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ENAMINE CHEMISTRY. I.
DIPOLAR CYCLOADDITION REACTION OF ENAMINES WITH NITRONES(1)

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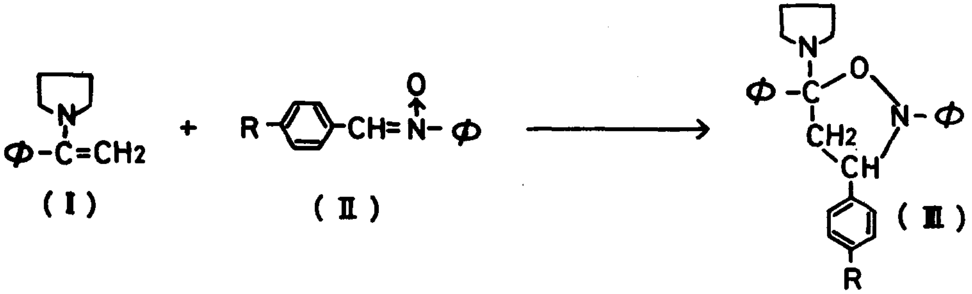
Since the work of Stork and his co-workers first appeared,(2) enamines have found increasingly important uses in organic syntheses. Particularly, cycloaddition reactions against enamines have received considerable attention recently. Although the reaction of nitrones with olefins to form isoxazolidines is well established,(3) we have little informations about the reaction of enamines with nitrones. The present paper deals with the cycloaddition reaction of enamines with N-phenyl-α-(p-substituted phenyl)nitrones.

When a benzene solution of 1-N-pyrrolidino-1-phenylethylene (I) and nitrones (II) was heated at 60°C for 1.5 hrs, the corresponding adduct, isoxazolidine compound (III), was obtained in a fairly good yield respectively.



(I) (II) (III)

The compound IIIa (R=H), m.p. 118–120°C, colorless needles, was obtained in 48.1% yield, and its structure was confirmed on the basis of elemental analysis, molecular weight and nmr spectrum. The mass spectrum showed the parent peak at m/e 370 and nmr spectrum in $CDCl_3$ exhibited multiplets at τ 2.5–3.3(15H), τ 5.3–5.8(1H), τ 6.5–7.5(6H) and τ 8.3(4H). The compounds IIIb (R=Cl), m.p. 124–125°C (decomp.), colorless needles and IIIc ($R=NO_2$), m.p. 142°C (decomp.), orange needles, were obtained in yields of 62.0 and 49% respectively. Their infrared and nmr spectra were similar to those of IIIa in the respective case. Considering from the nmr spectra, the compounds III are presumed to be a mixture of respective isomers.

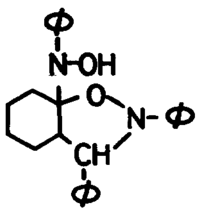
On the other hand, the reaction of 1-N-morpholino- (IV) and 1-N-piperidino-1-cyclohexene (V) with the nitrone IIa (R=H) in refluxing benzene solution produced the same product (VIa), colorless prisms melting at 124–124.5°C (decomp.), in 6.9 and 8.9 mole % respectively. Though the molecular formula of VIa did not agree with the expected isoxazolidine, it agreed with $C_{25}H_{26}O_2N_2$.

When a benzene solution of IV and IIa was heated for 100 hrs. at 60°C under a slow stream of nitrogen, VIa and colorless prisms (VIa′), m.p. 133–134°C (decomp.), were obtained in 28.4 and 7.8 mole % yield respectively. As the molecular formula of VIa′ also agreed with $C_{25}H_{26}O_2N_2$, the compound VIa′ is deduced to be an isomer of VIa. The infrared spectra of VIa and VIa′ showed bands of hydroxyl group at 3220 and 3400 cm^{-1} respectively.

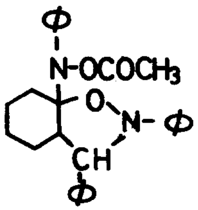
The acetylation of VIa with acetic anhydride in pyridine gave the monoacetyl derivative (VII), colorless needles melting at 139°C, whose infrared spectrum exhibited the characteristic bands at 1763 and 1190 cm^{-1} in the respective case.

When considered on the basis of the above observations, the structure of VIa seems to become consistent with the isoxazolidine compound replacing amine moiety by phenylhydroxylamine. Its formation course is, however, not clear.

A similar reaction of IV with IIb (R=Cl) afforded colorless prisms (VIII), m.p. 135°C, and colorless needles (IX), m.p. 187–187.5°C, in 13.5 and 3.2% yield respectively. The former was proved to be identical with _p_-chloro-

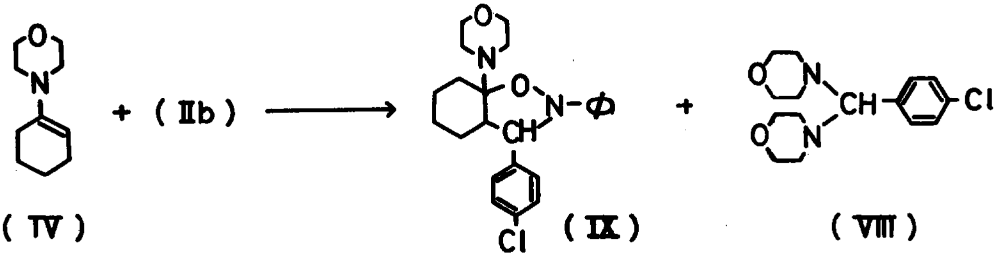


(VIa)



(VII)

benzylidene-bis-morpholine by the admixed melting point and by the infrared spectrum with an authentic sample.(4) The latter is confirmed to be the expected isoxazolidine compound by the nmr spectrum as well as by the elemental analysis.



On the other hand, the reaction of 1-N-pyrrolidino-1-cyclohexene (X) with IIa in benzene at 60-65°C for 4.5 hrs. produced two compounds, XIa and XIa′.(5) A similar reaction with IIb also gave two products, XIb and XIb′, whereas only one compound was obtained in the respective reaction with IIc or IId (R=OCH_3). The yields and physical properties of XI are summarized in Table I.

The nmr spectra of XI gave the corrected numbers and kinds of protons for the respective isoxazolidines and elemental analyses indicated that the compounds XIa and XIa′, and XIb and XIb′ are mutual isomers.

The nmr spectra are illustrated in Fig. 1 for XIb and XIb′. As is shown in Fig. 1, the H_3-proton signal of XIb and H_4-proton signal of XIb′ appeared at a field higher than that of XIb′ and XIb respectively. These differences could be understood in terms of the shielding effect of the respective phenyl

TABLE I

XI	R	Yield (%)	M.p. (°C)	Appearance	m/e(M)
a	H	60.4	147	colorless prisms	348
a′	H	+*	115	colorless prisms	—
b	Cl	44.0	164	colorless grains	382
b′	Cl	25.0	176.5	colorless needles	382
c	NO_2	59.5	172.5	orange needles	393
d	OCH_3	49.8	132	colorless grains	378

* + sign: Trace amount.

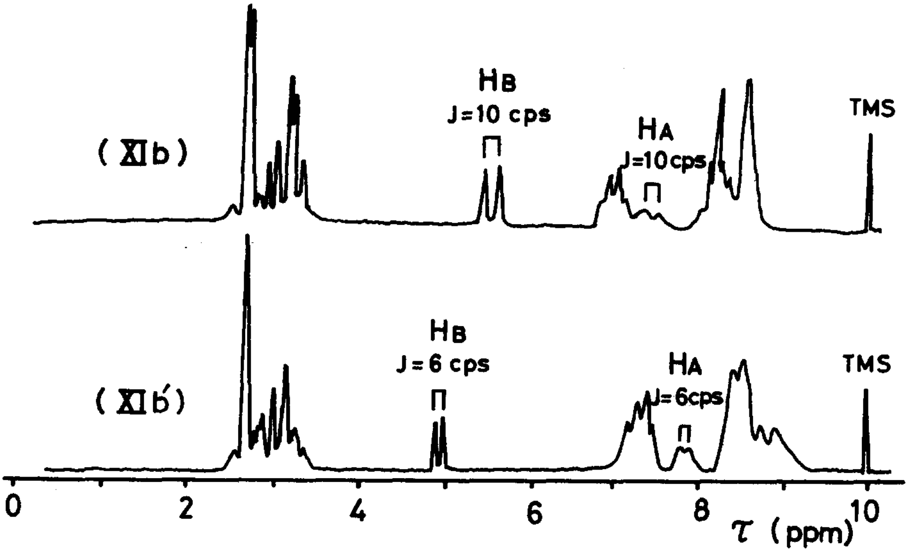
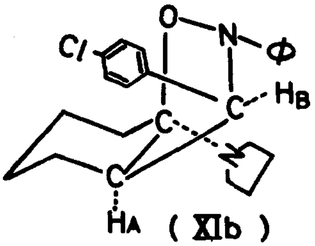
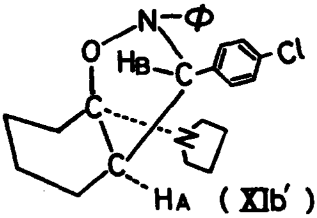


Figure 1 The nmr spectra of XIb and XIb′

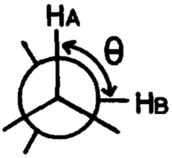
group on the nitrogen or carbon atom in the isoxazolidine ring. Considering from the appearance of broad doublets which are ascribed to the H_A-proton and also from the comparison of the observed and calculated values$^{(6)}$ of J_{AB}, the structures of XIb and XIb′ are respectively consistent with the conformation corresponding to the cis-adduct as follows.



(XIb)



(XIb′)



J_{AB}= 9.7c.p.s. Calcd. for θ = 20° J_{AB} = 6.0c.p.s. Calcd for θ = 135°

Here, if θ is 120° in the boat form of cyclohexane ring, the calculated value of J_{AB} amounts to 2.9 c.p.s. Consequently, the conformation of XIb′ could be understood by the twisted boat form in which θ is expanded from 120° to 135°.

TABLE II

XI	H_A (τ)	H_B (τ)	J_{AB} (c.p.s.)
XIa	7.40	5.59	10
XIb	7.36	5.50	10
XIb′	7.83	4.90	6
XIc	7.27	5.32	10
XId	7.16	5.56	10

On the basis of chemical shifts of H_A and H_B, and of the values of J_{AB} which are shown in Table II, it is deduced that the structures of XIa, XIc and XId correspond to that of XIb respectively.

All melting points were not corrected, but the results of elemental analyses were satisfactorily obtained for all compounds reported here.

REFERENCES

(1) Presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967.

(2) G. Stork, R. Terrell and J. Szmuszkovicz, J. Am. Chem. Soc., **76**, 2029 (1954).

(3) N. A. LeBel and J. J. Whang, J. Am. Chem. Soc., **81**, 6334 (1959).

(4) The authentic sample was prepared by the reaction of benzaldehyde with morpholine.

(5) It was independently reported by Y. Nomura et al. that the reaction of X with IIa in DMF gave the isoxazolidine, m.p. 146.7-148.5°C: at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967. However, they did not refer to both the reaction of X with other nitrones and the isomers of isoxazolidine.

(6) The calculated values for J_{AB} were given by the Wohl's equation in the respective case: Chimica, **18**, 213 (1964).

$J_{vic} = 11.3\cos^2\theta - 0.28$ ($0° \leq \theta \leq 90°$), $J_{vic} = 12.4\cos^2\theta - 0.28$ ($90° \leq \theta \leq 180°$)