The Preparation and Some Reactions of 1-Methyl-4-phenyl-3,4-epoxypiperidine

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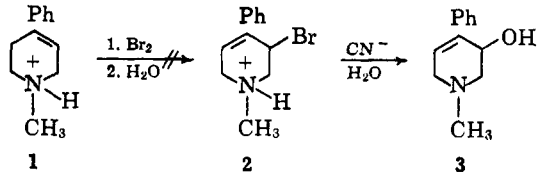
The addition of bromine to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (**1**) gave 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (**4**) and *not* 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide as reported previously.[2] The reaction of **4** with base gave the title epoxide **5** and *not* 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol. Chemical and physical evidence is presented in support of these structures.

The reaction of bromine with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide followed by treatment with water was reported to yield the allylic bromide, 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (**2**).[2] This halide was said to undergo a facile solvolysis with water in the presence of the stronger nucleophile, cyanide ion, to form the allylic alcohol, 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (**3**).[2] The preparations of the allylic bromide and alcohol **3** were attempted in this laboratory for the investigation of the displacement reaction, and the properties of these compounds were found to be inconsistent with structural assignments given previously.[2]



The initial product of the bromination was found to exhibit a broad absorption band at 3400 cm.$^{-1}$ in the infrared spectrum, and the ultraviolet absorption spectrum was consistent with the presence of a nonconjugated aromatic ring and not a substituted styrene system as required by structure **2**. The n.m.r. spectrum (Table I) gave no evidence of a hydrogen attached to aliphatic unsaturation, and the elemental analyses for the salt required one molecule of water more than structure **2**.

TABLE I

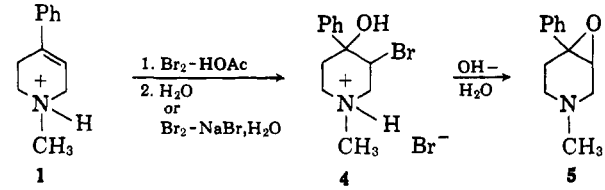
N.M.R. SPECTRAL DATA[a]

	Compd.			
Ring positions	**3a**	**4**	**5**	*cis*-**7**
1-Methyl	2.26 (s)	3.08 (s)	2.29 (s)	2.28 (s)
2-Methylene	2.39 (m)	3.68 (m) or 4.05 (m)	2.40 (m) or 2.89 (m)	2.55 (m)
3-Methine	4.23 (m)	4.85 (m)	3.21 (m)	3.98 (m)
4-Methine	...	...	...	2.57 (m)
5-Methylene or methine	6.00 (q)	2.34 (m)	1.96 (m)	1.51 (m)
6-Methylene	2.90 (m)	3.68 (m) or 4.05 (m)	2.40 (m) or 2.89 (m)	2.55 (m)
Hydroxyl	3.64 (s)	...	...	4.62 (s)
Phenyl	7.35 (m)	7.63 (m)	7.38 (m)	7.32 (m)

[a] Chemical shifts are in parts per million from tetramethylsilane (internal standard).

The reaction of the above hydrobromide with base at 0°[3] gave a solid product whose melting point corresponded with that reported for **3**; however, the infrared spectrum showed no bands above 3150 cm.$^{-1}$ or in the carbonyl region, and the n.m.r. spectrum (Table I) gave no evidence for a vinyl hydrogen. The ultraviolet absorption spectrum indicated an isolated aromatic ring. The elemental analyses were in agreement with those reported previously[2] and with the analytical values required by structure **3**. These data were consistent only with a cyclic ether.

The physical data suggested that the reaction sequence could better be represented by considering that the bromine and water treatment of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (**1**) had produced 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (**4**) which on reaction with base was converted to 1-methyl-4-phenyl-3,4-epoxypiperidine (**5**). This assumption was supported by the increase in yield of **4** from **1** when bromine–sodium bromide in water[4] was used for the initial reaction.



Confirmation of the structure of the product of **4** with base as the epoxide **5** was complicated by the fact that reactions of 3-halopiperidines under solvolytic conditions often occur with participation of the heterocyclic nitrogen to yield pyrrolidine derivatives.[5] Reaction of the suspected epoxide, **5**, with lithium aluminum hydride gave an alcohol, *cis*-**7**, which was not identical with 1-methyl-4-phenyl-4-piperidinol (**6**) or *trans*-1-methyl-4-phenyl-3-piperidinol (*trans*-**7**).[6] The same alcohol *cis*-**7** was formed by cleavage of the oxygen ring with hydrogen over Adams catalyst. The similarity of the infrared spectra of *trans*-**7** and *cis*-**7**, the n.m.r.

(1) This material represents a portion of the research to be presented as a thesis by W. E. Krueger to the Graduate Faculty of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree.

(2) S. M. McElvain and J. C. Safranski, Jr., *J. Am. Chem. Soc.*, **72**, 3134 (1950).

(3) At higher temperatures a second product **3a** was isolated in small yield which has the structure 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol. The properties of **3a** do not correspond with any of the compounds described in ref. 2.

(4) R. E. Lyle and G. G. Lyle, *J. Am. Chem. Soc.*, **76**, 3536 (1954); U. S. Patent, 2,683,145 (July 6, 1954). The alternative 1-methyl-4-bromo-4-phenyl-3-piperidinol cannot be ruled out; however, based on the mechanism of this reaction this is a very unlikely structure.

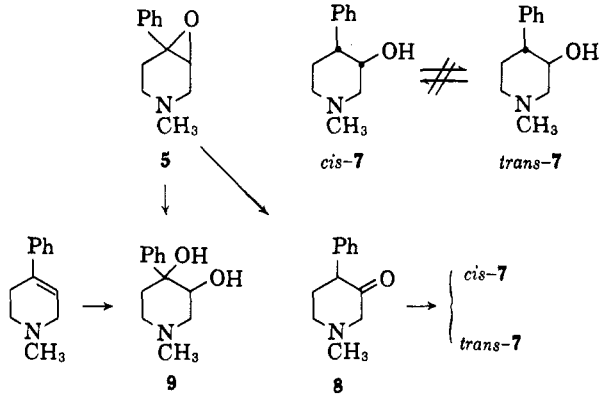
(5) R. Reitsema, *J. Am. Chem. Soc.*, **71**, 2041 (1949); R. Fuson and C. Zirkle, *ibid.*, **70**, 2760 (1948); J. Biel, L. G. Abood, W. K. Hoya, H. A. Leiser, P. A. Nuhfer, and E. F. Kluchesky, *J. Org. Chem.*, **26**, 4096 (1961); E. Smissman, R. P. Quintana, and J. H. Biel, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p. 35N; E. G. Brain, F. P. Doyle, and M. D. Mehta, *J. Chem. Soc.*, 633 (1961).

(6) The hydroboration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1**) produced *trans*-**7** (R. E. Lyle and C. K. Spicer, unpublished results, University of New Hampshire).

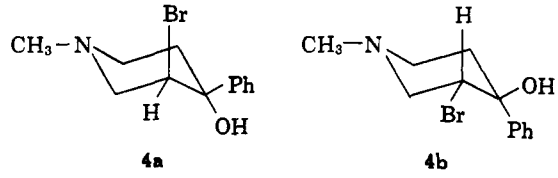
spectrum, and the anticipated stereochemistry of hydrogenolysis of an epoxide such as **5** suggested the structural assignment of *cis*-1-methyl-4-phenyl-3-piperidinol (*cis*-**7**) for this alcohol. Attempts to equilibrate the alcohols *cis*-**7** and *trans*-**7** failed starting with either alcohol.

The epimeric relationship of *cis*-**7** and *trans*-**7** was demonstrated by the formation of both alcohols by the reduction of 1-methyl-4-phenyl-3-piperidone (**8**) with lithium aluminum hydride. The ketone **8** was prepared by the rearrangement of **5** with boron trifluoride.

The reaction of the epoxide **5** with 1 *N* hydrochloric acid gave 1-methyl-4-phenyl piperidine-3,4-diol (**9**). This glycol was prepared directly from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by reaction with *m*-chloroperoxybenzoic acid in trifluoroacetic acid, further confirming the piperidine ring system in **5**.



It is further evident from a consideration of the n.m.r. spectra of the series **4**–**9** (see Table I) that these compounds contain a piperidine ring and not a pyrrolidine ring system. That rearrangement of the substituted 3-bromopiperidine system in **4** did not occur in competition with epoxide formation undoubtedly resulted because the conformation **4a**, which would allow epoxide formation, is energetically favored as compared with **4b**, which would be required for nitrogen participation and ring contraction.



Experimental

1-Methyl-3-bromo-4-phenyl-4-piperidinol Hydrobromide (4). **A.**—The reaction of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (**1**)[7] with bromine in acetic acid following the procedure of McElvain and Safranski[2] gave 80% of 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (**4**): m.p. 195–197°; $\lambda_{max}^{H_2O}$ 250, 256, 261, 268 mμ (log ε 2.17, 2.22, 2.07, 1.77).

Anal. Calcd. for $C_{12}H_{17}Br_2NO$: C, 41.04; H, 4.89. Found: C, 41.16; H, 5.16.

B.—A solution of 8.8 g. of **1** in 100 ml. of water in a standard three-neck set-up was treated with a solution of 10 g. of sodium bromide and 5.6 g. of bromine in 75 ml. of water added over a period of 0.5 hr. Evaporation of the solvent to one-half the volume caused the precipitation of 11.7 g. (95%) of **4**, m.p. 194–196°, isolated by filtration. Recrystallization from glacial acetic acid gave **4**, m.p. 196–197°, identical with that prepared by method A above.

1-Methyl-4-phenyl-3,4-epoxypiperidine (5). **A.**—A solution of 21.25 g. of 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (**4**) in 500 ml. of water in a 1-l. flask was cooled by an ice bath, and 52 ml. of a cooled 10% sodium hydroxide solution was added over a period of 5 min. The mixture was stirred for 0.5 hr., and anhydrous potassium carbonate was added until the solution was saturated. The insoluble solid was collected by filtration to give 10.6 g. (92.6%) of 1-methyl-4-phenyl-3,4-epoxypiperidine (**5**), m.p. 43–45°. An analytical sample of **5** was prepared by recrystallization from *n*-heptane at −70° to give white crystals: m.p. 45–46.5°; $\lambda_{max}^{i\text{-PrOH}}$ 253, 258, 264 mμ (log ε 2.20, 2.27, 2.13).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99. Found: C, 76.37; H, 8.05.

B.—Following the procedure of McElvain and Safranski[2] for the reaction of **4** with base an oily product was obtained which on standing overnight partially crystallized. The solid was separated by filtration to give 0.53 g. (10%) of crude 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (**3a**), m.p. 77–89°. Recrystallization of the solid from *n*-heptane gave **3a** as white needles, m.p. 104–106° (the melting point does not correspond with that of any of the products described by McElvain and Safranski[2]), $\lambda_{max}^{i\text{-PrOH}}$ 244 mμ (log ε 4.06).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99. Found: C, 76.31; H, 8.18.

The oil remaining from the isolation of **3a** was distilled under reduced pressure; and the fraction, b.p. 102–106° (1.2 mm.), 2.5 g., was found to be identical (by infrared and mixture melting point) with the **5** isolated by method A.

C.—To a slurry of 0.75 g. of lithium aluminum hydride in 75 ml. of anhydrous ether contained in a 200-ml., three-neck set-up was added 2.0 g. of **4**. The mixture was stirred for 6 hr. at room temperature, and the excess lithium aluminum hydride was decomposed with water. The precipitate was removed by filtration and was carefully washed with two 10-ml. portions of ether. The combined ether solutions were dried over anhydrous potassium carbonate and evaporated to give 1.02 g. of a pale yellow oil. Crystallization of the oil with *n*-heptane gave 0.92 g. (85.2%) of **5**, m.p. 44–46°, identical (by infrared and mixture melting point) in every respect with that isolated by method A.

Gas chromatographic analysis of the crude oil indicated that it was a mixture of approximately 90% **5** and 6.3% of the reduction product of **5**, 1-methyl-4-phenyl-3-piperidinol (*cis*-**7**) (*vide infra*).

***cis*-1-Methyl-4-phenyl-3-piperidinol (*cis*-7).** **A.**—To a slurry of 0.75 g. of lithium aluminum hydride in 50 ml. of 1,2-dimethoxyethane in a 200-ml. three-neck set-up was added 1.00 g. of solid 1-methyl-3-bromo-4-phenyl-4-piperidinol hydrobromide (**4**). The reaction mixture was heated under reflux for 2 hr., and, after cooling, the excess lithium aluminum hydride was decomposed with water. The precipitate was removed by filtration and washed with three 10-ml. portions of ether. The combined ether layers were dried over anhydrous potassium carbonate and evaporated to give 0.5 g. of a yellow oil. Crystallization of the oil from *n*-heptane gave 0.29 g. (58%) of *cis*-1-methyl-4-phenyl-3-piperidinol (*cis*-**7**), m.p. 95–97°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.45; H, 8.98.

The analysis of the crude oil by gas chromatography indicated that it was a mixture of approximately 60% *cis*-**7** and 20% **6** or *trans*-**7** (these compounds showed the same retention times on a 1-m. Carbowax 20M on Chromosorb W in series with a 1-m. silicone grease on Haloport F.)

B.—A solution of 1.0 g. of 1-methyl-4-phenyl-3,4-epoxypiperidine (**5**) in 10 ml. of ether was added dropwise to a slurry of 0.5 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. The reaction mixture was stirred at room temperature for 4 hr., and the excess lithium aluminum hydride was decomposed by addition of water. The resulting precipitate was separated by filtration and washed with two 10-ml. portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate and evaporated to give as residue 1.0 g. (98%) of *cis*-**7**, m.p. 94–97°. After recrystallization from *n*-heptane, the solid melted at 95–97° and was identical (by infrared and mixture melting point) with the *cis*-**7** obtained by method A. The analysis of the product prepared by method B indicated no impurity.

C.—A solution of 0.42 g. of 1-methyl-4-phenyl-3,4-epoxypiperidine (**5**) and 1 drop of perchloric acid in 25 ml. of methanol was hydrogenated over 0.023 g. of platinum oxide at ambient tem-

(7) C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.*, **78**, 425 (1956).

perature and pressure. After exposure to hydrogen for 24 hr., the reaction mixture was filtered, and the filtrate was dried over potassium carbonate and evaporated. The yellow residue was recrystallized from *n*-heptane to give 0.34 g. (80.9%) of *cis*-**7**, m.p. 95–97°. The product of this reaction was identical (by infrared and mixture melting point) in every respect with that obtained from methods A and B.

1-Methyl-4-phenyl-3-piperidone (8).—A solution of 2.5 g. of 1-methyl-4-phenyl-3,4-epoxypiperidine (**5**) in 25 ml. of ether was placed in a 200-ml. three-neck set-up, and 35 ml. of boron trifluoride etherate was added over a period of 5 min. The mixture was heated under reflux for 8 hr., cooled, and neutralized with 70 ml. of 5 *N* sodium hydroxide. Stirring was continued for 1 hr. The layers were separated, and the water layer was extracted with four 50-ml. portions of ether and four 50-ml. portions of chloroform. The organic layers were combined, dried over potassium carbonate, and evaporated to give 1.62 g. (65%) of crude 1-methyl-4-phenyl-3-piperidone (**8**).[8] The product was characterized as the oxime which was prepared by heating a mixture of 1.5 g. of crude **8**, 1.04 g. of hydroxylamine hydrochloride, and 0.60 g. of sodium hydroxide in a water–methanol solution. Concentration of the reaction mixture by evaporation gave 0.60 g. (37.5%) of **8** oxime, m.p. 166–168°, after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90. Found: C, 70.65; H, 8.11.

The Reduction of 1-Methyl-4-phenyl-3-piperidone (8) with Lithium Aluminum Hydride.—A solution of 5 g. of 1-methyl-4-phenyl-3-piperidone **8** in 15 ml. of 1,2-dimethoxyethane was added dropwise to a slurry of 1.0 g. of lithium aluminum hydride in 40 ml. of 1,2-dimethoxyethane. The reaction mixture was heated under reflux for 1 hr. and the excess lithium aluminum hydride was decomposed with water. The resulting precipitate was separated by filtration and washed with two 10-ml. portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate and evaporated to give 3.8 g. (76%) of a yellow oil. Gas chromatographic analysis of the crude product indicated that it was 53.6% *trans*-**7** and 20.3% *cis*-**7**. A picrate, m.p. 224–230°, isolated from the crude product was identical in every respect with the picrate of *trans*-**7**, m.p. 226–229°.[6]

1-Methyl-4-phenylpiperidine-3,4-diol (9). A.—A solution of 0.5 g. of 1-methyl-4-phenyl-3,4-epoxypiperidine (**5**) in 50 ml. of 1 *N* hydrochloric acid was stirred at room temperature for 10 hr. The mixture was saturated with potassium carbonate, and the precipitate which formed was removed by filtration. Recrystallization of the solid from acetone gave 0.47 g. (86.2%) of **9**, m.p. 157–159°. This compound seemed to be identical with the compound prepared by McElvain and Safranski[2] and was identified as **9**.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found[9]: C, 69.58; H, 8.32; N, 6.50.

B.—To a solution of 3.5 g. of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1**) in 4.8 g. of trifluoroacetic and 30 ml. of acetic acids was added a solution of 5.2 g. of *m*-chloroperoxybenzoic acid in 25 ml. of acetic acid. The reaction was exothermic and the addition required 15 min. After stirring at room temperature for 8 hr., the reaction was cooled in an ice bath; 325 ml. of 20% sodium hydroxide was added while maintaining the temperature below 40°. The mixture was extracted four times with 100-ml. portions of ether, and the ether extracts were dried over potassium carbonate. The solvent was removed from the extracts by distillation to give 3.15 g. of oily residue, which was shown by gas chromatographic analysis to contain about 37% unreacted **1**. The oily residue was dissolved in acetone, and deposited 1.35 g. (35.4%) of 1-methyl-4-phenylpiperidine-3,4-diol (**9**). On recrystallization from acetone the product was shown by infrared spectroscopy, melting point, and mixture melting point to be identical with the **9** prepared by opening the epoxide **5**.

Acknowledgment.—The authors wish to express appreciation to the National Heart Institute of the National Institutes of Health for partial support of this research by Grant HE-01713 and continuation grants. The *m*-chloroperoxybenzoic acid used in this research was generously supplied by FMC Corporation.

(8) This compound has been prepared previously but spectroscopic data were not available: for comparison, see S. M. McElvain and P. M. Laughton, *J. Am. Chem. Soc.*, **73**, 448 (1951).

(9) The analyses of **9** were obtained using an F and M carbon, hydrogen, and nitrogen analyzer, Model 180, and represent an average of three determinations.

Ring Closure of Ylidenemalononitriles. IV.[1,2a] Attempted Cyclizations of Saturated Malononitrile Derivatives

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Cyclization attempts employing concentrated sulfuric acid or polyphosphoric acid with saturated malononitrile derivatives obtained from the reduction of various ylidenemalononitriles produced only diamides and sulfonated products in the β-arylpropanonitrile and δ-arylpentanonitrile series, with one exception. A bulky *t*-butyl group in the former promoted cyclization to form an indenamine. The enamine was converted to an indanone, whose structure was proved by an unequivocal synthesis. Acylation reactions of the enamine gave only N-acylation followed by an intramolecular condensation to form pyrimidone derivatives. Steric effects on the cyclization of arylidenemalononitriles and their saturated analogs are discussed.

The formation of five- and six-membered rings by the cyclization of ylidenemalononitriles has been reported in previous papers.[1,3] It was noted that a bulky group R was essential in cyclizations forming five-membered rings (**1** → **2**).[3b] Benzylidenemalono- (PPA), whereas α-cyano-β-phenylcinnamonitrile (**1**, nitrile (**1**, R = H) did not yield cyclized products from concentrated sulfuric acid or polyphosphoric acid R = phenyl) cyclized to form 2-cyano-3-phenyl-1-indenone (**2**, R = phenyl, Z = CN) in an 80% yield. Since **1** contains a conjugated system, it was suggested that a bulky group was necessary to provide distortion of this ring-deactivating resonance system, thus facilitating electrophilic attack by the protonated nitrile group.[3c]

A bulky group was apparently not necessary in the formation of six-membered rings (**3** → **4**),[1] since good

(1) Previous paper, III: E. Campaigne, D. R. Maulding, and W. L. Roelofs, *J. Org. Chem.*, **29**, 1543 (1964).

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(3) (a) E. Campaigne and G. F. Bulbenko, *J. Org. Chem.*, **26**, 4703 (1961); (b) E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum, and D. R. Maulding, *ibid.*, **27**, 4428 (1962); (c) E. Campaigne, R. Subramanya, and D. R. Maulding, *ibid.*, **28**, 623 (1963); E. Campaigne and D. R. Maulding, *ibid.*, **28**, 1391 (1963).