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Thiamin Analogs. III. 4-Methyl-5-(hydroxymethyl)-thiazole[1]

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4-Methyl-5-(hydroxymethyl)-thiazole (I) was required for the synthesis of (Ig) (see preceding paper[3]). Its possible preparation by methods A-E was investigated.

A. Th-CHO (II)[4,5] $\xrightarrow{(i\text{-}C_3H_7O)_3Al}$ Th-CH_2OH (I)

B. $CH_3COCH_2CH_2OH$ (III) $\xrightarrow{Br_2\text{-}H_2O}$ $\xrightarrow{HCSNH_2}$ (I) + isomer (IV)

Ba. $CH_3COCH_2CH_2OCOCH_3$ (V) $\xrightarrow{SO_2Cl_2}$ $\xrightarrow{HCSNH_2}$ Th-CH_2OCOCH_3 (VI) + isomer (VII)

C. CH_3COCH_2Cl (VIII) $\xrightarrow{HCHO}$ $CH_3COCHClCH_2OH$ (IX) $\xrightarrow{HCSNH_2}$ (I)

D.[6] Th-$CH_2COOC_2H_5$ (X)[7,8] $\xrightarrow{NH_3}$ Th-CH_2CONH_2 (XI)[7,9] $\xrightarrow{Br_2\text{-}KOH}$ Th-CH_2NH_2 (XII) $\xrightarrow{HNO_2}$ (I)

E. $CH_3COCH{=}CH_2$ (XIII) $\xrightarrow{Br_2}$ $CH_3COCHBrCH_2BrX$ (IV) $\xrightarrow{HCSNH_2}$ Th-CH_2Br (XV)

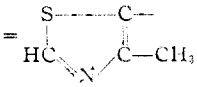
The patent literature[8b] claims the preparation of (I) from (XV) made according to E. We have not been able to realize the preparation of (XV) by this path. The preparation of (I) by method B has been reported by Pesina[10]; in our own work we have obtained (I) as well as its isomer, 4-(β-hydroxyethyl)-thiazole (IV), by this procedure.

Of the four successful syntheses (A, B, Ba, C) presented here, the first (A) is of interest inasmuch as the structure of (I) follows from its synthesis in this manner. Method C is by far the most convenient; it involves but few steps and the presence of isomer could not be detected in the product.

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

(2) Merck and Company, Inc., Fellow 1941-1942.

(3) Buchman and Richardson, THIS JOURNAL, **67**, 395 (1945).

(4) Th— = 

(5) Buchman and Richardson, THIS JOURNAL, **61**, 891 (1939).

(6) The Simonini reaction (*Monatsh.*, **13**, 329 (1892) [*Jahresber. Chem.*, 1463 (1892)] offers a shorter route to Th—CH_2OH from Th—CH_2COOH; this reaction was not investigated.

(7) Cerecedo and Tolpin, THIS JOURNAL, **59**, 1660 (1937).

(8) (a) Andersag and Westphal, U. S. Patent 2,139,570 (to Winthrop Chemical Co., Inc.); (b) I. G. Farbenindustrie, A.-G., English Patent 456,751 [*Chem. Zentr.*, **108**, I, 2868 (1937)]; (c) German Patent 702,436 (Andersag and Westphal inventors).

(9) Price and Pickel, (a) THIS JOURNAL, **63**, 1967 (1941); (b) U. S. Patent 2,209,092 (to National Oil Products Co.).

(10) Pesina, *J. Gen. Chem.* (U. S. S. R.), **9**, 804 (1939) [C. A., **34**, 426 (1940)].

Experimental[11]

4-Methyl-5-(hydroxymethyl)-thiazole (I) (Method A).—A specially purified thiazole aldehyde (II),[5] m. p. 75.6–76.1°, from isopropyl alcohol (picrate,[12] m. p. 105.0–105.6° from ether) was used in these experiments. Four grams of (II) was mixed with 75 cc. of isopropyl alcohol (distilled over a small amount of sodium) and 8 g. of aluminum isopropylate and the mixture distilled under a short column at such a rate that acetone was removed as formed. After two hours the distillate gave no further test for acetone with dinitrophenylhydrazine. Most of the isopropyl alcohol was then distilled off, 5 cc. of water and approximately 20 g. of potassium hydroxide were added to the residue and it was extracted repeatedly with ether until a portion of the extract gave no precipitate with ethereal picric acid. Solvent was removed *in vacuo* from the combined extracts and the residue distilled *in vacuo*, yield 3.2 g. (80%) of rather viscous oil, which on redistillation boiled almost entirely at 113–114° (2 mm.). After standing for about two months the substance crystallized, m. p. 65.8–66.2° from benzene.

Anal. Calcd. for C_5H_7NOS: C, 46.49; H, 5.46; N, 10.84. Found: C, 46.78; H, 5.43; N, 10.93.

Supercooled liquid (I) had d^{26}_4 1.240, picrate, yellow needles, m. p. 133.5–133.7° from alcohol (analysis for $C_{11}H_{10}N_4O_8S$), picrolonate, from components in methanol, m. p. 205.5–205.7° from alcohol (lit.[10] m. p. 196–197°).

Attempts to effect the catalytic reduction of (II) were unsuccessful; small amounts of (II) completely inhibited[13] the reduction of benzaldehyde (Adams platinum oxide catalyst). The reduction of (II) with aluminum amalgam and moist ether however led to a small yield of (I) which was isolated as the picrate (mixed m. p.).

(I) was converted to (VI) by treatment with excess of acetic anhydride and a drop of concentrated sulfuric acid. The reaction mixture was washed with ether and the base liberated from the aqueous solution of the residue with potassium carbonate, taken up in ether and converted to the picrate, m. p. 132.5–133.1°, rhombs from ethanol, which considerably depressed the m. p. when mixed with (I) picrate.

Anal. Calcd. for $C_{13}H_{12}N_4O_9S$: C, 39.00; H, 3.02; N, 14.00. Found: C, 39.27; H, 3.11; N, 14.09.

A mixture of 0.4 g. of (I) and 0.4 cc. of aqueous hydrobromic acid (saturated at 0°) was heated for ten hours in a sealed tube at 100°. The contents were evaporated *in vacuo* to a small volume, taken up in water and the base liberated with potassium carbonate, taken up in ether and dried over sodium sulfate. Even in solution (XV) reacted appreciably with itself; on evaporation (XV) was left as an oil, a powerful lachrymator (compare benzyl bromide), which in five to ten minutes was converted to a water soluble resin. Addition of ethereal picric acid to (XV) yielded the picrate which was recrystallized from ethyl acetate (recrystallization from water yielded (I) picrate, mixed m. p., m. p. 137.5–138.0°.

Anal. Calcd. for $C_{11}H_9BrN_4O_7S$: C, 31.36; H, 2.15; N, 13.30. Found: C, 31.74; H, 2.63; N, 13.74.

(I) was dissolved in three volumes of concentrated sulfuric acid and the mixture heated for two hours at 115°. After cooling and diluting with 4 cc. of water, the product was treated with excess of potassium carbonate and extracted with ether. From the concentrated extracts, ethereal picric acid threw down an oily picrate which soon

(11) All melting points are corrected.

(12) See ref. 3, footnote 21.

(13) Compare ref. 5, footnote 15.

crystallized and, after recrystallization from water, melted at 180.0–180.2°. The analysis gave figures for the dipicrate of di-[(4-methylthiazolyl-5)-methyl] ether.

Anal. Calcd. for $C_{22}H_{18}O_{15}S_2$: C, 37.82; H, 2.60; N, 16.04. Found: C, 38.12; H, 2.73; N, 16.37.

(I) (**Method B**).—Butanol-1-one-3 (III) was prepared according to directions in the literature[14a]; from 500 g. of acetone, 35 g. of product[15] was obtained, b. p. 65–70° at 8 mm. To 17.6 g. (0.2 mole) of (III) dissolved in 90 cc. of water, was added with stirring 32 g. (0.2 mole) of C. P. bromine, while the temperature was maintained at about 20° by external cooling with tap water. The bromine was added from a dropping funnel at such a rate[16] that the solution remained practically colorless during the initial part of the reaction; as the reaction proceeded the solution assumed an orange color; the same slow rate of addition was maintained throughout. After the addition (ten and three-quarters hours) the reaction mixture was decanted from about 1 cc. of heavy oil which had formed, was saturated with ammonium sulfate and extracted several times with ether. Evaporation of solvent at room temperature *in vacuo* yielded 30.0 g. (89%) of almost colorless oil (compare ref. 10).

Brominated (III) (15.0 g.) was mixed with 8.3 g. of crude thioformamide and 10 cc. of absolute alcohol; the reactants were kept at 0° during the mixing. After the mixture stood for one week in the ice-box and then for two days at room temperature, it was worked up,[3] yield of crude thiazole, b. p. 80–110° (2 mm.), 3.7 g.[17] (28% from (III)). Material thus obtained (6.45 g.) was added to a hot solution of the theoretical amount (11.5 g.) of picric acid in ethyl acetate. On cooling, needle crystals separated which were identified as (I) picrate[18] (mixed m. p.). The mother liquors on further cooling and standing deposited a mixture of needles and diamond-shaped tablets; separation was accomplished by seeding a supersaturated solution in ethyl acetate with either form, allowing it to crystallize, removing the crystals and obtaining the other form from the mother liquors. The diamond-shaped orange crystals, (IV) picrate, melted at 132.5–133.0° (from alcohol or ethyl acetate) and considerably depressed the m. p. when mixed with either (I) picrate or (VI) picrate.

Anal. Calcd. for $C_{11}H_{10}N_4O_8S$: C, 36.87; H, 2.81; N, 15.64. Found: C, 36.83; H, 2.88; N, 15.62.

These crystals exhibited dimorphism; when suddenly introduced into a bath at 123° they liquefied and after resolidification melted at 132.5; interesting is also the fact that small amounts of this picrate could be distilled without appreciable decomposition. From the above reaction, 3.0 g. of (IV) picrate was obtained together with 5.8 g. of its isomer. One may conclude that the bromination of butanol-1-one-3 (III) gave the 2- and 4-bromo derivatives in a ratio of approximately 2:1.

(I) (**Method Ba**).—Ten grams of (III) was acetylated conveniently by mixing with 20 g. of acetic anhydride and adding a drop of concentrated sulfuric acid. The reaction proceeded with evolution of heat; the mixture was allowed to stand for one-half hour and fractionated *in vacuo*, yield 9.0 g. of the acetate (V), b. p. (8 mm.) 76–78°[19] (analysis). This method of acetylation (compare ref. 14a) was found superior to methods involving acetylation in the presence of pyridine either with acetic anhydride[20] or with acetyl chloride. At room temperature (V) goes into solution slowly on shaking with water probably due to hydrolysis.

(V) (8.4 g.) dissolved in 8 cc. of C. P. benzene was chlorinated at room temperature by adding dropwise with stirring and under anhydrous conditions 8.7 g. of sulfuryl chloride. After removal of solvent *in vacuo*, 10.2 g. of oil[21] remained which was condensed in alcohol solution with 8 g. of crude thioformamide. The mixture was allowed to stand at room temperature for one week and then worked up[3]; yield of crude thiazole, b. p. (3 mm.) 90–99°, 1.8 g. (16%). This was treated with the theoretical amount of picric acid in ethyl acetate and the resulting picrates were recrystallized from alcohol; (VI) picrate was isolated (mixed m. p.).

Crude (VI)–(VII) mixture (2.5 g.) was saponified by heating for ten minutes with 10 cc. of 20% aqueous potassium hydroxide, yield of (I)–(IV) 0.6 g.[22] From this, (I) and (IV) were isolated as picrates (mixed m. p.s) by the procedure described above.

Chloroacetone (VIII).—In connection with the investigation described below, it was found that a commercial preparation of (VIII), although agreeing in b. p. and density with the literature description, nevertheless, reasoning from analytical results obtained, contained considerable amounts of *asym*-dichloroacetone which is known to have nearly the same b. p. (VIII), reasonably free from higher chlorinated products was made by chlorinating 2320 g. (40 moles) of C. P. acetone with a relatively small amount (320 g. = 2.37 moles) of sulfuryl chloride (practical grade). The latter was added slowly with stirring from a dropping funnel over a period of five and one-half hours, taking precautions to exclude moisture and maintaining the reaction flask immersed in an ice-bath. After removal of excess acetone *in vacuo*, the residue was washed with aqueous potassium carbonate solution, dried[23] over sodium sulfate and fractionated. The yield was 158 g., 72% based on sulfuryl chloride, b. p. 118–120°, d^{15}_4 1.135, d^{25}_4 1.123.[24]

2-Chlorobutanol-1-one-3 (IX).[25]—To a mixture of 62.5 g. of (VIII) (see above) and 1.7 g. of C. P. potassium carbonate, 29.0 g. of 37% aqueous formaldehyde (reagent grade) was added dropwise with stirring in an ice-bath over a period of four hours; the reaction was slightly exothermic. Stirring was continued for twenty-four hours at room temperature; the reaction mixture was then extracted with ether and the extracts dried over sodium sulfate and fractionated *in vacuo*. After removal of (VIII),

(14) (a) Bayer and Co., German Patent 223,207; *Friedlaender, Fortschr. Teerfarbenfabrikation*, **10**, 1007 [*Chem. Zentr.*, **81**, II, 347 (1910)]; (b) more recent literature see White and Haward, *J. Chem. Soc.*, 25 (1943).

(15) Unsuccessful attempts were made to improve upon this procedure; the method of Quattlebaum, U. S. Patent 2,064,564 (to Union Carbide and Carbon Corporation) gave poor results.

(16) When bromination was carried out more rapidly, the product, on treatment with thioformamide, gave no appreciable amount of thiazole (rapidly brominated acetopropyl alcohol [Buchman, THIS JOURNAL, **58**, 1803 (1936)] gave a relatively good yield of thiazole).

(17) Compare ref. 10; a parallel experiment in which the reactants were mixed at room temperature gave 2.75 g.

(18) In another experiment in which an evidently less pure sample of (III) was used, the picrate after several recrystallizations from alcohol and from ethyl acetate melted at 160.5–161.5°. *Anal.* Calcd. for $C_{13}H_{14}N_4O_8S$: C, 40.41; H, 3.65; N, 14.50. Found: C, 40.83; H, 3.73; N, 14.35. This material did not depress the m. p. of a like picrate (see ref. 3, footnote 33) obtained from a brominated crude acetone-acetaldehyde condensation product; evidently it is formed from brominated diacetone alcohol.

(19) The values in the literature are not in good agreement: b. p. (15 mm.) 96°[14a]; b. p. (30 mm.) 125–130[20]; b. p. (30 mm.) 98–102°; *Chem. Zentr.*, **104**, I, 1961 (1936).

(20) Compare Morgan and Holmes, *J. Chem. Soc.*, 2667 (1932).

(21) This material decomposed extensively when fractionated at 8 mm.

(22) There is evidence that the low yield was due to partial destruction of the thiazole ring by the strong caustic; saponification with acid should be satisfactory.

(23) (VIII) apparently forms a constant boiling mixture with water and acetone.

(24) Pure (VIII) would exhibit a somewhat lower density. The figures reported for (VIII) (d^{16} 1.162, Linnemann, *Ann.*, **134**, 171 (1865); d^{18} 1.158, Cloez, *Ann. chim. phys.*, [6] **9**, 158 (1886)) indicate a considerable admixture of dichloroacetone; it is doubtful whether any of the physical constants recorded for (VIII) are valid for the pure substance.

(25) The preparation of (IX) from (XIII) and hypochlorous acid appears to offer no advantages over the method described here. Although the reaction between (VIII) and formaldehyde has not previously been studied, the work of Pictet and Misner, *Ber.*, **45**, 1802 (1912), indicates the direction which the reaction would be expected to take; compare also H. O. L. Fischer, Baer, Pollock and Niedecker, *Helv. Chim. Acta*, **20**, 1214 (1937).

18.0 g. of distillate was obtained, b. p. 50–90° (2 mm.). This material is sufficiently pure for conversion to (I); on refractionation at 5 mm. there was considerable loss due to the instability of the compound; even on standing it was converted slowly to an insoluble substance. Analysis was carried out on a sample b. p. (5 mm.) 70°.

Anal. Calcd. for $C_4H_7ClO_2$: C, 39.20; H, 5.76. Found: C, 39.14; H, 5.45.

The residue from the above distillation crystallized on standing; the crystals were freed from oil (yield 3.5 g.) and recrystallized from toluene, white needles, m. p. 63.2–63.7°, readily soluble in water and the usual organic solvents except petroleum ether and carbon tetrachloride; on exposure to light the crystals turn reddish. The analysis indicates the probable formula $CH_3COCCl(CH_2OH)_2$.

Anal. Calcd. for $C_5H_9ClO_3$: C, 39.36; H, 5.95; Cl, 23.24. Found: C, 39.16; H, 5.81; Cl, 23.67.

(I) **(Method C).**—(IX) (4.0 g., b. p. 70–75° (5 mm.)) was mixed at 0° with 2.8 g. of crude thioformamide and 3.0 cc. of ethanol. After standing for two weeks, the mixture was worked up,[3] yield of base 0.95 g. (22%). From this, 2.0 g. of (I) picrate was obtained; no indication could be found of the presence of the isomeric picrate.

4-Methyl-5-(carbethoxymethyl)-thiazole (X).[26]—Ethyl levulinate (213 g. = 1.48 moles, b. p. 78–80° (8 mm.)) dissolved in 145 cc. of benzene (some experiments were run without solvent) was conveniently chlorinated by adding, with stirring at 0° and under anhydrous conditions, 200 g. (1.48 moles) of sulfuryl chloride over a period of four and one-half hours; careful fractionation of the product gave 203 g. (76%) of chloro ester,[27] b. p. 84–86° (8 mm.).

Chloroester (72 g.) was condensed with 52 g. of crude thioformamide and 20 g. of alcohol, the reaction mixture allowed to stand for two weeks and worked up,[3] yield 34.1 g. (45%) of crude (X), b. p. 112–114° (5 mm.). Thiazole (11.3 g.) made in this fashion was treated with 14 g. of picric acid in ethyl acetate and the crystalline picrate (20 g.) recrystallized from alcohol. The lemon-yellow picrate of (X) (6.3 g.) was obtained, m. p. 126.3–126.6° (ref. 7 gives m. p. 130°); the mixture of picrates in the mother liquors was separated by recrystallizing several times alternately from ethanol and from ethyl acetate. Additional (X) picrate was recovered together with a second similarly colored picrate (1.9 g.), m. p. 128.0–128.5° (mixed m. p. with (X) picrate 113–116°), isomeric[28] with (X) picrate.

Anal. Calcd. for $C_{14}H_{14}N_4O_9S$: C, 40.58; H, 3.41; N, 13.52. Found: C, 40.89; H, 3.38; N, 13.29.

(X) was regenerated from the picrate, b. p. 114–115° (3 mm.) (considerably higher than found for crude base), d^{25}_4 1.160, hydrochloride, m. p. 154–155°[7] from alcohol–ether; on long standing (X) deteriorates.

Anal. Calcd. for $C_8H_{11}NO_3S$: C, 51.87; H, 5.99; N, 7.56. Found: C, 51.4; H, 6.13; N, 7.80.

4-Methylthiazole-5-acetamide (XI) was prepared by treatment of (X) (regenerated from picrate) with 20% methyl alcoholic ammonia. More conveniently it was made[7,9] from crude distilled (X). Such ester (104 g.) was mixed with 650 cc. of 20% methyl alcoholic ammonia and the solution allowed to stand for two days at room temperature. After removal of solvent, the residue was recrystallized from dioxane,[29] yield 71 g. (80%), m. p. 137.2–137.7°[7,9] (analysis).

4-Methyl-5-(aminomethyl)-thiazole (XII).[30]—To a solution of 10.8 g. of bromine in 150 g. of 2.5 *N* potassium hydroxide was added 10.5 g. of (XI) while cooling in an ice-bath. After solution was complete, 22 g. of potassium hydroxide pellets was added and the mixture heated at 95° for one and one-half hours. (XII) was isolated by continuous extration with ether and distillation *in vacuo;* 1.4 g. (16%) was obtained, almost all of which boiled at 94–95° (5 mm.).

Anal. Calcd. for $C_5H_8N_2S$: C, 46.84; H, 6.29; N, 21.85. Found: C, 47.29; H, 6.20; N, 21.10.

(XII) is stable in a sealed container, dihydrochloride (analysis) m. p. 259.5–260.0° dec. from methanol–ether, monopicrate (analysis) m. p. 213–214° dec. from 90% ethanol.

Action of Nitrous Acid on (XII).—(XII) (0.95 g.) was dissolved in 10 cc. of an aqueous solution containing 4.17 cc. of concentrated sulfuric acid. The solution was cooled to *ca.* −40°, 0.55 g. of sodium nitrite in 2 cc. of water was added and the reaction mixture allowed to warm gradually to room temperature (one hour) and to stand for an additional three hours after which gas evolution had ceased. After neutralizing by gradual addition of potassium carbonate and making strongly alkaline with 6 *N* sodium hydroxide, the product was extracted with ether and the extracts evaporated, yield 0.3 cc. of oil not readily soluble in ether. This oil was converted with ethereal picric acid to the picrate, yellow pearly flakes from water, m. p. 220° dec. (rapid heating; 213–214° dec. on slow heating), yield 0.1 g.; no (I) picrate could be detected.[31]

Anal. Calcd. for $C_{16}H_{17}N_7O_{10}S_2 \cdot H_2O$ (tentative formula): C, 34.97; H, 3.49; N, 17.84; S, 11.67; loss in weight, 3.28. Calcd. for $C_{16}H_{17}N_7O_{10}S_2$: C, 36.16; H, 3.22; N, 18.45. Found (dried at room temperature *in vacuo*): C, 35.49; H, 3.54; N, 18.26; S, 11.86; loss in weight on drying at 80° *in vacuo*, 3.56. Found (dried at 80° *in vacuo*): C, 37.29; H, 3.46; N, 18.63.

Reaction[32] between 3,4-Dibromobutanone-2 (XIV) and Thioformamide.—Methyl vinyl ketone (XIII) was pre-

(26) The experimental work reported in this connection represents an extension of accounts in the literature.[7,8] In connection with earlier work (Buchman, Williams and Keresztesy, THIS JOURNAL, **57**, 1849 (1935)), these authors (unpublished) made a search for $ThCH_2COOH$ among the products of oxidation of the vitamin thiazole ($ThCH_2CH_2OH$) with nitric acid; none of this acid was found (compare oxidation[3] of $ThCH_2CH_2CH_2OH$). For comparison, $ThCH_2COOH$[7] and its esters[7] were synthesized (at Teachers College, Columbia University); the methyl ester was made by condensation of brominated methyl levulinate (Kondo, Ohno and Irie, *J. Pharm. Soc. Japan*, **57**, 78 (1937); compare Pauly, Gilmour and Will, *Ann.*, **403**, 150 (footnote) (1914)) with crude thioformamide and also by the action of diazomethane on the corresponding acid,[7] b. p. (3 mm.) 88–92°, b. p. (13 mm.) 128–130° (these values are not in agreement with the b. p. (18 mm.) 111° reported[1] by Cereceda and Tolpin) picrate, m. p. 141.0–141.5°[1] (analysis), difficultly soluble in ether (means of separation[12] from $ThCOOCH_3$ picrate). The reduction of (X) with sodium and alcohol (compare ref. 7, 8b, c) has been carried out by one of us (E. R. B.) and the reaction products subjected to biological assay; the presence of vitamin thiazole could not be detected (compare Erlenmeyer and Simon, *Helv. Chim. Acta*, **25**, 528 (1942)).

(27) Compare Conrad and Guthzeit, *Ber.*, **17**, 2286 (1884).

(28) The chlorination of levulinic ester proceeds therefore in two directions. The structures assigned to (X) and to (XI) follow from the conversion of (XI) into $ThCH_2CN$ and $ThCH_2CH_2NH_2$ (carried out in this Laboratory by Drs. E. M. Richardson and M. J. Schlatter; compare ref. 9). $ThCH_2CH_2NH_2$ has been independently synthesized by methods indicative of structure (Harington and Moggridge, *J. Chem. Soc.*, 443 (1939); compare ref. 8).

(29) A small amount (2.5 g.) of dioxane-insoluble material was also obtained, colorless crystals from methanol, m. p. 141–142° dec., readily soluble in water, less so in methanol and difficultly in ethanol. The substance arises from an impurity in crude (X). *Anal.* Calcd. for $C_7H_{10}N_4O_3S_2$: C, 11.88; H, 4.98; N, 27.70; S, 31.70. Found: C, 12.05; H, 4.98; N, 27.21; S, 30.80.

(30) Various modifications of the Hofmann reaction were tried; the above procedure (compare ref. 8) seemed to give the best consistent results. The instability of the thiazole ring under these conditions was demonstrated by tests made with 4-methylthiazole and with 2,4-dimethylthiazole. These substances react readily (with production of sulfate ion) at room temperature with aqueous or aqueous alkaline N-bromoacetamide.

(31) Compare Pyman, *J. Chem. Soc.*, **109**, 190 (1916).

(32) Acrolein dibromide was found (in experiments carried out by Dr. E. M. Richardson) to react with thioformamide in alcohol with almost explosive violence. Although the reactants were brought together under a variety of conditions, only insoluble products were obtained and there was no indication that any monomeric thiazole

pared by dehydration[33] of (III), yield 75%, b. p. 75–78°. (XIV)[34] was prepared by adding bromine diluted with petroleum ether to a solution of (XIII) in the same solvent until color persisted, keeping the temperature at about −15° (below this temperature the reaction rate was slow). After removal of solvent *in vacuo*, (XIV) remained as an almost colorless oil, yield 92%.

Ethanol solutions of (XIV) and of thioformamide were mixed at −50°, allowed to warm slowly to 5° and kept at this temperature for three days; a substantial crystalline deposit had formed. The basic products were taken up in acid, liberated with potassium carbonate and converted directly to picrates; no halogen containing picrate could be detected. The products[35] were not identified; however, it seems reasonably certain that (XV) (see above) was not formed by this reaction.

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Summary

The preparation of 4-methyl-5-(hydroxymethyl)-thiazole by several different methods has been investigated. A convenient two-step synthesis starting from chloroacetone has been developed.

derivative was formed. When acrolein dibromide was mixed with an equimolar amount of thiourea in the presence of absolute alcohol, no reaction (other than acetal formation) took place at room temperature. However, on warming on the steam-bath an apparently crystalline precipitate formed, only sparingly soluble in water, m. p. 235° dec. from aqueous ethanol (Found: C, 18.05; H, 2.65; N, 14.96). On treatment with aqueous potassium carbonate this solid was converted to an amorphous material insoluble in the usual solvents but soluble in acids. Hubacher (*Ann.*, **259**, 243 (1890)) had reported that acrolein dibromide does not react with thiourea.

(33) Décombe, *Compt. rend.*, **202**, 1685 (1936); compare ref. 14b.

(34) Schlotterbeck, *Ber.*, **42**, 2563 (1909).

(35) One condensation (carried out at 5°) gave 9.0 g. (from 40 g. of (XIV) and 17 g. of thioformamide) of viscous ether-soluble oily bases. On fractionation, 0.3 g. of material b. p. *ca.* 70° at 2 mm. was obtained which gave a halogen-free picrate, m. p. 154.5–154.8° from ethanol; the rest was considerably higher boiling. Another condensation carried out at room temperature gave a product which behaved in a similar fashion on distillation. The picrate however (also halogen-free) melted at 184.0–184.5° from water. *Anal.* (154° picrate): C, 35.97; H, 2.93; N, 14.71; S, 19.99. *Anal.* (184° picrate): C, 36.23; H, 2.78; N, 14.86; S, 19.94.

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Studies on Ionone. III. Structure of Ethyl Ionylidene-acetates[1]

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It has been reported in a preceding publication[2] that the important ionylidene acetaldehyde cannot be obtained by dry distillation of the mixed barium salts of ionylidene acetic acid and formic acid, but that ionone is obtained. It has also been stated that dry distillation of barium ionylidene-acetate leads invariably to α-ionone regardless of whether the ionylidene-acetic acid was prepared from α- or β-ionone in the Reformatsky condensation. Since both series thus converge, the question arises whether the transition from the β- to the α-series takes place in the course of the Reformatsky reaction or during the ensuing dry distillation. As has been indicated in the first paper of this series, spectrographic evidence points to the occurrence of this rearrangement during the synthetic reaction. The study of the ultraviolet absorption spectra of ethyl ionylidene-acetate forms the subject of the present communication.

The double bond of the carbethoxy group in ethyl α-ionylidene-acetate is conjugated with two ethylene bonds, whereas the cyclic double bond is not conjugated with this system and is not expected to influence the position of the main absorption band. Conversely, the C=O— bond of ethyl β-ionylidene-acetate is conjugated with three ethylene bonds; this should produce a difference, at the very least, of 25 mμ and up to 45 mμ, between the main absorption band of the two compounds.

Table I gives the absorption bands for the pair α-ionone–β-ionone and also for the pair of isomeric hydrocarbons $C_{14}H_{22}$ (formulas I and II) which we have prepared according to Kipping and Wild.[3]

TABLE I

ABSORPTION MAXIMA OF ETHYL IONYLIDENE-ACETATES AND RELATED COMPOUNDS

Graph	Compound (mol. wt.)	Max. wave length, mμ	Mol. extinction coefficient, $\epsilon_{max.}$
	Ionone (192.3)		
..	α-Isomer	228	15,550
..	β-Isomer	296	12,700
	Cyclocitrylidene-isobutene (190.3)		
1	α-Isomer	230	30,100
2	β-Isomer	281.5	21,900
	Ethyl ionylidene-acetate (262.4)		
3	Prepn. A	271	10,750
4	Prepn. B	284.5	12,550
5	Prepn. B (purified)	281.5	34,000
6	Prepn. C	269	27,200
7	Prepn. D	275	17,400

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(2) H. Sobotka, E. Bloch and E. Glick, THIS JOURNAL, **65**, 1961 (1943).

(3) Kipping and Wild, *J. Chem. Soc.*, 1239 (1940).