[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

# Synthesis of Derivatives of Alkylated and Arylated Piperidones and Piperidinols

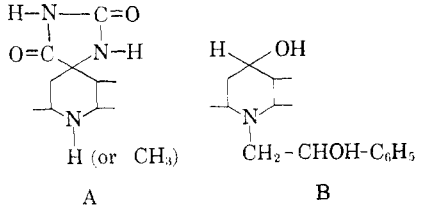
EVERETT A. MAILEY AND ALLAN R. DAY

*Received April 5, 1957*

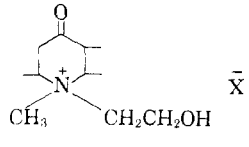
A number of new derivatives of substituted 4-piperidones have been prepared, including spirohydantoins, 1-phenacyl and 1-(2-hydroxyethyl) derivatives and quaternary compounds.

Earlier work has shown that spirohydantoins prepared from menthone and carvomenthone had marked anticonvulsant action in experimental animals.[1] In man, however, the compounds were ineffective. It is possible that this loss of activity in man may be due to lack of ability to absorb the material from the digestive tract. On this assumption it was decided to prepare spirohydantoins having other functional groups present which might facilitate their absorption. With this in mind, it seemed of interest to use a number of 4-piperidones as the starting ketones for the preparation of spirohydantoins (A), since the piperidone nucleus in a molecule may enhance nerve depressant action. This nucleus is present in such physiologically active compounds as cocaine, morphine and Demerol.

Although the preparation of spirohydantoins from 4-piperidones was the primary purpose of this investigation, several other compounds of possible physiological interest were made also. The main types prepared are shown below:




A B




C

Types B and C were prepared as potential adrenergic or cholinergic compounds.

The 2,2,6,6-tetramethyl-4-piperidone was prepared from phorone and ammonia by the method of Guerschi.[2] 1,2,2,6,6-Pentamethyl-4-piperidone was similarly prepared from phorone and methylamine.[2,3] 2,2,6-Trimethyl-4-piperidone was prepared from diacetoneamine acid oxalate and acetal.[4] 1-Methyl-3-carbethoxy-4-piperidone[5] was prepared by the Dieckmann condensation of methyldi(β-carbethoxyethyl)amine.[6] 1-Methyl-4-piperidone was prepared from the carbethoxy derivative by heating with hydrochloric acid.

The 2,6-diphenyl-4-piperidones were all prepared by the method of Noller and Baliah.[7] Benzaldehyde, the appropriate ketone, and ammonium acetate were heated in glacial acetic acid solution.

The spirohydantoins were prepared from the piperidones by the method of Bucherer.[8] In general the spirohydantoins from *N*-methylpiperidones melted slightly above 200° while those derived from piperidones having no substituents on nitrogen melted above 300°. All melted with decomposition.

The 4-piperidinols required in this study were obtained from the corresponding piperidones by hydrogenation with platinum as the catalyst or by reduction with lithium aluminum hydride. When 2,2,6-trimethyl-4-piperidone was reduced with lithium aluminum hydride it gave the *alpha* form of the alcohol, m.p. 137–138°. This had previously been obtained by a sodium amalgam reduction.[9] When 2,2,6-trimethyl-4-piperidone was hydrogenated over platinum at room temperature, the corresponding *beta* form was obtained, m.p. 158–159°. This form had also been isolated previously from a sodium amalgam reduction.[9] The remaining piperidinols were obtained in one form only.

The *N*-phenacyl derivatives of the piperidinols were prepared by heating with phenacyl bromide in ethanol or benzene solution. The *N*-phenacyl piperidinols were reduced with lithium aluminum

(1) E. S. Rothman and A. R. Day, *J. Am. Chem. Soc.*, **76**, 111 (1954).

(2) J. Guerschi, *Ber.*, **28**, 160 (1895).

(3) L. Orthner, *Ann.*, **456**, 251 (1927).

(4) A. T. King, F. A. Mason, and S. B. Schryver, British Patent **101,739** (1916).

(5) S. M. McElvain and K. Rorig, *J. Am. Chem. Soc.*, **70**, 1829 (1948); S. M. McElvain, *J. Am. Chem. Soc.*, **46**, 1725 (1924).

(6) R. Mozingo and J. H. McCracken, *Org. Syntheses*, Coll. Vol. III, 258 (1955).

(7) C. R. Noller and V. Baliah, *J. Am. Chem. Soc.*, **70**, 3853 (1948).

(8) H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, (2), **141**, 5 (1934).

(9) C. Harries, *Ann.*, **294**, 373 (1896).

hydride to the corresponding *N*-(2-hydroxy-2-phenylethyl)-4-piperidinols.

For the preparation of type C, the appropriate piperidine compound was heated with ethylene oxide to form the *N*-β-hydroxyethylpiperidine and the latter was converted to a quaternary compound by heating with methyl iodide.

## EXPERIMENTAL

The melting points recorded are uncorrected. They were taken in an apparatus similar to the one described by Wagner and Meyer[10] except that instead of using external heat an internal electrically heated coil made of Nichrome wire was used.

*Preparation of 4-piperidones.* See Table I. *2,2,6,6,-Tetramethyl-4-piperidone* (I). This compound, also known as triacetoneamine, was made from phorone and ammonia by the method of Guerschi.

TABLE I
SUBSTITUTED 4-PIPERIDONES

| Compound | Substituents | Yield, % | M.P., °C. | B.P., °C. |
|---|---|---|---|---|
| I | 2,2,6,6-Tetramethyl[2] | 75 | 58–59[a] | |
| II | 1,2,2,6,6-Pentamethyl[2,3] | 57 | | 78–82 at 2 mm. |
| III | 2,2,6-Trimethyl[4] | 87[b] | 181–183[c] | |
| IV | 1-Methyl-3-carbethoxy[5] | 58 | | 82–84 at 0.2 mm. |
| V | 1-Methyl[5] | 52 | | 43–44 at 6 mm. |
| VI | 2,6-Diphenyl-3-methyl[7] | 40 | 91–92[d] | |
| VII | 2,6-Diphenyl-3,3-dimethyl[7] | 50 | 114–115 | |
| VIII | 2,6-Diphenyl-3,5-dimethyl[7] | 72 | 131–133 | |
| IX | 1,3-Dimethyl-2,6-diphenyl[7] | 42 | 130–131 | |

[a] Melting point of monohydrate. [b] As acid oxalate. [c] Melting point of acid oxalate. [d] Literature gives 86–87°.

*1,2,2,6,6-Pentamethyl-4-piperidone* (II). The methods of Guerschi[2] and Orthner[3] were slightly modified for the preparation of this compound from phorone and methylamine. The initial reaction was carried out in an atmosphere of nitrogen. The removal of solvent, prior to fractionation of the reaction products, was also carried out in a stream of nitrogen.

*2,2,6-Trimethyl-4-piperidone* (III). It was prepared from diacetoneamine acid oxalate and acetal and isolated as its acid oxalate.[4] The free base was obtained by dissolving the oxalate salt in water and with cooling the solution was made strongly alkaline with 12*N* sodium hydroxide solution. The yellow oil was extracted with ether and the ethereal solution dried over potassium carbonate.

*1-Methyl-3-carbethoxy-4-piperidone* (IV). The procedures of McElvain and Rorig[5] and McElvain[6] were used to prepare this compound.

*1-Methyl-4-piperidone* (V). This compound was prepared from compound IV by a previously reported decarboxylation procedure.[5]

The following compounds were prepared by the method of Noller and Baliah:[7] *2,6-Diphenyl-3-methyl-4-piperidone* (VI), *2,6-diphenyl-3,3-dimethyl-4-piperidone* (VII), *2,6-diphenyl-3,5-dimethyl-4-piperidone* (VIII), *1,3-dimethyl-2,6-diphenyl-4-piperidone* (IX).

(10) E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem. Anal. Ed.*, 10, 584 (1939).

*Preparation of spirohydantoins from 4-piperidones.* These compounds were prepared from the 4-piperidones, ammonium carbonate and potassium cyanide in aqueous alcohol solution by the method of Bucherer.[8] Minor modifications were necessary in certain cases. In most cases it was found that the addition of more ammonium carbonate and potassium cyanide to the reaction mixture after 4 hr. of heating improved the yields. The following spirohydantoins were prepared for the first time (see Table II).

*7,7,9,9-Tetramethyl-1,3,8-triazaspiro[4.5]decane-2,4-dione* (X) *from Compound* I. The mixture was heated at 55–60° for 8 hr. White crystals appeared after 4–5 hr. After 8 hr., the mixture was cooled and the crystals removed. The crude hydantoin was dissolved in dilute sodium hydroxide solution and reprecipitated by the addition of hydrochloric acid. After filtering and drying, the hydantoin was finally recrystallized from a large volume of 50% aqueous ethanol.

The hydrochloride was prepared by heating the hydantoin with a minimum amount of water and concentrated hydrochloric acid until the solid dissolved. The solution was filtered and the filtrate cooled to precipitate the hydrochloride. The conversion was nearly quantitative. The hydrochloride was recrystallized from water.

*7,7,8,9,9-Pentamethyl-1,3,8-triazaspiro[4.5]decane-2,4-dione* (XI) *from Compound* II. In this case the mixture was heated at 55–60° for 18 hr. No crystals separated after 8 hr. Small amounts of ammonium carbonate and potassium cyanide were added and the heating continued for an additional 10 hr. The solution was reduced to about one-half its volume *in vacuo* and cooled to precipitate the hydantoin. The crude product was washed with water and recrystallized from 50% aqueous ethanol.

*7,7,9-Trimethyl-1,3,8-triazaspiro[4.5]decane-2,4-dione* (XII) *from Compound* III. The mixture was heated at 55–60° for 8 hr. After cooling, the product was removed and washed with water. It was dissolved in dilute sodium hydroxide solution and, after filtering, the filtrate was neutralized with hydrochloric acid to precipitate the hydantoin. The product was removed, washed thoroughly with water, and dried. The hydrochloride was prepared in the same way as the hydrochloride of X.

*6-Carbethoxy-8-methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione* (XIII) *from Compound* IV. In this case after heating the mixture at 55–60° for 1 hr., it separated into 2 layers and 50% aqueous ethanol was added until a homogeneous solution was obtained. The heating was then continued for 7 hr. The solvents were removed *in vacuo* and the residue recrystallized from 50% aqueous ethanol.

*8-Methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione* (XIV) *from Compound* V. The mixture was heated at 60–65° for 8 hr. The volume was then reduced about 50% *in vacuo* and the mixture cooled. The crude product was removed, washed with water, and dried. It was then recrystallized from 95% ethyl alcohol.

The same compound was obtained when 1-methyl-3-carbethoxy-4-piperidone was used in place of compound V and the mixture heated for 18 hr. Decarboxylation occurred during the reaction.

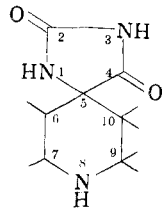
*6-Methyl-7,9-diphenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione* (XV) *from Compound* VI. The mixture was heated at 60–65° for 8 hr. After cooling, the product was removed, washed thoroughly with water, and recrystallized from a large volume of 50% aqueous ethanol.

*6,6-Dimethyl-7,9-diphenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione* (XVI) *from Compound* VII. The mixture was heated at 100° under pressure for 8 hr. After cooling, the product was removed, washed with 50% aqueous ethanol and with a little hot benzene. The dried product was dissolved in glacial acetic acid and heated with decolorizing carbon. After filtering, the filtrate was cooled and diluted with water to 3 times its volume. Aqueous ammonia was then added dropwise with cooling and stirring. The white solid, so obtained, was removed, washed, and dried.

*6,10-Dimethyl-7,9-diphenyl-1,3,8-triazaspiro[4.5]decane*

TABLE II

1,3,8-TRIAZASPIRO[4.5]DECANE-2,4-DIONES (SPIROHYDANTOINS)



| Compound | Substituents | Yield, % | M.P., °C. | Analyses, % Calcd. C | H | N | Cl | Found C | H | N | Cl |
|---|---|---|---|---|---|---|---|---|---|---|---|
| X | 7,7,9,9-Tetramethyl | 80 | 360–365 dec. | 58.64 | 8.50 | 18.65 | | 58.39 | 8.63 | 18.48 | |
| | Hydrochloride of X | | >360 dec. | 50.47 | 7.70 | 16.05 | 13.55 | 50.56 | 7.71 | 16.04 | 13.46 |
| XI | 7,7,8,9,9-Pentamethyl | 46 | 209–211 | 60.21 | 8.84 | 17.56 | | 60.00 | 9.11 | 17.39 | |
| XII | 7,7,9-Trimethyl | 95 | 360 dec. | 56.84 | 8.11 | 19.88 | | 56.69 | 8.22 | 20.04 | |
| | Hydrochloride of XII | | >360 dec. | 48.49 | 7.32 | 16.96 | 14.32 | 48.64 | 7.42 | 17.06 | 14.14 |
| XIII | 6-Carbethoxy-8-methyl | 50 | 230–232 | 51.75 | 6.71 | 16.46 | | 51.83 | 6.76 | 16.31 | |
| XIV | 8-Methyl | 34 | 254–256 | 52.45 | 7.15 | 22.94 | | 52.25 | 7.07 | 22.92 | |
| XV | 6-Methyl-7,9-diphenyl | 80 | 363–365 dec. | 71.63 | 6.31 | 12.56 | | 71.77 | 6.47 | 12.45 | |
| XVI | 6,6-Dimethyl-7,9-diphenyl | 79 | 323–325 dec. | 72.20 | 6.63 | 12.03 | | 72.44 | 6.64 | 11.86 | |
| XVII | 6,10-Dimethyl-7,9-diphenyl | 76 | >360 dec. | 72.20 | 6.63 | 12.03 | | 72.14 | 6.39 | 11.89 | |
| XVIII | 6,8-Dimethyl-7,9-diphenyl | 69 | 370–373 dec. | 72.20 | 6.63 | 12.03 | | 71.97 | 6.48 | 11.97 | |

TABLE III

SUBSTITUTED 4-PIPERIDINOLS

| Compound | Substituents | Yield, % | M.P., °C. | Analyses, % Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| XIX[11] | 2,2,6,6-Tetramethyl | 89 | 128–128.5[a] | | | | | | |
| XX[9] | 2,2,6-Trimethyl | | | | | | | | |
| | Alpha form | 79 | 137–138 | | | | | | |
| | Beta form | 97 | 160–161[a] | | | | | | |
| XXI | 2,6-Diphenyl-3-methyl | 82 | 125–126[b] | | | | | | |
| XXII | 2,6-Diphenyl-3,5-dimethyl | 83 | 133–134 | 81.10 | 8.23 | 4.98 | 81.30 | 8.05 | 4.75 |
| XXIII | 2,6-Diphenyl-3,3-dimethyl | 89 | 136.5–137.5 | 81.10 | 8.23 | 4.98 | 81.21 | 8.30 | 4.93 |
| XXIV | 1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl | 74 | 186–186.5 | 77.51 | 8.37 | 4.31 | 77.39 | 8.34 | 4.27 |

[a] Literature reports 158–159°. [b] Baliah and Ekambaram [*J. Indian Chem. Soc.*, **32**, 274 (1955)] report 123–124°.

*2,4-dione* (XVII) *from Compound* VIII. This compound was prepared in the same manner as XVI. The crude product was washed with 60% aqueous ethanol until colorless. The dry product was dissolved in a minimum amount of hot *6N* acetic acid. After filtering, the filtrate was diluted with water and treated with aqueous ammonia as in the case of XVI.

*6,8-Dimethyl-7,9-diphenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione* (XVIII) *from Compound* IX. The reaction mixture was heated at 60–65° for 18 hr. After cooling, the product was removed, washed with water, and dried. It was then recrystallized from 95% ethyl alcohol.

*Preparation of 4-piperidinols* (see Table III). *2,2,6,6-Tetramethyl-4-piperidinol* (XIX). 2,2,6,6-Tetramethyl-4-piperidone monohydrate in 95% ethyl alcohol was hydrogenated in the presence of platinum. The product was obtained by evaporating the alcohol solution *in vacuo* and recrystallizing the residue from benzene.[11]

*2,2,6-Trimethyl-4-piperidinol* (XX) (*α-form*). Lithium aluminum hydride (1.52 g., 0.04 mole) was added to 100 ml. of dry ether and the mixture stirred and refluxed for 30 min. Drying tubes were used to prevent moisture from reaching the reaction mixture. The external heat was removed and 14.1 g. (0.10 mole) of 2,2,6-trimethyl-4-piperidone in 100 ml. of dry ether was added dropwise. The mixture was then refluxed for an additional 15 min. Water (25 ml.) was added carefully to decompose the excess lithium aluminum hydride and then 100 ml. of 6*N* hydrochloric acid added to dissolve the basic aluminum precipitate. The two layers were separated and the aqueous layer made strongly alkaline with 12*N* sodium hydroxide solution. The alkaline solution was extracted with seven 100 ml. portions of butanol-1. The butanol was removed *in vacuo* and the residue was recrystallized from ethyl acetate. The product melted at 137–138°.[9]

*2,2,6-Trimethyl-4-piperidinol* (*β-Form*). The *β*-form was obtained by hydrogenating the ketone in 95% ethyl alcohol solution in the presence of platinum as a catalyst. After removing the ethyl alcohol *in vacuo*, the residue was recrystallized from ethyl acetate. The product melted at 160–161°.[9]

A mixture of the *α*- and *β*-forms melted at 121–123°.

*2,6-Diphenyl-3-methyl-4-piperidinol* (XXI). This compound was prepared from 2,6-diphenyl-3-methyl-4-piperidone hydrochloride by hydrogenation with platinum as the catalyst in 95% ethyl alcohol. The catalyst was removed

(11) E. Fischer, *Ber.*, **17**, 1789 (1884).

TABLE IV

SUBSTITUTED 1-PHENACYL-4-PIPERIDINOLS

| Compound | Substituents | Yield, % | M.P., °C. | Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|
| XXV | 2,2,6,6-Tetramethyl | 23 | 116.5–117.5 | 74.15 | 9.15 | 5.09 | 74.24 | 9.18 | 5.04 |
| XXVI | 2,6-Diphenyl-3,3-dimethyl | 75 | 124–126 | 81.19 | 7.32 | 3.51 | 81.35 | 7.38 | 3.48 |
| XXVII | 2,6-Diphenyl-3,5-dimethyl | 55 | 129.5–130 | 81.19 | 7.32 | 3.51 | 81.00 | 7.52 | 3.56 |
| | SUBSTITUTED 1-(2-HYDROXY-2-PHENYLETHYL)-4-PIPERIDINOLS | | | | | | | | |
| XXVIII | 2,2,6,6-Tetramethyl | 80 | 124–124.5 | 73.60 | 9.81 | 5.05 | 73.77 | 9.76 | 5.10 |
| XXIX | 2,6-Diphenyl-3,3-dimethyl | 57 | 197–198 | 80.76 | 7.78 | 3.49 | 80.88 | 7.95 | 3.54 |
| XXX | 2,6-Diphenyl-3,5-dimethyl | 40 | 303–305 | 80.76 | 7.78 | 3.49 | 80.98 | 7.93 | 3.50 |
| XXXI | 2,6-Diphenyl-3-methyl | 43 | 227–229.5 | 80.60 | 7.54 | 3.62 | 80.69 | 7.57 | 3.58 |

and the filtrate was made basic with ammonium hydroxide. The hot solution was then diluted with water to about 3 times its volume and allowed to cool. The product was collected, dried, and recrystallized from petroleum ether (65–100°).

The same compound was obtained by reduction with lithium aluminum hydride.

*2,6-Diphenyl-3,5-dimethyl-4-piperidinol* (XXII). The low solubility of 2,6-diphenyl-3,5-dimethyl-4-piperidone in ether led to the use of a Soxhlet extractor as a means of carrying out the reduction. Lithium aluminum hydride (3.8 g., 0.1 mole) was added to 500 ml. of dry ether. After refluxing for 30 min., a thimble containing 50 g. (0.18 mole) of the ketone was placed in the Soxhlet and refluxing was continued for 45 min. after all of the ketone had dissolved. The Soxhlet condenser was replaced with a straight condenser and 30 ml. of water was added very carefully to destroy the excess lithium aluminum hydride. Hydrochloric acid (200 ml., 6*N*) was then added and the solid removed by filtration. The solid was treated with 200 ml. of 95% ethyl alcohol and concentrated ammonium hydroxide added dropwise with stirring until a clear solution was obtained. After filtering, the filtrate was diluted with water to about 3 times its volume to precipitate the product. The latter was dried and recrystallized from petroleum ether (65–110°).

*2,6-Diphenyl-3,3-dimethyl-4-piperidinol* (XXIII). This piperidinol was prepared from 2,6-diphenyl-3,3-dimethyl-4-piperidone by the method described for XXI. The crude product was recrystallized from methanol.

*1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidinol* (XXIV). 1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidone was hydrogenated in glacial acetic acid using platinum as catalyst. After removing the solvent *in vacuo*, the residue was recrystallized from benzene.

*Preparation of N-Phenacyl Compounds* (see Table IV). *1-Phenacyl-2,2,6,6-tetramethyl-4-piperidinol* (XXV). A mixture of 10.5 g. (0.067 mole) of 2,2,6,6-tetramethyl-4-piperidinol, 6.66 g. (0.034 mole) of phenacyl bromide and 25 ml. of dry benzene was heated at 90–95° under pressure for 2 hr. After cooling, 50 ml. of dry benzene was added and the mixture was cooled overnight. The amine hydrobromide was removed and washed with a little dry benzene. The benzene solution was then extracted with 2*N* hydrochloric acid. The acid solution was cooled and while stirring was made alkaline by the addition of 6*N* sodium hydroxide. The precipitated phenacyl compound was either removed by filtration or by extraction with benzene, the benzene subsequently being removed *in vacuo*. The dried product was recrystallized from petroleum ether (65–110°).

*1-Phenacyl-2,6-diphenyl-3,3-dimethyl-4-piperidinol* (XXVI). The procedure for XXV was used for this preparation except that 2,6-diphenyl-3,3-dimethyl-4-piperidinol was used as the starting piperidinol and dry ethanol was used as the solvent. The filtrate from the hydrobromide was evaporated to dryness *in vacuo*. The residue was extracted with dry ether, the ether removed under reduced pressure, and the residue recrystallized from aqueous ethyl alcohol. The compound was dried *in vacuo* over phosphorus pentoxide.

*1-Phenacyl-2,6-diphenyl-3,5-dimethyl-4-piperidinol* (XXVII). This compound was prepared from 2,6-diphenyl-3,5-dimethyl-4-piperidinol and phenacyl bromide by heating in dry ethanol at 95°, under pressure, for 25 hr. The mixture was evaporated to dryness *in vacuo* and the residue extracted with dry ether. After removing the ether from the extract, the residue was recrystallized from aqueous ethyl alcohol.

*Reduction of N-phenacyl Compounds* (see Table IV). *1-(2-Hydroxy-2-phenylethyl)-2,2,6,6-tetramethyl-4-piperidinol* (XXVIII). Lithium aluminum hydride (0.38 g., 0.01 mole) in 100 ml. of dry ether was refluxed for 15 min. and 4.6 g. (0.0167 mole) of 1-phenacyl-2,2,6,6-tetramethyl-4-piperidinol in 100 ml. of dry ether was added dropwise. After the addition the mixture was heated to boiling for an additional 30 min. Water (25 ml.) was then cautiously added to destroy excess lithium aluminum hydride and finally 100 ml. of 6*N* hydrochloric acid was added and the mixture stirred for 15 min. The acid layer was separated and washed with ether. With cooling, the solution was then made strongly alkaline with 12*N* sodium hydroxide and extracted with ether. After removing the ether, the residue was recrystallized from 1:1 benzene-petroleum ether (65–110°).

*1-(2-Hydroxy-2-phenylethyl)-2,6-diphenyl-3,3-dimethyl-4-piperidinol* (XXIX). This compound was prepared from 1-phenacyl-2,6-diphenyl-3,3-dimethyl-4-piperidinol by the procedure used for making XXVIII up to the point where the 6*N* hydrochloric acid was added. After the addition of the acid, the solid was removed by filtration. It was mixed with 100 ml. of 95% alcohol; concentrated ammonium hydroxide was then added to neutralize the hydrochloride. The solution was diluted with water and cooled overnight. The precipitate so obtained was recrystallized from ethanol.

*1-(2-Hydroxy-2-phenylethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidinol* (XXX). This product was prepared from 1-phenacyl-2,6-diphenyl-3,5-dimethyl-4-piperidinol by the same method used for XXIX.

*1-(2-Hydroxy-2-phenylethyl)-2,6-diphenyl-3-methyl-4-piperidinol* (XXXI). In this case the 1-phenacyl-4-piperidinol was not isolated but was reduced directly to XXXI. 2,6-Diphenyl-3-methyl-4-piperidinol was condensed with phenacyl bromide in ethanol solution by the method used for making XXVII. The final ether extract of the phenacyl derivative was reduced directly with lithium aluminum hydride as described for the preparation of XXIX, except that the final product was recrystallized from methanol.

*Preparation of 1-(2-hydroxyethyl)-4-piperidones, 1-(2-hydroxyethyl)-4-piperidinols, and quaternary compounds. 1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidone* (XXXII). 2,6-Diphenyl-3,5-dimethyl-4-piperidone (14 g., 0.05 mole), 3.1 g. (0.07 mole) of ethylene oxide, and 19 ml. of methanol was heated at 90–95° under pressure for 24 hr. The solvent was removed *in vacuo* and the residue was

recrystallized from petroleum ether (65–110°). The yield was 68%, m.p. 149–159°.

*Anal.* Calcd. for $C_{21}H_{25}NO_2$: C, 78.00; H, 7.79; N, 4.33. Found: C, 78.09; H, 7.64; N, 4.26.

*1-(2-Hydroxyethyl)-2,6-diphenyl-3,3-dimethyl-4-piperidone* (XXXIII). A mixture of 14 g. (0.05 mole) of 2,6-diphenyl-3,3-dimethyl-4-piperidone, 3.52 g. (0.08 mole) of ethylene oxide, and 20 ml. of methanol was heated at 95–100° under pressure for 24 hr. After removing the solvent *in vacuo*, the viscous residue was covered with petroleum ether and allowed to stand in a refrigerator until the material crystallized. It was recrystallized from petroleum ether. The yield was 81%, m.p. 104–104.5°.

*Anal.* Calcd. for $C_{21}H_{25}NO_2$: C, 78.00; H, 7.79; N, 4.33. Found: C, 77.90; H, 7.59; N, 4.30.

*1-(2-Hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidinol* (XXXIV). Compound XXXII was hydrogenated in glacial acetic acid with platinum as a catalyst. The acetic acid was removed *in vacuo* and the residue was recrystallized from benzene. The yield was 74%, m.p. 186–186.5°.

*Anal.* Calcd. for $C_{21}H_{27}NO_2$: C, 77.51; H, 8.37; N, 4.31. Found: C, 77.39; H, 8.34; N, 4.27.

*1-(2-Hydroxyethyl)-1-methyl-2,6-diphenyl-3,5-dimethyl-4-ketopiperridinium iodide* (XXXV). A mixture of 0.5 g. (0.0015 mole) of 1-(2-hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidone and 3 g. (0.021 mole) of methyl iodide was heated at 100° under pressure for 68 hr. Excess methyl iodide was removed *in vacuo* and the residue was recrystallized from 95% ethyl alcohol. The yield was 46%, m.p. 203.5–204.5°.

*Anal.* Calcd. for $C_{22}H_{28}NO_2I$: C, 56.76; H, 6.06; N, 3.01; I, 27.26. Found: C, 56.90; H, 6.15; N, 3.02; I, 27.19.

*1-(2-Hydroxyethyl)-1-methyl-2,6-diphenyl-3,3-dimethyl-4-ketopiperridinium iodide* (XXXVI). A mixture of 9.6 g. (0.03 mole) of 1-(2-hydroxyethyl)-2,6-diphenyl-3,3-dimethyl-4-piperidone and 21.1 g. (0.15 mole) of methyl iodide was heated at 100° under pressure for 72 hr. Excess methyl iodide was removed *in vacuo* and the residue was recrystallized from ethanol-ether. The yield was 30%, m.p. 209.5–210.5°.

*Anal.* Calcd. for $C_{22}H_{28}NO_2I$: C, 56.76; H, 6.06; N, 3.01; I, 27.26. Found: C, 57.00; H, 6.07; N, 3.07; I, 27.06.

*1-(2-Hydroxyethyl)-1-methyl-2,6-diphenyl-3,5-dimethyl-4-hydroxypiperidinium iodide* (XXXVII). A mixture of 8.1 g. (0.025 mole) of 1-(2-hydroxyethyl)-2,6-diphenyl-3,5-dimethyl-4-piperidinol and 21.1 g. (0.15 mole) of methyl iodide was heated at 100° under pressure for 96 hr. Excess methyl iodide was removed *in vacuo* and the residue was recrystallized from dry ethanol. The yield was 53%, m.p. 219–220°.

*Anal.* Calcd. for $C_{22}H_{30}NO_2I$: C, 56.54; H, 6.47; N, 3.00; I, 27.15. Found: C, 56.43; H, 6.40; N, 2.88; I, 27.32.

*Preparation of p-nitro and p-aminobenzoates of* XIX *and* XX. These derivatives were prepared by the usual procedures, namely *p*-nitrobenzoylation in pyridine solution and subsequent reduction of the nitro group with hydrogen and palladium.

*p-Nitrobenzoate of 2,2,6,6-tetramethyl-4-piperidinol* (XXXVIII). The product was recrystallized from 95% ethyl alcohol; yield 49%, m.p. 128.5–129.5°.

*Anal.* Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.71; H, 7.24; N, 9.15. Found: C, 62.71; H, 7.12; N, 9.18.

*p-Aminobenzoate of 2,2,6,6-tetramethyl-4-piperidinol* (XXXIX). The product was recrystallized from water; yield 95%, m.p. 146–147°.

*Anal.* Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.30; H, 8.86; N, 9.96.

*p-Nitrobenzoate of 2,2,6-trimethyl-4-piperidinol* (XL). This compound was recrystallized from 95% ethyl alcohol; yield 48%, m.p. 93–94°.

*Anal.* Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.89; N, 9.58. Found: C, 61.50; H, 6.95; N, 9.47.

PHILADELPHIA 4, PA.

---

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Some Derivatives of ϵ-Caprolactam[1,2]

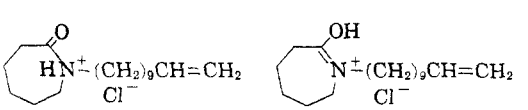
C. S. MARVEL AND WENDELL W. MOYER, JR.

*Received May 9, 1957*

A method for the *N*-alkylation of ϵ-caprolactam has been developed and used to produce the *N*-*n*-butyl, *N*-*n*-hexyl and the *N*-undecenyl derivatives. All of these amides showed markedly basic properties. Hydrolysis of *N*-undecenyl-ϵ-caprolactam with hydrochloric acid solution led to the formation of *N*-10(11?)-chloroundecyl-ϵ-aminocaproic acid which was characterized as the *N*-*p*-toluenesulfonyl derivative. *N*-*p*-Toluenesulfonyl-ϵ-aminocaproic acid was prepared and found to undergo cyclization forming *N*-*p*-toluenesulfonyl-ϵ-caprolactam when treated with either phosphorus pentachloride or sulfuric acid. The benzyl esters of *N*-benzoyl-ϵ-aminocaproic acid and *N*-formyl-ϵ-aminocaproic acid were synthesized.

In connection with the synthesis of a polyampholyte of regular structure, work was directed toward the preparation of a suitable intermediate from ϵ-caprolactam. Although this route to a polyampholyte proved to be infeasible, a number of previously unreported derivatives of ϵ-caprolactam were made.

A general procedure for the *N*-alkylation of ϵ-caprolactam was developed and the properties of the *N*-alkyl-ϵ-caprolactams were briefly investigated. All were found to have a pronounced basic character, forming perbromide and hygroscopic hydrogen chloride salts readily. In the case of *N*-undecenylcaprolactam a crystalline hydrochloride was isolated and the infrared absorption of this compound indicated it to be a mixture of the two isomers shown below. While ϵ-caprolactam itself and *N*-methyl-ϵ-caprolactam are easily hydrolyzed,



(1) Abstracted from a portion of the Ph.D. thesis of Wendell W. Moyer, Jr., University of Illinois, 1957.

(2) The work discussed herein was performed as a part of the synthetic rubber research project sponsored by the National Science Foundation.