solidified on cooling was recrystallized from petroleum ether, m. p. 55–57°.

Anal. Calcd. for $C_{10}H_{13}NO_2$: N, 7.82. Found: N, 7.54.

Cyclopentylacetic Acid.—When 17.9 g. of the above ester was reduced with the aid of Adams catalyst, there was obtained 15 g. of the saturated cyanoacetate. The ester (81 g.) was added dropwise with stirring to a boiling solution of 110 g. of potassium hydroxide in 130 ml. of water. The mixture was heated for six hours, cooled and acidified. The resulting di-acid was taken up in ether, washed with water and dried over sodium sulfate. The ether was removed and the residue heated to effect decarboxylation. The cyclopentylacetic acid was collected at 135–137° (27 mm.), yield, 47 g. (82%).

Summary

1. Twelve new 6-substituted thiouracils and their antithyroid activities are presented. Of the group 6-cyclopropyl-2-thiouracil and 6-cyclohexylmethyl-2-thiouracil appear to be the most interesting pharmacologically.

2. Ten new β-keto esters are described.

3. Convenient syntheses of cyclopentylacetic acid, cyclopentanecarboxylic acid and ethyl β-cyclopropyl-β-ketopropionate are reported.

4. A by-product formed in the reaction between crude ethyl β-cyclopropyl-β-ketopropionate and thiourea is shown to be 4,6-dicyclopropyl-2-thioketohydropyrimidine by an independent synthesis.

RENSSELAER, N. Y. RECEIVED MAY 9, 1947

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

The Synthesis of Some 6-Substituted-2-thiouracils[1]

BY WILBUR H. MILLER, ALICE M. DESSERT AND GEORGE W. ANDERSON

The synthesis of 5- and 6-substituted-2-thiouracils from β-oxoesters and thiourea has been reported recently by Anderson, *et al.*[2] These compounds were evaluated in rats as antithyroid drugs[3] and several were found to be more active than the parent compound, 2-thiouracil, which has been used extensively for the treatment of hyperthyroidism in man.[4] In this paper several new 6-substituted-2-thiouracils are described. Some are closely related to the more active compounds previously reported.[2] Others are of new types in which various heterocycles are used as substituents.

These thiouracils have been prepared by condensing thiourea with the appropriate β-oxoester. For the preparation of most of these esters the *t*-butyl malonate method was used.[5] In several cases the acyl derivative of diethyl malonate was isolated along with the β-oxoester and these compounds are described in Table I. The acid chlorides were prepared in good yield using the appropriate acid and benzoyl chloride[6] or thionyl chloride.

Ethyl β-oxo-γ-(*p*-nitrophenyl)-butyrate was readily prepared by the acetoacetic ester method (ref. 2, Method A), but only a 28% yield in one of three attempts was obtained by the *t*-butyl malonate method. In the two unsuccessful experiments after adding *p*-toluenesulfonic acid large amounts of *p*-nitrophenylacetic acid were formed, apparently by decomposition of its *t*-butyl ester. Subsequent experiments showed that this ester was readily decomposed to the acid by *p*-toluenesulfonic acid in benzene, whereas the ethyl ester was stable. The β-oxoester on reaction with thiourea gave a product which could not be purified.

When ethyl β-oxo-β-(3-pyridyl)-propionate was prepared by the *t*-butyl malonate method the yield was low (14%) and appreciable quantities of an unidentified by-product (m. p. 161.5–162.5°) were obtained. This β-oxoester was obtained much more easily by the reaction between ethyl nicotinate and ethyl acetate[7] (25%).

When ethyl β-oxo-β-mesitylpropionate reacted with thiourea the thiouracil was not obtained and 75% of β-oxoester was recovered unchanged. The condensation for thiouracil formation perhaps occurs stepwise as in pyrazolone formation,[8] first by elimination of water from the β-oxoester and thiourea followed by a splitting out of alcohol from the intermediate compound. The two methyl groups *ortho* to the carbonyl in the mesityl portion of the ester may interfere at the first stage of the condensation either sterically or by reducing the activity of the ester through inductive effects.

The unsaturated β-oxoesters, ethyl 3-oxo-4-hexenoate, ethyl cinnamoylacetate and ethyl 3-oxo-5-hexenoate, yielded no definite product on the attempted reaction with thiourea. The last, prepared from allylmagnesium bromide and ethyl cyanoacetate, was not a pure product although it boiled over a very narrow range (Table I). When this product reacted with thiourea a 46% crude yield of 6-amino-2-thiouracil was obtained indicating the presence of ethyl cyanoacetate. No other thiouracil was found. The unsaturated esters were considered to be unstable under the usual

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society at the Atlantic City Meeting, April 17, 1947.

(2) Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945).

(3) Astwood, Bissell and Hughes, *Endocrinology*, **37**, 456 (1945).

(4) Van Winkle, Hardy, Hazel, Hines, Newcomer, Sharp and Sisk, *J. Am. Med. Assoc.*, **130**, 343 (1946).

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

(6) Brown, *ibid.*, **60**, 1325 (1938).

(7) Clemo and Holmes, *J. Chem. Soc.*, 1739 (1934).

(8) Torrey and Zanetti, *Am. Chem. J.*, **44**, 397 (1910).

TABLE I

PROPERTIES OF ETHYL β-OXOESTERS AND SUBSTITUTED MALONATES

Ethyl β-oxo	B. p., °C.	Mm.	Method	Yield, %	Formula	Analyses, %[f] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
-γ-Methoxybutyrate	68–71	5	*t*-Butyl	40	$C_7H_{12}O_4$	52.5	51.8[g] 51.8	7.8	7.4 7.6
-γ-Ethylcaproate	95–96.5	9.3	*t*-Butyl	37	$C_{10}H_{18}O_3$	64.5	64.0	9.7	9.6
-γ-Phenylcaproate	126–128	1.5	*t*-Butyl	47	$C_{14}H_{18}O_3$	71.8	71.7	7.7	7.7
-γ-(*p*-Isopropylphenyl)-butyrate	135–140	0.5	*t*-Butyl	38	$C_{15}H_{20}O_3$	72.6	71.5[g] 71.5	8.1	8.3 8.1
-γ-(*p*-Chlorophenyl)-butyrate	139–140	1	*t*-Butyl	41	$C_{12}H_{13}O_3Cl$	59.9	59.2[g] 59.3	5.4	5.4
-β-(*m*-Chlorophenyl)-propionate	118–121	0.2	*t*-Butyl	43	$C_{11}H_{11}O_3Cl$	58.3	58.3	4.9	4.9
-γ-(2-Thienyl)-butyrate	143–145	5.5	[a]	22	$C_{10}H_{12}O_3S$	56.6	56.9	5.7	6.1
-γ-(*p*-Nitrophenyl)-butyrate	M. p. 78.5–79.5 (cor.)		*t*-Butyl	28					
			[b]	22	$C_{12}H_{13}O_5N$	57.4	57.5	5.2	5.4
-β-Mesitylpropionate	125–125.5	1.5	[c]	41	$C_{14}H_{18}O_3$	71.8	71.9	7.7	7.7
-4-Hexenoate	105–108	15	*t*-Butyl[d]	46	$C_8H_{12}O_2$	61.5	61.5	7.8	7.5
-5-Hexenoate	89–90	10	Cyanacetic ester[e]		$C_8H_{12}O_2$	61.5	57.3	7.8	7.3
Diethyl malonates									
-α-Ethylbutyryl	134–135.5	8.8	*t*-Butyl	17	$C_{13}H_{22}O_5$	60.4	60.9	8.6	8.6
-α-Phenylbutyryl	148–152	1.2	*t*-Butyl	14	$C_{17}H_{23}O_5$	66.4	66.6	7.5	7.2
-2-Thienylacetyl	150–152	1.5	*t*-Butyl		$C_{13}H_{16}O_5S$	54.9	54.8	5.7	5.7

[a] Combined procedure of Breslow, *et al.* (ref. 5) and Riegel and Lilienfeld (THIS JOURNAL, **67**, 1273 (1945)); see experimental. [b] Acetoacetic ethyl ester and acid chloride (Anderson, *et al.* (ref. 2, method A)). [c] Prepared originally from ω-cyano-2,4,6-trimethylacetophenone supplied through the courtesy of Dr. A. Weissberger of Eastman Kodak Co. Method of Allen, Van Allan and Wilson, THIS JOURNAL, **66**, 1808 (1944). Analysis is of compound recovered from attempted reaction with thiourea. [d] Compound prepared by Breslow, *et al.* (ref. 5). [e] Anderson, *et al.* (ref. 2, method F). Calcd. analysis for 50–50 mixture of ethyl cyanoacetate and ethyl-3-oxo-5-hexenoate, C, 57.3; H, 7.0. [f] Microanalyses were carried out under the direction of Dr. J. A. Kuck to whom we are indebted for these data. [g] All analyses reported in this paper are the average of two or more determinations. The two analyses are indicated in this case because of the variance from theory.

conditions for the condensation reaction. Even at room temperature for twenty-four hours using ethyl 3-oxo-4-hexenoate no definite compound could be isolated although satisfactory yields of 6-*n*-butyl-2-thiouracil were obtained with ethyl β-oxoenanthate.

Of the twelve new 6-substituted-2-thiouracils shown in Table II three show greater antithyroid activity than 2-thiouracil in rats, but only 6-α-ethylpropyl-2-thiouracil shows sufficient activity to be considered promising for the treatment of hyperthyroidism. While its activity is less than those reported for the 6-*n*-propyl- and 6-benzyl-2-thiouracils,[3] it is over five times as active as the isomeric *n*-amyl compound. The specificity of the benzyl compound is great since it is about ten

TABLE II

PROPERTIES OF 6-R-2-THIOURACILS

Substituted thiouracil R (= 6)	Antithyroid activity[a]	M. p., °C. (cor.)	Yield, %, from β-oxo-ester	Formula	Analyses, %[b] Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
Trifluoromethyl[c]	<0.01	247–249	40	$C_5H_3N_2OSF_3$	30.6	1.5	14.3	16.4	30.9	1.8	13.9	16.4
Methoxymethyl	1.0–1.5	221–222	6	$C_6H_8N_2O_2S$	41.8	4.7	16.3	18.6	41.9	4.8	16.3	18.3
α-Ethylpropyl	7	223–224	24	$C_9H_{14}N_2OS$	54.5	7.1	14.1	16.7	54.9	7.3	13.8	16.1
α-Phenylpropyl[d]	0.5–1.0	244–244.5	53	$C_{13}H_{14}N_2OS$	63.4	5.7	11.4	13.0	63.6	5.9	11.5	13.1
p-Isopropylbenzyl	*ca.* 0.5	229–229.5	63	$C_{14}H_{16}N_2OS$	64.6	6.2	10.8	12.3	64.9	6.5	10.6	12.4
p-Chlorobenzyl	0.2	242–243	64	$C_{11}H_9N_2OSCl$	52.3	3.6	11.1	12.7	52.7	3.9	10.9	12.7
m-Chlorophenyl	<0.1	266–266.5	21	$C_{10}H_7N_2OSCl$	50.3	3.0	11.7	13.4	50.7	3.2	11.7	13.0
m-Methoxyphenyl[e]	<0.03	292–293	22	$C_{11}H_{10}N_2O_2S$	56.4	4.3	12.0	13.7	56.8	4.7	11.7	13.4
p-Methoxyphenyl[e]	<0.03	226–227	32	$C_{11}H_{10}N_2O_2S$	56.4	4.3	12.0	13.7	56.6	4.7	12.1	13.4
2-Furyl[d,f]	0.5	298–300 dec	7	$C_8H_6N_2O_2S$	49.5	3.1	14.4	16.5	50.1	3.7	14.4	16.7
3-Pyridyl[d]	<0.1	296–298 dec.	16[g]	$C_9H_7N_3OS$	52.7	3.4	20.5	15.6	52.8	4.6	19.9	15.3
2-Thenyl	3	248–250	37	$C_9H_8N_2OS_2$	48.2	3.6	12.5	28.6	48.5	4.0	12.3	27.4

[a] Thiouracil = 1.00 (weight basis): Method of Astwood, *et al.*,[3] and data supplied by Dr. Astwood. [b] Microanalyses were carried out under the direction of Dr. J. A. Kuck, to whom we are indebted for these data. [c] Prepared from ethyl-β-oxo-β-trifluoromethylpropionate, b. p. 47–49° at 25 mm., obtained in 83% yield by method of Swarts, *Bull. Acad. Belgique*, **5**, 12 (1926). [d] Reported also in THIS JOURNAL, **70**, 497 (1948), by Jackman, Bergman and Archer of the Sterling-Winthrop Research Institute. [e] From β-oxoesters supplied through the courtesy of Dr. A. Weissberger of Eastman Kodak Company. [f] Prepared from ethyl β-oxo-β-(2-furyl)-propionate, b. p. 139–140° at 12 mm., obtained in 48% yield by method of Barger, Robinson and Smith, *J. Chem. Soc.*, 721 (1937). [g] 20% based on ester used since 22% of β-oxoester recovered unchanged.

times as active as the 6-phenyl- and the 6-phenethyl-2-thiouracils[2,3] and since substituents in the benzyl reduce the activity markedly (Table II). The discrepancy between the activities of the 6-(2-thenyl)- and the 6-benzyl compounds also is greater than expected from a similar comparison of compounds with other physiological activity.[9] Theories about these variations could be put forth on a much more valid basis if more were known about the blood concentrations of the various compounds.

Experimental

Acid chlorides were prepared in most cases using 1.5 moles of thionyl chloride for each mole of acid. The mixture was refluxed for four and one-half hours on a steam-bath in a flask with a condenser protected by a Drierite tube. Excess thionyl chloride was distilled *in vacuo* and then the product was fractionated: α-ethylbutyryl chloride,[10] b. p. 138–142° (80%); α-phenylbutyryl chloride,[11] b. p. 111–114° (15 mm.) (88%); *p*-isopropylphenylacetyl chloride,[12] b. p. 107–110° (5 mm.) (86%); *p*-chlorophenylacetyl chloride,[13] b. p. 127–129° (15 mm.) (91%); *m*-chlorobenzoyl chloride,[14] b. p. 104–106° (14 mm.) (91%); 2-thienylacetyl chloride,[12,15] b. p., 62–65° (3 mm.) (70%); *p*-nitrophenylacetyl chloride,[16] m. p. 47–48° cor. (54%); nicotinyl chloride,[17] b. p. 89–91° (15 mm.) (84%). Prepared using the benzoyl chloride method[6] without modification were: methoxyacetyl chloride,[18] b. p. 112–113° (57%); crotonyl chloride,[6] b. p. 120–122.5° (51%); and acrylyl chloride,[19] b. p. 73–74° (72%).

β-Oxoesters for the most part were prepared by Method B, Ref. 5. The difficulties encountered for two of the esters have been described above. A combination procedure was necessary in a third preparation, that of **ethyl β-oxo-γ-(2-thienyl)-butyrate** as indicated in Table I. In this case after adding *p*-toluenesulfonic acid only a little gas was evolved. The product was worked up and vacuum distilled. At this point it was shown that the batch of *t*-butylmalonate which had been used contained much diethyl malonate. Consequently our distillate was treated according to the Riegel–Lilienfeld method (Table I, *a*) for the decomposition of acylated malonic esters by heating with β-naphthalenesulfonic acid. Based on 2-thienylacetyl chloride an over-all yield of 22% of β-oxoester was obtained. The 2-thienylacetyl derivative of diethylmalonate was also isolated.

***t*-Butyl *p*-Nitrophenylacetate.**—In order to test the reactivity of this compound toward *p*-toluene sulfonic acid, it was prepared according to the general method for the preparation of *t*-butyl esters.[20] The product was a olid, and after two recrystallizations from alcohol, 7.1 g. or 30% yield, m. p. 37–38° cor., was obtained.

Anal. Calcd. C, 60.8; H, 6.4; N, 5.9. Found: C, 59.0; H, 6.4; N, 5.8.

One gram of *t*-butyl *p*-nitrophenylacetate, 1.4 cc. of benzene and 0.02 g. of *p*-toluenesulfonic acid monohydrate (Eastman Kodak Co.) were heated together under reflux and the gas evolved collected over water. After making correction for the blank 108 cc. of gas was obtained. Theory for isobutylene was 95 cc. The gas decolorized bromine water. *p*-Nitrophenylacetic acid, m. p. 150–154°, was recovered in 88% of the theoretical amount. When ethyl *p*-nitrophenylacetate, m. p. 64°,[21] was treated similarly it was recovered unchanged.

Thiouracils were prepared as described previously.[2] Those 6-substituted-2-thiouracils purified by recrystallization from water and the parts of boiling water required to dissolve them (crude) were: 6-trifluoromethyl, 50; 6-α-ethylpropyl, 200; and 6-methoxymethyl (after hot extraction with alcohol), 50. Those recrystallized from glacial acetic acid and the cc. per g. (crude product) were: 6-α-phenyl, 20; 6-*p*-chlorobenzyl, 100; 6-*m*-chlorophenyl, 20. Those purified by hot extraction with alcohol and then recrystallized from glacial acetic acid (cc. per g. of product) were: 6-(*p*-methoxyphenyl), 14; 6-(*m*-methoxyphenyl), 75; 6-(2-furyl), 50; 6-(2-thenyl), tarry product removed by alcohol extraction and discarded, residue recrystallized from 20 cc. acid per g. of resulting product. By carefully acidifying to *p*H 4 a solution of the sodium salt and extracting this residue with acetone 6-(3-pyridyl) was obtained and the resulting product was recrystallized from cellosolve, 75 cc. per g. The 6-(*p*-isopropylbenzyl) was purified by several hot extractions[2] with alcohol in which it is moderately soluble.

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Summary

1. The syntheses of several new 6-substituted-2-thiouracils and of several new β-oxoesters have been carried out. Certain of the β-oxoesters prepared could not be converted to thiouracils and the implications are considered.

2. The antithyroid activities of the new compounds varied widely. While several of the compounds were more active in rats than 2-thiouracil, only 6-α-ethylpropyl-2-thiouracil approaches the activity of the best compounds reported previously.

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(9) Steinkoph and Ohse, *Ann.*, **437**, 14 (1924); **448**, 205 (1926); Barger and Easson, *J. Chem. Soc.*, 2100 (1938); Blicke and Burckhalter, THIS JOURNAL, **64**, 477 (1942); Lands, Nash and Hooper, *J. Pharmacol.*, **86**, 129 (1946).

(10) Whitmore, *et al.*, THIS JOURNAL, **63**, 643 (1941).

(11) Rising and Schwartz, *ibid.*, **54**, 2021 (1932).

(12) A new compound; identification only by conversion to β-oxoester (Table I).

(13) Friedmann and Masse, *Biochem. Z.*, **27**, 108.

(14) Limpricht and Uslor, *Ann.*, **102**, 263; Hope and Riley, *J. Chem. Soc.*, **121**, 2513.

(15) From 2-thienylacetic acid, m. p. 60–61.5° cor. Calcd. for $C_6H_6O_2S$: C, 50.7; H, 4.3; S, 22.6. Found: C, 51.0; H, 4.4; S, 22.9. Blicke and Zienty [THIS JOURNAL, **63**, 2945 (1941)] give m. p. 75–76°.

(16) Wedekind, *Ann.*, **378**, 289.

(17) Hukusima, *J. Chem. Soc. Japan*, **61**, 121 (1940); total time of heating reaction mixture in our experiment 65 hours.

(18) Leiner, *Ber.*, **70B**, 1040 (1937).

(19) Rehberg, Dixon and Fisher, THIS JOURNAL, **67**, 208 (1945).

(20) Abramovitch, Shivers, Hudson and Hauser, *ibid.*, **65**, 986 (1943).

(21) Radziszewski, *Ber.*, **2**, 209 (1869).