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Summary

A number of 1-phenyl-2-alkylamino-1-propanols have been prepared by the catalytic hydrogenation of mixtures of norephedrine or

certain nuclear substituted derivatives with aldehydes or ketones, following the general method of Cope and Hancock. When the aminoalcohol contains a catechol nucleus, only ketones can be employed as the carbonyl component. A nuclear amino group may be alkylated simultaneously if an excess of carbonyl compound is employed.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

The Chemistry of the Benzylpyridines. I. 2-(4-Acetylbenzyl)- and 4-(4-Acetylbenzyl)-pyridines¹

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For the synthesis of new derivatives of benzylpyridines, 2-(4-acetylbenzyl)-pyridine (IA) and 4-(4-acetylbenzyl)-pyridine (IB) were required as intermediates. This paper describes the synthesis and proof of structure of these two compounds and several derivatives.

2-(4-Acetylbenzyl)- and 4-(4-acetylbenzyl)-pyridines were synthesized by the Friedel-Crafts reaction of the appropriate benzylpyridine and acetyl chloride. When the reaction was carried out by the conventional Friedel-Crafts procedure, using either nitrobenzene, carbon disulfide or acetylene tetrachloride as solvents, little or none of the expected acetyl products were obtained. However, in the absence of solvent and employing the same ratio of reactants as that described for the synthesis of 2,5-dichloroacetophenone,² namely, one part by weight of acetyl chloride and the benzylpyridine and two parts by weight of aluminum chloride, 60–70% yield of IA and IB were consistently obtained.

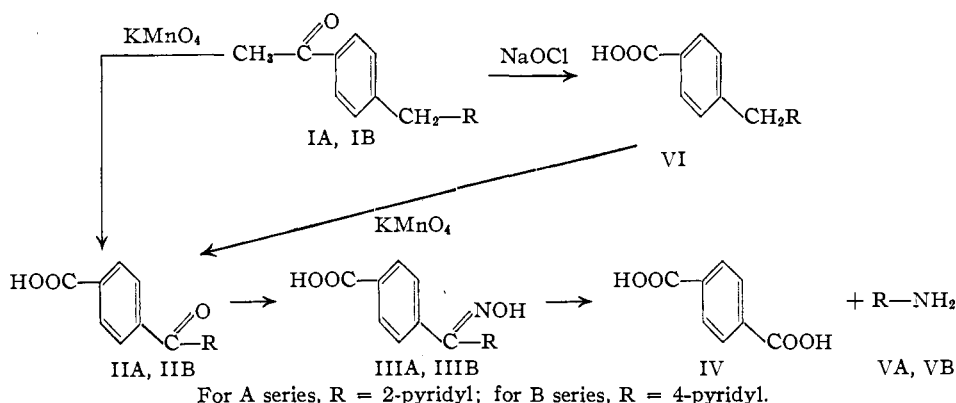
of IIA was subjected to the Beckmann rearrangement³ and the resulting amide, on hydrolysis yielded terephthalic acid (IV) and 2-aminopyridine (VA). These products were identified by known derivatives. Similarly, IB yielded IV and 4-aminopyridine (VB). The acidic product of the Beckmann rearrangement of IIIA and IIIB did not yield any phthalic acid indicating that no *o*-acetylbenzylpyridines were formed during the Friedel-Crafts reaction.

The oxidation of IA with sodium hypochlorite yielded the carboxylic acid VI, which could not be obtained analytically pure. Further oxidation of 2-(4-carboxybenzyl)-pyridine (VI) with alkaline permanganate resulted in the formation of the keto acid (IIA).

Experimental

All melting points are corrected.

2-(4-Acetylbenzyl)-pyridine (IA).—In a 2-l. flask equipped with a Hershberg type tantalum stirrer and a reflux condenser, was placed 200 g. of 2-benzylpyridine and 200 g. of acetyl chloride. The mixture was cooled in an ice-salt-bath and 400 g. of aluminum chloride was added slowly in small portions under anhydrous conditions. After all of the aluminum chloride had been added, the ice-bath was removed and the mixture was allowed to warm to room temperature and finally heated on the steam-bath for six hours. The brown viscous material was poured



The structure of the acetylbenzylpyridines was established by the following series of transformations. Oxidation of IA with alkaline permanganate yielded the keto acid IIA. The oxime

(1) Presented in abstract before the Division of Organic Chemistry of the American Chemical Society, Atlantic City Meeting, September 19, 1949.

(2) Sen and Bhargava, *J. Ind. Chem. Soc.*, **24**, 371 (1947).

(3) After this investigation had been completed, Huntress and Walter [*THIS JOURNAL*, **70**, 3702 (1948)] described the Beckmann rearrangement of 2-benzoylpyridine oxime.

(4) A large excess of sodium hydroxide is necessary in order to dissolve the aluminum hydroxide which precipitates.

titled over as a red oil; yield 153 g. (61%), b. p. 160–165° (1 mm.), n_D^{20} 1.5975.

Anal. Calcd. for $C_{14}H_{13}ON$: N, 6.63. Found: N, 6.85.

The picrate, prepared by adding an alcoholic solution of picric acid to an alcoholic solution of 2-(4-acetylbenzyl)-pyridine, melted at 137–138°.

Anal. Calcd. for $C_{20}H_{16}O_3N_4$: N, 13.17. Found: N, 13.32.

The semicarbazone melted at 166.5–167.5° after recrystallization from alcohol.

Anal. Calcd. for $C_{15}H_{15}ON_4$: N, 21.69. Found: N, 21.26.

In another experiment using 338 g. of 2-benzylpyridine, 338 g. of acetyl chloride and 676 g. of aluminum chloride, there was obtained 226 g. (60%) of 2-(4-acetylbenzyl)-pyridine.

4-(4-Acetylbenzyl)-pyridine (IB).—This compound was prepared as described for the isomeric 2-benzylpyridine derivative. From 51 g. of 4-benzylpyridine, 51 g. of acetyl chloride and 102 g. of aluminum chloride, 36.6 g. (57.5%) of 4-(4-acetylbenzyl)-pyridine (IB) was secured; b. p. 165–170° (1 mm.), n_D^{20} 1.5864.

Anal. Calcd. for $C_{14}H_{13}ON$: N, 6.63. Found: N, 6.52.

2-(4-Carboxybenzyl)-pyridine (IIA).—Twenty-five grams of 2-(4-acetylbenzyl)-pyridine (IA) in two liters of water containing 100 g. potassium permanganate and 25 ml. of 10% sodium hydroxide was refluxed with stirring for five hours. After cooling, the solution was neutralized carefully with dilute sulfuric acid and refluxed for an additional hour. The manganese dioxide was dissolved by the addition of sodium bisulfite solution and the precipitated acidic product was filtered; recrystallization from ethanol, m. p. 229.3–230.3°, yield 9 g. (36%).

Anal. Calcd. for $C_{13}H_9O_3N$: C, 68.72; H, 3.97; N, 6.16. Found: C, 68.79; H, 3.68; N, 6.14.

4-(4-Carboxybenzoyl)-pyridine (IIB).—This compound was obtained in 26% yield by the procedure described for the corresponding 2-isomer, m. p. 299–300° (dec.).

Anal. Calcd. for $C_{13}H_9O_3N$: N, 6.16. Found: N, 6.05.

Oxime of 2-(4-Acetylbenzoyl)-pyridine (IIIA).—To 8.5 g. (0.037 mole) of 2-(4-carboxybenzoyl)-pyridine (IIA) dissolved in 400 cc. of ethanol containing 50 g. of potassium hydroxide, 17 g. of hydroxylamine hydrochloride was added and the mixture was refluxed on the steam-bath for three hours. The alcohol was removed under reduced pressure, the residue dissolved in water and the aqueous solution made acid by partial neutralization with hydrochloric acid and finally with glacial acetic acid. The precipitated oxime was filtered and recrystallized from ethanol; yield 8 g. (90%), m. p. 236.5–237°.

Anal. Calcd. for $C_{13}H_{10}O_3N_2$: N, 11.57. Found: N, 11.32.

The oxime of 4-(4-carboxybenzoyl)-pyridine (IIIB) was prepared in a similar manner and 8 g. of the oxime, melting at 245–246°, was obtained from 8.5 g. of the ketone.

Anal. Calcd. for $C_{13}H_{10}O_3N_2$: N, 11.57. Found: N, 11.90.

Beckmann Rearrangement of Oxime IIIA.—A mixture of 7.5 g. of the oxime and 22.5 g. of phosphorus pentachloride was warmed on the steam-bath for two hours. The product was poured onto ice and neutralized with sodium hydroxide. The brown flocculent precipitate was filtered and air dried. Attempts to purify this amide were unsuccessful and the crude amide was hydrolyzed by refluxing with 125 ml. of 48% hydrobromic acid for twenty-two hours. On dilution with water, the acidic material

IV was precipitated and removed by filtration. The filtrate was made basic, extracted with ether and the ether removed by evaporation. The residue VA, a dark brown oil, was converted to the picrate, m. p. 225.3–225.8°. The mixed melting point with an authentic sample of the picrate of 2-aminopyridine showed no depression.

Two derivatives were made of the acidic material IV. The dimethyl ester melted at 139.5–141°, lit.⁵ m. p. 140–141°. The di-*p*-nitrobenzyl ester melted at 262–264°, lit.⁶ m. p. 263°.

Beckmann Rearrangement of Oxime (IIIB).—This rearrangement was carried out as described for the 2-isomer using the identical quantities and conditions. The acid fraction of the hydrolysis of the amide was identified as terephthalic acid by means of the dimethyl ester, m. p. 141–142°. The basic fraction was identified as 4-aminopyridine (VB) by conversion to the picrate, m. p. 212–215°, lit.⁷ m. p. 215–216°.

2-(4-Carboxybenzyl)-pyridine (VI).—Chlorine gas was bubbled into a mixture of 218 g. (5.48 moles) of sodium hydroxide, 300 cc. of water and 1250 g. of ice until 161 g. (4.5 moles) had been absorbed. One hundred and five grams (0.5 mole) of 2-(4-acetylbenzyl)-pyridine was added slowly with stirring, maintaining the temperature at 60–70°. After the addition, the mixture was heated on the steam-bath for two hours and the excess sodium hypochlorite was destroyed by the addition of 50 g. of sodium bisulfite in 200 cc. of water. The yellow solution was filtered and partly neutralized with hydrochloric acid. The clear yellow solution was finally made acid by the addition of glacial acetic acid. The product VI precipitated as an oil which soon solidified. After recrystallization from a benzene-alcohol mixture, the acid melted at 172.8–176.8°, yield 84 g. (79%).

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.58. Found: N, 7.01, 7.15.

The oxidation of 2 g. of 2-(4-carboxybenzyl)-pyridine (VI) using the alkaline permanganate procedure gave 1.5 g. of 2-(4-carboxybenzoyl)-pyridine (IIA), m. p. 227–228°.

2-(4-Carbomethoxybenzyl)-pyridine.—A solution of 41 g. (0.19 mole) of 2-(4-carboxybenzyl)-pyridine in 200 cc. of absolute methanol and 20 cc. of concentrated sulfuric acid was refluxed for six hours. Most of the methanol was removed by vacuum concentration and the residue was poured into ice water, made alkaline with sodium carbonate and extracted with ether. There was obtained 38 g. (88%) of an oil boiling at 150–160° (2 mm.), which subsequently crystallized. On recrystallization from petroleum ether, the ester was obtained as a white crystalline product melting at 53.6–55.2°.

Anal. Calcd. for $C_{14}H_{13}O_2N$: N, 6.16. Found: N, 6.33.

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Summary

The synthesis and proof of structure of 2-(4-acetylbenzyl)- and 4-(4-acetylbenzyl)-pyridines is described.

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(5) Huntress and Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 178.

(6) Lyons and Reid, *THIS JOURNAL*, **39**, 1740 (1917).

(7) Koenigs, Kinner and Weiss, *Ber.*, **57**, 1175 (1924).