at Indiana University, Bloomington, Indiana. The microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee and Het-Chem-Co., Harrisonville, Missouri.