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

THE PREPARATION OF ALPHA-, BETA- AND GAMMA-BENZYLPYRIDINES[1,2]

BY F. B. LAFORGE

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In a recent paper by Tattersfield and Gimingham[3] the announcement was made that benzylpyridines possess unusual insecticidal properties. The material used by these authors was a mixture of the α- and γ-benzylpyridines prepared by the method of Tschitschibabin.[4]

Since this method is extremely simple, and gives satisfactory yields, it would probably be capable of development into a commercial process should it be established that the benzylpyridines were of value as insecticides.

In order to provide material for insecticidal studies considerable quantities of this benzylpyridine mixture have been prepared. α-Benzylpyridine was separated by the picrate method, but a more convenient process than that described by Tschitschibabin was found for obtaining the γ-derivative. This consisted in the oxidation of the benzylpyridine mixture to the corresponding ketones, the separation of the γ-ketone by recrystallization of the picrate and reduction of the ketone back to the benzyl compound.

β-Benzylpyridine was prepared from β-pyridylphenyl ketone by reducing its oxime to the corresponding amine, from which the carbinol was obtained and reduced with hydriodic acid. By these methods, which are described below in detail, the three benzylpyridines were prepared in pure condition.

α- and γ-Benzylpyridine

The method of Tschitschibabin has been simplified by omitting the first treatment with sodium hydroxide and ether extraction, the hot reaction mixture being poured directly into water, which dissoves the hydrochlorides of the bases, leaving the tarry materials. The nearly colorless, aqueous solution is poured off and treated with sodium hydroxide solution. The bases are collected in ether and after evaporation of the solvent are distilled. The fraction boiling at 270–310° consists almost entirely of benzylpyridines. The portion boiling at 310–370° is probably a very indefinite mixture containing dibenzylpyridines.

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[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.

[3] Tattersfield and Gimingham, *Annals of Applied Biology*, **14**, 217 (1927).

[4] Tschitschibabin, *J. Russ. Phys.-Chem. Soc.*, **33**, 249 (1901); **47**, 1297 (1915); *Chem. Zentr.*, [2] **72**, 127 (1901); [2] **87**, 146 (1916).

The proportions employed were usually 72 g. of pyridine, 98 g. of benzyl chloride and 1 g. of copper-bronze powder. The yield of the benzylpyridine fraction is about 60 g. About 15 g. of the higher fraction and from 15 to 20 g. of pyridine are recovered. Analysis of the first fraction gave the following results.

Anal. Subs., 0.0989: CO_2, 0.3074; H_2O, 0.0576. Calcd. for $C_{12}H_{11}N$: C, 85.21; H, 6.51. Found: C, 84.77; H, 6.47.

The α-derivative may be prepared from the mixture of benzylpyridines in a pure state by fractional crystallization of the picrates.

The picrate mixture obtained from alcoholic solution consists of prisms and needles which do not differ much in solubility in any solvent. A rough separation may be made by quickly treating the mixture with a quantity of boiling water insufficient for complete solution. The undissolved portion consists mostly of the prisms of the α-compound. It is dissolved in warm acetone, from which large prisms of the α-compound crystallize on cooling. The solvent is poured off before the needles of the β-compound begin to be deposited. These prisms are finally recrystallized from alcohol and melt sharply at 139–140° (uncorr.).

The free base obtained from the picrate boiled at 275–276° (corr.), which boiling point is in agreement with the figures reported by Tschitschibabin.

The picrate of γ-benzylpyridine could not be separated from the mixture in a pure state by crystallization from benzene, as reported by that author. The pure base was, however, obtained by an indirect method.

The original mixture of the two benzylpyridines was oxidized to the ketones with potassium permanganate.[5] From the mixture of the two ketones the picrate of the γ-form is very easily separated from the picrate of the α-compound by crystallization from alcohol. It melts as reported by Tschitschibabin at 160°.

The free ketone was obtained from the picrate in the form of a white, crystalline solid. It was dissolved in ether and after removal of the solvent boiled at 315° (corr.). After recrystallization from petroleum ether it melted at 72°.

Reduction of the γ-Benzyl Ketone by the Method of Clemmensen.[6]—Eleven grams of the pure ketone was dissolved in about 200 cc. of 10% hydrochloric acid and heated with 50 g. of amalgamated zinc for ten hours on the steam-bath. The colorless solution was decanted and neutralized with sodium hydroxide solution. The precipitate which formed consisted of the zinc double salt of γ-benzylpyridine, together with some zinc hydroxide. It was filtered off and extracted repeatedly with 70% acetone, which dissolved the zinc double salt. The acetone was evaporated on the steam-bath, leaving the crystalline zinc compound, which is nearly insoluble in water. It is easily obtained

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[5] Tschitschibabin, *J. Russ. Phys.-Chem. Soc.*, **33**, 300 (1901); *Chem. Zentr.*, **73**, 206 (1902).

[6] Clemmensen, *Ber.*, **46**, 1837 (1913); **47**, 51 (1918).

pure by recrystallization from benzene. The yield of the pure compound was 11 g. It melts sharply at 161° (uncorr.).

Anal. Subs., 0.1403, 0.1790: CO_2, 0.3162, 0.3999; H_2O, 0.0652, 0.0812. Calcd. for $C_{24}H_{22}N_2 \cdot ZnCl_2$: C, 61.01; H, 4.66. Found: C, 61.46, 60.94; H, 5.15, 5.04.

The zinc double salt was boiled for ten minutes with a 50% potassium carbonate solution, and the resulting colorless oil was extracted with ether. The ether residue boiled at 287° (corr.) at 760 mm., which is the figure given by Tschitschibabin for γ-benzylpyridine. The yield was 6.5 g.

β-Benzoylpyridine.—β-Benzoylpyridine has been prepared by Bernthsen and Mettegang[7] and Jeiteles[8] from β-benzoylpyridinecarboxylic acid obtained by the condensation of quinolinic acid anhydride and benzene in the presence of aluminum chloride. It may be more conveniently prepared from β-pyridine cyanide and bromobenzene by the Grignard method.

Twenty grams of β-pyridine cyanide[9] in about 200 cc. of dry ether was slowly added with constant stirring to the Grignard reagent prepared from 38 g. of bromobenzene and 5.8 g. of magnesium in about 400 cc. of ether. A yellow precipitate separated which was decomposed by the slow addition of water. Saturated ammonium chloride solution was then added and the flask shaken until practically all of the solid had dissolved. The ethereal solution was dried and the solvent evaporated, leaving a red oil.

The quantity varied somewhat, but was usually about 35 grams. It contains the ketone, together with considerable quantities of impurities. If treated with fairly strong hydrochloric acid solution, it completely resinifies, but it may be separated into a basic and non-basic portion by suspending it in 150 to 200 cc. of water and carefully adding 10% hydrochloric acid with constant stirring until no more of the oil dissolves. It is best to pour off the solution after about 50 cc. of acid has been employed and to treat the undissolved oil with more dilute acid. The non-basic oil usually amounts to about 9 g. The acid solution yields about 25 g. of oil on addition of sodium hydroxide. This oil is still impure, but the major portion distils between 270 and 320°. The distillate, which weighed about 17 g., was dissolved in 300 cc. of hot alcohol and a hot alcoholic solution of picric acid was added. The picrate of the ketone crystallized even from the hot solution in balls of needles, which melt at 161° (uncorr.). The melting point was not changed by recrystallization. The yield was 24 g. The picrate was decomposed by suspending in 250 cc. of hot water and adding 30 cc. of concentrated ammonia. The ketone separated as a light yellow oil, which was taken up in ether and the ethereal solution washed with water and dried. The ether residue boiled between 318 and 319° (corr.).

Anal. Subs., 0.2108: CO_2, 0.6114; H_2O, 0.0993. Calcd. for $C_{12}H_9NO$: C, 78.70; H, 4.92. Found: C, 79.11; H, 5.24.

The oxime was prepared by dissolving 8 g. of the ketone in 60 cc. of an alcoholic solution of hydroxylamine prepared from 6 g. of the hydrochloride and 2 g. of sodium and filtering from the sodium chloride. After heating for several hours on the steam-bath the solution was concentrated to one-half of its volume and 2 volumes of water was added. The oxime crystallized in good yield and melted between 140 and 155°. It was recrystallized from benzene and melted at 161°.[8]

Anal. Subs., 0.1510: CO_2, 0.4066; H_2O, 0.0738. Calcd. for $C_{12}H_{10}N_2O$: C, 72.81; H, 5.05. Found: C, 73.44; H, 5.40.

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[7] Bernthsen and Mettegang, *Ber.*, **20**, 1209 (1887).

[8] Jeiteles, *Monatsh.*, **17**, 515 (1896).

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

β-Pyridylphenylmethylamine.—Sixteen and one-half grams of pure oxime were dissolved in 200 cc. of 95% alcohol, the solution was treated with 150 g. of zinc dust and 150 g. of glacial acetic acid was added alternately in small quantities over a period of about two hours. After the solution had stood overnight, the residue of zinc acetate and unaltered zinc was filtered off and washed with alcohol. The alcoholic solution was concentrated on the steam-bath with addition of water from time to time to expel the alcohol and most of the excess acid. The concentrated solution was treated with an excess of strong sodium hydroxide solution, and the separated oil was extracted with ether. The ether residue was distilled and yielded 14 g. of pure product, boiling at 329–331° (corr.), at 760 mm.

Anal. Subs., 0.1934: CO_2, 0.5565; H_2O, 0.1168. Calcd. for $C_{12}H_{12}N_2$: C, 78.26; H, 6.52. Found: C, 78.54; H, 6.71.

β-Pyridylphenylcarbinol.—The amine was transformed into the corresponding alcohol by dissolving it in about the calculated quantity of dilute hydrochloric acid and adding an aqueous solution of sodium nitrite, which caused a vigorous evolution of nitrogen. After standing for a few hours the solution was made alkaline with sodium hydroxide solution and the separated oil extracted with ether. The ether residue was a thick sirup which could not be made to crystallize. The yield was 9 g. from 11 g. of amine.

β-Benzylpyridine.—β-Benzylpyridine has been prepared by Tschitschibabin[10] by direct reduction of the corresponding ketones, but the fact is not mentioned in the reference books, and this compound was prepared by the method described before the original article was noted.

The crude sirupy carbinol was reduced by heating in a sealed tube for three and one-half hours with 30 g. of fuming hydriodic acid. The contents of the tube presented two layers. The heavy, black liquid, consisting of the periodide of benzylpyridine, insoluble in water, was separated, washed with water and decomposed by warming with concentrated sodium hydroxide solution. The separated dark oil was taken up in ether and the solution was shaken with sodium bisulfite to remove dissolved iodine. The ether residue was light brown and yielded on distillation 4.5 g. of the pure compound, boiling at 287–288° (corr.) at 760 mm. After standing for several days it crystallized to a solid cake. The analysis agrees for benzylpyridine. The picrate recrystallized from alcohol melts at 119° (uncorr.).

Anal. Subs., 0.1818: CO_2, 0.5661; H_2O, 0.1091. Calcd. for $C_{12}H_{11}N$: C, 85.21; H, 6.51. Found: C, 84.93; H, 6.67.

Summary

The method of Tschitschibabin for the preparation of α- and γ-benzylpyridine has been modified and a more convenient process found for the separation of the γ-derivative.

A new method is described for the preparation of β-benzylpyridine.

WASHINGTON, D. C.

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[10] Tschitschibabin, *Ber.*, **36**, 2711 (1903).