Tetrahedron, 1963. Vol. 19, pp. 2135 to 2143. Pergamon Press Ltd. Printed in Northern Ireland

STUDIES ON CONFORMATION—I

PREPARATION AND STEREOCHEMISTRY OF SOME 4-PIPERIDINOLS[1]

M. BALASUBRAMANIAN and N. PADMA

Department of Chemistry, Annamalai University,
Annamalainagar, India

(*Received* 13 *May* 1963)

Abstract—The reduction of a number of 4-piperidones by different methods afforded epimeric pairs of 4-piperidinols. Methods of formation, isomerization studies and the degree of adsorption on alumina indicate their conformation. The stereochemical course of the reductions is discussed.

THE principles of conformational analysis, as applied to cyclohexane derivatives, are also applicable to six-membered heterocyclic compounds having nitrogen, oxygen or sulphur in the ring.[2] Extensive studies on tropane alkaloids by Fodor *et al.*[3–5] have established that the piperidine ring mostly prefers the chair conformation. Investigations on cocaine epimers,[6] lupine alkaloids[7,8] and dihydrolysergic acids[9] also demonstrate a chair conformation for the piperidine ring. However, conformational studies on simple piperidine derivatives have been very much limited. Determination of molar Kerr constants showed that piperidine, N-methylpiperidine, N-phenylpiperidine and morpholine exist in the stable chair form.[10] Dipole moment measurements on 4-piperidinol[11] and N-ethyl-4-piperidone[12] also lead to the same conformation for the ring.

Some examples of the piperidine ring preferring a boat conformation are also known. 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol[13] and phenyl 3α-phenyl-3β-tropanyl ketone[14] have been shown to exist in the boat form. Pseudotropine is

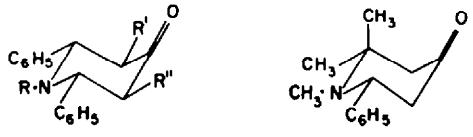
[1] Part of this work has been published as a preliminary communication in *Tetrahedron Letters* No. 14, 23 (1960).
[2] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10,** 44 (1956).
[3] G. Fodor, *Magyar Tud. Akad. Kem. Tud. Osztályának Közlémenyei* **3,** 311 (1953); **5,** 351 (1954).
[4] G. Fodor and K. Nádor, *Nature, Lond.* **169,** 462 (1952); *J. Chem. Soc.* 721 (1953).
[5] G. Fodor and O. Kovács, *J. Chem. Soc.* 724 (1953).
[6] S. P. Findlay, *J. Amer. Chem. Soc.* **75,** 4624 (1953); **76,** 2855 (1954).
[7] A. F. Thomas, H. J. Vipond and L. Marion, *Can. J. Chem.* **33,** 1290 (1955); J. Ratuský, A. Reiser and F. Sorm, *Chem. Listy* **48,** 1794 (1954); F. Galinovsky and H. Nesvadba, *Monatsh.* **85,** 1300 (1954).
[8] F. Galinovsky, P. Knoth and W. Fischer, *Monatsh.* **86,** 1014 (1955).
[9] A. Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann and Hs. H. Günthard, *Helv. Chim. Acta* **37,** 2039 (1954); J. B. Stenlake, *J. Chem. Soc.* 1626 (1955).
[10] M. Aroney and R. J. W. Le Fèvre, *J. Chem. Soc.* 3002 (1958); 2161 (1960).
[11] G. Fodor and J. Lestyán, *Magyar Kém. Folyóirat* **59,** 240 (1953).
[12] N. J. Leonard, D. F. Morrow and M. T. Rogers, *J. Amer. Chem. Soc.* **79,** 5476 (1957).
[13] R. E. Lyle, *J. Org. Chem.* **22,** 1280 (1957).
[14] M. R. Bell and S. Archer, *J. Amer. Chem. Soc.* **82,** 151 (1960).

considered to exist as an equilibrium mixture of chair and boat forms.[15] The present work was undertaken in order to study the conformation of some simple piperidine derivatives.

An elegant synthesis of 2,6-diaryl-4-piperidones has been developed by Baliah *et al.*[16–18] The condensation of an aliphatic ketone, an aromatic aldehyde and ammonia or an aliphatic primary amine afforded the 4-piperidones. Although some of these have been reduced to the 4-piperidinols,[19–21] a systematic investigation of their stereochemistry has not been carried out. The reduction of some of the piperidones by (1) sodium and n-butanol, (2) the Meerwein–Ponndorf–Verley (MPV) method and (3) lithium aluminium hydride is reported in this paper.

The stereochemistry of the 4-piperidones

Each of the 4-piperidones (I to VII), on reduction, afforded two epimeric 4-piperidinols. This shows that 2,6-diphenyl-4-piperidone and its N-methyl derivative have the *cis* orientation of the phenyl groups; a *trans* configuration should lead to a single 4-piperidinol. The *cis* orientation of the phenyl groups was also shown by the failure[21] to resolve 1-methyl-2,6-diphenyl-4-piperidone. In the chair conformation of the piperidone, the two phenyl groups should occupy the equatorial positions. Any contribution from the alternative chair conformation could be ruled out, since this would require the bulky phenyl groups to occupy 1,3-diaxial positions. Studies on cyclohexane derivatives showed that the phenyl group has a large preference for the equatorial position.[22] Consequently, *cis*-2,6-diphenyl-4-piperidone and its N-methyl derivative could be assumed to be anchored in a single chair conformation I and II, respectively. However, the possible contribution of a boat or a twist conformation cannot be ruled out.



VII

I R = R′ = R″ = H
II R = CH_3, R′ = R″ = H
III R = R′ = H, R″ = CH_3
IV R = R′ = CH_3, R″ = H
V R = H, R′ = R″ = CH_3
VI R = R′ = R″ = CH_3

[15] B. L. Zenitz, C. M. Martini, M. Priznar and F. C. Nachod, *J. Amer. Chem. Soc.* **74**, 5564 (1952); G. R. Clemo and K. H. Jack, *Chem. & Ind.* 195 (1953).
[16] C. R. Noller and V. Baliah, *J. Amer. Chem. Soc.* **70**, 3853 (1948).
[17] V. Baliah, A. Ekambaram and T. S. Govindarajan, *Current Sci. (India)* **23**, 264 (1954).
[18] V. Baliah and V. Gopalakrishnan, *J. Indian Chem. Soc.* **31**, 250 (1954); V. Baliah and T. S. Govindarajan, *Current Sci. (India)* **23**, 91 (1954); V. Baliah, V. Gopalakrishnan and T. S. Govindarajan, *J. Indian Chem Soc.* **31**, 832 (1954).
[19] V. Baliah and A. Ekambaram, *J. Indian Chem. Soc.* **32**, 274 (1955).
[20] E. A. Mailey and A. R. Day, *J. Org. Chem.* **22**, 1061 (1957).
[21] R. E. Lyle and G. G. Lyle, *J. Org. Chem.* **24**, 1679 (1959).
[22] A. C. Huitric and W. D. Kumler, *J. Amer. Chem. Soc.* **78**, 614 (1956); E. J. Corey, M. G. Howell, A. Boston, R. L. Young and R. A. Sneen, *Ibid.* **78**, 5036 (1956); E. L. Eliel and M. N. Rerick, *Ibid.* **82**, 1367 (1960).

In the condensation leading to the formation of 4-piperidones only a single isomer was obtained,[16–18] usually in a high yield, even though the possibility of the formation of a mixture of stereoisomers exists. This leads to the reasonable assumption that the condensation affords the thermodynamically more stable stereoisomer, namely, *cis*-2,6-diaryl-4-piperidones. In the case of 3-methyl-, 1,3-dimethyl-, 3,5-dimethyl- and 1,3,5-trimethyl-2,6-diphenyl-4-piperidone (III to VI), the methyl groups α to the carbonyl are also in the stable equatorial orientation. Each of these piperidones was recovered unchanged after treatment with refluxing ethanolic solution of sodium ethoxide.

1,2,2-Trimethyl-6-phenyl-4-piperidone, which was also included in this study, was prepared by the condensation of diacetonamine oxalate with benzaldehyde, followed by methylation of the product, 2,2-dimethyl-6-phenyl-4-piperidone.[23,24] This piperidone should be represented by the conformation VII; the alternative chair form would have severe 1,3-diaxial interaction between the axial methyl and phenyl groups.

Since these 4-piperidones are largely anchored in a single chair form, their reduction was expected to lead to stereoisomers with either an equatorial or axial hydroxyl. The equatorial hydroxyl would be *cis* to the phenyl groups and the axial hydroxyl would be *trans* to the phenyl groups. Consequently, establishment of the conformation of the hydroxyl would also lead to the configuration of the piperidinols.

Reduction with sodium and n-butanol

The products obtained in the reduction of the 4-piperidones with sodium and n-butanol was purified by chromatography on alumina. Each of the piperidones (I to VII) afforded a single alcohol, designated as the α-form. Except for small quantities of lower melting mixtures no other isomer could be isolated by chromatography. The results are recorded in Table 1. From the evidence accumulated in the field of steroids Barton[25] has shown that the reduction of polycyclic ketones with sodium and alcohol leads to a mixture in which the alcohol with an equatorial hydroxyl preponderates. Reduction of tropinone and related ketones with sodium and alcohol also afforded[26] the epimer with an equatorial hydroxyl as the major product. On this basis, the α-forms of the 4-piperidinols might be expected to have the hydroxyl in the equatorial orientation, the heterocyclic ring existing in the chair form. Consequently, the α-form would have the hydroxyl *cis* to the phenyl groups.

Reduction by the Meerwein–Ponndorf–Verley method

This method afforded two epimeric 4-piperidinols the α- and the β-form from each piperidone; the α-form was identical with the one obtained in the sodium/n-butanol reduction. On chromatography over alumina, the β-isomer was eluted first. In general, cyclohexanols with an equatorial hydroxyl group are more strongly adsorbed than those with an axial hydroxyl.[25,27] Therefore, the β-forms of the

[23] E. Fischer, *Ber. Dtsch. Chem. Ges.* **16,** 2236 (1883).
[24] P. W. Neber, A. Burgard and W. Thier, *Liebigs Ann.* **526,** 277 (1936).
[25] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).
[26] C. L. Zirkle, F. R. Gerns, A. M. Pavloff and A. Burger, *J. Org. Chem.* **26,** 395 (1961).
[27] H. E. Ungnade, *J. Org. Chem.* **13,** 361 (1948); S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* **77,** 5562 (1955).

TABLE 1. COMPOSITION OF THE PRODUCTS FROM THE REDUCTION OF 4-PIPERIDONES AND THE EQUILIBRATION OF THE 4-PIPERIDINOLS

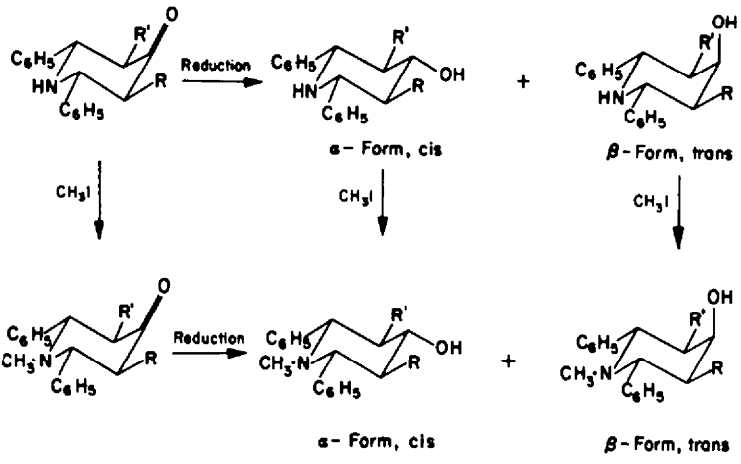
Piperidone reduced	Total recovery	Yield of the epimeric 4-piperidinols		Yield of the α-form from the equilibration mixture
		α-form	β-form	
	Reduction by sodium and n-butanol			
I	85%	80%	—	93%
II	95	73	—	85
III	87	64	—	88
IV	92	90		90
V	90	90	—	—
VI	99	89	—	—
VII	27	84	—	76
	Reduction by the MPV method			
I	80%	29%	53%	
II	94	30	56	
III	83	22	57	
IV	81	29	54	
V	82	—	73	
VI	87	16	74	
VII	91	—	88	
	Reduction by $LiAlH_4$			
I	98%	90%	—	
II	97	92	—	
III	97	86·5	—	
IV	93	86	—	
V	92	56	16	
VI	98	55	36	
VII	92	33	60	

4-piperidinols might be considered to have the axial hydroxyl (*trans* with respect to the phenyl groups). Such an assignment is also in agreement with the predominant formation of the α-form in the sodium/n-butanol reduction. Further evidence in favour of this assignment was obtained by subjecting the piperidinols to equilibration with sodium ethoxide in refluxing xylene. It was found that the β-form of the piperidinols obtained from piperidones I to IV and VII was epimerized to the corresponding α-isomer which was obtained in a high yield after chromatography of the equilibration mixture (see Table 1). However, neither the β- nor the α-form of 3,5-dimethyl-2,6-diphenyl- and 1,3,5-trimethyl-2,6-diphenyl-4-piperidinol underwent epimerization. The starting materials were recovered unchanged after heating with sodium ethoxide in refluxing xylene. On heating with potassium t-butoxide in decalin at 200° extensive decomposition occurred. Refluxing for 140 hours with aluminium isopropoxide in isopropanol also resulted in the recovery of the unchanged material.

The stereochemistry of the piperidinols bas been further confirmed by a study of their IR spectra and kinetics of acetylation with acetic anhydride in pyridine.[28] The

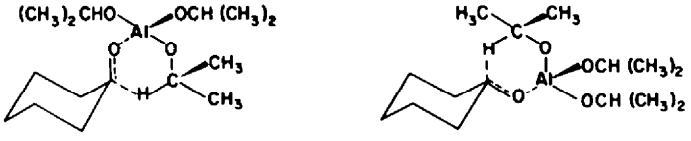
[28] M. Balasubramanian and N. Padma, unpublished work.

2,6-diphenyl-4-piperidinols were also inter-related by methylation with methyl iodide as shown below.



Considering the relative amounts of the two isomers formed in the MPV reduction, it will be seen from Table 1 that the β-forms were obtained in larger amounts than the α-forms. Since the β-forms have the axial hydroxyl, there is a general tendency for the MPV reduction to afford more of the epimer with the axial hydroxyl. This tendency is much greater in the case of the hindered ketones V to VII.

Generally, the MPV reduction is considered to proceed through a cyclic transition state, the reduction proceeding through the initial co-ordination of the carbonyl oxygen with aluminium followed by the transfer of a hydride ion to the carbonyl carbon.[29,30] On this basis two cyclic transition states (A and B) are possible for the reduction of a cyclohexanone. In A the hydride ion approaches the equatorial side of the developing cyclohexanol, leading to an axial hydroxyl and in B the approach is from the axial side, resulting in the formation of an equatorial hydroxyl.



A B

Examination of Courtald scale models reveals a greater hindrance to the axial approach of the isopropoxy hydrogen than to the equatorial approach. Consequently, a substituted cyclohexanone or any six-membered ring ketone with the ring anchored in a single chair conformation should lead to more of the isomer with an axial hydroxyl than that with an equatorial hydroxyl. This is supported by the present study.

Jackman *et al.*[30] studied the MPV reduction of some substituted cyclohexanones.

[29] R. B. Woodward, N. L. Wendler and F. J. Brutschy, *J. Amer. Chem. Soc.* **67**, 1425 (1945); R. E. Lutz and J. S. Gillespie, Jr., *ibid.* **72**, 344 (1950); W. von E. Doering and T. C. Aschner, *ibid.* **75**, 393 (1953); E. D. Williams, K. A. Krieger and A. R. Day, *ibid.* **75**, 2404 (1953).

[30] L. M. Jackman, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.* 2641 (1949).

According to them, as the apparent degree of steric hindrance of the carbonyl group increases owing to the proximity of bulky alkyl groups, the yield of the *cis* isomer (with an axial hydroxyl) increases. For example, they report the formation of 40% of *cis*-4-methylcyclohexanol, 50% of *cis*-2-methylcyclohexanol and 70% of neomenthol during the reduction of the corresponding methylcyclohexanones and menthone, respectively. Our results indicate that the presence of one methyl group, α to the carbonyl, in the piperidones does not make any appreciable change in the isomer ratio of the alcohols formed. On the other hand, the presence of two methyl groups at 3 and 5 positions of the 4-piperidone or an axial methyl group, β to the carbonyl, greatly increases the yield of the epimer with an axial hydroxyl. In contrast to these results, Hardy and Wicker[31] reported a 75% yield of *cis*-3,3,5-trimethylcyclohexanol (with an equatorial hydroxyl) in the reduction of dihydroisophorone by the MPV method. They also report the formation of only 37% of the *cis* alcohol from 2-methylcyclohexanone. However, in considering the stereoisomeric composition of the reduction product, the possibility of isomerization of the less stable alcohol to the more stable epimer under the catalysing influence of aluminium isopropoxide should be taken into account. Unless this possibility is excluded, the composition of the reduction product will not reflect the stereochemical course of the reduction. In the present study, it was found that no epimerization occurred if the duration of the reduction did not exceed 3 hr. An increase in the time of reduction led to more of the α-form. A similar observation was made by Beckett *et al.*[32]

Reduction with lithium aluminium hydride

The stereochemistry of reduction with $LiAlH_4$ and other complex metal hydrides has been the subject of several investigations.[31–34] Barton[25] suggested that an unhindered ketone is reduced chiefly to the more stable alcohol with the equatorial hydroxyl and a hindered ketone yields predominantly the epimer with the axial hydroxyl. Dauben *et al.*[34] proposed that the stereoisomeric composition of the products is controlled by (1) the steric hindrance to the approach of the reagent ('steric approach control') and (2) the relative thermodynamic stability of the stereoisomers formed ('product development control'). Beckett *et al.*[32] investigated the reduction of tropinone with complex metal hydrides and aluminium isopropoxide and their results largely support the conclusions reached by Dauben *et al.*[34]

It will be seen from Table 1 that piperidones, I to IV, on reduction with $LiAlH_4$, afforded only the more stable α-form. The almost similar yields of the α-form of the piperidinols, obtained from the 3-methyl-4-piperidones (III and IV) as well as the 3,5,-unsubstituted 4-piperidones (I and II), indicate that the presence of one methyl group, α to the carbonyl group has very little effect on the ratio of the epimers formed as in the case of the MPV reduction. The chief factor controlling the reduction of these piperidones with $LiAlH_4$ is the relative stability of the epimers formed. $LiAlH_4$

[31] K. D. Hardy and R. J. Wicker, *J. Amer. Chem. Soc.* **80**, 640 (1958).

[32] A. H. Beckett, N. J. Harper, A. D. J. Balon and T. H. E. Watts, *Tetrahedron* **6**, 319 (1959).

[33] H. R. Nace and G. L. O'Connor, *J. Amer. Chem. Soc.* **73**, 5824 (1951); D. J. Cram and F. A. Abd Elhafez, *Ibid.* **74**, 5828 (1952); D. S. Noyce and D. B. Denney, *Ibid.* **72**, 5743 (1950); D. M. S. Wheeler and J. W. Huffman, *Experientia* **16**, 516 (1960); see also N. G. Gaylord, *Reduction with Complex Metal Hydrides* pp 88–89, 149–151, 159. *Interscience*, New York, N.Y. (1956); L. F. Fieser and M. Fieser, *Steroids* p. 268. Reinhold, New York, N.Y. (1959).

[34] W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Amer. Chem. Soc.* **78**, 2579 (1956).

reduction of 3,5-dimethyl-4-piperidones (V and VI) has led to the formation of a larger proportion of the β-form. Since the resulting piperidinols failed to undergo epimerization, no conclusion is possible as to the factors responsible for the formation of larger amount of the β-forms from these piperidones. The preponderance of the less stable β-form in the reduction product of 1,2,2-trimethyl-6-phenyl-4-piperidone indicates that the axial methyl group in VII severely hinders the approach of the reagent from the axial side. Preferential approach from the equatorial side should lead to more of the less stable piperidinol with an axial hydroxyl.

EXPERIMENTAL

All m.ps. are uncorrected. E. Merck's Brockmann grade alumina was used for chromatography. Ethereal solutions were dried with anhydrous sodium sulphate.

2,6-*Diphenyl*-4-*piperidone* (I). Following the method of Baliah *et al.*[17] a mixture of acetone (58 g), benzaldehyde (212 g) and anhydrous ammonium acetate (77 g) in ethanol (95%, 80 ml) was heated on a water-bath with constant shaking until the contents became pale orange in colour. The reaction mixture was treated with ether (500 ml) and filtered. Addition of conc. hydrochloric acid (50 ml) to the clear filtrate afforded the hydrochloride of the piperidone (62 g, m.p. 216–217° with dec.) which was collected after washing several times with ethanol–ether (1:5). The free base, m.p. 104–105° (from ethanol) was obtained by treating a suspension of the hydrochloride in acetone with aqueous ammonia, followed by dilution with water.

1-*Methyl*-2,6-*diphenyl*-4-*piperidone* (II). A mixture of the above piperidone (10 g), anhydrous potassium carbonate (10 g) and methyl iodide (5 ml) in acetone (100 ml) was refluxed for 3 hr. After removal of the acetone by distillation, dilution with water and treatment with aqueous ammonia afforded the N-methyl-4-piperidone, m.p. 147–149° (from ethanol yield, 95%). Riedel[35] reports m.p. 152–153°.

3-*Methyl*-2,6-*diphenyl*-4-*piperidone* (III). A solution of anhydrous ammonium acetate (39 g) in glacial acetic acid (50 ml) was mixed with benzaldehyde (106 g) and methyl ethyl ketone (36 g), heated to boil and allowed to stand overnight. Addition of conc. hydrochloric acid afforded the hydrochloride (65 g) which melted at 224–226° with dec. after recrystallization from ethanol–ether. The free base, obtained by neutralization of the hydrochloride with aqueous ammonia, was recrystallized from ethanol, m.p. 96–97°. Noller and Baliah[16] report m.p. 86–87°.

1,3-*Dimethyl*-2,6-*diphenyl*-4-*piperidone* (IV). This was obtained in 97% yield by the methylation of the above piperidone with methyl iodide and anhydrous potassium carbonate in acetone, m.p. 130–131° (from ethanol); lit.[16] 130–131°.

3,5-*Dimethyl*-2,6-*diphenyl*-4-*piperidone* (V). Employing a mixture of diethyl ketone, benzaldehyde and anhydrous ammonium acetate, this was obtained as described in the lit.[16] The reaction mixture, on cooling, afforded the piperidone as long needles (yield, 75%). After recrystallization from ethanol, it melted at 132–133°, lit.[16] 131–133°.

1,3,5-*Trimethyl*-2,6-*diphenyl*-4-*piperidone* (VI). The 3,5-dimethyl-4-piperidone (V) was methylated by the usual procedure. The N-methyl derivative was recrystallized from ethanol, m.p. 91–92°. Noller and Baliah[16] report the same m.p.

1,2,2-*Trimethyl*-6-*phenyl*-4-*piperidone* (VII). 2,2-Dimethyl-6-phenyl-4-piperidone was prepared by the method of Fischer[36] by refluxing a solution of diacetoneamine hydrogen oxalate[36] (127 g) and benzaldehyde (127 g) in anhydrous ethanol (375 ml) for a period of 30 hr with frequent removal of the precipitated piperidone oxalate by filtration. The total yield of the oxalate amounted to 90 g. Treatment of this with aqueous potassium hydroxide, followed by ether-extraction and drying afforded the dimethyl-4-piperidone, recrystallized from ligroin as colourless prisms, m.p. 61–62°. This was immediately methylated with methyl iodide and potassium carbonate in acetone under reflux (1·5 hr). Acetone was removed in a current of dry air and the residue was diluted with water and made alkaline. The precipitated 1,2,2-trimethyl-6-phenyl-4-piperidone (yield, quantitative) was recrystallized from ethanol–water, m.p. 77–78°, lit[34] 78°.

Attempted isomerization of 3-*methyl and* 3,5-*dimethyl substituted* 4-*piperidones* (III to VI). Each piperidone (0·5 g) was treated under reflux (5 hr) with an ethanolic solution of sodium ethoxide

[35] J. D. Riedel, D. R. P. 269429, *Chem. Zentr.* **1**, 507, (1914).

[36] A. E. Everest, *J. Chem. Soc.* 588 (1919).

(prepared from 0·1 g of sodium and 10 ml of ethanol). After removal of the ethanol, the residue was extracted with ether, washed, dried and the base was precipitated as the hydrochloride. In all the cases more than 90% of the starting compound was recovered.

Reduction of 4-piperidones

With sodium and n-butanol. A solution of the piperidone (1 g) in n-butanol (80 ml) was heated to boil and sodium (25–30 equivalents) was added in small pieces at such a rate that the solution was kept refluxing. After the addition, the mixture was kept refluxing by external heating until sodium butoxide began to separate. Any unreacted sodium was destroyed by the addition of methanol. After dilution with water, the organic layer was separated, washed with water and the major portion of butanol was distilled off. The residue was taken up in ether, dried and treated with a saturated solution of hydrogen chloride in dry ether (5 ml). The precipitated hydrochloride was collected, washed with ether and treated, as a suspension in acetone, with aqueous ammonia. The acetone solution afforded the free base on dilution with water. The crystalline product was dried and subjected to chromatography.

TABLE 2. 4-PIPERIDINOLS AND THEIR PROPERTIES

No.	4-Piperidinol	M.p. (°C)	Crystalline form	Analyses Found C	Found H	Calc. C	Calc. H
1.	2,6-Diphenyl, α-form	123–124[a]	Needles	81·10	7·49	80·61	7·56
2.	2,6-Diphenyl, β-form	139–140[a]	Shining flakes	80·46	7·12	80·61	7·56
3.	1-Methyl-2,6-diphenyl, α-form	163–164[b]	Light feathers	81·14	7·60	80·85	7·92
4.	1-Methyl-2,6-diphenyl, β-form	171–172[b]	Needles	81·30	7·70	80·85	7·92
5.	3-Methyl-2,6-diphenyl, α-form	123–124[c]	Fine needles	81·1	7·7	80·85	7·92
6.	3-Methyl-2,6-diphenyl, β-form	93–94	Needles	81·1	8·1	80·85	7·92
7.	1,3-Dimethyl-2,6-diphenyl, α-form	72–74	Shining flakes	76·67	8·35	76·25	8·36
8.	1,3-Dimethyl-2,6-diphenyl, β-form	70–72	Short needles	76·15	8·97	76·25	8·36
9.	3,5-Dimethyl-2,6-diphenyl, α-form	133–134[d]	Needles	80·93	7·78	81·10	8·24
10.	3,5-Dimethyl-2,6-diphenyl, β-form	111–112[e]	Flakes	81·43	8·37	81·10	8·24
11.	1,3,5-Trimethyl-2,6-diphenyl, α-form	133–134[f]	Shining flakes	81·19	9·01	81·32	8·53
12.	1,3,5-Trimethyl-2,6-diphenyl, β-form	99–100[f]	Fine needles	81·30	8·66	81·32	8·53
13.	1,2,2-Trimethyl-6-phenyl, α-form	93–94	Flakes	75·95	10·23	76·70	9·65
14.	1,2,2-Trimethyl-6-phenyl, β-form	123–124	Stout needles	77·03	9·77	76·70	9·65

Nos. 1, 2, 3, 5, 6, 10, 11, 13 and 14 were recrystallized from light petroleum (b.p. 60–80°). Nos. 4, 7, 8, 9 and 12 were recrystallized from ethanol–water. Nos. 7 and 8 crystallized with a molecule of water.

[a] Baliah and Ekambaram[19] report m.p. 99–101° and 135–136° for their products obtained in the MPV reduction. [b] Lyle and Lyle[21] report m.p. 155–156° and 171–172° for the products obtained from the MPV reduction and $LiAlH_4$ reduction, respectively. [c] Lit[19] 123–124°. [d] Mailey and Day[20] obtained this isomer by $LiAlH_4$ reduction. [e] Lit[19] 110–111°. [f] Baliah and Ekambaram[19] report m.p. 126–128° and 90–92° for the two isomers from the MPV reduction.

The Meerwein–Ponndorf–Verley–reduction. The procedure of Wilds[37] was followed. The piperidone (0·02 mole) in isopropanol (40 ml) was added to a solution of aluminium isopropoxide in isopropanol (prepared from 2·2 g of aluminium and 80 ml of the alcohol), kept in a 500 ml flask fitted with a Liebig condenser with water drained off. A splash head was attached to the top of the condenser and a second condenser, set for downward distillation, was attached to the splash head. Refluxing and testing for acetone were carried out as described in the lit.[37] After a negative test for acetone (2–3 hr), most of the excess of isopropanol was removed by distillation under diminished pressure (water-pump) and the residue was hydrolysed with ice-cold water (200 ml) containing conc. hydrochloric acid (60 ml). After allowing to stand overnight, the solid that separated was removed by filtration. The filtrate, on concentration to half its bulk, afforded more of the solid. The product consisted of a mixture of hydrochlorides of the epimeric 4-piperidinols. The mixture was treated with aqueous ammonia and the resulting mixture of bases was separated by chromatography.

With lithium aluminium hydride. A suspension of $LiAlH_4$ (0·02 mole) in dry ether (25 ml) was stirred vigorously for 15 min. To the resulting slurry, a solution of the piperidone (0·5 g) in dry ether (50 ml) was added dropwise. The mixture was heated under reflux for 2 hr with stirring. Refluxing was maintained for 4–5 hr for the hindered ketones. After destroying the excess of hydride by cautious addition of ice-water, the ethereal layer was separated, dried and stripped of ether. The residue was subjected to chromatography.

Chromatographic separation of the mixture of epimeric 4-piperidinols. For 1 g of the mixture, 25 g of alumina was used. Elutions were carried out with light petroleum (b.p. 40–60°), light petroleum–benzene (1 : 1), benzene, benzene–ether (1 : 1) and ether in the order given. The reduction product was dissolved in the minimum quantity of benzene and fixed on the column. About four 20 ml fractions were collected with each eluent. The solvent was removed on a water-bath and the last traces were removed under red. press. The m.p. and the yield of each fraction were determined. The fractions melting at the same temp. were collected and further purified by crystallization from appropriate solvent or by rechromatography. The β-forms of the piperidinols were obtained from the light petroleum–benzene and benzene eluates and the α-forms from the benzene–ether and ether eluates.

N-*Methylation of the 4-piperidinols.* Each of the secondary amino alcohols was methylated with methyl iodide in refluxing acetone in the presence of anhydrous potassium carbonate. The resulting N-methyl-4-piperidinol was identical (m.p. and mixed m.p.) with the corresponding epimer obtained by the reduction of the N-methyl-4-piperidone.

Isomerization of the 4-piperidinols. The pure β-isomer of the piperidinol (0·5 g) was heated (5 hr) with sodium ethoxide (prepared from 2 g of sodium) and dry xylene (10 ml) in an oil bath at 150–160°. Xylene was removed by distillation under red. press. and the residue was treated with water, ether-extracted and dried. The piperidinol was precipitated as the hydrochloride. The base, after liberation, was purified by chromatography followed by recrystallization. The results are recorded in Table 1.

Acknowledgements—The authors are grateful to Professor V. Baliah for his interest and encouragement. They also thank the University Grants Commission for the award of a scholarship to one of them (N. P.).

[37] A. L. Wilds in *Organic Reactions* edited by R. Adams, Vol. II, p. 198. John Wiley, New York (1947).