Tetrahedron. Vol. 30, pp. 3827 to 3830. Pergamon Press 1974. Printed in Great Britain

THE OXIMATION OF *cis*-1-ALKYL-3-5-DIPHENYL-PIPERIDIN-4-ONES

R. ANDRISANO, A. S. ANGELONI and G. GOTTARELLI
Instituto di Chimica degli Intermedi dell 'Universita' Viale Risorgimento, 4-40136 Bologna, Italy

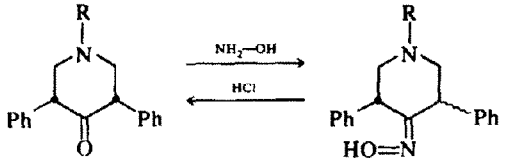
(*Received in the UK 29 January 1974; Accepted for publication 6 March 1974*)

Abstract—The oximation of 1-alkyl-3,5-diphenyl-piperidin-4-ones in which the phenyl groups are in a *cis* (bis-equatorial) configuration, leads to oximes having a *trans* configuration, with the phenyl *syn* to the oximic OH-group, in an *axial* arrangement.

Acid hydrolisis of the oximes affords about 90% of *cis*-1 and 10% of *trans*-2 1-alkyl-3,5-diphenyl-piperidin-4-ones.

Ketones **1** and **2** in acid and in alkaline media, undergo equilibration through keto-enolic tautomerism.

In previous papers[1,2] we described an oxime **3b** (R = Et) which was obtained from *cis*-1-ethyl-3,5-diphenyl-piperidin-4-one (**1b**) by oximation carried out in an acid medium. The oxime gave on hydrolisis with aqueous hydrochloric acid the ketone **1b** which was isolated in a high yield.



1a: R = Me
b: R = Et

3a: R = Me
b: R = Et

The oxime **3b** (R = Et) was resolved into optically active forms showing surprisingly high specific rotation:[2] the value of $[\alpha]_D = +247$ and -252 seemed abnormally high for a "geometrically enantiomorphous"[3] structure **3b** having both Ph groups in an equatorial position as in the starting ketone **1b**. In fact if the Ph rings are both in equatorial configuration these can not give rise to exciton optical activity, which, in analogous cases, is considered to be the cause for high specific rotations and strong circular dichroic absorption in the near UV.[4,5] Furthermore it was recently shown that oximation of cyclic ketones having equatorial Me groups, in position α with respect to the carbonyl, leads, if a single group is present, to the corresponding *anti* oxime, and if two equatorial groups are present, to a distortion of the ring of the oxime obtained.[6a]

These facts stimulated us to carry out a more detailed analysis on the stereochemistry of the system previously studied. The structure of ketones **1a,b** and of the oxime **3a,b**, was investigated by NMR; the optically active oxime **3b**, was further studied by CD and UV spectroscopy. The UV and CD spectra of (-) **3b** are shown in Fig 1: the values, remarkably high in the region below 230 nm, are of the same order as observed for other compounds containing two aromatic chromophores dissymmetrically disposed, whose optical activity was analysed in terms of exciton couplings.[4,5] Unfortunately **3b** possesses a tertiary amino and an oxime function which display absorption of light in the region at *ca* 215 nm, and do not allow a complete analysis of the CD spectrum, owing to the lack of knowledge about the electronic transitions involved in these absorptions; however, the positive and negative CD bands at 240 (max) and 210 nm (infl) are likely to be the components of the exciton

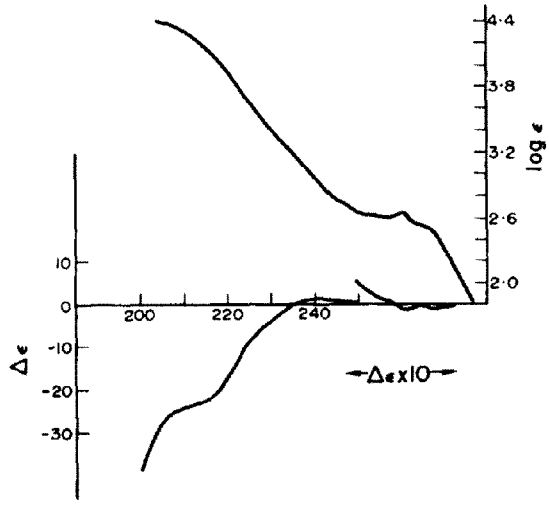
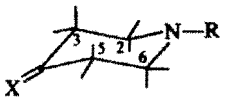


Fig 1. The UV (upper curve) and the CD spectrum of (−) **3b** in methanol.

Table 1. ^{1}H-NMR data



R = Et, Me
X = O; X = NOH *syn* to C(5)

			Chem. shifts in τ (ppm)							Coupling constants in c/s							
Comp.*	X	R	H(2)	H(3)	H(5)	H(6)	R	C_6H_5	OH	J_{2a2a}	J_{2a3a}	J_{2a3e}	J_{2e6e}	J_{5e6e}	J_{5a6e}	J_{5e6a}	J_{6a6e}	J_{5a6a}
			7·18a			7·18a												
1a	O	Me		5·52a	5·52a		7·54	2·5–2·8	—	−11·40	5·70	11·85	—	—	5·70	11·85	−11·40	—
			6·74e			6·74e												
			7·31a			7·31a	(CH_2)7·55											
1b	O	Et		5·90a	5·90			2·5–2·8	—	−11·55	5·70	11·90	—	—	5·70	11·90	−11·55	—
			6·65e			6·65e	(Me)8·88											
2a	O	Me	6·93	6·16	6·16	6·93	7·57	2·4–2·8	—	—	5·85		—	—	5·85		—	—
			7·52a			7·48a												
3a	NOH	Me		6·03	4·83		7·77	1·8–2·8	5·50	−10·50	4·80	12·00	1·80	1·35	—	—	−11·85	3·90
			7·03e			6·62e												
			7·46a			7·41a	(CH_2)7·61											
3b	NOH	Et		5·99a	4·73e			1·8–2·8	5·12	−10·65	4·80	11·90	1·80	1·35	—	—	−11·85	3·90
			6·87e			6·48e	(Me)8·95											

*1a, 1b and 2a in acetone-d 6 15% w/w at 30°; 3a and 3b in Py-d 5 15% w/w at 60°.

pattern caused by the coupling of the benzene-like B_{1u} transition of the two chromophores.

Such a spectrum is incompatible with a structure having the two Ph groups both in equatorial position, and only two possibilities are left: either the oxime **3b** has the Ph groups in an *axial*-equatorial arrangement, or the chair form is heavily distorted.[6a]

The parameters deduced from the NMR spectra of the ketones **1a,b**, are reported in Table 1.

An analisis of the $A_2B_2X_2$ type carried out on the aliphatic part of the spectra of **1a,b** leads to spectral parameters which are in agreement with a *cis*-(bis equatorial) configuration of the Ph groups in positions 3 and 5 (Ja a = 11·9 c/s; Je a = 5·7 c/s) as was previously observed.[2]

Furthermore in the spectra of **1a,b** a fine structure was evident which revealed the presence of "long-range" couplings, analogous to couplings reported in the literature for other cyclic systems.[7] If one considers the spectrum to be of the AA' BB' XX' type, one obtains a good agreement between experimental and simulated (with a LAOCN3 program[8]) spectra when the coupling constants J_{2e6e} = 1·6 c/s and $J_{2a6a} = J_{2a,6e}$ = 1·5 c/s are given.

The NMR spectra of **3a**, and **b** (Fig 2) are strictly similar, showing that the two derivatives have the same structure.

The chemical shift differences $\Delta\nu_{H_{3,5}} = 75$ c/s; $\Delta\nu_{H_{2a,6e}} = 23$ c/s; $\Delta\nu_{H_{2e6a}} = 3$ c/s are attributed to the anisotropy of the oximic group.[9]

The remarkable value of $\Delta\nu_{H_{3,5}}$ suggests that H_5 is in equatorial position,[10] *syn* to the oxime group (and H_3 in *axial* position consequently). On the other hand the vicinal coupling constants values (J_{2e3a} = 4·80; J_{2a3a} = 11·90; J_{5e6e} = 1·35; J_{5e6a} = 3·90) confirms the indications deduced on the ground of chemical shift differences.

It was in this way established that the "allilic strain"[6a] between the oximic OH group and the *syn* equatorial Ph ring is minimized through epimerisation of the latter. A similar behaviour on the other hand was observed during the formation of phenylhydrazones and hydrazones[6b] of similar ketones.

It is known that in ketones[11] and in particular in Mannich bases,[12] (the ketones **1** are cyclic Mannich bases), the H atoms in position α with respect to the CO undergo H-D exchange both in alkaline and in acid media through keto-enolic tautomerism.[11] In agreement with this, the hydrolysis of the oxime **3a**, carried out in D_2O and DCl (1 h) showed by NMR analysis, complete deuteration of the ketone **1a** obtained, at positions 3 and 5; also the ketone **1**, again in the same condition, gave complete deuteration. These facts showed that during the hydrolysis and the oximation reactions complete equilibration of the ketones **1a,b** could easily occur, and prompted us to consider the existence and the importance of the *trans* ketones **2a,b**, which, under acid catalysis would rapidly undergo partial or complete epimerisation to the more stable bis-equatorial derivatives **1a,b**.

Fortunately an NMR analysis of the crude mixture obtained from alkaline treatment of pure **1a** revealed the existence of *ca* 10% of a product whose spectrum was compatible with structure **2a**. The same product was found, in a smaller amount, in the crude ketone obtained by hydrolisis of the oxime **3a**. Careful fractionated crystallisation from ethanol allowed the separation of **2a** in pure form. The NMR spectrum of **2a** is very simple. The aliphatic protons give an A_2X_4 pattern because of

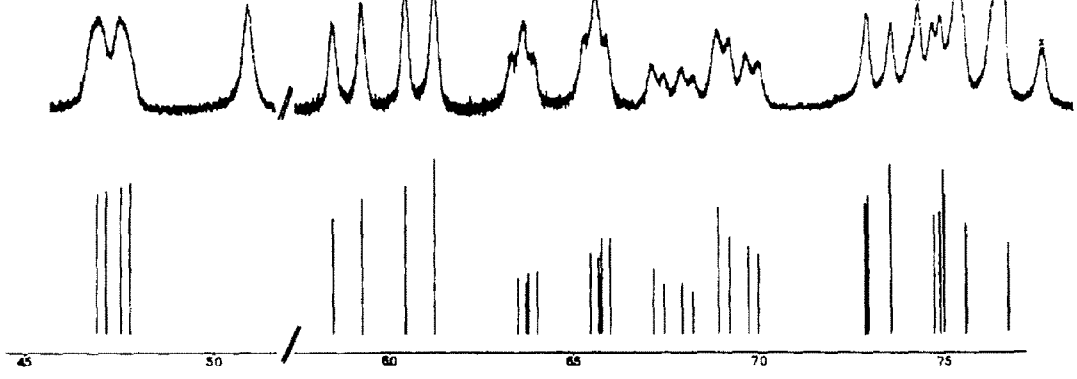
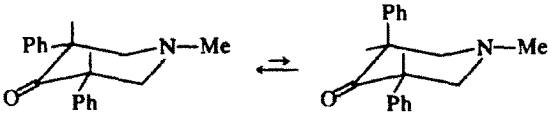


Fig 2. The observed (top) and calculated (bottom) aliphatic hydrogen part of the H'NMR spectrum of **3b**. The calculated spectrum uses the parameters of Table 1. The peacks marked are due to the CH_2 part of N-Et group. The peack at 5·1 ppm is due to the OH group.

the rapid ring inversion which makes equivalent the geminal protons in positions 2 and 6. Such an inversion is possible only if one admits a *trans* configuration of the Ph groups in positions 3 and 5. The average value of the coupling constant (J = 5·85 c/s) is in agreement with such a structure. Pure **1a** and pure **2a** in acid medium rapidly equilibrate to a mixture containing *ca* 80% of **1** and 20% of **2a**. In alkaline medium a higher amount of **2a** (*ca* 30%) is obtained. This is not unexpected because, by protonation the stereochemistry and the electronic properties of the nitrogen are drastically modified.

We believe that the experimental facts reported above are compatible with the following reaction Scheme:



1a **2a**

During the oximation reaction the bis equatorial ketones **1a,b** first equilibrates under acid catalysis.

Owing to the ground state difference in **1** and **2** and, or (if Curtin–Hammett principle is followed) the "1-3 allylic strain"[6] between the equatorial groups and the oxime OH group, only isomer **2** undergoes oximation leading to the oxime in which the OH group is on the side of the axial Ph group. During the reaction the equilibrium is continuously shifted to the right until no more of **1** is left. In this way, starting from **1**, only the oxime derived from **2** is obtained.

During the acid hydrolisis of the oximes **3a** and **b**, first **2** is obtained, which rapidly undergoes equilibration in the reaction medium.

EXPERIMENTAL

M.ps are uncorrected. H^1 NMR spectra were measured with a Jeol C 60 HL spectrometer, with TMS as internal standard. Optical rotations were measured with a Bendix N.P.L. automatic polarimeter.

CD and UV spectra were measured with a Jouan II dichrograph and with a Unicam SP 700 spectrophotometer respectively.

1 - Methyl and 1 - ethyl - 3,5 - diphenyl - piperidone - 4 - oxime. **3a,b.** These were obtained following the directions given in ref 2. Derivative **3a** was crystallized from EtOH and had m.p. 183-84°. (Found: C, 76·90; H, 7·13; N, 10·20. $C_{18}H_{20}N_2O$ requires: C, 77·10; H, 7·20; N, 10·00).

Resolution of 1 - ethyl - 3,5 - diphenyl - piperidone - 4 - oxime **3b.** The benzoyl-derivate of **3b**[2] was obtained, in quantitative yield, by treating a saturated soln of **3b** in dry ethyl ether with an equimolecular amount of sodium hydride, and then adding a small excess of benzoyl chloride dissolved in dry ether. The successive operations are identical to these described in Ref 2.

The oxime used in recording the CD spectrum had $[\alpha]_D = -262$ ($c = 0·12$ MeOH), m.p. 139–40°. Its NMR spectrum was identical to that of the racemic derivative.

cis and trans - 1 - Methyl - 3,5 - diphenyl - piperidin - 4 - ones **1a** *and* **2a.** A soln of **3a** (1 g) in 0·1 N HCl (20 ml) was refluxed for 1 h. After cooling, ethyl ether was added to the soln which was subsequently basified with 10% NaOH aq and immediately extracted with ethyl ether.

The ethereal extracts, after drying and evaporation of the solvent, left a residue which, crystallized from light petroleum (B.p. 40–60°) gave 0·4 g of **1a** m.p. 87° (Found: C, 81·32; H, 7·12; N, 5·52. $C_{18}H_{19}NO$ requires: C, 81·87; H, 7·22; N, 5·28%).

The solvent left from the crystallisation was evaporated and the residue crystallized from EtOH gave 0·1 g of **2a** m.p. 117–19 (Found: C, 81·85; H, 7·25; N, 5·35. $C_{18}H_{19}NO$ requires: C, 81·87; H, 7·22; N, 5·28%).

The equilibration of **1a** and **2a** was carried out by heating solutions of the pure compound (0·5 g) in 0·1 N HCl (10 ml) over a steam bath (1 h).

The solns were cooled with ice, ethyl ether was added and then 10% NaOH, until an alkaline pH was reached. After quick extraction with ether, drying and evaporation of the solvent, the residue was directly analized by NMR and gave a isomer ratio of *ca* 80:20 (**1:2**).

The equilibration was carried out also in alkaline medium: 0·5 g of ketone, 20 ml water, 20 ml EtOH 1 ml 10% NaOH and gave a isomer ratio of *ca* 70:30 (**1:2**).

Acknowledgments—We thank C.N.R. (Rome) for financial assistence and Dr. P. De Maria for discussion.

REFERENCES

[1]G. Gottarelli, *Tetrahedron Letters* No 32, 2813 (1965)
[2]R. Andrisano, A. S. Angeloni and G. Gottarelli, *Gazzetta* **97**, 1762 (1967)
[3]E. L. Eliel *Stereochemistry of Carbon Compounds* p. 321. Mc Graw-Hill, London (1962)
[4]S. F. Mason, *Some Newer Physical Methods in structural Chemistry* (Edited by R. Bonnett and J. G. Davis) p. 149. United Trade Press, London (1967)
[5]G. Gottarelli, S. F. Mason and G. Torre, *J. Chem. Soc.* 2349 (1970)
[6a]R. Haller and W. Ziriakus, *Tetrahedron* **28**, 2863 (1972); [b]T. L. Westman, R. Parades and W. S. Brey, *J. Org. Chem.* **28**, 3512 (1963)
[7]M. Barfield and B. Chakrabarti, *Chem. Rev.* **69**, 757 (1969); L. M. Jackman and S. Sternhell *Applications of NMR spectroscopy in Organic Chemistry.* Pergamon Press (1969)
[8]S. Castellano and A. A. Bothner-By, *J. Chem. Phys.* **41**, 3863 (1964)
[9]C. G. McCarty *The Chemistry of the carbon-nitrogen double bond* (Edited by S. Patai) p. 363. Interscience, N.Y. (1970)
[10]G. Carraro and L. Cavalli; *Annali di Chimica* **56**, 1093 (1966)
[11]R. P. Bell *Acid Bases* Ch. VI. Methuen, London (1961)
[12]R. Andrisano, A. S. Angeloni, P. De Maria and M. Tramontini, *J. Chem. Soc.* 2307 (1967)