

PIPERIDINE DERIVATIVES. PART III. 4-ARYLPIPERIDINES¹

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In a previous paper² the synthesis of 1-alkyl-2-aryl- and 1-alkyl-2-arylalkyl-piperidines from 1-alkyl-2-piperidones was described. Similar synthetic methods have been applied to 1-alkyl-4-piperidones to yield the isomeric 4-phenyl-piperidines I. As in the case of the 1-methyl-2-benzylpiperidine, the 1-methyl-4-phenylpiperidine structure may be considered inherent in the morphine nucleus II and hence it or its derivatives might be expected to have analgesic activity. This approach to the synthesis of simpler structure with compounds of morphine-like activity is not new. Eisleb and Schaumann (1) have described piperidine compounds of the structure III (R = alkyl, R¹ = alkoxy, alkyl, etc.), one of the compounds (III, R = CH₃, R¹ = C₂H₅O) being clinically employed under the name of Demerol. Since the inception of the program of work described here, Jensen & Lundquist (2) have described compounds of the structure I (R = methyl, R¹ = acyloxy, R² = H). The compounds are stated to have an activity in the case of I (R = methyl, R¹ = propionoxy, R² = H) which is five to ten times that of Demerol. A British Patent recently issued (3) describes 1,2,2,6,6-pentamethyl-4-phenyl-4-acetoxypiperidine for which analgesic activity is claimed.

The synthetic scheme employed is shown in Figure 1.

The reaction of the arylmagnesium halide or lithiumaryl with 1-alkyl-4-piperidones yields the piperidinols VI. The corresponding 2-piperidones² invariably gave 1,4,5,6-tetrahydropyridines, spontaneous dehydration occurring during the isolation of the reaction product. The alcohols VI can be readily dehydrated to the corresponding 1-alkyl-4-aryl-1,2,5,6-tetrahydropyridines, IX, by means of the usual reagents, such as potassium acid sulfate, hydrobromic acid, and thionyl chloride. The tetrahydropyridines IX are readily hydrogenated either with nickel or noble metal catalysts to the saturated piperidines VIII. The piperidinols VI can be readily acylated with acid anhydrides in pyridine or anhydrides catalyzed by a trace of sulfuric or perchloric acid. With acyl chlorides in pyridine less satisfactory results were obtained, partial dehydration usually occurring. Jensen and Lundquist (2) state that they could not prepare certain esters, amongst them the phenylacetic ester. We found this to be prepared without difficulty using phenylacetic anhydride, and it is possible that the remaining esters mentioned by them as unobtainable may be prepared by the same method.

The lithium or magnesium compounds V can be also directly acylated by modi-

¹ This paper was presented, in part, at the Medicinal Chemistry section of the Gibson Island Conferences of the A.A.A.S. 1946. Paper No. II, preceding article.

² Lee, Ziering, Heineman, and Berger, preceding paper.

TABLE I
1-SUBSTITUTED 4-ARYL-4-HYDROXYPIPERIDINES

| SUBSTANCE: 4-HYDROXYPIPERIDINES | M.P., °C.* | B.P., °C. | FORMULA | M.W. | ANALYSIS | | | | | |
|--|-------------------------|-----------|----------------------------|-------|------------|-------|------|-------|------|------|
| | | | | | Calculated | | | Found | | |
| | | | | | C | H | N | C | H | N |
| 1-Allyl-4-phenyl- | 86 | 135/2 mm. | $C_{14}H_{19}NO$ | 217.3 | 77.31 | 8.81 | | 77.87 | 7.48 | |
| 1-Methyl-4-(<i>o</i> -methoxyphenyl)- | 117-118 EtOAc | 130/1 mm. | $C_{13}H_{19}NO_2$ | 221.3 | 70.53 | 8.65 | | 70.4 | 8.5 | |
| 1-Methyl-4-(<i>m</i> -methoxyphenyl)- | 112-113 EtOAc | 162/3 mm. | $C_{13}H_{19}NO_2$ | 221.3 | 70.53 | 8.65 | | 70.89 | 8.79 | |
| 1-Methyl-4-(<i>p</i> -methoxyphenyl)- | 116 | 155/1 mm. | $C_{13}H_{19}NO_2$ | 221.3 | 70.53 | 8.65 | | | | |
| 1-Ethyl-4-(<i>p</i> -methoxyphenyl)- | 97 | 160/2 mm. | $C_{14}H_{21}NO_2$ | 235.3 | 71.44 | 8.99 | | 71.83 | 9.09 | |
| 1-Butyl-4-(<i>p</i> -tolyl)- | 87 | 155/2 mm. | $C_{18}H_{25}NO$ | 247.4 | 77.67 | 10.18 | | 77.37 | 9.86 | |
| 1-Ethyl-4-phenyl- | 87 | 143/1 mm. | $C_{13}H_{19}NO$ | 205.3 | 76.05 | 9.32 | | 76.04 | 9.41 | |
| 1-Benzyl-4-phenyl- | 103 base 216 (HCl) | | $C_{18}H_{21}NO \cdot HCl$ | 303.8 | 71.16 | 6.96 | | 71.60 | 6.68 | |
| 1-Butyl-4-phenyl- | 86-88 | | $C_{15}H_{21}NO$ | 233.3 | 77.22 | 9.93 | | 77.55 | 9.74 | 5.02 |
| 1-Butyl-4-benzyl- | 156-157 | | $C_{16}H_{23}ClNO$ | 283.9 | | | 4.94 | | | |
| 1-Isopropyl-4-phenyl- | 231 (HCl) 81 | 152/5 mm. | $C_{14}H_{21}NO \cdot HCl$ | 255.8 | 65.73 | 8.28 | | 66.23 | 8.82 | |
| 1-Butyl-4-(<i>p</i> -methoxyphenyl)- | 104 | | $C_{16}H_{23}NO_2$ | 263.4 | 72.95 | 9.57 | | 72.90 | 9.20 | |
| 1-Methyl-4-phenyl- | 111 | | $C_{12}H_{17}NO$ | 191.3 | 75.34 | 8.96 | | 75.53 | 8.89 | |
| 1-Butyl-4-(<i>m</i> -tolyl)- | 100 | | $C_{16}H_{25}NO$ | 247.4 | 77.67 | 10.18 | | 77.59 | 9.92 | |
| 1-Butyl-4-[naphthyl-(1)]- | 228-229 (HBr) (corr) | | $C_{19}H_{26}BrNO$ | 358.3 | 63.69 | 5.63 | | 62.7 | 7.0 | |
| 1-Butyl-4-(1'-butyl-4'-oxo-3'-piperidyl)- dihydrochloride | 188-190 | | $C_{18}H_{34}Cl_2N_2O_2$ | 381.4 | | | 7.35 | | | 7.06 |

* When not otherwise stated, bases crystallized from hexane and hydrochlorides from acetone. M.P.'s uncorrected.

TABLE II
1-ALKYL-4-SUBSTITUTED-4-PIPERIDINOL ESTERS

| SUBSTANCE: PIPERIDINE HYDROCHLORIDE | M.P., °C.* | FORMULA | M.W. | Calculated | | Found | | |
|---|-----------------|--|-------|------------|------|-------|------|------|
| | | | | C | H | C | H | N |
| 1-Propyl-4-phenyl-4-propionoxy- | 218-219 | C ₁₇ H ₂₃ NO ₂ ·HCl | 310.9 | 65.47 | 8.35 | 36.01 | 7.54 | |
| 1-Isopropyl-4-phenyl-4-propionoxy- | 220-221 | C ₁₇ H ₂₃ NO ₂ ·HCl | 310.9 | 65.47 | 8.35 | 35.66 | 8.51 | |
| 1-Allyl-4-phenyl-4-propionoxy- | 190-191 | C ₁₇ H ₂₃ NO ₂ ·HCl | 308.9 | 66.10 | 7.77 | 35.96 | 7.85 | |
| 1-Butyl-4-(<i>p</i> -tolyl)-4-propionoxy- | 196-197 | C ₁₉ H ₂₅ NO ₂ ·HCl | 340.9 | 66.94 | 8.86 | 37.49 | 8.78 | |
| 1-Ethyl-4-(<i>p</i> -methoxyphenyl)-4-propionoxy- | 164-165 | C ₁₇ H ₂₃ NO ₃ ·HCl | 328.9 | 62.09 | 7.91 | 32.12 | 7.85 | |
| 1-Methyl-4-phenyl-4-dimethylcarbamoxy- | 179-180 | C ₁₅ H ₂₁ N ₂ O ₂ ·HCl | 284.8 | 60.24 | 8.13 | 30.85 | 8.00 | |
| 1-Methyl-4-phenyl-4-acetoxy- | 212-213 | C ₁₄ H ₁₉ NO ₂ ·HCl | 269.8 | 62.32 | 7.47 | 32.42 | 7.45 | |
| 1-Butyl-4-phenyl-4-butyroxy- | 206-207 | C ₁₉ H ₂₅ NO ₂ ·HCl | 339.9 | 67.12 | 8.89 | 37.00 | 8.54 | |
| 1-Ethyl-4-phenyl-4-butyroxy- | 209-210 | C ₁₇ H ₂₃ NO ₂ ·HCl | 312.9 | 65.25 | 8.38 | 34.93 | 8.09 | |
| 1-Ethyl-4-phenyl-4-propionoxy- | 194-195 | C ₁₆ H ₂₁ NO ₂ ·HCl | 297.9 | 64.50 | 8.12 | 33.96 | 8.08 | |
| 1-Methyl-4-(<i>p</i> -methoxyphenyl)-4-propionoxy- | 120-121 | C ₁₆ H ₂₃ NO ₃ ·HCl | 313.9 | 61.23 | 7.71 | 31.20 | 7.76 | |
| 1-Methyl-4-phenyl-4-propionoxy- | 182-183 | C ₁₅ H ₂₁ NO ₂ ·HCl | 283.8 | 63.49 | 7.82 | 33.17 | 7.87 | |
| 1-Methyl-4-phenyl-4-butyroxy- | 192-193 | C ₁₆ H ₂₃ NO ₂ ·HCl | 297.9 | 64.50 | 8.12 | 34.47 | 7.81 | |
| 1-Benzyl-4-phenyl-4-propionoxy- | 210-211 | C ₂₁ H ₂₅ NO ₂ ·HCl | 359.9 | 70.08 | 7.28 | 30.50 | 6.65 | |
| 1-Butyl-4-phenyl-4-propionoxy- | 205-206 | C ₁₈ H ₂₇ NO ₂ ·HCl | 325.9 | 66.34 | 8.66 | 36.50 | 8.44 | |
| 1-Butyl-4-(naphthyl(1))-4-acetoxy- | 223.5 (corr) | C ₁₈ H ₂₃ ClNO ₂ | 361.9 | 69.69 | 7.80 | 39.7 | 7.44 | |
| 1-Butyl-4-(naphthyl(1))-4-propionoxy- | 212-213 | C ₂₂ H ₃₀ ClNO ₂ | 375.9 | 70.28 | 8.04 | 30.0 | 7.9 | |
| 1-Methyl-4-phenyl-4-benzoyloxy- | 214-215 | C ₁₉ H ₂₁ NO ₂ ·HCl | 331.9 | 68.80 | 6.64 | 38.45 | 6.65 | 4.12 |
| 1-Butyl-4-phenyl-4-carbethoxyoxy- | 173-174 | C ₁₈ H ₂₇ NO ₃ ·HCl | 341.9 | 63.25 | 8.20 | 33.40 | 7.91 | 3.96 |
| EtOAc | | | | | | | | |
| 1-Methyl-4-phenyl-4-β,β-dimethylacryloxy- | 210-211 | C ₁₇ H ₂₃ NO ₂ ·HCl | 309.9 | 65.90 | 7.76 | 36.13 | 7.53 | |
| 1-Butyl-4-phenyl-4-acetoxy- | 207-208 | C ₁₇ H ₂₃ NO ₂ ·HCl | 311.9 | 65.50 | 8.35 | 35.92 | 7.88 | 4.52 |
| 1-Butyl-4-phenyl-4-β-carbomethoxypropionoxy- | 126-128 | C ₂₀ H ₂₉ NO ₄ ·HCl | 383.9 | 62.60 | 7.80 | 32.86 | 7.80 | 3.87 |
| EtOAc | | | | | | | | |
| 1-Butyl-4-phenyl-4-ethoxyacetoxy- | 202-204.5 | C ₁₉ H ₂₉ NO ₃ ·HCl | 355.9 | 64.15 | 8.44 | 34.08 | 8.38 | 4.14 |

* When not otherwise stated crystallized from acetone.

cedures employed are described since otherwise the same methods were employed.

Pharmacological results. These will be described in detail in another place. The method of assay was substantially that of Ercoli and Lewis (5). Generally it may be said that the piperidinols VI showed only slight activity. The tetrahydroxyridines IX showed distinct activity, for example, in the case of 1-ethyl-4-*p*-methoxyphenyl-1,2,5,6-tetrahydroxyridine the activity was about $\frac{1}{30}$ of that of morphine. The saturated piperidines obtained by hydrogenation of these retained about the same activity, *p*-substitution still giving the highest activity, which was at its best with the more difficultly hydrolyzable acyloxy groups such as the *p*-dimethylcarbamoxy group.

TABLE III
1-ALKYL-4-PHENYL-1,2,5,6-TETRAHYDROXYRIDINE

| SUBSTANCE TETRAHYDROXYRIDINE | M.P., °C.* | FORMULA | M.W. | ANALYSIS | | | | | |
|--------------------------------------|-------------------------|--------------------------------------|-------|------------|------|------|-------|-----|------------|
| | | | | Calculated | | | Found | | |
| | | | | C | H | N | C | H | N |
| 1-Methyl-4- <i>o</i> -methoxyphenyl | b.p., oil 135/10 mm. | C ₁₃ H ₁₇ NO | 203.3 | 76.8 | 8.43 | | 76.05 | 8.2 | |
| 1-Methyl-4- <i>m</i> -hydroxyphenyl | HBr EtOAc | C ₁₂ H ₁₃ BrNO | 272.2 | 52.9 | 6.2 | Br | 52.8 | 5.8 | Br 29.3 |
| 1-Methyl-4- <i>p</i> -methoxyphenyl- | HCl | C ₁₃ H ₁₈ ClNO | 239.7 | | | 5.84 | | | 5.71 |
| 1-Methyl-4-phenyl- | HCl | C ₁₂ H ₁₅ ClN | 208.7 | 69.0 | 7.24 | | 68.6 | 7.8 | |
| 1-Ethyl-4- <i>p</i> -methoxyphenyl- | HCl | C ₁₄ H ₂₀ ClNO | 253.8 | 66.3 | 7.94 | | 65.9 | 7.7 | |

* Unless otherwise stated, crystallized from acetone.

Acylation of the piperidinols VI to obtain the esters VII is accompanied by an increase in activity. The fatty acid esters show the best activity. The peak activity is obtained with the propionyl group. 1-Methyl-4-phenyl-4-propionoxypiperidine is as active in the test at a dose level of 1 mg. as 25 mg. of Demerol or 3 mg. of morphine. The corresponding acetyl compound is $\frac{1}{25}$ as active and the butyryl $\frac{1}{5}$ as active. The same order of activity for these three compounds was also found by Jensen & Lundquist (2).

Increase in the length of the alkyl chain at R in the compounds VII retaining the propionoxy group at position 4 results in a decrease of both activity and toxicity, the therapeutic ratio remaining approximately constant. Compounds with unbranched 1-alkyl chains are all unstable in water. However, if the residue in the 1-position is branched as, for example, in 1-isopropyl-4-phenyl-4-

TABLE IV
 1-ALKYL-4-PHENYLPYPERIDINES

| SUBSTANCE | M.P., °C.* | FORMULA | M.W. | ANALYSIS | | | | | |
|---|-------------------|------------------------|-------|------------|------|------|-------|------|------|
| | | | | Calculated | | | Found | | |
| | | | | C | H | N | C | H | N |
| 1-Methyl-4- <i>o</i> -methoxyphenyl HCl | 240-242 | $C_{13}H_{20}ClNO$ | 241.7 | 64.6 | 8.3 | — | 63.9 | 7.7 | — |
| 1-Methyl-4- <i>o</i> -hydroxyphenyl HBr | 180-181 EtOAc | $C_{12}H_{18}BrNO$ | 272.2 | 52.9 | 6.7 | — | 52.3 | 6.7 | — |
| 1-Methyl-4- <i>p</i> -hydroxyphenyl HBr | 210 | $C_{12}H_{18}BrNO$ | 272.2 | 52.9 | 6.7 | — | — | — | — |
| 1-Methyl-4- <i>m</i> -hydroxyphenyl HBr | 206 | $C_{12}H_{18}BrNO$ | 272.2 | 52.9 | 6.7 | — | 53.1 | 6.3 | — |
| 1-Ethyl-4- <i>p</i> -methoxyphenyl | b.p. 116/1 mm. | — | — | — | — | — | — | — | — |
| 1-Methyl-4- <i>o</i> -dimethylcarbamoxy- phenyl HCl | 222 | $C_{16}H_{22}ClN_2O_2$ | 298.8 | — | — | 9.37 | — | — | 9.41 |
| 1-Methyl-4- <i>m</i> -dimethylcarbamoxy- phenyl HCl | — | $C_{16}H_{22}ClN_2O_2$ | 298.8 | 60.3 | 7.7 | — | 60.0 | 7.66 | — |
| 1-Methyl-4- <i>p</i> -dimethylcarbamoxy- phenyl HCl | 246 | $C_{16}H_{22}ClN_2O_2$ | 298.8 | — | — | 9.38 | — | — | 9.64 |
| 1-Ethyl-4-dimethylcarbamoxyphenyl HCl | 208 | $C_{18}H_{26}ClN_2O_2$ | 312.8 | 61.4 | 8.05 | — | 61.8 | 7.5 | — |

* Unless otherwise stated crystallized from acetone.

propionoxypiperidine, considerable stability is obtained. This compound can be kept at 40° in aqueous solution for months, whereas the corresponding 1-methyl compound is degraded very quickly.

Substitution in the phenyl nucleus of compounds VII gives material of lower activities. Methoxyl groups lower the activities to $\frac{1}{150}$ to $\frac{1}{200}$ of that of the unsubstituted compounds. With the methyl group as a substituent the dystherapeutic effect is less being least with the *m*-tolyl compound, here however the compound is only $\frac{1}{3}$ as active as the unsubstituted derivative.

In Stuart molecular models of compounds of the type of VII, where the propionoxy group occupies position 4, the acyloxy side chain is seen to simulate very closely the cyclohexane ring in models of the morphine skeleton. The oxygen of the CO group occupies a position almost identical with that of the ether-oxygen of morphine, and the two end-carbon atoms of the propionoxy group simulate positions of the carbon atoms 5 and 6 of morphine. In view of this and of the results in the 1-alkyl-4-phenyl-4-carbalkoxy (or 4 carbalkyl) series (III, R = alkyl, R' = alkyl or alkoxy) (1), it would appear that the minimal skeletal structure in the morphine molecule required for the high analgesic activity is represented by the 1-methyl-4-phenylpiperidine moiety, with the carbon atoms 5, 6, and 7 and the ether-oxygen atom.

Acknowledgment. The analysis of the compounds recorded here was performed in the Microanalytical Division of these Laboratories by Dr. Al Steyermark and his co-workers and the pharmacological results are due to Drs. R. H. K. Foster, N. Ercoli, and G. Lehmann and their co-workers of the Pharmacological Laboratory. We are glad to express our appreciation of their cooperation.

EXPERIMENTAL

1-Methyl-4-(p-methoxyphenyl)-4-hydroxypiperidine. To a three-necked flask provided with a ground sealed stirrer, dropping-funnel, and reflux condenser, was added 4.8 g. of magnesium and 150 cc. of dry ether. *p*-Bromoanisole (38 g.) in 50 cc. of dry ether was added dropwise to form the Grignard reagent in the usual manner. The ether solution was refluxed for one hour and to the reaction mixture, cooled in an ice-bath, 23 g. of 1-methyl-4-piperidone in 100 cc. of ether was added dropwise. After the addition, the mixture was refluxed for 8 hours, during which the gummy complex became solid. This was decomposed with 50 cc. of 20% hydrochloric acid. The ether layer was separated and the aqueous layer washed with ether. The aqueous layer was saturated with potassium carbonate and extracted with ether. The ether solution of the basic product was dried over sodium sulfate, and after removal of the ether, the residue was fractionated. 1-Methyl-4-hydroxy-4-*p*-methoxyphenylpiperidine boiled at 155° at 1 mm. It was crystallized from benzene and melted at 117–118°; yield 10 g.

1-Methyl-4-(p-methoxyphenyl)-1,2,5,6-tetrahydropyridine. 1-Methyl-4-hydroxy-4-*p*-methoxyphenylpiperidine (2.2 g.) was mixed with 2.7 g. of anhydrous potassium bisulfate and heated to 160° under vacuum at 10 mm. for 10 minutes. The flask was cooled, the contents dissolved in water and the solution saturated with potassium carbonate and extracted with ether, which was dried over potassium carbonate. After removal of the ether the 1-methyl-4-*p*-methoxyphenyl-1,2,5,6-tetrahydropyridine crystallized. It was recrystallized from Skellysolve B, m.p. 101°; yield 1 g. The hydrochloride melted at 178° uncorr.

1-Methyl-4-(p-methoxyphenyl)piperidine. 1-Methyl-4-*p*-methoxyphenyl-1,2,5,6-tetrahydropyridine (3.2 g.) was dissolved in 100 cc. of methanol and reduced in the presence of

5 g. of Raney nickel under a pressure of 50 lbs. of hydrogen at room temperature. The catalyst was filtered off and the alcohol was distilled off *in vacuo*. The residue was demethylated directly according to the procedure below.

1-Methyl-4-(p-hydroxyphenyl)piperidine. 1-Methyl-4-*p*-methoxyphenylpiperidine base (3 g.) was dissolved in a mixture of 15 cc. of acetic acid and 10 cc. of 48% hydrobromic acid. The mixture was refluxed for 4 hours. The acids were distilled off in vacuum and the residue was crystallized from alcohol, m.p. 210°; yield 3 g.

1-Methyl-4-p-(dimethylcarbamoylphenyl)piperidine. 1-Methyl-4-*p*-hydroxyphenylpiperidine hydrobromide (20 g.) was dissolved in 100 cc. of water and the solution saturated with potassium carbonate. The separated piperidine base was dissolved in ether. The ether solution was dried and the ether removed by distillation. The free phenolic base was dissolved in 50 cc. of dry pyridine and 9 g. of dimethylcarbamyl chloride were added. After heating on a steam-bath for 3 hours, a further 9 g. of dimethylcarbamyl chloride was again added and the solution heated for another hour. The solvent was then removed *in vacuo* and the residue dissolved in water, and the solution made alkaline with sodium hydroxide. The dimethylcarbamyl ester was extracted with ether. HCl gas was bubbled in to precipitate the hydrochloride, which was then crystallized from acetone; m.p. 245–247°; yield 18 g.

1-Methyl-4-(m-hydroxyphenyl)-1,2,5,6-tetrahydropyridine. 1-Methyl-4-(*m*-methoxyphenyl)-4-hydroxy piperidine (1 g.) was dissolved in 15 cc. of glacial acetic acid, 5 cc. of 48% hydrobromic acid was added, and the mixture was refluxed for 15 minutes. The acids were removed under vacuum and the pink residue dissolved in alcohol and crystallized by the addition of ethyl acetate; yield, 200 mg. of 1-methyl-4-(*m*-hydroxyphenyl)-1,2,5,6-tetrahydropyridine, m.p. 194–196°.

1-Isopropyl-4-piperidone. Isopropylamine (684 cc.) was dissolved in 1600 cc. of absolute alcohol and to the solution, cooled in an ice-bath, 2800 cc. of ethyl acrylate was added portionwise. The resulting solution was kept for 1 week at room temperature and then worked up in the usual manner (6). The di-(β -carbethoxyethyl)isopropylamine (7) distilled at 128°/2mm.; yield 1600 g.

In a 3-necked, 5-liter, round-bottom flask provided with a Hershberg stirrer, dropping-funnel and reflux condenser, 46 g. of sodium was powdered under 1000 cc. of dry toluene. The inside temperature was brought to 90° with an oil-bath, and 518 g. of di-(β -carbethoxyethyl)isopropylamine was added dropwise with stirring. As the condensation progressed the sodium salt of 1-isopropyl-3-carbethoxy-4-piperidone precipitated out. When the addition was complete the mixture was heated and stirred at 90° for 3 hours longer. The contents were cooled, 1000 cc. of water added, the toluene was separated, and the aqueous layer was acidified with 480 cc. of concentrated hydrochloric acid. The solution of 1-isopropyl-3-carbethoxy-4-piperidone hydrochloride was refluxed until a drop of the solution gave only a faint color with ferric chloride. Most of the water was removed in vacuum and the residue made alkaline with 50% sodium hydroxide solution to about pH 11. The mixture was then extracted with ether. The ether solution was dried over potassium carbonate and the ether removed. The residual oil on fractionation yielded 135 g. of 1-isopropyl-4-piperidone, b.p. 103°/25 mm.

1-Isobutyl-4-piperidone. Ethyl acrylate (1600 cc.) was added in portions to a cooled solution of 365 g. of isobutylamine in 500 cc. of alcohol. The resulting solution was kept for seven days at room temperature; the alcohol and excess ethyl acrylate were distilled off *in vac.* and the residue distilled in *vac.*, b.p. 130°/1 mm.; yield 1062 g.

The above di-ester (546 g.) was cyclized with 46 g. of sodium shot in 1300 cc. of toluene. As the condensation proceeded the sodium salt of the keto ester separated out. The reaction product was worked up as above to yield 191 g. of 1-isobutyl-4-piperidone, b.p. 105°/22 mm.

Anal. Calc'd for $C_9H_{17}NO$: C, 69.68; H, 10.98.

Found: C, 69.57; H, 11.28.

1-sec.-Butyl-4-piperidone. In a similar manner to that described above, 507 cc. of *sec.*-

butylamine, 500 cc. of alcohol, and 1087 cc. of ethyl acrylate yielded 400 g. of di-(β -carbethoxyethyl)-*sec.*-butylamine, b.p. 144°/2 mm. (7). The di-ester (400 g.) cyclized in a similar manner with 34.5 g. of sodium yielded, after hydrolysis with hydrochloric acid, 150 g. of 1-*sec.*-butyl-4-piperidone, b.p. 112°/23 mm.

Anal. Calc'd for $C_9H_{17}NO$: C, 69.68; H, 10.98.

Found: C, 69.26; H, 11.17.

1-Butyl-4-phenyl-4-hydroxypiperidine. The Grignard reaction was carried out with 3.6 g. of magnesium and 23.5 g. of bromobenzene in the usual manner. The flask was cooled in an ice-bath and 15.5 g. of 1-butylpiperidone-4 was added dropwise. On working up in the usual manner, 8 g. of 1-butyl-4-phenyl-4-hydroxypiperidine was obtained. After crystallization from Skellysolve B, the compound melted at 86–88°.

Alternate synthesis. Phenyllithium was prepared in the usual manner from 2.1 g. of lithium wire, 200 cc. of ether and 23.6 g. of bromobenzene. The reaction flask was kept under dry nitrogen throughout the reaction. The flask was cooled to -20° and 15.5 g. of 1-butyl-4-piperidone in 45 cc. of ether was slowly added. The reaction mixture was stirred for 2 hours at room temperature and finally decomposed with ice and 18% hydrochloric acid. An insoluble salt separated which was brought into solution with water. The ether solution was separated and discarded, after being extracted with dilute hydrochloric acid. The acid solutions were combined and alkalinized with 50% NaOH solution to pH 10. A crystalline base separated which was filtered off. The aqueous solution was extracted with ether and the ether solution dried and evaporated to yield a further crop of crystals. The 1-butyl-4-phenyl-4-hydroxypiperidine was recrystallized from Skellysolve B, melted at 86–88°; yield 17 g.

Propionate. 1-Butyl-4-phenyl-4-hydroxypiperidine (1 g.) was dissolved in 10 cc. of propionic anhydride and 1 drop of conc'd sulfuric acid added. The mixture was heated on a steam-bath for 3 hours, and the excess propionic anhydride removed in vacuum. The residue was taken up in water and alkalinized with sodium carbonate. The oil was extracted with ether and after drying over potassium carbonate, HCl gas was bubbled in. The hydrochloride was crystallized from acetone, m.p. 204–206°.

Methiodide. 1-Butyl-4-phenyl-4-propionoxypiperidine (2 g.) was dissolved in excess methyl iodide. An oil started to precipitate in a few minutes. After standing overnight ether was added and the oil crystallized. The product was recrystallized from ethyl acetate-methanol mixture and melted at 160–165°.

Anal. Calc'd for $C_{19}H_{29}INO_2$: C, 52.90; H, 6.96.

Found: C, 53.27; H, 6.74.

N-oxide. 1-Butyl-4-phenyl-4-propionoxypiperidine (5 g.) was dissolved in 100 cc. of chloroform and 2.3 g. of perbenzoic acid in 40 cc. of chloroform added. After standing overnight in the ice-box the chloroform was distilled off in vacuum and the residue dissolved in ether. HCl gas was bubbled into the ether solution to precipitate the hydrochloride, which was crystallized from acetone, m.p. 155–157°.

Anal. Calc'd for $C_{18}H_{27}NO_3 \cdot HCl$: C, 63.25; H, 8.20.

Found: C, 63.01; H, 8.13.

1-Isopropyl-4-phenyl-4-acetoxypiperidine hydrochloride by direct acylation of the lithium complex. Phenyllithium was prepared from 8.4 g. of lithium wire and 100 g. of bromobenzene in ether in the usual manner. The mixture was cooled with ice-water and 52 g. of 1-isopropyl-4-piperidone in dry benzene was added. The reaction mixture was refluxed for 1½ hours, the apparatus was arranged for distillation, and the ether distilled off until the temperature of the distillate reached 55–60°. One hundred cc. of additional benzene was added. The reaction was cooled to 5° with ice and water, and 100 cc. of acetic anhydride in 200 cc. of dry benzene was added. A yellow-green precipitate formed. At the end of the addition the entire reaction mass was thick and yellow-green in appearance. The reaction mass was diluted with 1 liter of dry benzene and the cooling bath removed and the reaction mixture brought to reflux temperature slowly. It was refluxed for 30 minutes and left to stand overnight. The next morning the entire mass was almost solid. Cooled with

ice-water, it was decomposed with 100 cc. of ice-water, and finally 100 cc. of concentrated HCl with ice was added. A very insoluble hydrochloride precipitated. This was dissolved in about 4 liters of water and extracted with ether. The ether extract was discarded. The aqueous solution was basified with cooling to pH 10 and extracted with ether. The ether solution was dried over sodium sulfate overnight, filtered, concentrated to dryness, and fractionated through a small Vigreux column at 3 mm. Six grams of forerun boiling at 86–150° was obtained. The product distilled at 151° (3 mm.); yield 52.5 g. (55% of theory). On standing, the basic product obtained crystallized spontaneously. It was recrystallized from ligroin (30–60°), and melted at 75–76°. The base obtained was converted to the hydrochloride and recrystallized from acetone and methanol to yield the colorless crystalline 1-isopropyl-4-phenyl-4-acetoxypiperidine hydrochloride, m.p. 205–206°.

Anal. Calc'd for $C_{18}H_{23}NO_2 \cdot HCl$ (297.5): C, 64.55; H, 8.07.

Found: C, 64.62; H, 7.96.

The corresponding 4-propionoxy derivative prepared in a similar manner was obtained in 40% yield. 1-Isopropyl-4-phenyl-4-propionoxy piperidine hydrochloride was crystallized from acetone and melted at 212–213°.

Anal. Calc'd for $C_{17}H_{23}NO_2 \cdot HCl$ (311.5): C, 65.50; H, 8.35; N, 4.50.

Found: C, 65.35; H, 8.40; N, 4.51.

1-Butyl-4-cyclohexylpiperidine hydrochloride. 1-Butyl-4-phenyl-4-propionoxypiperidine hydrochloride (5 g.) was added to 100 cc. of ethanol containing 5 g. of PtO_2 . The mixture was hydrogenated at 50 lbs. pressure at 80° until no more hydrogen was taken up. The mixture was filtered and the alcohol distilled off in vacuum. The residue was crystallized from acetone and melted at 240°.

Anal. Calc'd for $C_{23}H_{29}NO_2 \cdot HCl$: C, 71.23; H, 7.75; N, 3.61.

Found: C, 71.35; H, 7.34; N, 3.57.

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