To isolate caffeic acid, 5 g. of sample is dissolved in 50 ml. of *N* sodium hydroxide under an atmosphere of nitrogen and allowed to stand overnight at room temperature before acidification with an equivalent quantity of sulfuric acid. Caffeic acid is isolated from the saponification mixture by continuous extraction with ether, the ether removed by distillation, and the residue recrystallized from water, m. p. 218–220°.

After removal of the caffeic acid, quinic acid may be isolated by acetone extraction of the dry saponification residue or by formation of the copper acetate complex. Better yields are obtained by acid hydrolysis[11] of the hydrogenated chlorogenic or isochlorogenic acid, and the quinic acid is further identified by preparation of the 1,4,5-triacetylquinlactone.[12] The quinic acid derived from isochlorogenic acid is partially lactonized, but may be saponified to the correct titration value.

(11) A. Watanabe, *J. Pharm. Soc. Japan*, **56**, 71 (Abstracts in German) 13, (1936); *Chem. Zentr.*, **107**, 1, 4901 (1936); *cf. C. A.* **31**, 2062 (1936).

(12) Erwig and Koenig, *Ber.*, **22**, 1157 (1889).

Hydrogenation.—Chlorogenic and isochlorogenic acids were hydrogenated in absolute ethanol using 5% palladium on charcoal as a catalyst. The suspension after hydrogenation was filtered through Celite, the filtrate taken to dryness, and the residue taken up in water and lyophilized. The theoretical amount of hydrogen was absorbed by each compound without significant change in neutralization equivalent. However, the optical rotation of hydrogenated isochlorogenic acid $[\alpha]^{20}D$ −34 to −39°, was approximately that of chlorogenic or hydrochlorogenic acid, $[\alpha]^{20}D$ −37°.

Summary

A new compound, "isochlorogenic acid," has been isolated from green coffee. Evidence is presented for the proposed structure, 5-caffeylquinic acid, a position isomer of chlorogenic acid.

HOBOKEN, N. J. RECEIVED JANUARY 14, 1950

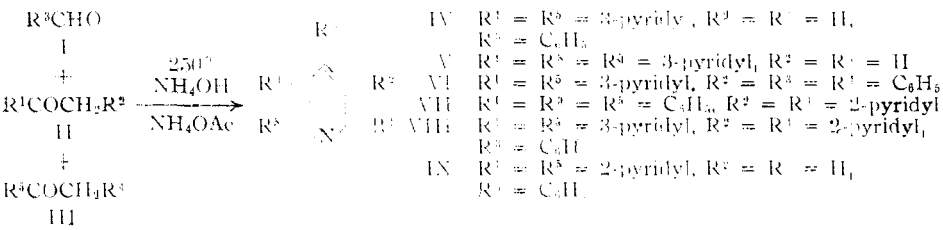
(CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS)

Pyridines. VI. Polypyridyls by the Chichibabin Synthesis[1]

BY ROBERT L. FRANK AND EDWARD F. RIENER

A recent investigation[2] of the Chichibabin synthesis of pyridines has demonstrated its particular usefulness for the preparation of symmetrically substituted aryl pyridines. The reaction has now been applied to the synthesis of pyridyl-substituted pyridines, or polypyridyls, some of which were desired for pharmacological studies.

Yields of the polypyridyls (IV–IX) were for the most part in the range 23–32%, comparable with those of the corresponding aryl pyridines[2] and satisfactory considering the simplicity of the procedure.



It has been shown that condensations of this type may occur[2,3] in two ways, either with the aldehyde (I) reacting so as to introduce the group R^3 at the *gamma* position of the pyridine, as in the above equation, or with the aldehyde (I) reacting at the *alpha* position to give products represented by Structures IV–IX in which R^1 (or R^5) and R^3 are interchanged. Thus the problem of assignment of structure arises in those examples in which R^1 (or R^5) is not identical with R^3, namely, IV, VI, VIII and IX.

In two previous examples,[2] as shown by unequivocal syntheses of aryl-substituted pyridines, the group introduced by the aldehyde (I) has been found to appear at the *gamma* position of the pyridine formed. A similar unequivocal synthesis, the reaction of benzaldi-(2-acetylpyridine) with hydroxylamine to form 2,5-di-(2-pyridyl)-4-phenylpyridine (IX), has now provided evidence for the correctness of Structure IX for the identical compound prepared by the Chichibabin reaction. Attempts to prepare the 1,5-diketones which would react with hydroxylamine to form structures IV, VI and VIII have been unsuccessful, so we are forced to assign these structures only tentatively, although with rather good assurance of their correctness.

Further information on the scope and limitations of the Chichibabin synthesis has been provided by this study. For example, the starting materials II and III must be identical or the products are complex mixtures, as evidenced by a number of reactions described in the Experimental Part. An additional limitation is that when formaldehyde is used as Compound I (R^3 = H), only tars are obtained. Compound I must be an aromatic aldehyde.[2]

The preparation of two polypyridyls (VII and VIII) gave rise to a side reaction not encountered in our previous study.[2] These compounds were formed in yields of only 5.4%. The explanation lies in the structures of the starting materials, 2-

(1) For the previous communication on pyridine chemistry see Frank and Phillips, THIS JOURNAL, **71**, 2804 (1949).

(2) Frank and Seven, *ibid.*, **71**, 2629 (1949).

(3) Chichibabin and co-workers, *J. prakt. Chem.*, **107**, 109, 122, 129, 132, 138, 145, 151 (1924).

phenacylpyridine and 2-picolyl 3-pyridyl ketone, respectively. These compounds, with carbonyl groups *beta* to 2-pyridyl groups, resemble 1,3-diketones and β-keto esters and are therefore cleaved by ammonium hydroxide at 250°. Evidence is the isolation of a 20% yield of benzoic acid and a smaller amount of 2-picoline from 2-phenacylpyridine in the Chichibabin synthesis of 3,5-di-(2-pyridyl)-2,4,6-triphenylpyridine (VII).

Experimental

2-Acetylpyridine.—2-Cyanopyridine was converted by ethanolysis to ethyl picolinate, a method we find more convenient than the oxidation of 2-picoline followed by esterification. Ethyl picolinate was then converted to 2-acetylpyridine by Claisen condensation with ethyl acetate, followed by hydrolysis and decarboxylation.[4]

Ethyl Picolinate.—Ninety grams (0.865 mole) of 2-cyanopyridine[5] was added cautiously to 1500 ml. of saturated ethanolic hydrogen chloride. The mixture was then refluxed for five hours, allowed to stand overnight, and filtered to remove precipitated ammonium chloride. The filter cake was washed well with ethanol and the washings added to the filtrate. The filtrate was concentrated *in vacuo* on a steam-bath to about 400 ml., cooled, poured into 500 ml. of water, and the whole neutralized with 28% ammonium hydroxide. The mixture was then extracted with three 300-ml. portions of ether, and the extracts dried over magnesium sulfate and fractionally distilled in a ten-inch helix-packed column. The yield of ethyl picolinate was 53 g. (40%), b. p. 124–127° (15 mm.); $n^{20}D$ 1.5108.

Chichibabin Syntheses.—These were performed as previously described[2] in a 500-ml. steel autoclave at 250° with reaction times of three hours. The molar ratio of 28% ammonium hydroxide of the expected product (based on 100% yield) was 10:1, and of ammonium acetate it was 0.13–0.29:1. Purifications of the individual products are described below.

4-Phenyl-2,6-di-(3-pyridyl)-pyridine (IV).—From 17.0 g. (0.16 mole) of freshly distilled benzaldehyde and 43.6 g. (0.36 mole) of 3-acetylpyridine[6] was obtained a solid which after washing with 200 ml. of water and 50 ml. of cold ethanol was recrystallized twice from ethanol with the use of Darco to yield 13.0 g. (26.3%) of fine microscopic needles, m. p. 221–222°. *Anal.*[7] Calcd. for $C_{21}H_{15}N_3$: C, 81.61; H, 4.85. Found: C, 81.57; H, 4.69.

2,4,6-Tri-(3-pyridyl)-pyridine (V).—From 15.0 g. (0.14 mole) of freshly prepared 3-formylpyridine[8] and 36.3 g. (0.298 mole) of 3-acetylpyridine[6] was obtained by the procedure just above 14.0 g. (32%) of tan crystals, m. p. 271–273°. An analytical sample, fine colorless microscopic needles, was obtained by recrystallization from nitromethane with the use of Darco, m. p. 273.5–274.5°. *Anal.* Calcd. for $C_{20}H_{14}N_4$: C, 77.42; H, 4.51. Found: C, 77.33; H, 4.51.

2,6-Di-(3-pyridyl)-3,4,5-triphenylpyridine (VI).—A mixture of 12.9 g. (0.12 mole) of benzaldehyde and 50.5 g. (0.251 mole) of benzyl 3-pyridyl ketone[9] yielded a mushy solid. This was washed with 100 ml. of water and 50 ml. of ether and recrystallized twice from ethyl acetate with the use of Darco to yield 12.5 g. (22.6%) of colorless needles, m. p. 278–279°. *Anal.* Calcd. for $C_{28}H_{23}N_3$: C, 85.90; H, 4.99. Found: C, 85.80; H, 4.75.

3,5-Di-(2-pyridyl)-2,4,6-triphenylpyridine (VII).—From 12.9 g. (0.12 mole) of benzaldehyde and 50.5 g. (0.251 mole) of 2-phenacylpyridine[10] was obtained by filtration of the aqueous reaction mixture a sticky mass of crystals. This was stirred with 100 ml. of ether and collected on a filter. Recrystallization from ethyl acetate, with the use of Darco, gave 3.0 g. (5.4%) of coarse colorless needles, m. p. 280–281°. *Anal.* Calcd. for $C_{33}H_{23}N_3$: C, 85.90; H, 4.99. Found: C, 85.88; H, 5.18.

The original aqueous portion was acidified with hydrochloric acid and yielded 6.0 g. (20% based on 2-phenacylpyridine) of benzoic acid. The filtrate from the original ether washings above was steam distilled; from the distillate was obtained the picrate of 2-picoline, m. p. 156–159°. A mixed m. p. with an authentic sample, m. p. 160–162°, was 159–161°.

2,6-Di-(3-pyridyl)-3,5-di-(2-pyridyl)-4-phenylpyridine (VIII).—A mixture of 1.06 g. (1.00 mole) of benzaldehyde and 5.0 g. (0.025 mole) of 2-picolyl 3-pyridyl ketone, available by the method of Burger and Walter,[9] yielded a suspension of crystals. These were washed with 10 ml. of ethanol, then 250 ml. of boiling water, dissolved in warm 5% hydrochloric acid, the solution filtered, and the greenish filtrate neutralized with ammonium hydroxide. The precipitate was washed with 50 ml. of boiling ethanol to give 0.39 g. of product, m. p. 277–278°. Recrystallization from ethyl orthoformate, with the use of Darco, gave 0.25 g. (5.4%) of colorless microscopic needles, m. p. 281.5°. *Anal.* Calcd. for $C_{31}H_{21}N_5$: N, 15.12. Found: N, 14.88.

2,6-Di-(2-pyridyl)-4-phenylpyridine (IX).—Attempts to prepare this pyridine in a steel autoclave were unsuccessful because of the tendency of the product to complex with iron. Use of a sealed glass tube containing 1.59 g. (0.0150 mole) of benzaldehyde, 4.54 g. (0.0375 mole) of 2-acetylpyridine, and the aforementioned proportions of ammonium hydroxide and ammonium acetate, heated within the steel autoclave, however, yielded a tarry mass which gave 1.7 g. of a tan residue on washing with 15 ml. of water and two 15-ml. portions of ethanol. Recrystallization from 36 ml. of nitromethane yielded 0.80 g. (17.2%) of granular crystals, m. p. 208°. *Anal.* Calcd. for $C_{21}H_{15}N_3$: C, 81.61; H, 4.85. Found: C, 81.80; H, 4.85.

Other Condensations.—The following combinations of starting materials, chosen to react in the Chichibabin synthesis to yield unsymmetrically substituted pyridines, gave products distilling in the expected boiling range, but these were always mixtures, regardless of the ratios of starting materials: acetophenone and paraldehyde, and 3-acetylpyridine paired with paraldehyde, formaldehyde, cinnamaldehyde and 1,3,3-triethoxybutane. 3-Acetylpyridine and benzalacetophenone gave fine needles (*ca.* 16%) which melted at 177–179° after many crystallizations from ethanol, methanol, and dioxane and which analyzed 1.37% low in carbon and 0.06% low in hydrogen for the expected 2,4-diphenyl-6-(3-pyridyl)-pyridine.

2,6-Di-(2-pyridyl)-4-phenylpyridine (IX) (by Means of Hydroxylamine).—A mixture of 0.33 g. (0.0010 mole) of benzaldi-(2-acetylpyridine),[11] 0.21 g. (0.0030 mole) of hydroxylamine hydrochloride and 3 ml. of absolute ethanol was sealed in a test tube and heated inside an autoclave for five hours at 160°. The black powder obtained was crystallized three times from nitromethane, with the use of Darco, to yield approximately 25 mg. (8%) of granular crystals, m. p. 207–208°. A mixed m. p. with the Chichibabin reaction product from 2-acetylpyridine and benzaldehyde was not depressed.

Summary

The Chichibabin synthesis of pyridines has been applied to the preparation of polypyridyls. Its scope for this purpose is discussed.

URBANA, ILLINOIS RECEIVED JANUARY 27, 1950

(4) Gilman, Tolman and Massie, THIS JOURNAL, **68**, 2399 (1946).

(5) Craig, *ibid.*, **56**, 231 (1934).

(6) Strong and McElvain, *ibid.*, **55**, 818 (1933).

(7) Microanalyses were performed by Miss Emily Davis, Mr. Maurice Dare and the Clark Microanalytical Laboratory.

(8) Panizzon, *Helv. Chim. Acta*, **24**, 24E (1941).

(9) Burger and Walter, THIS JOURNAL, **72**, 1988 (1950). We are indebted to these authors for a preview of their results.

(10) Kloppenburg and Wibaut, *Rec. trav. chim.*, **65**, 393 (1946).

(11) Engler and Engler, *Ber.*, **35**, 4061 (1902).