Thieno[2,3-*d*]pyrimidines. I. A New Method for the Preparation of Esters and Amides of Thieno[2,3-*d*]pyrimidine-6-carboxylic Acids

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A novel method for the preparation of esters and amides of thieno[2,3-*d*]pyrimidine-6-carboxylic acids was described. A typical example was the direct formation of ethyl 5-amino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylate (IIIa) from 4-chloro-2-methylthio-5-pyrimidinecarbonitrile (Ia) and ethyl mercaptoacetate in refluxing ethanol containing sodium carbonate. Displacement of the methylthio group in IIIa by various amines gave the corresponding amino derivatives. The reactions of IIIa and related compounds with acetylating agents such as acetic anhydride or chloroacetyl chloride gave various products. Treatment of 5-carbethoxy-4-chloro-2-phenylpyrimidine (IV) with methyl mercaptoacetate afforded the dechloro intermediate diester Va, which cyclized on reaction with sodium ethoxide to form methyl 5-hydroxy-2-phenylthieno-[2,3-*d*]pyrimidine-6-carboxylate (VIa). The synthesis was expanded to include the preparation of various new 2,4,5-trisubstituted thieno[2,3-*d*]pyrimidine-6-carboxylic acid esters and amides (Charts I-V).

The earliest preparation of a thieno[2,3-*d*]pyrimidine was described by Baker and co-workers (1), who reported that the action of methanolic ammonia on 2-formamido-3-carbomethoxythiophene gave a low yield (4%) of thieno-[2,3-*d*]pyrimidin-4-one. Subsequent to their report, other papers appeared in which the preparation of thieno[2,3-*d*]-pyrimidines was described. In these reports, suitably substituted 2-amino-3-carboalkoxy or 2-amino-3-cyanothiophenes were condensed with reagents that provided the remaining carbon-nitrogen fragment required for cyclization to the newly formed condensed pyrimidine system. Some of these reagents were triethylorthoformate-ammonia (2), formamidine (3), formamide (4), imidate esters (5), and urea (6). More recently, a unique method was reported by Roth (7) for the preparation of thieno[2,3-*d*]pyrimidines which involved the cyclodehydration of variously substituted 6-phenacylthiopyrimidines.

In the present paper we wish to report a novel method for the preparation of esters and amides of thieno[2,3-*d*]-pyrimidine-6-carboxylic acids *via* the reaction of 4-chloro-5-pyrimidinecarboxylic acid intermediates with variously substituted mercaptoacetic acid esters and amides (8a-c).

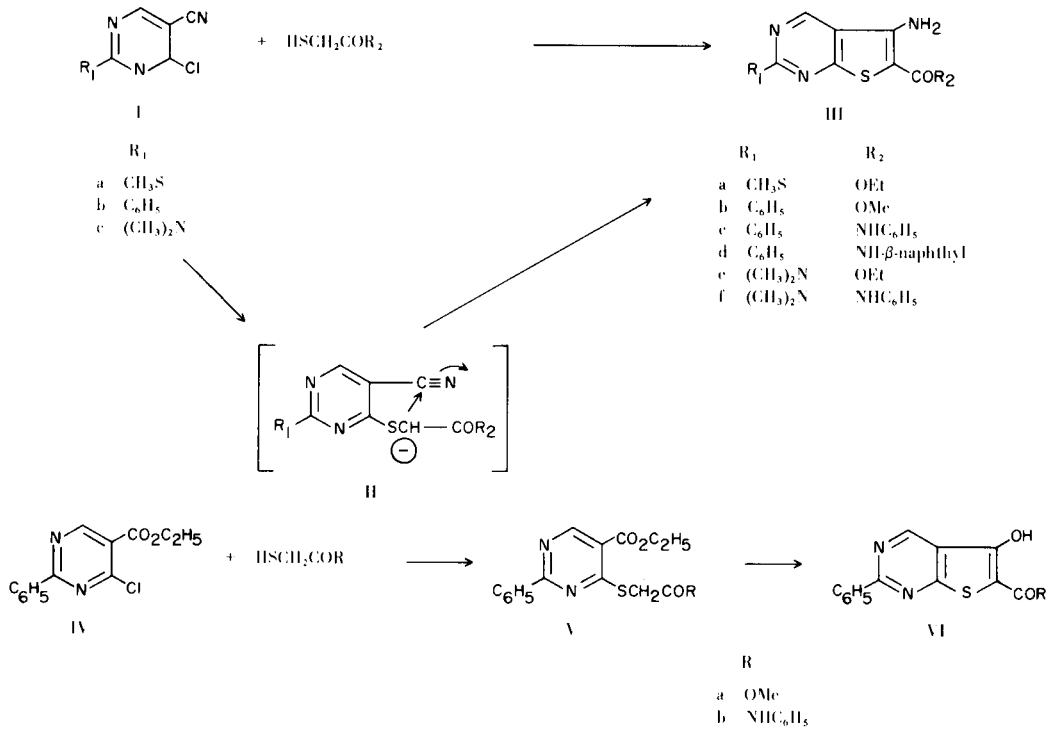
In a typical example, 4-chloro-2-methylthio-5-pyrimidinecarbonitrile (Ia) was allowed to react with one equivalent of ethyl mercaptoacetate in refluxing ethanol containing powdered sodium carbonate. The product which was formed directly was ethyl 5-amino-2-methylthiothieno-[2,3-*d*]pyrimidine-6-carboxylate (IIIa) (Scheme I). The postulated intermediate IIa was not isolated under the conditions of reaction, but cyclized directly to IIIa, presumably by a Dieckmann type process.

In contrast, when 5-carbethoxy-4-chloro-2-phenylpyrimidine (IV) was allowed to react with methyl mercaptoacetate under similar conditions, cyclization to the thieno-[2,3-*d*]pyrimidine failed to occur directly, even after several hours of reflux. The intermediate diester Va was obtained instead. Cyclization was effected by treatment of the latter product with sodium ethoxide in refluxing ethanol, affording a good yield of methyl 5-hydroxy-2-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate (VIa). Both the infrared and nuclear magnetic resonance spectra observed for IIIa and VIa were in accord with these structures.

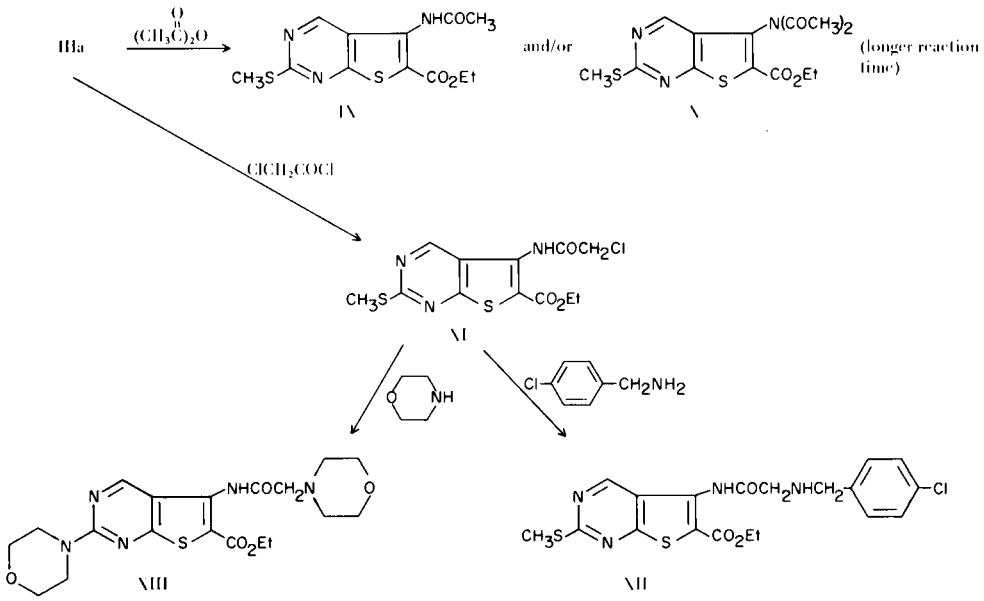
Other examples of thieno[2,3-*d*]pyrimidines synthesized by these two variations are shown in Scheme I and Table I. The synthesis of the 5-hydroxy derivatives VIa-b required a strong base such as sodium ethoxide to effect ring closure of the intermediates Va-b.

Replacement of the 2-methylthio group in these compounds by various amines was studied. Thus when IIIa was heated under reflux for several hours in 2-morpholinoethylamine without solvent, the corresponding 2-morpholinoethylamino derivative VIIa was obtained. Other

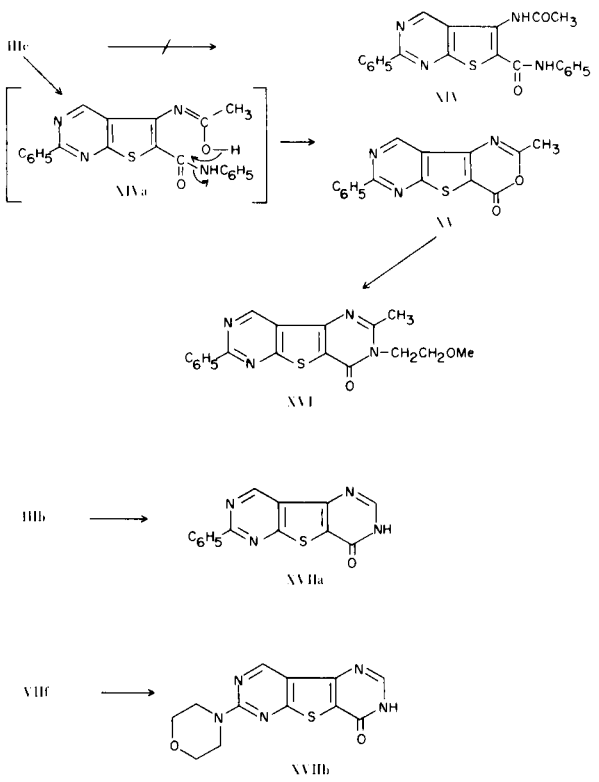
SCHEME I



SCHEME II



SCHEME III



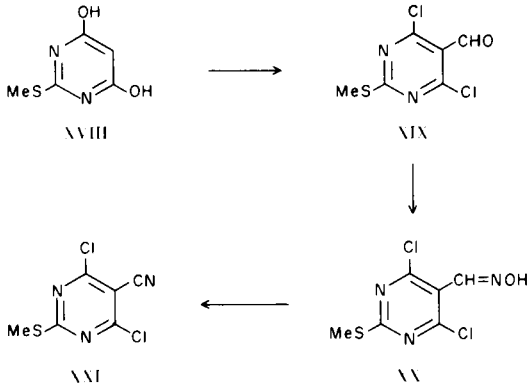
products (VIIb-f) obtained by this procedure, using various amines to displace the methylthio group, are given in Table II. In one example, *i.e.* when 2-hydroxyethylamine was employed, amide formation as well as displacement of the methylthio group occurred. The product thus afforded was 5-amino-*N*-2-hydroxyethyl-2-(2-hydroxyethylamino)-[2,3-*d*]pyrimidine-6-carboxamide (VIII).

When the acetylation of IIIa with acetic anhydride was carried out (Scheme II), either the monoacetyl derivative (IX) or the diacetyl derivative (X) was isolated, depending on the duration of reaction. With prolonged refluxing, the diacetyl derivative was the sole product obtained. Treatment of IIIa with chloroacetyl chloride afforded the corresponding chloroacetyl derivative (XI). Displacement reactions of the chloro group in XI were carried out. For example, with *p*-chlorobenzylamine in refluxing ethanol, amide XII was obtained. When an amine such as morpholine was used in this type of reaction without solvent at reflux temperature, displacement of the chloro group as well as the methylthio group resulted, giving XIII.

It is worthy to note that attempts to acetylate IIIc with acetic anhydride (Scheme III) under conditions similar to those used for the preparation of X failed to give the desired acetyl derivative XIV. Cyclization occurred instead to form the tricyclic pyrimidothienooxazine XV. Although the mechanism for this reaction is not apparent, the formation of XV could arise by the attack of the nucleophilic oxygen atom of the enol (XIVa) on the electrophilic carbonyl group of the carbanilide, resulting in the expulsion of aniline with resultant oxazine formation. The reaction of XV with 2-methoxyethylamine gave the pyrimidothienopyrimidine XVI. Two other examples of this ring system, XVIIa-b, were prepared by the action of formamide on thieno[2,3-*d*]pyrimidines IIIb and VIIf, respectively.

It was thought to be of pharmacologic interest to attach an amino, substituted amino, or methoxy group at the 4-

SCHEME IV



SCHEME V

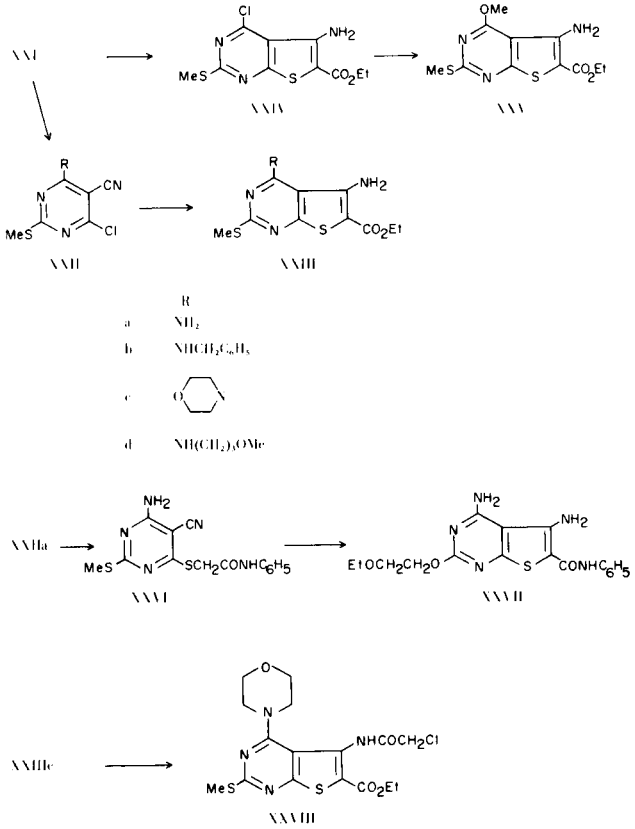
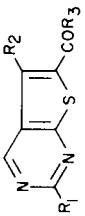


TABLE I



Compound	R_1	R_2	R_3	M.p., °C	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
IIIa	CH_3S	NH_2	OEt	190-192	88	$C_{10}H_{11}N_3O_2S_2$	44.59	4.12	15.60	23.81	44.84	4.01	15.57	23.86
b	C_6H_5	NH_2	OMe	233-235	52	$C_{14}H_{11}N_3O_2S$	58.93	3.89	14.74	11.24	59.00	4.03	14.66	11.04
c	C_6H_5	NH_2	NHC_6H_5	265-267.5	29	$C_{19}H_{14}N_4OS$	65.88	4.07	16.17	9.25	65.90	3.87	15.96	9.37
d	C_6H_5	NH_2	NH-β-naphthyl	268-270	44	$C_{23}H_{16}N_4OS$	69.68	4.07	14.13	8.09	69.40	4.27	14.12	7.86
e	$(CH_3)_2N$	NH_2	OEt	213-215	57	$C_{11}H_{14}N_4O_2S$	49.61	5.30	21.04	12.04	49.61	5.40	21.28	12.09
f	$(CH_3)_2N$	NH_2	NHC_6H_5	252-254	33	$C_{15}H_{15}N_5OS$	57.49	4.82	22.35	10.24	57.47	4.85	22.35	9.99
VIa	C_6H_5	OH	OMe	196-198	84	$C_{14}H_{10}N_2O_3S$	58.72	3.52	9.78	11.20	58.77	3.38	9.88	11.43
b	C_6H_5	OH	NHC_6H_5	272-274	41	$C_{19}H_{13}N_3O_2S$	65.69	3.77	12.10	9.23	65.43	3.93	11.85	9.16

position of the thieno[2,3-*d*]pyrimidine. This was done, beginning with a suitably substituted pyrimidine intermediate. For example, 4,6-dichloro-2-methylthio-5-pyrimidinecarbonitrile (XXI, Scheme IV) was prepared, starting from 4,6-dihydroxy-2-methylthiopyrimidine (XVIII), according to the general method described by Klotzer and Herberg (9). Treatment of XVIII with the Vilsmeier-Haack reagent, obtained from dimethylformamide and phosphoryl chloride, afforded 4,6-dichloro-2-methylthio-5-pyrimidinecarboxaldehyde (XIX). The aldehyde was converted to its oxime (XX), which in turn was dehydrated by the action of thionyl chloride to form XXI, the required key intermediate. Stepwise displacement of the chloro groups in XXI was carried out, first with ammonia or an amine, to afford the corresponding aminochloro- or substituted aminochloropyrimidines XXIIa-d (Scheme V). Thus, when these pyrimidines were treated with ethyl mercaptoacetate and sodium carbonate in refluxing ethanol in the usual way, the desired 4-substituted thieno[2,3-d]-pyrimidines XXIIIa-d, respectively, were obtained. The reaction of XXI with ethyl mercaptoacetate afforded ethyl 5-amino-4-chloro-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylate (XXIV). Treatment of XXIV with sodium methoxide resulted in the displacement of the chloro group by a methoxy group, giving ethyl 5-amino-4-methoxy-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylate (XXV). In one example, the reaction of 4-amino-6-chloro-2-methylthio-5-pyrimidinecarbonitrile (XXIIa) with 2-mercaptoacetanilide failed to give the thieno[2,3-*d*]pyrimidine directly, but gave instead the intermediate 2-(6-amino-5-cyano-2-methylthio-4-pyrimidinylthio)acetanilide (XXVI). When the latter product was treated with sodium 2-ethoxyethoxide in refluxing 2-ethoxyethanol, cyclization to the thieno[2,3-*d*]pyrimidine occurred readily, but replacement of the methylthio group by the base also resulted, giving 4,5-diamino-2-(2-ethoxyethoxy)thieno[2,3-*d*]pyrimidine-6-carboxanilide (XXVII).

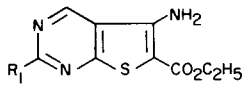
The reaction of XXIIIc with chloroacetyl chloride gave the corresponding chloroacetamido derivative XXVIII.

Several of the thieno[2,3-*d*]pyrimidines described in the present work were shown to be central nervous system depressants in test animals. One of them, XXVIII, showed a good anti-inflammatory response in the rat paw edema test.

EXPERIMENTAL

All melting points were determined in capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained in potassium bromide discs using a Perkin-Elmer spectrophotometer (Model 21). Ultraviolet absorption spectra were obtained with a Perkin-Elmer spectrophotometer (Model 450). Absorption maxima are given in millimicrons, with the molar extinction coefficients appearing in parentheses. Nuclear

TABLE II



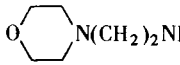
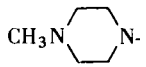
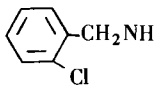
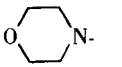
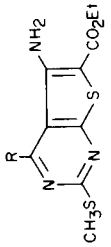
Compound	R_1	M.p., °C	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
VIIa		199-201	40	$C_{15}H_{21}N_5O_3S$	51.27	6.02	19.93	9.11	51.50	6.15	19.83	9.03
b	$C_6H_5(CH_2)_2NH$	188-190	20	$C_{17}H_{18}N_4O_2S$	59.63	5.30	16.36	9.36	59.41	5.26	16.06	9.39
c	$CH_3O(CH_2)_3NH$	208-210	26	$C_{13}H_{18}N_4O_3S$	50.31	5.84	18.05	10.33	50.51	5.62	18.13	10.55
d		202-204	33	$C_{14}H_{19}N_5O_2S$	52.32	5.96	21.79	9.98	52.54	5.96	22.07	10.28
e		198-201	31	$C_{16}H_{15}N_4O_2ClS$	52.96	4.17	15.44	8.34	52.94	4.14	15.20	8.68
f		200-202	14	$C_{13}H_{16}N_4O_3S$	50.63	5.23	18.17	10.40	50.77	5.00	18.08	10.31

TABLE III



Compound	R	M.p., °C	Yield, %	Formula	Calcd. C	H	N	S	Found C	H	N	S
XXIIIa	NH_2	256-258	21	$C_{10}H_{12}N_4O_2S_2$	42.24	4.25	19.70	22.55	42.24	4.26	19.74	22.34
b	$NHCH_2C_6H_5$	187-190	62	$C_{17}H_{18}N_4O_2S_2$	54.52	4.84	14.96	17.12	54.57	4.99	14.77	16.86
c		145-147	22	$C_{14}H_{18}N_4O_3S_2$	47.44	5.12	15.81		47.56	5.25	15.54	
d	$NHCH_2CH_2CH_2OMe$	118-120	32	$C_{14}H_{20}N_4O_3S_2$	47.17	5.66	15.72	17.99	47.14	5.30	15.66	17.84
XXIV	Cl	170-171	22	$C_{10}H_{10}ClN_3O_2S_2$	39.54	3.32	13.83	21.11	39.87	3.21	14.06	20.79

magnetic resonance spectra were obtained in dimethylsulfoxide, unless otherwise stated, using tetramethylsilane as the internal standard. The chemical shifts (δ) are given in ppm. The observed spectra are in accord with the assigned structures, and for brevity only essential spectral features are given for key compounds. The yields indicated are the results of single experiments and are not considered optimal.

4-Chloro-2-methylthio-5-pyrimidinecarbonitrile (Ia).

A mixture of 5 g. of 4-hydroxy-2-methylthio-5-pyrimidinecarbonitrile (10) in 50 ml. of phosphoryl chloride was heated under reflux with stirring for 5 hours. The excess phosphoryl chloride was distilled *in vacuo* on a rotary evaporator. Ice was added to the residue, and the crystalline product which formed was recrystallized from pentane, affording 5 g. (90%) of product, m.p. 61-63°; ir 4.55 μ (C≡N).

Anal. Calcd. for $C_6H_4ClN_3S$: C, 38.82; H, 2.17; N, 22.64. Found: C, 39.10; H, 2.22; N, 22.98.

4-Chloro-2-phenyl-5-pyrimidinecarbonitrile (Ib).

This compound was prepared in similar fashion from 5 g. of 4-hydroxy-2-phenyl-5-pyrimidinecarbonitrile (11) and 50 ml. of phosphoryl chloride. There was obtained 5.5 g. (100%) of product. Recrystallization from ethanol gave the analytical sample, m.p. 193-195°; ir 4.50 μ (C≡N).

Anal. Calcd. for $C_{11}H_6ClN_3$: C, 61.27; H, 2.80; N, 19.49; Cl, 16.44. Found: C, 61.56; H, 2.80; N, 19.70; Cl, 16.36.

5-Amino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (IIIa).

This compound typifies the preparation of compounds IIIa-f. To a mixture of 24.0 g. of Ia and 13.7 g. of anhydrous sodium carbonate in 100 ml. of ethanol was added 15.6 g. of ethyl mercaptoacetate. The reaction mixture was heated with stirring under reflux for 4 hours. The ethanol was removed by distillation in a rotary evaporator under vacuum. The residue was washed with 25 ml. of water and the mixture filtered. The filter cake after recrystallization from methanol afforded 27 g. of product m.p. 190-192°; ir, 2.95, 3.05 μ (doublet NH) and 5.92 μ (ester C=O); nmr, δ 7.49 (s, 2H, NH_2) disappears on deuteration, 1.33 (t, 3H, CH_3), 4.30 (q, 2H, CH_2), 2.61 (s, 3H, CH_3S).

4-Chloro-2-dimethylamino-5-pyrimidinecarbonitrile (Ic).

This compound was prepared as described by Schmidt and co-workers (10). From 13 g. of 4-hydroxy-2-dimethylamino-5-pyrimidinecarbonitrile and 150 ml. of phosphoryl chloride was obtained 10.5 g. (72%) of product, m.p. 143-148°. Recrystallization from benzene raised the m.p. to 147-149° (lit. [10] 149-150°).

4-Carboxymethylthio-2-phenyl-5-pyrimidinecarboxylic Acid, 4-Methyl Ester, 5-Ethyl Ester (Va).

To a mixture of 1.0 g. of anhydrous sodium carbonate in 50 ml. of ethanol was added 2.6 g. of 5-carbethoxy-4-chloro-2-phenylpyrimidine (8c) (IV) and 1.1 g. of methyl mercaptoacetate. The mixture was stirred and heated under reflux for 2 hours. On cooling the reaction mixture in ice a crystalline product was deposited. The precipitate was collected, washed with water, and recrystallized from ethanol, affording 1.8 g. of product (57%), m.p. 111-112°; ir 5.76 (methyl ester C=O) and 5.88 μ (pyrimidine ester C=O).

Anal. Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43; S, 9.65. Found: C, 57.65; H, 4.87; N, 8.21; S, 9.42.

5-Hydroxy-2-phenylthieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Methyl Ester (VIa).

To a solution of 1.3 g. of sodium in 100 ml. of absolute ethanol was added 18 g. of Va. The reaction mixture was cooled in ice and acidified with glacial acetic acid. The precipitate which resulted was removed by filtration and washed with water (3 x 25 ml.). The product amounted to 13.0 g. (84%), m.p. 184-187°. The analytical sample was obtained by recrystallization from methanol, m.p. 196-198°; uv 285 (3.56 x 10^4), 340 (1.00 x 10^3); ir 3.03 (OH stretch) and 5.92 μ (ester C=O); nmr (deuteriochloroform) 3.97 (s, 3H, OCH_3), 10.3 (s, 1H, OH), disappears on deuteration.

2-Phenyl-4-(phenylcarbamoyl)methylthio-5-pyrimidinecarboxylic Acid, Ethyl Ester (Vb).

This compound was prepared from 2.6 g. of IV, 1.67 g. of α-mercaptoacetanilide, and 1.0 g. of anhydrous sodium carbonate in 50 ml. of ethanol by the procedure described for the preparation of Va. The product amounted to 2.6 g. (67%). Recrystallization from aqueous dimethylformamide gave the analytical sample, m.p. 220-222°; ir 5.89 (ester C=O), 6.07 (amide I C=O) and 6.48 μ (amide II C=O).

Anal. Calcd. for $C_{21}H_{19}N_3O_3S$: C, 64.11; H, 4.87; N, 10.68; S, 8.15. Found: C, 64.15; H, 4.99; N, 10.48; S, 8.00.

5-Hydroxy-2-phenylthieno[2,3-*d*]pyrimidine-6-carboxanilide (VIb).

To a solution of 0.18 g. of sodium in 50 ml. of dry 2-ethoxyethanol was added 3.0 g. of Vb. The reaction mixture was heated under reflux with stirring for 2 hours. It was then cooled to room temperature, diluted with 50 ml. of water, and acidified by the addition of a slight excess of 30% hydrochloric acid. The solid which was deposited was removed by filtration and recrystallized from dimethylformamide. There was obtained 1.5 g. (41%) of product, m.p. 272-274° dec.; uv 290 (3.27 x 10^4), 355 (1.29 x 10^4); ir 6.15 (amide C=O) and 6.50 μ (amide II C=O).

5-Amino-2-(2-morpholinoethylamino)thieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (VIIa).

This compound typifies the preparation of compounds VIIa-f. To 40 ml. of 2-morpholinoethylamine was added 2.4 g. of IIIa. The resulting solution was heated under reflux for 4 hours, after which the reaction mixture was poured into 200 ml. of water. The resulting precipitate was collected and recrystallized from ethanol, affording 1.2 g. (40%) of product, m.p. 199-201°; uv 270 (shoulder, 1.39 x 10^4), 296 (3.23 x 10^4); ir 2.99, 307 (doublet NH_2) and 6.10 μ (ester C=O).

5-Amino-*N*-2-hydroxyethyl-2-(2-hydroxyethylamino)thieno[2,3-*d*]-pyrimidine-6-carboxamide (VIII).

To 40 ml. of ethanolamine was added 8.25 g. of IIIa. The reaction mixture was heated under reflux for 6 hours, then allowed to stand overnight, when a crystalline product was deposited. Recrystallization from aqueous dimethylformamide gave 3.2 g. (35%) of product, m.p. 244-246°; uv 268 (shoulder 1.37 x 10^4), 296 (3.00 x 10^4), 330 (shoulder 9.27 x 10^3); ir 6.2 (amide I C=O) and 6.6 μ (amide II C=O).

Anal. Calcd. for $C_{11}H_{15}N_5O_3S$: C, 44.43; H, 5.08; N, 23.55; S, 10.79. Found: C, 44.44; H, 5.07; N, 23.66; S, 10.75.

5-Acetylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (IX).

A mixture of 5.5 g. of IIIa and 50 ml. of acetic anhydride was heated under reflux for 3 hours. The mixture was cooled in ice and filtered, and the product which was collected was recrystallized from ethanol. There was obtained 2.8 g. (45%). The analytical sample had m.p. 173-176°; uv 242 (1.37 x 10^4), 278 (1.94 x 10^4), 330 (1.34 x 10^4); ir 5.85 (ester C=O) and 5.95 μ (amide C=O).

Anal. Calcd. for $C_{12}H_{13}N_3O_3S_2$: C, 46.29; H, 4.29; N, 13.49; S, 20.60. Found: C, 46.07; H, 4.18; N, 13.16; S, 20.49.

5-Diacetylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (X).

This compound was prepared in the manner described for the preparation of IX, except that the reflux time was extended an additional hour. There was obtained from 4.5 g. of IIIa 1.8 g. (31%) of X after recrystallization from ethanol, m.p. 134-136°; ir 5.85 (ester C=O) and 5.93 μ (amide C=O).

Anal. Calcd. for $C_{14}H_{15}N_3O_4S_2$: C, 47.58; H, 4.28; N, 11.89; S, 18.15. Found: C, 47.45; H, 4.28; N, 12.07; S, 18.39.

5-(α-Chloroacetamide)-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (XI).

A mixture of 5.5 g. of IIIa and 50 ml. of chloroacetyl chloride was boiled under reflux for 2 hours. The excess chloroacetyl chloride was removed by distillation under reduced pressure in a rotary evaporator. The residue amounted to 4.5 g. (64%). Recrystallization from dimethylformamide-methanol gave 1.6 g. of product, m.p. 194-197°; uv 244 (1.48 x 10^4), 287 (1.93 x 10^4), 330 (1.389 x 10^4); ir 5.85 (shoulder ester C=O) and 5.90 μ (amide C=O).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_3S_2$: C, 41.68; H, 3.50; N, 12.16; Cl, 10.25; S, 18.54. Found: C, 41.54; H, 3.47; N, 12.08; Cl, 10.50; S, 18.80.

5-[α-(*p*-Chlorobenzylamino)acetamido]-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (XII).

A mixture of 2.1 g. of anhydrous sodium carbonate, 2.8 g. of *p*-chlorobenzylamine and 6.9 g. of XI in 75 ml. of ethanol was heated under reflux for 3 hours. The excess ethanol was removed by distillation in a rotary evaporator *in vacuo*. Water (50 ml.) was added to the residue. The solid was collected and recrystallized from benzene-pentane, affording 0.5 g. (6%) of product, m.p. 144-146°; ir 5.92 (ester C=O), 6.1 (shoulder amide I C=O) and 6.45 μ (amide II C=O).

Anal. Calcd. for $C_{19}H_{19}ClN_4O_3S_2$: C, 50.60; H, 4.25; N, 12.42; Cl, 7.86; S, 14.22. Found: C, 50.99; H, 4.36; N, 12.57; Cl, 7.76; S, 14.15.

2-Morpholino-5-(α-morpholinoacetamido)thieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (XIII).

A mixture of 5 g. of XI and 20 ml. of morpholine was heated under reflux for 5 hours. To the dark-colored solution was added 30 ml. of methanol. The solution was treated with animal charcoal and filtered. The addition of water to the filtrate resulted in the deposition of a crystalline product. Recrystallization of this material from benzene-heptane afforded 0.5 g. (8%) of product, m.p. 179-182°; uv 246 (1.60 x 10^4), 294 (1.88 x 10^4), 355 (1.46 x 10^4); ir 5.85 (ester C=O), 6.01 (amide C=O) and 6.45 μ (amide II C=O).

Anal. Calcd. for $C_{19}H_{25}N_5O_5S$: C, 52.40; H, 5.79; N, 16.08; S, 7.36. Found: C, 52.48; H, 5.75; N, 15.90; S, 7.68.

2-Methyl-7-phenyl-4*H*-pyrimido[5′,4′:4,5]thieno[3,2-*d*][1,3]-oxazin-4-one (XV).

A solution of 2.1 g. of IIIc in 50 ml. of acetic anhydride was heated under reflux for 3 hours. The reaction mixture was cooled in ice and filtered. The product thus obtained was recrystallized from dimethylformamide, affording 1.1 g. (66%) of product, m.p. 264-267°; uv 277 (3.09 x 10^4), 3.15 (1.90 x 10^4); ir 5.72 μ

(lactone C=O).

Anal. Calcd. for $C_{15}H_9N_3O_2S$: C, 61.01; H, 3.07; N, 14.23; S, 10.86. Found: C, 60.87; H, 3.24; N, 14.28; S, 11.20.

3-(2-Methoxyethyl)-2-methyl-7-phenylthieno[2,3-*d*:4,5-*d'*]dipyrimidin-4(3*H*)-one (XVI).

Two grams of XV was added to 15 ml. of 2-methoxyethylamine and the mixture was heated under reflux for 5 minutes, during which time a precipitate was formed. The reaction mixture was cooled in ice and filtered. The precipitate was recrystallized from dimethylformamide, giving the product (0.5 g., 21%), m.p. 246-248°; uv 282 (3.79 x 10^4), 305 (1.99 x 10^4); ir 6.0 μ (lactam C=O).

Anal. Calcd. for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90; S, 9.10. Found: C, 61.05; H, 4.65; N, 15.96; S, 9.46.

7-Phenylthieno[2,3-*d*:4,5-*d'*]dipyrimidin-4(3*H*)-one (XVIIa).

A mixture of IIIb (1.0 g.) and formamide (10 ml.) was heated under reflux for 1½ hours and then cooled in ice. The yellow crystalline product which was deposited was recrystallized from 2-ethoxyethanol, affording 0.2 g. (20%) of product, m.p. >360°.

Anal. Calcd. for $C_{14}H_8N_4OS$: C, 59.99; H, 2.88; N, 19.99; S, 11.44. Found: C, 59.90; H, 2.84; N, 19.76; S, 11.22.

7-Morpholinothieno[2,3-*d*:4,5-*d'*]dipyrimidin-4(3*H*)-one (XVIIb).

This compound was prepared in the same fashion as XVIIa from 6.5 g. of VIIf in 100 ml. of formamide. The reaction time was 10 hours. The product, which was recrystallized from dimethylformamide, amounted to 2.1 g. (34%), m.p. > 360°; ir 6.03 μ (lactam C=O).

Anal. Calcd. for $C_{12}H_{11}N_5O_2S$: C, 49.82; H, 3.83; N, 24.21; S, 11.08. Found: C, 49.68; H, 4.09; N, 23.89; S, 10.72.

4,6-Dichloro-2-methylthio-5-pyrimidinecarboxaldehyde (XIX).

To 108 ml. of phosphoryl chloride chilled in ice was added 35 ml. of dimethylformamide. This mixture was allowed to stand at 20° for 1 hour and 25 g. of 4,6-dihydroxy-2-methylthiopyrimidine (12)(XVIII) was added in portions. After 30 minutes the reaction mixture was heated on a steam bath for 6 hours. The excess phosphoryl chloride was removed *in vacuo* and the residue was treated with ice and water. The crystalline product which resulted was collected on a filter and recrystallized from petroleum ether. The product amounted to 13.8 g. (39%), m.p. 82-84°; ir 5.90 μ (aldehyde C=O).

Anal. Calcd. for $C_6H_4Cl_2N_2OS$: C, 32.30; H, 1.81; N, 12.56; Cl, 31.79. Found: C, 32.48; H, 1.83; N, 12.16; Cl, 31.69.

4,6-Dichloro-2-methylthio-5-pyrimidinecarboxaldehyde, Oxime (XX).

To 15 ml. of glacial acetic acid was added 2.2 g. of XIX, 1 ml. of water, and 0.7 g. of hydroxylamine hydrochloride. The reaction mixture was warmed for a few minutes, then diluted with water to the precipitation point and cooled in ice. The crystalline product which was deposited amounted to 1.3 g. (55%). Recrystallization from petroleum ether gave the product, 0.7 g., m.p. 110-112°.

Anal. Calcd. for $C_6H_5Cl_2N_3OS$: C, 30.24; H, 2.12; N, 17.65; Cl, 29.78; S, 13.47. Found: C, 30.57; H, 2.09; N, 17.62; Cl, 29.84; S, 13.17.

4,6-Dichloro-2-methylthio-5-pyrimidinecarbonitrile (XXI).

A solution of 0.5 g. XX in 30 ml. of thionyl chloride was heated under reflux for 3 hours. The excess thionyl chloride was removed by distillation in a rotary evaporator *in vacuo*. The residue was recrystallized from aqueous ethanol, affording 0.2 g. (43%) of product, m.p. 103-104°; ir 4.55 μ (C≡N).

Anal. Calcd. for $C_6H_3Cl_2N_3S$: C, 32.74; H, 1.37; N, 19.09; Cl, 32.22; S, 14.57. Found: C, 32.98; H, 1.53; N, 18.90; Cl, 31.94; S, 14.78.

4-Amino-6-chloro-2-methylthio-5-pyrimidinecarbonitrile (XXIIa).

Ammonia gas was bubbled into a solution of 5 g. of XXI in 100 ml. of ethanol for 15 minutes, during which time a precipitate was deposited. The reaction mixture was heated for 15 minutes at 50° on a steam bath. The solvent was removed on a rotary evaporator *in vacuo*. The residue was recrystallized from methanol, giving 2.4 g. (52%) of product, m.p. 223-226°; ir 4.55 μ (C≡N).

Anal. Calcd. for $C_6H_5ClN_4S$: C, 35.91; H, 2.51; N, 27.92; S, 15.98. Found: C, 36.26; H, 2.87; N, 27.78; S, 15.66.

4-Benzylamino-6-chloro-2-methylthio-5-pyrimidinecarbonitrile (XXIIb).

To a solution of 10.7 g. of benzylamine in 20 ml. of absolute ethanol was added 11.3 g. of XXI. The mixture was heated with stirring under reflux for 1 hour, cooled, and filtered. The filter cake was washed with water and recrystallized from aqueous ethanol (8.6 g., 59%). The product melted at 164-166°; ir 3.05 (NH) and 4.55 μ (C≡N).

Anal. Calcd. for $C_{13}H_{11}ClN_4S$: C, 53.70; H, 3.81; N, 19.27; Cl, 12.19; S, 11.03. Found: C, 53.83; H, 3.77; N, 19.01; Cl, 12.16; S, 10.98.

4-Chloro-2-methylthio-6-morpholino-5-pyrimidinecarbonitrile (XXIIc).

This compound was similarly prepared from 10 g. of XXI and 7.2 g. of morpholine. After the initial heat of reaction had subsided, the reaction mixture was stirred at room temperature for 1 hour. The product (12 g., 98%) was recrystallized from ethanol, giving the analytical sample, m.p. 159-161°; ir 4.60 μ (C≡N).

Anal. Calcd. for $C_{10}H_{11}ClN_4OS$: C, 44.36; H, 4.10; N, 20.69; Cl, 13.10; S, 11.84. Found: C, 44.65; H, 3.94; N, 20.70; Cl, 13.15; S, 11.54.

4-Chloro-6-(3-methoxypropylamine)-2-methylthio-5-pyrimidinecarbonitrile (XXIId).

This compound was similarly prepared from 4.4 g. of XXI and 3.56 g. of 3-methoxypropylamine in 100 ml. of ethanol. The reaction mixture was heated under reflux for 3 hours with stirring. The excess ethanol was removed *in vacuo* and the residue recrystallized from methanol, affording 2.3 g. (42%) of product, m.p. 80-82°; ir 3.02 (NH) and 4.53 μ (C≡N).

Anal. Calcd. for $C_{10}H_{13}ClN_4OS$: C, 44.03; H, 4.80; N, 20.54; Cl, 13.00; S, 11.76. Found: C, 43.80; H, 4.72; N, 20.33; Cl, 13.00; S, 11.62.

5-Amino-4-chloro-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (XXIV).

To a mixture of 2.3 g. of XXI and 1.1 g. of anhydrous sodium carbonate in 75 ml. of ethanol was added 1.2 g. of ethyl mercaptoacetate. The reaction mixture was heated under reflux for 3 hours and the solvent removed *in vacuo* on a rotary evaporator. The yellow residue was triturated with 50 ml. of water and filtered. The product was recrystallized from ethanol, giving 0.7 g. (22%) of product, m.p. 170-171°; uv 299 (3.38 x 10^4), 345 (7.18 x 10^3); ir 2.92, 3.03 (doublet NH_2) and 5.95 μ (ester C=O).

Anal. Calcd. for $C_{10}H_{10}ClN_3O_2S_2$: C, 39.54; H, 3.32; N, 13.83; Cl, 11.67; S, 21.11. Found: C, 39.87; H, 3.21; N, 14.06; Cl, 12.05; S, 20.79.

Similarly prepared were compounds XXIIIa-d, starting with the

appropriate 4-chloro-2-methylthio-6-substituted amino-5-pyrimidinecarbonitriles and allowing them to react with an equivalent of ethyl mercaptoacetate in refluxing ethanol containing sodium carbonate.

5-Amino-4-methoxy-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (XXV).

To a solution of 0.46 g. of sodium in 50 ml. of methanol was added 3.1 g. of XXIV. The reaction mixture was heated with stirring under reflux for 2½ hours, cooled, and filtered. The collected solid was washed with water and recrystallized, first from dimethylformamide and then from 2-propanol. The product amounted to 1.1 g. (36%), m.p. 179-181°; uv 280 (2.95×10^4), 345 (1.39×10^4); ir 2.90, 3.02 (doublet NH_2) and 5.95 μ (ester C=O).

Anal. Calcd. for $C_{11}H_{13}N_3O_3S_2$: C, 44.13; H, 4.38; N, 14.03; S, 21.42. Found: C, 43.66; H, 4.26; N, 14.24; S, 21.79.

2-(6-Amino-5-cyano-2-methylthio-4-pyrimidinylthio)acetanilide (XXVI).

A mixture of 3.7 g. of XXIIa, 3.3 g. of 2-mercaptoacetanilide, and 2.1 g. of anhydrous sodium carbonate in 150 ml. of ethanol was heated under reflux for 2 hours. The precipitate which formed during this period was removed by filtration washed with water, and recrystallized from dimethylformamide-methanol. There was obtained 2.5 g. (45%) of product, m.p. 225-257°; ir 3.00, 3.08 (doublet NH_2), 4.58 (C≡N), 6.05 (amide C=O) and 6.55 μ (amide II C=O).

Anal. Calcd. for $C_{14}H_{13}N_5OS_2$: C, 50.74; H, 3.95; N, 21.13; S, 19.35. Found: C, 50.82; H, 3.91; N, 21.21; S, 19.06.

4,5-Diamino-2-(2-ethoxyethoxy)thieno[2,3-*d*]pyrimidine-6-carboxanilide (XXVII).

To a solution of 0.7 g. of sodium in 150 ml. of 2-ethoxyethanol was added 9.0 g. of XXVI. The reaction mixture was heated with stirring under reflux for 1 hour, cooled, and 200 ml. of water added. The crystalline product which was deposited (1.0 g., 10%) was recrystallized from ethanol and then from 2-propanol, m.p. 224-226°; ir 2.99, 3.05 (doublet NH_2), 6.18 (amide C=O) and 6.55 μ (amide II C=O).

Anal. Calcd. for $C_{17}H_{19}N_5O_3S$: C, 54.68; H, 5.13; N, 18.75; S, 8.59. Found: C, 54.43; H, 5.00; N, 18.85; S, 8.87.

5-(2-Chloroacetamido)-2-methylthio-4-morpholinothieno[2,3-*d*]-pyrimidine-6-carboxylic Acid, Ethyl Ester (XXVIII).

A mixture of 4 g. of XXIIIc and 15 ml. of chloroacetyl chloride in 100 ml. of benzene was heated under reflux for 5 hours. The reaction mixture was allowed to stand overnight at room temperature, during which time crystals formed. Recrystallization from 2-propanol and then ethanol gave 1 g. (22%) of product, m.p. 161-163°; uv 271 (2.25×10^4), 320 (1.54×10^4); ir 5.90 (ester C=O), 5.98 (amide C=O) and 6.4 μ (amide II C=O).

Anal. Calcd. for $C_{16}H_{19}ClN_4O_4S_2$: C, 44.59; H, 4.44; N, 13.00; Cl, 8.23; S, 14.88. Found: C, 44.36; H, 4.42; N, 13.09; Cl, 8.42; S, 14.83.

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