Tetrahedron Letters No.40, pp. 3549-3552, 1969. Pergamon Press. Printed in Great Britain.

ENAMINES. VI(1)
THE REACTION OF ENAMINES WITH SCHIFF BASES AND ITS STEREOCHEMISTRY.

Shuji Tomoda, Yoshito Takeuchi and Yujiro Nomura
Department of Chemistry, College of General Education,
University of Tokyo, Komaba, Meguro, Tokyo, Japan

(Received in Japan 8 July 1969; received in UK for publication 31 July 1969)

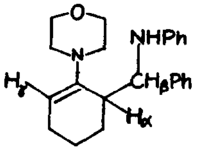
Although enamines are known to be excellent addends in many Michael type reactions, the reaction of enamines with Schiff bases has hitherto never been found in the literatures. We now would like to report the reaction and its stereochemical consequence.

Reaction of 1-morpholino-1-cyclohexene (Ia) or 1-morpholino-4-tert.-butyl-1-cyclohexene (Ib) with benzylideneaniline (II) was carried out at room temperature by standing overnight in absolute methanol. Substituted enamines (IIIa,b) were obtained (yield; about 30%) whose structures were confirmed by elementary analysis and spectroscopic data. Upon elution with benzene containing a little water through silica gel column, IIIa and IIIb were easily hydrolysed to β-aminoketones (IVa) and (IVb), respectively.

Reaction of 1-pyrrolidino-1-cyclohexene (V) with II, however, gave an unexpected product (VI), which was easily formed by mixing V and 2,6-dibenzylidenecyclohexanone in methanol.

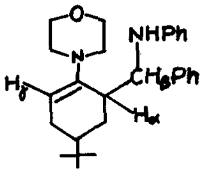
The illustrative data for the structural proof of IIIa,b , IVb, and VI are shown below ;

IIIa



m.p. 136-8°C.
Found; C: 79.10%, H: 7.97%, N: 7.85%.
Calc'd for $C_{23}H_{28}N_2O$; C: 79.21%, H: 8.09%, N: 8.04%.
IR(nujol) ν(N-H) 3246 cm^{-1}, ν(C=C) 1649 cm^{-1}.
UV(in methanol) λmax 249 mμ(εmax=18,100), 299 mμ(εmax=2,550)
NMR(in $CDCl_3$) H_β 5.71 τ(d., $J_{\alpha\beta}$=7.9 Hz.), H_γ 4.96 τ(t.)

IIIb



m.p. 155-6°C.

Found; C: 79.59%, H: 9.57%, N: 6.79%.

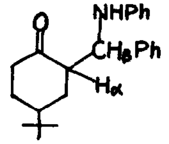
Calc'd for $C_{27}H_{36}N_2O$; C: 80.15%, H: 8.97%, N: 6.92%.

IR(nujol) ν(N-H) 3244 cm^{-1}, ν(C=C) 1653 cm^{-1}.

UV(in methanol) λmax 249 mμ(εmax=14,800),299 mμ(εmax=2,230)

NMR(in $CDCl_3$) H_β 5.84 τ(d., $J_{\alpha\beta}$=10.5 Hz.), H_γ 5.00 τ(q.)

IVb



m.p. 132-2.5°C.

Found; C: 82.47%, H: 8.69%, N: 4.53%.

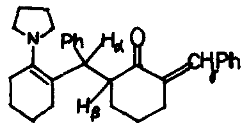
Calc'd for $C_{23}H_{29}NO$; C: 82.34%, H: 8.71%, N: 4.77%.

IR(nujol) ν(N-H) 3220 cm^{-1}, ν(C=O) 1705 cm^{-1}.

UV(in methanol) λmax 248 mμ(εmax=12,700),296 mμ(εmax=1,900)

NMR(in $CDCl_3$) H_α 5.36 τ(d., $J_{\alpha\beta}$=7.7 Hz.)

VI



m.p. 174-6.5°C(decomp.)

Found; C: 84.46%, H: 8.62%, N: 3.04%.

Calc'd for $C_{30}H_{35}NO$; C: 84.66%, H: 8.29%, N: 3.29%.

IR(nujol) ν(C=O) 1642 cm^{-1}.

UV(in methanol) λmax 300 mμ

NMR(in $CDCl_3$) H_α 6.66 τ(d., $J_{\alpha\beta}$=10.1 Hz.), H_γ 3.10 τ(s.)

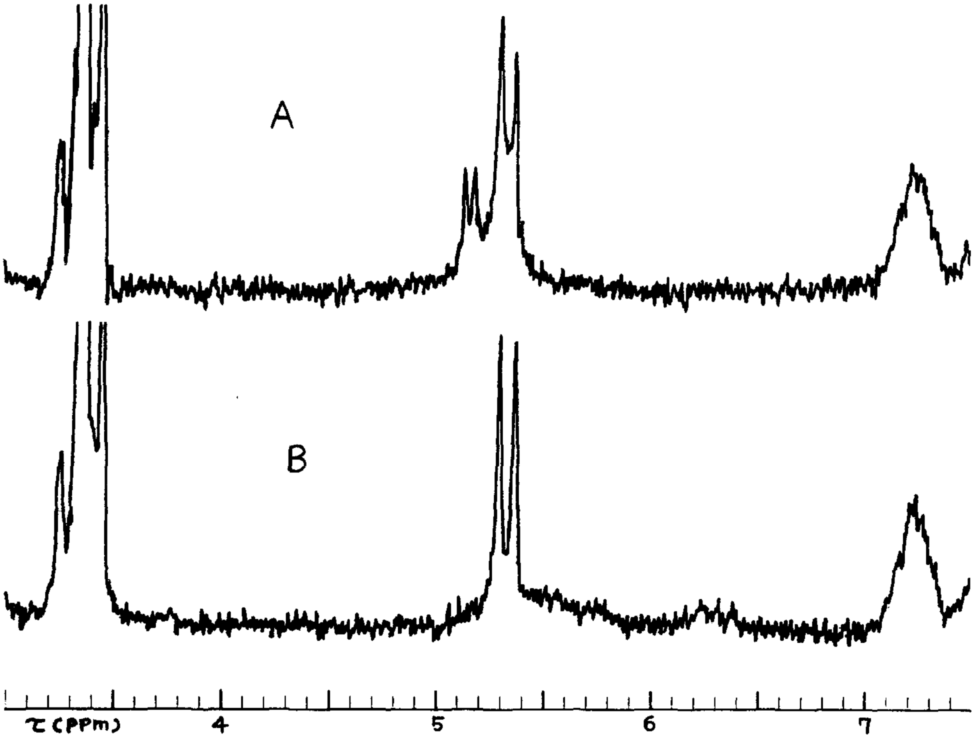
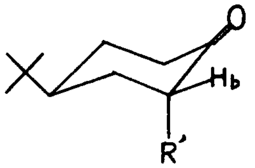
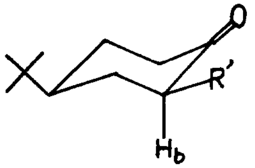


Fig. 1. 100 MHz. nmr spectra of IVa (3). A; Prepared according to the lit.(2). B; Prepared from enamine. (Region due to the benzyl protons only.)

2-(1-Anilinobenzyl)cyclohexanone (IVa) prepared according to the literature (2) from cyclohexanone, benzaldehyde and aniline, m.p. 116-134°C(found; C: 81.62%, H: 8.07%, N: 4.96%. $C_{19}H_{21}NO$ requires; C: 81.68%, H: 7.58%, N: 5.01%. Recrystallized four times from ethanol.), lit. m.p. 139°C(from ethanol), showed a pair of doublets of benzyl proton (H_β) in its nmr spectrum, whereas IVa, m.p. 141-3°C obtained by hydrolysis of IIIa showed only one doublet (Fig. 1). Thus the former seems to be a mixture of diastereomeric isomers due to two asymmetric carbons. IVb also showed only one doublet of benzyl proton. These observations promoted us to examine the nmr spectra to clarify the stereospecificity of the reaction. The results of nmr measurements are listed in Table 1 from which we can draw a conclusion that only the trans isomer (IVb-A) shown below was formed during the course of the reaction.



(IVb-A)



(IVb-E)

(R'=-CHPh-NPh)

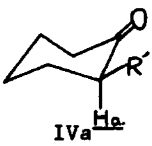
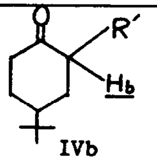
τ_{Ha} or τ_{Hb}	 IVa	 IVb	τ_{Hb} − τ_{Ha}
$\tau(CDCl_3)$	7.23	7.50	+0.27
$\tau(C_6D_6)$	7.58	7.50	-0.08
$\Delta\tau$ *	+0.35	0.00	

Table 1. The τ values and their solvent dependence of the protons at the α-position in IVa and IVb. $^*\Delta\tau = \tau(C_6D_6) - \tau(CDCl_3)$.

The following facts are particularly noteworthy;

1). The value +0.27 ppm in the last column of Table 1 can be explained assuming that the most probable configuration at position-2 of IVb should be IVb-A shown above, since the signal of the axial proton at the α-position of substituted cyclohexanone generally appears at lower field by about 0.3 ppm than that of the equatorial proton (4). (The ring is assumed to exist predominantly in the chair form and R' in IVa is largely equatorial on steric grounds.)

2). The $\Delta\tau$ values ($\Delta\tau$ is defined as indicated in Table 1.) are +0.35 and 0.00 ppm for IVa and IVb, respectively. According to the carbonyl plane rule (5,6), the

$\Delta\tau$ value of the axial proton (~+0.3 ppm) at the α-position of cyclohexanone ring is always greater than that of the equatorial proton (~0 ppm). Consequently, the trans configuration (IVb-A) would be more probable.

Considering that the cyclohexane ring is anchored by tert.-Bu throughout the reaction and subsequent hydrolysis, it is clear that the Schiff base approaches to the ring from the axial direction. According to Johnson (7), the alkylation of the enamine of 4-substituted cyclohexanone with a series of halides gave largely the trans-2,4-dialkylcyclohexanone after hydrolysis and the ratio of the trans to the cis isomer probably reflects the relative amounts of axial and equatorial attack that take place by alkyl halides. Axial approach is to be expected as the preferred reaction path and our results agree well with this consequence.

We continue to explore the full scope of the reaction of enamines with Schiff bases. The results of the further investigation will be reported later.

<u>ACKNOWLEGEMENT</u> The authors wish to thank Dr. F. Furusaki, in their laboratory, for giving the compound IVa and helpful suggestions.

REFERENCES

(1). Y. Nomura, T. Shimura and Y. Takeuchi, Bull. Chem. Soc. Japan, <u>37</u>, 892 (1964).

(2). F. Pirrone, Gazz. Chim. Ital., <u>66</u>, 429 (1936).

(3). Proton nmr spectra were determined in $CDCl_3$ or C_6D_6 (concentration; about 120 mg in 1 ml solvent) with TMS as an internal standard by a JNM-4H-100 spectrometer.

(4). N. S. Bhacca, D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry." pp. 164-171, Holden Day Inc., San Francisco, 1964.

(5). J. D. Connolly, R. M. McCrindle, Chem. and Ind., 1965, 379.

(6). D. H. Williams, N. S. Bhacca, Tetrahedron, <u>21</u>, 2120 (1965).

(7). F. Johnson, Chem. Rev., <u>68</u>, 375 (1968), and references therein.