Preparation of 4-Pyrimidinethiones from Acyl Isothiocyanate-Enamine Adducts

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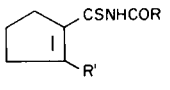
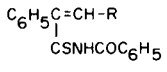
Adducts formed from benzoyl isothiocyanate and 1-morpholinocyclopentene or β-(*N*,*N*-diethylamino)styrene and that prepared from acetyl isothiocyanate and 1-pyrrolidinocyclopentene gave 4-pyrimidinethiones when treated with primary amines or ammonia. In some cases intermediates, the products of amine exchange, were isolated. These intermediates were readily cyclized to 4-pyrimidinethiones with dilute alkali.

Preparations of 4-pyrimidinethiones have recently been reported involving the reaction of acyl isothiocyanates with primary and secondary enamines (1-3). The reaction of benzoyl isothiocyanate with 1-morpholinocyclohexene was shown to give 5,6,7,8-tetrahydro-2-phenyl-1,3-benzoxazine-4-thione (4), which, upon treatment with primary amines or ammonia, yielded 5,6,7,8-tetrahydro-2-phenyl-4-quinazolinethiones (5). Recent work in this laboratory has shown that 4-thiouracils can be prepared by direct treatment of ethoxycarbonyl isothiocyanate-tertiary enamine adducts with primary amines or ammonia (6). This paper deals with the similar use of adducts prepared from acetyl and benzoyl isothiocyanate in the synthesis of 4-pyrimidinethiones.

The enamine adducts I-III were stable solids and were used for subsequent work. Acetyl isothiocyanate gave, with other enamines, products that were oils at room temperature. These were not further investigated (7). The properties of the adducts I-III (as well as intermediates IV-VII) are shown in Table I.





I R = C_6H_5; R' = 

II R = CH_3, R' = 

III R = $N(C_2H_5)_2$

IV R = C_6H_5; R' = NHC_6H_5

V R = C_6H_5; R' = $NH(CH_2)_2OH$

VI R = $NHCH_2C_6H_5$

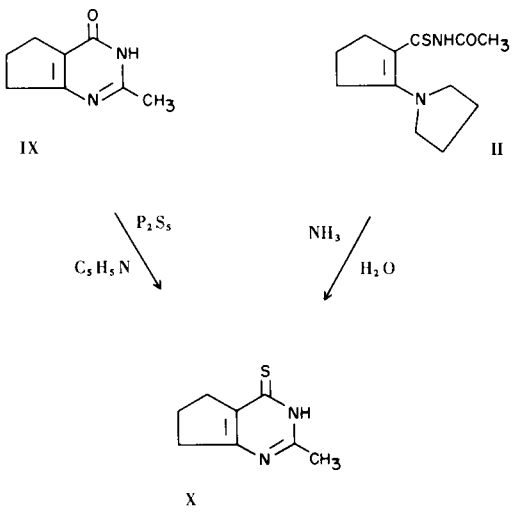
VII R = NHC_6H_{11} (cyclohexyl)

Treatment of I-III with an excess of primary amine or ammonia at room temperature led to the 4-pyrimidinethiones listed in Tables II and III. In a few cases, the products isolated proved to be the uncyclized intermediates (IV-VII) resulting from simple replacement of the secondary amine moiety by that of the primary amine. The intermediates readily cyclized to the pyrimidine derivatives in the presence of dilute alkali (*e.g.*, IV → XI, Scheme B). The adduct I with a large excess of aqueous 2-aminoethanol produced directly 6,7-dihydro-1-(2-hydroxyethyl)-5*H*-cyclopenta[*d*]pyrimidine-4(1*H*)-thione. However, with a much smaller excess (*ca.* 10%) of 2-aminoethanol in ethanol, compound I yielded the intermediate V.

The assigned structures of the compounds in Table II and III were supported by microanalytical data and spectra, including the nmr spectra of representative products. Supporting chemical evidence is illustrated in Schemes A and B. The known 6,7-dihydro-2-methyl-5*H*-cyclopenta[*d*]pyrimidin-4(3*H*)-one (IX) (8) was prepared and thiated to give a product identical with that obtained from II with concentrated ammonia (X). Benzoyl isothiocyanate and cyclopentanone anil formed an adduct which was indistinguishable from the product IV obtained from I with aniline (9).

The isolation of the uncyclized intermediates supported a stepwise amine exchange-cyclization mechanism for the conversion of adducts I-III into 4-pyrimidinethiones. A similar sequence was suggested for 4-thiouracil formation (6,10).

SCHEME A



SCHEME B

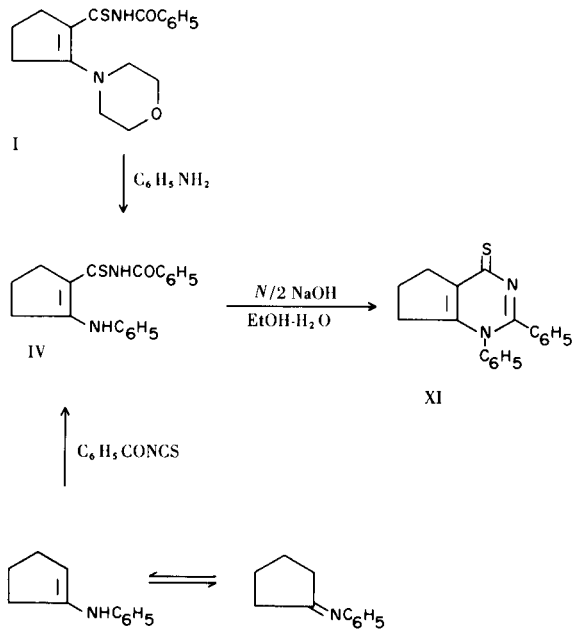


TABLE I

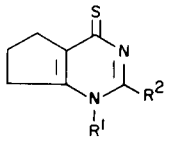
Intermediates

Structure	Yield(a) %	M.p.(b) °C	Recrystn. Solvent	Molecular Formula	Elemental Analysis Calcd C	H	N	S	Found C	H	N	S	λ max (c)	ε x 10^{-3}
I(d)	96	129-130 dec(e)		$C_{17}H_{20}N_2O_2S$									308 436 (e)	11.4 9.9
II	84	154-155 dec	Methanol-ethyl acetate	$C_{12}H_{18}N_2OS$	60.5	7.6	11.8	13.5	60.6	7.6	12.0	13.3	300 406	9.8 14.7
III	52	131-132 dec	Chloroform-ligroin(f)	$C_{20}H_{22}N_2OS$	71.0	6.6	8.3	9.5	70.8	6.7	8.2	9.3	300 405	18.3 17.1
IV	92	168-170 dec	Chloroform-ethanol	$C_{19}H_{18}N_2OS$	70.8	5.6	8.7	9.9	70.5	5.8	8.6	9.8	303 425	11.7 15.1
V	63	135-136 dec	Methanol	$C_{15}H_{18}N_2O_2S$	62.1	6.3	9.7	11.0	62.2	6.2	9.5	10.8	288 405	14.0 21.0
VI	75	140-144 dec	Chloroform-ligroin(f)	$C_{23}H_{20}N_2OS$	74.2	5.4	7.5	8.6	74.1	5.7	7.3	8.3	302 398	16.1 20.0
VII	85	165-166 dec	Chloroform-ethanol	$C_{22}H_{24}N_2OS$	72.5	6.6	7.7	8.8	72.4	6.7	7.5	8.8	282(g) 300 400	12.3 12.5 18.3

(a) Crude material. (b) Uncorrected. (c) Solvent, chloroform. (d) Previously reported without m.p. See reference 11. (e) Determined from crude material. (f) Precipitation by addition of ligroin (b.p. 35-60°) to a chloroform solution. (g) Shoulder.

TABLE II

6,7-Dihydro-5*H*-cyclopenta[*d*]pyrimidine-4-(1*H*)-thiones



						Elemental Analysis									
						Calcd				Found				λ max	ε x 10^{-3}
R^1	R^2	Yield %(a)	M.p. °C (b)	Recrystn. Solvent	Molecular Formula	C	H	N	S	C	H	N	S	(c)	
H (d)	C_6H_5	79	195-197 dec	Methanol	$C_{13}H_{12}N_2S$	68.4	5.3	12.3	14.1	68.4	5.4	12.1	14.0	243 308 354	19.4 12.4 5.5
CH_3	C_6H_5	76	240-244 dec	Acetonitrile	$C_{14}H_{14}N_2S$	69.4	5.8	11.6	13.2	69.2	5.8	11.4	13.4	249 342	8.2 17.5
C_6H_5	C_6H_5	80 (e)	243-245 dec	Ethanol	$C_{19}H_{16}N_2S$	75.0	5.3	9.2	10.5	74.8	5.0	8.9	10.7	253 345	10.6 19.0
CH_2CH_2OH	C_6H_5	80 (f)	227-229 dec	Ethanol	$C_{15}H_{16}N_2OS$	66.2	5.9	10.3	11.8	66.0	5.9	10.5	12.0	245 342	9.7 24.4
CH_2CH_2 	C_6H_5	40	200-201 dec	Ethanol	$C_{19}H_{23}N_3OS$	66.8	6.8	12.3	9.4	66.7	6.9	12.0	9.1	246 343	10.3 24.3
H (d)	CH_3	89	234-236 dec	Methanol	$C_8H_{10}N_2S$	57.8	6.1	16.9	19.3	57.6	6.1	16.8	19.4	290 338	9.4 10.6
CH_3	CH_3	77	203-205 dec	Methanol-ethyl acetate	$C_9H_{12}N_2S$	60.0	6.7	15.6	17.8	60.0	6.6	15.6	18.0	239 339	6.9 23.7
CH_2CH_2OH	CH_3	72	243-245 dec	Dimethyl-formamide	$C_{10}H_{14}N_2OS$	57.1	6.7	13.3	15.2	57.3	6.6	13.6	15.0	343 (g)	25.2
CH_2CH_2COOH	CH_3	82	208-209 dec	Water	$C_{11}H_{14}N_2O_2S$	55.4	5.9	11.8	13.5	55.5	6.2	11.8	13.7	239 338	7.4 22.6

(a) Crude material. (b) Uncorrected. (c) Solvent, ethanol unless otherwise indicated. (d) Referred to in the text as the 3*H* form. (e) Yield obtained from IV. (f) Yield obtained directly from I with 2-aminoethanol. Obtained from V with dilute alkali in 71% yield. (g) Solvent, DMF.

EXPERIMENTAL

Ultraviolet spectra were determined using a Cary Model 14 or Model 11MS Spectrophotometer. Infrared spectra were obtained from potassium bromide discs using a Baird-Atomic Model NK-1 Spectrophotometer unless otherwise indicated. The nmr spectra were determined with a Varian A-60 instrument using tetramethylsilane as internal standard.

1-(*N*-Benzoylthiocarbamoyl)-2-morpholinocyclopentene (I).

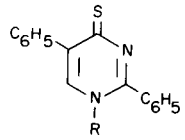
This material was prepared by the method of Hünig, Hübner and Benzig (11) and was used without purification, m.p. 129-130° dec. Infrared, 3.15 (NH), 5.95 μ (C=O). The nmr spectrum (deuteriochloroform) showed no vinyl protons and was otherwise consistent with structure I.

1-(*N*-Acetylthiocarbamoyl)-2-pyrrolidinocyclopentene (II).

To a solution of 13.7 g. (0.10 mole) of 1-pyrrolidinocyclopentene in 10 ml. of dry ether was added dropwise, with cooling, 10.1 g. (0.10 mole) of acetyl isothiocyanate in 10 ml. of the same solvent. The mixture was stirred for 2 hours in the cold and the orange product was collected, washed with ether, then with 100 ml. of cold methanol, and finally with more ether. The product weighed 20.0 g., m.p. 149-150° dec. Recrystallization from ethyl acetate containing a little methanol gave II as orange prisms, m.p. 154-155° dec. Infrared, 3.15 (NH), 5.95 μ (C=O); nmr (deuteriochloroform), δ 1.3-2.0 (β-CH_2 of both rings), 2.10 (CH_3CO), 2.51-2.82 (CH_2 adjacent to double bond), 3.50 (multiplet, CH_2-N), 9.0 (NH).

TABLE III

2,5-Diphenyl-4-(1*H*)-pyrimidinethiones



R	Yield % (a)	M.p. (b) °C	Recrystn. Solvent	Molecular Formula	Elemental Analysis Calcd. C	H	N	S	Found C	H	N	S	λ max (c)	ε x 10^{-3}
CH_3	73	214-216 dec	Chloroform-ethanol	$C_{17}H_{14}N_2S$	73.4	5.1	10.1	11.5	73.4	5.0	9.9	11.5	351 (d)	16.9
CH_2CH_2OH	60	221-223 dec	Chloroform-ethanol	$C_{18}H_{16}N_2OS$	70.1	5.2	9.1	10.4	69.9	5.5	9.1	10.3	243 348	16.0 18.3
$CH_2CH_2CH_3$	81	206-208 dec	Acetonitrile	$C_{19}H_{18}N_2S$	74.5	5.9	9.1	10.5	74.4	5.9	9.0	10.2	240 348	14.9 16.8
$CH_2C_6H_5$	95 (e)	225-227 dec	Acetonitrile	$C_{23}H_{18}N_2S$	77.9	5.2	7.9	9.0	77.7	5.2	7.8	8.9	352 (d)	19.2
C_6H_{11}	82 (f)	215-217 dec (g)	Ethanol	$C_{22}H_{22}N_2S$	76.3	6.4	8.1	9.3	76.0	6.5	8.1	9.2	237 348	16.8 20.0

(a) Crude material. (b) Uncorrected. (c) Solvent, ethanol unless otherwise indicated. (d) Solvent, chloroform. (e) Yield obtained from VI. (f) Yield obtained from VII. (g) Sintered at 201°.

α-(*N*-Benzoylthiocarbamoyl)-β-(*N*,*N*-diethylamino)styrene (III).

The reactants (0.10 mole of each) (12) were combined in dry ether as above but without cooling. The red oil which initially separated solidified on stirring yielding a red solid, 17.7 g., m.p. 121-122° dec. Dilution of a chloroform solution of the product with ligroin (b.p. 35-60°) gave III as red prisms, m.p. 131-132° dec. Infrared, 3.02 (weak, NH), 5.92 μ (C=O); nmr (deuteriochloroform), δ 1.05 and 3.10 (C_2H_5), 7.38 (C_6H_5), 8.43 (β-CH), 8.7 (NH).

α-Benzoylthiocarbamoyl-β-benzylaminostyrene (VI).

A suspension of III, 3.38 g. (0.01 mole), in 40 ml. of ethanol was treated with 2 ml. of benzylamine. The mixture was stirred at room temperature for 2 hours, during which time the suspension turned from red to yellow-orange. The product (VI) was isolated by filtration, washed with a small amount of methanol, and air-dried, yield 2.78 g., m.p. 140-144° (transition, residue melted at 200-207°). Dilution of a chloroform solution of the product with ligroin (b.p. 35-60°) gave material of unchanged m.p. Infrared, 3.00 (NH), 5.92 μ (C=O); nmr (deuteriochloroform), δ 4.53 (doublet, CH_2-N), 7.34 (single peak with smaller peaks at the base, C_6H_5 and β-CH), 8.7 and 13.0 (NH). Signals due to the diethylamino group were absent.

1-Benzyl-2,5-diphenyl-4(1*H*)-pyrimidinethione.

The above intermediate (VI, 3.00 g., 8.05 mmoles) was warmed and swirled on a steam bath with 30 ml. of 0.5 *N* sodium hydroxide in 50% aqueous ethanol until a uniform suspension was obtained. The mixture was stirred at room temperature for 2 hours, filtered, and the solid was washed with ethanol, yield, 2.72 g., m.p. 225-227° dec. The infrared spectrum of the crude material showed no NH or C=O absorption (13). Recrystallization from acetonitrile gave yellow needles of unchanged m.p. Nmr (DMSO-d_6), δ 5.20 (CH_2-N), *ca.* 6.9-7.7 (C_6H_5), 7.95 (H-6).

1-Anilino-2-(*N*-benzoylthiocarbamoyl)cyclopentene (IV).

A mixture of I, 4.00 g. (0.0126 mole), 3 ml. of aniline and 35 ml. of ethanol was stirred until the red starting material was replaced by a yellow-orange product yielding 3.77 g. of IV, m.p. 164-165° dec. Recrystallization from chloroform-ethanol gave yellow-orange needles, m.p. 168-170° dec.

Cyclopentanone anil was prepared by azeotropic water removal from a refluxing benzene solution of cyclopentanone, excess aniline and a trace of *p*-toluenesulfonic acid giving a yield of 44%, b.p. 69-72° (0.3 mm).

Dropwise addition of cyclopentanone anil to an equimolar amount of benzoyl isothiocyanate in 1,2-dimethoxyethane gave a yellow-orange product (50% yield). This substance, after recrystallization, was shown to be identical with that obtained from I by mixture m.p. and comparison of infrared spectra (9).

Conversion of this product to XI was achieved with 0.5 *N* sodium hydroxide in 50% aqueous ethanol as described above for the cyclization of VI.

6,7-Dihydro-2-methyl-5*H*-cyclopenta[*d*]pyrimidine-4-(3*H*)-thione (X).

The enamine adduct (II), 6.00 g. (0.0251 mole) was stirred in 70 ml. of aqueous ammonia until it dissolved. A small amount of ethanol was added to the mixture to hasten solution. After standing overnight, the solution was concentrated and acidified to yield 3.72 g. of X as a light tan solid, m.p. 234-236° dec. Recrystallization from methanol afforded yellow needles of the same m.p.

The 4-oxo analogue (IX) was prepared by the method of Thompson (8) and thiated in 43% yield with phosphorous pentasulfide in refluxing pyridine. The product, after purification, was proved to be identical with that obtained from II by mixture m.p. and comparison of infrared spectra.

6,7-Dihydro-2-phenyl-5*H*-cyclopenta[*d*]pyrimidine-4-(3*H*)-thione.

Treatment of I with saturated ethanolic ammonia gave the product as the white, unstable ammonia salt, which rapidly decomposed on standing to the yellow ammonia-free material.

6,7-Dihydro-1-methyl-2-phenyl-5*H*-cyclopenta[*d*]pyrimidine-4-(1*H*)-thione.

To a stirred suspension of 15.0 g. (0.0474 mole) of I in 50 ml. of ethanol was added 100 ml. of 20% aqueous methylamine. The red suspension was rapidly replaced by a flocculent yellow precipitate. The mixture was stirred for one hour, filtered and the product was washed with ethanol-water (1:1), yield, 8.79 g., m.p. 230-235° dec. Recrystallization from acetonitrile gave yellow needles, m.p. 240-244° dec. The infrared spectrum showed no NH or C=O; nmr (DMSO-d_6), δ 2.00 (multiplet, C-6 protons), *ca.* 2.7-3.2 (C-5 and C-7 protons), 3.49 (CH_3-N), 7.60 (C_6H_5).

6,7-Dihydro-1-(2-hydroxyethyl)-2-methyl-5*H*-cyclopenta[*d*]pyrimidine 4-(1*H*)-thione.

A suspension of 2.00 g. (8.06 mmoles) of II in 20 ml. of ethanol was treated with 2 ml. of 2-aminoethanol. The mixture was stirred for 1.5 hours, during which time its color turned from orange to yellow. The product amounted to 1.27 g., m.p. 240-243° dec. Recrystallization from dimethylformamide gave yellow plates, m.p. 243-245° dec.

1-(2-Carboxyethyl)-6,7-dihydro-2-methyl-5*H*-cyclopenta[*d*]pyrimidine-4-(1*H*)-thione.

The enamine adduct (II), 2.38 g. (0.01 mole), and β-alanine, 1.78 g. (0.20 mole), were dissolved in 25% trimethylamine (aqueous) diluted with dimethylformamide (1:1). The solution was allowed to stand overnight and then was evaporated at reduced pressure. The residue was taken up in water and acidified giving 1.96 g. of solid, m.p. 205-207° dec. Recrystallization from water afforded yellow needles, m.p. 208-209° dec.

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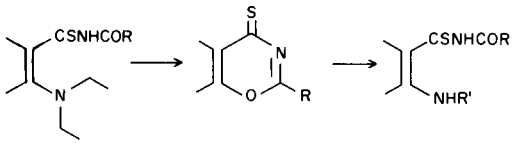
(6) R. W. Lamon, *J. Heterocyclic Chem.*, 5, 839 (1968).

(7) The product obtained from the tertiary enamines of cycloheptanone and benzoyl isothiocyanate was 6,7,8,9-tetrahydro-2-phenyl-5*H*-cyclohepta[*e*]-1,3-oxazine-4-thione, the analogue of the product reported in reference 4. The preparation will be discussed in a forthcoming communication.

(8) Q. E. Thompson, *J. Am. Chem. Soc.*, 80, 5483 (1958).

(9) The infrared spectrum of IV showed bands at 3.20 (NH) and 6.12 μ. The position of the latter band was at a higher wavelength than other carbonyl bands observed in similar compounds described here. This shift and a broad weak band at 3.85 μ may be due to internal hydrogen bonding involving an enolic form.

(10) It is possible, in view of the work described in references 4 and 5, that the amine exchange step occurs *via* a 1,3-oxazine-4-thione intermediate, *i.e.*:



(11) S. Hünig, K. Hübner and E. Benzig, *Chem. Ber.*, 95, 926 (1962).

(12) The preparation of β-(*N*,*N*-diethylamino)styrene has been described by S. Mannich and H. Davidsen, *Ber.*, 69, 2106 (1936).

(13) Determined on a Perkin-Elmer "Infracord" Spectrophotometer.

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