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Reaction of N-(1-Cyanoalkyl)alkylideneamine N-Oxide with Dipolarophiles and Nucleophiles. III.[1] 1,3-Dipolar Cyclo-addition of N-(1-Cyanoalkyl)alkylideneamine N-Oxide

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The addition reaction of nitrones to multiple bonds have been published mostly on aromatic nitrones.[3-6] N-(1-Cyanoalkyl)alkylideneamine N-oxide (I) is an interesting, stable aliphatic aldonitrone which undergoes a nucleophilic addition reaction with a nitrogen nucleophile.[1]

To compare the reactivities of aliphatic and aromatic nitrones, we studied the 1,3-dipolar cyclo-addition of I. N-(1-Cyanoisobutyl)isobutylideneamine N-oxide (Ia) was mainly used as a typical nitrone in this work.

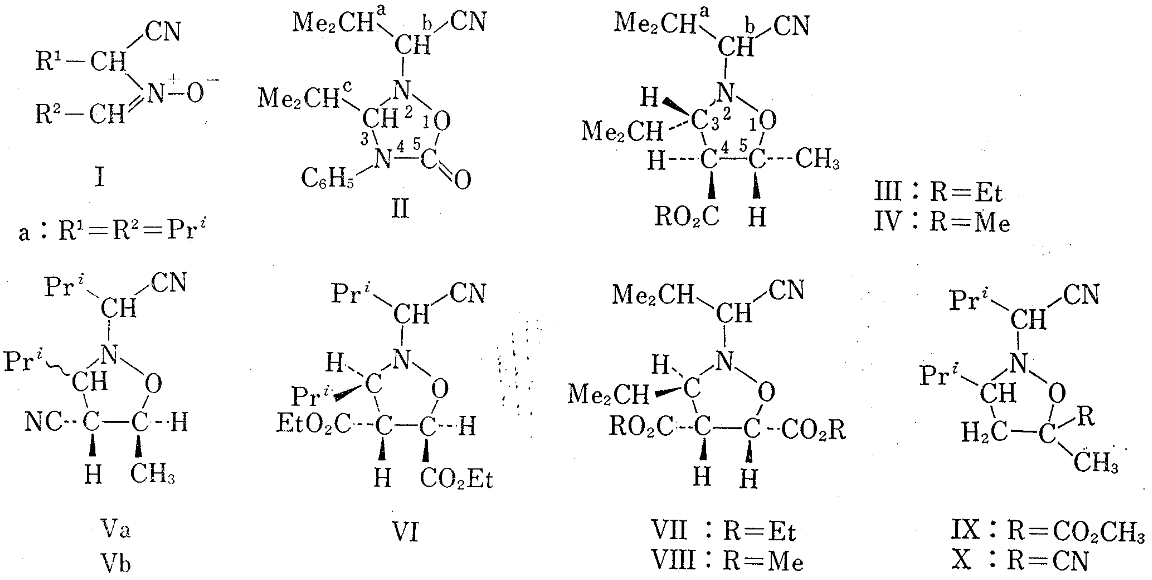

Chart 1

Result and Discussion

Isocyanates are reactive dipolarophiles, which are known to react with various aromatic nitrones to give 1,2,4-oxadiazolidones.[5-7] Phenylisocyanate reacted with Ia to give the 1:1 adduct (II) in high yield. The infrared (IR) spectrum of II showed characteristic bands due to $C\equiv N$ and $C=O$ groups at 2250 and 1755 cm^{-1}, respectively. In the nuclear magnetic

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[1] Part II: M. Masui, C. Yijima, and K. Suda, *Chem. Pharm. Bull.* (Tokyo), **20**, 2150 (1972).

[2] Location: *Toneyama, Toyonaka, Osaka-fu.*

[3] R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).

[4] R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 633 (1963).

[5] J. Harmer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964).

[6] G.R. Delpierre and M. Lamchen, *Quart. Rev.*, **19**, 329 (1965).

[7] H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).

resonance (NMR) spectrum, signals due to H_3 and H_b were observed at 5.21 ($J_{3,c}=3.2$ Hz) and 3.89 ppm ($J_{a,b}=5.1$ Hz), respectively, as doublets. The observed coupling constant between H_3 and H_c is smaller than the usual vicinal coupling constant (6—8 Hz). This implies that the rotation of the substituent on C_3 is considerably hindered by substituents on the two adjacent nitrogen atoms of the ring.

The reactions of Ia with alkyl isocyanates, phenylthioisocyanate and carbon disulfide gave no 1,3-adduct.

In the reaction of nitrones with unsymmetrical olefins, two possible isoxazolidines should be produced, depending on the orientation of the addition. The orientation has been claimed to be subject to electronic and steric control.[8]

α,β-Disubstituted olefins also reacted with Ia to give isoxazolidine derivatives in fairly good yield (Table). The orientation and configuration of the adducts were determined by their NMR spectra. In the NMR spectrum of III, signals at 3.40 (double doublet, $J_{3,4}=4.2$ Hz), 2.67 (double doublet, $J_{4,5}=8.4$ Hz) and 4.32 ppm (double quartet) were assigned to

TABLE. Isoxazolidines

Compound	Dipolarophile	Yield (%)	React. time (hr)	bp/mmHg (mp) (°C)	Formula	Analysis (%) Found) (Calcd.		
						C	H	N
III	ethyl crotonate	63	12	112—116/1	$C_{15}H_{26}O_3N_2$	63.38 (63.80)	9.31 (9.28)	10.11 (9.92)
IV	methyl crotonate	86	9	138—143/3	$C_{14}H_{24}O_3N_2$	62.77 (62.66)	9.03 (9.02)	10.16 (10.44)
V	crotonitrile	62	40	124—128/1	$C_{13}H_{21}ON_3$	66.06 (66.35)	8.96 (9.00)	17.79 (17.86)
VI	dimethyl malate	54	54	148—152/1 (76—76.5)	$C_{15}H_{24}O_5N_2$	57.93 (57.67)	8.03 (7.74)	9.09 (8.97)
VII	diethyl malate	75	24	(78)	$C_{17}H_{28}O_5N_2$	59.98 (59.98)	8.21 (8.29)	8.41 (8.23)
VIII	diethyl fumalate	50	16	165—175/5-6	$C_{17}H_{28}O_5N_2$	60.71 (59.98)	8.36 (8.29)	8.38 (8.23)
IX	methyl methacrylate	90	9	157—158/16—17	$C_{14}H_{24}O_3N_2$	62.92 (62.66)	8.88 (9.02)	10.39 (10.44)
X	methacryronitrile	80	40	113—118/1	$C_{13}H_{21}ON_3$	66.49 (66.35)	9.22 (9.00)	17.79 (17.86)
XI	styrene	80	11	141—148/1	$C_{17}H_{24}ON_2$	74.71 (74.96)	8.87 (8.88)	10.14 (10.29)
XII	*p*-chlorostyrene		200	165—168/1	$C_{17}H_{23}ON_2Cl$	66.77 (66.54)	7.31 (7.56)	9.13 (9.13)
XIII	methyl acrylate	93	7	145—148/3	$C_{13}H_{22}O_3N_2$	61.54 (61.39)	8.64 (8.72)	10.64 (11.02)
XIV	ethyl acrylate	97		162/11	$C_{14}H_{24}O_3N_2$	62.79 (62.66)	8.90 (9.02)	10.50 (10.44)
XV	acrylonitrile	91	20	152—158/4	$C_{12}H_{19}ON_3$	64.92 (65.12)	8.61 (8.65)	18.81 (18.99)
XVI	acrylamide	92	20	(70—72)	$C_{12}H_{21}O_2N_3$	60.63 (60.22)	8.84 (8.85)	17.59 (17.56)
XVII	allyl chloride	93	18	122—128/1	$C_{12}H_{21}ON_2Cl$	59.06 (58.88)	8.62 (8.65)	11.32 (11.45)
XVIII	allylbenzene		54	158—164/1	$C_{18}H_{26}ON_2$	75.75 (75.48)	9.08 (9.15)	9.99 (9.78)
XIX	*n*-butyl vinylether	97	25	115—121/1	$C_{15}H_{28}O_2N_2$	67.36 (67.12)	10.47 (10.52)	10.30 (10.44)
XX	*n*-hexene	64	65	120—124/1	$C_{15}H_{28}ON_2$	71.53 (71.38)	11.28 (11.18)	11.30 (11.10)

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[8] Y. Nomura, F. Furusaki, and Y. Takeuchi, *Bull. Chem. Soc. Japan*, **46**, **1913** (1970).

H_3, H_4 and H_5, respectively. Huisgen, *et al.* have reported[9] that $J_{3,4}=6.8$—6.9 Hz (*trans*), $J_{4,5}=8.5$—9.0 Hz (*trans*) for isoxazolidines derived from α,N-diphenylnitrone and esters of crotonic acid, and $J_{3,4}=8.2$ Hz (*cis*), $J_{3,4}=6.2$ Hz (*trans*) for 2,3-diphenyl-5-cyanoisoxazolidine. In addition, the 1,3-dipolar cyclo-addition is known to be *cis*-stereoselective.[4] Therefore, the relative positions of H_3 and H_4, and H_4 and H_5 in III are both considered to be *trans* positions. The reverse-oriented adduct was not found at any temperature used. Thus, the orientation is subject to electronic control. Compound (IV) showed the same orientation and configuration as III.

The presence of two isomeric isoxazolidines, in a ratio of Va: Vb=2: 1, was deduced from the NMR spectrum of V, the product of Ia with crotonitrile. Two doublets centered at 1.41 and 1.38 ppm with a coupling constant of 5.8 Hz were assigned, respectively, to the methyl group on C_5 of each isomer. These two isomers are *cis* and *trans* isoxazolidines with respect to H_3 and H_4, since the addition of crotonitrile is *cis*-stereoselective.

Compound (VI), formed from Ia and fumarate showed signals due to H_3, H_4 and H_5 at 3.35 (double doublet, $J_{3,4}=3.5$ Hz), 3.43 (double doublet, $J_{4,5}=6.0$ Hz) and 4.76 ppm (doublet), respectively. It has been reported that isoxazolidines derived from aromatic nitrones and esters of fumaric acid or maleic acid, show $J_{3,4}$ (*cis*)$=8.0$ Hz and $J_{4,5}$ (*trans*)$=7.5$ Hz.[10] On the other hand, for isoxazolidines derived from aromatic nitrones and N-phenylmaleimide, Iwakura, *et al.* reported that the *trans* coupling constant of H_3 and H_4 is zero.[11] Therefore, the relative positions of H_3 and H_4, and H_4 and H_5 in VI are both *trans* positions. In the case of VII obtained from Ia and maleate, signals due to H_a, H_b, H_c and H_5 were observed at 2.79 (multiplet), 4.65 (doublet), 1.92 (octet) and 4.86 ppm (doublet), respectively. Two protons due to H_3 and H_4, overlapping each other, were observed at 3.77—3.88 ppm and they were assigned to 3.84 and 3.82 ppm, respectively, by irradiation at H_c (1.92 ppm) and H_5 (4.86 ppm). Further irradiation at 3.82 ppm (H_4) changed the doublet at 4.86 ppm (H_5) to a sharp singlet. The coupling constants between the ring protons, $J_{3,4}=3$ Hz, and $J_{4,5}=10.5$ Hz, reveal that the relative position of H_3 and H_4 is the *trans* position, and that of H_4 and H_5 is the *cis* position. These assignments are also reasonable from the steric point of view. In general, aldonitrones exist in the *trans* form,[5] and this generalization also seems to apply to our nitrone, judging from the NMR data.[12] Assuming that the 1,3-dipolar cyclo-addition of Ia to dicarboxylates proceeds by a concerted one step mechanism,[4] the steric hindrance of R^2 should be greater than that of R^1 since R^2 is nearer to the reaction center than R^1. Thus, VIa or VIIa is more favourable than VIb or VIIb in the transition state.

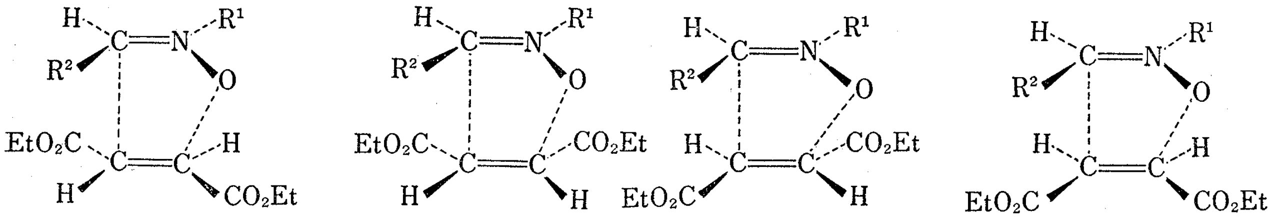
VIa VIIa VIb VIIb

Chart 2

For further investigation of the reactivities of I, the reactions of Ia with α-substituted olefins were carried out and the corresponding isoxazolidines were obtained in high yield.

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[9] R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968).
[10] R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **102**, 736 (1969).
[11] Y. Iwakura, K. Uno, and T. Hongu, *Bull. Chem. Soc. Japan*, **42**, 2882 (1969).
[12] M. Masui and C. Yijima, *J. Chem. Soc.* (*C*), **1967**, 2022.

The isoxazolidines derived from α-disubstituted olefins IX—X have no signal between 4—5 ppm. This shows that there is no proton on C_5 next to the oxygen atom of the isoxazolidines.

The isoxazolidines derived from mono-substituted olefins (XI)—(XX) showed one proton signal due to H_5 between 4.0—5.5 ppm as a multiplet.

Though, the temperature-dependence of the orientation has been reported for the addition reaction of 5,5-dimethyl-pyrroline 1-oxide and ethylacrylate,[13] the reaction of Ia with this ester proceeds only in one direction. Thus, steric effect is dominant in the addition reaction of Ia with α-substituted olefins. Configurational analysis of the adducts could not be made because of the complexity of the spectra, but followings were remarkable.

X is a mixture of the two diastereoisomers on C_5 and its methyl signals were found at 1.66 and 1.70 ppm in a ratio of 4: 1. XII, XVIII and XX are also a mixture of the diastereoisomers and in those NMR spectra α-proton of the nitrile group of the respective isoxazolidine was observed at 3.4—3.7 ppm as two doublets. For example, XII obtained after 200 hours refluxing in benzene showed the signals at 3.64 and 3.55 ppm in a ratio of 1: 1. On the other hand, XII obtained at room temperature showed the signals in a ratio of 1: 3, and a further 5 hours refluxing of this mixture with *p*-chlorostyrene gave the signals in a ratio of 1: 2. The behaviour like this has been reported on the reaction of dihydroisoquinoline N-oxide and methyl methacrylate.[9]

These results support the idea that the 1,3-dipolar cyclo-addition of aliphatic acyclic nitrone is reversible and that the configuration of the adducts is subject to kinetic and thermodynamic control.

Experimental

NMR spectra were measured with a Hitachi Perkin–Elmer R-20A spectrometer and JMN-PS-100 spectrometer using materials as solutions in CCl_4 with tetramethylsilane as an internal reference. IR spectra were measured in a Hitachi ETI-GS spectrometer. All melting points and boiling points are given as uncorrected values.

1,3-Dipolar Cyclo-addition of N-(1-Cyanoisobutyl)isobutylideneamine N-Oxide (Ia) to Phenylisocyanate——A mixture of 2 g of Ia, 2.5 g of phenylisocyanate and 40 ml of dry benzene was refluxed for 8 hr. The benzene was evaporated off at room temperature and the resulting crystalline solid was washed several times with small portions of petroleum ether. Recrystallization from methanol gave II, mp 124—126° (3.5 g, 97% yield). *Anal.* Calcd. for $C_{16}H_{21}O_2N_3$: C, 66.87; H, 7.37; N, 14.62. Found: C, 66.69; H, 7.34; N, 14.80. IR ν_{max}^{Nujol} cm^{-1}: 2250 (C≡N), 1755 (C=O). NMR (ppm): 5.21 (H_3, doublet, $J=3.2$ Hz), 3.89 (H_b, doublet, $J=5.1$ Hz).

1,3-Dipolar Cyclo-addition of (Ia) to Olefins ——General Method: Unless otherwise stated, all operations were carried out as follows.

A solution of Ia and an olefin in a mole ratio of from 2: 3 to 1: 2 in benzene, was refluxed. The solvent and excess olefin were evaporated off under reduced pressure, leaving an isoxazolidine, which was purified by distillation under reduced pressure (Table). If the isoxazolidine was impure, it was applied to a silica gel column and eluted with benzene. The eluent was concentrated and redistilled under reduced pressure. The isoxazolidines obtained are summarized in Table.

Preparation of III——a) A mixture of 2.0 g of Ia and 2.0 g of ethyl crotonate was refluxed for 12 hr at 140—150°. Evaporation of excess ethyl crotonate gave a colored oil. A solution of the oil in benzene was applied to a silica gel column. The product was eluted with benzene. The eluate was concentrated and distilled on a water bath under reduced pressure to obtain (III). IR ν_{max}^{liquid} cm^{-1}: 1727 (C=O), 2240 (C≡N).

IV was also obtained by this method.

b) A mixture of 3.0 g of Ia, 3.0 g of ethyl crotonate and 10 ml of dry benzene was stood for 20 days at room temperature. Evaporation of the benzene at below 50° under reduced pressure gave a syrup. Rapid distillation of the syrup at 130—135°/1 mmHg gave only III.

IV, IR ν_{max}^{liquid} cm^{-1}: 1732 (C=O). NMR (ppm): 3.39 (1H, d. d., H_3), 2.67 (1H, d. d., H_4), 4.32 (1H, d. q., H_5), 3.69 (3H, s., OCH_3), 1.25 (3H, d., CH_3), $J_{3,4}=4.3$ Hz, $J_{4,5}=8.4$ Hz, $J_{5,CH_3}=6.1$ Hz, $J_{3,CHMe_2}=7.3$ Hz.

VI, recrystallized from petroleum ether. NMR (ppm): 4.68 (1H, d., H_5), $J_{4,5}=10$ Hz, 3.72, 3.68 (3H × 2, s., OCH_3).

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13) G.R. Delpierre and M. Lamchen, *J. Chem. Soc.*, **1963**, 4693.

VII, recrystallized from petroleum ether. NMR (ppm): 4.14, 4.11 (2H$\times$2, q., OCH_2Me), J=7.1 Hz.

VIII, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=O). NMR (ppm): 4.22, 4.19 (2H$\times$2, q., OCH_2Me), J=7.1 Hz.

IX, IR ν_{max}^{liquid} cm^{-1}: 1744 (C=O). NMR (ppm): 1.46 (3H, s., 5-CH_3), 3.76 (3H, s., OCH_3).

X, A mixture of Ia (1 g), methacrylonitrile (0.8 g) and dry benzene (20 ml) was stood for 7 days, and then refluxed for 40 hr. The solvent was evaporated off under reduced pressure, and the residue was applied to a silica gel column. The product was eluted with benzene. Concentration of the eluate and then distillation of the residue under reduced pressure gave X as a mixture of the diastereoisomers. NMR: 5-CH_3, two singlets at 1.70 and 1.66 ppm in a ratio of 1: 4.

XI, IR ν_{max}^{liquid} cm^{-1}: 1605, 758, 704 (C_6H_5). NMR (ppm): 7.29 (5H, s., C_6H_5).

XII——a) A mixture of Ia (1 g), *p*-chlorostyrene (0.9 g) and dry benzene (10 ml) was refluxed for 200 hr, and then treated according to the general method. IR ν_{max}^{liquid} cm^{-1}: 1600, 1493, 828 (C_6H_4). NMR (ppm): –CH(CN)N, 3.64 (d., J=7.2 Hz) and 3.55 (d., J=8.1 Hz), in a ratio of 1: 1.

b) A solution of Ia (1 g), *p*-chlorostyrene (0.9 g) and dry benzene (10 ml) was stood for 5 days at room temperature, and then hexane was added. Unreacted (Ia) was filtered off and the filtrate was concentrated to a syrup and then applied to a silica gel column. The column was eluted first with benzene–hexane (1: 3, v/v), to remove the unreacted *p*-chlorostyrene and then with benzene. The eluate with benzene was concentrated and distilled under reduced pressure giving (XII) as a mixture of the diastereoisomers. NMR: –CH(CN)N, two doublets centered at 3.64 and 3.55 ppm in a ratio of 1: 3. This isoxazolidine was refluxed with *p*-chlorostyrene (0.5 g) for 5 hr. The solution was concentrated, chromatographed and distilled by the method described above. After this treatment the ratio of diastereoisomers in the resulting isoxazolidine had changed to 1: 2.

XIII, IR ν_{max}^{liquid} cm^{-1}: 1745 (C=O). NMR ($CDCl_3$) (ppm): 3.76 (3H, s., OCH_3).

XIV, IR ν_{max}^{liquid} cm^{-1}: 1738 (C=O). NMR (ppm): 4.16 (2H, q., OCH_2Me, J=6.8 Hz), 1.24 (3H, t., OCH_2–CH_3).

XVI, A solution of Ia (1 g) and acrylamide (0.5 g) in dry benzene (20 ml) was refluxed for 20 hr, and the solvent was evaporated off under reduced pressure. The residue was applied to a silica gel column and eluted with acetone–petroleum ether (1: 4, v/v). The eluate was concentrated under reduced pressure and the residue was recrystallized from ether–petroleum ether giving XVI. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390, 3350, 3240, 3150, 1688, 1660 ($CONH_2$). NMR ($CDCl_3$) (ppm): 6.4 (2H, broad singlet, NH_2), 3.66 (1H, d., –CH(CN)N, J=7.9 Hz).

XVII, NMR (ppm),: 3.50 (2H, d., –CH_2Cl).

XVIII——a) A mixture of Ia (1 g), allylbenzene (1 g) and dry benzene (20 ml) was refluxed for 54 hr. The solvent was evaporated off and the resulting syrup was distilled under reduced pressure. IR ν_{max}^{liquid} cm^{-1}: 1603, 1498, 754, 707 (C_6H_5). NMR: –CH(CN)N, 3.46 (d., J=6.4 Hz) and 3.41 ppm (d., J=7.7 Hz), in a ratio of 1: 2.

b) A solution of Ia (1 g) and allylbenzene (1 g) in dry benzene (10 ml) was stood for 5 days at room temperature and then hexane was added. Unreacted (Ia) was filtered off and the filtrate was concentrated to a syrup. It was applied to a silica gel column which was eluted with benzene–hexane (1: 3, v/v) and then benzene. The benzene in the latter eluate was evaporated off and the residue was distilled under reduced pressure. NMR: –CH(CN)N, two doublets centered at 3.46 and 3.41 ppm, in a ratio of 1: 3.

XX, NMR: –CH(CN)N, 3.46 (d., J=6.4 Hz) and 3.40 ppm (d., J=7.5 Hz), in a ratio of *ca.* 1: 1.