but they exclude the possibility that it could be 2,5-methylene-D-mannitol or a stereoisomer of that substance.

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 43.15; H, 7.27.

4-Acetoxymethyl-5-acetoxy-6-di-(acetoxymethyl)-1,3-dioxane.—A solution of 1.0 g. of the substituted 1,3-dioxane in a mixture of 10 cc. of pyridine and 15 cc. of acetic anhydride was allowed to stand overnight at room temperature and then poured into 500 cc. of ice water. The aqueous solution was extracted with chloroform and the washed and dried extract upon concentration yielded 1.7 g. (89%) of a sirup which crystallized readily. The compound, which is soluble in acetone, chloroform, ether, pyridine, benzene and dioxane and insoluble in water, was recrystallized from 10 parts of alcohol in the form of rods, melting at 93–94° and showing a specific rotation $[\alpha]^{20}D$ +12.4° in chloroform (*c*, 1.0) and +20.4° in acetone (*c*, 1.0).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 47.5; molecular weight, 362. Found: C, 49.73; H, 6.24; CH_3CO, 47.3; molecular weight (Rast), 313.

Summary

The acetolysis of 2,5-diacetyl and 2,5-dibenzoyl-1,3:4,6-dimethylene-dulcitols yields a tetraacetyl-di-(acetoxymethyl)-dulcitol and a 2,5-dibenzoyl-diacetyl-di-(acetoxymethyl)-dulcitol, respectively. The acetolysis of the trimethylene-D-mannitol of Schulz and Tollens yields a diacetyl-di-(acetoxymethyl)-methylene-D-mannitol. Upon saponification of the latter compound 2,5-methylene-D-mannitol, a new type of acetal of a carbohydrate, is formed. The isolation of this substance indicates that under the conditions of acetolysis employed, the methylene hemiacetal linkages that are formed through primary hydroxyl groups are more easily ruptured than those formed through secondary hydroxyl groups and suggests the tentative structural assignments of 1,2,5,6-tetraacetyl-3,4-di-(acetoxymethyl)-dulcitol, 1,6-diacetyl-2,5-dibenzoyl-3,4-di-(acetoxymethyl)-dulcitol, and 1,6-diacetyl-2,5-methylene-3,4-di-(acetoxymethyl)-D-mannitol to the acetolysis products.

Proof of the structure of 2,5-dimethylene-D-mannitol has been obtained (1) through its oxidation by per-iodic acid to form sirupy methylene-bis-2-D-glycerose, which upon reduction is converted into a crystalline methylene-bis-2-glycerol; (2) through the lead tetraacetate oxidation of its 1,6-dibenzoyl derivative to produce the formaldehyde acetal of 3-benzoyl-D-glyceric aldehyde, which was characterized as the crystalline disemicarbazone; and (3) through the condensation of its 1,6-dibenzoyl derivative with benzaldehyde to yield 1,6-dibenzoyl-2,5-methylene-3,4-benzylidene-D-mannitol which proved to be identical with the mixed diacetal prepared by condensing the known 1,6-dibenzoyl-3,4-benzylidene-D-mannitol with paraformaldehyde.

Evidence is presented for the assignment of 1,3:2,5:4,6-trimethylene-D-mannitol as the structural formula for the long known trimethylene-D-mannitol of Schulz and Tollens.

An interesting reaction, apparently an intramolecular aldol condensation of methylene-bis-2-D-glycerose to produce 4-hydroxymethyl-5-hydroxy-6-formyl, hydroxymethyl-1,3-dioxane, which upon reduction yields crystalline 4-hydroxymethyl-5-hydroxy-6-di-(hydroxymethyl)-1,3-dioxane, has been described.

BETHESDA, MARYLAND RECEIVED AUGUST 16, 1943

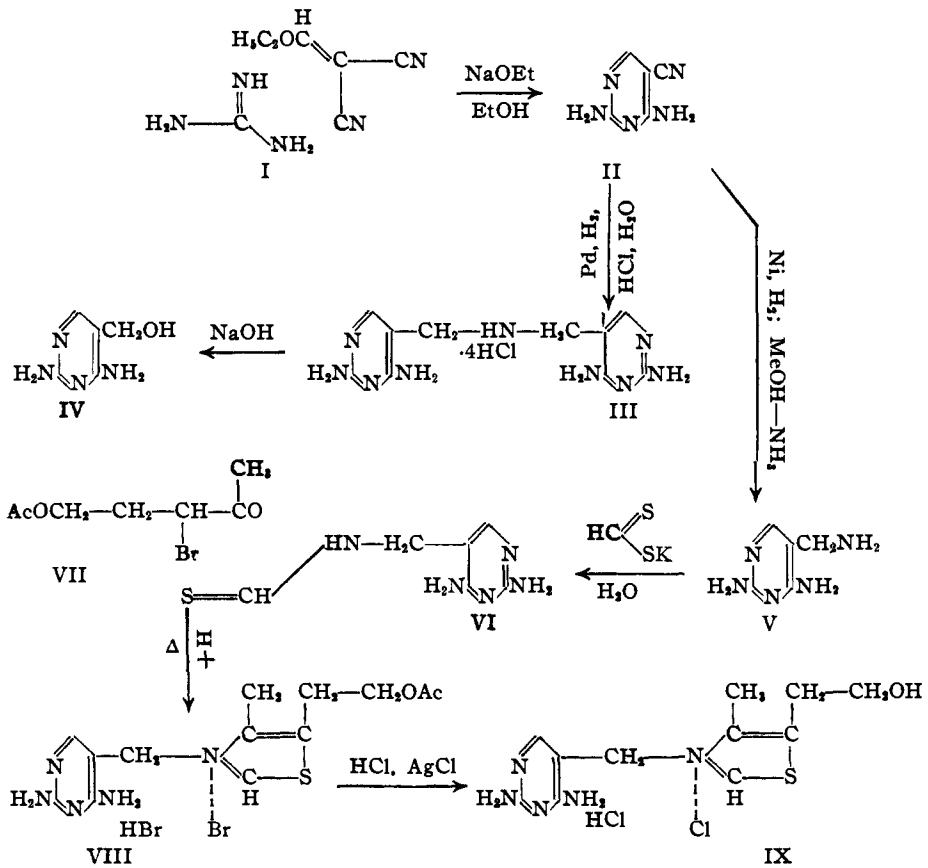
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

2,4-Diamino-5-(4-methyl-5-β-hydroxyethylthiazolium chloride)-methylpyrimidine Hydrochloride, a New Analog of Thiamin

BY WOLFGANG HUBER

Within the last seven years well over two score homologs and analogs of thiamin have been prepared. These compounds can be conveniently classified into the following groups indicating the place of change in comparison with the original thiamin molecule: (1) change of substituents in the pyrimidine ring[1,2,3,4,5]; (2) change of substituents in the thiazole ring[1,6,3,7,8,5]; (3) change of substituents in the pyrimidine and the thiazole rings[3,5]; (4) change of the carbon bridge connecting the pyrimidine and thiazole rings[3]; (5) replacement of either the pyrimidine or thiazole ring by another ring system.[9,10,11,12,13] The pharmacological and biochemical evaluation of a large number of thiamin homologs and analogs has been reported in the literature.[3,5,12,14] One cannot fail to draw the conclusion from these reports that the antineuritic specificity of the vitamin is shared by a surprisingly large number of more or less related compounds although the actual activity of the vitamin is duplicated only in the very closely related homologs and some of the esters.

(1) Todd and Bergel, *J. Chem. Soc.*, 1559 (1936).
(2) Andersag and Westphal, *Ber.*, **70**, 2043 (1937).
(3) Schultz, *Z. physiol. Chem.*, **265**, 113 (1940).
(4) Perina and Ziegel, *Proc. Sci. Inst. Vitamin Research*, U. S. S. R., **3**, No. 1, 94 (1941); *C. A.*, **36**, 3008.
(5) Stein, Sampson, Cline and Stevens, THIS JOURNAL, **63**, 2059 (1941).
(6) Buchman and Richardson, *ibid.*, **61**, 891 (1939).
(7) Slobodin and Ziegel, *J. Gen. Chem.* (U. S. S. R.), **11**, 1019 (1941).
(8) Price and Pickel, THIS JOURNAL, **63**, 1067 (1941).
(9) Schmelkes and Joiner, *ibid.*, **61**, 2562 (1939).
(10) Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939).
(11) Tracy and Elderfield, *ibid.*, **6**, 54 (1941).
(12) Baumgarten and Dornow, *Ber.*, **73**, 44, 353 (1940).
(13) Tota and Elderfield, *J. Org. Chem.*, **7**, 309 (1942).
(14) Robbins, *Proc. Nat. Acad. Sci.* U. S., **27**, 419 (1941).



It seemed of interest to study the change of general biological behavior which would be effected by the replacement of the methyl group in the 2-position of the pyrimidine part of the thiamin molecule by groups other than alkyl. The present report deals with the preparation of 2,4-diamino - 5 - (4 - methyl - 5 - β - hydroxy - ethyl - thiazolium chloride)-methylpyrimidine hydrochloride. The synthesis is represented by the accompanying equations.

2,4-Diamino-5-cyanopyrimidine was prepared according to the method of Grewe[15] and Huber and Hoelscher[16] by the condensation of a guanidine salt with ethoxymethylenemalononitrile (I) in ethanol in the presence of enough sodium ethoxide to form the free guanidine base. The reduction of the nitrile (II) to the corresponding primary amine (V) can be achieved catalytically by a number of methods such as hydrogenation with platinum oxide or palladium-charcoal in the presence of mineral acids; these procedures give only moderate yields of 2,4-diamino-5-aminomethylpyrimidine salts. The primary amine (V) can be obtained in over 90% yields, however, by catalytic hydrogenation in the presence of Raney nickel in an alcoholic solution saturated with ammonia.

(15) Grewe, *Z. physiol. Chem.*, **243**, 89 (1936).
(16) Huber and Hoelscher, *Ber.*, **71**, 87 (1934).

Hydrogenation with palladium-charcoal in alcohol containing hydrochloric acid leads invariably to the formation of considerable amounts of the secondary amine (III). This is stable only in the form of its salts. Every attempt to form the free base resulted in the loss of ammonia and in the formation of a compound $C_8H_8N_4O$ for which the structure of 2,4-diamino-5-hydroxymethylpyrimidine is proposed (IV). The similar di-(2-methyl-4-amino-5-pyrimethyl)-amine has been observed to hydrolyze similarly[17] to give the known 2 - methyl - 4 - amino - 5 - hydroxymethylpyrimidine[2] which was identified by comparison with an authentic sample. Considering the similarity of the 5-pyrimethyl to the benzyl group, this rupture of a carbon to nitrogen linkage by hydrolyzing agents is not too surprising. It is in analogy with the observation of Kharasch and Howard[18] on the instability of the carbon to nitrogen linkage in substituted methylamines and numerous other findings reported in the literature.[19]

The dihydrochloride of the primary amine (V) readily undergoes condensation with potassium dithioformate[20] in aqueous solution in the presence

(17) Huber, unpublished results.
(18) Kharasch and Howard, THIS JOURNAL, **56**, 1370 (1934).
(19) For a summary, see Houben–Weyl, "Die Methoden der organischen Chemie," second ed., 1924, Vol. 4, p. 446–469.
(20) Levy, *Atti Acad. Lincei, Classe Sci., fis., mat. nat.*, **32**, I. 569 (1923).

of enough potassium carbonate to neutralize the mineral acid to give 2,4-diamino-5-thioformylaminomethylpyrimidine (VI) in excellent yields. The latter was condensed with γ-bromo-γ-acetopropyl acetate (VII) in the presence of formic acid to (VIII). For practical purposes the latter can be converted without isolation in a one-step procedure into the vitamin analog (IX).

This modified process increased considerably the yield of the condensation product in comparison with the standard procedure[1,2] and was found to be applicable also in the preparation of thiamin itself and a number of its homologs and analogs.[17]

TABLE I

2,4-DIAMINO-5-(4-METHYL-5-β-HYDROXYETHYLTHIAZOLIUM CHLORIDE)-METHYLPYRIMIDINE HYDROCHLORIDE CALCULATED AS THIAMIN HYDROCHLORIDE, %

Sample	Color method	Thiochrome method
1	60	28
	31	30
	56	24.4
	36	26.4
2	50	29.4
	44	28.8

Table I shows the results of several assays by the thiochrome method[21] and the color method with diazotized *p*-aminoacetophenone.[22] The discrepancy of results and the inconsistency of individual figures in the color test show that analytical methods used in the determination of thiamin, cannot *per se* be adopted for the determination of even closely related analogs.

The vitamin analog (IX) was assayed according to the official U. S. P. Curative method[23] for a seven-day period in a dosage of 25 γ and was found to be inactive at this level.

Experimental[24]

Ethoxymethylenemalononitrile (I).—The method of Diels[25] was found hard to control and gave rather poor yields. The following modification was found to be reliable in a great number of experiments.

Sixty-six grams of redistilled malononitrile, 152 g. of ethyl orthoformate and 220 g. of acetic anhydride were mixed in an oversized flask and heated to 110° inner temperature with stirring. Heating was discontinued until the vigorous reaction had subsided and the inner temperature of the mixture had dropped to 95°. The solvent was removed from the clear yellow reaction mixture by distillation until the inner temperature of the mixture had risen to 115°. The last trace of solvent was then removed by a vacuum distillation (100°, 15 mm.). The residue was then cooled to 80°, 1.0 g. of charcoal and 35 ml. of absolute ethanol were added and the mixture was refluxed for five minutes with stirring. After filtering while hot and washing the filtercake with 3 ml. of hot absolute ethanol, the filtrate was cooled in ice with stirring until crystallization was complete. After filtration and washing with ice-cold ethanol the white crystalline material was dried to constant weight *in vacuo*; yield, 80.0 g. From the mother liquor on cooling to −10° an additional crop of equally pure material was obtained: over-all yield; 88.6 g. or 72.6%; m. p. 67–68°.

2,4-Diamino-5-cyanopyrimidine (II).—Twelve and two-tenths grams of guanidine nitrate was added in portions and with stirring to a cold solution (5°) of 2.3 g. of sodium in 100 cc. of absolute alcohol. To complete the formation of the free guanidine base stirring and cooling were continued for ten minutes. The precipitated sodium nitrate was then filtered by suction, washed with 15 ml. of ice-cold absolute ethanol and the clear colorless filtrate was cooled to −5°. Twelve grams of ethoxymethylenemalononitrile was added in four portions to the cold solution with stirring. Immediate reaction took place, turning the solution yellow and raising the temperature, which was kept below 15° by cooling. After about thirty minutes the pyrimidine began to precipitate in the form of a yellow solid. The temperature was then allowed to rise and the reaction allowed to run to completion by eight hours of additional stirring at room temperature. After removal of about 60 ml. of ethanol and subsequent cooling, the solid precipitate was filtered and washed thoroughly with ice-cold 70% aqueous ethanol. The light amber solid was purified by dissolving it in glacial acetic acid in the presence of charcoal; after filtration it was reprecipitated by neutralizing the solution with ammonia. The cyanopyrimidine was thus obtained in clustered white needles, m. p. 318° (dec.); 7.5 g. or 54% yield.

Anal. Calcd. for $C_5H_5N_5$: N, 51.85; Found: N, 51.49.

The hydrochloride was obtained from dilute ethanol in the presence of hydrochloric acid as white leaflets which did not melt up to 360°.

Anal. Calcd. for $C_5H_6N_5Cl$: N, 40.81; Cl, 20.69. Found: N. 40.58; Cl, 20.50.

The picrate, when recrystallized from water, formed yellow needles; m. p. 281-283° (dec.).

2- or 4-Amino-2- or 4-acetylamino-5-cyanopyrimidine.—Five grams of 2,4-diamino-5-cyanopyrimidine was mixed with 50 ml. acetic anhydride and refluxed for three hours. The clear red solution was decolorized with charcoal and filtered while hot. From the light yellow filtrate a white precipitate was obtained on cooling. It was filtered with suction and pressed as dry as possible and dissolved in hot water. The aqueous solution was decolorized with charcoal and then neutralized with ammonia. The monoacetyl derivative of 2,4-diamino-5-cyanopyrimidine crystallized on cooling in clustered white needles; 4.8 g. or 72% yield; m. p. 238°.

Anal. Calcd. for $C_7H_7ON_5$: N, 39.54; AcOH, 33.89. Found: N, 39.40; AcOH, 34.00.

2,4-Diacetylamino-5-cyanopyrimidine.—Two and five-tenths grams of 2,4-diamino-5-cyanopyrimidine was mixed with 30 ml. of acetic anhydride and heated in a bomb tube for four hours at 200°. The deep red, partly charred mixture was taken up in excess hot water, decolorized repeatedly with charcoal and finally made neutral with ammonia. After concentration to a small volume and cooling, a white precipitate was formed, which was filtered and pressed dry. After recrystallization from a small volume of hot water, 2,4-diacetylamino-5-cyanopyrimidine was obtained as white needles; 2.6 g. or 64% yield; m. p. 197–198°.

Anal. Calcd. for $C_9H_9O_2N_5$: N, 31.96; AcOH, 54.74. Found: N, 31.70; AcOH, 54.40.

2,4-Diamino-5-aminomethylpyrimidine (V).—To a suspension of 7 g. of 2,4-diamino-5-cyanopyrimidine in 130 ml. of methanol containing 13 g. of dry ammonia 8 g. of freshly prepared Raney nickel was added. The reduction was carried out in a small steel autoclave with vigorous shaking under a pressure of 60 lb. of hydrogen at room temperature. The nitrile soon went into solution, while toward the end of the reaction some white precipitate was formed. The required amount of hydrogen was taken up in two hours. Catalyst and precipitate were filtered and washed thoroughly with methanol. The clear yellow filtrate was decolorized with charcoal and the solvent re-

(21) Hennessy and Cerecedo, THIS JOURNAL, **61**, 179 (1939).
(22) Auerbach, *J. Am. Pharm. Assoc.*, **29**, 313 (1940).
(23) U. S. Pharmacopeia XI, 1939 Supplement, p. 129.
(24) The melting points reported here are not corrected.
(25) Diels, Gartner and Kaack, *Ber.*, **55**, 3441 (1922).

moved *in vacuo*. The residue was taken up in 20 ml. of water, filtered from insoluble material (recovered nitrile) if necessary, and made strongly acid with concentrated hydrochloric acid. Most of the solvent was removed *in vacuo* and the 2,4-diamino-5-aminomethylpyrimidine dihydrochloride precipitated with excess ethanol; 8.9 g. or 81% yield. For analysis the dihydrochloride was recrystallized from dilute ethanol; m. p. 278–280° (dec.).

Anal. Calcd. for $C_6H_{11}N_5Cl_2$: N, 33.02; Cl, 33.49. Found: N, 32.85; Cl, 33.50.

If the reduction was carried out under a pressure of 200 lb. of hydrogen, it was finished in much shorter time and no precipitate (secondary amine) was found.

The reduction was also carried out with platinum oxide and palladium on zirconium oxide in either ethanol containing dry hydrochloric acid or glacial acetic acid. In these reactions the hydrogenation required a much longer time and was often incomplete because of poisoning of the catalyst by the acid. Invariably considerable amounts of secondary amine were found.

Di-(2,4-diamino-5-pyrimethyl)-amine (III).—The mixture of Raney nickel and precipitate as obtained from the above hydrogenation was triturated with 50% acetic acid until the color of the catalyst was a pure black. The latter was removed by filtration, the yellow filtrate decolorized with charcoal and made strongly acid with hydrochloric acid. Acetic acid and water were removed *in vacuo* and the di-(2,4-diamino-5-pyrimethyl)-amine tetrahydrochloride precipitated with ethanol. After recrystallization from aqueous ethanol the compound crystallized in white needles; m. p. 357° (dec.).

Anal. Calcd. for $C_{10}H_{19}N_9Cl_4$: N, 30.95; Cl, 34.88. Found: N, 30.84; Cl, 34.96.

If the hydrogenation of the nitrile (I) was carried out in aqueous hydrochloric acid in the presence of palladium on zirconium oxide di-(2,4-diamino-5-pyrimethyl)-amine is obtained exclusively and in good yield.

2,4-Diamino-5-hydroxymethylpyrimidine (IV).—Two grams of di-(2,4-diamino-5-pyrimethyl)-amine tetrahydrochloride was dissolved in 20 ml. of water and the cold solution was neutralized with 10% sodium hydroxide. Evolution of ammonia occurred with simultaneous precipitation of a white solid. The material was filtered and washed with cold water; 1.28 g. or 90% yield. The product was crystallized from a large volume of water and then melted at 265° (dec.). The hydrochloride was obtained from dilute ethanol in glittering platelets; m. p. 327° (dec.).

Anal. Calcd. for $C_6H_9N_4OCl$: N, 31.73; Cl, 20.11. Found: N, 32.05; Cl, 20.10.

The picrate is obtained from water in very fine needles; m. p. 244–246° (dec.).

2,4-Diamino-5-thioformylaminomethylpyrimidine (VI).—To the cooled solution of 9.2 g. of 2,4-diamino-5-aminomethylpyrimidine dihydrochloride in 28 ml. of water, 6.2 g. of anhydrous potassium carbonate in 20 ml. of water was added as quickly as possible. Immediately thereafter a solution of 6.1 g. of potassium dithioformate in 18 ml. of water was added, keeping the temperature below 15° during the addition. The clear amber solution turned cloudy after a few minutes with a simultaneous evolution of hydrogen sulfide. To complete the reaction stirring was continued for six hours at room temperature. The solid precipitate was filtered, washed thoroughly with water and dried. It was then dissolved in 40 ml. of warm 50% acetic acid, decolorized with charcoal, filtered and neutralized with 28% ammonium hydroxide while warm. On cooling the 2,4-diamino-5-thioformylaminomethylpyrimidine crystallized in white, glittering platelets; 7.7 g. or an 86% yield; m. p. 181–182° (dec.).

Anal. Calcd. for $C_6H_9N_5S$: N, 38.25; S, 17.48. Found: N, 38.09; S, 17.26.

On addition of the calculated amount of alcoholic hydrochloric acid to a solution of 2,4-diamino-5-thioformylaminomethylpyrimidine in aqueous methanol in the cold, the monohydrochloride was obtained in the form of white needles. After recrystallization from ethanol the material melted at 205–206° (dec.).

Anal. Calcd. for $C_6H_{10}N_5SCl$: N, 31.89; S, 14.58; Cl, 16.17. Found: N, 31.67; S, 14.69; Cl, 16.00.

γ-Bromo-γ-acetopropyl Acetate (VII).—It was found that of the large number of halogenated acetopropanols and esters described in the literature this compound, on condensation with 5-thioformylaminopyrimidines, gave the best yields of thiamin, its analogs and homologs.[17] Since its preparation[26] as described in the scientific and patent literature was found to be incomplete and to give rather poor yields the following modified procedure was developed. This makes it possible to obtain the crude γ-bromo-γ-acetopropyl acetate in a pure enough state for further reaction, thus avoiding a cumbersome and yield-impairing final purification by high vacuum distillation. One hundred twenty grams of pure acetopropyl acetate[27] was dissolved, with stirring, in 600 ml. of dry ether and the solution cooled to 5°. Then 133 g. of bromine was dropped into the well-stirred solution at a rate that kept the inner temperature below 10°. This required about one and a half hours. After all the bromine had been added the stirring was continued at room temperature until the color of the solution had faded to a light yellow. This required about thirty minutes. Then 300 ml. of fresh ether was added and the solution was twice extracted with 200 ml. of ice water to remove the bulk of the hydrobromic acid. Finally the ethereal solution was extracted with 200 ml. of ice-cold 2% sodium bicarbonate solution and dried with 60 g. of calcium chloride for six hours in a dark container at a temperature below 20°. The ether was then removed *in vacuo* at 20°, the reaction product being protected from light. The residue was dried *in vacuo* at room temperature for thirty minutes. The crude γ-bromo-γ-acetopropyl acetate thus obtained was a light yellow oil; 164 g. or 88% yield.

Anal. Calcd. for $C_7H_{11}O_3Br$: Br, 35.85. Found: Br, 36.42.

The bromo ester should preferably be used as soon as possible, because even short storage, especially with exposure to light, will cause decomposition which is indicated by intense discoloration to a dark brown. The bromo ester should be handled carefully because it is a respiratory irritant and can cause severe dermatitis on prolonged contact with the skin.

2,4-Diamino-5-(4-methyl-5-β-hydroxyethylthiazolium chloride)-methylpyrimidine Hydrochloride (IX).—Into a solution of 6.8 g. of γ-bromo-γ-acetopropyl acetate, as obtained above, in 10 ml. of anhydrous formic acid was stirred at 40° 5 g. of 2,4-diamino-5-thioformylaminomethylpyrimidine. The reaction proceeded with evolution of heat which brought the inner temperature to 60°. The semi-solid mixture was maintained at 45° for two hours and then heated to 60° for an additional three hours. The clear amber solution crystallized on cooling. The reaction product was taken up in 25 ml. of 5% aqueous hydrochloric acid and the red solution extracted twice with 10 ml. of methylene chloride to remove unreacted γ-bromo-γ-acetopropyl acetate and soluble decomposition products. After addition of charcoal the aqueous layer was stirred at 40° for thirty minutes. Decolorization and saponification of the acetyl group were thus achieved. The process was repeated and the clear light yellow filtrate was then shaken at room temperature with 4 g. of freshly prepared silver chloride for one hour. The silver bromide was filtered and washed with 5 ml. of hot water. The nearly colorless filtrate was concentrated in vacuum to a total volume of 9 ml., the inner temperature being raised to 90° toward the end. Then the vacuum was discontinued and the crude hydrochloride (VII) was precipitated by addition of 75 ml. of hot absolute ethanol. After twelve hours of cooling the precipitate was filtered, washed with a total of 15 ml. of ice cold absolute ethanol in small portions and dried in the oven at 60°; 7.1 g. or an 80% yield; m. p., 241–243° (dec.). After recrystallization from dilute ethanol and decoloriza-

(26) Andersag and Westphal, *loc. cit.*, Buchman, U. S. Patents 2,218,349 and 2,218,350 (1941).

(27) Pakendorf, *Compt. Rend. Acad. Sci.*, U. R. S. S., **27**, 956 (1940); *C. A.*, **35**, 1382 (1941).

tion with charcoal, 2,4-diamino-5-(4-methyl-5-β-hydroxyethylthiazoliumchloride)-methylpyrimidine hydrochloride was obtained in white needles; m. p. 245–247° (dec.).

Anal. Calcd. for $C_{11}H_{17}ON_5SCl_2$: C, 39.05; H, 5.02; N, 20.71; Cl, 21.00. Found: C, 39.18; H, 4.84; N, 20.60; Cl, 21.24.

The compound formed a picrate which after recrystallization from water melted at 197–199° (dec.).

2,4-Diamino-5-(4-methyl-5-β-hydroxyethylthiazolium bromide)-methylpyrimidine Hydrobromide (VIII).—This compound was obtained when the reaction product of the above condensation was taken up with 10% aqueous hydrobromic acid. The red solution was extracted with methylene chloride, warmed to 40° for one hour to saponify the acetyl group and finally decolorized with charcoal. From the highly concentrated filtrate the compound was precipitated with excess ethanol. After recrystallization from dilute ethanol 2,4-diamino-5-(4-methyl-5-β-hydroxyethylthiazolium bromide)-methylpyrimidine hydrobromide was obtained in white needles; m. p. 214–216° (dec.).

Anal. Calcd. for $C_{11}H_{16}ON_5SBr_2$: N, 16.43; Br, 37.56. Found: N, 16.29; Br, 37.64.

Acknowledgment.—The author is grateful to Drs. O. W. Barlow and H. R. Street for the biological assays, to Dr. E. Danziger for most of the analyses and to Mr. A. Astrack for technical assistance.

Summary

An analog of thiamin having an amino group instead of the methyl group in the C-2 position of the pyrimidine ring has been prepared. It was assayed according to the official curative method and found to be void of Vitamin B_1 activity at a level of 25 γ.

RENNSELAER, N. Y. RECEIVED JULY 10, 1943

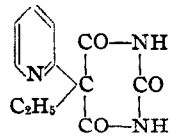
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

5-Ethyl-5-(2-pyridyl)-barbituric Acid

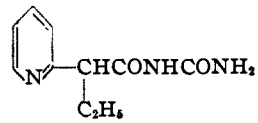
BY S. M. McELVAIN AND M. A. GOESE

In an earlier paper[1] from this Laboratory unsuccessful attempts to condense ethyl ethyl-2-pyridylmalonate with urea by means of sodium ethoxide, both in the dry state and in alcoholic solution, were reported. The only reaction product that could be obtained was α-(2-pyridyl)-butyramide, formed through the cleavage of the malonic ester to the corresponding acetic ester followed by the ammonolysis of this latter ester.

In this work which is now reported it has been found possible to prepare 5-ethyl-5-(2-pyridyl)-barbituric acid (I) in low (10%) yields from this sensitive malonic ester by carrying out the reaction in the less efficient alcoholizing medium, *t*-butyl alcohol. It also was found advantageous to add the condensing agent, sodium *t*-butoxide, in fractional amounts as the condensation proceeded and to arrange the apparatus to permit continuous distillation of the alcohol in order to remove as much as possible of the ethyl alcohol as it is formed in the condensation



I



II

The main product of the reaction between urea and ethyl-2-pyridylmalonic ester in *t*-butyl alcohol is the α-(2-pyridyl)-butyrylurea (II) which results from the condensation of the corresponding butyric ester with urea.

With sodium isopropoxide in isopropyl alcohol as the condensing agent the yield of the barbituric acid dropped to 5% of the theoretical. Under these conditions the α-(2-pyridyl)-butyramide was the principal reaction product as it was when ethyl alcohol and sodium ethoxide were used.[1] The yield of the barbituric acid was not improved by the use of guanidine instead of urea, a variation which Cope and Hancock[2] have found beneficial in the preparation of barbituric acids from certain alkali-sensitive malonic esters.

5-Ethyl-5-(2-pyridyl)-barbituric acid is being studied pharmacologically by Mr. E. E. Swanson of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. Preliminary tests indicate that this barbituric acid has no hypnotic or anesthetic action when administered intraperitoneally or intravenously to white rats.

Experimental

Diethyl Ethyl-2-pyridylmalonate.—This ester was prepared from diethyl ethylmalonate by the same procedure and in approximately the same yields (15–20%) as previously reported.[1] The product obtained boiled at 136–138° (2 mm.) and contained 33.6% ethoxyl (calcd. 33.9%). The use of reduced copper, as recommended by Schickh, Binz and Schultz[3] for the preparation of 2-methoxy-3-aminopyridine from 2-chloro-3-aminopyridine, gave no improvement in yields. In connection with the preparation of this pyridylmalonic ester it is interesting to note that Kuhn and Richter[4] report that they were unable to obtain any of the pyridylmalonic ester by the condensation of 2-bromopyridine with the unsubstituted malonic ester.

5-Ethyl-5-(2-pyridyl)-barbituric Acid.—In a 250-ml. 3-neck round-bottom flask fitted with a dropping funnel, mechanical stirrer and a condenser set for downward distillation, was placed 4.8 g. (0.08 mole) of urea, 10.6 g. (0.04 mole) of ethyl-2-pyridyl-malonic ester, 1 g. of sodium *t*-butoxide and 100 ml. of dry *t*-butyl alcohol. This mixture was heated to the boiling point of the alcohol and the latter slowly distilled at the rate of about 100 ml. per hour from the reaction flask. The distilled alcohol was re-

(1) Walter and McElvain, THIS JOURNAL, 57, 1891 (1935).

(2) Cope and Hancock, *ibid.*, 61, 776 (1939).

(3) Schickh, Binz and Schultz, *Ber.*, 69, 2593 (1936).

(4) Kuhn and Richter, THIS JOURNAL, 57, 1927 (1935).