Synthesis of Thieno- and Furo-pyrimidinethiones

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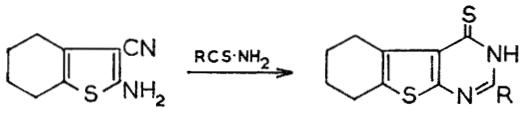
Substituted thiophens carrying adjacent amino- and cyano-groups have been converted into the corresponding pyrimidinethione derivatives in 30—70% yield by condensation with thioamides. Acylation of the thiophen followed by cyclisation in acidic solution gave the corresponding pyrimidones. The same reactions were used successfully with analogous furan compounds.

PYRIMIDINE-4-THIONES have received considerable attention because of their close structural relationship with 6-mercaptopurines, which exhibit antimitotic activity.[1-4] Recently Zoltewicz and Sharpless [5] have reported a one-step synthesis of fused pyrimidinethiones from *o*-amino-nitriles and thioamides under strongly acid conditions. This is an extension of the synthesis already reported by Taylor and Zoltewicz.[6] Todd and his co-workers [7] have studied the reaction of ethyl aminomethylenecyanoacetate with thioacetamide in the presence of sodium ethoxide. In this case the principal product isolated was ethyl 4-amino-2-methylpyrimidine-5-carboxylate. This great divergence in the nature of the products formed under different conditions prompted us to reinvestigate the Zoltewicz and Sharpless procedure and to study the scope of this reaction.

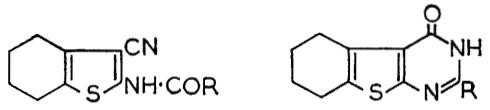
When 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-carbonitrile [8] (I) and thioacetamide were heated under reflux in glacial acetic acid saturated with dry hydrogen bromide, the product isolated was the benzothienopyrimidinethione (II) (33%). Under similar conditions, treatment of (I) with thiobenzamide afforded a product with the correct analysis for the hydrobromide of (III). When (I) was heated under reflux with thiobenzanilide, thioacetanilide, or acetanilide in glacial acetic acid–hydrogen bromide, quantitative amounts of aniline hydrobromide were formed as the only isolable product; the rest was an intractable tar in each case.



(I) (II) R = Me (III) R = Ph

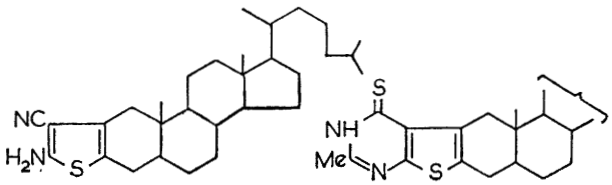
Acylation of (I) with acetic anhydride and benzoyl chloride gave the amides (IV) and (V) respectively. When these were heated under reflux in ethanol saturated with dry hydrogen chloride, the pyrimidones (VI) and (VII) were formed [9] (*ca.* 70%).

We have extended the thioacetamide method for the synthesis of thienopyrimidinethiones to the preparation



(IV) R = Me (V) R = Ph (VI) R = Me (VII) R = Ph

of a steroid derivative of type (IX). Cholestan-3-one under Gewald's conditions [8] gave the corresponding thieno-derivative (VIII), which on treatment with thioacetamide under acidic conditions [5] afforded the pyrimidinethione (IX).



(VIII) (IX)

Attempts to synthesise 2-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-3-carbonitrile (X) from cyclopentanone by use of Gewald's conditions [8] failed. However, under similar conditions, 2-amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-3-carbonitrile (XI) was obtained (45%) from cycloheptanone. Ready conversion of (XI) into the pyrimidinethione (XII) was achieved by refluxing with thioacetamide in glacial acetic acid–dry hydrogen bromide. Ethyl acetoacetate could also be converted into the corresponding ethyl 5-amino-4-cyano-3-methylthiophen-2-carboxylate (XIII) by heating under reflux with sulphur, malononitrile, and diethylamine in ethanol.[8] Acylation of (XIII) with acetic anhydride

[1] J. H. Burchenal, R. R. Ellison, M. L. Murphy, D. A. Karnofsky, M. P. Sykes, T. C. Tan, A. C. Mermann, M. Yuceoglu, W. P. L. Myres, I. Krakoff, and N. Alberstadt, *Ann. New York Acad. Sci.*, 1954, **60**, 359.

[2] H. E. Skipper, J. R. Thomson, D. J. Hutchinson, F. M. Schabel, and J. J. Johnson, *Proc. Soc. Exp. Biol. Med.*, 1957, **95**, 135.

[3] H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel, *Cancer Res.*, 1959, **19**, 425.

[4] R. K. Robins, *J. Medicin. Chem.*, 1964, **7**, 186.

[5] J. A. Zoltewicz and T. W. Sharpless, *J. Org. Chem.*, 1967, **32**, 2681, and references cited therein.

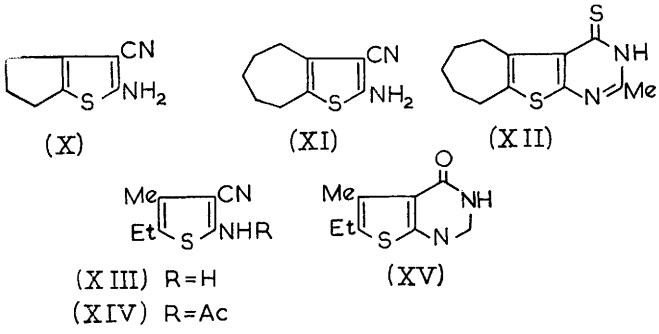
[6] E. C. Taylor and J. A. Zoltewicz, *J. Amer. Chem. Soc.*, 1961, **83**, 248.

[7] G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 1943, 388; see also H. M. Wuest and M. Hoffer, U.S.P. 2,271,503/1941 (*Chem. Abs.*, 1942, **36**, 3632).

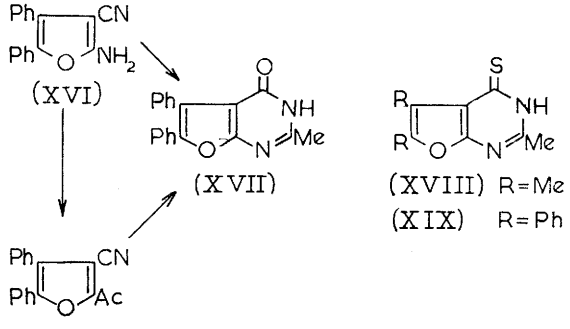
[8] K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.*, 1966, **99**, 94.

[9] See also E. C. Taylor and Y. Shvo, *J. Org. Chem.*, 1968, **33**, 1719.

afforded the amide (XIV), which when heated under reflux with ethanol saturated with dry hydrogen chloride gave the thienopyrimidone (XV). Treatment of (XIII) with thioacetamide in glacial acetic acid–dry hydrogen bromide did not give the expected thiopyrimidone. Only (XV) could be isolated in this reaction (78%). This conversion of (XIII) into (XV) probably arises by the acetylation of (XIII) with glacial acetic acid followed by cyclisation.[10] A similar conversion under these conditions has been reported by Zoltewicz and Sharpless.[5]



Efforts were then directed towards the synthesis of pyrimidinethiones from 2-aminofuran-3-carbonitriles. These compounds could be synthesised from *o*-hydroxyketones.[11] When (XVI) was treated with thioacetamide the product isolated was identified as (XVII); no pyrimidinethione could be recovered. This product was identical with the pyrimidone formed by acetylation of (XVI) followed by cyclisation in absolute ethanol saturated with dry hydrogen chloride. 2-Amino-4,5-dimethylfuran-3-carbonitrile [11] when similarly treated with thioacetamide, however, gave the pyrimidinethione (XVIII).



A useful variation of the synthesis of pyrimidinethiones from thioamides and *o*-amino-nitriles was the use of trifluoracetic acid in place of glacial acetic–dry hydrogen bromide. The subsequent work-up is convenient and the yields are better. When (XVI) was heated under reflux with thioacetamide in trifluoracetic acid, the hydrofluoride of the pyrimidinethione (XIX) was obtained, which gave the free base (XIX) on basification with ammonium hydroxide. The hydrogen fluoride for the salt formation must come from the breakdown of trifluoroacetic acid. An analogous reaction with (I) gave the monohydrate of (II) (40%).

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer Infracord. N.m.r. spectra were recorded with a Varian A60A spectrometer and mass spectra with a 21-103C CEC mass spectrometer. Microanalyses were performed by MHW Laboratories, Garden City, Michigan, and A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mülheim (Ruhr), West Germany.

2-Aminothiophen-3-carbonitriles were prepared by the method of Gewald, Schinke, and Bottcher.[8]

2'-Aminocholest-2-eno[3,2-6]*thiophen-4'-carbonitrile* (VIII) was obtained (30%) from cholestan-3-one; m.p. 235° (Found: C, 77·45; H, 9·45, N, 6·2; S, 6·95. $C_{30}H_{46}N_2S$ requires C, 77·25; H, 9·85; N, 6·0; S, 6·85%).

2-Amino-5,6,7,8-tetrahydro-4H-cyclohepta[b]*thiophen-3-carbonitrile* (XI) was obtained (45%) from cycloheptanone; m.p. 114° (from ethanol) (Found: C, 62·4; H, 6·4; N, 14·5; S, 16·6. $C_{10}H_{12}N_2S$ requires C, 62·5; H, 6·25; N, 14·6; S, 16·65%).

Ethyl 5-amino-4-cyano-3-methyl-2-thiophen-2-carboxylate (XIII) was obtained (63%) from ethyl acetoacetate; m.p. 210° (decomp.) (from aqueous dimethylformamide) (Found: C, 51·2; H, 4·8; N, 13·2; S, 15·3. $C_9H_{10}N_2O_2S$ requires C, 51·45; H, 4·8; N, 13·35; S, 15·25%).

2-Aminofuran-3-carbonitriles were synthesised according to the procedure developed by Gewald.[10]

Synthesis of Thieno- and Furo-pyrimidones.—(*a*) The *o*-aminonitriles were acylated with acetic anhydride or benzoyl chloride and pyridine in benzene solution: *2-acetamido-4,5,6,7-tetrahydrobenzo*[b]*thiophen-3-carbonitrile* (IV) (85%), m.p. 216—217° (from ethanol) (Found: C, 56·0; H, 5·4; N, 12·85; S, 14·6. $C_{11}H_{12}N_2OS$ requires C, 56·0; H, 5·5; N, 12·7; S, 14·5%); *2-benzamido-4,5,6,7-tetrahydrobenzo*[b]*thiophen-3-carbonitrile* (V) (87%), m.p. 237° (from dimethylformamide (Found: C, 67·9; H, 5·05; N, 9·85; S, 11·3. $C_{16}H_{14}N_2OS$ requires C, 68·1; H, 5·0; N, 9·9; S, 11·3%); *ethyl 5-acetamido-4-cyano-3-methylthiophen-2-carboxylate* (XIV) (60%), m.p. 232° from dimethylformamide (Found: C, 52·05; H, 4·55; N, 10·85; S, 12·65. $C_{11}H_{12}N_2O_3S$ requires C, 52·4; H, 4·8; N, 11·1; S, 12·7%).

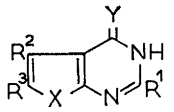
(*b*) A moderately dilute solution of the acylated *o*-aminonitrile in absolute ethanol was saturated with dry hydrogen chloride and then heated under reflux for 0·5 hr. After 12 hr. at room temperature, the mixture was poured into ice–water; ammonium hydroxide was added to raise the pH to 10 and the precipitate was filtered off. Crystallisation of the crude material from ethanol or dimethylformamide–methanol mixture afforded the required compounds.

Physical and analytical data for the pyrimidones and pyrimidinethiones are recorded in the Table.

Synthesis of Pyrimidinethione by Use of Trifluoroacetic Acid.—A solution of 2-amino-4,5-diphenylfuran-3-carbonitrile (XVI) (3·5 g.) and thioacetamide (4·0 g.) in trifluoroacetic acid was heated overnight on a steam-bath. The mixture was cooled and then poured into excess of

[10] M. T. Bogert and W. F. Hand, *J. Amer. Chem. Soc.*, 1902, **24**, 1031.
[11] K. Gewald, *Chem. Ber.*, 1966, **99**, 1002.

Thieno- and furo-pyrimidinethiones and -pyrimidones



	R^1	R^2	R^3	X	Y	Yield (%)	M.p. (solvent)	Analysis [a] (%)
(II)	Me	$[CH_2]_4$		S	S	33	298—300° * (DMF) †	C, 55·75 (55·95); H, 5·05 (5·1); N, 11·65 (11·85); S, 27·15 (27·1)
(III)	Ph	$[CH_2]_4$		S	S	50 [b]	268—270 * (DMF)	C, 50·7 (50·65); H, 4·15 (3·95); N, 7·3 (7·4); S, 16·8 (16·9)
(XII)	Me	$[CH_2]_5$		S	S	25	>340 (EtOH)	C, 57·3 (57·6); H, 5·45 (5·3); N, 11·05 (11·2); S, 25·8 (25·55)
(IX)	Me	Cholest-2-eno		S	S	30	220 * (DMF)	C, 75·4 (75·25); H, 9·5 (9·85)
(VI)	Me	$[CH_2]_4$		S	O	60	270—271 (DMF)	C, 60·05 (60·0); H, 5·35 (5·5); N, 12·85 (12·7); S, 14·5 (14·5)
(VII)	Ph	$[CH_2]_4$		S	O	65	287 (DMF)	C, 68·1 (68·1); H, 5·1 (5·0); N, 9·65 (9·9); S, 11·05 (11·3)
(XV)	Me	Me	CO_2Et	S	O	78	257 (DMF)	C, 52·9 (52·6); H, 4·9 (4·75); N, 11·05 (11·1); S, 12·85 (12·7)
(XVIII)	Me	Me	Me	O	S	80	275 * (DMF–H_2O)	C, 55·5 (55·65); H, 5·15 (5·2); N, 14·35 (14·45) S, 16·3 (16·5)
(XIX)	Me	Ph	Ph	O	S	50 [c]	300 * (DMF)	C, 67·45 (67·7); H, 4·1 (4·0); N, 8·3 (8·6); S, 9·45 (9·2)
(XVII)	Me	Ph	Ph	O	O	40	348 * (DMF)	C, 75·4 (75·5); H, 4·6 (4·6); N, 9·35 (9·25)

[a] Calc. values in parentheses. [b] Values calc. for hydrobromide. [c] Values calc. for hydrofluoride.

* Decomp. † Dimethylformamide.

ice–water. Crystallisation of the yellow solid from dimethylformamide afforded (XIV) (50%), m.p. 300° (decomp.).

Similarly (I) (1·78 g.) and thioacetamide (2 g.) in trifluoroacetic acid (20 ml.) were heated for 4 hr. on a steam-bath. The mixture was poured into ice–water. The yellow solid was stirred with ammonium hydroxide for 15 min. and finally washed with water. Two crystallisations from from ethanol gave analytically pure monohydrate of the thiopyrimidone (II) (40%), m.p. 186—187°.

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