α-Phenylpyrrolidine.—Twelve grams of phenylaminochlorobutane hydrochloride was dissolved in water and a strong solution of potassium hydroxide added. The oil which separated reacted suddenly with evolution of heat to form α-phenylpyrrolidine. The product was extracted with ether and the solution dried with solid potassium hydroxide. The ether residue boiled at 236–238° (uncorr.) at 757 mm. The yield was 8 g.

Anal. Subs., 0.1400: CO_2, 0.4155; H, 0.1154. Calcd. for $C_{10}H_{13}N$: C, 81.63; H, 8.84. Found: C, 80.94; H, 9.15.

α-Phenyl-N-methylpyrrolidine.—Four grams of α-phenylpyrrolidine was dissolved in 25 cc. of methyl alcohol containing 4 g. of methyl iodide. After twelve hours the solvent was evaporated and the residue treated with strong potassium hydroxide solution. Most of the oil was soluble in ether but a part remained undissolved. The ethereal solution was dried with solid potassium hydroxide and the ether evaporated, leaving 2.6 g. of base, which distilled at 760 mm. at 225–227° (uncorr.). The yield of pure product was 2.2 g.

Anal. Subs., 0.1460: CO_2, 0.4374; H_2O, 0.1161. Subs., 0.1560: N, 11.2 cc. at 29° and 762 mm. Calcd. for $C_{11}H_{15}N$: C, 81.99; H, 9.31; N, 8.69. Found: C, 81.71; H, 8.83; N, 8.23.

Summary

A number of pyrrolidine derivatives have been prepared with reference to their chemical relation to nicotine and tested as contact insecticides. Methods are described for the preparation of α-methyl- and α-phenylpyrrolidine and α-phenylpyrroline and their N-methyl derivatives. The various intermediary compounds and the results of several unsuccessful attempts to prepare substituted pyrrolidines are described in the experimental part.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

THE PREPARATION AND PROPERTIES OF SOME NEW DERIVATIVES OF PYRIDINE[1,2]

BY F. B. LAFORGE

RECEIVED MAY 18, 1928 PUBLISHED SEPTEMBER 5, 1928

In a previous article it was pointed out that whereas nicotine, which is β-pyridyl-α-N-methylpyrrolidine, stands out as one of the few known organic compounds possessing insecticidal properties of a very high order, none of the several other substituted pyrrolidines which have been tested approach it in toxicity.

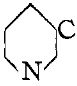
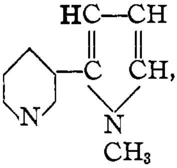
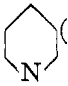
It is natural to inquire whether or not the pyrrolidine group is essential to the specific toxic effect of nicotine on insects and whether or not some

---

[1] A study of the insecticidal action of these compounds is being made in coöperation with Dr. C. H. Richardson, Deciduous Fruit Insect Investigations, Bureau of Entomology.

[2] Presented at the Insecticide Symposium, St. Louis meeting of the American Chemical Society, April, 1928.

other groups attached to the pyridine radical would result in compounds of the same order of toxicity.

Accordingly, a number of new synthetic pyridine derivatives were prepared and tested on insects. All these derivatives were of a very low order of toxicity. On the other hand, three known compounds derived from nicotine itself, metanicotine, $CH{=}CHCH_2CH_2NHCH_3$, nicotyrine,  and dihydrometanicotine, $(CH_2)_4NHCH_3$, were of high toxicity, the first compound being almost equal to nicotine itself in this respect. The other two, although less toxic than metanicotine, still exhibited this property to a degree which far exceeded that of any purely synthetic pyridine derivative which we have prepared and tested. These synthetic compounds are all open chain pyridylamino derivatives which were obtained by reduction of the oximes or hydrazones of pyridyl ketones.

Since considerable quantities of these ketones were required for the investigations, it was necessary to develop satisfactory methods for their preparation. A number of pyridyl ketones have been described by Engler,[3] who prepared them by distillation of pyridinecarboxylic acid calcium salts with the calcium salts of the fatty acids, and by Pinner[4] by the condensation of pyridinecarboxylic acid esters with the esters of fatty acids in the presence of sodium ethylate and cleavage of the resulting pyridoylacetic esters. The method of Engler gives low yields of very impure products. Pinner does not state his yields, but numerous attempts to prepare pyridyl ketones by the method described by him were unsuccessful. Even when every precaution was taken in carrying out the reaction, the yields were at the best exceedingly small and usually nothing but nicotinic acid could be recovered from the reaction product.

The method by which methyl and propyl pyridyl ketones were finally prepared leaves something to be desired, but it was adequate for the preparation of several hundred grams of these compounds.

Nicotinic acid hydrochloride or the free acid prepared from the cheaper nitrate was the starting material. It was esterified and the ester transformed into the acid amide which was converted into the cyanide. These operations are described by R. Camps, but as the directions given by that author are somewhat inadequate, some slight changes in the methods were introduced.

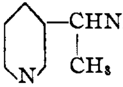
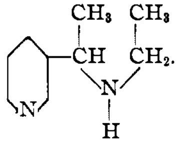
According to Blaise,[5] aromatic cyanides react with the Grignard reagent,

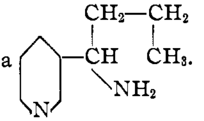
[3] Engler, *Ber.*, **22,** 597 (1889), **24,** 2541 (1891).

[4] Pinner, *Ber.*, **34,** 4234 (1901).

[5] Blaise, *Compt. rend.*, **333,** 1217 (1900).

producing fairly good yields of the aromatic alkyl ketones. This method was used for the preparation of pyridyl ketones.

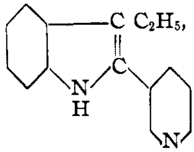
β-Pyridylethylamine,  was prepared by reduction of the β-pyridyl methyl ketoxime and from this the corresponding N-ethyl derivative was obtained. The resulting compound differs from nicotine in that it has an open four carbon chain instead of the closed pyrrolidine ring, and it is not methylated on the nitrogen atom. It may be represented by the formula 

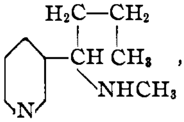
β-Pyridylpropyl ketone was prepared from β-pyridine cyanide and *n*-propyl iodide by the Grignard reaction. As the oxime of the ketone could not be obtained in crystalline form, the hydrazone was prepared and reduced to the β-pyridylbutyl amine represented by the formula 

The hydrazone of this ketone as described by Engler was prepared from the crude ketone, and was made for the purpose of isolating the ketone itself in pure condition.

It was found that a crystalline hydrazone could be obtained easily from the crude ketone prepared by the Grignard reaction, but it differed in its chemical and physical properties from the one described by Engler. Its melting point (130°) differed from that recorded by Engler (182°), and it could not be changed even by repeated recrystallization.

Engler prepared the pure ketone from his hydrazone by decomposition with concentrated hydrochloric acid.

When the same treatment was applied to the hydrazone prepared by us, it resulted in a quantitative yield of a crystalline base, which is in all probability 1-pyridyl-2-ethylindol  analogous to the methylindol from acetone hydrazone.

The amine resulting from the reduction of the hydrazone was methylated on the nitrogen to β-pyridylbutyl-N-methylamine,  which differs from nicotine in that an open chain of the same number of carbon atoms is substituted for the N-methylpyrrolidine ring.

Ethyl Nicotinate.—The following method, which is a slight modification of the one described by R. Camps,[6] was found most convenient for the preparation of ethyl nicotinate. Eighty grams of nicotinic acid hydrochloride or 70 g. of the free acid was dissolved in a mixture of 150 g. of absolute alcohol and 150 g. of concentrated sulfuric acid, and the solution was heated for about four hours in a flask on the steam-bath. The

---

[6] R. Camps, *Arch. Pharm.*, **240**, 366 (1902).

solution was cooled and divided roughly into three portions, which were poured onto cracked ice. Ammonia was then added in a quantity sufficient to render the solution strongly alkaline. Generally some ester separated as an oily layer but most of it remained dissolved. The solution was extracted four times with ether, the last two or three ether extracts being used to extract the other portions.

The ethereal solutions were washed with water and dried with potassium carbonate, after which the solvent was removed. The yield of pure ester boiling between 222 and 224° was always from 71 to 75 g. If pure material is used to start with, it is not necessary to distil the ester if it is to be used for the preparation of the amide.

Nicotinic Acid Amide.—Since the directions for the preparation of this derivative are rather inadequate, it seems desirable to add a few details to those given by Camps.

One hundred grams of nicotinic ester was covered with about 1.5 volumes of concentrated aqueous ammonia saturated at 0°. The flask was kept loosely closed for about eighteen hours, after which time the lower layer generally dissolved on shaking. The solution was again saturated with ammonia gas and allowed to stand for several hours. The process was again repeated, after which, as a rule, crystals of the amide began to appear in the solution. At this stage the contents of the flask was evaporated to dryness in a dish on the steam-bath. The crystalline cake was ground and further dried at 120°. The yield was nearly quantitative.

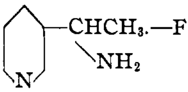
β-Pyridine Cyanide.—In the preparation of the cyanide from the amide, a few details should be added to those given by Camps.[6]

Eighteen grams of powdered amide and 25 g. of phosphorus pentoxide were placed in a distilling flask of about 150 cc. capacity and mixed by shaking. The mixture was subjected to distillation in a vacuum of about 30 mm. The heating must be done by means of an oil-bath, the temperature of which is rapidly raised to about 300°. The oil-bath was then removed and the heating continued with a free flame as long as a distillate was obtained. The cyanide crystallized on cooling to a snow-white solid which was redistilled at ordinary pressure. All but a trace boiled at 201° at 760 mm. The yield was consistently from 19.5 to 20.5 g. This cyanide was used for the preparation of pyridyl ketones.

β-Pyridylmethyl Ketone.—Twenty grams of β-pyridyl cyanide dissolved in about 100 cc. of dry ether was slowly added with vigorous stirring to the solution of Grignard reagent prepared from 40 g. of methyl iodide and 7 g. of magnesium in about 150 cc. of ether. A voluminous yellow precipitate of the addition compound was produced. At this stage most of the ether is distilled off and replaced by an equal quantity of dry benzene. After boiling for about an hour, the contents of the flask was decomposed by the addition of water followed by about 100 g. of 40% sulfuric acid. The red aqueous solution was made alkaline with sodium hydroxide and subjected to steam distillation until about 2 liters of distillate was collected. The distillate was acidified with hydrochloric acid and concentrated to 60 cc. on the steam-bath. The solution was treated with sodium hydroxide and the separated oil extracted with ether. The dried ethereal solution yielded about 14 g. of oily residue, which was distilled at ordinary pressure. The yield of pure product varied from 11 to 12 g. The boiling point, 217–220°, agreed with that found by Engler.

β-Pyridylmethyl Ketoxime.—Fifteen grams of the ketone was dissolved in 75 cc. of a solution of hydroxylamine prepared from 9 g. of the hydrochloride. After standing for about twelve hours the solution was heated on the steam-bath for a short time and then evaporated to a sirup.

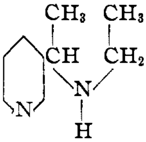
The residue crystallized on cooling to a solid cake, which was washed with benzene and then recrystallized from the same solvent. The yield of pure product was 15 g. It melted at 113°. Engler gives 112° as the melting point of the compound.

β-Pyridylethylamine, 

—Five grams of the oxime was dissolved in 75 cc. of 95% alcohol and 40 g. of zinc dust and 40 g. of glacial acetic acid were added alternately in small portions over a period of several hours. After about twenty-four hours the undissolved zinc and zinc acetate were filtered off and washed with alcohol. The alcoholic solution was evaporated to a small volume and after the addition of water the evaporation was repeated several times to remove as much as possible of the acetic acid. Strong potassium hydroxide solution was added to the concentrated solution and the separated oil extracted with ether. The dried ethereal solution yielded on evaporation about 4.5 g. of residue, practically all of which distilled between 219 and 221° at 765 mm.

Anal. Subs., 0.2370, 0.1632: CO_2, 0.5951, 0.4087: H_2O, 0.1738, 0.1165. Subs., 0.1350: N, 27.4 cc. at 23° and 772 mm. Calcd. for $C_7H_{10}N_2$: C, 68.84; H, 8.19; N, 22.95. Found: C, 68.48, 68.29; H, 8.14, 7.93; N, 23.13.

The picrate formed in aqueous solution melted at 186–187°.

β-Pyridylethyl-N-ethylamine, 

—Four grams of the primary amine, was added to 5 g. of ethyl iodide in 10 cc. of absolute alcohol and the solution was allowed to stand for forty-eight hours at room temperature.

The alcohol was expelled on the steam-bath, the residue was dissolved in 25 cc. of water and made strongly alkaline with potassium hydroxide. The separated oil was only partly soluble in ether. The ether residue was dissolved in about 15 cc. of 10% hydrochloric acid, and the solution was cooled and treated with a solution of 4 g. of sodium nitrite in 10 cc. of water.

The nitroso compound separated as an oil on addition of sodium hydroxide solution. It was extracted with ether and the ether residue was heated for one-half hour on the steam-bath with 7 cc. of concentrated hydrochloric acid. The secondary amine was separated by the addition of concentrated potassium hydroxide solution and extraction with ether. The dried ethereal solution gave 3 g. of crude product on evaporation. It was twice distilled at 773 mm. and yielded 2 g. of product boiling between 223 and 226°. In another experiment 16 g. of the primary amine gave 8 g. of the ethyl derivative.

Anal. Subs., 0.2114: N, 35.0 cc. at 19° and 767 mm. Calcd. for $C_9H_{14}N$: N, 18.67. Found: 19.11.

β-Pyridylpropyl Ketone.—Twenty grams of β-pyridine cyanide in 100 cc. of dry ether was slowly added to the Grignard reagent prepared from 7.7 g. of magnesium and 55 g. of *n*-propyl iodide. The reaction product was boiled for two hours and then cooled with ice and decomposed with water and finally with saturated ammonium chloride solution. Nearly all of the yellow precipitate formed in the reaction dissolved. The ethereal solution was separated and dried, yielding about 28 g. of crude product. The fraction which distilled between 235 and 260° contained the ketone.

It was redistilled and the fraction of 240–248° was analyzed for nitrogen, but the figures obtained on several preparations ranged from 10.9 to 11.3% instead of the theoretical 9.4% for $C_9H_{11}NO$. Closer figures could not be obtained on analysis of the steam distilled product. Therefore the crude product was converted into the phenyl hydrazone.

β-Pyridylpropyl Ketone Phenylhydrazone.—This derivative has been described by Engler, who prepared it from the impure ketone which he obtained by distillation of the mixture of nicotinic and propionic acid calcium salts. The author employed the hydrazone for the purpose of isolating the pure ketone, which is stated to be easily obtainable by cleavage of the hydrazone with hydrochloric acid.

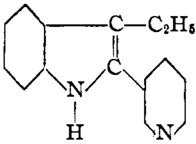
Thirty grams of the crude ketone fraction boiling between 235 and 260° was heated for two hours on the steam-bath with 25 g. of phenylhydrazine. Crystallization took place on cooling. The crude product was extracted with 50% alcohol and then recrystallized by dissolving in the necessary quantity of hot 95% alcohol and adding an equal volume of hot water. The recrystallized substance melted at 129–130°. The yield was 24 g. For analysis it was twice recrystallized from acetic ester without altering its melting point. Engler gives 182° as the melting point of the hydrazone.

Anal. Subs., 0.1248: CO_2, 0.3450; H_2O, 0.0835. Calcd. for $C_{15}H_{17}N_3$: C, 75.31; H, 7.11. Found: C, 75.40; H, 7.43.

Semicarbazone of β-Pyridylpropyl Ketone.—The semicarbazone was obtained by heating the crude ketone in alcoholic solution with the calculated quantity of semicarbazide. The resulting product recrystallized from water melted at 169–170°.

Anal. Subs., 0.1845: N, 44.2 cc. at 21° and 768 mm. Calcd. for $C_{10}H_{14}N_4O$: N, 27.19. Found: 27.43.

1-β-Pyridyl-2-ethylindol,



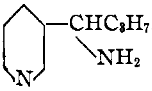
—When the hydrazone is brought into contact with strong hydrochloric acid, it instantly changes to a bright yellow, crystalline product difficultly soluble in water.

The resulting compound was dissolved in hot water, and on addition of alkali the free base was obtained as a pure white, crystalline solid melting sharply at 158°.

Anal. Subs., 0.1821: CO_2, 0.5383; H_2O, 0.1000. Subs., 0.2058: N, 22.9 cc. at 24° and 764 mm. Found: C, 80.80; H, 6.10; N, 12.48.

These figures agree for a compound of the formula $C_{15}H_{14}N_2$, differing from that of the hydrazone, $C_{15}H_{17}N_3$, by —NH_3. It seems altogether probable that the substance is an indol derivative of the formula given above, for which the theory requires C, 81.08; H, 6.30; N, 12.61.

1-β-Pyridylbutylamine,



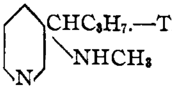
—Twenty-three grams of the hydrazone was dissolved in 300 cc. of 95% alcohol and 200 g. of zinc dust and 200 g. of glacial acetic acid were added alternately in small quantities over a period of several hours. After standing for about eighteen hours, the solution was filtered and the undissolved material was washed with alcohol. The filtrate was concentrated on the steam-bath to a small volume and the evaporation was repeated to remove most of the acid. The solution was finally concentrated to a sirup, which was dissolved in 150 cc. of water, cooled and treated with saturated sodium hydroxide solution until the precipitate of zinc hydroxide which at first formed had almost completely dissolved.

At the same time the amine, together with the aniline formed in the process, separated as an oily layer, which was extracted with ether. The dried ethereal solution yielded 16 g. of the mixture.

The aniline was separated by suspending the oil in 60 cc. of water and adding dilute hydrochloric acid until the aqueous solution was acid to litmus paper. The undissolved aniline was extracted with ether and the pyridyl amine was recovered from the acid solution by addition of sodium hydroxide and extraction with ether. The yield of crude product was 13 g., 9.4 g. of which boiled between 247 and 251°.

Anal. Subs., 0.1678: CO_2, 0.4438; H_2O, 0.1372. Subs., 0.1532: N, 24.0 cc., at 23° and 778 mm. Calcd. for $C_9H_{14}N_2$: C, 72.00; H, 9.33; N, 18.67. Found: C, 72.13; H, 9.09; N, 18.15.

1-β-Pyridylbutyl-N-methylamine,



—Thirteen grams of the primary amine was dissolved in 40 cc. of water, the solution was cooled with ice and 12 g. of dimethyl sulfate was added in small portions with constant shaking. After several hours a solution of potassium hydroxide was added and the reaction product was extracted with ether. The dried ethereal solution was evaporated and the resulting oil, which weighed 11 g., was distilled. The yield of the product boiling between 240 and 250° was 6.5 g. It was redistilled at 760 mm. and the fraction boiling between 244 and 247° was taken for analysis.

Anal. Subs., 0.1422: CO_2, 0.3810; H, 0.1213. Subs., 0.1735: N, 26.4 cc. at 26° and 765 mm. Calcd. for $C_{10}H_{16}N_2$: C, 73.17; H, 9.75; N, 17.07. Found: C, 73.08; H, 9.48; N, 16.91.

Metanicotine.—This derivative was prepared according to the method of Pinner.[7] It boiled between 275 and 278° at 760 mm. As a check on its purity, its optical activity was determined: 1.1368 g. of substance in 10.275 g. of water rotated in a 1dm. tube $-0.062°$, indicating that the quantity of nicotine in the preparation could not be greater than 3%.

Dihydrometanicotine.—Löffler[8] has prepared this compound by reduction of metanicotine with hydriodic acid. It may be obtained more easily by direct reduction with hydrogen in the presence of reduced platinum oxide catalyst by the method of Adams.[9]

Fourteen grams of metanicotine in 100 cc. of alcohol and 14.4 cc. of concentrated hydrochloric acid absorbed the required quantity of hydrogen in about one hour. The alcohol was evaporated and the base set free with potassium hydroxide and extracted with ether. The ether residue weighed 14 g., 12 g. of which distilled within 1.5° of the boiling point (258–259°) recorded by Löffler.

Summary

A new method is described for the preparation of pyridyl alkyl ketones by the use of the Grignard reaction. Methyl- and propylpyridylamines were obtained by reduction of the corresponding oximes or hydrazones. Although these compounds are chemically very similar to nicotine, they were, nevertheless, of low toxicity to insects, as were also their N-alkyl substitution products.

Metanicotine, nicotyrin and dihydrometanicotine were of a high order of toxicity, the first mentioned being only slightly below that of nicotine.

WASHINGTON, D. C.

---

[7] Pinner, *Ber.*, **27**, 2865 (1894).

[8] Löffler, *Ber.*, **42**, 3431 (1909).

[9] Adams, THIS JOURNAL, **45**, 1072 (1923).