recrystallized twice from petroleum ether by seeding with previously crystallized material. The final sample had melting point 60–61.5°. *Anal.*[4p] Calcd. for $C_{16}H_{12}O$: C, 87.2; H, 5.5. Found: C, 86.7; H, 5.8.

In one demethylation experiment the benzene solution of the products was extracted with alkali. Acidification of the alkaline extract gave only a small quantity of II; the bulk of II was found in the neutral fraction.

An infrared absorption spectrum showed a strong band in the 2.8 micron region, thus establishing the presence of a hydroxyl group.[7]

1,9-Benzoxanthene from 2′-Hydroxy-1-phenylnaphthalene.—A mixture of 3.0 g. of II and 0.3 g. of palladium-on-charcoal[6] was heated in a nitrogen atmosphere for two hours at 320–350°. The mixture was treated with benzene and filtered. To the concentrated benzene solution there was added 0.7 g. of 2,4,7-trinitrofluorene.[10] On cooling there separated 1.3 g. of dark brown crystals, m. p. 178–190°. Recrystallization from acetic acid gave 1.0 g. of the crystalline complex of 1,9-benzoxanthene and 2,4,7-trinitrofluorenone, m. p. 214.0–214.6°. The complex was dissolved in benzene and the solution poured onto a column of activated alumina. The benzoxanthene was eluted with benzene and the benzene solution evaporated to dryness, leaving 0.41 g. (13.5%) of III. Two crystallizations from ethanol gave the compound in long needles, m. p. 107.5–108.0°. *Anal.*[4p] Calcd. for $C_{16}H_{10}O$: C, 88.1; H, 4.6. Found: C, 87.8; H, 4.6.

Diphenylene Oxide from *o*-Phenylphenol.—A mixture of 5.00 g. of *o*-phenylphenol[11] was heated with 0.5 g. of 30% palladium-on-charcoal catalyst at 285–290° for three hours. The mixture was treated with petroleum ether and filtered. The filtrate was washed with aqueous alkali; acidification of the alkaline extract gave 4.25 g. of recovered phenylphenol. The petroleum ether solution containing the neutral material was dried and chromatographed on a mixture of activated alumina and celite. The components of the mixture were selectively eluted from the column by using mixtures of petroleum ether–benzene containing increasing quantities of benzene; percolate receivers were changed at 100-cc. intervals. The solutions in all receivers were separately evaporated to dryness and the residue, if any, weighed and its melting point determined. The first fractions gave a total of 140 mg. of material, m. p. 66–69°; mixed melting point with diphenyl gave no depression. The later fractions gave a total of 400 mg. (8%) of diphenylene oxide, m. p. 81.5–83.0°; mixed melting point with authentic diphenylene oxide gave no depression. When 5.0 g. of phenylphenol was heated in a sealed tube at 315° for fourteen hours with 0.5 g. of palladium charcoal, a yield of 14% pure diphenylene oxide and 8% diphenyl was obtained. The balance of the material was unconverted phenylphenol.

(10) Orchin and Woolfolk, THIS JOURNAL, **68**, 1727 (1946).

(11) Gift from the Dow Chemical Company.

Summary

Liquid phase treatment of 2-(1-naphthyl)-cyclohexanone with palladium-on-charcoal gave a small yield of a compound whose properties were identical with those reported for 1,9-benzoxanthene. 2′-Hydroxy-1-phenylnaphthalene was probably the intermediate in this conversion since on similar treatment it also gave the compound presumed to be 1,9-benzoxanthene.

o-Phenylphenol when treated with palladium-on-charcoal gave diphenylene oxide. The intramolecular loss of hydrogen between an aromatic hydroxyl group and a suitably situated aromatic nucleus appears to be a general reaction.

1-*o*-Anisylnaphthalene was synthesized in 69% yield in two steps by condensing 1-tetralone with *o*-anisylmagnesium bromide and treating the resulting carbinol with palladium-on-charcoal.

PITTSBURGH, PENNSYLVANIA RECEIVED MAY 2, 1947

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

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

BY MARY JACKMAN, A. J. BERGMAN AND S. ARCHER

Recently Astwood[1a] has shown that certain 6-alkyl- and 6-aralkyl-2-thiouracils, prepared by Anderson and co-workers[2] were powerful goitrogens. In the 6-alkyl-2-thiouracil series maximum activity was reached when the substituents ranged from ethyl through butyl and then dropped off rapidly. The most potent compounds, 6-*n*-propyl-2-thiouracil and 6-benzyl-2-thiouracil (an aralkyl derivative) appeared to be about ten times as active as thiouracil, heretofore considered to be the best antithyroid drug. Astwood screened only one 6-cycloalkyl derivative, namely, 6-cyclohexyl-2-thiouracil, and found that it was equal to thiouracil in effectiveness.

In the course of our work in this field we had occasion to prepare and test some thiouracils joined at the six position, either directly or through an aliphatic chain to alicyclic, heterocyclic and aromatic rings. In addition, 6-methylthiomethyl-2-thiouracil was prepared. The β-keto esters required for condensation with thiourea were prepared by one of the methods given below, depending upon the availability of the starting materials.

$$RCOOC_2H_5 + CH_3COOC_2H_5 \xrightarrow{NaOC_2H_5} RCOCH_2COOC_2H_5 \quad (A)$$

$$RCOCl + CH_3COCHNaCOOC_2H_5 \longrightarrow RCOCH(COCH_3)COOC_2H_5 \xrightarrow{NH_3} RCOCH_2COOC_2H_5 \quad (B)$$

$$RCOCH_3 + (C_2H_5)_2CO_3 \xrightarrow{NaNH_2} RCOCH_2COOC_2H_5 \quad (C)$$

Ethyl furoylacetate[3] and ethyl nicotinoylacetate[4] were prepared according to method A and then condensed with thiourea to form the corresponding

(1) Presented at the Atlantic City meeting of the American Chemical Society, April, 1947.

(1a) Astwood, Bissell and Hughes, *Endocrinology*, **37**, 460 (1945).

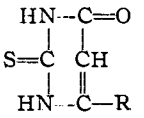
(2) Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945).

(3) Wahl and Dahl, *Bull. soc. chim.*, [4] **13**, 279 (1913).

(4) Strong and McElvain, THIS JOURNAL, **55**, 818 (1933).

TABLE I

THIOURACILS



R =	Yield, %	M. p., °C. (cor.)	Solvent	Analyses, % Calcd. N	Calcd. S	Found N	Found S	Activity
Cyclopropyl	60	236–239	Water	16.60	19.07	16.76	19.17	10
Cyclobutyl	77	211–212	Water	15.38	17.59	15.27	17.63	3
Cyclopentyl	69	220–222	Acetic acid-water	14.28	16.34	14.34	16.19	1–2
Cyclohexylmethyl	38	238–239.5	Acetic acid-water	12.49	14.29	12.50	14.37	5
Cyclohexylethyl	63	194–195.4	Alcohol	11.76	13.45	11.72	13.41	<1
Cyclohexylpropyl	72	181.5–182.8	Alcohol	11.10	12.70	10.84	12.64	1
Cyclopentylmethyl	68	197–200	Acetic acid-water	13.23	15.25	13.36	15.00	1
α-Phenylethyl	59	204.5–206	Acetic acid-water	12.06	13.80	12.12	14.00	2
α-Phenylpropyl	80	241.5–242.5	Acetic acid-water	11.38	13.02	11.44	12.78	1
Methylthiomethyl	60	231–233	Acetic acid-water	14.88	34.06	14.60	32.91[a]	<1
Furyl	23	284–286	Alcohol	14.43	16.51	14.56	16.38	1
β-Pyridyl·HCl	27	*ca.* 291	Hydrochloric acid	14.67	13.26	14.52	13.32[b]	<0.1

[a] When crystallized from dilute dioxane a strong mercaptan odor was noticed indicating that some decomposition was occurring. [b] The free base was obtained in the usual manner and crystallized from dilute acetic acid; m. p. >230°. *Anal.* Calcd.: N, 20.47; S, 15.62. Found: N, 20.30; S, 15.98. The base was suspended in water and hydrochloric acid added until it had all dissolved, the solution was filtered to remove traces of suspended matter and the hydrochloride was then thrown down by the addition of more acid.

TABLE II

β-KETO ESTERS, $RCOCH_2COOC_2H_5$

R =	Method	Yield, %	B. p. °C.	Mm.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Cyclopropyl	C[a]	57	99–101	11	61.52	7.75	61.71	7.68
Cyclobutyl	B	19	112–115	19	63.51	8.29	63.90	8.02
Cyclopentyl	B	36	91–94	1.8	65.19	8.76	65.03	8.54
Cyclohexylmethyl	B	41	143–145	12	67.89	9.49	67.80	9.42
Cyclohexylethyl	B	27	115–118	0.8	68.99	9.80	69.30	9.64
Cyclohexylpropyl	B	17	139–142	2	69.96	10.07	70.06	10.07
Cyclopentylmethyl	B	28	105–106	2	66.64	9.15	66.20	8.89
α-Phenylethyl	B[b]	35	148–154	1.2	70.89	7.32	70.48	7.33
α-Phenylpropyl	B[b]	41	124–133	1.5	71.77	7.74	71.82	7.71
Methylthiomethyl	B[c]	12	142–150	29	47.70	6.87	48.05	7.06

[a] The yield of keto ester when prepared by method B was 24%. Both esters yielded identical thiouracils. [b] The required acids were prepared from ethyl phenylmalonate using the appropriate iodide as the alkylating agent, thus

$$C_6H_5CH(COOC_2H_5)_2 + RI \longrightarrow C_6H_5CR(COOC_2H_5)_2 \longrightarrow C_6H_5CR(COOH)_2 \longrightarrow C_6H_5C(R)COOH$$

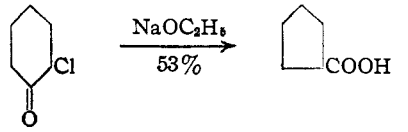
[c] The acid chloride was prepared according to the equations

$$HSCH_2COOH \longrightarrow CH_3SCH_2COOH \longrightarrow CH_3SCH_2COCl$$

thiouracils. It was hoped that a water-soluble thiouracil would prove to be active. Accordingly, 6-(3-pyridyl)-2-thiouracil was converted to the hydrochloride and tested as such. However, it was found that this substance was devoid of any antithyroid action.

With one exception, all of the other β-keto esters were prepared according to equation B. The method used was a slight modification of previously described procedures.[2,5] Whenever a water-insoluble amide was expected as a by-product in the ammonolysis step, the reaction mixtures were concentrated and the residues taken up in petroleum ether to effect a separation of the keto esters from solid material.

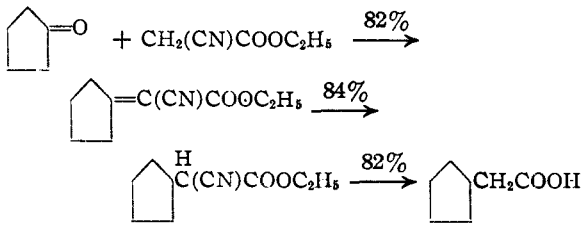
Cyclopentanecarboxylic acid was prepared conveniently from chlorocyclohexanone and sodium ethoxide, a reaction first described by Favorski.[6] The acid fraction obtained from the action of two moles of the base on one of the chloro-ketone was practically pure cyclopentanecarboxylic acid. The neutral fraction appeared to be a complex mixture and was not examined further. The next



higher homolog was prepared by a three-stage synthesis from cyclopentanone in over-all yields of 57%.

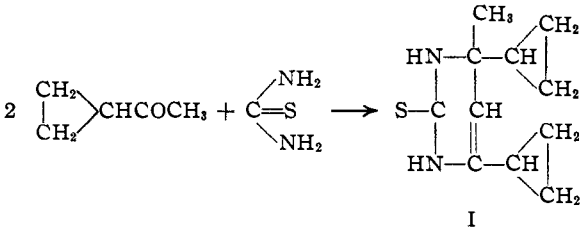
(5) Archer and Pratt, THIS JOURNAL, **66**, 1656 (1944).

(6) Favorski, *Chem. Zentr.*, **86**, I, 984 (1915).



Ethyl β-cyclopropyl-β-ketopropionate was prepared according to method B in 24% over-all yield based on the acid chloride. The carbethoxylation of cyclopropyl methyl ketone in the presence of sodium amide proved to be a more convenient synthesis since the yield in this one step method was 57%. Cyclopropyl methyl ketone condensed readily with ethyl oxalate to form the corresponding glyoxalate which, however, proved to be resistant to decarbonylation in the presence of iron and powdered soft glass.

In one experiment in which an impure sample of ethyl β-cyclopropyl-β-ketopropionate was used in the preparation of the thiouracil, an alkali-insoluble by-product separated when the reaction mixture was poured into water. This substance, m.p. 204–206°, was recovered unchanged after refluxing in either acid or basic media. We suggest that the compound is the thiotetrahydropyrimidine (I) since it could be prepared from cyclopropyl methyl ketone and thiourea in sodium ethylate solution.



I

This is in accord with the observations of Folkers and Johnson[7] who found that the major product arising from the interaction of acetophenone and urea was 4,6-diphenyl-4-methyl-2-oxotetrahydropyrimidine. This compound was also quite stable to the usual hydrolytic agents. Thiourea and acetophenone behaved similarly.[8] We are inclined to believe that (I) was formed from the ketone present as an impurity present in the keto-ester, since it was not encountered when pure ester was used in the preparation of 6-cyclopropyl-2-thiouracil.

Experimental[9]

Ethyl β-Cyclopropyl-β-ketopropionate.—To a stirred suspension of finely divided sodium amide (23.4 g.) in 150 ml. of dry ether cooled in an ice-bath there was added 25.2 g. of cyclopropyl methyl ketone. The mixture was then gently refluxed for one-half hour, cooled, and 70.8 g. of ethyl carbonate was added dropwise. The mixture was then refluxed for two hours, cooled and alcohol added to destroy excess sodium amide. The solution was added to 500 g. of ice and acidified to congo red. The organic layer was separated and the aqueous part extracted three times with ether. The combined ethereal extracts were washed with water, dilute sodium carbonate solution, again with water and then dried. After removal of the ether and a forerun consisting largely of ethyl carbonate the keto-ester was collected at 97.5–101° (11 mm.), 27 g. (57%). On redistillation almost all was collected at 99–101° (11 mm.).

Ethyl γ-Cyclopropyl-α,γ-diketobutyrate.—A mixture of 73 g. of ethyl oxalate and 42 g. of cyclopropyl methyl ketone was added dropwise to a solution of 11.5 g. of sodium in 150 ml. of absolute alcohol while the temperature was maintained below 40°. A yellow solid separated during the course of the reaction and after stirring for three hours the mixture was allowed to stand overnight. The pasty mass was added to 1.5 liters of water and the suspension was acidified with dilute sulfuric acid. When all the solid had disappeared the oil was drawn off and the aqueous layer then extracted with benzene. The combined organic layers were concentrated and the residue distilled at reduced pressure. Fifty grams of glyoxalate was collected at 149–154° (23 mm.) (55%). A fraction of b. p. 149° (23 mm.) was analyzed.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.59; H, 6.42.

6-Cyclopropyl-2-thiouracil.—After 131 g. of thiourea had dissolved in a stirred, boiling solution of 56.7 g. of sodium in 1225 ml. of absolute ethanol, 192 g. of *crude* ethyl β-cyclopropyl-β-ketopropionate was added dropwise in the course of one hour. Heating and stirring were continued overnight. Most of the alcohol was then removed and the residue added to 3 liters of water. The insoluble fraction was removed by filtration and the clear filtrate acidified to *p*H 3. The solid that separated was collected and crystallized from boiling water, wt. 97 g. (42%), m. p. 234–235° (cor.).

The alkali-insoluble fraction which weighed 14 g. was crystallized from alcohol twice; m. p. 204–206°. The melting point was not depressed when mixed with the compound described below.

Anal. Calcd. for $C_{11}H_{16}N_2S$: C, 63.43; H, 7.74; N, 13.45. Found: C, 63.51, 63.33; H, 7.97, 7.86; N, 13.26.

4,6-Dicyclopropyl-4-methyl-2-thiotetrahydropyrimidine.—A solution of 9.2 g. of sodium, 15.2 g. of thiourea and 32.8 g. of cyclopropyl methyl ketone in 200 ml. of ethanol was refluxed for three and one-half hours before being poured into 2 liters of water. The solid was filtered and recrystallized several times from ethanol, m. p. 207–208.2° (cor.).

Anal. Calcd. for $C_{11}H_{16}N_2S$: N, 13.45; S, 15.39. Found: N, 13.20; S, 15.38.

Cyclopentanecarboxylic Acid.—To a stirred solution of 83 g. of sodium in 2 liters of absolute alcohol there was added dropwise 240.5 g. of chlorocyclohexanone[10] over a period of several hours. The mixture was left overnight before the alcohol was removed on the steam-bath and replaced by an equal volume of water. The aqueous solution was extracted with ether and then acidified to *p*H 3. The oily acid that separated was gathered in ether, washed with water, dried over sodium sulfate and distilled. The acid boiled at 120–123° (27 mm.), wt. 110 g. (53%).

Ethyl Cyclopentylidenecyanoacetate.—A solution of 56.5 g. of ethyl cyanoacetate, 50.5 g. of cyclopentanone, 3.85 g. of ammonium acetate and 6 g. of acetic acid in 50 ml. of dry benzene was refluxed in an apparatus described by Cope[11] until the formation of water was complete. The mixture was cooled, extracted thoroughly with water and distilled to yield 72.3 g. (82%) of the unsaturated ester, b. p. 152–156° (18 mm.). The compound which

(7) Folkers and Johnson, THIS JOURNAL, **55**, 3367 (1933).

(8) Dziewonski, *et al.*, *C. A.*, **30**, 5227 (1936).

(9) All melting and boiling points are uncorrected unless otherwise specified. Analyses carried out under the supervision of M. E. Auerbach of this laboratory.

(10) Newman, Farbman and Hipsher, "Organic Syntheses," **25**, 22 (1945).

(11) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1943).

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).