thiazine[2] have been prepared. Methods used were similar to those which had been employed for the acylation of phenols. Acetyl derivatives were prepared by the use of acetic anhydride.[3] Other acylations were effected by permitting the materials to react in pyridine solution,[4] but no heating was required.

Phenothiazine.—"Phenothiazine (Regular) Lot 18-10402-1-769" was generously provided by E. I. du Pont de Nemours & Company. Recrystallizations from benzene yielded a product melting at 179°.

Nitro Derivatives.[5]—3-Nitrophenothiazine-5-oxide and 3,7-dinitrophenothiazine were prepared by recorded methods; 3,7-dinitrophenothiazine-5-oxide was obtained as a by-product in the preparation of the mononitro oxide.

Acyl Derivatives of Phenothiazine and Substituted Phenothiazines

(A) **10-Benzenesulfonylphenothiazine:** glistening, colorless needles from ethanol, 30% yield, m. p. 170–170.5°. *Anal.* Calcd. for $C_{18}H_{13}O_2NS_2$: S, 18.87. Found: S, 19.0.

(B) **10-Acetyl-3-nitrophenothiazine-5-oxide:** dark red irregular crystals from nitrobenzene (precipitated by the addition of 90–120° ligroin), 90% yield, sublimes *ca.* 250°, dec. above 360°. *Anal.* Calcd. for $C_{14}H_{10}O_4N_2S$: S, 10.59. Found: S, 9.6.

(C) **10-Benzoyl-3-nitrophenothiazine-5-oxide:** dark red irregular crystals from nitrobenzene (precipitated by the addition of 90–120° ligroin), crude yield nearly quantitative, sublimes *ca.* 270°, dec. above 360°. *Anal.* Calcd. for $C_{19}H_{12}O_4N_2S$: S, 9.14. Found: S, 9.12.

(D) **10-Benzenesulfonyl-3,7-dinitrophenothiazine:** as small red irregular platelets from nitrobenzene (precipitated by the addition of benzene), 40% yield, dec. above 300°. *Anal.* Calcd. for $C_{18}H_{11}O_6N_3S_2$: S, 14.94. Found: S, 14.96.

(2) In this report the nomenclature system listed recently by *Chemical Abstracts* [**37**, 7807 (1943)] and used by Gilman and Shirley [THIS JOURNAL, **66**, 888 (1944)] has been followed.

(3) Hazlet and Kornberg, THIS JOURNAL, **61**, 3037 (1939).

(4) Hazlet, *ibid.*, **59**, 287 (1937).

(5) Kehrmann and Nossenko, *Ber.*, **46**, 2809 (1913).

DEPARTMENT OF CHEMISTRY
STATE COLLEGE OF WASHINGTON
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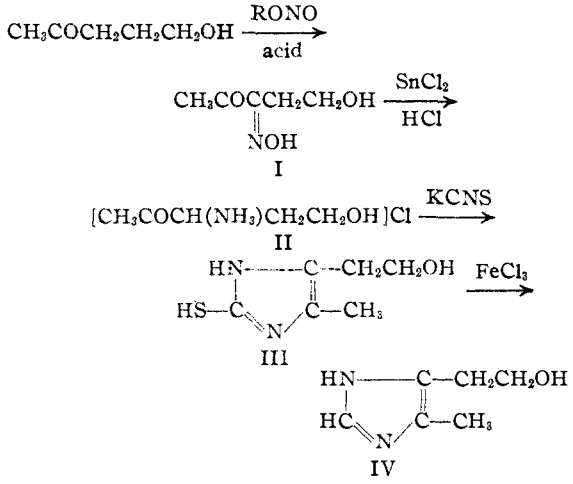
Thiamin Analogs. IV.[1] 4(5)-Methyl-5(4)-(β-hydroxyethyl)-imidazole

BY SIDNEY W. FOX,[2] HERBERT SARGENT AND EDWIN R. BUCHMAN

This communication deals with the synthesis of (IV), the imidazole[3] analog of the vitamin B_1 thiazole. Its preparation was accomplished by the following steps, which are based on reactions well known in the field of imidazole chemistry.[4]



Studies carried out at this Institute by Dr. James Bonner show that (IV) is unable to function as the vitamin thiazole in supporting growth of either pea roots or *Phycomyces Blakesleeanus*.

Experimental[5]

3-Oximinopentanol-5-one-2 (I).[6]—To a mixture of 58 g. of γ-acetopropanol[7] and 1.8 cc. of concentrated hydrochloric acid, 45 g. of butyl nitrite was added over a period of fifteen minutes, with the temperature maintained at 45–50° by means of an ice-bath. After the addition the mixture was allowed to stand for an additional fifteen minutes; 50 g. of ice and 48 g. of 33% sodium hydroxide solution were then added and the mixture stirred for one-half hour. The aqueous layer was separated and extracted twice with ether, after which it was brought to *p*H 6 by addition of dilute sulfuric acid while the temperature was kept below 10° by external cooling. The resulting mixture was continuously extracted with ether and the ether extract evaporated *in vacuo;* from the residual sirup 7 g. (9% from acetopropanol) of crude (I) crystallized on standing; m. p. 91.5° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.97; H, 6.94; N, 10.33.

The mother liquors containing additional amounts of (I) were utilized without further purification for conversion to (IV); attempts to distill them led to extensive decomposition.

3-Aminopentanol-5-one-2 Hydrochloride (II).[8]—In a flask surrounded by a bath at −15° was placed 75 g. of stannous chloride, 100 cc. of concentrated hydrochloric acid and 180 g. of mossy tin. To this was added 14. g. of (I) at such a rate that the reaction temperature did not rise above 0° (about ten minutes). The resulting mixture was allowed to stand at room temperature for one-half hour and then heated to boiling for several minutes. The liquid was decanted, the tin was washed with water and the combined aqueous solutions, after diluting to about 1300 cc., treated with hydrogen sulfide until precipitation of tin

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

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(3) Tracy and Elderfield (*Science*, **92**, 180 (1940); *J. Org. Chem.*, **6**, 54 (1941)) have prepared the pyridine analog of thiamine; see Robbins, *Proc. Natl. Acad. Sci.*, **27**, 419 (1941); also Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939); Schmelkes, *Science*, **90**, 113 (1939); Schmelkes and Joiner, THIS JOURNAL, **61**, 2562 (1939); Baumgarten and Dornow, *Ber.*, **73**, 44 (1940); Dornow, *ibid.*, **73**, 156, 353 (1940). A pyrimidine analog has been synthesized (Tota and Elderfield, *J. Org. Chem.*, **7**, 309 (1942); see Robbins, *Proc. Natl. Acad. Sci.*, **28**, 352 (1942)) and attempts to prepare a pyrazine analog have been recorded (*J. Org. Chem.*, **7**, 313 (1942)). Schultz (*Z. physiol. Chem.*, **256**, 113 (1940)) has reported on the physiological activity of the selenazole analog.

(4) Compare, for instance, Garforth and Pyman, *J. Chem. Soc.*, 489 (1935).

(5) All melting points are corrected.

(6) The structure of this compound is based on analogy; see Gabriel and Posner, *Ber.*, **27**, 1040 (1894); Fileti and Ponzio, *ibid.* **28R**, 555 (1895). Its preparation directly from α-acetobutyrolactone will be discussed in another connection.

(7) Knunyantz, Chelintzev and Osetrova, *Compt. rend. acad. sci.*, (U. R. S. S.), [N. S.] **1**, 312 (1934); *C. A.*, **28**, 4382 (1934).

(8) Compare Künne, *Ber.*, **28**, 2036 (1895); Gabriel and Pinkus, *ibid.*, **26**, 2199 (1893).

sulfide was complete. After filtration, the filtrate was evaporated *in vacuo* to yield a yellow sirup which was used directly for the next step in the synthesis.

In another similar preparation, the sirup was treated with absolute alcohol and anhydrous ether and allowed to crystallize in an icebox. The small amount of crystalline material separating was recrystallized from *n*-butanol–ether, needles m. p. 134° dec. Due to the unstable nature of (II), satisfactory analytical figures were not obtained.

2-Mercapto-4(5)-methyl-5(4)-(β-hydroxyethyl)-imidazole (III)[8] was obtained in good yield from the unstable crystalline (II). More conveniently it was prepared as follows: The crude sirup resulting from the reduction of 14 g. of (I) was taken up in 50 cc. of ethanol, 10 g. of potassium thiocyanate and 10 cc. of water were added and the mixture was heated for two hours in a bath maintained at about 60°. The reaction mixture was transferred to an evaporating dish, evaporated at about 50° and the residual dry yellow powder extracted with hot alcohol. The extracts were evaporated to a sirup which was taken up in a small amount of water and the solution allowed to stand in the icebox. After two days 9.6 g. of substantially pure (III) had crystallized out (56% from (I)), m. p. 201° from *n*-butyl alcohol, absorption maxima at 263 mμ, 209 mμ, minimum at 230 mμ (in water).[9]

Anal. Calcd. for $C_6H_{10}N_2OS$: C, 45.54; H, 6.37; N, 17.71. Found: C, 45.64; H, 6.41; N, 17.60.

Mother liquors from various preparations of (I) (60 g. of oil and crystals) were reduced essentially as given above and, after detinning and evaporation, the residue (containing large amounts of ammonium chloride) was heated for twenty-four hours with 60 g. of potassium thiocyanate and 65 cc. of water in a bath maintained at 100°. After evaporation the reaction mixture was extracted with 250 cc. of hot absolute alcohol, the extract cooled and filtered from potassium thiocyanate. After concentration to about 150 cc., an additional amount of potassium thiocyanate was filtered off and the filtrate seeded; after reworking of the mother liquors a total of 16 g. of (III) was obtained.

4(5)-Methyl-5(4)-(β-hydroxyethyl)-imidazole (IV).—To a solution of 3.2 g. of crude (III) dissolved in 100 cc. of water was added a solution of 19.6 g. of anhydrous ferric chloride[10] in 100 cc. of water. After heating the mixture at 100° for one-half hour, 300 cc. of sodium carbonate solution was added and after filtration the filtrate was concentrated *in vacuo*. The residue was extracted with two 100-cc. portions of hot absolute alcohol, the extract[11] evaporated to a small volume, 3.6 g. of picric acid added and the mixture heated and allowed to cool. The resulting picrate was recrystallized from alcohol; yield 3.0 g. (41%) m. p. 157.5°.

Anal. Calcd. for $C_{12}H_{13}N_5O_8$: C, 40.57; H, 3.69; N, 19.71. Found: C, 40.68; H, 3.61; N, 19.75.

The picrate was treated with dilute hydrochloric acid and the mixture extracted with ethyl acetate to remove picric acid. Next, excess sodium carbonate was added, the whole evaporated *in vacuo* and the residue extracted with hot absolute alcohol. After evaporation of the alcohol the residue was taken up in hot ethyl acetate and the ethyl acetate solution evaporated to a small volume. On long standing, crystals of (IV) separated, m. p. 96.5° from ethyl acetate (crystallization takes place very slowly); solution in water practically transparent above 250 mμ, $\lambda_{max.}$ 222 mμ, ε 6308,[12] character of spectrum not appreciably affected by *p*H change.

Anal. Calcd. for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.07; H, 7.76; N, 22.10.

(9) 2-Mercaptoimidazole exhibited $\lambda_{max.}$ 252 mμ, 208 mμ, $\lambda_{min.}$ 223 mμ (in water); 2-ethylmercapto-4-methylimidazole $\lambda_{max.}$ 251 mμ, 224 mμ, $\lambda_{min.}$ 235 mμ (in water).

(10) Compare Pyman, *J. Chem. Soc.*, **99**, 2172 (1911).

(11) In other experiments (IV) was isolated directly from such extracts without going through the picrate.

(12) A sample of 4-methylimidazole was found to have $\lambda_{max.}$ 215 mμ (in water).

The authors are indebted to Dr. J. Bonner for the results of his tests and to Dr. R. T. Major of Merck and Company, Inc., for his generous support of the investigation.

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Nicotinic Acid Esters

BY JEROME G. KAUFMAN[1]

Esters of nicotinic acid can be obtained by direct esterification of reaction mixtures that result when nicotine, quinoline or β-picoline is oxidized in the liquid phase. This direct synthesis is of interest because of the importance of these esters as intermediates in the preparation of the widely used nicotinamide. In addition, the esters, since they are capable of hydrolytic conversion to nicotinic acid in the body, can be classified as biologically active pyridine derivatives. It has been demonstrated that ethyl nicotinate, when administered orally, exhibits anti-black-tongue activity.[2]

This Laboratory[3] has shown that good yields of nicotinic acid are obtained when nicotine, quinoline or β-picoline is oxidized by concentrated sulfuric acid in the presence of mercuric sulfate or selenium. In order to isolate the nicotinic acid formed, the sulfuric acid, always used in excess, is neutralized, and the product is precipitated as copper nicotinate. The latter is then converted to nicotinic acid in the usual way. If nicotinic acid esters were desired, it was necessary to esterify by any of the known methods.[4,5,6,7]

Experimental

Methyl Nicotinate.—A mixture of 650 cc. of 95% sulfuric acid, 75 g. of selenium and 129 g. (1 mole) of quinoline was heated together for one hour. The maximum temperature attained was 300°. During this time 240 cc. of water was distilled over. To the cooled mass was added 300 cc. of methanol, after which the mixture was refluxed for six hours on the steam-bath. The reaction mixture was then poured onto three times its volume of cracked ice, made alkaline with ammonium hydroxide, and extracted with ether. The combined ether extracts were washed with water and dried over anhydrous potassium carbonate. After the ether was removed, the product was vacuum-distilled. It yielded 82.5 g. of methyl nicotinate (b. p. (3 mm.) 70–72°), which immediately crystallized to beautiful white crystals in the receiver (m. p. 38°). The yield was 60.2%.

Ethyl Nicotinate.—With essentially the same procedure as described for methyl nicotinate, 83 g. of ethyl nicotinate (b. p. (4 mm.) 72–74°) was obtained; this yield was 55%.

Propyl Nicotinate.—Substitution of *n*-propyl alcohol for the methanol and ethanol used in the preceding experi-

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(2) Woolley, Strong, Madden and Elvehjem, *J. Biol. Chem.*, **124**, 715 (1938).

(3) Woodward, Badgett and Kaufman, *Ind. Eng. Chem.*, **36**, 544 (1944).

(4) Pollak, *Monatsh.*, **16**, 46 (1895).

(5) Engler, *Ber.*, **27**, 1787 (1894).

(6) Camps, *Arch. Pharm.*, **240**, 353 (1902).

(7) LaForge, THIS JOURNAL, **50**, 2477 (1928).