TABLE I

PYRIDINE DERIVATIVES

2-Substituent	B. p., °C.	Mm.	M. p., °C., or $n^{20}D$	Yield, %	Derivative M. p., °C.	Formula	Analyses, % Calcd.	Found
β-Dimethylaminoethylamino-	105	4	1.5320	78.5[a]	223–224[e]	$C_9H_{14}N_3 \cdot 2HCl$	Cl, 29.79	29.78
β-Diethylaminoethylamino-	112–134	4		51[a]	170–171[g]	$C_{11}H_{18}N_3 \cdot 2HCl$	Cl, 26.65	26.62
γ-Aminopropylamino-	128	2	1.5750	20.7[b] 68.2[d]	204.5–205.0[f]	$C_8H_{12}N_3 \cdot 3$ p. a.[g]	N, 20.03	20.28
γ-(2-Pyridylamino)-propylamino-	220–225	1	113.5–114.0	33.8[c] 9.7[d]	218[f]	$C_{13}H_{14}N_4$	N, 24.50	24.35
ζ-Aminohexylamino-	147–148 162	1 3		28[b] 66.5[c]	165–166[f]	$C_{11}H_{18}N_3 \cdot 3$ p. a.[g]	N, 19.17	19.37
ζ-(2-Pyridylamino)-hexylamino-	205–220 185–198	3 1	149–149.7	31[b] 16[c]	222[f]	$C_{16}H_{22}N_4$	N, 20.71	20.66
γ-Diethylaminopropylamino-	105–107	0.8	1.5309	40[b]	163.5–164[f]	$C_{12}H_{21}N_3$	N, 20.26	20.03
γ-Di-*n*-butylaminopropylamino-	144–150	2	1.5087	26[b]	149–150[f]	$C_{16}H_{29}N_3 \cdot 3$ p. a.[g]	N, 17.28	17.11
γ-Piperidinopropylamino-	135	0.5	1.5505	48[b]	168.5–169[f]	$C_{12}H_{21}N_3 \cdot 2HCl$	N, 14.37 Cl, 24.26	14.28 24.19
γ-Morpholinopropylamino-	154–156	2	55–58	48[b] 74[c] 35[a]	220[f]	$C_{12}H_{19}N_3O$	N, 18.98	18.82
γ-Morpholinopropylamino-5-bromo-	182–185	1	76–77	51.6[b]	170–171[f]	$C_{12}H_{18}N_3OBr$	N, 13.99	14.10
δ-Morpholinobutylamino-	139–144	1	1.5455	28[b] 92.5[g]	191–192[f]	$C_{12}H_{21}N_3O \cdot 3$ p. a.[g]	N, 18.21	18.33
Di-(γ-piperidinopropyl)amino-	186–192	1	1.5337	48[b]	167.5–168[f]	$C_{21}H_{36}N_4 \cdot 3$ p. a.[g]	N, 17.91	18.11
p-Diethylaminophenylamino-	185–200	2	.....	40[b]	231[e] dec.	$C_{14}H_{19}N_3 \cdot 2HCl$	N, 13.36	13.21
p-Methoxyphenylamino-	.....	..	84	42[a]	165–166[f]	$C_{12}H_{12}N_2O$	N, 13.97	13.76
α-Methyl-γ-morpholinopropylamino-	165–168	2.5	45–47	40[b]	165–166[f]	$C_{13}H_{21}N_3O$	N, 17.85	17.84
α-Methyl-γ-piperidinopropylamino-	138–142	3	.....	48[b]	145–146.5[g]	$C_{14}H_{23}N_3 \cdot 2HCl$	N, 13.71	13.55
δ-Piperidinobutylamino-	148–152	2	1.5351	63.5[d]	148–149[e]	$C_{14}H_{23}N_3 \cdot 2HCl$	N, 13.71	13.78
γ-(β-Morpholinoethylamino)-propylamino-	170–171	2	1.5525[h]	30[c]	178[f]	$C_{14}H_{24}N_4O \cdot 3HCl$	N, 14.98	14.90
γ-(β-Diethylaminoethoxy)-propylamino-	140–142	1	1.5185	68.5[c]	111–112[f]	$C_{14}H_{25}N_3O$	N, 16.71	16.68

[a] Method I. [b] Method II. Equal molar amounts of reactants were used. [c] Method II. One molar excess of aliphatic diamine used. [d] Synthesized according to Method II. Two molar excess of aliphatic diamine used. [e] Hydrochloride. [f] Picrate derivative. [g] Yield based on the amount of aliphatic diamine used. [h] This material solidified on standing to a white, low melting solid. [i] The abbreviation p. a. is used for picric acid, $C_6H_3N_3O_7$.

mixture was then warmed with 20 g. of powdered sodium hydroxide in pyridine, the mixture filtered, and the filtrate distilled through a Claisen flask. After the pyridine and hexamethylenediamine had distilled over, 38.4 g. (66.5%) of 2-(ζ-aminohexylamino)-pyridine (b. p. 162–165 at 3 mm.) and 6.8 g. (16%) of 1,6-di-(2-pyridylamino)-hexane (b. p. 195–200 at 3 mm.) were collected. Both products solidified on cooling, the first to a low melting solid and the second, on crystallization from methanol, gave clusters of needles melting at 149–149.7°. Both gave crystalline picrates, the first melting at 165–166° and the second at 222°. The latter compound gave a hydrochloride which melted at 216°; Sharp[5] reported 216–218°.

Summary

Twenty basically-substituted 2-aminopyridine derivatives have been synthesized from 2-bromopyridine and an aminoalkylamine or from 2-aminopyridine and an aminoalkyl halide.

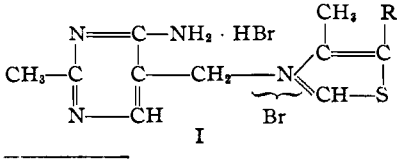
STATE COLLEGE, PA. RECEIVED NOVEMBER 4, 1944

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 994]

Thiamin Analogs. II. 4-Methylthiazole Analogs[1,2]

BY EDWIN R. BUCHMAN AND EDWIN M. RICHARDSON

The thiamin (vitamin B_1) molecule may be represented by formula (I)



I

(a) R = —H
(b) = —C_2H_5
(c) = —CH=CH_2
(d) = —CHOHCH_3
(e) = —$CH_2CH_2CH_2OH$
(f) = —$CH_2CHOHCH_3$
(g) = —CH_2OH

in which R = —CH_2CH_2OH. The present paper reports the synthesis and antineuritic properties of the seven vitamin analogs (Ia) to (Ig). These analogs were prepared by condensing the appropriate thiazole with a bromopyrimidine derivative, following the procedure used by Williams and Cline[3] in their synthesis of the vitamin. Compound (Ia) has previously been reported on by Bergel and Todd,[4] who obtained it by another method, the

(1) Paper XXII in the R. R. Williams series.

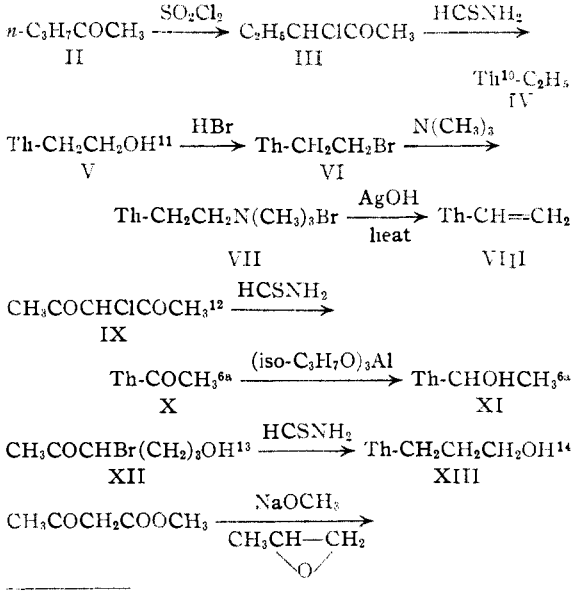
(2) The data relating to analogs (Ia)–(If) were presented before the Organic Division of the American Chemical Society at the Dallas meeting, April 1938. Analog (Ig) prepared by Dr. Herbert Sargent is included in the present paper.

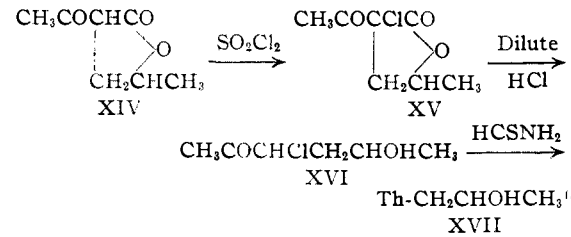
(3) Williams and Cline, THIS JOURNAL, **58**, 1504 (1936); Cline, Williams and Finkelstein, *ibid.*, **59**, 1052 (1937).

(4) Bergel and Todd, *J. Chem. Soc.*, 1504 (1937).

preparation of (Ie)[5] and of (Ig)[6] has been disclosed[6a] in a number of patents, and in addition physiological data[6a] on (Ic)[7] and on (Ig)[7] have been published.

4-Methylthiazole was obtained by a method given in the literature[8]; for the preparation of 4-methyl-5-hydroxymethylthiazole, see the following paper.[9] The synthesis of the remaining thiazole intermediates was carried out as indicated on the accompanying chart; wherever the synthetic route was not entirely free of ambiguities the constitution of the final product was independently confirmed (see Experimental).





Mr. W. L. Sampson of the Merck Institute for Therapeutic Research has tested the thiamin analogs for antineuritic activity by the rat curative method.[16] None of the substances exhibited vitamin B_1 potency in doses up to 500 γ. Thus even a small change in the nature of the thiazole-attached group R results in complete inactivity.[17]

Experimental[18]

The Synthesis of Thiazoles[19] from Crude Thioformamide.[20]—Extensive use has been made of this method

(5) The preparation of (Ie) is claimed both by the Williams-Cline[3] and by the Todd-Bergel[4] methods: (a) I. G. Farbenindustrie, A.-G., English Patent 471,416 (1937) [*C. A.*, **32**, 1051 (1938), *Chem. Zentr.*, **109**, 1, 939 (1938)]; (b) French Patent 816,432 (1937) [*C. A.*, **32**, 1870 (1938)]; (c) I. G. Farbenindustrie, A.-G. (Andersag and Westphal, inventors), German Patent 685,032 (1939) [*C. A.*, **34**, 3763 (1940)]; (d) Andersag and Westphal (to Winthrop Chemical Company, Inc.) U. S. Patent, 2,209,244 (1940) [*C. A.*, **35**, 282 (1941)]; (e) I. G. Farbenindustrie, A.-G., German Patent (Österreich) 159,315 (1940).

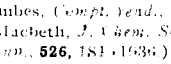
(6) The preparation of (Ig) by the Williams-Cline[3] method is reported: ref. 5a, c, e.

(6a) Since this paper was written, Bamngarten, Dornow, Gutschmidt and Krehl, *Ber.*, **75**, 442 (1942) [*C. A.*, **37**, 3091 (1943)], have described the preparation of (Id); biological assays indicated that the substance has no true antineuritic action. Our own findings substantiate the work of the German investigators.

(7) Schultz, *Z. physiol. Chem.*, **265**, 113 (1940); material supplied by Andersag and Westphal. The preparation of (Ic) has not been described.

(8) Clarke and Gurin, THIS JOURNAL, **57**, 1876 (1935).

(9) Buchman and Sargent, *ibid.*, **67**, 400 (1945).

(10) Th— = 

(11) Buchman, *ibid.*, **58**, 1893 (1936).

(12) (a) Combes, *Compt. rend.*, **111**, 273 (1890); [*Ber.*, **23R**, 687 (1890)]; (b) Macbeth, *J. Chem. Soc.*, **121**, 1120 (1922); (c) Neber and Wörner, *Ann.*, **526**, 181 (1936).

(13) Bergmann and Miekeley, *Ann.*, **432**, 341 (1923).

(14) Previously prepared by another method: I. G. Farbenindustrie, A. G., English Patent 456,735 (1936) [*C. A.*, **31**, 2232 (1937), *Chem. Zentr.*, **108**, I, 2819 (1937)].

(15) This compound is mentioned in the patent literature, English Patent 456,735 [*C. A.*, **31**, 2232 (1937), *Chem. Zentr.*, **108**, I, 2819 (1937)]; its preparation has not been described.

(16) The negative results are in agreement with previous reports on (Ia),[4] (Ic)[7] and (Id).[6a] For (Ig) Schultz[7] reported antineuritic potency with pigeons; the discrepancy may be traced to the difference in test object. For other physiological properties of compounds described in this paper see: Bonner, *Am. J. Botany*, **25**, 543 (1938); Bonner and Buchman, *Proc. Natl. Acad. Sci.*, **24**, 431 (1938); Bonner and Erickson, *Am. J. Botany*, **25**, 685 (1938); Knight and McIlwain, *Biochem. J.*, **32**, 1241 (1938); A. Lwoff and M. Lwoff *Compt. rend. soc. biol.*, **127**, 1170 (1938); A. Lwoff and Dusi, *ibid.*, **128**, 238 (1938); Ochoa and Peters, *Biochem. J.*, **32**, 1502 (1938), Robbins and Kavanah, *Proc. Natl. Acad. Sci.*, **24**, 145 (1938); Bonner and Buchman, *ibid.*, **25**, 164 (1939); Summary: Schopfer, *Ergeb. Biol.*, **16**, 74 (1939). Compounds (Ia), (Ie) and (If) were found to have substantially no vitamin activity with *Propionibacterium pentosaceum* (private communication from C. H. Werkman). The hydroxythiazoles were tested with a like result on a *Neurospora* mutant requiring vitamin thiazole (private communication from E. L. Tatum).

(17) Compare Stein, Sampson, Cline and Stevens, THIS JOURNAL, **63**, 2059 (1941).

(18) All melting points are corrected. A portion of the work reported was carried out by the senior author at The Johns Hopkins University. In connection with the preparation of cocarboxylase analogs (unpublished), the greater part of the experiments described here has been repeated in this Laboratory by Drs. H. Sargent and M. J. Schlatter; supplementing observations due to these investigators have been included in the present paper.

(19) See (a) Willstätter and Wirth, *Ber.*, **42**, 1908 (1909); (b)[8]; (c)[11]; (d) Cerecedo and Tolpin, THIS JOURNAL, **59**, 1660 (1937), (e) Buchman and Richardson, *ibid.*, **61**, 891 (1939); (f) Stevens and Stein, *ibid.*, **62**, 1045 (1940); (g) Buchman, Reims and Sargent, *J. Org. Chem.*, **6**, 768 (1941); (h) Todd, Bergel and Jacob, *J. Chem. Soc.*, 1555 (1936); (i) Harington and Moggridge, *ibid.*, 443 (1939); (j) Erlenmeyer and co-workers, *Helv. Chim. Acta*, **20**, 204 (1937); **22**, 938 (1939); **23**, 197 (1940); **25**, 362, 528 (1942); (k) Ochiai and co-workers, *J. Pharm. Soc. Japan*, **59**, 228, 462 (1939) [*C. A.*, **34**, 101 (1940)]; *Ber.*, **73**, 28 (1940); (l) Pesina, *J. Gen. Chem.* (U. S. S. R.), **9**, 804 (1939) [*C. A.*, **34**, 426 (1940)]; (m)[9]; (n)[6a]; numerous recent patents. On the basis of experience in this laboratory the method may be recommended almost without reserve for the preparation of thiazoles unsubstituted in the 2-position; compare however: (o) McLean and Muir, *J. Chem. Soc.*, 383 (1942); (p) Erlenmeyer and Morel, *Helv. Chim. Acta*, **25**, 1074 (1942); the reaction[9] between thioformamide and 3,4-dibromobutanone-2 or 2,3-dibromopropanal.

(20) Gabriel, *Ber.*, **49**, 1115 (1916). Although the purity of the thioformamide used undoubtedly influences the yield of thiazole obtained, this factor has not yet been investigated thoroughly; the Gabriel preparation (may be kept for several days at 0° without apparent deterioration) was found satisfactory in the cases discussed here.

in this Laboratory. Because of the unstable nature of thioformamide, it is essential that its reaction with an α-halogen ketone be carried out at the lowest feasible temperature. Most α-chloro ketones react smoothly at room temperature; in the case of α-bromo ketones and of especially reactive α-chloro ketones, it was found advisable to bring the reactants together at 0° or below and to provide for external cooling since the reaction may be strongly exothermic. Unless otherwise specified the α-halogen ketone was mixed at 0° with 1.5 to 2 times the theoretical of crude thioformamide and a small amount of absolute alcohol. The reaction mixture was allowed to stand for periods up to seven days in the ice box (omit in the case of less reactive halogen ketones), and then for periods up to two weeks at room temperature (reaction usually complete in three to four days). The product was then treated with excess 6 *N* hydrochloric acid and washed with ether to remove non-basic material. The ether extract rarely contained any significant amount of unreacted α-halogen ketone. However, in order to recover from it small amounts of thiazole, it was extracted with small portions of aqueous hydrochloric acid and the hydrochloric acid extracts combined with the main reaction product. This latter was made alkaline by the addition of a large excess of concentrated aqueous alkali (alkali carbonate was used in the case of thiazole esters and other thiazoles altered by caustic alkali). Usually the thiazole separated as an oil; solid alkali hydroxide or alkali carbonate was added to saturation and the base extracted with ether. Since most thiazoles readily give a precipitate[21] when treated with ethereal picric acid, in the case of these substances the extraction was continued until a negative test was obtained with this reagent. The ether solution was dried over sodium sulfate or caustic alkali (the latter can be used only in case of simple alkyl thiazoles; in the case of hydroxyalkyl thiazoles, there is a certain amount of interaction) and distilled. Final purification was effected by fractionation, usually *in vacuo*, or in special cases by conversion to a crystalline derivative and regeneration.

4-Methylthiazole was prepared[8] from chloroacetone in 32% yield, b. p. (743 mm.) 132.1–132.4°, d^{25}_4 1.112, picrate, m. p. 184.5°[19a,c] (analysis).

3-Chloropentanone-2 (III)[22] (a).—The chlorination of 43 g. (0.5 mole) of methyl *n*-propyl ketone (II) (b. p. 101–102°) diluted with 50 cc. of C. P. benzene was accomplished by adding 63 g. (0.5 mole) of sulfuryl chloride over a twenty-minute period while excluding moisture, stirring and keeping the temperature at 20° by external cooling. The reaction mixture was fractionated *in vacuo*, 26.5 g. (44% yield) of (III) boiling at 62–66° (56 mm.) being obtained.

(b) Twenty-five grams of α-chloro-α-ethylacetoacetic ester (b. p. (2 mm.) 58–60°, obtained in 86% yield by chlorination[23] of ethyl α-ethylacetoacetate in benzene solution with sulfuryl chloride) was heated under reflux from a bath at 100° with 80 cc. of glacial acetic acid and 20 cc. of concentrated C. P. hydrochloric acid[24]; gas was given off slowly. After twenty hours of heating, the reaction mixture was cooled, neutralized with alkali and extracted with ether. Fractionation of the ether extract gave 1.6 g. of (III), the major portion of which boiled at 61–62° (56 mm.), 130–132° (745 mm.), and 8 g. of unchanged α-chloro-α-ethylacetoacetic ester.

4-Methyl-5-ethylthiazole (IV) was made from (III) prepared by each of the above methods; the products obtained were identical in all respects. Chlorinated (II) (26.5 g.) was condensed with 20 g. of thioformamide and 25 cc. of alcohol. Refractionation of the resulting 11 g. of crude thiazole gave 8.8 g. (29%), b. p. 78–79° (25 mm.), b. p. 169.5–170° (745 mm.), d^{25}_4 1.042.

Anal. Calcd. for C_6H_9NS: C, 56.65; H, 7.13; N, 11.01. Found: C, 56.57; H, 6.82; N, 11.14.

The picrate was recrystallized from alcohol, m. p. 164.7–165.1°; the methiodide from methanol–ether, m. p. 130.5–131.5°. (IV) was also obtained from $ThCH_2$-CH_2Cl.[11] One gram of the latter was heated at 140–150° in a sealed tube for eight hours with 10 cc. of 57% aqueous hydriodic acid. The resulting solution was then stirred at 0° while 6 g. of zinc dust and 7 cc. additional of hydriodic acid were added over twenty-four hours. The mixture was made alkaline and steam distilled; extraction of the distillate with ether gave a small amount of base from which picrate and methiodide were prepared. These were shown (mixed m. p.[25]) to be identical with material made from (III).

4-Methyl-5-(β-bromoethyl)-thiazole (VI).—Ten grams of vitamin thiazole[11] (V) was cautiously mixed with 100 cc. of hydrobromic acid (aqueous solution saturated at room temperature), the mixture placed in a sealed tube and heated for twelve hours at 100°. The contents of the tube were evaporated on a steam-bath at reduced pressure to a small volume, cooled and diluted with water. Excess potassium carbonate was added and the liberated base taken up in ether, dried over sodium sulfate and distilled from a bath at below 110°,[26] yield 11.3 g. (78%), b. p. 87–88° (2 mm.).[27]

Anal. Calcd. for C_6H_8BrNS: C, 34.96; H, 3.91. Found: C, 34.82; H, 4.13.

The stable picrate was recrystallized from ethanol–water, m. p. 128.3–128.5°. (VI) has only a limited stability; after twelve hours at room temperature it had become cloudy and on longer standing was entirely converted to a solid polymer.[28]

[β-(4-Methylthiazolyl-5)-ethyl]-trimethylammonium Bromide (VII).—Freshly distilled (VI) (11.3 g.) was mixed with 50 cc. of trimethylamine solution (36% in benzene) and heated in a sealed tube for twelve hours at 100°. The crystalline product was filtered off, washed with ether and dried, yield 11.0 g. (76%), m. p. 228.0–228.5° from absolute ethanol.

Anal. Calcd. for $C_9H_{17}BrN_2S$: C, 40.76; H, 6.46; N, 10.56. Found: C, 40.99; H, 6.69; N, 10.60.

The corresponding chloride was made from $ThCH_2$-CH_2Cl[11]; after twenty-four hours of heating at 100° with 36% trimethylamine solution the yield of product was 60% (unreacted chlorothiazole was recovered). The quaternary chloride is an extremely hygroscopic crystalline solid, easily soluble in water and alcohol.

4-Methyl-5-vinylthiazole (VIII).—Ten grams of (VII) (chloride could also be used) was dissolved in 30 cc. of water, silver oxide from 10 g. of silver nitrate was added and the suspension shaken for one hour. After filtering and washing with a little water, the filtrate (*ca.* 70 cc.) was treated with 6 g. of potassium hydroxide and the resulting solution refluxed for thirty minutes.[29] The decomposition

(21) Four exceptions of similar structure have been noted: $Th^{19}COOCH_3$, $ThCOOC_2H_5$, ThCHO and $ThCOCH_3$. The picrates of these compounds are quite appreciably soluble in ether and crystallize from the solution only on strong cooling; $ThCOOCH_3$ picrate, m. p. 107.6–107.8° from isopropyl ether.

(22) (a) Conrad, *Ann.*, **186**, 241 (1877); (b) Vladesco, *Bull. soc. chim.*, [3] **6**, 832 (1891); (c) Korschun, *ibid.*, [4] **3**, 595 (1908), the b. p. 63° (95 mm.) reported is in error.

(23) Compare (a) Forster and Newman, *J. Chem. Soc.*, **97**, 1365 (1910), the b. p. (0.3 mm.) 64° reported is in error; (b) Macbeth, *ibid.*, **123**, 1125 (1923).

(24) *Cf.* ref. 22a; under these conditions α-ethylacetoacetic ester is readily converted to (II). That α,α-disubstituted acetoacetic esters offer greater resistance to hydrolysis has been recognized; see for instance, Hudson and Hauser, THIS JOURNAL, **63**, 3163 (1941).

(25) The picrates of (IV) and of (V) give only a very small m. p. depression when mixed.

(26) Higher temperatures resulted in extensive polymerization.

(27) Ref. 14 and also German Patent 702,831 (1941) (Andersag and Westphal inventors) issued to I. G. Farbenindustrie, A.-G. describe the preparation of this compound by another method, b. p. 95° (3 mm.), picrate m. p. 129°.

(28) $ThCH_2CH_2Cl$, previously reported[11] to be stable, is in fact much more stable than (VI). On long standing, however, it also polymerizes and some samples have been observed to pass to a solid.

(29) Aqueous solutions of the quaternary base are unstable; an attempt to evaporate such a solution prior to decomposition resulted in a much poorer yield.

took place smoothly; (VIII) separated as an oil which was isolated by extracting with ether and distilling at reduced pressure, b. p. 76–78° (21 mm.), yield 2.6 g. (55%), d^{22}_4 1.090.

Anal. Calcd. for C_6H_7NS: C, 57.56; H, 5.64; N, 11.19. Found: C, 57.23; H, 5.23; N, 10.71.

The base on standing at room temperature was soon converted to a thick viscous polymer (*cf.* styrene). The picrate was recrystallized from ethanol, m. p. 162.2–162.7°, not appreciably altered on standing.

4-Methyl-5-acetylthiazole (X).[6a]—Sulfuryl chloride (62.5 g. = 0.5 mole) was added slowly at room temperature with stirring over a period of four hours to 50 g. (0.5 mole) of acetylacetone (b. p. 69–70° (99 mm.)) mixed with 50 cc. of C. P. benzene. Fractionation of the product yielded 53 g. (79%)[30] of chloroacetylacetone (IX), b. p. 56–59° (28 mm.).

Twenty-five grams of (IX) reacted with 17 g. of thioformamide; 15.3 g. (55%) of product was obtained, the major portion of which boiled at 96–97° (9 mm.) and crystallized on standing, m. p. 27.5°.

Anal. Calcd. for C_6H_7NOS: C, 51.04; H, 5.00; N, 9.92. Found: C, 51.26; H, 4.95; N, 10.08.

(X) has a characteristic odor, picrate,[21] m. p. 107.6–108.0° from ethyl acetate–ether.

4-Methyl-5-(α-hydroxyethyl)-thiazole (XI).[6a,31]—Five grams of (X) together with 8.5 g. of aluminum isopropoxide and 110 cc. of absolute isopropyl alcohol were introduced into a flask equipped with fractionating column and distilled at such a rate (bath temperature 120–140°) that the acetone formed during the reaction was removed. After four hours of heating the distillate gave no further test for acetone. The material in the flask was treated with a small amount of water and solid potassium hydroxide and repeatedly extracted with ether. The combined extracts were dried with sodium sulfate and distilled *in vacuo* yielding 3.9 g. (78%) of product boiling for the most part at 103–104° (2 mm.).

Anal. Calcd. for C_6H_9NOS: C, 50.32; H, 6.34; N, 9.78. Found: C, 50.85; H, 6.17; N, 9.51.

(XI) is a quite viscous oil d^{25}_4 1.172, picrate, m. p. 142.1–143.1° from alcohol.

Pentanol-4-one-2[32] was brominated in aqueous solution with one molecular equivalent of bromine and the product extracted with ether. After drying the extract and removing solvent *in vacuo*, the crude bromide was condensed with thioformamide to give a small yield of thiazole which was converted to the picrate, m. p. 117.2–117.7°[33] after recrystallization from ethanol and from ethyl acetate.

Anal. Calcd. for $C_{12}H_{12}N_4O_8S$: C, 38.71; H, 3.25; N, 15.05. Found: C, 38.91; H, 3.51; N, 14.69.

This picrate is presumably derived from 4-(β-hydroxypropyl)-thiazole formed from a bromo ketone consisting mainly of 1-bromopentanol-4-one-2 (*cf.* bromination[9] of ketobutyl alcohol).

4-Methyl-5-(γ-hydroxypropyl)-thiazole (XIII).—5-Methyl-1,2-dihydropyrane[34] (30 g., b. p. 106.3–106.4°) was mixed with 150 cc. of water, to which a few drops of hydrobromic acid had been added, and stirred at room temperature for one-half hour. A slightly exothermic reaction took place and after fifteen minutes the organic phase had disappeared. The resulting acetobutyl alcohol solution[35] was treated (compare ref. 13) with 50.0 g. (2% excess) of bromine which was added slowly with stirring over a period of one and one-half hours while the temperature was maintained at 5–10°; a second phase appeared when about half the bromine had been added. The crude product (XII) was isolated by extraction with ether, the extracts were dried over sodium sulfate and solvent was removed at 30 mm. and temperatures below 50°; yield 52.2 g. of only slightly colored oil.

This material was cooled to −10° and mixed with 25 g. of thioformamide and 30 cc. of methanol which also had been cooled to −10°. The condensation proceeded smoothly and yielded 23.3 g. of distilled thiazole (48% from the dihydropyrane). The base was converted to the picrate by addition to the theoretical amount of picric acid in ethyl acetate, yield 49.5 g. (86%), m. p. 105.6–106.2° from alcohol, analysis for $C_{18}H_{14}N_4O_8S$.

A careful search failed to disclose any significant amount of isomeric picrate in the mother liquors (in one experiment a few crystals of material m. p. 140–141° were obtained from mother liquors; the amount did not suffice for purification); thus the monobromination of acetobutyl alcohol gives essentially one product. The free base was regenerated from the picrate by treating with aqueous hydrochloric acid, removing picric acid with ethyl acetate and liberating from the hydrochloride with alkali as usual, yield 88%, b. p. 122–124° (2 mm.), d^{26}_4 1.150.

Anal. Calcd. for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.28; H, 7.04; N, 8.90.

(XIII) (1.4 g.) was treated with 14 cc. of concentrated nitric acid and the mixture heated for six and one-half hours at 40°. After evaporation *in vacuo*, the residue was dissolved in water and sulfate ion quantitatively removed by addition of an equivalent amount of barium nitrate solution. The resulting solution was again evaporated, taken up in a small volume of dilute potassium hydroxide solution and concentrated hydrochloric acid added cautiously. β-(4-Methylthiazolyl-5)-propionic acid (0.75 g.) precipitated, was washed with water and recrystallized from methanol using Norite, m. p. 179.0–179.5°.

Anal. Calcd. for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18 Found: C, 49.04; H, 5.65; N, 8.49.

A portion of the acid was methylated with ethereal diazomethane and the product sublimed in a small still. The methyl ester (oily), picrate, m. p. 120–121°, on heating for fourteen hours in a sealed tube at 120–130° with saturated methyl alcoholic ammonia, gave the corresponding amide, m. p. 97–98°[36] from dioxane–ether.

α-Aceto-γ-valerolactone (XIV).[37]—To a solution of 69 g. (3 moles) of sodium in 1000 cc. of absolute methanol, 348 g. (3 moles) of methyl acetoacetate was first added, and then over a period of seventy-five minutes 173 g. (3 moles) of propylene oxide (b. p. 33.5°) slowly with stirring (ice-bath, anhydrous conditions). The temperature was allowed to rise slowly to room temperature and after standing for twelve hours the solvent was removed under water pump vacuum. The white solid residue was dissolved in ice-water and the solution acidified with sulfuric acid at 0° and extracted repeatedly with ether. The extracts after drying over sodium sulfate were fractionated *in vacuo*, b. p. 120–128° (15 mm.), yield 162.5 g. (38%); refractionated material boiled at 125° (15 mm.).

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.85; H, 7.33.

α-Chloro-α-aceto-γ-valerolactone (XV).—The above 162.5 g. of (XIV) was mixed with 150 cc. of C. P. benzene

(30) These conditions are apparently superior to those given in the literature.[12c]

(31) Reduction of (X) with aluminum amalgam gave a small amount of a crystalline substance (pinacol) and other oily material boiling higher than the desired alcohol.

(32) Claisen, *Ber.*, **25**, 3164 (1892); *Ann.*, **306**, 324 (1899); Wuhl and Maag, *Ber.*, **43**, 3283 (1910).

(33) In another similar experiment a picrate, m. p. 160.0–160.5°, was obtained; it did not depress the m. p. when mixed with the picrate of like properties obtained[9] from crude ketobutyl alcohol.

(34) Lipp, *Ann.*, **289**, 187 (1896).

(35) A solution containing acetobutyl alcohol may conveniently be prepared by heating 5-methyl-4-carbethoxy-1,2-dihydropyrane (Perkin, *J. Chem. Soc.*, **51**, 709 (1887)) with an equal volume of 0.6 *N* hydrochloric acid for one hour at 100°.

(36) The preparation of this compound (m. p. 96°) by another method has been reported, ref. 14; Andersag and Westphal (to Winthrop Chemical Company, Inc.) U. S. Patent 2,139,570 (1938); I. G. Farbenindustrie, A.-G., German Patent 704,236 (1941).

(37) This compound, made by the method described here, is referred to in English Patent 459,453 (1937) issued to I. G. Farbenindustrie, A.-G. It is erroneously termed α-aceto-β-methylbutyrolactone (*C. A.*, *Zentr.*, **108**, I, 4827 (1937)).

and 154.5 g. of sulfuryl chloride was added slowly with stirring at 0° over a period of four and one-half hours taking precautions to exclude moisture. The reaction mixture was distilled *in vacuo* yielding 178 g. (88%) of (XV), b. p. 78–84° (3 mm.). A portion b. p. 83° (3 mm.), was analyzed.

Anal. Calcd. for $C_7H_9ClO_3$: C, 47.60; H, 5.14; Cl, 20.08. Found: C, 47.22; H, 5.08; Cl, 20.51.

3-Chlorohexanol-5-one-2 (XVI).[38]—To 30 g. of (XV), 300 cc. of water and 60 cc. of C. P. concentrated hydrochloric acid were added, and the mixture heated under reflux from a bath at 100° for one and one-half hours during which carbon dioxide was evolved and the chloro lactone went into solution. After having been saturated with ammonium sulfate, the solution was repeatedly extracted with ether, and the extracts dried over sodium sulfate and distilled, yield 17.7 g. (69%) b. p. 69–75° (2 mm.).

Anal. Calcd. for $C_6H_{11}ClO_2$: C, 47.85; H, 7.36; Cl, 23.54. Found: C, 47.71; H, 7.33; Cl, 23.17.

4-Methyl-5-(β-hydroxypropyl)-thiazole (XVII).[39]—The reaction between 19.5 g. of (XVI) and 12 g. of thioformamide gave 5.0 g. of crude (XVII) (24%). This was purified[40] (compare (XIII)) via the picrate, m. p. 166.5–167.0° from ethanol, analysis for $C_{13}H_{14}N_4O_8S$. The regenerated thiazole boiled at 105° (2 mm.), d^{23}_4 1.149.

Anal. Calcd. for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.96; H, 6.81; N, 8.72.

The base readily gave a positive iodoform test which is in agreement[41] with the assigned structure and that of α-aceto-γ-valerolactone.

Preparation of Thiamin Analogs.—Equal weights of 2-methyl-6-amino-5-bromomethylpyrimidine dihydrobromide (obtained from Merck and Co., Inc., and giving analytical figures close to those expected), the appropriate thiazole, and of *n*-butyl alcohol were heated[3] for fifteen to twenty minutes in a bath maintained at 115–120° while stirring occasionally to ensure intimate mixing. Usually complete solution took place and, in the course of the reaction, the analog crystallized out. The solid product was thoroughly washed with anhydrous ether and with small portions of cold absolute alcohol, after which it was recrystallized, preferably with the aid of decolorizing charcoal. Suitable solvents included methanol, methanol–ethanol and aqueous ethanol. No attempt was made to study the reaction from standpoint of yield; the yields of pure analog actually obtained varied from 9% in the case of (Ic) to 31% in the case of (Ib). Further pertinent data are given in the accompanying table.

TABLE I

	Formula	Melting point °C.	From
Ia[h]	$C_{10}H_{14}Br_2N_4S$[a]	274 dec.	Ethanol–water
Ib	$C_{13}H_{18}Br_2N_4S$[b]	256 dec.	Methanol–water
Ic	$C_{13}H_{14}Br_2N_4S$[c]	248 dec.	Ethanol–water
Id	$C_{13}H_{16}Br_2N_4OS\cdot{}^1/_2H_2O$[d]	251 dec.[k]	Ethanol–water
Ie	$C_{13}H_{20}Br_2N_4OS\cdot{}^1/_2H_2O$[e]	228.5[i]	96% ethanol
If	$C_{13}H_{20}Br_2N_4OS\cdot{}^1/_2H_2O$[f]	237 dec.	96% ethanol
Ig	$C_{11}H_{16}Br_2N_4OS\cdot{}^1/_2H_2O$[g]	231[j] dec.	Ethanol–water

[a] *Anal.* Calcd.: C, 31.43; H, 3.69; N, 14.66. Found: C, 31.45; H, 3.56; N, 14.62. [b] *Anal.* Calcd.: C, 35.13; H, 4.42; N, 13.66. Found: C, 34.84; H, 4.42; N, 13.76. [c] *Anal.* Calcd.: C, 35.31; H, 3.95; N, 13.73. Found: C, 35.21; H, 4.22; N, 13.31. [d] *Anal.* Calcd.: C, 33.11; H, 4.40; N, 12.87. Found: C, 32.31; H, 4.42; N, 12.83 (the carbon value was consistently low on this sample). [e] *Anal.* Calcd.: C, 34.75; H, 4.71; N, 12.47. Found: C, 34.67; H, 4.78; N, 12.52. [f] *Anal.* Calcd.: C, 34.75; H, 4.71; N, 12.47. Found: C, 35.08; H, 4.75; N, 12.57. [g] *Anal.* Calcd.: C, 31.37; H, 4.07; N, 13.30. Found: C, 31.51; H, 4.05; N, 13.37. [h] A 77% yield of crude Ia was obtained by allowing the pyrimidine hydrobromide to stand for six months at room temperature with an excess of thiazole. [i] Ref. 5 gives m. p. 226°. [j] Ref. 6 gives m. p. 227°. [k] Ref. 6a gives m. p. 231° dec.

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Summary

The preparation is described of seven thiamin analogs differing from the vitamin only with respect to the group attached to the thiazole ring in the 5-position. When tested on rats, none of these analogs was found to possess vitamin B_1 activity.

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(38) The stability of this compound is noteworthy. Stevens and Stein have shown[19f] that 3-chloropentanol-5-one-2 has a great tendency to pass into a dimeric ether. Note also that (XV) (compare also hydrolysis[11] of α-chloro-α-acetobutyrolactone) is easily hydrolyzed whereas α-chloro-α-ethylacetoacetic ester (above) is not.

(39) An attempt to prepare 4-methyl-5-acetonylthiazole failed; chlorination of acetonylacetone with sulfuryl chloride yielded much tar; compare Gray (*J. Chem. Soc.*, **79**, 682 (1901)).

(40) The crude thiazole exhibited to a significant extent the biological activity associated with vitamin thiazole (V); the picrate was recrystallized until negative results were obtained in the *Phycomyces* test.[16]

(41) See Fuson and Tullock, THIS JOURNAL, **56**, 1638 (1934).