diphenylpteridine have been prepared for the purpose of finding a soluble derivative which would retain a high degree of antifolic acid activity.

The absorption spectra of these compounds in solution, some of their solubility characteristics and their inhibitory indices against *S. faecalis* are reported.

2. It has been found that a sulfinomethylamino group confers water solubility with the retention of antifolic acid activity. The introduction into the 2,4-diamino-6,7-diphenylpteridine molecule of any of the solubilizing groups investigated results in some lowering of antifolic acid activity.

3. Several conclusions have been drawn regarding the effect on antifolic acid activity of certain structural changes in the 2,4-diamino-6,7-diphenylpteridine molecule.

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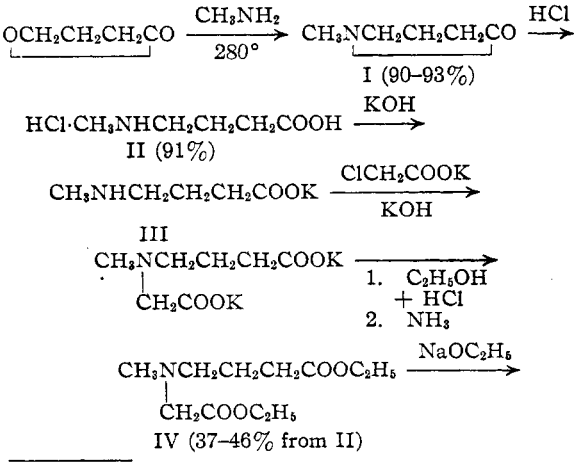
[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

# Piperidine Derivatives. XX. The Preparation and Reactions of 1-Methyl-3-piperidone

By S. M. McElvain and John F. Vozza

The recent report[1] on the reactions of 1-methyl-4-piperidone, particularly those with a variety of aromatic aldehydes, indicated a study of similar reactions with the unsymmetrical isomer, 1-methyl-3-piperidone (VI). The preparation of this latter compound from 1-methyl-4-carbethoxy-3-piperidone (V), obtained by the cyclization of the diester (IV) was reported earlier[2] from this Laboratory. It seemed of special interest to determine the reactivity of VI in the presence of basic catalysts inasmuch as the previous workers[2] had shown that, due to the relative inertness of the $\alpha$-aminomethylene group, the cyclization of IV produced the keto-ester V rather than the isomer, 1-methyl-2-carbethoxy-3-piperidone.

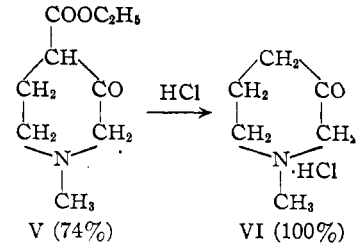
In the earlier work[2] the diester IV was prepared by the interaction of ethyl $\gamma$-bromobutyrate with sarcosine ester. In the present work a more satisfactory preparation of IV has been developed from butyrolactone, which is now commercially available.[3] The complete series of reactions from this lactone to the piperidone VI is




(1) McElvain and Rorig, This Journal, **70**, 1820 (1948).

(2) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

(3) From the Cliffs Dow Chemical Company, Marquette, Michigan.



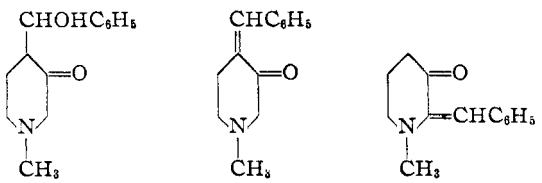

V (74%) VI (100%)

The sequence from II to IV was found necessary, as it was not possible to obtain an ester of II; all attempts to prepare the ester gave the pyrrolidone (I). The amino-acid, however, is quite stable in the form of its salts II and III. The cyclization of IV was found to proceed most satisfactorily with sodium ethoxide; sodium hydride, which produced excellent yields of 1-methyl-3-carbethoxy-4-piperidone,[1] gave very poor yields (*ca.* 10%) of V.

The condensation of benzaldehyde with VI in alkaline, 60% ethanol was rapid and a crystalline product, which gave analytical values approximating an equimolecular mixture of the 4-carbinol (VII) and the 4-benzal derivative (VIII), was obtained in approximately 70% yield. No other products could be separated from this reaction. This mixture of VII and VIII could not be separated by recrystallization; a product with a constant melting range, 123–128°, was obtained. However, when this material was converted to the hydrochloride salts, the free bases liberated into ether, and the resulting solution concentrated, the benzal derivative VIII, m. p. 112–113°, separated. From the ether filtrate the carbinol VII was obtained as a glass, which gave a crystalline hydrochloride that melted at 192–202°, indicating that it was a mixture of the two possible racemates. Two other observations are worthy of note: (a) an ethereal solution of the carbinol VII containing a small amount of the benzal derivative (VIII) gave, on standing, a crystalline precipitate, m. p. 123–128°, and (b) this latter product also separated from an alkaline 60% ethanol solution of VII on

standing. These results lead to the conclusion that this reaction product is a molecular complex of VII and VIII, which is destroyed when the components are converted to their hydrochlorides, and which forms sufficiently slowly to permit separation of the components immediately after their liberation from the non-associated salts.

Both VII and VIII show a similar instability (as indicated by rapid darkening) to light and air as has been noted[2] for the free base of VI. The structures of VII and VIII were shown by their reduction to 1-methyl-4-benzylpiperidine, derivatives of which were compared to those obtained from an authentic sample prepared from 4-benzylpyridine.




VII VIII IX

The carbinols VII are as resistant to dehydration as are those obtained from 1-methyl-4-piperidone.[1] The 4-benzal derivative (VIII), however, is readily hydrated to VII, treatment of a moist ethereal solution of VIII with hydrogen chloride being sufficient to effect the reaction. This peculiar reactivity of the benzal linkage of VIII was noticeable in its hydrogenation: in alcohol solution it absorbed hydrogen very slowly and incompletely, while in dioxane solution it was rapidly, but incompletely, hydrogenated, possibly because of a complex formation between a hydroxylic reduction product and unchanged VIII.

The condensation of benzaldehyde with VI in an ethanolic solution of hydrogen chloride was much slower than the base catalyzed reaction. The dark-colored reaction product was readily recrystallized to colorless crystals, m. p. 165–166°, the analyses of which were corresponded to a monobenzal derivative of VI. This purified material was obtained in 43% yield, and no other product could be isolated from the reaction mixture. In spite of the narrow melting range of this salt it was shown to be a mixture of the hydrochlorides of VIII and the isomeric 2-benzal derivative IX by the following reactions: (a) conversion of the salt to the free base produced a pale-yellow oil that could not be induced to crystallize (VIII melts at 112–113°), but was reconverted to the original hydrochloride mixture, m. p. 164–165°, by hydrogen chloride; (b) reduction failed to give a single 1-methyl-benzylpiperidine, but a product, the methiodide of which had properties similar to a mixture of the methiodides of 1-methyl-2- and 1-methyl-4-benzylpiperidines; (c) the picrate of the reduction product behaved as a mixture of authentic picrates of 1-methyl-2- and -4-benzylpiperidines that contained a higher proportion of the 4-isomer.

The exclusive formation of the 4-derivatives of 1-methyl-3-piperidone with an alkaline catalyst indicates that the reactivity of the 2-methylene group is inhibited by the attached basic nitrogen as is the acetic ester–methylene group[2] of IV in the Dieckmann cyclization. In acid medium, however, some of the 2-derivative (IX) is formed, which indicates that a positive charge on the nitrogen of the piperidone promotes reaction at the 2-position. It is also of interest to note that none of the dibenzal derivative, which was the main or exclusive product with 1-methyl-4-piperidone,[1] could not be isolated from any of the reactions of benzaldehyde with VI.

It also seemed of interest to determine the behavior of the 3-piperidone toward such a Grignard reagent as phenylmagnesium bromide. With this reagent, the isomeric 1-methyl-2-piperidone is reported[4] to yield the dehydration product, 1-methyl-2-phenyl-1,4,5,6-tetrahydropyridine, of the expected tertiary carbinol when the initial Grignard reaction product is decomposed with acids. Under these conditions, however, the 1-methyl-4-phenyl-4-hydroxypiperidine may be obtained from the 4-piperidone.[5] The 3-piperidone (VI) behaves as does its 4-isomer with phenylmagnesium bromide. The carbinol, 1-methyl-3-phenyl-3-hydroxypiperidine, was obtained in 59% yield as a viscous oil, which, because of its sensitivity to air, was analyzed in the form of the methiodide. The hydrochloride of this compound was readily acetylated to the corresponding 3-acetoxy derivative.

## Experimental

**1-Methyl-2-pyrrolidone (I).**—A steel bomb containing 172 g. (2 moles) of butyrolactone[3] was placed in a bath of acetone and Dry Ice. After the bomb and its contents were thoroughly cooled, 124 g. (4 moles) of liquid methylamine was added, the bomb closed and heated at 280° for four hours. After removing the excess methylamine with the aspirator, the reaction mixture was distilled, yielding 175–185 g. (90–93%) of 1-methyl-2-pyrrolidone,[6] b. p. 201–202°.

The hydrochloride of I, precipitated from ether with hydrogen chloride and recrystallized from absolute ethanol,[2] melted at 86–88°.

**γ-N-Methylaminobutyric Acid Hydrochloride (II).**—A solution containing 179 g. (1.8 moles) of 1-methyl-2-pyrrolidone and 250 ml. of concentrated hydrochloric acid was refluxed in an oil-bath for eight hours. The water and excess acid then were removed at diminished pressure on the steam-bath. The solid residue was shaken with 250 ml. of cold, dry acetone, which does not dissolve the amino-acid hydrochloride but facilitates its subsequent crystallization from ethanol. Crystallization from ethanol yielded 250 g. (90%) of colorless crystals, m. p. 120–121°.[7]

Several attempts to esterify the secondary amino-acid hydrochloride (II) by heating it in the presence of ethanolic hydrogen chloride failed to yield the desired ester. Also various attempts to form the N-benzoyl derivative of II by the Schotten–Baumann reaction and modified versions of this general procedure failed to give the desired produc..

(4) Lee, Ziering, Heineman and Berger, *J. Org. Chem.*, **12**, 885 (1947).

(5) Jensen and Lundquist, *Dansk. Tidsskr. Farm.*, **17**, 173 (1943), *C. A.*, **40**, 4086 (1946).

(6) Späth and Lintner, *Ber.*, **69**, 2727 (1936).

(7) Gansser, *Z. physiol. Chem.*, **61**, 59 (1909).

Table I

1-Methyl-2-benzylpiperidine (A), 1-Methyl-4-benzylpiperidine (B) and Derivatives

| Compound | B. p., °C. (mm.) | M. p., °C. | Formula | Analyses, % Calcd. C | Calcd. H | Calcd. I | Found C | Found H | Found I |
|---|---|---|---|---|---|---|---|---|---|
| A | 128–129 (13)[a,b,c] | ..... | ..... | ... | .. | .. | ... | .. | .. |
| Picrate of A | ..... | 180–181[b,c] | ..... | ... | .. | .. | ... | .. | .. |
| Methiodide of A | ..... | 225–226[d] | $C_{14}H_{22}IN$ | 50.75 | 6.65 | 38.4 | 50.65 | 6.52 | 38.1 |
| Hydriodide of A | ..... | 120–121 | $C_{13}H_{20}IN$ | ... | .. | 40.1 | ... | .. | 40.0 |
| B | 125–126 (7) | ..... | ..... | ... | .. | .. | ... | .. | .. |
| Picrate of B | ..... | 184–186 | $C_{19}H_{22}N_4O_7$ | 54.54 | 5.26 | .. | 54.24 | 5.46 | .. |
| Methiodide of B | ..... | 206–207 | $C_{14}H_{22}IN$ | 50.75 | 6.65 | 38.4 | 50.86 | 6.54 | 38.0 |
| Hydriodide of B | ..... | 128–129 | $C_{13}H_{20}IN$ | ... | .. | 40.1 | ... | .. | 40.2 |

[a] Anker, Cook and Heilbron, *J. Chem. Soc.*, 917 (1945). [b] Ref. 4. [c] Bryans and Pyman, *J. Chem. Soc.*, 549 (1929). [d] This compound was obtained also when an ethereal solution of 2-benzylpiperidine was treated with methyl iodide. Anker, *et al.*,[a] p. 918, report a similar product, but state that they obtained 1-methyl-2-benzylpiperidine (A) from it on treatment with sodium hydroxide. This is obviously an error, as the methiodide, m. p. 226°, is not converted to A by alkali as is the hydroiodide, m. p. 120–121°.

**Ethyl γ-(Methyl-N-carbethoxymethylamino)-butyrate (IV).**—To a 5-l. three-necked flask, equipped with a dropping funnel and mechanical stirrer and immersed in an ice–salt-bath, was added a solution of 358 g. (6.4 moles) of potassium hydroxide in 200 ml. of water. When the alkaline solution had cooled to 0°, a solution of 246 g. (1.6 moles) of II in 800 ml. of absolute ethanol was added slowly, and the temperature of the stirred mixture kept below 12°. A solution of 154 g. (1.6 moles) of monochloroacetic acid in 200 ml. of absolute ethanol then was added at such a rate that the temperature of the reaction mixture did not rise above 12°. The contents of the flask was allowed to warm slowly to room temperature as the ice melted, and stirring was continued for forty-eight hours. The reaction mixture then was made distinctly acid to congo red with hydrochloric acid and filtered to remove the potassium chloride that had separated from solution. The filtrate was taken to dryness under reduced pressure on the steam-bath, leaving a clear, light-brown, semi-solid material. This was dissolved in 500 ml. of absolute ethanol, and the solution was added to 1800 ml. of absolute ethanol that had been saturated with hydrogen chloride. The mixture was shaken vigorously and allowed to stand at room temperature for two days, after which it was refluxed on the steam-bath for *only* two hours, as it was found that a longer period of heating was unfavorable to the yield. After the reflux period, the alcohol and excess hydrogen chloride were removed under reduced pressure on the steam-bath until only a thick viscous mass remained in the flask. The flask and its contents then were cooled in an ice-bath and 200 ml. of ether added, after which a solution of liquid ammonia in ether was added slowly until a strong odor of ammonia persisted. Each addition of ammonia was accompanied by vigorous stirring and agitation in order to bring about intimate contact between the ether layer and the more dense lower layer. The liberation of IV was accompanied by the precipitation of ammonium chloride. After an excess of ammonia had been added, the liquid was decanted from the precipitated solid and the latter extracted with three 100-ml. portions of ether; it was necessary to centrifuge the ether–salt suspension to separate the ether in the last extraction. After removing the ether and residual alcohol, the product was distilled through a Vigreux column under reduced pressure. The forerun, principally 1-methyl-2-pyrrolidone (I), was collected up to 131° (10 mm.); it amounted to about 25% of the starting salt (II). The diester (IV) was collected at 133–137° (10 mm.); $n^{25}D$ 1.4380, and weighed 135 g. The residue in the flask was dissolved in ethanol and treated with excess hydrogen chloride. After separating a small amount of ammonium chloride, a white crystalline material was recovered from the ethanol solution. This material was found to be the hydrochloride of a half-ester of the dibasic acid of IV. Its melting point, 121–122°, was similar to that of II (120–121°), but a mixture of equal parts of these two salts melted at 92–103°.

*Anal.* Calcd. for $C_9H_{18}ClNO_4$: Cl, 14.8; N, 5.8. Found: Cl, 14.6; N, 5.2.

By re-esterifying this half-ester hydrochloride and processing the esterification mixture according to the procedure described above, an additional 35 g. of IV was obtained. The total amount, 170 g., represents a 46% yield.

The ethereal solution of ammonia was used to liberate IV from its hydrochloride, as it was found that aqueous solutions of alkali bases resulted in considerably lower yields of the product.

**1-Methyl-2- and 1-Methyl-4-benzylpiperidines.**—2-Benzylpiperidine and 4-benzylpiperidine were prepared by the hydrogenation[8] of the corresponding benzylpyridines.[9] These piperidines were N-methylated catalytically over copper–chromium oxide.[10] 4-Benzylpiperidine was also methylated with methyl iodide. The properties and analyses of these tertiary amines and their derivatives are listed in Table I.

**The Base-catalyzed Condensation of Benzaldehyde with 1-Methyl-3-piperidone (VI).**—To a solution of 10 g. (0.067 mole) of VI[2] in 70 ml. of 60% ethanol were added 7 g. (0.067 mole) of freshly purified benzaldehyde and 7.5 g. of solid potassium hydroxide. The mixture was shaken vigorously for fifteen minutes during which time a yellow, crystalline material separated. The reaction mixture then was allowed to stand in the dark at room temperature for four days. After separating the solid material by filtration, the filtrate was diluted with 100 ml. of water, causing a cloudiness to develop in the solution. As only a small amount of oil (0.1 g.) had separated after several days, it was discarded. The crude, yellow solid, m. p. 109–121° dec. was dissolved in ether to separate it from the potassium chloride which had crystallized from solution with it. After two recrystallizations from absolute ether, the yellow material attained a constant melting point range, 123–128° dec. and weighed 10.7 g.

*Anal.* Calcd. for $C_{13}H_{15}NO$ (VIII): C, 77.58; H, 7.51. Calcd. for $C_{13}H_{17}NO_2$ (VII): C, 71.20; H, 7.82. Found: C, 74.06; H, 7.65.

A solution of 9.2 g. of the product, m. p. 123–128°, from the preceding experiment in 300 ml. of absolute ether was treated with an excess of hydrogen chloride. This treatment caused the yellow color of the solution to disappear and a white solid separated, leaving a clear, colorless supernatant liquid. A solution of this hydrochloride in 25 ml. of water was treated with an excess of potassium carbonate and the liberated water-insoluble free base taken up in 50 ml. of ether. This solution was concentrated to the point where crystals began to separate from solution and then cooled for an hour in the refrigerator. The white, crystalline 1-methyl-4-benzal-3-piperidone (VIII), m. p. 112–113°, that separated weighed 4.0 g.

(8) Adkins, *et al.*, This Journal, **56**, 2425 (1934).
(9) Crook, *ibid.*, **70**, 416 (1948).
(10) Schwoegler and Adkins, *ibid.*, **61**, 3499 (1939).

*Anal.* Calcd. for $C_{13}H_{15}NO$: C, 77.58; H. 7.51. Found: C, 77.68; H, 7.34.

The ether filtrate, from which VIII had been separated, was treated with hydrogen chloride. A white precipitate of 4.9 g. of **phenyl-4-(1-methyl-3-keto-piperidyl)-carbinol (VII) hydrochloride**, m. p. 192–202° dec., separated.

*Anal.* Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.06; Cl, 13.9. Found: C, 60.84; H, 6.88; Cl, 13.6.

This hydrochloride was also obtained from the monobenzal derivative (VIII). A solution of 100 mg. of VIII in 50 ml. of moist ether was treated with an excess of hydrogen chloride. A white solid, m. p. 176–197° dec., separated from solution. This product gave the following analysis: C, 61.21; H, 6.98.

**1-Methyl-4-benzal-3-piperidone (VIII) from VII.**—A solution of 0.8 g. of the hydrochloride of VII in 5 ml. of 60% ethanol was treated with 0.3 g. of solid potassium hydroxide. After shaking the mixture vigorously for fifteen minutes, it was allowed to stand in the dark for four days. From the reaction mixture 0.38 g. of the product, m. p. 124–128°, was obtained. The hydrochloride (0.4 g.) of this material, after conversion to the free base yielded 0.15 g. of VIII, m. p. 111–113°, by the procedure described above.

**Reduction of 1-Methyl-4-benzal-3-piperidone (VIII) to 1-Methyl-4-benzylpiperidine.**—A solution of 1.0 g. of VIII in 50 ml. of dixoane was hydrogenated over 0.5 g. of Raney nickel at room temperature and atmospheric pressure. The initial absorption of hydrogen was very rapid but became slower after the first five minutes. Addition of another portion (0.3 g.) of catalyst did not increase the rate of hydrogenation. At the end of thirty minutes, when 67% of the theoretical amount of hydrogen had been absorbed, the hydrogenation stopped. After removing the catalyst, the solution was taken to dryness under reduced pressure on the steam-bath. The residue was dissolved in 10 ml. of dilute hydrochloric acid and placed in a 50-ml. flask, which contained 2.0 g. of amalgamated zinc (prepared by shaking zinc with a solution of 0.1 g. of mercuric chloride in 10 ml. of water and 1 ml. of hydrochloric acid). The reaction mixture was refluxed for three hours during which time 8 ml. of hydrochloric acid was added in four 2-ml. portions. The solution then was decanted from the unreacted zinc amalgam and treated with excess solid potassium carbonate. The aqueous solution was shaken with ether and the supernatant liquids decanted from the inorganic salt. After shaking the suspension with 30 ml. of ether, the mixture was filtered and the precipitate washed several more times with ether. The aqueous solution was extracted twice more with ether and discarded. After drying the ether solution of the amine over anhydrous sodium sulfate, it was concentrated to 10 ml., a few drops of ethanol added, and then treated with methyl iodide. A solid, m. p. 158–208°, separated from solution. After four recrystallizations from ethanol, the product melted at 200–205°. A mixture of this material and an authentic sample of 1-methyl-4-benzylpiperidine methiodide (m. p. 206–207°) melted at 203–208°.

A solution of 4 g. of VIII in 35 ml. of dioxane absorbed two equivalents of hydrogen at 3000 p. s. i. of hydrogen at 250° over 1 g. of copper–chromium oxide. After separating the catalyst, the solvent was removed under reduced pressure on the steam-bath, leaving a light-brown, semi-solid material. A solution of 0.5 g. of this product in 15-ml. of colorless hydriodic acid was heated in a sealed tube at 250° from three hours. After cooling, the tube was opened and the reaction mixture was transferred to a 50-ml. flask. It was heated to about 50° and then treated with solid sodium sulfite until the solution became colorless and the water-insoluble material that had formed during the heating went into solution. The colorless solution then was treated with excess potassium hydroxide and extracted with two 25-ml. portions of ether. After drying the ether solution over anhydrous sodium sulfate, it was concentrated to 10 ml., a few drops of ethanol were added, and then it was treated with methyl iodide. An oil separated on standing; it was dissolved in a small amount of ethanol, and after adding a few drops of ether it was set aside. After several hours a solid, m. p. 185–197°, was deposited. After two crystallizations from an ethanol–ether mixture, it melted at 200–204°. A mixture of this product and the methiodide of 1-methyl-4-benzylpiperidine melted at 201–206°.

**Reduction of VII to 1-Methyl-4-benzylpiperidine.**—A solution of 0.5 g. of the carbinol (VII) hydrochloride in 20 ml. of ethanol and 16 ml. of hydrochloric acid was added to 2 g. of amalgamated tin. The mixture was refluxed gently for sixteen hours. After separating the unreacted metal, the alcohol and water were removed from the reaction mixture. The residue then was dissolved in 25 ml. of water and made basic to litmus paper with potassium hydroxide. The water-insoluble amine was extracted from the water with two 25-ml. portions of ether. After removing the ether, the amine was dissolved in 10 ml. of dilute hydrochloric acid and the solution was added to 2 g. of amalgamated zinc. The reaction mixture was refluxed for three hours during which time 10 ml. of hydrochloric acid was added in 2-ml. portions. After separating the unreacted metal, the reaction mixture was processed as described in the preceding procedure, yielding a crude methiodide, m. p. 192–203°. After two crystallizations from alcohol–ether, this product melted at 199–205°. A mixture of this material and the methiodide of 1-methyl-4-benzylpiperidine melted at 200–206°.

**The Acid-catalyzed Condensation of Benzaldehyde with 1-Methyl-3-piperidone (VI).**—A solution of 7.5 g. (0.05 mole) of VI and 10.6 g. (0.1 mole) of freshly distilled benzaldehyde in 30 ml. of absolute ethanol was saturated with hydrogen chloride and allowed to stand in the dark at room temperature. No sign of reaction was observed for several hours when a red color began to develop. The following day a crystalline deposit was noticed in the reaction mixture, and the supernatant liquid was a blood-red. The reaction mixture was allowed to stand for three weeks before the solid was filtered. This material, m. p. 162–166°, became colorless after three crystallizations from ethanol. The purified product, m. p. 163–166°, weighed 5.1 g., and represented a 43% yield of hydrochloride of a monobenzal derivative.

*Anal.* Calcd. for $C_{13}H_{16}ClNO$: C, 65.77; H, 6.73; Cl, 15.0. Found: C, 65.40; H, 6.79; Cl, 14.6.

The filtrate was distilled under reduced pressure in a water-bath kept below 35° to remove the ethanol. After dissolving the residue in 100 ml. of water, the solution was shaken with ether to remove the residual benzaldehyde. On making the red aqueous solution basic to litmus paper with potassium carbonate, a dark brown color developed and a dark oil separated. The oil was extracted from the water with benzene and, after drying over anhydrous sodium sulfate, it was treated with hydrogen chloride; 3.0 g. of a dark amorphous solid, m. p. 60–73° dec., separated and the blood-red color reappeared in the solution. All attempts to isolate a pure product from this solid material were unsuccessful.

To further characterize the reaction product, a solution of 2.4 g. of the salt, m. p. 165–166°, in 30 ml. of ethanol and 40 ml. of water was hydrogenated over a previously reduced 5% palladium chloride–charcoal catalyst. The absorption of hydrogen was slightly more rapid at the outset, but then proceeded at a uniform rate until the theoretical amount was absorbed in seven hours. After separating the catalyst, the solution was taken to dryness under reduced pressure on the steam-bath, leaving a light-brown, glassy material. This product was dissolved in 15 ml. of water and after the addition of 6.0 g. of amalgamated zinc and 15 ml. of hydrochloric acid, the mixture was refluxed gently for four hours during which time another 15 ml. of hydrochloric acid was added. After decanting the solution from the unreacted metal, it was made basic to litmus paper with excess potassium carbonate. The water-insoluble amine was then extracted from the aqueous suspension of inorganic salts with three 25-ml. portions of ether. The ether solution of the amine was dried over anhydrous sodium sulfate and concentrated to 40 ml.

A 15-ml. aliquot of this ether solution was evaporated to remove the solvent and the residue dissolved in 10 ml. of ethanol. This solution was treated with a saturated ethanolic solution of picric acid. The crude picrate, m. p. 137–145°, after two crystallizations from ethanol, melted at 149–150°. It gave analytical values corresponding to those of a 1-methylbenzylpiperidine picrate and is subsequently designated as mixture A.

*Anal.* Calcd. for $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.26. Found: C, 54.58; H, 5.20.

A mixture of equal parts of the authentic picrates of 1-methyl-2-benzylpiperidine (m. p. 180.5–181.5°) and 1-methyl-4-benzylpiperidine (m. p. 184–186°) melted at 156–161°. A mixture of A and this known synthetic mixture melted at 133–143°. A solution of equal amounts of the two authentic picrates in ethanol yielded a product, m. p. 154–163°, which melted at 155–165° and 158–165° after two recrystallizations from ethanol. A mixture of the product from the second recrystallization and A melted at 138–149°. From the filtrates of the recrystallizations of the known mixture, a sample melting at 179–181° was obtained. This product depressed the melting point of the authentic picrate of 1-methyl-2-benzylpiperidine to 157–173°, but when mixed with the picrate of 1-methyl-4-benzylpiperidine the mixture melted at 181–185°. Similarly, the melting point of A (149–150°) was not depressed by either the sample obtained from the filtrate or by the authentic picrate of 1-methyl-4-benzylpiperidine; the latter combination melted at 152–169° and the former at 148–158°. However, the melting point of A was depressed to 140–152° by the picrate of 1-methyl-2-benzylpiperidine.

To the remainder of the ether solution containing the reduction products of benzalpiperidones was added 3 ml. of ethanol and 2 ml. of methyl iodide. A solid product X, m. p. 181–186°, was separated by filtration; from the filtrate another product Y, m. p. 185–191°, was obtained after standing in the refrigerator for thirty minutes. Both X and Y gave analytical values for the methiodide of a 1-methylbenzylpiperidine.

*Anal.* Calcd. for $C_{14}H_{22}IN$: C, 50.75; H, 6.65. Found: X, C, 50.68; H, 6.43; Y, C, 50.97; H, 6.44.

A solution containing equal parts of authentic samples of the methiodides of 1-methyl-2-benzylpiperidine (m. p. 225–226°) and 1-methyl-4-benzylpiperidine (m. p. 206–207°) in ethanol yielded a product, m. p. 171–178°. From a succession of crystallizations of this product from ethanol, samples melting at 187–196°, 184–188°, 183–187°, 181–186° and 183–188° were obtained. A mixture of X and Y melted at 182–185°. A mixture comprised of the product (m. p. 183–188°) obtained from the last crystallization of the known mixture and the mixture of X and Y melted at 179–185°.

From the above observations on the melting behavior of these picrates and methiodides, it may be concluded that a mixture of 1-methyl-2-benzyl- and 1-methyl-4-benzylpiperidines were obtained from the reduction of the product isolated from the acid-catalyzed condensation of VI with benzaldehyde.

**1-Methyl-3-hydroxy-3-phenylpiperidine Methiodide.**—To a suspension of 7.0 g. (0.05 mole) of 1-methyl-3-piperidone hydrochloride (VI) in 75 ml. of thiophene-free benzene was added 15 ml. of a saturated solution of potassium carbonate. The mixture was stirred vigorously until the evolution of carbon dioxide ceased. The aqueous layer was separated and extracted with three 15-ml. portions of benzene. The combined benzene solution was distilled on the steam-bath until the volume was reduced to approximately 80 ml. in order to remove all water. The dry benzene solution of the piperidone then was added dropwise to a Grignard reagent, which had been prepared under nitrogen from 1.5 g. (0.06 atom) of magnesium and 9.6 g. (0.06 mole) of freshly distilled bromobenzene. The reaction mixture was stirred during the addition of the piperidone and then for two hours while refluxing gently on the steam-bath. The flask and its contents then were immersed in an ice-bath, and a solution of 15 ml. of hydrochloric acid in 35 ml. of water added slowly. The mixture was transferred to a separatory funnel and shaken thoroughly and after separation, the aqueous layer extracted with ether. It then was made basic with potassium hydroxide and the water-insoluble oil extracted with chloroform. After removing the chloroform, the product was distilled and 5.3 g. (60%) of **1-methyl-3-hydroxy-3-phenylpiperidine**, b. p. 106–108° (0.4 mm.), was collected.

This product darkened quite rapidly on exposure to air. Consequently, it was converted to the methiodide by treating an ether–ethanol solution of the compound with methyl iodide. This salt, after one crystallization from ethanol, melted at 239.5–240.5°.

*Anal.* Calcd. for $C_{13}H_{20}INO$: C, 46.85; H, 6.00; I, 38.1. Found: C, 47.02; H, 6.09; I, 37.7.

The hydrochloride of the carbinol was prepared by passing hydrogen chloride into an ethereal solution of the compound. The resultant solid was hygroscopic; m. p. 134–136° dec. All attempts to purify this product sufficiently for consistent analyses were unsuccessful.

**1-Methyl-3-phenyl-3-acetoxypiperidine Hydrochloride.**—To a solution of 3.0 g. of the hydrochloride, obtained in the above procedure, in 15 ml. of glacial acetic acid was added 15 g. of acetyl chloride and the mixture refluxed gently for two hours. After removing the acetic acid and excess acetyl chloride under reduced pressure on the steam-bath, a white solid material remained in the flask. The product was crystallized from an alcohol–ether mixture, yielding 1.9 g. of white crystals of **1-methyl-3-phenyl-3-acetoxypiperidine hydrochloride**, m. p. 188–189°. A second crop of crystals, m. p. 179–182°, weighing 0.5 g. was recovered from the filtrate.

*Anal.* Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.34; H, 7.42; N, 5.19; Cl, 13.2. Found: C, 61.96; H, 7.70; N, 5.12; Cl, 13.2.

## Summary

An improved procedure for the preparation of ethyl γ-(N-methyl-N-carbethoxymethylamino)-butyrate (IV) from butyrolactone is described.

The condensation of 1-methyl-3-piperidone (VI) with benzaldehyde in basic medium yielded only the 4-substituted derivatives, 1-methyl-4-benzal-3-piperidone (VIII) and the corresponding carbinol VII. In acidic medium these reactants gave a mixture of VIII and its 2-benzal isomer (IX). None of the dibenzal derivative was obtained from either of these reactions.

The 3-piperidone (VI) reacts with phenylmagnesium bromide to yield 1-methyl-3-phenyl-3-hydroxypiperidine, which was isolated as the methiodide and as the 3-acetoxy derivative.

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