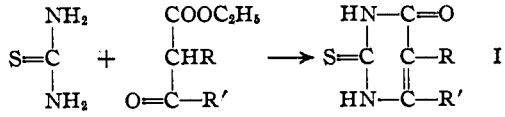
[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. X. Antithyroid Compounds. Synthesis of 5- and 6-Substituted 2-Thiouracils from β-Oxoesters and Thiourea[1]

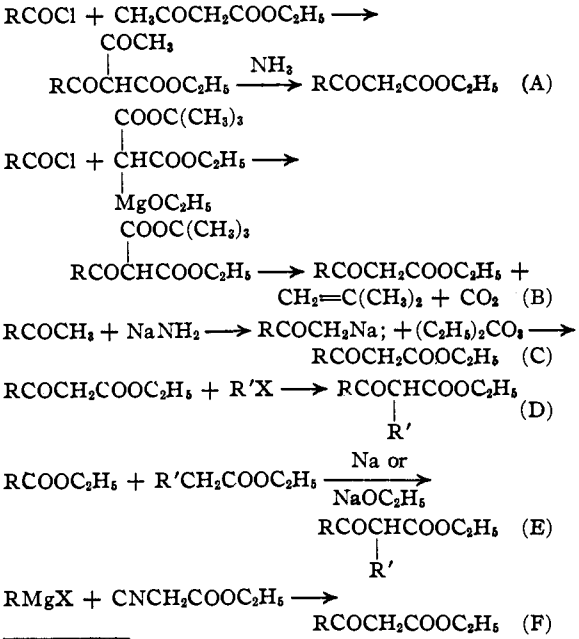
BY GEORGE W. ANDERSON, I. F. HALVERSTADT, WILBUR H. MILLER AND RICHARD O. ROBLIN, JR.

The application of thiourea and 2-thiouracil[2,3,4,5] to the treatment of hyperthyroidism in man suggested a study[6] of the preparation and properties of a series of substituted thiouracils. 2-Thiouracil was selected as the parent compound for this investigation because Astwood[7] found it to be among the most effective of a large group of substances which appear to block the synthesis of thyroxine by the rat thyroid gland.[8]

5- and 6-substituted 2-thiouracils were prepared by condensing thiourea with β-oxo esters as indicated.



The intermediate oxo esters (see Experimental) were synthesized by one of several standard procedures depending on convenience and availability of raw materials.



(1) Presented in part at the Gibson Island Conference on Medicinal Chemistry, July 6, 1945.

(2) Astwood, *J. Am. Med. Assoc.*, **122**, 78 (1943).

(3) Williams and Bissell, *Science*, **98**, 156 (1943).

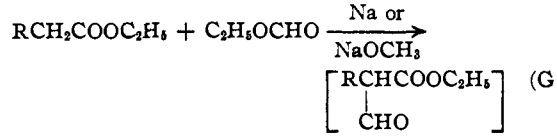
(4) Himsworth, *Lancet*, **II**, 465 (1943).

(5) *Cf.* Astwood, *J. Clin. Endocrinol.*, **4**, 229 (1944).

(6) This investigation was carried out in collaboration with Dr. E. B. Astwood and co-workers at the Department of Pharmacology, Harvard Medical School, Boston, Massachusetts.

(7) Astwood, *J. Pharmacol.*, **78**, 79 (1943).

(8) For a review of this subject see Roblin, *Chem. Rev.*, in press.



In general, method B[9] gives the best results when only small quantities of the β-oxo esters are required, because a single product is obtained in excellent yield. The limiting factor is the relative unavailability of ethyl *t*-butyl malonate. Method A[10] yields ethyl acetoacetate as a by-product and hence is not so suitable for the preparation of the lower boiling β-oxo esters. If the required ketone is available method C[11] is very convenient, although it sometimes leads to a troublesome mixture of esters. In those cases where two or more β-oxo esters of similar boiling point are formed, method E is not very satisfactory. Method F[12] is preferable for the preparation of moderate quantities of ethyl β-oxovalerate.[13]

Considerable variation in the yields of thiouracils (Table I) was observed depending on the character of the intermediate oxo ester. The low yields of the simple 5-substituted thiouracils were undoubtedly due to poor yields of the intermediate α-formyl esters (Method G), which were not isolated. In one experiment in the preparation of 5-isopropyl-2-thiouracil a significant increase in yield was obtained when the reaction mixture in the formation of α-formylisobutyric ester was cooled by ice water. This modification was not tried for the other formyl esters. Unidentified by-products were obtained in the syntheses of the longer chain (*n*-butyl, amyl and hexyl) 6-substituted thiouracils. Possibly the low yield of 5,6-trimethylene-2-thiouracil occurred as a result of a competitive opening of the ring of cyclopentanonecarboxylic ester during the reaction with thiourea. Butyrolactone was formed as a by-product in the condensation of α-acetobutyrolactone with thiourea in the synthesis of 5-β-hydroxyethyl-6-methyl-2-thiouracil.

5-Cyano-2-thiouracil was obtained in a yield of 14% from the condensation of ethyl α-cyano-β-ethoxyacrylate[14] and thiourea. Johnson and Ambler[15] reported that this condensation yielded

(9) Breslow, Baumgarten and Hauser, THIS JOURNAL, **66**, 1286 (1944).

(10) Bouveault and Bongert, *Bull. soc. chim.*, [3] **27**, 1088 (1902).

(11) Levine and Hauser, THIS JOURNAL, **66**, 1768 (1944).

(12) Blaise, *Compt. rend.*, **132**, 978 (1901); Willstätter and Clarke, *Ber.*, **47**, 298 (1914).

(13) This work was completed before the publication of the new method of Riegel and Lilienfeld, THIS JOURNAL, **67**, 1273 (1945).

(14) de Bollemont, *Bull. soc. chim.*, [3] **25**, 20 (1901).

(15) Johnson and Ambler, THIS JOURNAL, **33**, 981 (1911).

TABLE I

PROPERTIES OF 5-R, 6-R'-2-THIOURACILS

Substituted thiouracil R (=5)	R' (=6)	Anti-thyroid activity[m]	M. p., °C. (cor.)	Yield, % from β-oxo ester	Formula	Analyses, %[n] Calcd. C	H	N	S	Found C	H	N	S
Ethyl		3.5	190–192	4[a]	$C_6H_8N_2OS$	46.1	5.2		20.5	46.5	5.2		20.8
n-Propyl		2.0	161–163	10[a]	$C_7H_{10}N_2OS$	49.4	5.9	16.5		49.5	6.1	16.5	
i-Propyl		2.5	242–244	6[a]	$C_7H_{10}N_2OS$	49.4	5.9	16.5		49.3	5.9	16.4	
n-Butyl		0.6	151.5–153.5	6[a]	$C_8H_{12}N_2OS$	52.2	6.5	15.2		52.5	6.7	15.5	
	Methyl[c]	1.0	>300	63	$C_5H_6N_2OS$	42.2	4.3			42.4	4.4		
	Ethyl[d]	8	228.5–230.5	78									
	n-Propyl	11	218–219	70	$C_7H_{10}N_2OS$	49.4	5.9	16.5	18.8	49.2	5.7	16.4	19.0
	i-Propyl	9	179–180	45	$C_7H_{10}N_2OS$	49.4	5.9		18.8	49.2	5.8		18.9
	n-Butyl	3	207.5–209	31	$C_8H_{12}N_2OS$	52.2	6.6	15.2		52.1	6.4	15.4	
	i-Butyl	5	220.5–221.5	36	$C_8H_{12}N_2OS$	52.2	6.6		17.4	52.5	6.8		17.3[b]
	s-Butyl	6	222–224	55	$C_8H_{12}N_2OS$	52.2	6.6	15.2	17.4	52.3	6.5	15.2	17.3
	t-Butyl	9	178–180	43	$C_8H_{12}N_2OS$	52.2	6.6		17.4	52.2	6.4		17.5[b]
	n-Amyl[e]	1.3	153–154.5, 163–164	33									
	n-Hexyl[f]	0.18	144.5–145.5	27									
	Cyclohexyl	1.2	282–285	69	$C_{10}H_{14}N_2OS$	57.1	6.7		15.3	57.0	6.7		15.3[b]
	Phenyl[g]	1	263–264.5	45									
	p-Chlorophenyl	<0.01	289–291	21	$C_{10}H_7N_2OSCl$	50.3	3.0	11.7	13.4	50.2	3.2	11.4	13.5
	Benzyl[h]	10	223–224	71									
	Phenethyl	1.2	223.5–225.5	41	$C_{12}H_{12}N_2OS$	62.0	5.2	12.1	13.8	62.0	5.2	11.9	13.9
Methyl	Methyl[i]	1.2	283–285	42									
Methyl	Ethyl	3.5	223–224	48	$C_7H_{10}N_2OS$	49.4	5.9		18.8	49.7	6.0		18.9
Ethyl	Methyl[j]	0.9	216–218	53									
Ethyl	Ethyl	2.0	214.5–215.5	41	$C_8H_{12}N_2OS$	52.2	6.6		17.4	52.1	6.3		17.4
Trimethylene		0.3	336–337 d.	10	$C_7H_8N_2OS$	50.0	4.8		19.1	50.2	4.8		18.8
Cyano		<0.001	285 d.	14[k]	$C_5H_3N_3OS$	39.2	2.0		20.9	39.0	2.1		20.9
Carbethoxy[l]		<0.001	253–254	49	$C_7H_8N_2O_3S$	42.0	4.0			42.0	4.1		
β-Hydroxyethyl	Methyl	<0.01	265–267	13	$C_7H_{10}N_2OS$	45.1	5.4	15.0	17.2	45.3	5.8	15.1	17.1

[a] Over-all yield based on the aliphatic ester used. [b] Micro sulfurs were not reproducible; these results are from macro determinations. [c] Wheeler and McFarland, *Am. Chem. J.*, **42**, 105 (1909); prepared by Miss Anne Turrentine. [d] Robinson and Tomlinson, *J. Chem. Soc.*, 1283 (1935). [e] Yanai and Naito, *J. Pharm. Soc., Japan*, **61**, 99–107 (1941). [f] Johnson, THIS JOURNAL, **36**, 1898 (1914). [g] Johnson and Hemingway, *ibid.*, **37**, 380 (1915); prepared by Miss Anne Turrentine. [h] See ref. (31). [i] Chi and Kao, THIS JOURNAL, **58**, 769 (1936). [j] Johnson and Bailey, *ibid.*, **35**, 1010 (1913). [k] From ethyl α-cyano-β-ethoxyacrylate. See Experimental. [l] Ballard and Johnson, THIS JOURNAL, **64**, 795 (1942). [m] Thiouracil = 1.00 (weight basis); Astwood, Bissell and Hughes, *Endocrinology*, in press. [n] Micro analyses were carried out under the direction of Dr. J. A. Kuck, to whom we are indebted for these data.

only 2-mercapto-4-amino-5-carbethoxypyrimidine. While we have found that the reaction proceeds mainly in this direction, the cyano compound is also formed and can be obtained readily since it is fairly soluble in hot water whereas the former compound is almost completely insoluble.

A number of the alkyl thiouracils, particularly those substituted in the 6-position, showed considerably greater antithyroid activity in rats than 2-thiouracil itself. Maximum activity appeared to be reached when the alkyl group contained three or four carbon atoms. Of the aralkyl derivatives the 6-benzyl was highly active whereas the 6-phenethyl was about equal to 2-thiouracil. The introduction of other types of substituents usually resulted in complete loss of antithyroid action. The reason for the differences in activity is not known at present. Several of the 6-alkyl compounds as well as 6-benzyl-2-thiouracil are sufficiently more active than 2-thiouracil to warrant further study.

Experimental

Method A. Ethyl β-Oxocaproate.—The procedure of Fischer, Goldschmidt and Nüssler[16] was improved. A slurry of 0.84 mole of sodium ethyl acetoacetate in 500 ml. of dry ether (Hershberg stirrer) was treated with 0.84 mole of *n*-butyryl chloride in three hours, allowed to stand overnight, treated with 200 cc. of water and extracted with ether. The extract (600 cc.) was cooled in iced water, and treated with 40 g. of gaseous ammonia during two and one-half hours while it warmed to 25°. It was washed with water, stirred vigorously with 200 cc. of 10% hydrochloric acid for two and one-half hours, then washed with water and dilute sodium bicarbonate solution and concentrated on a steam-bath. The reddish residual liquid was extracted with five 50-cc. portions of saturated sodium bisulfite solution, washed with water, taken up in ether, dried and distilled. There was no forerun of ethyl acetoacetate and 51.7 g. (39%) of ethyl β-oxocaproate was collected at 93–94° (15 mm.).

Ethyl γ-Methyl-β-oxovalerate,[17] b. p. 89–93° (15 mm.) (41%), was also synthesized by this method but in the other cases, **ethyl β-oxoenanthate,**[18] b. p. 97–101° (9 mm.) (40%), **ethyl β-oxocyclohexanepropionate,**[19] b. p. 133–134° (10 mm.) (40%) and **ethyl β-oxo-γ-phenylbutyrate,**[20] b. p. 128–131° (3 mm.) (31%), the bisulfite extraction was unnecessary since the ethyl acetoacetate was easily separated in the fractional distillation. In the latter two cases the expected amide by-products were isolated, cyclohexanecarboxamide, m. p. 183–184° (31%) (m. p. 184–185° after recrystallization from water), and phenylacetamide, 150–154° (21%) (m. p. 160–161° after recrystallization from ethyl acetate). These amides did not depress the melting points of authentic samples.

(16) Fischer, Goldschmidt and Nüssler, *Ann.*, **486**, 31 (1931).

(17) Kroeker and McElvain, THIS JOURNAL, **56**, 1172 (1934).

(18) Blaise and Luttringer, *Bull. soc. chim.*, [3] **33**, 1103 (1905).

(19) Wahl and Meyer, *ibid.*, [4] **3**, 959 (1908)] gave 138–142° (13 mm.) and Zelinsky and Schwedoff, [*Ber.*, **40**, 3055 (1907)] gave 135–137° (18 mm.).

(20) Borsche and Hahn, *Ann.*, **537**, 244 (1939).

Method B.—**Ethyl β-oxovalerate**[9] (60%), **ethyl γ-methyl-β-oxocaproate,** b. p. 92–97° (10 mm.) (49%) (*Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.8; H, 9.3. Found: C, 62.8; H, 9.3), **ethyl β-(4-chlorophenyl)-β-oxopropionate,**[21] b. p. 132–142° (1 mm.) (82%) and **ethyl β-oxo-δ-phenylvalerate,**[22] b. p. 136–144° (61%) (*Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.9; H, 7.4), were prepared by this procedure.

Method C.—The following compounds were synthesized: **ethyl γ-methyl-β-oxocaproate,**[11] b. p. 96–100° (14 mm.) (68%), **ethyl γ,γ-dimethyl-β-oxovalerate,**[11] b. p. 91–95° (14.5 mm.) (43%), **ethyl β-oxocaprylate,**[21] b. p. 114–120° (14 mm.) (57%) and **ethyl β-oxopelargonate,**[11] b. p. 120–126° (10 mm.) (61%).

Method D.—**Ethyl α-methylacetoacetate,**[23] b. p. 75–77° (15 mm.) (45%), **ethyl α-ethylacetoacetate,**[24] b. p. 79–82° (12 mm.) (58%), and **ethyl α-ethyl-β-oxovalerate,** b. p. 83–85° (8 mm.) (75%) (*Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.8; H, 9.3. Found: C, 62.5; H, 9.3) were obtained by this method.

Method E was employed for the preparation of **ethyl α-methyl-β-oxovalerate,**[25] b. p. 81–83° (11 mm.) (26%) and **2-carbethoxycyclopentanone,**[26] b. p. 106–109° (12.5 mm.) (71%).

Method F. Ethyl β-oxovalerate.—The procedure was patterned after Willstätter and Clarke's[12] modification of Blaise's[12] synthesis. The preparation is given in detail because the yields recorded in the literature for this reaction have varied widely and Hauser and Hudson[27] have stated that the method does not appear to be satisfactory.

The Grignard reagent was prepared in the usual manner from 38.9 g. (1.60 atoms) of magnesium and 141 cc. (272 g., 1.74 moles) of ethyl iodide in 250 cc. of dry ether, the diluted halide being added in four hours while the temperature was held near 30° by a cold water-bath. The ethylmagnesium iodide solution was stirred vigorously (Hershberg stirrer) and maintained at 25–30° while 66 cc. (72 g., 0.62 mole) of redistilled ethyl cyanoacetate diluted with 100 cc. of dry ether was added in two and one-half hours. The homogeneous, bluish-green, slightly viscous oil was allowed to stand for sixty hours (no change in appearance) and then decomposed by the addition of saturated ammonium chloride solution.[28] A total of 250 cc. of ammonium chloride solution, 250 cc. of water, and 120 cc. of concentrated hydrochloric acid were added in that order to clarify the aqueous layer. It was extracted several times with ether, strongly acidified with 50 cc. of concentrated hydrochloric acid and again ether extracted. The ether extracts were combined and vigorously stirred with 200 cc. of 10% hydrochloric acid for three hours at room temperature in order to hydrolyze any β-imino ester. The aqueous layer was separated and extracted once with ether. The ether layers were combined, washed with water and saturated sodium bicarbonate solution, dried with sodium sulfate and distilled, the fraction from 75–90° at 9.5 mm. being collected. Careful redistillation of this slightly yellowish 54.9 g. fraction yielded 52.0 g. (58%) of water white product, boiling sharply at 77–77.5° at 8.5 mm. This ester was also prepared in 60% yield by method B and in 12% yield by method E.[29] It was found that only 20–35% of the β-oxo ester present was isolated by shaking with a saturated aqueous solution of cupric acetate. This copper salt melted at 148–149° (cor.).[30]

(21) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2252 (1941).

(22) Henze and Holder, *ibid.*, **66**, 1545 (1944).

(23) Brühl, *J. prakt. Chem.*, [2] **50**, 128 (1894).

(24) Conrad and Limpach, *Ann.*, **192**, 155 (1878).

(25) Roberts and McElvain, THIS JOURNAL, **59**, 2007 (1937).

(26) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 119.

(27) Hauser and Hudson, "Organic Reactions," Vol. I, Roger Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 300.

(28) Decomposition with water might have led to equivalent results.

(29) Wahl and Doll, *Bull. soc. chim.*, [4] **13**, 267 (1913).

(30) Dupont, *Compt. rend.*, **148**, 1524 (1909), found m. p. 144–145°.

Thiouracils

6- and 5,6-Alkyl Substituted Thiouracils.—Sodium metal (2.3 g., 0.10 g. atom) was dissolved in 50 cc. of anhydrous ethanol and 5.33 g. (0.07 mole) of thiourea and 0.05 mole of the appropriate β-oxo ester were added to the clear solution. The mixture was heated on a steam-bath and yielded a clear solution in about ten minutes. Shortly afterward a precipitate began to form and did not change greatly in appearance after two hours. The total time of heating was six to seven hours and the mixture was allowed to stand overnight. It was distilled *in vacuo* at 40–50° until near dryness and the residue was dissolved in 50 cc. of water. The product was precipitated by the addition of 7 cc. of concentrated hydrochloric acid and subsequent acidification to *p*H 4 with glacial acetic acid. The crude thiouracil was filtered off, washed and dried at 80°.

Most of the crude thiouracils were purified by recrystallization from boiling water. The compound and the parts of boiling water required to dissolve it (crude) are: 6-ethyl, 25; 6-*n*-propyl, 60; 6-*i*-propyl, 20; 6-*n*-butyl, 80; 6-*i*-butyl, 140; 6-*s*-butyl, 110; 6-*t*-butyl, 30; 6-*n*-amyl, 200; 6-*n*-hexyl, 350; 5,6-dimethyl, 65; 5-methyl-6-ethyl, 35; 5-ethyl-6-methyl, 45; 5,6-diethyl, 95; 5,6-trimethylene, 190; and 5-β-hydroxyethyl-6-methyl, 75. In the cases of 6-*n*-amyl and 6-*n*-hexyl better yields were obtained if the crude products were fractionally crystallized by continuous hot ether extraction, the impurities being more soluble than the thiouracil. It was found that fractions so obtained melting 10–15° below the melting point of the pure product could not be efficiently purified by ether extraction but could be obtained in pure state and in good recovery by a single recrystallization from boiling water. These crystals from water were flaky and an additional hot extraction with ether yielded smaller, more compact crystals which were much easier to handle.

6-Methylthiouracil was purified by solution in aqueous alkali and precipitation with acid. 6-Cyclohexylthiouracil was purified by continuous hot extraction with ethanol, 10 cc./g. 6-Benzylthiouracil was hot extracted continuously with 5 cc./g. of ethanol to remove most of the yellow color and a colorless product was obtained by recrystallization from glacial acetic acid, 10 cc./g. The following were crystallized from glacial acetic acid (cc./g.): 6-phenyl, 25; 6-*p*-chlorophenyl, 50; and 6-phenethyl, 10.

5-Propyl-2-thiouracil.—The procedure was modified from that of Johnson and Ambelang[31] for the synthesis of 5-benzyl-2-thiouracil. A solution of 28.6 cc. (25 g. or 0.192 mole) of ethyl valerate and 30.8 cc. (28.4 g. or 0.384 mole) of ethyl formate was added during four hours to a stirred mixture of 4.85 g. (0.21 g. atom) of sodium wire in 100 cc. of dry ether. Hydrogen was evolved, the reaction mixture darkened, and for a time spontaneous refluxing was noted. Six hours after the start, little reaction was apparent and the mixture stood overnight. Solvent and unreacted esters were removed at room temperature using successively water vacuum and Hy-vac pump. Nine and seventy-five hundredths grams (0.128 mole) of powdered thiourea and 85 cc. of absolute ethanol were added to the residue and the mixture refluxed for seven hours on a steam-bath. Ethanol was removed *in vacuo* with slight external warming and the dried residue dissolved in 100 cc. of water. The brown solution was acidified with hydrochloric acid and the resulting oily mixture extracted with ether; none of the desired product was obtained from the aqueous fraction. After the dried ether solution was distilled *in vacuo*, the oily residue was filtered during six hours, leaving 4.9 g. of solid. This was boiled with 50 cc. of water using Norit and 3.4 g. of product (10% yield based on ethyl valerate) was obtained on cooling. Further recrystallizations did not alter the m. p. of 161–163.5° (cor.).

The same procedure was used to prepare 5-*n*-butyl-2-thiouracil and 5-isopropyl-2-thiouracil. The yield of the 5-isopropyl compound was so poor (1.6%) that another preparation was run and the flask immersed in an ice-bath during the more vigorous part of the reaction of the esters.

(31) Johnson and Ambelang, THIS JOURNAL, **60**, 2941 (1938).

The yield was considerably better (6.3%) and suggests that this modification should be considered in other similar preparations.

5-Ethyl-2-thiouracil was prepared by a somewhat different procedure. The sodium salt of methyl formylbutyrate was obtained by condensation of 90 g. (1.5 moles) of methyl formate and 152 g. (1.5 moles) of methyl butyrate with 81 g. (1.5 moles) of sodium methylate in 250 cc. of anhydrous ether by allowing to stand four days, analogous to the preparation of the corresponding ethyl ester by Johnson and Menge.[32] When 57 g. (0.75 mole) of thiourea was added with stirring, there was little change even on four hours of standing. The ether was distilled off and 200 cc. of absolute alcohol was added. Part of the solvent was distilled off to raise the reflux temperature to 72°. After an hour of refluxing, the product was cooled and dissolved in 250 cc. of water. This was allowed to stand overnight, separated from a few cc. of oil and acidified with acetic acid. Overnight chilling gave 11.35 g. of product, and concentration of the filtrate gave a mixture of the thiouracil with thiourea. This was recrystallized from water to remove the thiourea and then combined with the first fraction. Three recrystallizations from water, using Darco, and one from isopropanol yielded 8.45 g. (3.6%, based on the methyl butyrate used) of colorless 5-ethyl-2-thiouracil, m. p. 190–192° (cor.) with preliminary softening about 175°.

It was found that the sodium salt of methyl formylbutyrate would not react with thiourea in aqueous solution. It did react with an aqueous solution of methyl isothiourea (made from the sulfate and sodium hydroxide) to give an 8% yield of 2-methylthio-4-oxy-5-ethylpyrimidine, m. p. 187–191° (cor.). This was demethylated at 210° by dry hydrogen chloride to give a product melting at 189–191° which did not depress the melting point of 5-ethyl-2-thiouracil obtained above, but did depress the starting material. Another but unidentified product, m. p. about 205°, was also obtained.

5-Cyano-2-thiouracil.—Sodium metal (4.22 g., 0.184 g. atom) was dissolved in 200 cc. of absolute ethanol and 13.5 g. (0.178 mole) of thiourea was added and the mixture was cooled. Thirty grams of ethyl α-cyano-β-ethoxyacrylate[14] (0.178 mole) was added quite slowly. The dark orange solution was refluxed for one hour on the steam-bath and left overnight at room temperature. The clear solution was concentrated under vacuum to 75 cc. and diluted with 400 cc. of water. Precipitates obtained by cooling and neutralization to about *p*H 7, and by concentration of the filtrates, totaled 23.7 g. This was heated with 350 cc. of water and the whole acidified to *p*H 3 to yield 18.9 g. of product corresponding to a crude yield of 54% of 2-mercapto-4-amino-5-carbethoxypyrimidine. This product was purified by recrystallization from 4% hydrochloric acid and subsequent extraction of the product by hot water, m. p. 277° dec. (cor.).[33] Johnson and Ambler[15] gave m. p. 260–265° dec.

The 5-cyano-2-thiouracil was obtained by acidifying the filtrate from the crude 4-amino compound above. The solution was acidified to about *p*H 3 and by cooling and further concentration a total of 7.2 g. of precipitate was obtained. This was recrystallized from 150 cc. of water. The results indicated that the 5-cyano-2-thiouracil was not completely free from its sodium salt at this point and that the aqueous solution should have been acidified to below a *p*H of 2. Finally, 4.1 g. of product was recrystallized from 100 cc. of water and 3.7 g., m. p. 282–283° dec. (cor.), settled out on cooling. This was 14% of the theoretical. The analysis is given in Table I.

2-Mercapto-4-amino-5-pyrimidinecarboxylic Acid.—The ethyl ester, 6.4 g., was saponified by refluxing in 100 cc. of 95% alcohol and 60 cc. of 10% sodium hydroxide for two and one-half hours. The product from acidifying to *p*H 2 was purified by recrystallization from 5% hydrochloric acid followed by extraction with boiling water to remove any hydrochloric acid; yield 4.3 g. (78%); m. p. 276–279° dec. (cor.) with slight effervescing at 267°.

Anal. Calcd. for $C_5H_5N_3O_2S$: C, 35.1; H, 2.9; S, 18.7. Found: C, 34.7; H, 3.1; S, 18.5.

Neither 2-mercapto-4-amino-5-pyrimidinecarboxylic acid nor its ethyl ester was active as an antithyroid compound.

Acknowledgment.—We are indebted to Dr. E. B. Astwood, Pratt Diagnostic Hospital, Boston, Mass., for the data on antithyroid activity and for valuable advice and suggestions.

Summary

The synthesis of a series of 5- and 6-substituted 2-thiouracils from β-oxo esters and thiourea is described. Various methods for the preparation of the intermediate β-oxo esters have been evaluated.

The antithyroid activity of the substituted 2-thiouracils has been shown to vary with the nature and position of the substituent. Some of these derivatives are more potent than the parent compound in rats, and warrant further study.

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(32) Johnson and Menge, *J. Biol. Chem.*, **2**, 109 (1906).

(33) *Anal.* Calcd. for $C_7H_9N_3O_2S$: C, 42.2; H, 4.5; S, 16.1. Found: C, 42.1; H, 4.5; S, 15.9.