To a solution of 61 g. (0.25 mole) of the above diketo ester in 200 ml. of methanol was added 12.5 g. (0.25 mole) of 100% hydrazine hydrate. Heat was evolved, and the solution boiled spontaneously. After removal of the methanol the ethyl 5-(β-carbethoxyethyl)-3-pyrazolecarboxylate was distilled in vacuum to yield 56 g. (93.5%) of viscous colorless liquid which soon crystallized; b. p. 180° (0.5 mm.), m. p. 70–72°. A sample was recrystallized from petroleum ether, m. p. 72–73°.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: N, 11.66. Found: N, 12.17.

The above ester, 55 g., was saponified with sodium hydroxide solution and the 5-(β-carboxyethyl)-3-pyrazolecarboxylic acid was precipitated with hydrochloric acid. The yield was 42.5 g. (100%). A sample, recrystallized from water, melted at 243–244° dec.

Anal. Calcd. for $C_7H_8N_2O_4$: N, 15.23. Found: N, 15.15.

A sample of the acid was sublimed twice in vacuum at a temperature of about 200–230°. It remained unchanged, m. p. 243–244° dec.

Anal. Calcd. for $C_7H_8N_2O_4$; neut. equiv., 92.08. Found: neut. equiv., 93.57.

A sample of the acid was boiled for several hours in quinoline and another sample was boiled in glacial acetic acid. In neither case was there any evidence of decarboxylation.

Acknowledgment.—The author is indebted to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses reported here, and to Frank Streightoff and Dr. H. M. Lee for the biological tests.

Summary

3-Pyrazolealanine, 3-β-aminoethylpyrazole, 4-pyrazolealanine and 4-β-aminoethylpyrazole have been synthesized.

These pyrazole compounds appear to have no significant biological activity.

INDIANAPOLIS, INDIANA RECEIVED JUNE 2, 1949

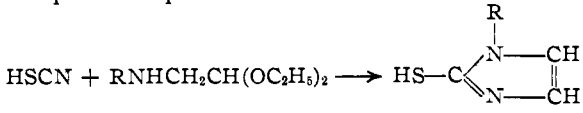
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies on Imidazoles. IV.[1] The Synthesis and Antithyroid Activity of Some 1-Substituted-2-mercaptoimidazoles

BY REUBEN G. JONES, EDMUND C. KORNFELD, KEITH C. MCLAUGHLIN AND ROBERT C. ANDERSON

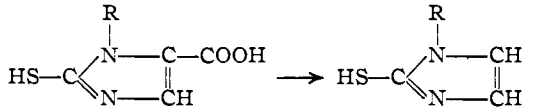
A large amount of synthetic work on antithyroid drugs appears to have been directed toward the preparation of 2-thiouracil types.[2] However, in 1945, Astwood[3] showed that 2-mercaptoimidazole had antithyroid activity about one and one-half times that of thiouracil when tested in rats. In connection with other work a number of 1-substituted-2-mercaptoimidazoles became available, and it appeared to be worthwhile to prepare others of this series and submit them to pharmacological testing.

Easson and Pyman have described a general method of preparing 1-substituted-2-mercaptoimidazoles by the reaction of primary amines with acetalylisothiocyanate.[4] Earlier, Marckwald and others had synthesized compounds of this type from isothiocyanates and aminoacetal.[5] The reaction of thiocyanic acid with N-substituted aminoacetals has proved to be a most useful method for obtaining the greater number of the compounds reported in Table I.



This is designated as method A in the table. The requisite N-substituted aminoacetals were readily prepared by heating chloro- or bromoacetal with primary amines.

Another satisfactory method (B) of synthesizing some of the compounds of Table I consisted of the decarboxylation of 1-substituted 2-mercapto-5-imidazolecarboxylic acids.



The acids were heated to about 250° at which temperature the decarboxylation was rapid, and the yields of the desired products were practically quantitative. Surprisingly the resulting 2-mercaptoimidazoles, in the absence of air, appeared to be quite stable at these elevated temperatures.

The antithyroid activities of a number of the compounds of Table I as determined by the rat test[6] are recorded in the last column. Although 2-mercaptoimidazole appears to be somewhat less active in rats than is propylthiouracil, Astwood has recently found[7] that in man 2-mercaptoimidazole and 1-methyl-2-mercaptoimidazole are much more active.

In addition to the compounds of Table I, three related members were synthesized (see Experimental) and tested. These together with their activities were: 4(or 5)-methyl-2-mercaptoimidazole,[8] 0.05; 4(or 5)-ethyl-2-mercaptoimidazole, 0.1; and 1-methyl-5-ethyl-2-mercaptoimidazole, 0.5. After the completion of this work

(1) For the preceding paper of this series see THIS JOURNAL, **71**, 2444 (1949).

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

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

(4) Easson and Pyman, *J. Chem. Soc.*, 1806 (1932).

(5) (a) Marckwald, *Ber.*, **25**, 2354 (1892); (b) Wohl and Marckwald, *ibid.*, **22**, 568, 1353 (1889).

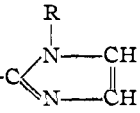
(6) Astwood, *J. Pharmacol.*, **78**, 79 (1943).

(7) Stanley and Astwood, *Endocrinology*, **44**, 588 (1949).

(8) Gabriel and Pinkus, *Ber.*, **26**, 2203 (1893).

TABLE I

1-SUBSTITUTED-2-MERCAPTOIMIDAZOLES



R	Empirical formula	Method of prepn.	Yield, %[a]	M. p., °C.[b]	Nitrogen, % Calcd.	Found	Activity Thiouracil = 1.0
H[c]	$C_3H_4N_2S$	A, B	78–91	218–220	[d]		0.5
CH_3[e]	$C_4H_6N_2S$	A, B	84–99	146–148	24.54	24.21	.5
C_2H_5	$C_5H_8N_2S$	A	98	79–80	21.86	21.60	.5
C_3H_5[f]	$C_6H_8N_2S$	A	36	73–74	19.99	19.99	
n-C_3H_7	$C_6H_{10}N_2S$	A	85	115–116	19.70	19.40	.05
i-C_3H_7	$C_6H_{10}N_2S$	B	95	168–169	[g]		
n-C_4H_9	$C_7H_{12}N_2S$	A	70	80–81	17.93	17.92	
i-C_4H_9	$C_7H_{12}N_2S$	A	90	137–138	17.93	17.69	.05
s-C_4H_9	$C_7H_{12}N_2S$	A	98	166–167	17.93	17.51	
t-C_4H_9	$C_7H_{12}N_2S$	A	19	189–190	17.93	17.77	
$(CH_3)_2NCH_2CH_2$[h]	$C_7H_{13}N_3S$·HCl	A	53	188–189	20.23	20.27	
2-C_5H_4N[i]	$C_8H_7N_3S$·2HCl	A	66	159–160	16.80	16.28	
C_6H_5[e]	$C_9H_8N_2S$	A, B	85–97	179–180	15.90	16.55	
C_6H_{11}[j]	$C_9H_{14}N_2S$	B	89	173–174	[k]		
$C_6H_5CH_2$	$C_{10}H_{10}N_2S$	A, B	87–96	145–146	[l]		.2
$C_5H_{11}CH(CH_3)$[m]	$C_{10}H_{18}N_2S$	A	86	72–73	14.13	13.83	
$C_6H_5CH_2CH_2$	$C_{11}H_{12}N_2S$	A	80	166–167	13.72	14.00	

[a] Where two figures are given the yields are for methods A and B, respectively. [b] Melting points are not corrected. [c] See Ref. 5a. [d] Calcd.: S, 32.02. Found: S, 32.03. [e] See ref. 5b. [f] Allyl. After recrystallization from water this compound was white but upon exposure to air it gradually decomposed turning dark red. [g] Calcd.: S, 22.54. Found: S, 23.09. [h] This compound was isolated as the monohydrochloride by addition of one equivalent of hydrochloric acid to the reaction mixture followed by evaporation to dryness and extraction of the residue with hot absolute alcohol. It was recrystallized from absolute alcohol. [i] 2-Pyridyl. Isolated as the dihydrochloride. [j] Cyclohexyl. [k] S, 17.69. Found: S, 17.80. [l] See Jones, THIS JOURNAL, **71**, 383 (1949). [m] 2-Heptyl.

TABLE II

N-SUBSTITUTED AMINOACETALS, $RHNCH_2CH(OC_2H_5)_2$

R	Empirical formula	Yield, %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_{25}	Nitrogen, % Calcd.	Found
CH_3[a]	$C_7H_{17}NO_2$	65	164–166	750				
C_2H_5	$C_8H_{19}NO_2$	55	71–73	16	1.4857	0.8792	8.69	8.74
C_3H_5[b]	$C_9H_{19}NO_2$	81	195–200	750				
n-C_3H_7[b]	$C_9H_{21}NO_2$	70	78–80	13				
n-C_4H_9[b]	$C_{10}H_{23}NO_2$	82	94–97	12				
i-C_4H_9	$C_{10}H_{23}NO_2$	59	85–87	12	1.4195	.8922	7.40	7.84
s-C_4H_9	$C_{10}H_{23}NO_2$	72	86–87	12	1.4224	.8687	7.40	7.54
t-C_4H_9	$C_{10}H_{23}NO_2$	90	190	750	1.4135	.8631	7.40	7.48
$(CH_3)_2NCH_2CH_2$	$C_{10}H_{24}N_2O_2$	70	104–106	12	1.4304	.8921	13.71	13.66
2-C_5H_4N[c]	$C_{11}H_{18}N_2O_2$	52	115–118	0.6	1.5123	1.043	13.32	13.20
C_6H_5[d]	$C_{12}H_{19}NO_2$	66	108–110	0.4				
$C_6H_5CH_2$[e]	$C_{13}H_{21}NO_2$	82	162–164	20				
$C_5H_{11}CH(CH_3)$[f]	$C_{13}H_{29}NO_2$	74	125–127	10	1.4265	0.8582	6.06	5.79
$C_6H_5CH_2CH_2$	$C_{14}H_{23}NO_2$	60	142–145	3	1.4122	0.9565	5.90	6.12

[a] See ref. 11. [b] See ref. 12. [c] 2-Pyridyl. [d] See ref. 13a. [e] See ref. 13b. [f] 2-Heptyl.

a paper by Jackman and others[9] appeared describing the synthesis and antithyroid activity of an additional number of 2-mercapto-4(or 5)-substituted-imidazoles.

The 1-substituted-2-mercapto-5-imidazole carboxylic acids of Table III (Experimental) and their methyl or ethyl esters[10] were tested and found to have no antithyroid activity.

(9) Jackman, Klenk, Fishburn, Tullar and Archer, THIS JOURNAL, **70**, 2884 (1948).

(10) Jones, *ibid.*, **71**, 644 (1949).

Acknowledgment.—The authors are grateful to Drs. Ewald Rohrmann, K. K. Chen and D. C. Hines for advice and to W. L. Brown, H. L. Hunter and W. J. Schenck for the microanalyses.

Experimental

N-Substituted Aminoacetals.—The preparation of the compounds presented in Table II consisted of heating diethyl chloro- or bromoacetal with an excess of the appropriate primary amine as de-

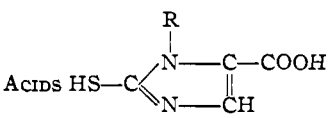
scribed by Knorr,[11] Paal and Gember[12] and others.[13] The following is a description of a typical experiment.

In a pressure vessel (autoclave or sealed tube) was placed 60 g. (0.3 mole) of bromoacetal and 88 g. (1.0 mole) of N,N-dimethylethylenediamine,[14] and the mixture was heated at 120° for sixteen hours. The product was removed from the reaction vessel, shaken with 100 ml. of 50% aqueous potassium hydroxide, and the organic layer was dried with potassium carbonate. Distillation of this liquid gave 35 g. of unreacted N,N-dimethylethylenediamine and 42 g. of dimethylaminoethylaminoacetal, b. p. 104-106° (12 mm.). The sample for analysis distilled at 105° (12 mm.).

1-Substituted-2-mercapto-5-imidazolecarboxylic Acids.—These acids, presented in Table III, were obtained by saponification of the corresponding methyl or ethyl esters[10] as has been described previously.[10]

TABLE III

1-SUBSTITUTED-2-MERCAPTO-5-IMIDAZOLECARBOXYLIC ACIDS



R	Empirical formula	Yield, %	M. p. °C.[a]	Nitrogen, % Calcd.	Found
H	$C_4H_4N_2O_2S$	96	235–236	19.43	19.43
i-C_3H_7	$C_7H_{10}N_2O_2S$	97	203–204	15.40	14.76
C_6H_{11}[b]	$C_{10}H_{14}N_2O_2S$	98	203–204	12.38	12.00
$C_6H_5CH_2$	$C_{11}H_{10}N_2O_2S$	97	221–222	11.96	11.69

[a] Melting points dec. are not corrected. [b] Cyclohexyl.

1-Substituted-2-mercaptoimidazoles. A. From Substituted Aminoacetals and Thiocyanic Acid.—The following example is illustrative of method A used for preparing the compounds of Table I.

To a solution of 19 g. (0.1 mole) of N-*n*-butylaminoacetal in 100 ml. of alcohol was added 12 g. (0.12 mole) of potassium thiocyanate and 55 ml. (0.11 mole) of 2 *N* hydrochloric acid. The mixture was heated on the steam-bath overnight and then evaporated to dryness *in vacuo*. The residue was extracted with hot acetone which, after evaporation, left the crude 1-*n*-butyl-2-mercaptoimidazole.

The crude products were purified in a number of ways. Those which were not too soluble in water, including the butyl and higher homologs, were taken up in dilute aqueous sodium hydroxide. The solution was treated with carbon, filtered and acidified to precipitate the product. Acetone, ethyl acetate or mixtures of one of these with petroleum ether were good solvents for recrystallizing the compounds.

B. Decarboxylation of 1-Substituted-2-mercapto-5-imidazolecarboxylic Acids.—Method B for the preparation of compounds in Table I is illustrated by the following typical experiment.

In a two-liter round-bottom flask was placed 300 g. of 2-mercapto-4(or 5)-imidazolecarboxylic acid. This was heated with a soft flame and stirred with a glass rod until all had melted and foaming had stopped. The melt was cooled under nitrogen or carbon dioxide and the solid was taken up in 2.5 l. of boiling absolute alcohol. The alcohol solution was boiled with a liberal quantity of decolorizing carbon, filtered, evaporated almost to dryness *in vacuo*, and 1 l. of petroleum ether was added to the residue. The white crystalline solid was collected on a filter and air-dried. It was analytically pure.

α-Bromobutyraldehydediethylacetal.—The method described by Kuhn and Grundmann[15] for the preparation of α-bromo-*n*-valeraldehydediethylacetal was employed using freshly distilled *n*-butyraldehyde. The product was obtained in 58% yield; b. p. 88–91° (21 mm.).

Anal. Calcd. for $C_8H_{17}BrO_2$: Br, 35.50. Found: Br, 35.59.

α-Aminobutyraldehydediethylacetal.—α-Bromobutyraldehydediethylacetal, 200 g., was mixed with 100 ml. of methanol in a 1-l. high pressure autoclave, and the bomb was cooled in Dry Ice–methanol. About 450 ml. of liquid ammonia was then added, and the bomb was closed. The reaction mixture was heated for seven hours at 120–130°. After the autoclave had been opened the ammonia was allowed to evaporate, and the methanol was distilled *in vacuo*. The mixture was diluted with ether, and a concentrated aqueous solution containing 70 g. of potassium hydroxide was added slowly with stirring. The ether solution was decanted, and the remaining sludge was extracted twice with ether. The extracts (600 ml.) were dried over potassium hydroxide, and the ether was evaporated. The residue was distilled *in vacuo;* b. p. 79–84° (24 mm.); yield, 98 g. (68%).

Anal. Calcd. for $C_8H_{19}NO_2$: N, 8.69. Found: N, 8.47.

2-Mercapto-4(5)-ethylimidazole.—This was prepared from butyraldehydediethylacetal and thiocyanate as described above. The yield was 38 g. (84%), and the product was recrystallized from either dilute ethanol or water; m. p. 165–167°.

Anal. Calcd. for $C_5H_8N_2S$: N, 21.86. Found: N, 21.26.

α-Methylaminobutyraldehydediethylacetal.—α-Bromobutyraldehydediethylacetal, 341 g., was charged into a cold 1-l. autoclave with 450 ml. of liquid methylamine, and the mixture was heated for seventeen hours at 115°. The product was isolated as described above for the amino homolog; b. p. 85–90° (25 mm.); yield, 189 g. (71%). The acetal contained a trace of the bromide starting material which was not removed by fractionation; however, it was adequately pure for conversion to the mercaptoimidazole.

2-Mercapto-1-methyl-5-ethylimidazole.—This compound was prepared as described above for the other 2-mercaptoimidazoles. The yield was 71%; m. p. 208–210°.

Anal. Calcd. for $C_6H_{10}N_2S$: N, 19.70. Found: N, 19.01.

Summary

A series of 1-substituted-2-mercaptoimidazoles has been synthesized, and some of the compounds have been tested for antithyroid activity in rats.

INDIANAPOLIS, INDIANA RECEIVED JUNE 9, 1949

(11) Knorr, *Ber.*, **32**, 729 (1899).

(12) Paal and Gember, *Arch. Pharm.*, **246**, 306 (1905).

(13) (a) Wohl and Lange, *Ber.*, **40**, 4727 (1907); (b) Rügheimer and Schön, *ibid.*, **41**, 17 (1908).

(14) Turner, THIS JOURNAL, **68**, 1607 (1946).

(15) Kuhn and Grundmann, *Ber.*, **70**, 1894 (1937).