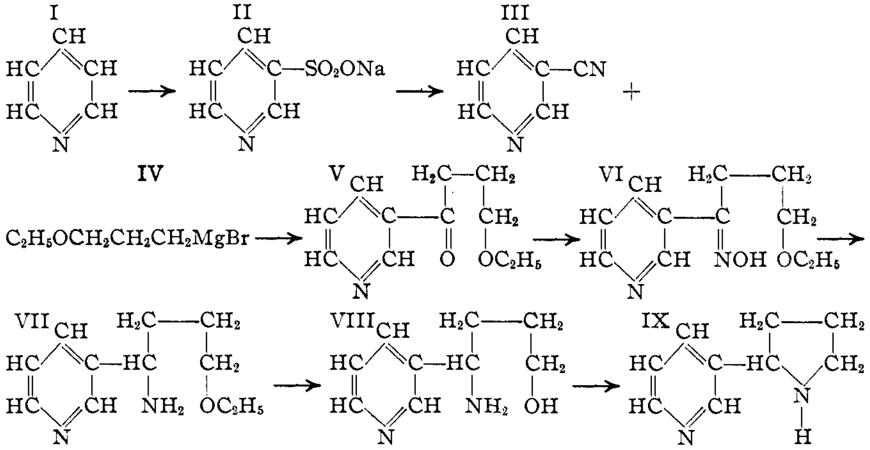
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

A New Synthesis of Nornicotine and Nicotine

BY LYMAN C. CRAIG[1]

Nornicotine was desired as one of the compounds in a series being prepared in this Laboratory for a study of structure and physiological properties. Two rather recent syntheses by demethylation of nicotine are in the literature. Polonovski and Polonovski[2] treated the peroxide of nicotine with an acid anhydride according to their general method for the removal of methyl groups. Later Braun and Weissbach[3] partially removed the methyl group by heating nicotine with a high boiling organic acid and by excellent work isolated the nornicotine in pure form from a mixture containing also metanicotine. The properties reported by the later workers for nornicotine did not agree with those reported by the first. In either method removal of the methyl radical depends on treatment that is very severe for so reactive a structure as that of nicotine.

The synthesis of Braun and Weissbach gives a product that is partially racemized. Optical activity has been shown to play a considerable role in the physiological action of nicotine[4] and most probably would also in nicotine. The racemic form is most suitable for the study at hand as a possible varying synergistic effect should be avoided. To obtain the racemic form directly and in order to give further proof of the identity of the compound, synthesis by yet another method seemed desirable. The following synthesis was proposed and carried out in this Laboratory.



The properties of compound IX and those of its derivatives correspond throughout with those reported by Braun and Weissbach.

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[1] National Research Fellow.

[2] Polonovski and Polonovski, *Compt. rend.*, **184**, 1333 (1927).

[3] Braun and Weissbach, *Ber.*, **63**, 2018 (1930).

[4] Mayor, *Ber.*, **37**, 1335 (1904); Macht, *Nat. Acad. Sci.*, **15**, 63–70 (1929).

Methylation of IX with methyl iodide gives a small yield of an oil whose properties correspond with those of nicotine and a mixed melting point of the picrate with the picrate of natural nicotine confirms the identity. Hence the work represents a complete new synthesis of racemic nicotine from pyridine.

The above synthesis can easily be modified to prepare alpha nicotine and other compounds closely related to nicotine. Such a study is under way and will be reported in a later paper.

Experimental

Sulfonation of Pyridine.—Pyridine has been sulfonated with sulfuric and fuming sulfuric acid by a number of workers,[5] who used a variety of catalysts. As none of these methods gave a yield which exceeded 25% of the theoretical when repeated in this Laboratory the following directions which afforded 35–40% yields consistently are given.

To 400 g. of pyridine, 100 g. of water and 30 g. of vanadyl sulfate in a three-liter distillation flask, 600 g. of concentrated sulfuric acid is cautiously added and the mixture heated over a free flame until the sulfuric acid begins to distil over. It is cooled and 800 g. of 20% fuming sulfuric acid added. The flask is heated gently for two hours and finally at the full force of a Bunsen burner until most of the sulfuric acid has distilled off and the contents of the flask weigh approximately 900 g. The residue is diluted, treated with a suspension of calcium hydroxide until neutral to litmus and filtered. After evaporation of the filtrate to a thick sirup on a steam-bath it is converted to the sodium salt with an equivalent of sodium carbonate in solution and the calcium carbonate filtered off. The filtrate is evaporated and finally dried in an oven at 140° for twenty-four hours, after which it can be ground to a powder.

β-Pyridyl-γ-ethoxypropyl Ketone.—γ-Bromopropyl ethyl ether prepared according to the directions of Noyes[6] forms a Grignard reagent smoothly in the usual way as contrasted to γ-bromopropyl phenyl ether which gives a quantitative yield of phenol. The Grignard reagent prepared from 60 g. of the bromide is allowed to drop into 45 g. of nicotinic acid nitrile[7] dissolved in 150 cc. of anhydrous ether. After standing several hours the yellow voluminous precipitate is filtered off and washed with ether. It is then suspended in ether and hydrochloric acid added until the solid is dissolved, after which an excess of ammonia is added. The ether layer is fractionated: 15 g. of nitrile, 26 g. of compound boiling at 140–144° (5 mm.) and 15 g. of a high boiling residue are obtained. Upon fractionation of the second fraction practically the entire amount distils at 141–143° (5 mm.).

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.4; H, 7.83. Found: C, 68.4; H, 7.96.

The yield is 37% of the theoretical when calculated from the bromide or 47% from the nitrile. The compound has not heretofore been reported in the literature.

β-Pyridyl-γ-ethoxypropyl ketone is a colorless oil which is slightly soluble in water and soluble in strong acids. It reacts with phenylhydrazine, semicarbazide and hydroxylamine but none of these derivatives are crystalline.

1-[β-Pyridyl]-1-amino-4-ethoxybutane.—To a solution containing 24 g. of β-pyridyl-γ-ethoxypropyl ketone and 240 cc. of 90% alcohol, 17 g. of hydroxylamine hydrochloride is added. After refluxing overnight the alcohol is distilled off on the steam-

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(5) Fischer, *Ber.*, **15**, 62 (1882); **16**, 1183 (1882); Wiedel and Murmann, *Monatsh.*, **16**, 751 (1895); Meyer and Ritter, *ibid.*, **35**, 765 (1914); British Patent 335,817, Nov. 26, 1928; *Chem. Abstracts*, **25**, 1537 (1931).

(6) Noyes, *Am. Chem. J.*, **19**, 766 (1897).

(7) Prepared from sodium β-pyridine sulfonate by the method of Fischer (5a). Sodium cyanide is preferable to potassium cyanide and gives a yield of 34% of the theoretical.

bath and 25 cc. of water added; 30% sodium hydroxide is then slowly added until the insoluble oil which first appears is entirely redissolved. Too much caustic at this point will reprecipitate an oil. The solution is extracted twice with ether and the oxime precipitated from the caustic with carbon dioxide. Extraction with ether gives 19 g. of a red colored oil. All attempts to induce crystallization failed. It is a non-distillable oil and as it does not lend itself readily to purification an analysis was not made.

The oily oxime (19 g.) is dissolved in 200 cc. of 95% alcohol and a few pieces of iron filings added. The mixture is constantly stirred and maintained at a temperature not above 35° while 108 g. of glacial acetic acid is allowed to drop slowly into the solution over a period of two to three hours and 108 g. of zinc dust added from time to time in small portions. After standing for several hours the zinc and zinc acetate are filtered off and washed with alcohol. The filtrate is concentrated and finally heated at 15 mm. pressure on a water-bath to remove the excess acetic acid. The viscous residue is diluted with water and solid potassium hydroxide added until the precipitated zinc is mostly dissolved. The oil which separates is drawn off, dried over solid potassium hydroxide and distilled; 15 g. distil at 148–155° (5 mm.). The yield is 85% of the theoretical. Upon refractionation the major portion distils at 151–152° (5 mm.). A report of the compound could not be found in the literature.

Anal. Calcd. for $C_{11}H_{18}N_2O$: C, 67.9; H, 9.37. Found: C, 67.6; H, 9.77.

1-[β-Pyridyl]-1-amino-4-ethoxybutane is a colorless, odorless oil that is soluble in water in all proportions and also in organic solvents. The picrate is oily and could not be made to crystallize. An oxalate upon repeated recrystallization from alcohol melts at 155°. Phenyl isothiocyanate reacts vigorously with the base but the product could not be made to crystallize.

Reduction of the phenylhydrazone of β-pyridyl-γ-ethoxypropyl ketone with zinc and acetic acid gives the same base but in much smaller yield.

Nornicotine.—A solution of 15 g. of 1-[β-pyridyl]-1-amino-4-ethoxybutane and 60 cc. of 48% hydrobromic acid is heated under an air condenser by means of an oil-bath maintained at 150–155° for twelve hours. The excess acid is then removed by distillation under reduced pressure, finally on the steam-bath and at 15 mm. pressure. The viscous sirup is treated with a small amount of water and then potassium hydroxide until the basic oil is entirely precipitated. In order to prevent decomposition the temperature should not rise above 35°. The basic layer is then fractionated before drying as an attempt to dehydrate with solid potassium hydroxide resulted in tar formation. The water is first distilled off at 30 mm. pressure and finally 9 g. of oil boiling at 139–140° (12 mm.) distils. The properties and also those of the picrate and phenylthiourea correspond throughout with those reported by Braun and Weissbach[3] for nornicotine. The yield is 55% of the theoretical.

Racemic Nicotine.—A solution of 5 g. of nornicotine and 7 cc. of methyl alcohol is treated with an equivalent of methyl iodide in an equal volume of methyl alcohol. After standing for four days, the dark colored solution is poured into 150 cc. of ether, shaken well and allowed to settle. The clear ether solution is decanted from the viscous brown colored oil and fractionated. One gram of material distils at 113–115° (10 mm.) which has all the characteristics of nicotine. A picrate is slightly soluble in 95% alcohol and melts at 219°. A mixed melting point with the picrate of natural nicotine melts at the same temperature. Nornicotine is a stronger base than nicotine. Therefore in the above synthesis the unreacted nornicotine is in the ether-insoluble oil along with the quaternary derivative while the nicotine is liberated as the ether-soluble free base.

Summary

The Fischer synthesis of nicotinic acid nitrile has been improved and

shown to be a convenient synthesis. β-Pyridyl-γ-ethoxypropyl ketone and 1-[β-pyridyl]-1-amino-4-ethoxybutane are reported for the first time.

A complete new synthesis from pyridine of nornicotine and racemic nicotine is reported.

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Organic Reactions with Boron Fluoride. IV. Ether Cleavage in the Presence of Organic Acids

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Introduction

Hinton and Nieuwland have recently shown that boron fluoride catalyzes the reaction between alcohols and acids to form esters.[1] In view of the fact that alcohols, acids and esters form covalent compounds[2] with boron trifluoride, the esterification reaction reported by them may be looked upon as an alkylation reaction depending upon the presence of an alcohol-boron fluoride compound of the type $ROH \cdot BF_3$. These compounds possess marked acid properties[3,4] and may be considered to be alkoxy fluoboric acids.

Boron fluoride also forms covalent compounds with ethers.[2,5] With diethyl ether a compound of the formula $(C_2H_5)_2O \cdot BF_3$ is formed which boils at 126°. Looking upon the latter compound as the ethyl ester of ethoxyfluoboric acid[6] it was thought that it too should show certain alkylation properties. In a broader sense such a reaction would be a case of ether cleavage. To test this hypothesis a study of esterification of organic acids with ether and boron fluoride was undertaken.

The literature reports numerous cases of ether cleavage. Such reactions occur with acid chlorides[7] at elevated temperatures in the presence of certain catalysts, with acid bromides at high temperatures without catalysts, and with acid iodides still more readily.[8] Meerwein and Maier-Hüser[7] showed that ethers can be cleaved with acid anhydrides in the presence of certain catalysts. In this manner they obtained ethyl acetate from diethyl ether and acetic anhydride in the presence of boron fluoride. In the presence of anhydrous hydrogen bromide ether reacts with certain

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(1) Hinton and Nieuwland, THIS JOURNAL, **54**, 2017 (1932).

(2) Bowlus and Nieuwland, *ibid.*, **53**, 3835 (1931).

(3) Vogt, Foohey and Nieuwland, *ibid.*, **52**, 1018 (1930).

(4) Vaughn, Bowlus and Nieuwland, *Proc. Ind. Acad. Sci.*, **40**, 203 (1930).

(5) Gasselin, *Ann. chim. phys.*, [7] **3**, 11 (1894).

(6) Sugden and Waloff, *J. Chem. Soc.*, 1492 (1932).

(7) Reviewed by Meerwein and Maier-Hüser, *J. prakt. Chem.*, **134**, 51 (1932).

(8) Gustus and Stevens, THIS JOURNAL, **55**, 378 (1933).