Tetrahedron Letters No.14, pp. 23-26, 1960. Pergamon Press Ltd. Printed in Great Britain

CONFORMATION OF SOME 4-HYDROXYPIPERIDINES

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(Received 1 June 1960)

ALTHOUGH a number of substituted 4-hydroxypiperidines are known,[1,2] a thorough study of the conformation of such compounds is limited to tropine and ψ-tropine.[3] Conformational analysis is made difficult in this type of compounds due to the flexibility of the heterocyclic ring. Baliah *et al.*[4] synthesized a number of 2,6-diaryl-4-piperidones. The bulky aromatic substituents in these compounds should restrict the ring to a single chair form, particularly when they are *cis* and occupy equatorial positions. The failure to resolve 1-methyl-2,6-diphenyl-4-piperidone has been ascribed to the *cis* relationship of the two phenyl groups.[5] The same configuration can be expected for similar

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[1] A. Ziering and J. Lee, *J.Org.Chem.* **12**, 911 (1947); and earlier papers; I.N. Nazarov, D.V. Sokolov and V.N. Rakcheeva, *Izv.Akad.Nauk SSSR, Otdel.Khim.Nauk* 80 (1954); *Chem.Abstr.* **49**, 6248 (1955); and earlier papers.

[2] V. Baliah and A. Ekambaram, *J.Indian Chem.Soc.* **32**, 274 (1955).

[3] W. Klyne, *Progress in Stereochemistry* Vol. 1, p. 80. Butterworths, London (1954).

[4] C.R. Noller and V. Baliah, *J.Amer.Chem.Soc.* **70**, 3853 (1948); V. Baliah and V. Gopalakrishnan, *J.Indian Chem.Soc.* **31**, 250 (1954); V. Baliah, V. Gopalakrishnan and T.S. Govindarajan, *J.Indian Chem.Soc.* **31**, 832 (1954); V. Baliah, A. Ekambaram and T.S. Govindarajan, *Curr.Sci. (India)* **23**, 264 (1954); V. Baliah and A. Ekambaram, *Sci. & Cult. (India)* **20**, 193 (1954).

[5] R.E. Lyle and G.G. Lyle, *J.Org.Chem.* **24**, 1679 (1959).

piperidones. The reduction of these compounds by the Meerwein - Ponndorf - Verley (MPV) method has been reported[2] to yield isomeric 4-hydroxypiperidines, designated as α- and β-forms. Assuming a chair conformation for the ring, the hydroxyl would be equatorial in one form and axial in the other. We report in this communication a study of the conformation of these hydroxy compounds.

The piperidones were reduced by (1) the MPV method, (2) sodium and n-butanol and (3) lithium aluminium hydride. The MPV method gave a mixture of α- and β-forms which were separated by chromatographic adsorption on alumina. The other two methods gave chiefly a single isomer, the α-form. This was also purified by chromatography. It may be noted that most of the compounds obtained by earlier workers[2,5] were not adequately pure.

Reduction of 2,6-diphenyl-4-piperidone, A by the MPV method gave Iα [m.p. 123-124°, lit.[2] 99-101°; γ cm^{-1} (CS_2) 3546 (free OH), 3247 (bonded OH)]. (Found: C, 81.10; H, 7.49. $C_{17}H_{19}NO$ requires C, 80.61; H, 7.56.) and Iβ [m.p. 139-140°, lit.[2] 135-136°; γ cm^{-1} (CS_2) 3571 (free OH)]. (Found: C, 80.46; H, 7.12. $C_{17}H_{19}NO$ requires C, 80.61; H, 7.56). 1-Methyl-2,6-diphenyl-4-piperidone, B gave IIα [m.p. 163-164°, lit.[5] 170-172.5°; γ cm^{-1} (CS_2) 3584 (free OH), 3205 (bonded OH)]. (Found: C, 81.14; H, 7.60. $C_{18}H_{21}NO$ requires C, 80.85; H, 7.92) and IIβ [m.p. 170-171°, lit.[5] 155-156°; γ cm^{-1} (CS_2) 3560 (free OH)]. (Found: C, 81.30; H, 7.70. $C_{18}H_{21}NO$ requires C, 80.85; H, 7.92). Repeated chromatography of IIα on alumina did not improve the melting point. Lyle and Lyle[5] report the product from the MPV reduction melting at 155-156° as a pure isomer but it should be a mixture of the two forms. Our product from the MPV method melted at 140-150° before separation of the two forms. Reduction of A and B with sodium and n-butanol or with $LiAlH_4$ furnished a single isomer in each case, Iα and IIα respectively. Heating of Iβ or IIβ with sodium ethoxide in refluxing xylene gave the corresponding α-form in high yield. The alcohols IIα and IIβ were also obtained by the methylation of Iα and Iβ with methyl iodide and potassium carbonate in refluxing acetone.

Reduction of 3,5-dimethyl-2,6-diphenyl-4-piperidone, C by the MPV method yielded chiefly IIIβ [m.p. 111-112°, lit.[2] 110-111°; γ cm^{-1} (CS_2) 3560 (free OH)]. (Found: C, 81.43; H, 8.37. $C_{19}H_{23}NO$ requires C, 81.10; H, 8.24) and a small amount of IIIα [m.p. 132-133°, lit.[6] 133-134°; γ cm^{-1} (CS_2) 3571 (free OH), 3247 (bonded OH)]. (Found: C, 80.93; H, 7.78. $C_{19}H_{23}NO$ requires C, 81.10; H, 8.24). Whereas reduction with sodium and n-butanol furnished only IIIα, reduction with $LiAlH_4$ gave IIIα along with a small quantity of IIIβ. Similar results were obtained with 1,3,5-trimethyl-2,6-diphenyl-4-piperidone, D. The MPV method gave IVα [m.p. 133-134°, lit.[2] 126-128°; γ cm^{-1} (CS_2) 3571 (free OH), 3333 (bonded OH)]. (Found: C, 81.19; H, 9.01. $C_{20}H_{25}NO$ requires C, 81.32; H, 8.53) and IVβ [m.p. 99-100°, lit.[2] 90-92°; γ cm^{-1} (CS_2) 3571 (free OH)]. (Found: C, 81.30; H, 8.66. $C_{20}H_{25}NO$ requires C, 81.32; H, 8.53), sodium and n-butanol gave only IVα and $LiAlH_4$ yielded a mixture consisting chiefly of IVα. Methylation of IIIα and IIIβ with CH_3I gave IVα and IVβ respectively. Equilibration of either the α- or the β-form of III or IV with sodium ethoxide in xylene gave unchanged starting materials and under more severe conditions (potassium t-butoxide in decalin at 200°) extensive decomposition occurred.

Reduction of unhindered cyclic ketones with $LiAlH_4$ or with sodium and alcohol has been shown to yield predominantly equatorial alcohols.[7,8] It is

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[6] E.A. Mailey and A.R. Day, J. Org. Chem. 22, 1061 (1957).

also well known[7] that equilibration of secondary alcohols with alkali gives a mixture consisting predominantly of thermodynamically the more stable equatorial alcohol. These facts indicate that the hydroxyl groups in Iα and IIα are equatorial and those in Iβ and IIβ are axial. Similar conformations follow for IIIα, IVα, IIIβ and IVβ also, though they could not be subjected to epimerization. Such an assignment of conformation is consistent with their infra-red spectra and their behaviour towards adsorption on alumina. The equatorial alcohol is more strongly adsorbed on alumina than the axial alcohol.[7] In the present work the β-forms were eluted first, thus suggesting that the hydroxyl in them has axial disposition. Infra-red absorption of the α-forms gives two bands in the region 3600-3200 cm^{-1}, a sharp band due to the free hydroxyl group and a broad band due to the bonded hydroxyl, whereas the β-forms give a single sharp band. Hydrogen bonds are known to form more readily when the hydroxyl is equatorial, since it is then sterically more accessible.[9]

The authors are grateful to Professor V. Baliah for his interest and encouragement. Our thanks are also due to Professor T.R. Govindachari, Presidency College, Madras, for the infra-red measurements. One of us (N.P.) thank the University Grants Commission for the award of a scholarship.

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[7] D.H.R. Barton, J. Chem. Soc. 1027 (1953).

[8] W.G. Dauben, E.J. Blanz, Jr., J. Jiu and R.A. Micheli, J. Amer. Chem. Soc. **78**, 3752 (1956).

[9] E.E. Pickett and H.E. Ungnade, J. Amer. Chem. Soc. **71**, 1311 (1949); E.G. Peppiatt and R.J. Wicker, J. Chem. Soc. 3122 (1955); E.L. Eliel, J. Chem. Educ. **37**, 130 (1960).