[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Thiazole Analogs of Pyridoxine

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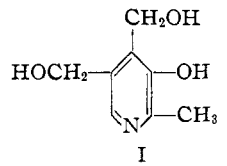
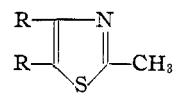
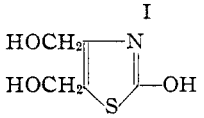
The synthesis of thiazole[2] and pyrimidine[3] analogs of pyridoxine (I) was undertaken originally to make the compounds available for antimalarial tests.[4] The present paper reports the preparation of 2-methyl-4,5-bis-(hydroxymethyl)-thiazole (II), and describes numerous experiments designed to lead to the corresponding 2-hydroxy compound (III).



I

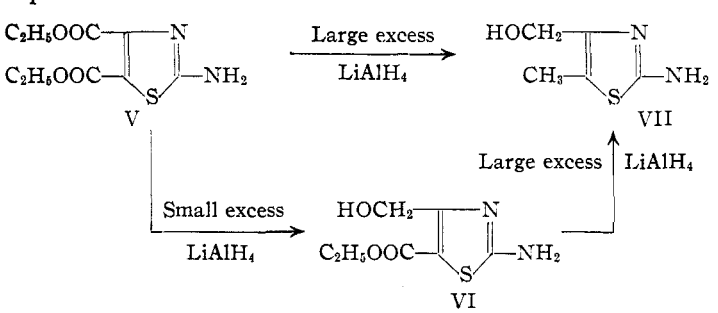


II, R = CH_2OH
IV, R = $COOC_2H_5$



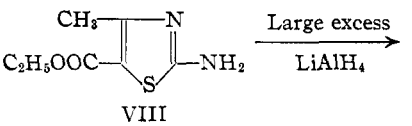
III

Compound II was obtained readily by reduction of the corresponding 4,5-dicarbethoxy derivative (IV) with lithium aluminum hydride. It was anticipated that application of this method to the corresponding 2-amino compound (V), would lead to a similar reduction, and that III could then be obtained by conversion of the amino substituent to a hydroxyl; the reduction however led to an unexpected result.

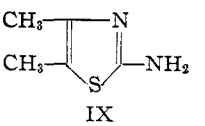


A small excess of lithium aluminum hydride[5] attacked only one ester group of V, giving VI, which could be converted by a large excess of reducing agent to the methyl-hydroxymethyl compound (VII); the latter was also formed from the dicarbethoxy compound (V) by a large excess of lithium aluminum hydride.

The structures assigned to VI and VII are supported by analogy with the reactions of similar compounds. It was found, for example, that 2-amino-4-methyl-5-carbethoxythiazole (VIII) was unaffected by a small excess of lithium aluminum hydride, but was converted by a large excess of the reagent to the 4,5-dimethyl derivative (IX) (identified by comparison with a known sample[6]).



VIII



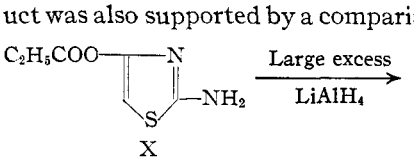
IX

This showed that the 5-carbethoxy group was subject to hydrogenolysis to yield a 5-methyl derivative.

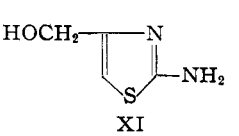
It was also found that reduction of 2-amino-4-carbethoxythiazole (X) by lithium aluminum hydride, under conditions which reduced the 5-carbethoxy group to methyl as above, yielded only 2-amino-4-hydroxymethylthiazole (XI) (identified by comparison with an authentic sample).

Furthermore, investigation of the action of lithium aluminum hydride on a number of benzene derivatives, containing an amino group and an ester or carbonyl group, showed that under similar conditions only those with the amino group ortho or para to the oxygen function yielded products in which the oxygen function had been converted to a methyl (or methylene) by hydrogenolysis.[7] This indicated that the 5-carbethoxy group in V would be the one attacked, since the 2-amino-5-carbethoxythiazoles are isosteres of *p*-aminobenzoic acid.

Structure VI for the reduction product was also supported by a comparison of its ultra-



X



XI

(1) Abbott Laboratories Fellow, 1948–1950.

(2) Tarbell, Hirschler and Carlin, THIS JOURNAL, **72**, 3138 (1950).

(3) McCasland, Tarbell, Carlin and Shakespeare, *ibid.*, **68**, 2390 (1946); McCasland and Tarbell, *ibid.*, **68**, 2393 (1946).

(4) Reasons for anticipating antimalarial activity in pyridoxine analogs are given in ref. 3.

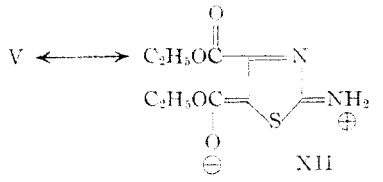
(5) Calculated as the amount in excess of that necessary to react with the active hydrogens and to reduce the ester groups to carbinols.

(6) The 2-amino-4,5-dimethylthiazole for comparison was prepared, applying the general method of Dodson and King, THIS JOURNAL, **68**, 871 (1946), from sulfuryl chloride, methyl ethyl ketone and thiourea. Evidence presented in the experimental section indicates that the product was the 4,5-dimethylthiazole and not the isomeric 4-ethyl compound.

(7) Conover and Tarbell, *ibid.*, **72**, 3586 (1950).

violet absorption spectrum with those of a number of similar compounds of known structure. Table I shows that all of the 2-amino-5-carbethoxythiazoles examined show, as the free bases, λ_{max} of 300–306 mμ, while 2-amino-4-carbethoxythiazole has λ_{max} at 289 mμ. The 2-aminothiazoles without unsaturated groups in the 4- or 5-positions show λ_{max} at 256–266.[8]

Some conclusions of more general application can be drawn from the data in Table I. The marked bathochromic effect of the 5-carbethoxy group in 2-aminothiazoles must be due to increased resonance interaction through forms such as XII.[9] The absorption spectrum of 2,4-dimethyl-



XII

5-carbethoxythiazole (λ_{max} at 260 mμ) shows that both the 2-amino and 5-carbethoxy groups are necessary for absorption at 300 mμ. It is unlikely that the 2-amino-5-carbethoxythiazoles exist in the tautomeric 2-iminothiazoline form, because one cannot write structures allowing resonance interaction between the two groups on this basis (neglecting improbable ionic structures).

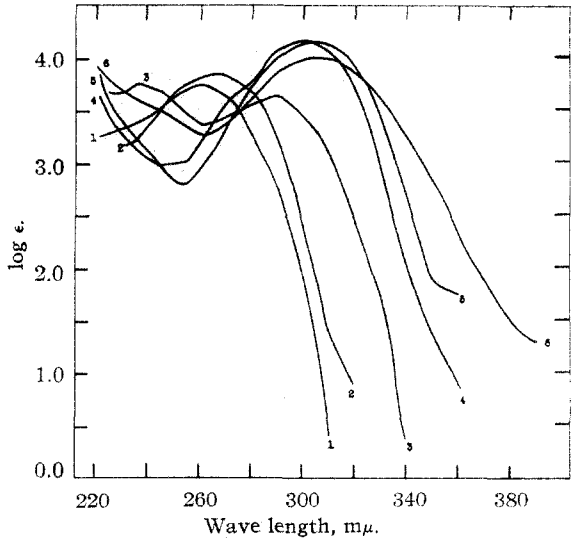


Fig. 1.—Molar extinction curves in 95% ethanol: (1), 2-amino-4-hydroxymethyl-5-methylthiazole (VII); (2), 2-amino-4,5-dimethylthiazole hydrochloride; (3), 2-amino-4-carbethoxythiazole (X); (4), 2-amino-4-methyl-5-carbethoxythiazole (VIII); (5), 2-amino-4-hydroxymethyl-5-carbethoxythiazole (VI); (6), 2-amino-4,5-dicarbethoxythiazole (V).

(8) 2-Aminothiazole itself shows λ_{max}, at 255 mμ (Vandenbelt and Doub, THIS JOURNAL, **66**, 1633 (1944), while the hydrochlorides of 2-aminocyclopentenothiazole and 2-aminocyclohexenothiazole have λ_{max} near 270 mμ (Erlenmeyer and Schoenauer, *Helv. Chim. Acta*, **24**, 172E (1941)).

(9) *Cf.* Raffauf, THIS JOURNAL, **72**, 753 (1950).

TABLE I

ULTRAVIOLET ABSORPTION CURVES OF THIAZOLES IN 95% ALCOHOL

Compound, substituents 2-	4-	5-	λ_{max} mμ	log E
CH_3	CH_3	COOEt	260	3.96
CH_3	COOH	COOH	261	3.88
NH_2[b]	CH_3	CH_3	266	3.85
NH_2	CH_2OH	CH_3	259	3.73
NH_2[a]	CH_2OH	H	256	3.75
NH_2[b]	CH_2OH	H	257	3.72
NH_2[b]	CH_3	H	259	3.76
NH_2	COOEt	H	289	3.61
NH_2[c]	COOEt	H	249	3.96
NH_2	CH_2OH	COOEt	306	4.15
NH_2	CH_3	COOEt	300	4.16
NH_2[c]	CH_3	COOEt	274	4.08
NH_2	COOEt	COOEt	306	4.01
NH_2[b]	COOEt	COOEt	306	4.08
NH_2[c]	COOEt	COOEt	288	3.63

[a] Obtained by addition of calculated amount of sodium hydroxide to solution of the hydrochloride. [b] As monohydrochloride. [c] Taken in 95% alcohol saturated with hydrogen chloride.

The absorption curve of 2-amino-4,5-dicarbethoxythiazole hydrochloride is practically identical with that of the free base, and hence it seems unlikely that the 2-amino group has been altered.[10] The 2-aminothiazoles with saturated groups or hydrogens in the 4- and 5-positions likewise show no hypsochromic shift after formation of the monohydrochloride.[11] It is probable that, as in the aminoacridine series,[12] the first proton goes to the ring nitrogen, and does not affect the chromophoric system of the compound. In more strongly acid solutions (alcohol saturated with hydrogen chloride) λ_{max} for 2-amino-4,5-dicarbethoxythiazole is shifted to 288 mμ; while under the same conditions the maximum for 2-amino-4-methyl-5-carbethoxythiazole is shifted to 274 mμ. These hypsochromic shifts are doubtless due to dihydrochloride formation which prevents the contributions from resonance structures such as XII. It might be expected that under these conditions both of the maxima should lie at around 260 mμ; that they do not, may be the result of incomplete salt formation.

2-Amino-4-carbethoxythiazole (X) absorbs at shorter wave length than the 2-amino-5-carbethoxythiazoles. This is not surprising since resonance interaction between 2-amino and 4-carbethoxy groups may only be represented by resonance structures of relatively high energy (*e. g.*, meta bonded[13] or quadripolar). However the amino and carbethoxy substituents can also interact in-

(10) Conversion of aromatic amines to their salts is usually accompanied by a marked hypsochromic shift (Ferguson, *Chem. Revs.*, **43**,396 (1948)).

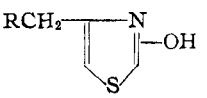
(11) 2-Aminothiazole shows no change in λ_{max}, on salt formation (Vandenbelt and Doub, ref. 7).

(12) Craig and Short, *J. Chem. Soc.*, 419 (1945); Turnbull, *ibid.*, 441 (1945); Craig, *ibid.*, 534 (1946).

(13) *Cf.* Doub and Vandenbelt, THIS JOURNAL, **71**, 2414 (1949).

dependently with the thiazole ring system, causing λ_{max} to lie at longer wave length than that of either of the corresponding monosubstituted compounds.[13] In support of this view it was found that λ_{max} of X shifts to 249 mμ in strong acid, thus it appears certain that the amino group is involved in the bathochromic shift of the absorption maximum of the free base.

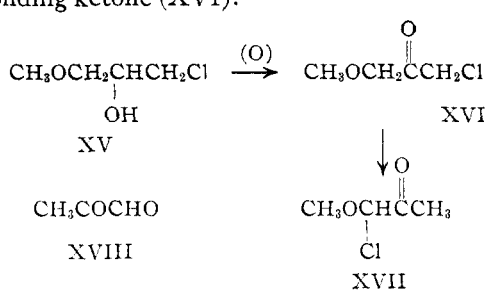
Several other approaches to the structure III were investigated. In one of these 2-hydroxy-4-chloromethylthiazole (XIII)[14] was to be converted



XIII, R = Cl
XIV, R = OCH_3

to the methoxy compound (XIV), which it was hoped could be converted by formylation or chloromethylation in the 5-position to a precursor of III.[15] The action of sodium methoxide on XII under a variety of conditions appeared to cause polymerization, and none of the desired ether was obtained; attempts to replace the chlorine by hydroxyl, ethoxyl, acetoxyl and amino likewise failed. The chloro compound (XIII) appeared to have a very reactive halogen; it formed a precipitate rapidly with sodium iodide in acetone, and reacted with amines to form high-melting salts of undetermined composition.

Another scheme involved the oxidation of 1-methoxy-3-chloro-2-propanol (XV) to the corresponding ketone (XVI).



The product of oxidation of XV proved to be very unstable, and did not condense to form a thiazole derivative under any conditions tried. A number of derivatives obtained from the oxidation product with phenylhydrazine, semicarbazide and similar reagents, which were prepared to furnish analytical evidence for structure XVI, were found to be indistinguishable, in every case, from the corresponding derivatives of methylglyoxal (XVIII). This suggests that, although the chloromethoxyacetone (XVI) may have been formed initially by oxidation of XV, it rearranged to the isomeric structure (XVII) before or during reaction with the carbonyl reagents, to form derivatives of methylglyoxal.

(14) Ganapathi and Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 362 (1945).

(15) Friedel-Crafts acylation and the Gattermann reaction occur with 2-hydroxy-4-methylthiazole (Ochiai and Nagasawa, *Ber.*, **72**, 1470 (1939)).

Experimental[16]

Diethyl α-bromoöxaloacetate was prepared by bromination of diethyl oxaloacetate sodium salt (Eastman Kodak Co. Practical) in chloroform solution; the yield of material with b. p. 109–111° (6 mm.), $n^{20}D$ 1.4682, was 31%.[17] A residue in the distilling flask was believed to be tetraethyl dioxalosuccinate, reported[18] formed under similar conditions.

The chloro compound was prepared in similar yield by treatment of the sodium salt in chloroform with sulfuryl chloride; b. p. 98–102° (2 mm.), $n^{20}D$ 1.4480.[19]

2-Methyl-4,5-dicarbethoxythiazole (IV).—A mixture of 20 g. of diethyl α-chloroöxaloacetate and 20 g. of thioacetamide in 100 cc. of chloroform was stirred at 0° for five hours, then allowed to stand for thirty-six hours at room temperature. Solids were removed and the remaining solution concentrated to a dark oil. This was shaken with water, the oil layer filtered free of sulfur, and combined with an ethereal extract of the filtered aqueous layer. Removal of the ether from the dried extracts left 16.2 g. (74%) of foul-smelling oil, a sample of which was converted to the diacid, m. p. 172–173° (dec.).[20]

2-Methyl-4,5-bis-(hydroxymethyl)-thiazole (II).—A solution of 4.8 g. of crude 2-methyl-4,5-dicarbethoxythiazole (IV) in 100 cc. of benzene was added cautiously to 75 cc. of 0.65 *m* lithium aluminum hydride (145% excess) and the mixture stirred for one hour. The product was isolated by the wet ether method.[21] The dark oil which remained after removal of the solvent was taken up in ethanol, treated with charcoal and crystallized by cooling in a Dry Ice-bath. The collected tan solid (1.2 g., 38%) was obtained, after several crystallizations from benzene, as white needles, m. p. 106–107°. *Anal.* Calcd. for $C_6H_9NO_3S$: C, 45.26; H, 5.70. Found: C, 45.56; H, 5.69.

The bis-phenylurethan, recrystallized several times from benzene–acetone and hexane–acetone, was obtained as white crystals, m. p. 155–156°. *Anal.* Calcd. for $C_{20}H_{19}N_3O_4S$: C, 60.44; H, 4.82. Found: C, 60.62; H, 4.74.

2-Amino-4,5-dicarbethoxythiazole (V).—Diethyl α-bromoöxaloacetate (26.7 g.) was placed in a 500-cc. flask, and 7.6 g. of thiourea was added rapidly with stirring; 5 cc. of ethanol was added, which started an exothermic reaction. The mixture was stirred for twelve hours, the ethanol removed *in vacuo*, and the residue treated dropwise with 5% sodium hydroxide until the mixture was slightly basic. The neutralization was accompanied by heat evolution and the formation of a highly colored by-product, the amount of which was minimized by cooling and avoiding a large excess of base. The tan solid which separated was washed with water and dried *in vacuo;* the yield of material of m. p. 107–108° was 15.8 g. (65%). Several recrystallizations from benzene raised the m. p. to 111–112°.[22]

The picrate, after repeated recrystallizations from ethanol–pentane and chloroform–pentane, melted at 171–172° with decomposition. *Anal.* Calcd. for $C_{15}H_{15}N_5O_{11}S$: C, 38.06; H, 3.19. Found: C, 38.24; H, 3.0.

The thiazole was also made in 61% yield from diethyl chloroöxaloacetate, substituting 7 *m* ammonium hydroxide for sodium hydroxide.

Lithium Aluminum Hydride Reduction of 2-Amino-4,5-dicarbethoxythiazole (V). A. 2-Amino-4-hydroxy-

(16) Melting points corrected; analyses by Mrs. G. Sauvage and Micro-tech Laboratories.

(17) Brühl, *Ber.*, **36**, 1732 (1903), reports a b. p. of 140–145° (11 mm.); the refractive index is not reported.

(18) Sutter, *Ann.*, **499**, 47 (1932).

(19) Wislicenus, *Ber.*, **43**, 3529 (1910), gave the b. p. as 150–152° (56 mm.); the refractive index is not available.

(20) Roubleff, *Ann.*, **259**, 253 (1890), reported the m. p. as 169°.

(21) Isolation procedure A-1, ref. 7. (The use of aqueous base for hydrolysis of the reaction mixture was less satisfactory. Because of the solubility of the product in water, it was found necessary in this case to employ continuous ether extraction of the water layer for a week or more to effect the isolation.)

(22) Roubleff, ref. 20, reports a m. p. of 112°, but gives few details.

methyl-5-carbethoxythiazole (VI).—To a solution of 4.0 g. of 2-amino-4,5-dicarbethoxythiazole in 600 cc. of dry ether at −10–0° was added dropwise over a period of forty-five minutes 50 cc. of 0.59 *m* lithium aluminum hydride solution (25% excess). After standing at room temperature for an hour, the yellow addition product was decomposed by the addition of 1500 cc. of wet ether; the inorganic hydroxides, which were dark colored, were collected and leached with boiling acetone, and the acetone solution was combined with the ether filtrate. Evaporation yielded 1.0 g. of yellow solid, m. p. 173–176°, which was raised to 182–183° by repeated crystallization from alcohol with norite decolorization. *Anal.* Calcd. for $C_7H_{10}N_2O_3S$: C, 41.57; H, 4.98; N, 13.86. Found: C, 41.21; H, 4.96; N, 14.00.

The picrate, after several crystallizations from chloroform, melted with decomposition at 165–166°. *Anal.* Calcd. for $C_{13}H_{13}N_5O_{10}S$: C, 36.20; H, 3.04. Found: C, 36.20; H, 3.00.

Many further experiments were run in an effort to reduce the diester to the desired dialcohol. Using 10–20% more reducing agent than the calculated 1.5 moles per mole of diester, runs were made in mixtures of ether and dibutyl ether at 25–55°, and reaction times varying from one to eighteen hours. The above product was obtained in all cases, but less pure and in lower yield.

B. **2-Amino-4-hydroxymethyl-5-methylthiazole (VII).**—The diester (V) (1.0 g.) in 40 cc. of ether was allowed to stand 24 hours at room temperature in the presence of 50 cc. of 0.59 *m* lithium aluminum hydride (400% excess); there was obtained 200 mg. of material, m. p. 149–154°; after four crystallizations from alcohol, the material was colorless, and melted at 158–159°. *Anal.* Calcd. for $C_5H_8N_2OS$: C, 41.65; H, 5.59; N, 19.43. Found: C, 41.50; H, 5.24; N, 19.58.

The reaction mixture was examined carefully for the presence of another product but none could be isolated. Considerable tar was found.

Reduction of 2-Amino-4-hydroxymethyl-5-carbethoxythiazole (VI).—Treatment of 0.23 g. of VI in 125 cc. of ether with 2.4 cc. of 0.59 *m* lithium aluminum hydride (0.0% excess) yielded 0.200 g. of starting material. However, treatment of 0.20 g. of VI in 150 cc. of benzene with 4.0 cc. of 0.65 *m* lithium aluminum hydride solution (120% excess) gave, after 24 hours, 0.012 g. (8%) of solid, which, after crystallization from ethanol, was shown to be identical by mixed m. p. with the 2-amino-4-hydroxymethyl-5-methylthiazole described in the preceding paragraph.

2-Amino-4-methyl-5-carbethoxythiazole (VIII) was prepared by the method of Zürcher[23] in 76% yield.

The picrate, after four crystallizations from ethanol–acetone, melted at 213–214° with decomposition. *Anal.* Calcd. for $C_{13}H_{13}N_5O_9S$: C, 37.59; H, 3.15. Found: C, 37.87; H, 3.00.

2-Amino-4,5-dimethylthiazole (IX) by Reduction of 2-Amino-4-methyl-5-carbethoxythiazole (VIII).—A solution of 4.0 g. of 2-amino-4-methyl-5-carbethoxythiazole (VIII) in 1000 cc. of benzene was treated with 63 cc. of 1.2 *m* lithium aluminum hydride (250% excess); after standing for 36 hours, the oil which was obtained was converted into a hydrochloride. This material (1.5 g.), after Darco treatment and five crystallizations from ethanol, formed white needles, melting with decomposition at 269–270°, and showed no depression on admixture with an authentic sample of the hydrochloride of 2-amino-4,5-dimethylthiazole. In order to obtain a derivative for comparison which mel ed without decomposition, 1.15 g. of the hydrochloride was converted to the free base with 5% alkali, and the base in 5 cc. of alcohol refluxed for five minutes with 2.5 g. of *p*-nitrobenzaldehyde. After standing a day at room temperature, 0.95 g. (52%) of bright orange needles of the Schiff base was obtained, which, after five crystallizations from alcohol, melted sharply at 171–172°. *Anal.* Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24. Found: C, 55.46; H, 4.38. A mixed m. p. with the Schiff base prepared in the same manner from authentic 2-amino-4,5-dimethylthiazole did not show any depression.

There appeared to be no simple product of the reduction besides the dimethyl compound. Considerable tar (1.2 g.) was formed. Treatment of the 2-amino-4-methyl-5-carbethoxythiazole with an 88% excess of lithium aluminum hydride at room temperature or with a 20% excess at 88° (in ether, benzene and dibutyl ether) yielded only starting material.

2-Amino-4,5-dimethylthiazole (IX).—Sulfuryl chloride (34 g.) was added dropwise with cooling to a mixture of 18 g. of methyl ethyl ketone and 38 g. of thiourea; chloroform was added as needed to make stirring possible. After the addition was complete (thirty minutes) the mixture stood twelve hours, and was heated on the steam-bath to remove the solvent and sulfur dioxide. The sticky mass which resulted was treated with excess 5% alkali, and extracted with two 200-cc. portions of ether; the hydrochloride was precipitated from the dried extracts with a stream of dry hydrogen chloride. (This method of isolation allowed a clean separation of product from unreacted thiourea.) The hydrochloride (13.0 g., 32%) was shown by mixed m. p. (269–270°) to be identical with that prepared in the usual way[24] by the condensation of 3-chlorobutanone-2 and thiourea; the Schiff bases obtained from both samples of the thiazole with *p*-nitrobenzaldehyde (see above) were also shown to be identical. The hydrochloride of the isomeric 2-amino-4-ethylthiazole melts at 85–86°.[25]

Reduction of 2-Amino-4-carbethoxythiazole (X) to 2-Amino-4-hydroxymethylthiazole (XI).—Reduction of 0.25 g. of 2-amino-4-carbethoxythiazole[26] with 540% excess of lithium aluminum hydride for 18 hours in benzene yielded, by the usual procedure, 0.050 g. (21%) of a hydrochloride which, after crystallization from ethanol, melted at 164–165°. A mixed m. p. with an authentic sample of 2-amino-4-hydroxymethylthiazole hydrochloride[27] showed no depression. The hydrochloride of 2-amino-4-methylthiazole is apparently not described, but treatment of the free base in the usual way gave a hydrochloride of m. p. 170–171°. A mixture of this material and the hydrochloride of the reduction product melted at 130–135°. The 2-amino-4-methylthiazole was prepared by heating equivalent amounts (0.03 mole) of thiourea and redistilled chloroacetone in eight volumes of ethanol until the thiourea dissolved, then the mixture remained at room temperature one week. On evaporation of the ethanol a near quantitative yield of the hydrochloride was obtained. After one crystallization of the hydrochloride from ether–ethanol, the free base was liberated with dilute ammonium hydroxide then isolated by ether extraction; it melted without further purification at 43–44°.[28]

2-Hydroxy-4-chloromethylthiazole (XIII).—The published procedure,[14] which is not satisfactory, was modified as follows. Solid ammonium thiocarbamate[14] (23.5 g.) was added in two separate batches to a solution of 33.0 g. of α,α'-dichloroacetone with stirring at 0°. Each addition required an hour, with a period of six hours between the two. Five drops of 0.1 *N* sodium hydroxide in saturated barium hydroxide was added during the eight-hour period. After 12 hours at 8°, the ethanol was removed *in vacuo*, the brown solid remaining was leached with water, and the residue was dried. It was extracted with ether in a Soxhlet until only a dark resin remained in the thimble. The crude material obtained by removal of the ether from the extract was recrystallized from acetone with norite treatment, and by cooling the acetone solution in a Dry Ice-bath white crystals were obtained,

(23) Zürcher, *Ann.*, **250**, 289 (1889).

(24) Jensen and Thorsteinsson, *Dansk. Tids. Farm.*, **15**, 41 (1941).

(25) Prijs, Ostertag and Erlenmeyer, *Helv. Chim. Acta*, **30**, 2110 (1947).

(26) Steude, *Ann.*, **261**, 22 (1891).

(27) Sprague, Land and Ziegler, THIS JOURNAL, **68**, 2155 (1946).

(28) For smaller quantities at least, this procedure seemed preferable to that of Byers and Dickey, "Organic Syntheses," Coll., Vol. II, pp. 31-32.

m. p. 146°. The yields obtained by this method ranged from 50–70%; the reported yield[14] was 22%, m. p. 150–151°.

The residue from the ether extraction was apparently polymeric, failed to melt at 320°, was quite insoluble in water and organic solvents, but was soluble in base.

2-Hydroxy-4-chloromethylthiazole phenylurethan melted, after crystallization from pentane–ethyl ether, at 119.5–120.5°. *Anal.* Calcd. for $C_{11}H_9N_2O_2SCl$: C, 49.16; H, 3.38. Found: C, 49.35; H, 3.21.

Oxidation of 1-Methoxy-3-chloro-2-propanol (XV).—1-Methoxy-3-chloro-2-propanol[29] was oxidized by sodium dichromate and sulfuric acid.[30] The product was separated from the reaction mixture by ether extraction, and following conventional treatment of the extracts it was purified by fractional distillation. The main fraction boiled 72–73° (25 mm.), or 39–40° (6 mm.). Several refractionations gave a colorless lachrymatory liquid $n^{20}D$ 1.4470, the refractive index of which remained constant on further refractionation. On standing it darkened with evolution of hydrogen chloride; no satisfactory analysis was obtained, presumably because of this decomposition.

The oxidation product reacted readily to form typical ketone derivatives. On the basis of mixed m. p. observations these products were proved to be identical with the corresponding bis-derivatives of methyglyoxal. (The latter were prepared from chloroacetone by refluxing with an ethanol solution of the appropriate reagent.) The following types of derivatives were prepared from the oxidation product: *p*-nitrophenylhydrazone, m. p. 296–297° (dec.); 2,4-dinitrophenylhydrazone m. p. 292–293° (dec.); phenylhydrazone m. p. 145–146°; semicarbazone, m. p. 250–251.5° (dec.). The melting points of the corresponding bis-derivatives of methylglyoxal are reported in the literature as follows: *p*-nitrophenylhydrazone, m. p. (dec.) values given vary from 277 to 302°[31]; 2,4-dinitrophenylhydrazone, m. p. 299–300°[32] (dec.); phenylhydrazone, m. p. 148°[33]; semicarbazone, m. p. 254°.[34]

(29) Fourneau and Ribas, *Bull. soc. chim. France*, **39**, 1584 (1926); Koelsch, THIS JOURNAL, **65**, 2460 (1943); Flores-Gallardo and Pollard, *J. Org. Chem.*, **12**, 831 (1947).

(30) *Cf.* Conant and Quayle, "Organic Syntheses," Coll. Vol. I, pp. 211–213.

(31) See "Beilstein," Vol. XV, p. 472.

(32) Bülow and Seidel, *Ann.*, **439**, 48 (1924).

(33) Wohl and Lange, *Ber.*, **41**, 3612 (1908).

(34) Knöpfer, *Monatsh.*, **32**, 753 (1911).

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Summary

1. 2-Methyl-4,5-dicarbethoxythiazole has been reduced to 2-methyl-4,5-bis-(hydroxymethyl)-thiozole, an analog of pyridoxine.

2. 2-Amino-4,5-dicarbethoxythiazole has been reduced with lithium aluminum hydride to 2-amino-4-hydroxymethyl-5-carbethoxythiazole. Both of these compounds have been reduced to 2-amino-4-hydroxymethyl-5-methylthiazole.

3. 2-Amino-4-methyl-5-carbethoxythiazole has been reduced with lithium aluminum hydride to 2-amino-4,5-dimethylthiazole, which has also been prepared by the reaction of sulfuryl chloride, methyl ethyl ketone and thiourea.

4. 2-Amino-4-carbethoxythiazole has been reduced to 2-amino-4-hydroxymethylthiazole by lithium aluminum hydride.

5. The ultraviolet absorption curves of a group of thiazoles have been observed and interpreted. These support the structures assigned to the reduction products of 2-amino-4,5-dicarbethoxythiazole. The effect of resonance interactions of substituents on the wave length of maximum absorption has been discussed. Modifications of this effect due to salt formation have also been considered.

6. The oxidation of 1-methoxy-3-chloro-2-propanol gives a product which reacts to give derivatives of methylglyoxal.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGY AND VITAL ECONOMICS, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY]

The Synthesis of 6,7-Diethyl-9-(D-1[1]-ribityl)-isoalloxazine[1]

BY JOHN P. LAMBOOY

Since the classical studies of flavin syntheses done by Kuhn and Karrer and their co-workers, which culminated in the synthesis of riboflavin[2] in 1935, no effort has been made to find additional analogs of riboflavin which might possess riboflavin-like activity. During this original period of interest a relatively large number of analogs were synthesized which differed from riboflavin in respect to the form, number or position of the substituents on the benzene ring portion or with respect to the form of the sugar portion of the molecule.

Of particular interest are 6-methyl-9-(D-1[1]-ribityl)-isoalloxazine,[3] 7-methyl-9-(D-1[1]-ribityl)-isoalloxazine,[4] 6-ethyl-7-methyl-9-(D-1[1]-ribityl)-isoalloxazine,[5] 7-ethyl-9-(D-1[1]-ribityl)-isoalloxazine,[5] 6,7-dimethyl-9-(D-1[1]-arabityl)-isoalloxazine,[6] 6,7-dimethyl-9-(L-1[1]-arabityl)-isoalloxazine[6,7,8] and 7-methyl-9-(D-1[1]-sorbityl)-isoalloxazine[8] in that they have been found to have biological activity under certain conditions. In addition to riboflavin, 6-methyl-9-(D-1[1]-ribityl)-isoalloxazine, 7-methyl-9-(D-1[1]-ribityl)-isoalloxazine and 6-ethyl-7-methyl-9-(D-1[1]-ribityl)-isoalloxazine have been found to support growth

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(2) Kuhn, Reinemund, Weygand and Ströbele, *Ber.*, **68**, 1765 (1935); Karrer, Becker, Benz, Frei, Salomon and Schöpp, *Helv. Chim. Acta*, **18**, 1435 (1935).

(3) Karrer and Strong, *ibid.*, **18**, 1343 (1935).

(4) Karrer, Salomon, Schöpp and Benz, *ibid.*, **18**, 1143 (1935).

(5) Karrer and Quibell, *ibid.*, **19**, 1034 (1936).

(6) Kuhn and Weygand, *Ber.*, **68**, 1282 (1935); Karrer and Meerwein, *Helv. Chim. Acta*, **19**, 264 (1936).

(7) Kuhn, Rudy and Weygand, *Ber.*, **68**, 166, 625 (1935).

(8) Karrer, Schöpp, Benz and Pfaehler, *Helv. Chim. Acta*, **18**, 69, 522 (1935).