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The Preparation of Some Substituted Thiohydantoins and Thioimidazoles

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It has been shown that proper substitution at the six position in 2-thiouracil resulted in increased antithyroid activity.[1] Astwood showed that 2-thiohydantoin was half and 2-thioimidazole one and one half times as active as 2-thiouracil in goitrogenic potency.[2] It seemed likely then that appropriately substituted thiohydantoins and thioimidazoles would show greater activity than the parent heterocycles. Accordingly, a number of 5-alkyl-2-thiohydantoins and 4-alkyl-2-thioimidazoles have been prepared for pharmacological screening.

Alkylthiohydantoins have been prepared by Wheeler and co-workers[3] by the interaction of amino acids and ammonium thiocyanate in acetic anhydride to give, first, the 1-acetyl-5-alkyl-2-thiohydantoins, which upon boiling with hydrochloric acid suffer loss of the acetyl group. Most of the amino acids which were needed were prepared by the method of Albertson.[4] In all cases the intermediate acetyl bodies were subjected to hydrolytic cleavage without purification. In the few instances where oily acetylthiohydantoins were encountered the quenched reaction mixture was extracted with chloroform and further processed as described in the experimental part.

The 4-alkyl-2-thioimidazoles were prepared from the corresponding aminomethyl alkyl ketone hydrochlorides and potassium thiocyanate.[5] The usual methods of preparing amine ketones (*e. g.*, bromination followed by a Gabriel synthesis or nitrosation followed by reduction) give compounds substituted on the methylene rather than on the terminal methyl group. To assure the desired orientation of the amino radical the following method of synthesis was used

$$RCOCH_2COOC_2H_5 \xrightarrow{HNO_2} RCOC(NOH)COOC_2H_5 \xrightarrow[(CH_3CO)O]{Zn} RCOC(HNHCOCH_3)COOC_2H_5 \xrightarrow{HCl} RCOCH_2NH_2\cdot HCl$$

Several of the keto-esters were prepared from available alkyl methyl ketones by carbethoxylation with ethyl carbonate in the presence of sodium hydride, a method recently described by Soloway and LaForge.[6] Previously, Levine and Hauser[7] had shown that sodium amide may also be used as a condensing agent in this synthesis. Our yields were in line with those reported by the latter authors rather than the high figures given by LaForge. However, our conditions differed insofar as we avoided the use of ether as a solvent, a factor we thought undesirable in large preparations.

Although there does not seem to be much doubt that carbethoxylation occurred predominantly at the methyl group, the subsequent reactions to which the keto-esters were submitted afforded additional evidence that such was the case. If reaction took place at the methylene group then alkyl acetoacetic esters would have resulted. These esters, upon nitrosation, reductive acetylation and hydrolysis would then have been transformed to amino acids[8] rather than to the amino ketones which were actually obtained.

Hauser[7] was able to convert pinacolone to ethyl trimethylacetoacetate with the aid of sodium amide as the condensing agent but sodium hydride proved to be ineffective here. The desired aminoketone was prepared by the Gabriel synthesis. It was found that aluminum amalgam used as the catalyst by Hill and Kropa[9] for the bromination of pinacolone in ether could be replaced by aluminum chloride without loss in yield. The reaction with potassium phthalimide and subsequent hydrolysis proceeded smoothly to give the amino ketone hydrochloride contaminated with a small amount of phthalic acid. Treatment with potassium thiocyanate yielded 4-*t*-butyl-2-thioimidazole which could readily be obtained in a pure state.

The pharmacological data indicate that replacement of the hydrogen by other groups in the five position of 2-thiohydantoin did not result in any significant increase in activity. On the other hand, in the 2-thioimidazole series beneficial effects were noticed. The best compound was 4-*n*-propyl-2-thioimidazole which was about three times as active as the unsubstituted heterocycle or five times more potent than thiouracil.

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Experimental

5-*n*-Butyl-2-thiohydantoin.—The following procedure was used when the intermediate acetylthiohydantoins were not obtained in crystalline form. A mixture of 20 g. of norleucine and 20 g. of ammonium thiocyanate in a solution of 100 ml. of acetic anhydride containing 10 ml. of acetic acid was refluxed for twenty minutes and then poured onto

(1) (a) Anderson, Halverstadt, Miller and Roblin, THIS JOURNAL, **67**, 2197 (1945); (b) Miller, Dessert and Anderson, *ibid.*, **70**, 500 (1948); (c) Jackman, Bergman and Archer, *ibid.*, **70**, 497 (1948).

(2) Astwood, Bissell and Hughes, *Endocrinology*, **37**, 462 (1945).

(3) Wheeler, Nicolet and Johnson, *Am. Chem. J.*, **46**, 456 (1911).

(4) Albertson, THIS JOURNAL, **68**, 450 (1946).

(5) (a) Gabriel and Pincus, *Ber.*, **26**, 2203 (1893); (b) Jackson and Marvel, *J. Biol. Chem.*, **103**, 191 (1933).

(6) Soloway and LaForge, THIS JOURNAL, **69**, 2677 (1947).

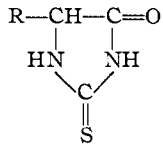
(7) Levine and Hauser, *ibid.*, **66**, 1768 (1944).

(8) The amino acid synthesis developed by Bouveault and Locquin, *Bull. soc. chim.*, [3] **31**, 1180 (1904), and since used by Hamlin and Hartung, *J. Biol. Chem.*, **145**, 389 (1942), is based on such a series of reactions.

(9) Hill and Kropa, THIS JOURNAL, **55**, 2509 (1933).

TABLE I

5-ALKYL-2-THIOHYDANTOINS

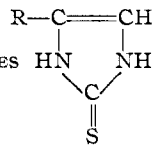


R =	Yield, %[a]	Solvent	M. p., °C. (cor.)	Analyses, % Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	Activity thiouracil = 1
Methyl	25	H_2O	163–165[b]	21.53	21.26	24.63	24.85	1
Ethyl	21	H_2O	164–166	19.30	19.10	22.05	22.20	<1
n-Propyl	21	H_2O	155–156.5	17.71	17.51	20.26	20.51	<1
i-Propyl	44	H_2O	138–140[c]	17.71	17.38	20.26	20.11	1
n-Butyl	48	H_2O—C_2H_5OH	134.4–135.4	16.27	16.00	18.62	18.33	<1
s-Butyl	32	H_2O—C_2H_5OH	131–133	16.27	16.21	18.62	18.72	1
i-Butyl	60	H_2O—C_2H_5OH	174–176[c]	16.27	16.03	18.62	18.78	1–2
n-Amyl	41	H_2O—C_2H_5OH	131.5–132	15.05	14.86	17.22	17.00	1
n-Hexyl	60	H_2O—C_2H_5OH	143.5–144.5	14.01	13.70	16.01	15.93	1
Benzyl	60	H_2O—C_2H_5OH	184–184.5[d]			15.39	15.61	<1
Cyclohexylmethyl[e]	41	H_2O—C_2H_5OH	224.4–225.7	13.14	12.93	15.03	15.24	0.1
Methylthioethyl	48	H_2O	149.5–151	14.73	14.45	33.70	33.80	0.5

[a] Yield of analytically pure material based on amino acid. [b] Wheeler (ref. 3) reported m. p. = 158–159°. [c] Komatsu, *C. A.*, **9**, 2087 (1915), reported 129–130° for the m. p. of the *i*-propyl compound and 169–170° for the *i*-butyl. [d] Johnson and O'Brien, *J. Biol. Chem.*, 12, 211 (1912), reported m. p. as 185°. [e] The amino acid, 2-amino-3-cyclohexylpropionic acid was prepared by amination of the corresponding bromo acid.

TABLE II

4-ALKYL-2-THIOIMIDAZOLES



R =	Yield, %	Solvent	M. p., °C. (cor.)	Analyses, % Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	Activity[b] thiouracil = 1
n-Propyl	50	H_2O	183–184	19.70	19.88	22.55	22.60	4–5
i-Propyl	50	H_2O	149.6–150	19.70	19.41	22.55	22.79	0.8
i-Butyl	45	H_2O	188.4–189.4[a]	17.93	19.64	20.52	20.65	0.8
n-Amyl	30	Ether–pet. ether	111–113[a]	16.46	16.64	18.83	18.88	<1
n-Hexyl	60	Ether–pet. ether	115.2–116	15.20	14.92	17.40	17.37	0.2
Cyclopentyl	49	H_2O—C_2H_5OH	218–220.8	16.65	16.23	19.05	19.24	0.5
Cyclohexylmethyl	17	C_2H_5OH	231.2–232.5	14.27	13.98	16.33	15.95	<1
Benzyl	42	H_2O—C_2H_5OH	222.8–224[a]	14.73	14.72	16.85	16.66	1.1

[a] Akabori and Numano, *J. Chem. Soc. Japan*, **53**, 200 (1932), who prepared these thioimidazoles by a different sequence of reactions, reported the *i*-butyl derivative to melt at 183–184°, the *n*-amyl at 114–115.5° and the benzyl at 221–222°. [b] The activity of the *t*-butyl compound (see Experimental Part) was not yet known.

one liter of cold water. When all the excess anhydride was destroyed the remaining oil was taken up in chloroform and the solution then concentrated *in vacuo*. Then 200 ml. of 10% hydrochloric acid was added to the residue and the whole boiled under reflux for forty minutes. On cooling the thiohydantoin crystallized. It was filtered off and purified by recrystallization from dilute ethanol.

Ethyl *n*-Butyrylacetate.—In a nitrogen atmosphere 40 g. of sodium hydride was added in one portion to 300 g. of ethyl carbonate in a flask equipped with an efficient stirrer. Then 86 g. of methyl *n*-propyl ketone was dropped into the stirred mixture over a period of thirty minutes. During the course of the addition the temperature rose from 25° to 50° and was maintained at this point for an additional three hours. The next morning the excess condensing agent was destroyed by the cautious addition of 50 ml. of ethanol and the mixture then poured onto 2500 ml. of water. The mixture was made acid to congo red and the oil layer then removed with the aid of ether. The solution was washed with water, sodium bicarbonate solution and again with water. After drying over sodium sulfate the ethereal solution was distilled first at atmospheric pressure to remove volatile material and then at reduced pressure to give 65 g. of keto-ester, b. p. 93–96° at 14 mm. (41%).

It was subsequently discovered that when the reaction mixture was held at 58–60° for the first ninety minutes and then raised to 80–90° for the next two hours the yield rose to 60%. The following esters were prepared by the above described procedure. Ethyl 3-oxo-4-methylpentanoate from methyl isopropyl ketone in 37% yield, b. p. 85° at 16 mm. Ethyl 3-oxo-5-methylhexanoate from methyl isobutyl ketone in 64% yield, b. p. 93–96° at 15 mm. Ethyl 3-oxooctanoate from methyl *n*-amyl ketone in 35% yield, b. p. 85–90° at 3 mm. Ethyl 3-oxononanoate from methyl *n*-hexyl ketone in 37% yield, b. p. 92–97° at 1 mm.

The remainder of the keto-esters were prepared as described previously.[1c]

1-Amino-3-cyclohexyl-2-propanone Hydrochloride.—To a solution of 71.2 g. of ethyl 3-oxo-4-cyclohexylbutyrate in 44 ml. of acetic acid cooled in an ice–salt-bath a solution of 22 g. of sodium nitrite in 50 ml. of water was added at such a rate that the temperature was kept below 30°. Then 120 g. of ice and 60 ml. of acetic anhydride were

added followed by the portionwise addition of 39 g. of zinc dust. During the latter operation the temperature was held at 10–20°. Stirring was continued for two hours as the mixture warmed up to room temperature. The solids were removed by filtration and the filter cake washed with water and then chloroform. The combined filtrates were extracted with more chloroform and the organic layers then combined and washed with water and sodium carbonate solution. The chloroform was removed and the residual oil was then refluxed for nine hours with 250 ml. of 10% hydrochloric acid. The warm mixture was clarified by filtration over a bed of filter-cel and then taken to dryness. The dark oil was azeotropically distilled with absolute alcohol and the crude hydrochloride was dissolved in alcohol and precipitated by the addition of dry ether. There was obtained 10 g. of crude aminoketone hydrochloride which was satisfactory for conversion to the thioimidazole. In a similar fashion the following amino ketones were prepared.

1-Amino-2-pentanone Hydrochloride.—Obtained from ethyl 3-oxohexanoate, m. p. 163–164°.

Anal. Calcd. for $C_5H_{11}NO\cdot HCl$: Cl, 25.77. Found: Cl, 25.92.

1-Amino-3-phenyl-2-propanone Hydrochloride.—Obtained from ethyl 3-oxo-4-phenylbutanoate, m. p. 190–193°.

Anal. Calcd. for $C_9H_{11}NO\cdot HCl$: Cl, 19.10. Found: Cl, 19.22.

1-Amino-3-methyl-2-butanone Hydrochloride.—Obtained from ethyl 3-oxo-4-methylpentanoate, m. p. 161.5–163°.

Anal. Calcd. for $C_5H_{11}NO\cdot HCl$: Cl, 25.77. Found: Cl, 26.28.

1-Amino-4-methyl-2-pentanone Hydrochloride.—Obtained from ethyl 3-oxo-5-methylhexanoate, m. p. 179–180°.

Anal. Calcd. for $C_6H_{13}NO\cdot HCl$: Cl, 23.38. Found: Cl, 23.60.

1-Amino-2-heptanone Hydrochloride.—Obtained from ethyl 3-oxoöctanoate, m. p. 159–162°.

Anal. Calcd. for $C_7H_{15}NO\cdot HCl$: Cl, 21.40. Found: Cl, 21.68.

1-Amino-2-octanone Hydrochloride.—Obtained from ethyl 3-oxononanoate, m. p. 151–154°.

Anal. Calcd. for $C_8H_{17}NO\cdot HCl$: Cl, 19.73. Found: Cl, 20.20.

Aminomethyl Cyclopentyl Ketone Hydrochloride.—Obtained from ethyl 3-oxo-3-cyclopentylpropanoate, m. p. 185–186°.

Anal. Calcd. for $C_7H_{13}NO\cdot HCl$: Cl, 21.67. Found: Cl, 21.62.

4-Cyclohexylmethyl-2-thioimidazole.—A solution of 8.0 g. of the crude hydrochloride as prepared above and 5.4 g. of potassium thiocyanate in 9 ml. of water was warmed at 90° for two hours. The precipitate that separated on cooling was collected and recrystallized from ethanol with the aid of charcoal to constant melting point.

Bromopinacolone.—A solution of 40 g. of pinacolone in 500 ml. of dry ether containing 1.0 g. of aluminum chloride was cooled to zero degrees before being treated with 63 g. of bromine over a period of one-half hour. After stirring an additional thirty minutes the mixture was poured onto water and after separation of the layers the organic phase was washed thoroughly with water. The ether solution was dried over sodium sulfate and then distilled to give 47.3 g. (58%) of bromoketone, b. p. 47–49° at 1 mm.

Phthalimidopinacolone.—A mixture of 47.3 g. of bromopinacolone, 48.0 g. of potassium phthalimide and 150 ml. of dry benzene was stirred under reflux for ten hours. The cooled suspension was filtered, the solid washed with benzene and the combined filtrates then treated with petroleum ether until turbid. The crystalline mass which separated on cooling was collected; m. p. 100–102°, wt. 40.8 g. (63.5%).

Anal. Calcd. for $C_{14}H_{15}NO_3$: N, 5.71. Found: N, 5.72.

4-*t*-Butyl-2-thioimidazole.—A solution of 23 g. of phthalimidopinacolone, 128 ml. of concentrated hydrochloric acid, 130 ml. of water and 90 ml. of acetic acid was refluxed for ten hours before being concentrated to dryness. The residue was warmed with 100 ml. of water and then chilled. The phthalic acid that separated was removed by filtration and the filtrate concentrated to dryness. After azeotropic distillation with alcohol the hydrochloride of the amino ketone was dissolved in alcohol and ether added to precipitate 7.4 g. of amino ketone hydrochloride.

The salt was added to a warm solution of 6.3 g. of potassium thiocyanate in 10.5 ml. of water and the resulting mixture warmed on the steam-bath for two hours. On cooling the thioimidazole separated. It was filtered, washed with water and dried; wt. 3.9 g. (39%). After recrystallization from alcohol the substance melted at 234.2–235.4° (cor.).

Anal. Calcd. for $C_7H_{12}N_2S$: N, 17.93; S, 20.52. Found: N, 18.33; S, 20.72.

Summary

1. The preparation of several substituted thiohydantoins and thioimidazoles for antithyroid screening has been described. Although no significant increase in antithyroid activity was noted over the parent substance in the thiohydantoin series, 4-*n*-propyl-2-thioimidazole proved to be about three times as active as 2-thioimidazole itself.

2. The carbethoxylation of methyl ketones with sodium hydride was further extended and was successful in all cases tried but pinacolone.

3. The preparation of some 1-aminomethyl ketones was also described.

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