Summary

1. Vitamin B_1 contains two basic groups, one of which is of the same order of strength as the nitrogen in the quaternary salt of its basic cleavage product and in 4-methylthiazole ethiodide.

2. The vitamin and the methiodide of its basic cleavage product, like 4-methylthiazole ethiodide, form pseudo bases in alkaline solutions, but this phenomenon is not exhibited by a 2-methyl substituted thiazolium base or by simple thiazoles.

NEW YORK CITY RECEIVED JULY 6, 1935

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 130]

The Dehydrogenation of Nicotine in Toluene as a Solvent

BY AVERY A. MORTON AND DAVID HORVITZ[1]

The experiments reported in this paper show that nicotine can be dehydrogenated by sulfur in boiling toluene as a solvent. This temperature is the lowest at which a dehydrogenation by sulfur or selenium has been carried out and is one of the few instances of the application of such a reaction to an alkaloid.[2] The object of this work was to perfect the exceedingly important method of dehydrogenation by lowering the temperature, controlling the concentrations, and changing the solvent so that the correctness of conclusions relative to the carbon framework of organic compounds might be subject to less doubt.[3] It was also desired to extend the application of dehydrogenation to nitrogen-containing compounds. Nicotine was chosen as suitable for study because the product of the proposed reaction is already known, having been prepared from nicotine by oxidation with potassium ferricyanide[4] or silver oxide[5] or by dehydrogenation over platinized asbestos at 320°.[6] Fusion of nicotine with sulfur has also been carried out by Cahours and Étard.[4]

Under the mild conditions attending the use of toluene as a solvent the amount of hydrogen sulfide evolved corresponds to 69% of the theoretical as given in equation 1 for the formation of nicotyrine, $C_{10}H_{10}N_2$. Actually nicotyrine was

$$C_{10}H_{14}N_2 + 2S = C_{10}H_{10}N_2 + 2H_2S \qquad (1)$$

obtained in only about 2.5% yield, the larger amount of material being thiodinicotyrine[7] $C_{20}H_{18}N_4S$ (equation 2), from which nicotyrine can be obtained by distillation over copper.[4] The yield of this substance when purified was about 18%.

$$2C_{10}H_{14}N_2 + 6S = C_{20}H_{18}N_4S + 5H_2S \qquad (2)$$

No appreciable quantities of tar were formed. The remainder of the material appeared to be unchanged nicotine and possibly products not completely dehydrogenated. Cahours and Étard[4] obtained this sulfur compound by the action of sulfur on nicotine in the absence of a solvent but failed to observe any nicotyrine.

Under a wide variety of conditions such as were possible by changing the concentrations and quantities of reagents the amount of hydrogen sulfide liberated could not be increased. Addition of acid at the end of the experiment failed to reveal any combined hydrogen sulfide. Iron, which has been claimed by Cheung[8] to break up sulfur addition compounds at higher temperatures, had no effect on the velocity or extent of hydrogen sulfide evolution. The addition of a small quantity of diphenylguanidine in the hope that it would act catalytically was found to inhibit greatly the rate and the completion of the reaction. Other solvents, boiling within the range of 99–121°, which were tried were epichlorohydrin, tetrachloroethylene, glacial acetic acid, and a gasoline fraction (99–102° b. p.). These solvents were far inferior to toluene both in the quantity of hydrogen sulfide formed and in the freedom from tarry products. Even the addition of acetic acid to toluene retarded greatly the rate of gas evolution although the total amount finally ap-

---

[1] From the thesis of David Horvitz submitted in partial fulfilment of the requirements for the degree of Bachelor of Science, 1934.

[2] See Blount [*J. Chem. Soc.*, 124 (1935)] for leading references to the application of dehydrogenation of alkaloids by selenium.

[3] See Vocke, *Ann.*, **497**, 248 (1932); Cook and Hewett, *J. Chem. Soc.*, 1103 (1933); 365 (1934); Clemo and Ormston, *ibid.*, 352 (1933), for criticisms of the present method of fusion.

[4] Cahours and Étard, *Bull. soc. chim.*, **34**, 449 (1880).

[5] Blau, *Ber.*, **27**, 2535 (1894).

[6] Wibaut and Overhoff, *Rec. trav. chim.*, **47**, 935 (1928).

[7] This compound was named thiotetrapyridine by Cahours and Étard on the basis of the erroneous belief that nicotyrine contained two pyridine rings. A more correct name would be thiodinicotyrine.

[8] Cheung, *Bull. inst. pin*, 108 (1929); *C. A.*, **23**, 3467 (1929).

proached the same value obtained for toluene alone.

The success of this study has given encouragement to extend the use of solvents to the cases of cholesterol and abietic acid, which have heretofore given compounds of disputed structure[9] or yielded small amounts[10] of substances. Strychnine is also being investigated by this method. Solvents which boil higher than toluene are preferred in these cases. The results will be published shortly. The work on nicotine is being reported at this time because the recent paper of Blount,[2] in which the dehydrogenation of an alkaloid by selenium is mentioned, indicates a growing interest in this field.

Experiments

Choice of Solvent and Conditions.—Preliminary tests showed that no hydrogen sulfide was evolved when 0.5 g. of sulfur was refluxed for fifteen hours with 15 ml. each of epichlorohydrin, tetrachloroethylene, gasoline (99–102° fraction), glacial acetic acid, and toluene. Under the same conditions isopropyl propionate reacted with sulfur. Of the five suitable solvents toluene proved the best with respect to freedom from tarry products and quantity of hydrogen sulfide evolved when tested by refluxing 20 ml. of each with 0.5 g. (0.016 mole) of sulfur and 0.97 g. (0.006 mole) of nicotine (freshly distilled) for fifty hours. The hydrogen sulfide evolved was absorbed in ammoniacal zinc sulfate and titrated with standard iodine solution. Systematic variation of the quantities of sulfur, nicotine, and solvent showed that the largest quantity of sulfide gas, amounting to 69% calcd. according to equation 1, was obtained with 0.01 mole (1.6 g.) of nicotine, 0.225 mole (0.80 g.) of sulfur, and 20 ml. of toluene. Higher concentrations of nicotine produced some tar. Addition of 1.1 g. of alcoholized iron powder caused a somewhat decreased rate and quantity of gas. Diphenylguanidine, 0.2 g., reduced the total evolution of gas by 30%. Glacial acetic acid, 2.4 g., cut down the velocity to a fifth at the start but affected the amount finally obtained by only 11%. A huge excess of sulfur, amounting to over 100 times the theoretical, had no appreciable influence. No odor of methyl mercaptan was detected in any experiment.

Isolation of Nicotyrine and Thiotetrapyridine.—The quantities given above as being best were increased 25 times. The reaction was carried out by refluxing in a 2-liter flask heated in an oil-bath. At the end of ninety-one hours the evolution of gas had practically ceased. The resulting dark green solution was heated on a steam-bath under the vacuum created by a water pump until the distillation of toluene had ceased. The dark green viscous residue stood for two days without crystallization, a procedure which had been effective in causing solidification in other experiments. After placing the flask over solid carbon dioxide for two hours and then allowing to stand overnight, a large deposit of green crystals resulted. The supernatant liquid was poured off and the crystals washed with ether. They were then recrystallized twice from warm alcohol, yielding 7.6 g. of bright yellow crystals. The melting point after a third recrystallization remained at 151.5–153.5°. Cahours and Étard give 155° for this compound, thiodinicotyrine. Since no previous determination of its molecular weight had been made, the boiling point elevation in benzene was observed with the differential thermometer apparatus of Menzies: found with 0.0939 g. in 35.4 ml. of solvent, 303; with 0.1640 g., 314; calculated for $C_{20}H_{18}N_4S$, 346.

Upon distilling the solution, which had been poured off from the crude product, under 17 mm. vacuum a considerable additional amount of hydrogen sulfide was evolved. The fraction boiling from 143 to 153°, amounting to 1 ml., was collected. When redistilled at atmospheric pressure the main portion boiled at 268–274°. It is not as pure as the nicotyrine prepared by Wibaut and Overhoff[6] who found a boiling point of 280°. It was recognized as consisting chiefly of nicotyrine by its insolubility[11] in water, and by the melting point of its picrate derivative, which after six recrystallizations from alcohol melted at 160–161°. Blau gives 163–164; Wibaut 168–169°.

The above method of separation of the products proved much superior to extraction of the toluene solution with 5% alkali followed by distillation at atmospheric pressure of the toluene solution. Some nicotyrine was obtained together with tar and decomposition products. An attempt to precipitate the thiodinicotyrine by adding alcohol to the toluene concentrate before the crystals had formed was made. In spite of the fact that thiodinicotyrine is insoluble in alcohol, no crystals separated even on seeding and standing for several days at low temperatures.

Conclusions

Toluene has been found to be preferred over several other solvents of similar boiling point as a medium for the dehydrogenation of nicotine by sulfur. The temperature is lower than any hitherto employed for this purpose. The products are thiodinicotyrine and a small quantity of nicotyrine with practically no tarry materials.

CAMBRIDGE, MASS. RECEIVED JULY 12, 1935

---

[9] Diels and Rickert, *Ber.*, **68**, 267, 325 (1935).

[10] Vesterberg, *ibid.*, **36**, 4200 (1903); Virtanen, *Ann.*, **424**, 198 (1921); Ruzicka and Meyer, *Helv. Chim. Acta*, **5**, 581 (1922).

[11] For a comparison with other possible dehydrogenation products see Pinner and Wolffenstein, *Ber.*, **25**, 1430 (1892); Pinner, *ibid.*, **28**, 456 (1895); Pictet and Crépieux, *ibid.*, **31**, 2018 (1898); Pictet and Rotschy, *ibid.*, **34**, 696 (1901).