A New Synthesis of 4-Thiouracils

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Ethoxycarbonyl isothiocyanate has been found to form adducts with enamines which, on treatment with primary amines or ammonia, undergo apparent "amine exchange" and cyclization to 4-thiouracil derivatives. Evidence for the 4-thiouracil structure includes both spectral data and chemical transformations.

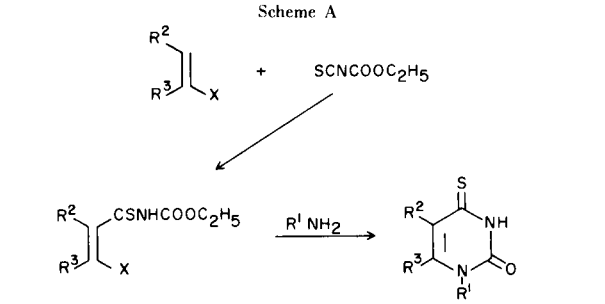
Much work has been done recently in the preparation of 4-pyrimidinethiones and related compounds from acyl isothiocyanates and enamines (1-3). Of particular relevance to the present work are the reports of Goerdeler and co-workers concerning the synthesis of certain 4-thiouracils (2,3). Their methods involved the cyclization of adducts formed from certain primary and secondary enamines and phenoxycarbonyl isothiocyanate. It is the purpose of the present paper to report a similar, but potentially more general, method for the synthesis of the 4-thiouracil ring.

Adducts formed from the reaction of ethoxycarbonyl isothiocyanate and tertiary enamines (henceforth referred to as enamine adducts) were found to undergo apparent "amine exchange" and cyclization in the presence of primary amines or ammonia. As shown in Scheme A, the products obtained were 4-thiouracils. Cyclic enamine adducts gave 4-thiouracils condensed with an alicyclic ring. Assigned structures were supported by analytical and spectral data and confirmed by chemical transformations.

Ethoxycarbonyl isothiocyanate is stable and conveniently prepared. Earlier procedures call for preparation from ethyl chloroformate and potassium thiocyanate in hot acetone (4). In the present work it was found that yields as high as 61% could be obtained by heating the reactants in acetonitrile.

Ethoxycarbonyl isothiocyanate gave the expected enamine adducts in ether or ether-petroleum ether mixtures. Table I lists the enamines used, their literature sources, and appropriate data for their adducts. Reactions of cyclic enamines with electron-deficient olefins are accompanied by a shift of the double bond toward the β'-position (5). A similar shift has been shown to occur to a major extent in the reaction of phenyl isocyanate with 1-(*N*-morpholino)-cyclohexene (6). The nmr spectra of enamine adducts I-III, run in deuteriochloroform, confirmed the structures illustrated. Lack of vinyl proton signal showed that the double bond did not rearrange. Adducts II and III were unstable at room temperature, the crystalline substances gradually changing to oils in a few days. Refrigerated samples remained intact for many months. As a precaution, analytical samples were kept cold and analyzed as soon as possible.

Scheme A



I n = 3; X = N O

II n = 4; X = N

III n = 4; X = N O

IV R^2 = H; R^3 = C_6H_5; X = N O

V R^2 = C_6H_5; R^3 = H; X = $N(C_2H_5)_2$

VI R^2 = CH_3; R^3 = H; X = N

VII R^2 = $COOC_2H_5$; R^3 = CH_3; X = $N(CH_3)_2$

R^2R^3 = $(CH_2)_n$

VIII R^1 = H; R^2 = CH_3; R^3 = H

IX R^1 = CH_2CH_2OH; R^2 = $COOC_2H_5$; R^3 = CH_3

R^2R^3 = $(CH_2)_n$

X n = 4; R^1 = CH_2CH_2OH

XI n = 4; R^1 = C_6H_5

XII n = 3; R^1 = CH_3

XIII n = 3; R^1 = H

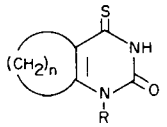
TABLE I

Enamine-Ethoxycarbonyl Isothiocyanate Adducts

Enamine (Reference) (a)	Yield of Adduct % (b)	M.p., °C (c)	Recrystn. Solvent	Molecular Formula	Calcd. C	H	N	S	Found C	H	N	S
1-(*N*-Piperidino)-propene (10)	64	115-116	Ether	$C_{12}H_{20}N_2O_2S$	56.2	7.9	10.9	12.5	56.0	7.5	10.6	12.3
1-(*N*-Pyrrolidino)-butene (11)	74	75-77	Ether	$C_{12}H_{20}N_2O_2S$	56.2	7.9	10.9	12.5	56.0	7.9	11.1	12.7
β-(*N*,*N*-Diethylamino)-styrene (10)	89	113-114	Ether-ethanol	$C_{16}H_{22}N_2O_2S$	62.7	7.2	9.1	10.5	62.4	7.5	8.8	10.4
α-(*N*-Morpholino)-styrene (11)	91	162-163 dec.	Ethanol	$C_{16}H_{20}N_2O_3S$	60.0	6.3	8.7	10.0	60.1	6.2	8.6	9.9
1-(*N*-Morpholino)-cyclopentene (12)	92	124-125	Methanol	$C_{13}H_{20}N_2O_3S$	54.9	7.1	9.9	11.3	54.8	6.9	10.0	11.6
1-(*N*-Morpholino)-cyclohexene (13)	84	86-87	Ether-ligroin	$C_{14}H_{22}N_2O_3S$	56.4	7.4	9.4	10.7	56.0	7.3	9.1	10.5
1-(*N*-Pyrrolidino)-cyclohexene (14)	87	78-80	Ether	$C_{14}H_{22}N_2O_2S$	59.6	7.9	9.9	11.4	59.4	7.8	9.8	11.3
Ethyl β-(*N*,*N*-diethylamino)crotonate (15)	83	148-150 dec.	Ethanol	$C_{12}H_{20}N_2O_4S$	50.0	7.0	9.7	11.1	50.2	6.9	9.5	11.0

(a) Preparation and properties of enamines have been reviewed by Stork. See Ref. 5. (b) Yields based on crude material. (c) Uncorrected.

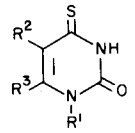
TABLE II



R	n	Yield % (a)	M.p., °C (b)	Recrystn. Solvent	Molecular Formula	Calcd. C	H	N	S	Found C	H	N	S	λ max (c)	ε x 10^{-3}
H	3	100	> 265 dec.	Ethanol	$C_7H_8N_2OS$	50.0	4.8	16.7	19.1	50.0	4.9	16.4	19.0	244	3.5
														335	20.3
CH_3	3	100	245-249 dec.	Chloroform	$C_8H_{10}N_2OS$	52.7	5.5	15.4	17.6	52.6	5.7	15.6	17.8	345 (d)	23.2
C_6H_5	3	95	> 280 dec.	Chloroform-ethanol	$C_{13}H_{12}N_2OS$	63.9	5.0	11.5	13.1	63.7	4.9	11.4	13.5	345 (d)	36.4
CH_2CH_2OH	3	89	236-238 dec.	Ethanol	$C_9H_{12}N_2O_2S$	50.9	5.7	13.2	15.1	50.9	6.0	13.0	15.2	248	3.9
														341	22.7
$CH_2COOC_2H_5$	3	91	183-184	Ethanol	$C_{11}H_{14}N_2O_3S$	52.0	5.6	11.0	12.6	51.8	5.5	10.8	13.0	248	3.6
														338	22.5
H	4	96	282-286 dec.	Ethanol	$C_8H_{10}N_2OS$	52.7	5.5	15.4	17.6	52.6	5.4	15.2	17.8	242	3.7
														334	19.1
CH_3	4	84	241-245 dec.	Ethanol	$C_9H_{12}N_2OS$	55.1	6.2	14.3	16.3	54.9	6.3	14.7	16.6	245	4.1
														340	20.1
C_6H_5	4	89	287-294 dec.	Chloroform-ethanol	$C_{14}H_{14}N_2OS$	65.1	5.5	10.9	12.4	65.0	5.6	10.7	12.6	342 (d)	24.0
CH_2CH_2OH	4	84	234-235 dec.	Ethanol	$C_{10}H_{14}N_2O_2S$	53.1	6.2	12.4	14.2	53.0	6.0	12.3	14.0	246	3.5
														340	20.8
$CH_2CH_2N\langle\rangle O$	4	80	212-213 dec.	Ethanol	$C_{14}H_{21}N_3O_2S$	56.9	7.2	14.2	10.9	56.7	7.2	14.2	10.7	245	4.0
														340	20.8
$CH_2COOC_2H_5$	4	70	171-172	Ethanol	$C_{12}H_{16}N_2O_3S$	53.7	6.0	10.4	12.0	53.6	5.8	10.1	11.6	245	3.2
														338	19.9

(a) Yields based on crude material. (b) Uncorrected. Ranges are not given where decomposition occurs evenly over a wide area of temperature. (c) Solvent, ethanol unless otherwise indicated. (d) Solvent, chloroform.

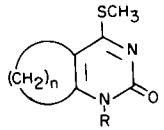
TABLE III

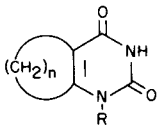


R^1	R^2	R^3	Yield % (a)	M.p., °C (b)	Recrystn. Solvent	Molecular Formula	Calcd. C	H	N	S	Found C	H	N	S	λ max (c)	ε x 10^{-3}
H	C_2H_5	H	88	>250 dec.	Methanol	$C_6H_8N_2OS$	46.1	5.2	17.9	20.5	46.2	5.4	17.9	20.5	243 333	3.8 15.5
CH_3	C_2H_5	H	90	171-172	Ethanol	$C_7H_{10}N_2OS$	49.4	5.9	16.5	18.8	49.7	6.3	16.3	18.6	247 338	4.2 17.6
C_6H_5	C_2H_5	H	83	235-236	Ethanol	$C_{12}H_{12}N_2OS$	62.0	5.2	12.1	13.8	62.1	5.2	11.8	14.0	252 340	5.6 23.0
CH_2CH_2OH	C_2H_5	H	88	213-215	Ethanol	$C_8H_{12}N_2O_2S$	48.0	6.0	14.0	16.0	47.0	6.3	13.8	16.2	246 338	4.0 18.5
$CH_2CH_2N(C_2H_5)_2$	C_2H_5	H	54	124-125	Ethanol-water	$C_{12}H_{21}N_3OS$	56.4	8.3	16.5	12.6	56.3	8.1	16.2	12.5	247 342	4.3 19.1
CH_3	C_6H_5	H	89	282-283	Aceto-nitrile	$C_{11}H_{10}N_2OS$	60.5	4.6	12.8	14.7	60.7	4.4	12.6	15.0	273 350 (d)	5.7 15.3
C_6H_5	C_6H_5	H	88	219-220	Ethanol	$C_{16}H_{12}N_2OS$	68.6	4.3	10.0	11.4	68.4	4.1	9.9	11.7	265 352 (e)	6.9 18.8
CH_2CH_2N O	C_6H_5	H	83	167-168	Ethanol	$C_{16}H_{19}N_3O_2S$	60.6	6.0	13.2	10.1	60.3	5.7	13.1	9.8	268 348	5.8 16.8
CH_2CH_2OH	$COOC_2H_5$	CH_3	80	147-148	Water	$C_{10}H_{14}N_2O_4S$	46.5	5.5	10.9	12.4	46.6	5.4	10.7	12.7	256 338	3.6 18.1

(a) Yields based on crude material. (b) Uncorrected. (c) Solvent, ethanol unless otherwise indicated. (d) Solvent, DMF. (e) Solvent, chloroform.

TABLE IV



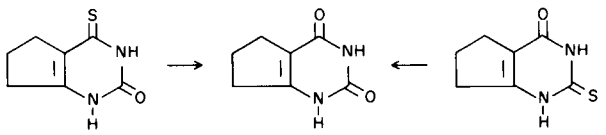
R	n	Yield % (a)	M.p., °C (b)	Recrystn. Solvent	Molecular Formula	Calcd. C	H	N	S	Found C	H	N	S	λ max	ε x 10^{-3}
C_6H_5	4	96	228-230 dec.	Dichloro-methane-ligroin	$C_{15}H_{16}N_2OS$	66.2	5.9	10.3	11.8	66.1	6.1	10.0	12.0	270 312 (c)	10.8 11.8
CH_3	3	85	141-142	Dichloro-methane-ligroin	$C_9H_{12}N_2OS$	55.1	6.2	14.3	16.3	54.8	5.9	14.2	16.1	226 264 312 (c)	9.5 9.1 11.5
															
C_6H_5	4	95	287-288 dec.	Chloroform-ethanol	$C_{14}H_{14}N_2O_2$	69.4	5.8	11.6		69.0	5.9	11.3		270 (d)	12.2
CH_3	3	73	248-249 dec.	Ethanol	$C_8H_{10}N_2O_2$	57.8	6.1	16.9		57.8	6.2	17.0		273 (e)	9.4
H	3	91	> 310 dec.	Ethanol-water	$C_7H_8N_2O_2$	55.3	5.3	18.4		54.9	5.4	18.2		268 (e)	11.6

(a) Yields based on crude material. (b) Uncorrected. (c) Solvent, methanol. (d) Solvent, chloroform. (e) Solvent, ethanol.

Allowing the enamine adducts to stand in aqueous or alcoholic primary amine or ammonia solutions gave 4-thiouracils of the types shown in Scheme A. In at least one case, dimethylformamide was found to be a useful solvent. The enamine adduct (IV) from α-(*N*-morpholino) styrene was unreactive under these conditions. By contrast, the adduct (V) obtained from β-(*N*,*N*-diethylamino)styrene gave good yields of the expected 5-phenyl-4-thiouracils. The lack of reactivity of IV establishes a limitation on the method of steric and/or electronic origin. Tables II and III list the 4-thiouracils prepared in the present work, with appropriate data.

The structures of the products were supported in each case by combustion analyses and infrared spectra. The ultraviolet absorption curves of all the proposed 4-thiouracils were consistent with each other and with the known 4-thiothymine, allowing for possible substituent and solvent effects (Tables II and III). The nmr spectra of a representative group of products were consistent with assigned structures. The products were soluble in cold, dilute alkali. That the secondary amine moiety of the enamine adduct was eliminated during the reaction with primary amine was shown by the synthesis of the identical substance (X) from 2-aminoethanol with either II or III. In addition, cyclohexanone anil and ethoxycarbonyl isothiocyanate, when heated together in 1,2-dimethoxyethane, gave, in poor yield, a substance identical with that obtained from aniline and III (7). Products formed from methylamine and I and aniline and III were desulfurized by standard methylation-hydrolysis procedures. Thiation of the resulting products gave the original proposed 4-thiouracils (XI and XII). The product obtained from alcoholic ammonia and enamine adduct VI was identical with an authentic specimen of 4-thiothymine (VIII) (8). The known 6,7-dihydro-4(3*H*)-oxo-5*H*-cyclopenta[*d*]pyrimidine-2(1*H*)-thione (XIV, Scheme B) was

Scheme B

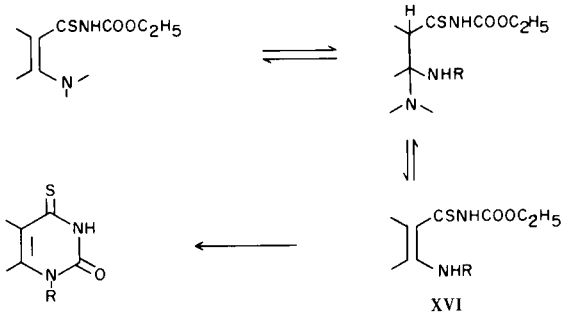


XIII XV XIV

prepared (9) and hydrolyzed in aqueous chloroacetic acid. The product obtained from enamine adduct I and ammonia gave a chloroacetic acid hydrolysis product identical with that obtained from XIV (XV). The enamine-ammonia reaction product must therefore have possessed structure XIII. The latter material could be regenerated by thiation with phosphorus pentasulfide in damp pyridine. An interesting extension of the title method was the preparation of the 4-thiouracil IX from the adduct (VII) obtained from ethyl β-dimethylaminocrotonate. The adduct was allowed to stand overnight with excess 2-aminoethanol in dimethylformamide, giving IX in 80% yield.

A possible mechanism for the enamine adduct cyclization reaction is illustrated in Scheme C. The path illustrated seems reasonable since ready cyclization of structures analogous to XVI is well documented (1-3).

Scheme C



XVI

EXPERIMENTAL (16)

Ethoxycarbonyl Isothiocyanate.

A mixture of 700 ml. of dry acetonitrile and 194 g. (2.0 moles) of potassium thiocyanate was warmed on a steam bath and treated, portion-wise, with 217 g. (2.0 moles) of ethyl chloroformate. Heating was continued until the reaction mixture became hot and the inorganic precipitate thickened rapidly. At this point the mixture became yellow. The heat source was removed and the reaction allowed to run its course. The mixture was permitted to cool slowly to room temperature, chilled, and suction-filtered. The filtrate was concentrated under reduced pressure and the residual oil distilled, yield, 161 g., b.p. 51-55° (13 mm.). Redistillation at 10 mm. showed that the bulk of the material distilled at 44-46°. The infrared spectrum agreed with the published curve (17).

1-(*N*-Carbethoxythiocarbamoyl)-2-(*N*-morpholino)cyclopentene (I).

To a cooled solution of 15.3 g. (0.10 mole) of 1-(*N*-morpholino)cyclohexene in 60 ml. of dry ether was added, dropwise, 13.1 g. (0.10 mole) of ethoxycarbonyl isothiocyanate diluted with 15 ml. of dry ether. A red-orange precipitate appeared during the addition. The mixture was stirred in the cold for 3-4 hours, filtered, washed thoroughly with dry ether, and air-dried, yield, 26.2 g., m.p. 123-124°. Two recrystallizations from methanol gave an analytical sample as red crystals, m.p. 124-125°.

Enamine adducts II, IV, V, and VII were similarly prepared. Products III, VI, and that of 1-(*N*-pyrrolidinobutene) were prepared in ether-petroleum ether. If no precipitate occurred in the cold, stirring at room temperature for several hours and then chilling the mixture gave satisfactory yields.

The nmr spectrum of I (in deuteriochloroform) showed the expected triplet (δ 1.30) and quartet (δ 4.18) due to the ethyl

group. In addition, multiplets were observed centered at δ 1.80 and 2.73 (homoallylic and allylic protons of the cyclopentene ring) and at 3.33 and 3.80 (protons of the morpholine ring) with the appropriate relative areas. The NH signal appeared at 9.5. The nmr spectra of II and III showed, analogously, expected signals for the cyclohexene ring protons and the protons of the cyclic amine moieties. The signals for the lone NH protons appeared at δ 8.50 and 10.8, respectively.

6,7-Dihydro-1-methyl-2(1*H*)-oxo-5*H*-cyclopenta[*d*]pyrimidine-4(3*H*)-thione (XII).

Ten grams (0.036 mole) of I was treated with sufficient 40% aqueous amine to effect solution. After standing at room temperature for 12 hours, the solution was concentrated under reduced pressure to remove most of the methylamine. Dropwise acidification with concentrated hydrochloric acid to *p*H 3 precipitated the product, which amounted to 6.5 g. Two recrystallizations from chloroform gave analytically pure material as yellow prisms, m.p. 245-249° dec.

5,6,7,8-Tetrahydro-2(1*H*)-oxo-1-phenyl-4(3*H*)-quinazolinethione (XI).

Eight grams (0.027 mole) of III was partially dissolved in 50 ml. of ethanol. The stirred mixture was treated with 6 ml. of aniline and complete solution of the mixture occurred. In a few minutes, the product precipitated. The mixture was stirred for an additional 30 minutes and the solid was isolated by filtration. After the solid had been thoroughly washed with ethanol and air-dried, the product weighed 6.2 g. It darkened above 270° and liquefied at 280-282°. Two recrystallizations from chloroform-ethanol gave pure material as yellow plates, m.p. 287-294° dec.

Cyclohexanone anil was prepared by the azeotropic water-removal method in benzene and showed b.p. 103° at 1 mm. The infrared spectrum was identical with that published (18). Refluxing this substance with ethoxycarbonyl isothiocyanate for 1 hour gave a poor yield (15%) of a substance having m.p. 287-294° dec., with no change on admixture of XV. The infrared spectra of the products were identical.

5-Carbethoxy-1-(2-hydroxyethyl)-6-methyl-4-thiouracil (IX).

Five grams (0.017 mole) of VII was dissolved in dimethylformamide and 3.5 ml. of 2-aminoethanol was added. After standing overnight, the mixture was concentrated under vacuum, the residue taken up in 60 ml. of water, and the solution acidified. The off-white precipitate weighed 3.6 g., m.p. 145-147°. Two recrystallizations after treatment with charcoal gave pale yellow prisms, m.p. 147-148°.

4-Thiothymine (VIII).

The enamine adduct (VI) was dissolved in ethanol and treated with excess ethanolic ammonia. After several hours, the partially precipitated product was removed and a nearly equal amount was isolated by concentration of the mother liquor, solution of the residue in water, and acidification (yield, 86%). The combined solids were recrystallized from boiling water as fine yellow needles, m.p. 306-307° dec.; λ max (DMF) 338 mμ (ε, 16,300). Authentic 4-thiothymine, prepared by the thiation of thymine (8), did not depress the melting point on admixture. The infrared spectra of the two products were identical.

Methylation of XI and XII and Hydrolysis of the Methylation Products.

The methylation of XI and XII was accomplished by dissolving the starting material in an equivalent of aqueous alkali and treating it with a slight excess of methyl iodide. The product formed from XI precipitated immediately. The methylation product of XII was obtained by extraction of the reaction mixture with chloroform, drying and concentrating the extract, and stirring the residue with 1:1 ether-petroleum ether. Table IV gives appropriate data for these compounds.

The methylation products mentioned were hydrolyzed by suspending them in 2*N* hydrochloric acid and refluxing for 2 hours. Yields and other pertinent data are given in Table IV.

Regeneration of XI and XII by Thiation.

The desulfurized products of XI and XII were rethiated to give the starting materials in 65 and 48% yields, respectively. The procedures used were analogous to the procedure used in the thiation of thymine (8). The crude products were crystallized from chloroform-ethanol and chloroform, respectively, and the identity of these products with original XI and XII was demonstrated by mixture melting points and comparison of infrared spectra.

6,7-Dihydro-4(3*H*)-oxo-5*H*-cyclopenta[*d*]pyrimidine-2(1*H*)-thione (XIV).

This material was prepared in 35% yield by the procedure of Polonovski and Libermann (9), m.p. > 310° dec. (lit. 340° dec.); λ max (ethanol), 282 mμ (ε, 18,400).

Chloroacetic Acid Hydrolysis of XIII and XIV to 6,7-Dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4(1*H*,3*H*)-dione (XV).

Refluxing XIV with an equal weight of chloroacetic acid in 8 volumes of water gave the desulfurized product XV (see Table IV).

The product (XIII) obtained from I and ammonia was subjected to the same hydrolysis procedure. The product had m.p. > 310° dec. Its infrared spectrum and x-ray powder diffraction pattern were identical with those of the hydrolysis product of XIV.

Thiation of XV.

The hydrolysis product of XIV (1.52 g., 0.010 mole) was refluxed with 6.66 g. (0.030 mole) of phosphorus pentasulfide in 80 ml. of pyridine for 2.5 hours. During the reflux period a total of 0.8 ml. of water (19) was added with an eye dropper, a few drops at a time. The reaction mixture was allowed to cool and stand overnight, and the liquid was decanted from a solid residue and concentrated. The resulting crude product was dissolved in ethanol (300 ml.) and treated with charcoal. The yellow solution was concentrated until crystallization commenced, yield, 0.925 g. (55.0%), m.p. and mixed m.p. with XIII > 265° dec. The x-ray powder diffraction diagrams of the two products were identical.

Acknowledgment.

The author wishes to thank the following individuals for special assistance: Dr. T. H. Regan, for nmr data and interpretations; Miss Thelma J. Davis, for assistance in interpretation of infrared spectra; and Mr. S. Marino, for the x-ray powder diffraction photographs.

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Received August 30, 1968 Rochester, New York 14650