Formation of 4-Benzamidoisoxazole Derivatives[1)]

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The titled compounds (**3**) were synthesized by the reaction of nitrile oxides with 1-azirines and also the reaction of aliphatic nitro compounds with dibenzoylmethane derivatives in the presence of acetyl chloride and sodium methoxide. The structure of **3** was established by single crystal X-ray analysis. A mechanism of the formation for **3** is proposed.

This is dealing with an one-pot synthesis of 4-benzamidoisoxazole derivatives **3** through the reaction of nitrile oxides **1**[2)] with 1-azirines **2**.[3,4)] **3** was synthesized by the two methods as follows: (I) Nitrile oxides **1a—1c**, which are isolated or generated in situ by the acylation[5)] of aliphatic nitro compounds **4a—4c** with acetyl chloride, are allowed to react with 2-benzoyl-1-azirines (**2a—2c**) in the presence of NaOMe. In this case furazan 2-oxides (**6**),[2)] dimers of **1**, were obtained as main products. (II) Dibenzoylmethanes (**5a, 5b**) are reacted with two molecular equivalents of **4a, b** in the presence of acetyl chloride and NaOMe also (Scheme 1). The results of these procedures are summarized in Table 1.

The structure of **3** was determined by single crystal X-ray analysis with **3e** (Fig. 1) and also by alternative preparations of **3c** and **3g** from **9f** and **9g**[6)] respectively (III) (Scheme 1). Compound **3c** obtained via (I) was identical to that obtained from the reaction (III).

The postulated mechanism of the formation of **3** was illustrated by Scheme 2: Nitrile oxide **1** generated from **4** reacts with dibenzoylmethane derivative **5** in an 1,3-dipolar cycloaddition to give an isoxazoline intermediate **10**. A fission of N-O bond[7)] of **10** in basic conditions followed by elimination of benzoic acid affords nitrene intermediate **11**, which isomerizes[8)] to 1-azirine **2**. Subsequently, nucleophilic attack of methoxide anion to **2** gives aziridine intermediate **12**. Furthermore a fission of C-C bond[9)] of **12** gives olefinic intermediate **13**, which cyclizes with another **1** to finally lead to **3**.

This mechanism was also supported by the following experimental results: i) Isolated nitrile oxide **1b** reacts with **5a** to give the corresponding 1-azirine **2b**.[10)] ii) Isoxazoles (**7** and **8**) were isolated as by-products in

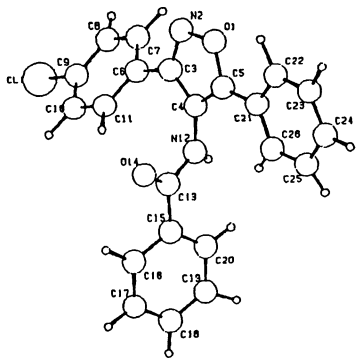


Fig. 1. Molecular structure of the compound **3e**.[15)]

Table 1. Yields and Spectral Data of the Derivatives of Benzamidoisoxazoles and Related Compounds

	R^1	R^2	R^3	Mp θ_m/°C	Yield/% I	II	III	IR cm^{-1}	MS, m/z	^{1}H NMR δ/ppm (NH and Me)
3a	H	H	H	202—203	20[b)]	16		3210, 1650	340(M^+)	7.60
3b	CH_3	H	H	188—190	13,[a)] 23[b)]			3240, 1640	354(M^+)	7.55, 2.37
3c	CH_3	CH_3	H	216—219	18[a)]	28	76	3240, 1650	368(M^+)	7.53, 2.33, 2.40
3d	CH_3	CH_3	CH_3	238—241	35[b)]	41		3260, 1650	382(M^+)	7.42, 2.40, 2.37(2Me)
3e	Cl	H	H	176—178	5[b)]			3260, 1660	374(M^+), 376(M^++2)	7.50
3g	CH_3	H	CH_3	223—224			91	3220, 1650	368(M^+)	7.45, 2.33(2Me)
14a	H	H	H	153—155		92		1660	354(M^+)	3.47
14b	CH_3	H	H	155—157		76		1660	368(M^+)	2.45, 3.47
14c	CH_3	CH_3	H	176—178		83		1660	382(M^+)	2.22, 2.45, 3.45
14d	CH_3	CH_3	CH_3	213—214		58		1660	396(M^+)	2.34(2Me), 2.43, 3.45
15a	—	—	—	222—224		64		3230, 1640	342(M^+)	7.50, 8.43, 8.80
15b	—	—	—	211—213		67		3370, 3300, 1630	356(M^+)	3.24, 6.63, 7.00
16a	—	—	—	173—175[c)]		14		—	—	—
16b	—	—	—	130—132		60		3440, 1720, 1690	357(M^+)	—
17	—	—	—	201—202		74		3260, 1630	324(M^+)	—

a) The yields of **3** by the reaction of (**1**+**2**→**3**). b) The yields of **3** by the reaction of (**4**+**2**→**3**). c) Lit. 173.5—174.5 °C (Ref. 14). All compounds had elemental analyses (C,H,N) within ±0.3% of theoretical values.

Table 2. The Positional Parameters and Equivalent Isotropic Thermal Parameters with Their Estimated Standard Deviation in Parentheses

Atom	x(×10⁴)	y(×10⁴)	z(×10⁴)	B_{eq}/Å²
O1	1679(1)	1789(4)	8110(2)	3.25(0.04)
N2	1978(1)	1606(5)	7109(3)	3.24(0.05)
C3	2560(2)	2069(6)	7470(3)	2.88(0.06)
C4	2657(2)	2564(6)	8681(3)	2.77(0.05)
C5	2095(2)	2389(6)	9048(3)	2.91(0.06)
C6	3013(2)	2080(6)	6642(3)	2.97(0.06)
C7	2854(2)	2795(7)	5502(4)	3.72(0.07)
C8	3289(2)	2858(7)	4742(4)	4.15(0.07)
C9	3881(2)	2222(7)	5135(4)	3.93(0.07)
C10	4050(2)	1468(7)	6243(4)	4.00(0.07)
C11	3610(2)	1409(6)	7006(4)	3.48(0.07)
C12	3217(1)	3230(5)	9339(3)	2.83(0.05)
C13	3615(2)	2077(6)	10035(3)	3.14(0.06)
C14	3510(1)	467(4)	10124(3)	4.86(0.06)
C15	4192(2)	2981(6)	10668(3)	3.06(0.06)
C16	4694(2)	1834(7)	11052(4)	4.07(0.07)
C17	5245(2)	2618(8)	11637(4)	4.96(0.08)
C18	5287(2)	4463(7)	11848(4)	4.10(0.07)
C19	4794(2)	5560(7)	11472(4)	3.97(0.07)
C20	4241(2)	4820(6)	10875(4)	3.64(0.07)
C21	1855(2)	2699(6)	10151(3)	3.24(0.06)
C22	1248(2)	2203(7)	10235(4)	4.41(0.08)
C23	1014(2)	2525(8)	11277(4)	5.34(0.09)
C24	1382(2)	3354(8)	12227(4)	5.24(0.09)
C25	1982(2)	3845(8)	12145(4)	4.88(0.09)
C26	2225(2)	3518(7)	11106(4)	4.30(0.08)
Cl	4433(1)	2391(2)	4191(1)	5.68(0.02)

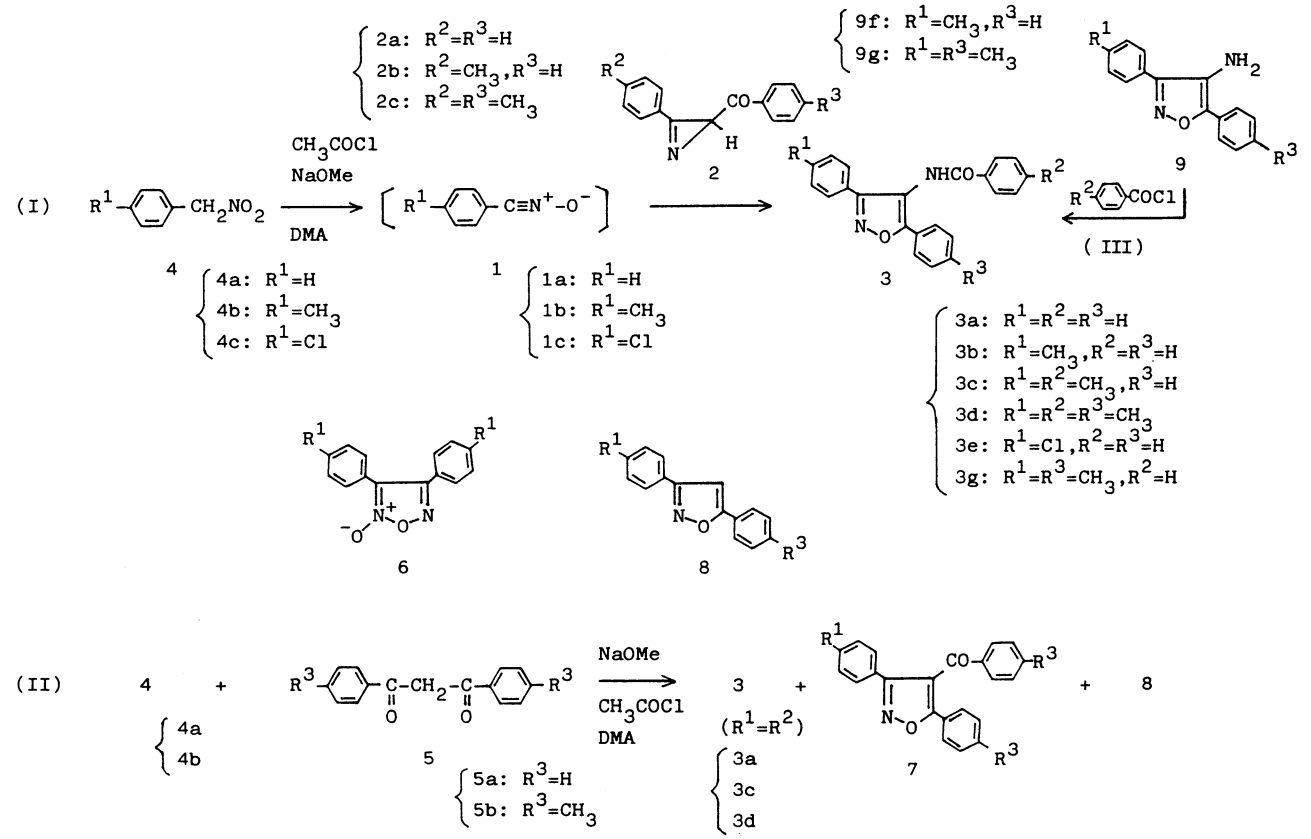
the reaction (II). This result shows that the above mechanism includes intermediate **10**, for **7** is a dehydroxy compound of **10**, and **8** is considered to be formed from **11**.[8]

The reactivity of **3** was also studied as follows: i) *N*-Methylations of **3a—3d** were carried out with CH_3I to afford **14a—14d** in good yields as summarized in Table 1. ii) Hydrogenation of **3** with Raney Ni afforded β-aminoenone (**15**), which was hydrolyzed to give **16** and/or imidazole **17** (Scheme 3).

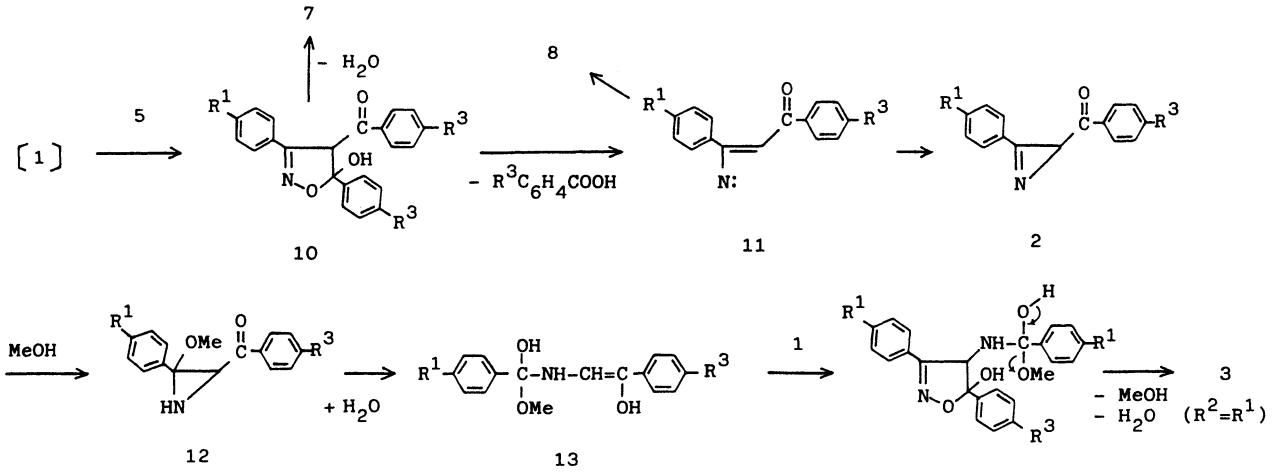
The authors (Z. and H.) reported[11] previously the reaction of **1** with **2** to give **3** and assigned the structure of **3** to 4*H*-1,2,4-oxadiazine derivative based on spectroscopic analysis and also a ring opening reaction mentioned above. However, the structure of **3** was established to be 4-benzamido-3,5-diarylisoxazole, as illustrated in Fig. 1 by X-ray analysis. Accordingly,the authors (Z. and H.) correct the structure of **3** herein.

Table 3. Bond Length and Torsional Angle for the Bond Connecting the Conjugated Groups

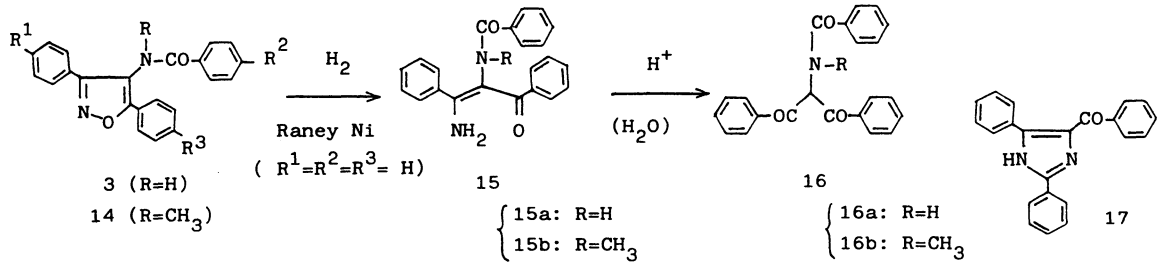
A-X-Y-B	Bond length (l/Å) X-Y	Torsional angle (ϕ/°) along X-Y
N2-C3-C6-C7	1.474 (6)	42.9 (5)
O1-C5-C21-C22	1.458 (6)	6.6 (5)
C3-C4-N12-C13	1.419 (4)	−97.6 (4)
N12-C13-C15-C20	1.506 (5)	20.8 (5)



Scheme 1.



Scheme 2.



Scheme 3.

Experimental

Reaction of *p*-Tolunitrile Oxide (1b) with 3-Benzoyl-2-phenyl-1-azirine (2a). General Procedure for Method(I): To a solution of **2a**[12] (57.0 mg, 0.26 mmol) in anhydrous *N,N*-dimethylacetamide (DMA) (5 cm^3) was added freshly prepared **1b**[13] (37.0 mg, 0.26 mmol) and 1 mol dm^{-3} NaOMe in MeOH (0.52 cm^3) with ice-cooling. After stirring at room temperature overnight, the reaction mixture was partitioned between ice-water (20 cm^3) and benzene (10 cm^3). The aqueous phase was extracted with benzene (3×10 cm^3), dried (Na_2SO_4) and concentrated to dryness. The residue (46.2 mg) was separated by column chromatography on silica gel with AcOEt-hexane (5 : 1) as an eluent to afford 3,4-di-*p*-tolylfurazan 2-oxide (**6b**) (20.1 mg, 54%) and 4-benzamido-5-phenyl-3-(*p*-tolyl)isoxazole (**3b**) (11.9 mg, 13%): mp 188—190 °C (EtOAc-hexane).

Reaction of Phenylnitromethane (4a) with 3-Benzoyl-2-phenyl-1-azirine (2a): To a solution of **4a** (137 mg, 1.0 mmol) in anhydrous DMA (15 cm^3) was added 1 mol dm^{-3} NaOMe in MeOH (1.0 cm^3), acetyl chloride (0.70 cm^3, 1.0 mmol), **2a** (221.0 mg, 1.0 mmol) with ice-cooling. After further addition of 1 mol dm^{-3} NaOMe in MeOH (4.0 cm^3), the reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was poured into ice-water (20 cm^3). After neutralization with 1 mol dm^{-3} HCl, the aqueous phase was extracted with benzene (3×15 cm^3), dried (Na_2SO_4) and concentrated to dryness. The residue (284 mg) was chromatographed on silica gel with EtOAc-hexane (5 : 1) as an eluent to give 3,5-diphenylisoxazole (**8a**) (79.0 mg, 35%), 3,4-di-*p*-tolylfurazan 2-oxide (**6a**) (13.0 mg, 54%), and 4-benzamido-3,5-diphenylisoxazole (**3a**) (68.0 mg, 20%): mp 202—203 °C (MeOH-H_2O).

Reaction of Phenylnitromethane (4a) with Dibenzoylmethane (5a). General Procedure for Method(II): To a solution of **4a** (548 mg, 4.0 mmol) in anhydrous DMA (20 cm^3) was added 1 mol dm^{-3} NaOMe in MeOH (4 cm^3), acetyl chloride (0.29 cm^3, 4.1 mmol), **5a** (448 mg, 2.0 mmol) with ice-cooling. After further addition of 1 mol dm^{-3} NaOMe in MeOH (16 cm^3), the reaction mixture was poured into ice-water (120 cm^3). After neutralization with 1 mol dm^{-3} HCl, the aqueous phase was extracted with benzene (3×40 cm^3), dried (Na_2SO_4) and concentrated to dryness. The residue (887.5 mg) was chromatographed on silica gel with benzene-EtOAc (20 : 1) as an eluent to give **8a** (140.5 mg, 32%), 4-benzoyl-3,5-diphenylisoxazole (**7a**) (195.3 mg, 30%), methyl benzoate (33.0 mg, 12%), acetophenone (28.0 mg, 12%) and **3a** (108.2 mg, 16%).

X-Ray Analysis of 4-Benzamido-3-(*p*-chlorophenyl)-5-phenylisoxazole (3e): X-Ray specimen of **3e** of approximate dimensions 0.35×0.1×0.06 mm was recrystallized from hexane-EtOAc. Diffraction intensities were measured using Cu $K\alpha$ radiation monochromated by a graphite plate. The crystal data are: 4-Benzamido-3-(*p*-chlorophenyl)isoxazole, $C_{22}H_{15}N_2O_2Cl$, MW=374.8. Monoclinic, space group $P2_1/n$, Z=4. Unit cell dimensions, a=21.833(10), b=7.339(5), c=11.448(7) Å, β=99.02(6)°, U=1812 Å^3. D_{cal}=1.374 g cm^{-3}, μ for Cu $K\alpha$=31 cm^{-1}. Number of observed reflections as above the 2δ(I) level was 2390 out of 3947 within the 2θ range of 6° through 156°. The crystal structure was determined by the direct method and refined by the method of block-diagonal matrix least-squares to an R value of 0.058 including 27 heavier atoms and 42 hydrogen atoms. The hydrogens were

located on the difference electron-density map and their positional and isotropic temperature factors were included in the least-squares refinement. The molecular structure of **3e** is shown in Fig. 1. The molecule consists of an isoxazole ring(A), two phenyl groups (B and C, B ring bears a chlorine atom at *p*-position), and a benzamido group (D). The dimensions of each part of the molecule are quite normal. The torsional angles along the bonds connecting each group are listed in Table 3.

***N*-Benzoylation of 4-Amino-5-phenyl-3-(*p*-tolyl)isoxazole (9f):** A mixture of **9f** (30 mg, 0.12 mmol), *p*-toluoyl chloride (19 mg, 0.12 mmol) and K_2CO_3 (18 mg, 0.12 mmol) in a ether-benzene-H_2O (1 : 3 : 1) mixed solution was stirred at 0—5 °C for 15 h. The mixture was poured into ice-water and extracted with toluene (5 $cm^3 \times 3$), dried (Na_2SO_4) and concentrated to dryness. The residue (47.4 mg) was chromatographed on silica gel with hexane-EtOAc (3 : 1) as an eluent to give **3c** (33.6 mg, 76%): mp 218—220 °C (MeOH-H_2O).

***N*-Methylation of 3a:** A mixture of **3a** (20 mg, 0.06 mmol), KOH (3.9 mg, 0.06 mmol), and 18-crown-6 (0.25 mg, 0.001 mmol) in benzene (2 cm^3) was refluxed for 2 h. After the addition of CH_3I (14 mg, 0.1 mmol) in benzene (1 cm^3), the reaction mixture was refluxed for 4 h and concentrated in vacuo. After washing with H_2O, the crude product was recrystallized from EtOAc-hexane to give 4-(*N*-methylbenzamido)-3,5-diphenylisoxazole (**14a**) (19.0 mg, 92%).

Reductive Ring Opening Reaction of 3a: A solution of **3a** (100 mg, 0.26 mmol) in MeOH (30 cm^3) was hydrogenated (1 atm, r.t.) for 3 h in the presence of activated Raney Ni-Tl. After the solution was filtered, the filtrate was concentrated to dryness. The residue (95.2 mg) was chromatographed on silica gel with hexane-EtOAc (3 : 1) as an eluent to furnish 3-amino-2-benzamido-1,3-diphenyl-2-propen-1-one (**15a**) (64.6 mg, 64%).

Hydrolysis of 15a: A mixture of **15a** (50 mg, 0.15 mmol) and 1 mol dm^{-3} HCl (1 cm^3) in MeOH (2 cm^3) was refluxed for 2h. After cooling, the reaction mixture was diluted with 5 cm^3 of cooled H_2O, and the resultant precipitates were collected. 2-Benzamido-1,3-diphenyl-1,3-propanedione (**16a**) (7.0 mg, 14%): mp 173—175 °C (MeOH) (lit,[14] 173.5—174.5 °C). The filtrate was neutrallized with 2 mol dm^{-3} NaOH and the resultant precipitates were collected. 2-Benzoyl-3,5-diphenylimidazole (**17**) (37.0 mg, 74%): mp 201—202 °C (MeOH).

References

1) The Synthetic Reactions of Aliphatic Nitro Compounds XXV. Presented at the 54th Annual Meeting of Chemical Society of Japan, Tokyo, April 1987. (Part XXIV: S. Zen, T. Nishino, K. Harada, H. Nakamura, and Y. Iitaka, *Chem. Pharm. Bull.*, **31**, 4181 (1983).

2) For reviews, a) P. Caramella and P. Grünanger, "1,3-Dipolar Cycloaddition Chemistry," ed by A. Padwa, John Wiley & Sons, New York (1984), Vol. 1, Chap. 3, pp. 291—392; b) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963); C. Grundmann, "The Chemistry of the Cyano Group," ed by Z. Rappoport, Interscience Publishers, New York (1970), pp. 832—846.

3) For reviews, a) V. Nair and K-H Kim, *Heterocycles*, **7**, 353 (1977); b) A. Hassner, *Heterocycles*, **14**, 1517 (1980).

4) V. Nair, *Tetrahedron Lett.*, **1971**, 4831.

5) K. Harada, E. Kaji, and S. Zen, *Chem. Pharm. Bull.*, **28**, 3296 (1980)

6) V. D. Piaz, S. Rinzauti, and P. Lacrimini, *Synth. Commun.*, **1975**, 664.

7) G. Bianchi, R. Gandolfi, and P. Grünanger, *J. Heterocycl. Chem.*, **5**, 49 (1968).

8) A. N. Nesmeyanov, M. I. Rybinskaya, and I. G. Kelekhsaeva, *Izvest. Akad. Nauk, SSSR*, **1969**, 866.

9) A. Padwa, O. Eastman, and L. Hamilton, *J. Org. Chem.*, **33**, 1317.

10) S. Zen and K. Harada, *Chem. Pharm. Bull.*, **30**, 366 (1982).

11) S. Zen and K. Harada, *Chem. Lett.*, **1982**, 1711.

12) E. F. Ullman and B. Singh, *J. Am. Chem. Soc.*, **88**, 1844 (1966).

13) G. Barbaro, G. Battaglia, and A. Dondoni, *J. Chem. Soc. B*, **1970**, 588; A. Quilico, "Five and Six-membered Compounds with Nitrogen and Oxygen," ed by R. H. Wiley, Intersciences, New York (1962), p. 21.

14) D. Y. Curtin and M. L. Poutsma, *J. Am. Chem. Soc.*, **84**, 4887 (1962).

15) Tables of anisotropic thermal parameters, coordinates of hydrogen atoms are deposited as Document No. 8817 at the Office of the Editor of Bull. Chem. Soc. Jpn.