[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

PIPERIDINE DERIVATIVES
X. THE PHENYLPIPERIDYLCARBINOLS

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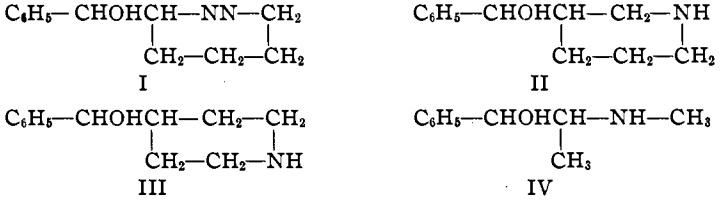
Since the publication[1] of the summarized work of Chen and others on the pharmacological properties of ephedrine, a number of papers have appeared in the chemical literature in which the preparation and properties of certain synthetic homologs of this important drug have been described.[2] These synthetic compounds in general have been of the type $ArCHOH-CHR_1NHR_2$, where Ar is a phenyl or alkyl substituted phenyl radical and R_1 and R_2 are various alkyl radicals. In certain cases R_1 is a phenylalkyl radical.

This paper describes the preparation and properties of the three phenylpiperidylcarbinols (I, II, III) as an effort to extend the synthetic ephedrine-like compounds to other types of structure. The relationship between the structure of these carbinols and ephedrine (IV) seemed interesting on



account of the fact that the secondary amino group could be placed at different positions relative to the secondary alcohol group without increasing the carbon content of the molecule or altering materially the characteristic ephedrine-like structure.

The phenyl-2-, -3- and -4-piperidylcarbinols were obtained by the catalytic reduction of 2-, 3- and 4-benzoylpyridine hydrochlorides using Adams' platinum-oxide platinum black catalyst. The 2-benzoylpyridine was so weakly basic that due to the hydrolysis of its hydrochloride the catalyst was rendered inactive by the precipitation of the free base upon it. This difficulty was overcome by carrying out the reduction with an excess of hydrochloric acid in the solution. No similar difficulty was encountered in the reduction of the 3- and 4-benzoylpyridine hydrochlorides.

The reduction of 2-benzoylpyridine produced both diastereoisomeric racemic phenyl-2-piperidylcarbinols. One isomer (A) melted at 141–142°

[1] Chen and Kao, *J. Am. Pharm. Assocn.*, **15**, 625 (1926).

[2] Adams, Hyde and Browning, THIS JOURNAL, **50**, 2287 (1928); Johnson and Manske, *ibid.*, **51**, 1906 (1929); Fourneau and Barrelet, *C. A.*, **24**, 352 (1930); de Buruaga, *C. A.* **24**, 596 (1930)

and the other (B) melted at 171–173°. Both isomers were isolated as the free bases and in the ratio of about three parts of A to one part of B. It was found that isomer A could be changed into isomer B to some extent by heating at 100° for forty-eight hours with 25% hydrochloric acid. The separation and purification of these racemic diastereoisomers are made possible by the fact that the hydrochloride of B is much more soluble in an alcohol–ether mixture than the hydrochloride of A, while the free base, B, is considerably less soluble than the free base A in water containing 4% alcohol. The details of the isolation and the conversion of the lower-melting into the higher-melting isomer are given in the experimental part of the paper. The amount of material that was available did not allow for any extended search to be made for the diastereoisomeric phenyl-3-piperidylcarbinols; consequently only one of these racemic mixtures was obtained. Obviously such isomerism would not be present in a structure such as phenyl-4-piperidylcarbinol.

The 2- and 4-benzoylpyridines were prepared by the oxidation of 2- and 4-benzylpyridines. 3-Benzoylpyridine was prepared from nicotinic acid by the method of LaForge.[3]

Pharmacological Properties.—The isomeric phenylpiperidyl carbinols are being studied pharmacologically by Messrs. Edward E. Swanson and Charles L. Rose of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. They have reported that each of these carbinols has the same pharmacological properties as ephedrine, but is somewhat less active. The details of this pharmacological investigation will be published by them elsewhere.

Experimental

All melting points and boiling points herein given are corrected.

The 2- and 4-benzyl- and benzoylpyridines were prepared by a modification and, it is believed, an improvement of the methods which have been described by Tschitschibabin[4] and LaForge[3] for these compounds. Since specific directions were not found in the available literature, the procedures which proved most satisfactory are given below in considerable detail.

2-Benzylpyridine.—A mixture of 300 g. of benzyl chloride, 200 g. of dry pyridine and 3 g. of powdered copper was placed in a 2-liter flask fitted with a reflux water condenser and thermometer dipping into the contents of the flask. The mixture was slowly heated to 70°, after which the heat of the reaction caused the temperature to continue to rise to about 115°, when the liquid began to boil. At the first indication of boiling, the flask was surrounded by an ice-bath and cooled for three to five minutes until the violent reaction was over. The water condenser was then replaced by an air reflux condenser and the flask contents heated rapidly in an oil-bath to 225–230°, then slowly to 240–245°. A small amount of liquid distilling out of the top of the flask was discarded. The temperature was held at 240–245° for three hours, after which time the reaction

[3] LaForge, THIS JOURNAL, **50**, 2484 (1928).

[4] Tschitschibabin, *Chem. Centr.*, **72**, II, 127 (1901); **73**, I, 206 (1902); **87**, II, 146 (1916).

mixture was cooled to 75–100°, poured into 750 cc. of warm water which contained 50 cc. of concd. hydrochloric acid and chilled in an ice-bath. The black solution was poured off from a small amount of tar, made alkaline with sodium hydroxide, extracted with benzene, and the benzene solution dried over potassium hydroxide. After evaporation of the solvent, the material was distilled, giving about 175 g. of crude benzylpyridines boiling between 260 and 310°, together with some higher-boiling material which was discarded. The 260–310° fraction was carefully fractionally distilled at atmospheric pressure through a 6-inch Vigreaux column sealed onto a flask. After three fractionations, the following fractions were obtained

279–282°.....65–75 g.	285–288°.....17–23 g.
282–285°.....28–31 g.	288–299°.....12–20 g.

The fractions boiling between 282 and 299° were used in the preparation of 4-benzoylpyridine (see below).

Fifty grams of the 279–282° fraction was added to a solution of 105 g. of picric acid in 3 liters of alcohol and refluxed for thirty minutes. The solution was then quickly cooled to about 32° in an ice-bath with stirring and the impure 2-benzylpyridine picrate which precipitated quickly filtered off. This crude picrate was dissolved in 3 liters of hot alcohol, cooled in an ice-bath with stirring to about 32° and again rapidly filtered. A second recrystallization from the same quantity of alcohol, but cooled to 20° before filtering, yielded 57–59 g. of pure 2-benzylpyridine picrate, m. p. 139.5–140.5°. If the relative amount of alcohol used in recrystallization was decreased or the solutions cooled to lower temperatures than indicated, additional recrystallizations were found to be necessary.

A suspension of 40 g. of 2-benzylpyridine picrate in about 1 liter of hot water was made strongly alkaline with ammonium hydroxide. The 2-benzylpyridine separated as an oil and, after cooling to 40°, was extracted with benzene. After drying over potash, the benzene was distilled off, leaving 16 g. of 2-benzylpyridine which boiled at 276.8–277.2° (737 mm.).

2-Benzoylpyridine.—Eighty-eight grams of 2-benzylpyridine was suspended in about 2 liters of water contained in a 3-necked flask fitted with reflux condenser, mechanical stirrer and thermometer which dipped below the surface of the liquid. To this suspension 115.5 g. of potassium permanganate was added in five or six portions, each portion being added only after the preceding one was practically decolorized. The temperature was held at 70° until after addition of the last portion of the oxidizing agent, and then raised to 100° until all the permanganate had reacted. After cooling, the liquid was layered over with benzene, stirred vigorously and the benzene solution of 2-benzoylpyridine drawn off, dried over potassium hydroxide and the solvent evaporated. The residue on distillation yielded 85–89.5 g. of 2-benzoylpyridine that boiled at 170–172° (10 mm.).[5]

This 2-benzoylpyridine gave a picrate from alcoholic solution that melted at 121–123°. After two recrystallizations from alcohol, the melting point of this picrate was 122–123°. Tschitschibabin[4] reports the melting point of this particular picrate as 130°. Further recrystallization, however, did not change the melting point. The purity of the compound obtained in the present work was checked by preparing some 2-benzoylpyridine from pure picolinic acid by the procedure described below for the preparation of 3-benzoylpyridine from nicotinic acid. The 2-benzoylpyridine so obtained gave a picrate which also melted at 122–123° and a mixture of the picrates prepared by the two methods melted at the same temperature.

2-Benzoylpyridine Hydrochloride.—When 2-benzoylpyridine was dissolved in

[5] *Cf.* Wolffenstein and Hartwich, *Ber.*, **48**, 2043 (1915).

ether and dry hydrogen chloride passed in, a liquid hydrochloride separated that was difficult to crystallize. After solution in acetone and evaporation under diminished pressure to remove excess hydrochloric acid, the thick liquid was allowed to stand for three weeks, when about half had crystallized. One recrystallization from anhydrous acetone gave a white, crystalline hydrochloride, m. p. 126–128°.

Anal. Subs., 0.4567, 0.3917: AgCl, 0.2987, 0.2563. Calcd. for $C_{12}H_{10}ONCl$: Cl, 16.15. Found: Cl, 16.18, 16.19.

4-Benzoylpyridine.—The fractions of the benzylpyridine boiling between 282 and 299° were oxidized with potassium permanganate in a similar manner to that described above in the preparation of 2-benzoylpyridine. The crude 4-benzoylpyridine was added to a solution of double its weight of picric acid in sufficient alcohol to retain the picrate in solution at the boiling point. On cooling, nearly pure 4-benzoylpyridine picrate separated. One to two recrystallizations from the minimum quantity of boiling alcohol necessary for solution gave pure 4-benzoylpyridine picrate which melted at 159–160°. This picrate was decomposed as in the case of the 2-benzylpyridine picrate, yielding 4-benzoylpyridine, b. p. 313.5–314° (742 mm.), which solidified immediately to a white solid that melted without recrystallization, at 71.5–72.5°. In one run the three higher-boiling fractions of crude benzylpyridines were oxidized and purified separately, the yields of 4-benzoylpyridine being

75 g. of the 282–285° fraction gave 22.5 g. of 4-benzoylpyridine
38.5 g. of the 285–288° fraction gave 17.0 g. of 4-benzoylpyridine
31.5 g. of the 288–299° fraction gave 15.6 g. of 4-benzoylpyridine

In other runs the three fractions were combined before oxidation and there was obtained 32–33 g. of 4-benzoylpyridine for each 100 g. of material boiling between 282–299°.

4-Benzoylpyridine Hydrochloride.—Dry hydrogen chloride was passed into a solution of 10 g. of 4-benzoylpyridine in 250 cc. ether. The white, crystalline hydrochloride was recrystallized once from alcohol–ether, yielding 10 g. of the hydrochloride, m. p. 195–197°.

Anal. Subs., 0.5494, 0.7821: AgCl, 0.3575, 0.5097. Calcd. for $C_{12}H_{10}ONCl$: Cl, 16.15. Found: Cl, 16.10, 16.12.

3-Benzoylpyridine was made by the method given by LaForge.[3] The only variation from his procedure was that the 3-benzoylpyridine was purified as the hydrochloride instead of as the picrate. The purified hydrochloride melted at 160–162°.

Anal. Subs., 0.3581, 0.4013: AgCl, 0.2321, 0.2598. Calcd. for $C_{12}H_{10}ONCl$: Cl, 16.15. Found: Cl, 16.03, 16.01.

Phenyl-2-piperidylcarbinol.—The 2-benzoylpyridine is very weakly basic and a solution of its hydrochloride in water appears cloudy due to hydrolysis. On attempting to reduce a solution of the hydrochloride in water with platinum-oxide platinum black catalyst which had previously been reduced in water, the catalyst collected in small clumps and no hydrogen was absorbed. The addition of a 75% excess of hydrochloric acid would usually cause the catalyst to whip up into suspension and reduction then proceeded normally. To determine the optimum conditions for reduction in hydrochloric acid solution, the following experiments were made. In each case 0.100 g. of platinum-oxide catalyst was placed in 10 cc. of water and shaken with hydrogen until the brown oxide was reduced to black platinum. Then 5 g. of 2-benzoylpyridine, together with the indicated excess of hydrochloric acid was added, with enough water to make the total volume given in the table. Each sample of catalyst was taken from the same lot of freshly prepared catalyst, and the same initial hydrogen pressure (41 lb.) was used in each case. The results that were obtained are shown in Table I.

TABLE I

THE REDUCTION OF 2-BENZOYLPYRIDINE WITH VARYING AMOUNTS OF HYDROCHLORIC ACID

Excess of hydrochloric acid, %	Total volume of solution, cc.	Time of reduction, hours
10	45	13
10	75	No reduction
25	75	7.5
50	75	5.5
75	75	5
100	75	4
125	75	4
150	75	11.5

It is seen from the above data that 100–125% excess of hydrochloric acid over that necessary to form the hydrochloride is the optimum amount of acid for the reduction of this concentration of 2-benzoylpyridine. It is also apparent from the first two runs that a dilution from 45 cc. to 75 cc. of the benzoylpyridine hydrochloride solution containing a 10% excess of hydrochloric acid causes sufficient hydrolysis of the hydrochloride to the free base to prevent the reduction. In this connection it may be of interest to point out that Craig and Hixon[6] found that pyrrole could be more efficiently reduced to pyrrolidine in the presence of an excess of hydrochloric acid.

The two diastereoisomeric phenyl-2-piperidylcarbinols designated as A and B were separated as follows: 10 g. of 2-benzoylpyridine was reduced in 100% excess of hydrochloric acid, the catalyst filtered off and the water removed by evaporation under diminished pressure. The residual hydrochloride was recrystallized by dissolving in 5 cc. of absolute alcohol for each gram of hydrochloride and precipitating with 6 cc. of dry ether for each cc. of alcohol used. Four such recrystallizations gave 4.04 g. of the hydrochloride of A, m. p. 200–202°. On dissolving in a small amount of water and making alkaline with sodium hydroxide, 3.26 g. of the free base was obtained. One recrystallization from water containing 4% of alcohol gave 2.5 g. of A, m. p. 141–142°.

Anal. Subs., 0.2377, 0.2000: CO_2, 0.6544, 0.5514: H_2O, 0.1921, 0.1617. Calcd. for $C_{12}H_{17}ON$: C, 75.39; H, 8.90. Found: C, 75.08, 75.19; H, 8.98, 8.98. 0.6119 g. (1 mol) of this carbinol reacted with 0.6555 g. (2.01 mols) of acetic anhydride.[7]

The alcohol–ether filtrate from the first recrystallization of the hydrochloride of A contains most of the hydrochloride of B, the latter of which is the more soluble. On evaporation of the solvent and conversion to the free base, there remained 3.75 g. of base. After three recrystallizations of the free base from the minimum quantity of water containing 4% of alcohol, 0.81 g. of B, m. p. 171–173°, was obtained.

Anal. Subs., 0.2210, 0.2098: CO_2, 0.6086, 0.5805: H_2O, 0.1808, 0.1700. Calcd. for $C_{12}H_{17}ON$: C, 75.39; H, 8.90. Found: C, 75.10, 75.46; H, 9.09, 9.00. 0.4865 g. (1 mol) of the carbinol reacted with 0.4899 g. (1.89 mols) of acetic anhydride.

Evaporation of all filtrates from the purification of A and B and conversion to the free base gave 4.5 g., from which an additional quantity of A and B could be recovered by a repetition of the above method of separation.

Conversion of A into B.—One-half gram of A was heated at 100° for forty-eight

[6] Craig and Hixon, THIS JOURNAL, **52**, 804 (1930).

[7] The carbinol and a 3- to 4-fold excess of acetic anhydride contained in a sealed tube were heated overnight on a steam-bath, then dissolved in water and the excess acetic acid titrated with standard potassium hydroxide.

hours in 5 cc. of 25% hydrochloric acid. The solvent was removed under diminished pressure and the hydrochloride converted to the free base with sodium hydroxide. After three recrystallizations from water containing 4% of alcohol, there remained 0.032 g. of the B isomer that melted at 171–173°.

Phenyl-3-piperidylcarbinol Hydrochloride.—Ten grams 3-benzoylpyridine hydrochloride was reduced in aqueous solution with 0.5 g. of platinum-oxide platinum black catalyst. The reduction required fifteen hours for completion. After filtering off the catalyst and removing water under diminished pressure, the hydrochloride was purified by recrystallization from an alcohol–ether mixture. After five recrystallizations, 3 g. of product, m. p. 190–192°, was obtained.

Anal. Subs., 0.3558, 0.4267: AgCl, 0.2241, 0.2680. Subs., 0.2715: CO_2, 0.6338; H_2O, 0.1805. Calcd. for $C_{12}H_{18}ONCl$: Cl, 15.58; C, 63.30; H, 7.91. Found: Cl, 15.58, 15.54; C, 63.67; H, 7.56.

Phenyl-4-piperidylcarbinol Hydrochloride.—A solution of 10 g. of 4-benzoylpyridine hydrochloride in water absorbed the theoretical quantity of hydrogen in five hours when shaken with 0.5 g. of catalyst. After removal of solvent and one recrystallization from an alcohol–ether mixture, 10.2 g. of phenyl-4-piperidylcarbinol was obtained; m. p. 191–193°.

Anal. Subs., 0.2821, 0.3207: AgCl, 0.1768, 0.2016. Calcd. for $C_{12}H_{18}ONCl$: Cl, 15.58. Found: Cl, 15.50, 15.55.

Phenyl-4-piperidylcarbinol.—Ten grams of phenyl-4-piperidylcarbinol hydrochloride on conversion to the free base gave, after one recrystallization from water containing 4% of alcohol, 6.4 g. of the free base, m. p. 166–167°.

Anal. Subs., 0.2469, 0.2150: CO_2, 0.6805, 0.5936: H_2O, 0.2005, 0.1736. Calcd. for $C_{12}H_{17}ON$: C, 75.39; H, 8.90. Found: C, 75.17, 75.30; H, 9.02, 8.97. 0.9545 g. (1 mol) of the carbinol reacted with 1.004 g. (1.97 mols) of acetic anhydride.

Summary

1. The isomeric phenylpiperidylcarbinols have been prepared and described. In the case of the phenyl-2-piperidylcarbinol the two diastereoisomers have been isolated.

2. These carbinols have structures analogous to ephedrine and it has been found that although they are somewhat less active they all possess the same pharmacological properties as this important drug.

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