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Reaction of N-(1-Cyanoalkyl)alkylideneamine N-Oxide with Dipolarophiles and Nucleophiles. II.[1] 1,3-Addition Reaction with Carboxamides

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N-(1-Cyanoalkyl)alkylideneamine N-oxide reacts with carboxamides to give N-(1-cyanoalkyl)-N-(1′-carboxamido-alkyl)hydroxylamines. The reaction is catalyzed by strong bases. On warming in solvents these adducts readily decompose to the starting nitrones and amides, and the decomposition is accelerated by elevation of temperature.

The cyclo-additions of nitrones to unsaturated compounds have been extensively studied by many workers[3] and many of the features of these reactions are now well understood. The reactions of Grignard's reagents,[4] hydrogen cyanide,[5] or nitromethane[6] with nitrones, which do not involve cyclo-addition, have also been studied and these reactions are thought to be nucleophilic additions of carbon nucleophiles to nitrones. Except for our previous communication,[7] there have been no reports on the addition of nucleophlies other than carbon nucleophiles to nitrones.

The present paper describes detailed experiments on the addition of several carboxamides to nitrones.

Result and Discussion

As we have already briefly reported, N-(1-cyanoalkyl)alkylideneamine *N*-oxide (I) reacts with formamide in a 1:1 molar ratio to give an adduct (II). Formamide is known to react with unsaturated bonds in two different fashions as follows.[8,9] Hence, the adduct seems to be a hydroxylamine involving either a secondary amide or a primary amide moiety.

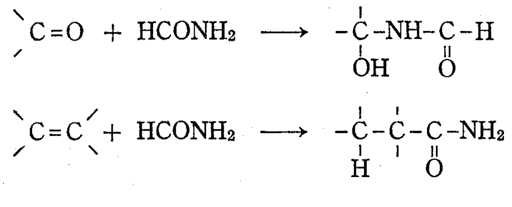

Chart 1

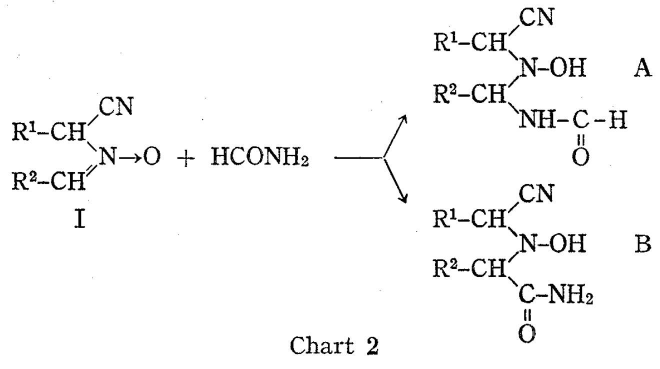

Chart 2

In the spectra of the adducts (II) two characteristic absorptions are observed at 1522—1528 and 1204—1216 cm^{-1}, which correspond to amide II and amide III bands, respectively, of secondary amides.

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[1] Part I: M. Masui, K. Suda, M. Yamauchi, and C. Yijima, *J. Chem. Soc. Perkin I*, in press.

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

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

[4] A. Dornov, H. Gehrt, and F. Ische, *Ann.*, **585**, 220 (1954); G.E. Utzinger and F.A. Regenass, *Helv. Chim. Acta*, **37**, 1892 (1954).

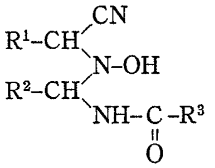
[5] M. Masui, Y. Tsuda, and C. Yijima, *J. Chem. Soc.*, **1961**, 4063.

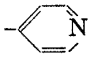
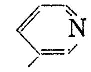
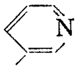
[6] R. Bonnett, R.F.C. Brown, V.M. Clark, I.O. Sutherland, and A. Todd, *J. Chem. Soc.*, **1959**, 2094.

[7] M. Masui, C. Yijima, and K. Suda, *Chem. Pharm. Bull.* (Tokyo), **19**, 865 (1971).

[8] G.A. Crowe and C.C. Lynch, *J. Am. Chem. Soc.*, 72, 3622 (1950).

Table I. IR Spectral Data on II



II	R¹	R²	R³	IR (cm⁻¹, KBr)					
				OH and NH		C≡N	C=O	Amide II	Amide III
a	Pr^n	Pr^i	H	3360	3200	2230	1652	1522	1216
b	Pr^n	Pr^n	H	3355	3190	2230	1651	1526	1212
c	Pr^i	Pr^n	H	3345	3210	2240	1656	1528	1210
d	Pr^i	Pr^i	H	3350	3220	2240	1659	1526	1216
e	Pr^i	Me	H	3340	3205	2240	1641	1529	1230
f	Et	Pr^n	H	3350	3200	2240	1647	1522	1204
g	Et	Pr^i	H	3355	3190	2230	1668	1523	1214
h	Pr^i	Pr^i		3350	3190	2230	1645	1528	1303
i	Pr^i	Pr^i		3295	3175	2230	1630	1532	1303
j	Pr^n	Pr^i		3265	3190	2230	1635	1532	1297

The nuclear magnetic resonance (NMR) spectrum of (IIg) showed a rather broad doublet due to the proton of a secondary amide at τ 1.67. There are two possible explanations of this phenomenon: (1) the rotation around the C-N bond is hindered or (2) the N-H proton exchanges slowly so that it is coupled to protons on adjacent carbons. The results shown in Fig. 1 and Table II support the latter possibility. The triplet at τ 5.71 and doublet at τ 1.86 were assigned to the proton b and the formyl proton e, respectively. Both protons couple with the proton on the adjacent nitrogen. On D_2O treatment, the OH proton signal at τ 1.57 immediately disappeared, but the NH proton signal decreased gradually, and with concomitant gradual replacement of the signals b and e by a new doublet and a singlet, respectively.

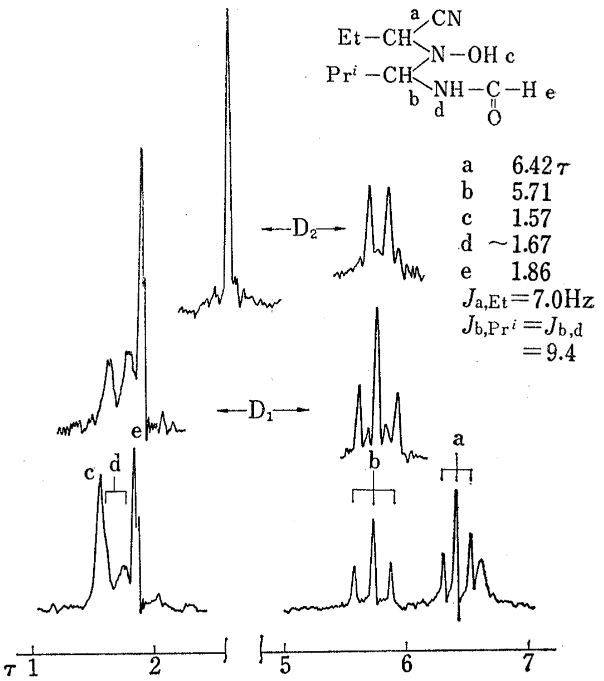


Fig. 1. NMR Spectrum of IIg (DMSO$_{d\text{-}6}$)

D_1: ten minutes after D_2O treatment
D_2: five hours after D_2O treatment

Thus, the adduct is not B but A.

When R² was a normal alkyl chain, proton b on theasymmetrical centre gave rise to a complicated multiplet which could not be assigned definitely.

All the primary amides investigated other than formamide are crystalline solids at room temperature, so their reactions with I were studied in various solvents. Among the many amides tested, nicotinamide and isonicotinamide also gave 1:1 adducts which were confirmed

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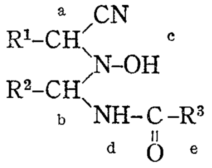
9) E. Eland and J. Rokach, *J. Org. Chem.*, **30**, 3361 (1965).

to be (IIh—j) from their infrared (IR) spectra. On reaction of I with other amides no adducts could be isolated.

TABLE II. Chemical Shift (τ) and Coupling Constant (*J*, Hz) of II



II[a]	a	b	c	d	e	$J_{\mathrm{aR}}\mathrm{R}^1$	$J_{\mathrm{bR}}\mathrm{R}^2$	$J_{\mathrm{dR}}\mathrm{R}^3$	J_{bd}
a	6.33	5.70	1.58	~1.69	1.88	6.5	9.5	1.7	9.5
b	6.28	~5.25	1.56	~1.65	1.93	6.8		1.7	
c	6.61	~5.30	1.58	~1.65	1.95	8.4		1.7	
d	6.66	5.74	1.61	~1.68	1.88	8.3	9.5	1.8	9.5
f	6.35	~5.28	1.57	~1.68	1.96	6.9		1.4	
g	6.42	5.71	1.57	~1.67	1.86	7.0	9.4	1.6	9.4
h	6.55	5.50	1.56	~1.13		8.7	9.4		9.4
i	6.54	5.49	1.58	~1.21		8.7	9.6		9.6
j	6.23	5.49	1.58	~1.21		7.2	9.8		9.8
k[b]	6.61	5.73	1.49	~1.52	5.85	8.2	9.3	1.8	9.3

[a] measured in DMSO$_{d-6}$ [b] $R^1=R^2=Pr^i$, $R^3=-CH_2Cl$

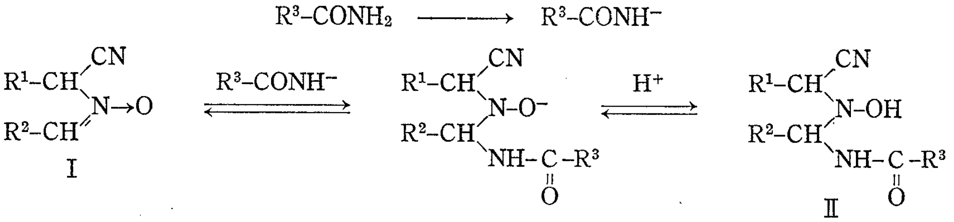
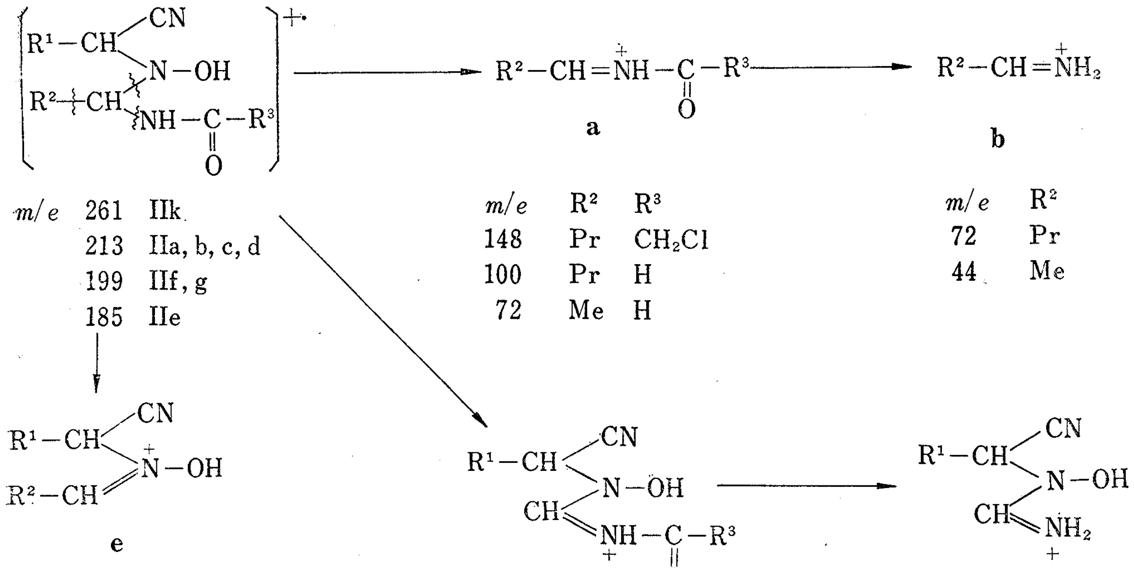


Chart 3



m/e	
261	IIk
213	IIa, b, c, d
199	IIf, g
185	IIe

a

m/e	R^2	R^3
148	Pr	CH_2Cl
100	Pr	H
72	Me	H

b

m/e	R^2
72	Pr
44	Me

e

m/e	R^1	R^2
169	Pr	Pr
155	Et	Pr
131	Pr	Me

c

m/e	R^1	R^3
170	Pr	H
156	Et	H
218	Pr	CH_2Cl

d

m/e	R^1
142	Pr
128	Et

Chart 4

The reaction seemed to involve addition of amide anion ($RCONH^-$) to the nitrone, so the catalytic effect of bases on the reaction was studied in dry ethanol. Sodium ethoxide was found to be the most effective catalyst, and only when it was used did Id give IIk with chloroacetamide. The other bases tested, such as sodium hydroxide and pyperidine, were much less effective.

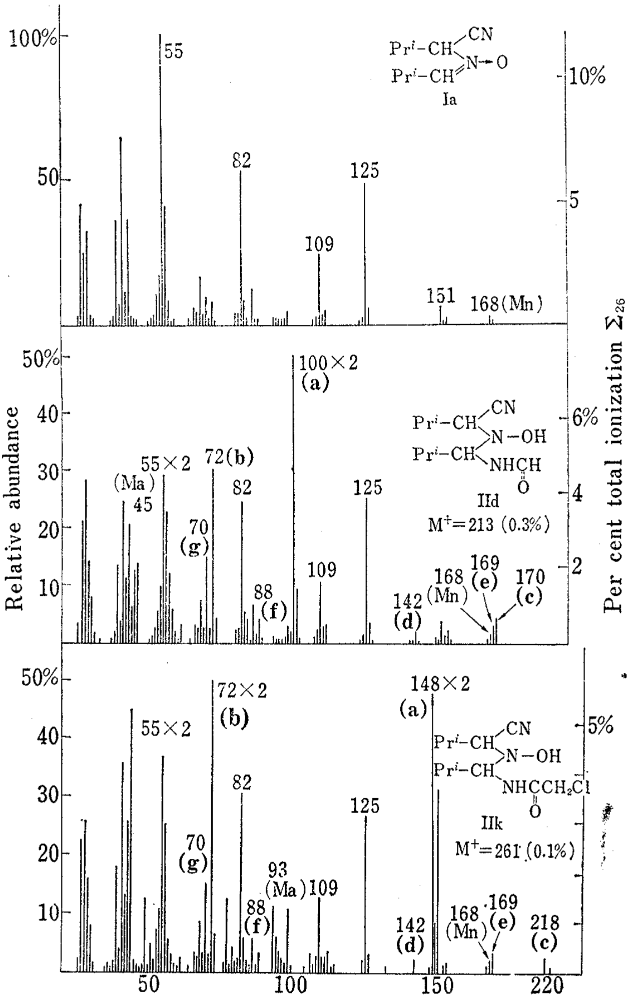


Fig. 2. Mass Spectra of N-(1-Cyanoisobutyl)isobutylideneamine N-Oxide (Ia), N-(1-Cyanoisobutyl)-N-(1′-formamidoisobutyl)hydroxylamine (IId) and N-(1-Cyanoisobutyl)-N-(1′-chloracetamidoisobutyl)hydroxylamine (IIk)

The measurement were made with an ionization energy of 70 eV and the temperature of the ion source was 210°

On warming in solvents such as ethanol or benzene, II readily liberated the original nitrone and elevation of temperature accelerated the decomposition.[10] Nitrones are known to be transformed readily into the hydrazones of the corresponding carbonyl compounds on treatment with 2,4-dinitrophenylhydrazine.[11] When the reagent was added to a warm ethanolic solution of II, the hydrazone of the parent aldehyde precipitated almost immediately. However, at room temperature, an ethanolic solution of II only gave the hydrazone after shaking for 10 to 20 minutes. These results suggest that the reaction of I with carboxamides involves nucleophilic attack of the amide anions on I, and the products readily decompose to the starting compounds.

The thermal decomposition of II to I and the amides can also be deduced from the mass spectra of II (Fig. 2). Molecular ions of the nitrone (Mn) and the amide (Ma) are both seen in the spectra of IId and IIk, and the peaks derived from the individual nitrone and amide are also found in the spectra of II.[12] The molecular ion peak of II is itself very weak and its intensity is generally less than 0.5% of that of the base peak. The following results were obtained by comparing the spectra of II with various R^1, R^2, and R^3, and confirming the fragments **a**, **b**, **c**, **d**, and **e** by high resolution mass spectrometry. The most characteristic peak of II is usually the base peak. It is due to fragment **a** resulting from the cleavage of the C-N bond next to the carboxamide moiety. The rearrangement of fragment **a** to form fragment **b** probably occurs in one of two different ways depending on the nature of R^3 (Chart 5). The metastable ion peaks, *m/e* 52 and 35, respectively, support the rearrangement.

Other characteristic peaks are **c** and **e**. The fragment **c** results from C-C cleavage next to the two nitrogen atoms. The rearrangement of fragment **c** to form **d** is the same as that

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10) The melting point for II reported previously[7] should be termed the decomposition point.
11) F. Kroehnke, *Angew. Chem.*, **65**, 612 (1953); *idem*, *ibid.*, **75**, 181 (1963).
12) M. Masui and C. Yijima, *Chem. Pharm. Bull.* (Tokyo), **17**, 1517 (1969).

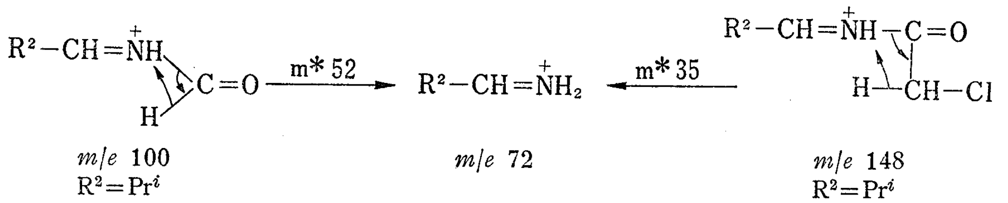

Chart 5

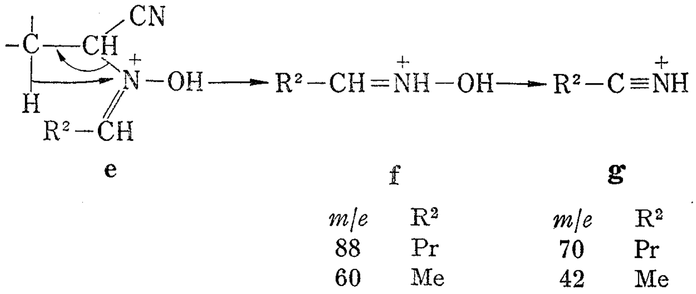

Chart 6

of fragment **a** to form **b**. The formation of the ion **e** can be understood by supposing that the nitrogen atom of the hydroxylamine moiety has a positive charge. However, the fate of fragment **e** is uncertain, since if dehydration or removal of ·H or ·OH is possible at any stage during the fragmentations, the resulting ions should be identical with those of the nitrone. In the mass spectra of IIc and IIe, fragments **f** and **g** were noticed by high resolution measurement, and so fragmentation like that shown in Chart 6, may occur.

Experimental

IR spectra were measured in KBr with a Hitachi ETI-G3 spectrometer, NMR spectra were measured with a Hitachi Perkin-Elmer R-20A spectrometer, and mass spectra with a Hitachi RMU-6D mass spectrometer. High resolution measurements were made with a Hitachi RMU-7L mass spectrometer with an ionization energy of 70 eV. The temperature of the ion source was 150°.

N-(1-Cyanoalkyl)-N-(1′-formamidoalkyl)hydroxylamine (IIa—g)——a) N-(1-Cyanoalkyl)alkylideneamine N-oxide (I) (2 g) was dissolved in excess formamide (10 ml) and stood at room temperature for one to two weeks to allow crystallization of the product. This was separated from the mixture by filtration (maximum 1.8 g), rinsed with a small portion of ether (3 ml × 3) and then recrystallized from ethylacetate–ethanol (5:1 v/v). A high temperature must be avoided during recrystallization.

b) I (1 g) and formamide (2.2 g) were dissolved in dry ethanol (10 ml) containing Na (12 mg) and stood for a day at room temperature. The ethanol was removed *in vacuo* at low temperature and the resulting oil was chromatographed on silica gel (Mallincrodt). Elution with benzene–ethylacetate (3:1 v/v) gave (II), (100 mg).

N-(1-Cyanoisobutyl)-N-(1′-nicotinamidoisobutyl)hydroxylamine (IIi)——N-(1-Cyanoisobutyl)isobutylideneamine N-oxide (2 g) and nicotinamide (1.5 g) were dissolved in solvents, such as ethanol, acetone, ethylacetate or benzene,and refluxed for two days and then warmed at 50° for a day. The solvents were evaporated off *in vacuo* at low temperature and the resulting paste was rinsed with a small portion of ether (3 ml × 3) and then water (3 ml × 3). Unreacted amide was recovered from the latter, (550 mg). The residue was recrystallized from ethylacetate, (900 mg). IIh and IIj were obtained by the same procedure.

N-(1-Cyanoisobutyl)-N-(1′-chloroacetamidoisobutyl)hydroxylamine (IIk)——N-(1-Cyanoisobutyl)isobutylideneamine N-oxide (500 mg) and chloroacetamide (350 mg) were dissolved in dry ethanol (30 ml) containing Na (10 mg) and the mixture was stood for 6 days at room temperature. The resulting paste was applied to a silica gel column. Elution with benzene–ethylacetate (4:1 v/v) gave the adduct which was recrystallized from benzene–petroleum ether (61 mg), mp 100—102°. *Anal.* Calcd. for $C_{11}H_{20}O_2N_3Cl$: C, 50.47; H, 7.73; N, 16.05. Found: C, 50.68; H, 7.77; N, 16.14.

Investigation of the Catalysis of the Reaction——N-(1-Cyanoisobutyl)isobutylideneamine N-oxide (1 g) and formamide (2 ml) were dissolved in ethanol (60 ml) and the mixture was divided into five parts. Four of these were mixed with Na, NaOH, piperidine and acetic acid (*ca.* 1×10^{-4} mol), respectively and one received no addition. The reaction was followed by thin layer chromatography on silica gel with ether as solvent. With Na the product ($Rf = 0.77$) was found after one hour, with NaOH or piperidine after 15 hours, with acetic acid after 22 hours and without catalyst after 24 hours.

Thermal Decomposition of II to the Corresponding Nitrone (I)——(IId) was dissolved in dry ethanol and heat at 70° for 1—2 hours. A thin–layer chromatogram on silica gel with ether as solvent showed two main spots due to IId ($Rf=0.77$) and Id ($Rf=0.60$). Then, 2,4-dinitrophenylhydrazine was added to the solution. The hydrazone separated immediately and was recrystallized from ethanol–water, mp 182—183°. It was identified as the hydrazone of isobutyraldehyde by determination of the mixed melting point. IIc gave the corresponding hydrazone mp 122° (from ethanol–water).

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