[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, MEDICAL RESEARCH DIVISION, SHARP AND DOHME, INC.]

Derivatives of 2-Amino-4-methylthiazole

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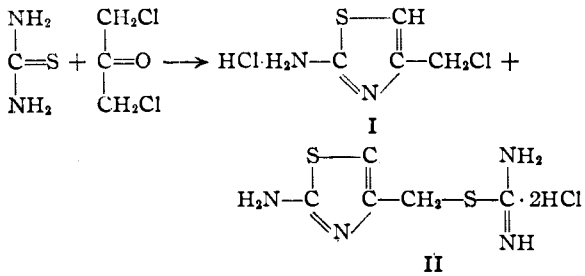
Derivatives of 2-amino-4-methylthiazole containing functional substituents on the methyl group were required as starting materials for further syntheses. A number of compounds of this type were prepared and the compounds in which the substituent is chloro, dialkylamino, hydroxy or alkylmercapto are described in this paper.

2-Amino-4-chloromethylthiazole served as a convenient starting material for the introduction of most of the substituent groups. For the synthesis of this compound the reaction between α,γ-dichloroacetone and thiourea was investigated. Previously Suter and Johnson[1] had found that α,γ-dichloroacetone reacted in a normal fashion with aromatic thioamides to yield 2-aryl-4-chloromethylthiazoles. However, Sheppard and Brigham[2] have reported the formation of 2-thiono-5-ketohexahydropyrimidine (III) from the reaction of thiourea with α,γ-dichloroacetone. In the present work, an investigation of this reaction has failed to disclose any product having the properties expected of the pyrimidine III. All conditions that we have tried have led to satisfactory yields of either the hydrochloride of 2-amino-4-chloromethylthiazole (I) or the di-hydrochloride of S-(2-amino-4-thiazolylmethyl)-isothiourea (II). No



I

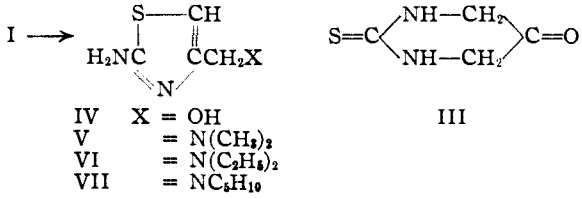
II

satisfactory explanation of this discrepancy in results is apparent. It is noteworthy, however, that although Sheppard and Brigham did not report the presence of chlorine in their product and observed a different behavior toward hot aqueous silver nitrate solution, the other properties of their compound (alcohol solubility, melting point and nitrogen and sulfur content) were similar to those of II.

When equimolecular amounts of α,γ-dichloroacetone and thiourea reacted in acetone solution at room temperature, I was obtained in 50–60% yields together with a small amount of II. The use of two equivalents of thiourea in alcohol solution led to an 85% yield of II. In alcohol solution the chloromethylthiazole I reacted readily with thiourea to give a nearly quantitative yield of the isothiourea II. From these results it is evident that 2-amino-4-chloromethylthiazole (I) is the primary product of the reaction between thiourea and α,γ-dichloroacetone and that the isothiourea II is a secondary product formed by the reaction of I with thiourea.

An isothiourea structure similar to II was assigned by Conrad and Schmidt[3] to the compound that they obtained by the reaction of β,δ-dibromolevulinic acid and thiourea.

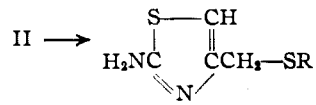
The chloromethyl group of I is very reactive toward a number of reagents. On heating with water, I was converted smoothly to 2-amino-4-hydroxymethylthiazole (IV). Reaction with dimethylamine, diethylamine or piperidine gave the corresponding tertiary amines V–VII. Because of the difficulty of isolating pure products the yields of the amines were only 30–50%. Under similar conditions no crystalline product was obtained when morpholine was used.



IV X = OH
V = $N(CH_3)_2$
VI = $N(C_2H_5)_2$
VII = NC_5H_{10}

III

The preparation of the mercapto compounds VIII–XII was accomplished through the use of the isothiourea II. The isothiourea structure was substantiated by its cleavage by alkali to the thiol, 2-amino-4-mercaptomethylthiazole (VIII). Although VIII was not isolated, its presence was indicated by a positive nitroprusside test for the mercapto group and by the production in good yield of the disulfide by the action of mild oxidizing agents. Treatment of II in alkaline solution with alkylating agents such as methyl sulfate, ethyl bromide, chloroacetic acid or ethyl chloroacetate gave the mercapto compounds, IX–XII.



VIII R = —H
IX = $—CH_3$
X = $—C_2H_5$
XI = $—CH_2CO_2H$
XII = $—CH_2CO_2C_2H_5$

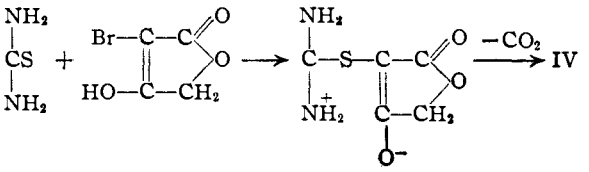
The reaction of α-bromotetronic acid with thiourea served as an alternate method for the synthesis of 2-amino-4-hydroxymethylthiazole. In aqueous solution this reaction gave a crystalline, bromine-free product that did not contain the char-

(1) Suter and Johnson, *Rec. trav. chim.*, **49**, 1066 (1930).

(2) Sheppard and Brigham, THIS JOURNAL, **58**, 1046 (1936).

(3) Conrad and Schmidt, *Ann.*, **285**, 210 (1895).

acteristic diazotizable amino group of 2-aminothiazoles and that exhibited properties and a nitrogen content consistent with the formulation as an inner enol-isothiouronium salt XIII. In the presence of acid, XIII slowly evolved carbon dioxide and 2-amino-4-hydroxymethylthiazole (IV) was formed.



XIII

The tertiary amino derivatives V–VII were prepared also by a second method which is an extension of the usual Traumann[4] synthesis of 2-aminothiazole and its derivatives. Dialkylaminoacetone hydrobromides were brominated and the crude bromoaminoacetones were treated with thiourea to yield thiazoles that were identical with those obtained from the reaction of 2-amino-4-chloromethylthiazole with the corresponding secondary amines. Although the yields of crude bromoaminoacetones were low, the yields of thiazoles from the bromo ketones were generally good. In the case of the diethylamino derivative X this was the more satisfactory method of preparation. No attempt was made to purify the bromoacetones and to ascertain their exact structure. The identity of the thiazoles that were prepared by both methods shows that a primary bromo compound XIV was formed. Because of the low yield of bromoaminoacetones, the concurrent formation of some secondary bromide resulting from the entry of bromine into a methylene group is not excluded.

$$CH_3COCH_2NR_2 \longrightarrow BrCH_2COCH_2NR_2 \xrightarrow{\text{Thiourea}} \text{V-VII}$$

XIV

The 2-aminothiazole structures for the products I and II are supported by their properties and the properties of the products prepared from them. The preparation of some of these by alternate methods lends additional support. Furthermore, all of these compounds that have a free amino group in the 2-position undergo diazotization and coupling with dimethyl-α-naphthylamine to give an unstable color that has been found to be characteristic of a large number of 2-aminothiazoles. Conclusive proof of the 2-aminothiazole structure was obtained by the catalytic dechlorination of I to give 2-amino-4-methylthiazole.

Experimental[5]

The diazotization and coupling test used for characterization of the 2-aminothiazoles was carried out in the following manner:

Five drops of 0.1% sodium nitrite solution was added to a solution of about 5 mg. of the amine in 5 ml. of water and one drop of concentrated hydrochloric acid. After one minute of shaking several ml. of 0.25% alcoholic α-naphthyldimethylamine was added without mixing. The color (usually blue or purple) developed at the interface of the two solutions. The characteristic color usually changed to brown after a few minutes. When the sample was too large the brown color frequently appeared immediately and obscured the characteristic color obtainable with a more dilute solution.

2-Amino-4-chloromethylthiazole Hydrochloride I.—A solution of 25.4 g. (0.2 mole) of α,γ-dichloroacetone in 100 ml. of acetone was stirred while a solution of 15.2 g. (0.2 mole) of thiourea in 500 ml. of acetone was dropped in at a fairly rapid rate. A clear oil began to separate when the addition was about one quarter complete. The mixture stood overnight during which time the oil solidified to a mass of white crystals. After decantation of the acetone, the solid was stirred with 200 ml. of anhydrous ethanol. The insoluble residue of the isothiourea II weighed 5.8 g., m. p. 250–253° dec. The alcohol extract was stirred vigorously while it was diluted with 300 ml. of ligroin. The product separated as an oil which soon crystallized. Seventeen and eight-tenths grams of crystals, m. p. 145–146°, was obtained. An additional 3.8 g., m. p. 144–145°, was obtained by diluting the acetone mother liquor with ligroin and reprecipitating the crude solid as described above. The total yield was 58.5%. Two recrystallizations from a mixture of ethanol and ethyl acetate raised the melting point to 148–149°.

Anal. Calcd. for $C_4H_6N_2Cl_2S$: N, 15.14; Cl, 38.32; S, 17.33. Found: N, 15.06; Cl, 38.55; S, 17.24.

The diazotization test gave a blue color.

2-Amino-4-methylthiazole.—Three and seven-tenths grams (0.02 mole) of 2-amino-4-chloromethylthiazole hydrochloride was dissolved in 50 ml. of ethanol and hydrogenated in the presence of 0.3 g. of 10% palladized charcoal. When the absorption of hydrogen had become very slow, the solution was filtered and 0.3 g. of fresh catalyst was added. Three 0.3-g. portions of catalyst were used. The absorption of hydrogen ceased after the consumption of 0.0233 mole. The catalyst then was removed by filtration and the alcohol solution evaporated to dryness. The residue was dissolved in 5 ml. of water, the solution made basic with 20% sodium hydroxide and extracted with ether. After drying over magnesium sulfate the ether was evaporated and the residue distilled *in vacuo*. The distillate, b. p. 124–126° (20 mm.), m. p.[6] 45–46°, weighed 1.1 g. Acetylation with acetic anhydride gave a product, m. p. 134–135°, that did not depress the melting point of an authentic sample of 2-acetamido-4-methylthiazole.[6]

S-(2-Amino-4-thiazolylmethyl)-isothiourea Dihydrochloride. A. From I.—One and eight-tenths grams (0.01 mole) of 2-amino-4-chloromethylthiazole hydrochloride was added to a boiling solution of 0.76 g. (0.01 mole) of thiourea in 20 ml. of ethanol. After about five minutes a crystalline precipitate began to form and after refluxing for one hour the mixture was cooled and filtered. The white crystalline product, m. p. 255° dec., weighed 2.45 g. Recrystallization from a mixture of acetone and dilute hydrochloric acid gave 1.9 g., m. p. 254–255° dec.

Anal. Calcd. for $C_5H_{10}N_4Cl_2S_2$: N, 21.76; Cl, 27.15. Found: N, 21.35; Cl, 27.24.

B. From α,γ-Dichloroacetone.—Seventy-six grams (1.0 mole) of thiourea was added to a solution of 63.5 g. (0.5 mole) of α,γ-dichloroacetone in 500 ml. of ethanol and the mixture was warmed on a steam-bath until an exothermic reaction started. Crystallization began after several minutes. The mixture was cooled in an ice-bath, filtered and the crystals were washed with acetone and dried at 70°. The product, m. p. 249–250° dec., weighed 110 g. (84%).

This compound was sparingly soluble in cold ethanol. With cold aqueous silver nitrate solution it gave a white

(4) Traumann, *Ann.*, **249**, 47 (1888).

(5) The melting points reported in this paper are uncorrected.

(6) Young and Crookes, *J. Chem. Soc.*, **89**, 67 (1906).

precipitate that was unchanged after heating to boiling.[7] The diazotization test gave a purple color. A solution of the isothiourea in dilute sodium hydroxide solution gave a violet color with sodium nitroprusside.

2-Amino-4-dimethylaminomethylthiazole V. A.—To a solution of 20 g. (0.45 mole) of dimethylamine in 100 ml. of anhydrous ethanol was added 21.8 g. (0.12 mole) of 2-amino-4-chloromethylthiazole hydrochloride. After standing overnight at room temperature the solution was heated under reflux for one-half hour and then evaporated to dryness *in vacuo*. The residue was dissolved in 75 ml. of water and made strongly alkaline with 20% sodium hydroxide solution to precipitate 15.9 g. of brown crystals, m. p. 147–149°. Recrystallization from benzene gave 10.2 g. (53%) of pale yellow crystals, m. p. 150–151.5°.

Anal. Calcd. for $C_6H_{11}N_3S$: N, 26.73. Found: N, 26.57.

B.—Hydrogen bromide was passed into an isopropyl ether solution of 8.2 g. of dimethylaminoacetone[8] until precipitation was complete. The hydrobromide was partially purified by dissolving it in isopropyl alcohol and precipitating it by dilution with isopropyl ether. It then was dissolved in 10 ml. of glacial acetic acid and stirred while a solution of 4.8 g. of bromine in 5 ml. of acetic acid was added. After fifteen minutes the hydrobromide of the bromoketone was precipitated as an oil by diluting the solution with isopropyl ether. The crude oily hydrobromide was twice reprecipitated from isopropyl alcohol with isopropyl ether to give 3.9 g. of crystalline material, m. p. 122–124°. The 1-bromo-3-dimethylamino-2-propanone hydrobromide thus obtained was used without further purification.

A solution of 1.95 g. of the bromoketone hydrobromide and 0.6 g. of thiourea in 15 ml. of water was allowed to stand at room temperature for one-half hour. The addition of an excess of 20% sodium hydroxide solution precipitated 0.85 g. (76%) of 2-amino-4-dimethylaminomethylthiazole, m. p. 150–152°.

A mixture of the thiazoles prepared by the two methods showed no depression in melting point. Both preparations gave a red color in the diazotization test.

2-Amino-4-diethylaminomethylthiazole VI.—A.—A solution of 5.5 g. (0.03 mole) of 2-amino-4-chloromethylthiazole hydrochloride (I) in 50 ml. of ethanol was stirred vigorously while 15 g. (0.21 mole) of diethylamine dissolved in 15 ml. of ethanol was added dropwise. A crystalline precipitate began to form in about half an hour. The next day the solvent was removed by distillation *in vacuo*. The residue was dissolved in dilute hydrochloric acid, the solution covered with a layer of ether and made strongly alkaline with 20% sodium hydroxide solution. The mixture was shaken, the layers separated and the ether extract dried with anhydrous sodium sulfate. Evaporation of the ether left a residue of oil which was dissolved in 15 ml. of 6 *M* hydrochloric acid. The solution was made basic and extracted. Evaporation of the ether extract again left an oil that partially solidified when stirred. Recrystallization from hexane yielded 1.8 g. of sticky brown crystals. This was dissolved in 20 ml. of isopropyl alcohol and the solution then was saturated with hydrogen chloride. Upon cooling, the solution deposited 2.3 g. of white crystalline hydrochloride, m. p. 206–207° dec. Recrystallization from a mixture of ethanol and ethyl acetate yielded 1.7 g. of crystals, m. p. 206–207°. The free base was prepared from the hydrochloride and, after two recrystallizations from hexane, 0.4 g. of white needles, m. p. 63.5–64.5°, was obtained.

B.—Twenty-four grams of diethylaminoacetone was converted to the hydrobromide and brominated by the procedure used with dimethylaminoacetone. Twenty-nine grams of 1-bromo-3-diethylamino-2-propanone hydrobromide, m. p. 124–125° dec., was obtained after reprecipitation from alcohol solution by dilution with isopropyl ether.

A solution of 28.8 g. (0.10 mole) of the bromoketone hydrobromide and 8.4 g. (0.11 mole) of thiourea in 50 ml. of water was allowed to stand at room temperature for one hour. The solution was made basic with 20% sodium hydroxide solution and the yellow oil that separated was taken up in ether and dried with anhydrous sodium sulfate. The ether was evaporated and the residue recrystallized from hexane to yield 12.65 g. (69%) of the aminothiazole, m. p. 62–63.5°. After three recrystallizations from hexane, it melted at 63.5–64.5°.

Anal. Calcd. for $C_8H_{15}N_3S$: N, 22.71. Found: N, 22.56.

The product that was obtained from both procedures gave a blue color in the diazotization test and a mixed melting point showed no depression.

2-Amino-4-piperidinomethylthiazole, VII. A.—Twelve grams (0.14 mole) of piperidine was added to a solution of 9.25 g. (0.05 mole) of 2-amino-4-chloromethylthiazole hydrochloride (I) in 100 ml. of anhydrous alcohol. After standing at room temperature overnight, the alcohol was distilled *in vacuo*. The dark semi-solid residue was suspended in 60 ml. of water and acidified with hydrochloric acid to obtain a clear brown solution which was partially decolorized by two treatments with "Norit." The addition of an excess of 20% sodium hydroxide precipitated brown crystals of the aminothiazole. This was dissolved in dilute hydrochloric acid, decolorized and precipitated with sodium hydroxide to give 4 g. (40%) of light yellow crystals, m. p. 158–161°. Recrystallization from dilute alcohol gave material melting at 163°.

Anal. Calcd. for $C_9H_{15}N_3S$: N, 21.30. Found: N, 19.95, 20.06, 21.32, 20.93 (by Kjeldahl procedure).

The **dihydrochloride** was prepared by dissolving the base in alcoholic hydrogen chloride solution and precipitating the salt by dilution with petrolum ether. After recrystallization from ethanol it melted with effervescence at 217–219°.

Anal. Calcd. for $C_9H_{17}N_3Cl_2S$: Cl, 26.26. Found: Cl, 26.21.

B.—Ten grams of the crude hydrobromide of piperidinoacetone[9] was dissolved in acetic acid and brominated by the procedure that was used with dimethylaminoacetone. One-half gram of crystalline bromoketone hydrobromide was obtained by dissolving the orange-colored oily product in ethanol and diluting the solution with ether. Purification was not attempted because of the small amount of material obtained.

One gram of the crude 1-bromo-3-piperidino-2-propanone hydrobromide was added to a solution of 0.4 g. of thiourea in 10 ml. of water. After one hour the solution was made basic with 20% sodium hydroxide to precipitate 0.4 g. of 2-amino-4-piperidinomethylthiazole, m. p. 158–159°. Reprecipitation from dilute hydrochloric acid with alkali gave 0.1 g., m. p. 159.5–161°. The dihydrochloride melted at 215–217°.

The base and the dihydrochloride did not depress the melting point of samples prepared by method A. All samples gave a blue-purple color in the diazotization test.

***bis*-(2-Amino-4-thiazolylmethyl)-disulfide.**—A solution of 13.05 g. of the isothiourea II in 80 ml. of 10% sodium hydroxide solution was stirred at 10° while 6% hydrogen peroxide was added slowly. The addition of hydrogen peroxide was continued until a few drops of the reaction mixture no longer gave a purple color with alkaline sodium nitroprusside. The disulfide that separated during the reaction was removed by filtration, washed with water, and dried at 70°. Recrystallization from 50% ethanol gave 5.9 g. (82%) of white crystals, m. p. 165–166°. Another recrystallization raised the melting point to 165.5–166.5°.

Anal. Calcd. for $C_8H_{10}N_4S_4$: N, 19.32. Found: N, 19.16.

(7) Sheppard and Brigham (ref. 2) state that the compound which they considered to be 2-thiono-5-ketohexahydropyrimidine (III) reacted with cold aqueous silver nitrate to give a white precipitate that turned black when heated.

(8) Magee and Henze, THIS JOURNAL, **60**, 2148 (1938).

(9) Stormer and Burkert, *Ber.*, **28**, 1250 (1895).

2-Amino-4-methylmercaptomethylthiazole, IX.—A solution of 13.05 g. of the isothiourea II was stirred at ice-bath temperature in a nitrogen atmosphere while 4.9 ml. of methyl sulfate was added. After standing overnight the mixture was filtered, the solid washed with water and dried. The crude product then was boiled with 60 ml. of benzene and the solution was filtered to remove a small amount of insoluble material. The product was precipitated by the addition of hexane. The white crystals thus obtained melted at 76.5–78°, and weighed 5.4 g. (67%). Another recrystallization from a mixture of benzene and hexane raised the melting point to 79.5–80.5°.

Anal. Calcd. for $C_5H_8N_2S_2$: N, 17.50. Found: N, 17.35.

2-Amino-4-ethylmercaptomethylthiazole, X.—A solution of 6.5 g. of the isothiourea II and 3 ml. of ethyl bromide in 40 ml. of ethanol was stirred in a nitrogen atmosphere while 40 ml. of 10% aqueous sodium hydroxide was dropped in rapidly. After fifteen minutes the solution was transferred to an evaporating dish and heated on a steam-bath in a stream of air until most of the alcohol had evaporated. The oily precipitate which solidified upon cooling was collected on a filter, washed with water and dried at 70°. It weighed 4.28 g. and melted at 89–93°. Recrystallization was effected by dissolving the crude product in 15 ml. of ethanol and adding water until solution was barely complete at the boiling point. The cooled solution deposited an oil which soon solidified to 3.45 g. (79%) of white crystals; m. p. 93–94°. After another recrystallization, the melting point was 93.5–95°.

Anal. Calcd. for $C_6H_{10}N_2S_2$: N, 16.10. Found: N, 16.08.

2-Amino-4-thiazolylmethylmercaptoacetic Acid, XI.—Two and six-tenths grams (0.01 mole) of the isothiourea II, 1 g. (0.011 mole) of chloroacetic acid and 1.6 g. (0.04 mole) of sodium hydroxide were dissolved in 20 ml. of water and heated on a steam-bath. After one hour, the test for mercapto group became negative. The solution was acidified to about *p*H 4 with hydrochloric acid and cooled. The white solid was removed by filtration and a second crop was obtained by cautiously adding hydrochloric acid to the filtrate until the precipitate just began to redissolve. Recrystallization from water gave 1.45 g. (71%) of light yellow crystals, m. p. 166–168°.

Anal. Calcd. for $C_6H_8O_2N_2S_2$: N, 13.79. Found: N, 13.67.

Ethyl 2-Amino-4-thiazolylmethylmercaptoacetate, XII. A.—A solution of 6.5 g. of the isothiourea II in 30 ml. of water and 15 ml. of 20% sodium hydroxide solution was stirred at ice-bath temperature while 3.3 g. of ethylchloroacetate was added. After ten minutes the solution was extracted with two 50-ml. portions of ether. The extract was dried with anhydrous sodium sulfate and the oily residue remaining after evaporation of the ether was stirred until it solidified. Recrystallization from a benzene–hexane mixture yielded 2.5 g. (49%) of pale yellow crystals, m. p. 65–69°.

B.—Seventeen and four-tenths grams of the acid XI was dissolved in 60 ml. of 10% ethanolic hydrogen chloride solution. The solution became warm and quickly set to a mass of crystals. After standing overnight the mixture was refluxed for two hours during which time all of the solid dissolved. The alcohol was evaporated and the solid residue was stirred with 75 ml. of water and an excess of 20% sodium hydroxide solution. The suspension was shaken with ether to remove the ester. The clear aqueous solution upon acidification yielded 7.6 g. of unesterified acid. The ether extract was dried with anhydrous sodium sulfate and evaporated. The oily residue was triturated with hexane until it crystallized and then was recrystallized from a benzene–hexane mixture to yield 6.9 g. (61.5%) of white crystals, m. p. 66.5–68.5°. After another recrystallization the melting point was 68–69°.

Anal. Calcd. for $C_8H_{12}O_2N_2S_2$: N, 12.07. Found: N, 11.98.

2-Amino-4-hydroxymethylthiazole. A.—Two grams of 2-amino-4-chloromethylthiazole hydrochloride was dissolved in 20 ml. of water, the solution was boiled for ten minutes and then evaporated to dryness on a steam-bath. The residue was redissolved in several ml. of water and again evaporated to dryness. After three evaporations, the residue was triturated with ethanol and again evaporated to dryness, leaving 1.7 g. of tan solid. The solid was twice reprecipitated from ethanol by dilution with isopropyl ether and finally recrystallized from ethanol to give 0.6 g. of white crystalline **hydrochloride**, m. p. 161–163° with effervescence.

Anal. Calcd. for $C_4H_7ON_2ClS$: N, 16.82; Cl, 21.32. Found: N, 16.91; Cl, 21.26.

Alcoholic sodium hydroxide solution was added to 4.5 g. of the hydrochloride until the solution was slightly alkaline. After removal of the sodium chloride by filtration, the solution was evaporated to dryness *in vacuo*. The residue was extracted with boiling benzene containing a small amount of ethanol and the extract was filtered and allowed to cool. The brown crystalline material that separated was dissolved in boiling benzene, decolorized with "Norit" and allowed to crystallize. Seven-tenths gram of white crystals of **2-amino-4-hydroxymethylthiazole**, m. p. 98–99°, was obtained.

Anal. Calcd. for $C_4H_6ON_2S$: N, 21.52. Found: N, 21.29.

A **diacetyl derivative** was prepared by warming 0.7 g. of the base in 1.2 ml. of acetic anhydride and 5 ml. of glacial acetic acid for one-half hour. The mixture was diluted with 6 ml. of water, and neutralized with ammonium hydroxide to precipitate 0.8 g. of crystalline material, m. p. 145–148°. Two recrystallizations from benzene gave 0.25 g. of white crystals, m. p. 149–150°.

Anal. Calcd. for $C_8H_{10}O_3N_2S$: N, 13.08. Found: N, 13.09.

B.—Nine grams (0.05 mole) of α-bromotetronic acid[10] was added to a solution of 4 g. (0.053 mole) of thiourea in 50 ml. of water. The solution became quite warm and within an hour a precipitate of fine white needles began to form. The amount of precipitate increased during the next twelve hours and then began to diminish slowly. Slight evolution of gas was observed as the solution cleared. The solution had become clear thirty-six hours after the reactants were mixed. The solution was concentrated *in vacuo*, and the thick pasty residue was transferred to a suction filter with acetone. The acetone washings were concentrated to small volume and the precipitate was combined with the first crop, giving a total of 5.9 g. (56%). The crude material was recrystallized by dissolving it in boiling ethanol and adding benzene until the solution just cleared when reheated to boiling. On cooling slowly, the solution precipitated 4.3 g. of 2-amino-4-hydroxymethylthiazole hydrobromide as fine white crystals, m. p. 165–166°. After another recrystallization, it melted at 166–166.5°.

Anal. Calcd. for $C_4H_7ON_2BrS$: N, 13.27; Br, 37.87. Found: N, 13.17; Br, 37.50.

One gram of the hydrobromide was converted to a **dibenzoyl derivative** by dissolving it in sodium hydroxide solution and shaking with benzoyl chloride until no more precipitate formed. After several recrystallizations from water, it melted at 177–178°.

Anal. Calcd. for $C_{18}H_{14}O_3N_2S$: N, 8.23. Found: N, 8.24.

A **diacetyl derivative** was prepared by heating the hydrobromide with a mixture of acetic anhydride, glacial acetic acid and fused sodium acetate at 80° for fifteen minutes. It melted at 149–150.5°, and did not depress the melting point of a sample prepared under A.

Enol Isothiouronium Salt XIII.—α-Bromotetronic acid (5.4 g.) (0.029 mole) and 2.3 g. (0.03 mole) of thiourea were dissolved in 15 ml. of water. The temperature rose rapidly to 50° and after three hours in the refrigerator the mixture solidified to a mass of crystals. The solid was transferred to a filter and washed with three 4-ml. portions of

(10) Kumler, THIS JOURNAL, **60**, 859 (1938).

cold water and two 5-ml. portions of acetone. The solid weighed 2.4 g. (48%) and melted with decomposition at 213–214° when placed in a bath at 200° and heated at a rate of about 2° per minute. After two recrystallizations from water, it melted at 220–224° with decomposition. This compound contained sulfur but gave no precipitate with acidified silver nitrate solution and produced no color in the diazotization test.

Anal. Calcd. for $C_5H_6O_3N_2S$: N, 16.10. Found: N, 15.98.

One gram of enol salt was suspended in 7.5 ml. of 4 *N* hydrochloric acid. After standing for twenty-four hours, the solid had not dissolved completely. Two ml. of water and a few drops of concentrated hydrochloric acid were added and the mixture was warmed slightly to obtain a clear solution. After standing for another day the solution was evaporated to dryness and the residue was extracted with 30 ml. of ethanol. The extract was diluted with 60 ml. of hexane and on cooling, 0.43 g. of 2-amino-4-hydroxymethylthiazole hydrochloride was obtained, m. p. 157–158°. After two recrystallizations from ethanol the melting point was 162–163°.

Summary

2-Amino-4-chloromethylthiazole (I) was prepared by the reaction of equimolecular quantities α,γ-dichloroacetone and thiourea. S-(2-Amino-4-thiazolylmethyl) isothiourea (II) was obtained when two equivalents of thiourea was used.

2-Amino-4-*t*-aminomethylthiazoles were prepared by the reaction of I with secondary amines and also by the reaction of thiourea with brominated *t*-aminoacetones.

2-Amino-4-hydroxymethylthiazole was obtained by the hydrolysis of I and also through the reaction of α-bromotetronic acid with thiourea.

2- mino-4-alkylmercaptomethylthiazoles were synthesized by treating alkaline solutions of the isothiourea II with alkylating agents.

GLENOLDEN, PENNSYLVANIA RECEIVED MARCH 1, 1946

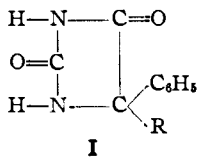
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

5-R-Thiomethyl- and 5-R-Sulfonylmethyl-5-phenylhydantoins

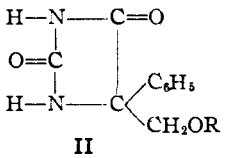
BY LOREN M. LONG

Since the discovery by Putnam and Merritt[1] of the anticonvulsant activity of 5,5-diphenylhydantoin (Dilantin), a large number of compounds have been prepared and tested[2] in an effort to find additional substances of value in the treatment of convulsive seizures. It has been found that numerous substituted hydantoins possess anticonvulsant activity while exhibiting little or no hypnotic activity. In contrast the barbituric acids such as phenobarbital which possess anticonvulsant activity are also powerful hypnotics. It is partly for this reason that so many of the compounds studied have been hydantoins.

Many of the hydantoins which are active have structure (I) where R may be a simple alkyl or a substituted alkyl.

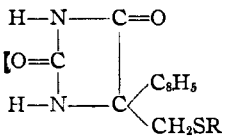


I

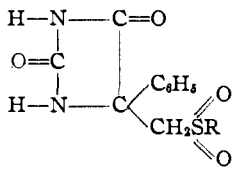


II

One group of compounds prepared by Henze[3,4] which possesses a high degree of activity throughout the series may be represented by formula (II) where R denotes various alkyl groups. Because of this fact and since sulfur containing compounds such as ethyl phenyl sulfide and sulfone have proved to be effective in reducing convulsive seizures,[4] it was considered worth while to prepare a number of compounds represented by (III) and (IV) for anticonvulsant testing.



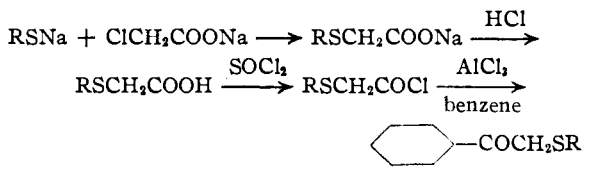
III



IV

The synthesis of these hydantoins necessitated the preparation of a series of α-R-thioacetophenones shown in Table I. Literature investigation revealed that α-*n*-butylthioacetophenone had been prepared by Whitner and Reid.[5] With slight variation their procedure, which involves the reaction of sodium mercaptan with phenacyl chloride, was adequate for the preparation of the entire series.

However, several of the ketones were prepared also by an alternate method illustrated by the reactions



Although the yields obtained in the various steps were good, the over-all yields were lower than those obtained in the first method. The products obtained by the two methods are identical.

Conversion of the ketones to the corresponding hydantoins was carried out by the method of

(1) Putnam and Merritt, *Science*, **85**, 525 (1937).

(2) Merritt and Putnam, *Epilepsia*, **3**, 51 (1945).

(3) Rigler and Henze, THIS JOURNAL, **58**, 474 (1936).

(4) Merritt, Putnam and Bywater, *Arch. Neurol. Psychiat.*, **54**, 319 (1945).

(5) Whitner and Reid, THIS JOURNAL, **43**, 638 (1921).