[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

A Synthesis of 3-Phenylpiperidines

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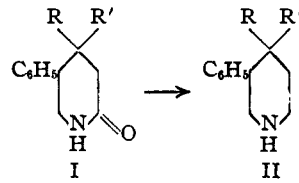
Compounds of marked physiological activity are common among substances derived from β-phenylethylamine. Most of the simple derivatives are sympathomimetic, but the β-arylethylamine nucleus may be discerned in alkaloids having widely varied types of activity. A considerable physiological activity is likewise a property of certain derivatives of piperidine. It therefore appeared worth while to prepare for pharmacological testing a group of substances derived from 3-phenylpiperidine, a compound in which both pharmacogenic nuclei are combined.

The present paper reports a general method for the preparation of substituted 3-phenylpiperidines and describes the synthesis of several members of this hitherto almost unknown class of compounds.[1]

The steps in the synthesis consist of (1) a Michael reaction, (2) a catalytic reduction,[2] and (3) a reduction with sodium and butyl alcohol.[3]

$$C_6H_5CH_2CN + RR'C{=}CHCOOC_2H_5 \longrightarrow C_6H_5CH(CN)CRR'CH_2COOC_2H_5 \longrightarrow$$



I II

It is noteworthy that the reduction of the cyano group (step 2) is accompanied by the formation of practically no secondary amine. Apparently, the primary amine first formed undergoes intramolecular reaction with the ester group so rapidly that it cannot react with the unreduced nitrile still present.

Similar reductions have been described in which γ-lactams are formed, for example, the reduction of ethyl β-cyano-β-phenylpyruvate to 1,2-diketo-3-phenylpyrrolidine,[4] of ethyl β-cyanopropionate to pyrrolidone, and of ethyl β-cyano-β-phenylpropionate to 4-phenylpyrrolidone.[5] However, the formation of a δ-lactam in an analogous way has not been reported previously.[6]

The present work suggested that the formation of secondary amines in the catalytic reduction of nitriles might be avoided by the use of esters as solvents, but experiments have shown that such is not the case.

Piperidones and piperidines (formulas I and II) in which R and R′ are H, H; CH_3, H; CH_3 CH_3; C_6H_5, H; and $COOC_2H_5$, H have been prepared. Those in which R and R′ are different have been isolated in stereoisomeric forms; in all cases the higher melting piperidone and the piperidine obtained from it have been designated as α-forms, the corresponding isomers as β-forms. Studies are now in progress which may lead to the assignment of the proper configuration to each substance.

Before the synthesis described above was developed, a number of others were investigated. None of these was successful, but some of the negative results are worthy of note. γ-Phenylbutyrolactone was recovered unchanged after it had been heated at 250° with potassium cyanide; this was unexpected in view of the reaction of γ-valerolactone and the especially smooth reaction of phthalide[7] with potassium cyanide. No reaction took place between hydrocyanic acid and aqueous sodium β-benzoylpropionate or between hydrocyanic acid and alcoholic ethyl β-benzoylpropionate.[8] Ethyl formylphenylacetate reacted with ethyl β-aminocrotonate, but no pure substance could be isolated from the oily product; analogy with the formation of 4-hydroxy-3-phenylquinoline from the anil of ethyl formylphenylacetate[9] suggested that ethyl 4-hydroxy-2-methyl-5-phenylnicotinate might be formed in the present experiment. α-Phenyl- and α,β-diphenylglutaronitriles yielded no simple piperidines on catalytic reduction, and it was evident that intermolecular reaction had taken place.

Experimental

5-Phenylpiperidone-2.—The reduction of methyl γ-cyano-γ-phenylbutyrate[10] (31.5 g.) in 20 ml. of ethanol containing 1 g. of Raney nickel, with hydrogen at about 200 atm. and at 150° was complete after forty-five minutes. The catalyst was removed by filtration, and the lactam was isolated by distillation. There was obtained 24.1 g. (88%) of a colorless product that boiled at 225–230° at 20 mm. and solidified in the receiver. Recrystallized from benzene–ligroin it formed flat needles that melted at 127–129°; it was very soluble in alcohol.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.4. Found: C, 75.6; H, 7.1.

3-Phenylpiperidine.—To a solution of 15 g. of 5-phenylpiperidone in 200 ml. of hot *n*-butyl alcohol[11] contained in a 1-liter flask bearing a large-bore condenser was added 20 g. of sodium in one portion. The flask was shaken vigorously at intervals after the initial reaction had moderated, so that the sodium was kept finely divided. This was especially important toward the end of the reaction, when the separated sodium butoxide caused the mixture to become semi-solid. The use of a larger quantity of butyl alcohol was found to affect the yield adversely. When the sodium had dissolved, the mixture was cooled and 40 ml. of water was added cautiously through the con-

(1) The only representative previously described is 3-phenylpiperidine itself [Walters and McElvain, THIS JOURNAL, **55**, 4625 (1933)], and the procedure used for synthesizing this substance is not easily applicable to the preparation of related compounds.

(2) For an attempted piperidine synthesis involving a somewhat similar route, which failed because no satisfactory method of reducing a cyano group was then available, see Wohl and Maag, *Ber.*, **43**, 3280 (1910); *cf.* Rupe and Gisiger, *Helv. Chim. Acta*, **8**, 338 (1925); Rupe and Heckendorn, *ibid.*, **9**, 982 (1926).

(3) Ladenburg, *Ber.*, **20**, 2215 (1887); Wallach, *Ann.*, **324**, 286 (1902).

(4) Rupe and Pieper, *Helv. Chim. Acta*, **12**, 637 (1929).

(5) Winans and Adkins, THIS JOURNAL, **55**, 4167 (1933).

(6) *Cf.*, Rupe and Stern, *Helv. Chim. Acta*, **10**, 859 (1927).

(7) Wislicenus, *Ann.*, **238**, 102 (1886).

(8) Only one form of this ester resulted, whether it was prepared through the silver salt of the acid, or by Fischer esterification.

(9) Wislicenus, *ibid.*, **413**, 248 (1917).

(10) Koelsch, THIS JOURNAL, **65**, 438 (1943).

(11) Numerous experiments indicated that the presence of even small quantities of water in the alcohol caused the yields of piperidines to drop off markedly. Best results were obtained by the use of alcohol which had been fractionated and then treated with sodium butoxide and butyl phthalate.

denser. The mixture was shaken well, and the lower aqueous layer was separated and discarded. The organic layer was acidified with hydrochloric acid, and the butyl alcohol was removed by steam distillation. An excess of sodium hydroxide was added, and the oily amine was separated using ether. Distillation gave 7.8 g. (57%) of a product which boiled at 139–142° at 19 mm. (reported 255–256° at 740 mm.) and melted at 14–15°. The hydrochloride melted at 143–144° (reported 146–147°).

The **benzoyl derivative,** prepared with benzoyl chloride and aqueous sodium hydroxide and crystallized from ether-ligroin, formed colorless prisms that melted at 89–90°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.5; H, 7.2. Found: C, 81.6; H, 7.0.

4-Methyl-5-phenylpiperidone-2.—Ethyl γ-cyano-γ-phenylisovalerate[12] (40 g.) dissolved in ethanol (50 ml.) and reduced (Raney nickel) at 155° gave a mixture from which was isolated 19.7 g. of the α- and 11.8 g. of the β-form of the piperidone. In larger experiments (165 g.) using no solvent and at 165°, reduction was slow (six hours), and there was obtained about 20% of unchanged cyanoester, 33% of the α-, and 35% of the β-form of the piperidone.

The products were isolated by removing the alcohol under reduced pressure and replacing it with toluene, in which the α-isomer was almost insoluble. The easily soluble β-isomer usually crystallized only after all impurities had been removed by vacuum distillation, although it could be precipitated from the undistilled products by careful treatment of the toluene mother liquors with ligroin.

The **α-isomer** separated from alcohol in the form of colorless plates that melted at 210–212°; the **β-isomer** crystallized from benzene–ligroin in the form of small prisms that melted at 89–92°. Both substances boiled at 210–220° at 10 mm.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.2; H, 7.9. Found: (α-form) C, 76.4; H, 8.2; (β-form) C, 76.3; H, 8.0.

4-Methyl-3-phenylpiperidine.—The α-form of 4-methyl-5-phenylpiperidone (15 g.) reduced in 200 ml. of butyl alcohol with 20 g. of sodium gave 11.1 g. (80%) of the corresponding piperidine, a colorless oil that boiled at 143–144° at 22 mm. and crystallized on cooling to 10°. The amine rapidly gained in weight on exposure to air, and concordant analyses were not obtained.

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.2; H, 9.7. Found: C, 81.5, 80.6; H, 9.5, 9.3.

The **hydrochloride** formed small colorless prisms from a mixture of alcohol and ether; m. p. 189–190°.

Anal. Calcd. for $C_{12}H_{18}ClN$: C, 68.1; H, 8.6. Found: C, 68.1; H, 9.1.

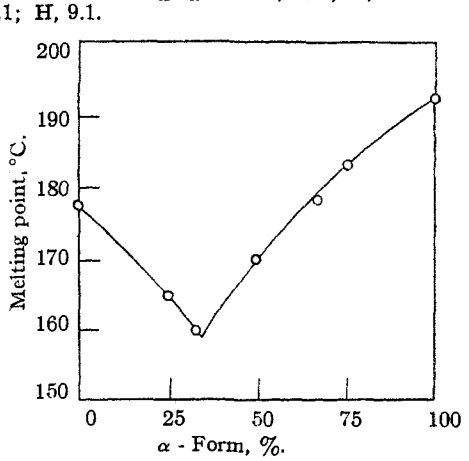


Fig. 1.—Melting points (capillary) of mixtures of the α- and the β- forms of 4,5-diphenylpiperidone-2.

(12) The present experiments indicate that this ester, a liquid previously described,[10] is a mixture.

The **benzoyl derivative,** crystallized from ethanol and then from benzene–ligroin, formed colorless prisms that melted at 129–130°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.7; H, 7.5. Found: C, 81.6; H, 7.7.

The **picrate** (not analyzed) melted at 188–189°.

Reduction of 15 g. of the β-form of 4-methyl-5-phenylpiperidone with 20 g. of sodium in 200 ml. of butyl alcohol gave 10.9 g. (78%) of the **β-form** of 4-methyl-3-phenylpiperidine, b. p. 151–153° at 23 mm., which was a limpid oil even at −10° and which like the α-isomer gained in weight on exposure to the air.

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.2; H, 9.7. Found: C, 81.7; H, 9.8.

The **hydrochloride** was much less soluble in water than was the hydrochloride of the α-isomer. Crystallized from dilute hydrochloric acid, it formed white needles that melted at 250–252°.

Anal. Calcd. for $C_{12}H_{18}ClN$: C, 68.1; H, 8.5. Found: C, 68.0; H, 9.0.

The **benzoyl derivative** crystallized from ether–ligroin in the form of small colorless prisms that melted at 100–101°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.7; H, 7.5. Found: C, 81.6; H, 7.8.

The **picrate** (not analyzed) melted at 217–218.5°.

4,4-Dimethyl-5-phenylpiperidone-2.—Ethyl γ-cyano-β,β-dimethyl-γ-phenylbutyrate[10] was reduced (Raney nickel) in alcohol at 165° and 100 atm. The product, crystallized from benzene–ligroin and then from water containing a little alcohol, formed colorless needles that melted at 167–169°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.4; N, 6.9. Found: C, 76.9; H, 8.3; N, 7.1.

Reduced with sodium and butyl alcohol, the above lactam gave **4,4-dimethyl-3-phenylpiperidine** in good yield. The base was isolated in the form of its hydrochloride, which melted at 274–276°.

Anal. Calcd. for $C_{13}H_{20}NCl$: Cl, 15.7. Found: Cl, 15.8.

The **benzoyl derivative** crystallized from ether–ligroin in the form of fine white needles that melted at 108–110°.

Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.8; H, 7.8; N, 4.8. Found: C, 81.7; H, 7.7; N, 4.9.

4,5-Diphenylpiperidone-2.—The reduction of the higher melting form (100–101°) of ethyl γ-cyano-β,γ-diphenylbutyrate[10] in alcohol with Raney nickel at 165° and 150 atm. gave mainly the α-form of 4,5-diphenylpiperidone-2, and the reduction of the lower melting cyanoester (57–59°) gave mainly the β-form of the piperidone. But in both cases the isomeric piperidone was also formed, indicating that some inversion took place. Therefore, in most experiments the mixture of diastereoisomeric esters obtained by condensing benzyl cyanide with ethyl cinnamate was not separated but was reduced directly. The piperidones were separated by many crystallizations alternately from alcohol and benzene; the α-isomer was much less soluble than the β- in alcohol, and it was nearly insoluble in benzene. Figure 1, constructed using synthetic mixtures of the two piperidones, was used to follow the separations.

The **α-form,** white plates from alcohol or colorless prisms from toluene, melted at 192–194°. The **β-form** separated from benzene in the form of needles that fell to a white powder on drying; it sintered at 174° and melted at 177–178°.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.3; H, 6.8. Found: (α-form) C, 81.4; H, 6.9; (β-form) C, 81.7; H, 6.8.

3,4-Diphenylpiperidine.—The reduction of 12 g. of the α-form of 4,5-diphenylpiperidone-2 in 125 ml. of butyl alcohol with 12.3 g. of sodium gave 9.25 g. (86%) of the pure α-form of 3,4-diphenylpiperidine, and the reduction of 10.7 g. of the β-piperidone gave 8.8 g. (93%) of the β-piperidine. But the separation of the piperidones was very tedious, and it was found much more practical to reduce

the mixed piperidones and to separate the resulting mixed piperidines. The crude mixed piperidines were distilled (b. p. 205–215° at 10 mm.), and the less soluble β-form was largely removed by crystallization from ligroin (90–110°). The solvent was distilled under reduced pressure, and the remaining bases were dissolved in three times their weight of alcohol. The solution was neutralized with concd. aqueous hydrochloric acid and then diluted with four volumes of ether. Scratching caused the separation of the less soluble hydrochloride of the α-piperidine. The hydrochlorides remaining in solution were reconverted to the free bases and the whole process was repeated. The separation could be carried out easily and quantitatively, since the more soluble base gave the less soluble hydrochloride.

The **α-isomer** boiled at 230–240° at 23 mm.; crystallization from dilute alcohol gave white plates that melted at 83–84°.

Anal. Calcd. for $C_{17}H_{19}N$: C, 86.1; H, 8.0. Found: C, 85.7; H, 8.1.

The **hydrochloride** was rather difficultly soluble in cold water, but it separated from this solvent as an unfilterable mass of microscopic plates. From alcohol–ether, it formed white plates that melted below 100° and then resolidified. Dried for three hours at 80° under reduced pressure, it melted at 197–199°; analysis indicated that a small amount of solvent was still retained.

Anal. Calcd. for $C_{17}H_{20}NCl$: C, 74.6; H, 7.3. Found: C, 73.8, 73.7; H, 7.3, 7.1.

The **N-methyl derivative,** obtained by boiling the hydrochloride with twice its weight of 40% formalin for thirty hours, boiled at about 195° at 15 mm. and melted at 79–80° after it had been crystallized from alcohol.

Anal. Calcd. for $C_{18}H_{21}N$: C, 86.0; H, 8.37. Found: C, 86.1; H, 8.14.

The **hydrochloride** of the N-methyl derivative formed fine colorless needles from alcohol–ether that melted at 203–206°.

Anal. Calcd. for $C_{18}H_{22}ClN$: C, 75.1; H, 7.65. Found: C, 75.0; H, 7.62.

The **N-benzoyl derivative** formed colorless needles that melted at 138–139° after it had been crystallized from dilute alcohol.

Anal. Calcd. for $C_{24}H_{23}NO$: C, 84.5; H, 6.8. Found: C, 84.2; H, 6.9.

The β-form of 3,4-diphenylpiperidine melted at 115–116° after it had been crystallized from alcohol.

Anal. Calcd. for $C_{17}H_{19}N$: C, 86.1; H, 8.0. Found: C, 85.8; H, 8.1.

The hydrochloride was an oil, difficultly soluble in water but easily soluble in alcohol–ether. The **nitrate** crystallized from water in the form of colorless needles that melted completely in a bath at 150°, then resolidified and melted again at 160–164°. Dried under reduced pressure at 132°, the salt melted at 165–166°.

Anal. Calcd. for $C_{17}H_{18}N + HNO_3$: C, 68.0; H, 6.7. Found: C, 68.1; H, 6.7.

The **N-methyl derivative,** obtained by heating a mixture of the nitrate with twice its weight of formalin in an oil-bath at 100° for twenty-four hours, boiled at 200–210° at 15 mm. and solidified on long standing. It melted at 54–57°.

Anal. Calcd. for $C_{18}H_{21}N$: C, 86.0; H, 8.3. Found: C, 85.6; H, 8.0.

The hydrochloride and the nitrate of the N-methyl derivative were both oils, difficultly soluble in water.

The **N-benzoyl derivative** formed colorless prisms that melted at 159–160°.

Anal. Calcd. for $C_{24}H_{23}NO$: C, 84.5; H, 6.8. Found: C, 84.7; H, 6.9.

4-Carbethoxy-5-phenylpiperidone-2.—The reduction (Raney nickel) of ethyl β-carbethoxy-γ-cyano-γ-phenylbutyrate[10] (285 g.) in 250 ml. of alcohol at 165° gave a mixture of the two isomeric piperidones. Most (85 g.) of the α-isomer separated directly from the reduction mixture when it was cooled; an additional quantity (32 g.) was obtained by distilling the solvent under reduced pressure and replacing it with benzene and ligroin. After it had been recrystallized from alcohol, the **α-isomer** melted at 162–163° and distilled at 244° at 9 mm.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9. Found: C, 67.8; H, 7.0.

The **β-isomer** (32 g.) was isolated from the mother liquors by distillation (b. p. 210–250° at 2 mm.) followed by crystallization from ether; it formed colorless needles that melted at 74–77°.[13]

3-Phenylisonipecotic Acid.—The α-form of 4-carbethoxy-5-phenylpiperidone-2 (30 g.) in 250 ml. of butyl alcohol was reduced with 25 g. of sodium. Then 60 ml. of water was added, and the aqueous layer, which was found to contain no organic material, was separated. The butyl alcohol was removed with steam, and the residual aqueous solution was diluted to 100 ml. and brought to *p*H 4.5 by adding acetic acid. The precipitated amino acid was removed, and the mother liquor was concentrated to one-half its volume, giving a second crop (2.5 g.) of the same amino acid.[14] The product did not melt, but sublimed about 360° with slight decomposition; it was readily soluble in dilute hydrochloric acid and in dilute sodium carbonate. For analysis it was sublimed at 25 mm. and boiled out with alcohol, in which it was difficultly soluble.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.3; H, 7.3. Found: C, 70.0; H, 7.4.

The **methyl ester,** prepared by Fischer esterification, crystallized from water in the form of cotton-like needles that melted at 62–63°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8. Found: C, 71.1; H, 7.6.

The **methyl ester hydrochloride,** slightly pink needles from methanol, melted at 253–255° with gas evolution.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.2; H, 7.1. Found: C, 61.3; H, 7.0.

The author thanks Mr. E. E. Renfrew for carrying out most of the analyses reported in this paper.

Summary

Intermolecular condensation with the formation of secondary amines does not occur when γ-cyanoesters are reduced; instead, piperidones are formed.

This reaction has been made the basis of a new piperidine synthesis, illustrated in the present paper by the preparation of several derivatives of 3-phenylpiperidine.

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(13) A detailed study of this substance and the related piperidine, and a proof that the compounds do not contain a five-membered ring will be reported in a forthcoming paper with Dr. E. J. Prill.

(14) The mother liquor still contained 3-phenylpiperidyl-4-methanol. This base,[13] isolated by salting out with solid sodium hydroxide and extracting with ether, was distilled (b. p. 215–218° at 24 mm.) and then crystallized from ether; yield, 4.3 g. It sintered at 98° and melted at 110°. $C_{13}H_{17}NO$ required C, 75.4; H, 8.9. Found: C, 74.4; H, 9.0.