thiazines 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. Other acylations were effected by permitting the materials to react in pyridine solution, 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. 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 Thiazines

(A) 10-Benzensulfonylphenothiazine: glistening, colorless needles from ethanol, 30% yield, m. p. 170-170.5°. Anal. Calcd. for C_{10}H_{10}O_{3}N_{3}S: C, 45.79; H, 6.92; N, 17.20; S, 14.94. Found: C, 45.97; H, 6.94; N, 17.20; S, 14.96.

(B) 10-Acetyl-3-nitrophenothiazine-5-oxide: dark red irregular crystals from benzene (precipitated by the addition of 90-120° ligroin), 90% yield, sublimes ca. 270°, dec. above 380°. Anal. Calcd. for C_{10}H_{10}O_{3}N_{3}S: C, 44.09; H, 6.84; N, 16.47; S, 14.20. Found: C, 44.03; H, 6.82; N, 16.44; S, 14.22.

(C) 10-Benzyol-3-nitrophenothiazine-5-oxide: as small red irregular platelets from nitrobenzene (precipitated by the addition of benzene), 40% yield, dec. above 300°. Anal. Calcd. for C_{10}H_{10}O_{3}N_{3}S: C, 45.97; H, 6.94; N, 17.20; S, 14.94. Found: C, 45.91; H, 6.88; N, 17.15; S, 14.88.

(3) In this report the nomenclature system listed recently by Chemical Abstracts [97, 8707 (1943)] and used by Gilman and Shirley (This Journal, 66, 898 (1944)) has been followed.

(4) Hazlet and Romberg, THIS JOURNAL, 61, 6037 (1939).

(5) Hazlet, ibid., 59, 257 (1937).

(6) Kehrmann and Noscek, Ber., 46, 2806 (1913).

DEPARTMENT OF CHEMISTRY
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Thiamin Analogs. IV. 4-(5)-Methyl-5-(4)-(ß-hydroxyethyl)-imidazole
BY SIDNEY W. FOX, HERRERT SARGENT AND EDWIN R. BUCHMAN

This communication deals with the synthesis of (IV), the imidazole analog of the vitamin Bi thiazole. Its preparation was accomplished by the following steps, which are based on reactions

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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 alcohol and anhydrous ether and allowed to crystallize in an icebox. The small amount of crystalline material separating was recrystallized from n-butanol—absolute alcohol and anhydrous ether and allowed to crystallize (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 thioctyanate and 10 cc. of water were added and the mixture was heated for two hours in a bath maintained at about 60°C. The reaction mixture was transferred to an evaporating dish, evaporated at about 100°C for one-half hour, and the residue was taken up in hot alcohol. The extracts were evaporated to a sirup which was taken up in 100 cc. of hot absolute alcohol, the extract cooled and filtered from potassium thioctyanate. After concentration to a small volume, the extract was heated together for one hour. The maximum temperature attained was 200°C. 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 carbonate. After the ether was removed, the product was vacuum-distilled. It yielded 75 g. of methyl nicotinate (b. p. 38°C/240°C), which immediately crystallized to beautiful white crystals in the receiver (m. p. 71.9°C).

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.

NOTES

The Laboratory has shown that high yields of nicotinic acid esters are obtained when nicotine, quinoline or β-picoline is oxidized with 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 purify by any of the known methods.

Experimental

Methyl Nicotinate.—A mixture of 650 cc. of 85% sulfuric acid, 75 g. of selenium and 120 g. (1 mole) of quinoline was heated together for one hour. The maximum temperature attained was 300°C. During this time about 240 cc. of water was distilled over. 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°C), which immediately crystallized to beautiful white crystals in the receiver (m. p. 71.9°C).

The yield was 60.2 g.

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

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

(1) Present address: Van Ameringue-Haeblv, Inc., Elizabeth, N. J.
(4) Pollak, Monatsh., 16, 46 (1905).
(5) Engler, Ber., 17, 1787 (1894).

Nicotinic Acid Esters

By Jerome G. Kaufman

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.

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