ISOLATION OF AZIRINO[1,2-a]INDOLE DERIVATIVES BY THE THERMOLYSIS OF 2-ALKENYL-3-AZIDO-2-CYCLOHEXEN-1-ONES

Michihiko Noguchi,* Kenjiro Onimura, and Shoji Kajigaeshi
Department of Industrial Chemistry, Faculty of Engineering,
Yamaguchi University, Tokiwadai, Ube 755, Japan

Abstract——The thermal reaction of 2-alkenyl-3-azido-2-cyclohexen-1-ones **1** in toluene gave azirino[1,2-a]indole derivatives **3** as major products together with indoles **2**.

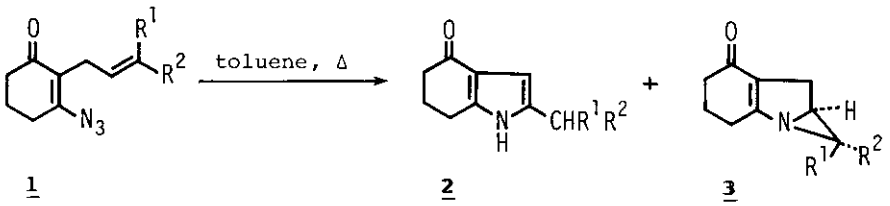
Cycloaddition reactions of organic azides or nitrenes to unsaturated double bond have been investigated as a synthetic means of nitrogen heterocycles.[1] In particular, recent advances in azide-diene cycloaddition of ω-azidodiene provided an important and versatile methodology for pyrrolizidine alkaloid synthesis.[2] Some investigations on the reaction pathway revealed that dipolar cycloaddition of azide to olefin preceded to yield triazoline derivative, which lost nitrogen with formation of aziridine and/or imine.[3] However, there were few reports on the synthetic utilities of vinyl azide-olefin or -diene cycloadditions,[4] because the cycloaddition competed with the conversion to vinyl nitrene accompanied with azirine formation or Curtius-type rearrangement.[5] For example, the thermal reaction of α-azidostyrene in acrylonitrile gave azirine, 1-vinylaziridine, and/or 1-pyrroline derivatives.[4b] An intramolecular variant of this reaction was also done; the thermal reaction of 2-allyl-3-azido-2-cyclohexen-1-one (**1a**) in MeOH gave 2-allyl-2-amino-3,3-dimethoxycyclohexanone, stemmed from azirine intermediate, and 2-methyl-4-oxo-4,5,6,7-tetrahydroindole (**2a**).[4a]

To elucidate the synthetic utility of intramolecular vinyl azide-olefin cycloaddition, we reinvestigated the thermal reaction of 2-alkenyl-3-azido-2-cyclohexen-1-ones **1** in toluene, and found that the aziridine formation was a main pathway and the reaction was sensitive to the stereo-electronic factor of alkenyl moiety of **1**.

The reaction of **1a** in toluene under reflux gave **2a** and 1a,2,3,4,5,6-hexahydro-3-oxo-1H-azirino-[1,2-a]indole (**3a**) in 20 and 21% yields, respectively. For a better understanding of the reaction profiles, similar thermolysis of 2-(trans-cinnamyl)- (**1b**), 2-(trans-2-butenyl)- (**1c**), and 2-(3-methyl-2-butenyl)-3-azido-2-cyclohexen-1-one (**1d**) was examined. In these cases, 1H-

azirino[1,2-a]indoles (**3b–d**) were obtained as major products together with the corresponding indoles (**2b–d**), but none of the products from azirine intermediate were isolated (Table 1).

Table 1. Thermolysis of 2-Alkenyl-3-azido-2-cyclohexen-1-ones **1** in Toluene



1 **2** **3**

			Reaction	Yield (%)[a]	
	R^1	R^2	Time (min)	**2**	**3**
a	H	H	15	20	21
b	H	Ph	40	10	37[b]
c	H	Me	30	trace	63[c]
d	Me	Me	30	9	80

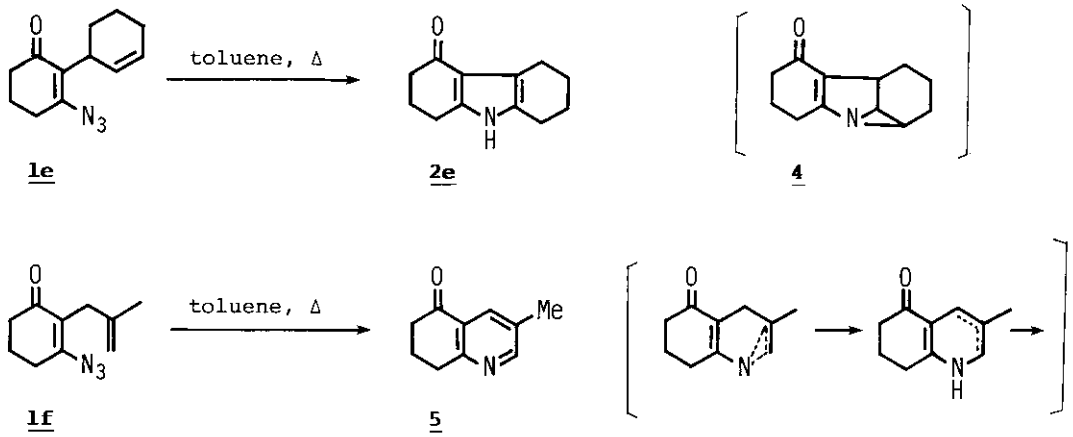
a) Isolated yield. b) Single isomer. c) Mixture of exo/endo (4/1) isomers.

The structural elucidation of the 1H-azirino[1,2-a]indoles (**3**) was accomplished on the basis of their analytical and spectral data, e.g., the ^{13}C nmr spectrum of **3a** showed six sp^3-carbon signals except for olefin and carbonyl carbon signals.

The azirinoindoles (**3**) were not so stable; on standing at room temperature for a long period or heating in some solvents gave only polymeric products. This means that the indoles (**2**) were not secondary products from azirinoindoles (**3**). The thermolysis of **1b** in THF under reflux for 1 day gave **2b** (16%), **3b** (18%), and the recovered **1b**, but triazoline derivative was not formed. Some attempts to detect triazoline intermediates in ^1H nmr spectra of reaction mixtures have failed, and only starting azides and products were seen. In order to obtain any evidence for reaction mechanism, the photolysis of **1a** was examined. The irradiation (high pressure mercury lamp) of the solution of **1a** in benzene gave **2a** (trace), **3a** (50 %), and the unreacted **1a**.

These results indicate that a nitrene intermediate might be responsible for the formation of these products.[6] A similar reaction pathway had been demonstrated by Tamura and his co-workers[4a,5b] in the thermolysis and photolysis of 2-alkyl- and 2-allyl-3-azido-2-cyclohexen-1-ones.

Similar thermolysis of 3-azido-2-(2-cyclohexenyl)-2-cyclohexen-1-one (**1e**) gave carbazole (**2e**) in 67% yield. The inspection of molecular model of azirino[2,3,1-jk]carbazole (**4**) elucidated that the formation of **4** would be unfavorable due to its ring strain. On the other hand, 3-azido-2-(2-methyl-2-propenyl)-2-cyclohexen-1-one (**1f**) was heated under reflux in toluene to yield 3-methyl-5,6,7,8-tetrahydro-5-oxoquinoline (**5**) in 38% yield, which may be formed via the nucleophilic attack of C-C double bond to nitrene yielding a dihydropyridine ring.



1e **2e** **4**

1f **5**

The development of this intramolecular vinyl azide-olefin cycloaddition reaction and further investigations on the reaction mechanism are now in progress.

EXPERIMENTAL[7]

2-Alkenyl-1,3-cyclohexanediones were prepared similarly to the method for 2-allyl-1,3-cyclohexanedione.[8]

Preparation of 3-azido-2-alkenyl-2-cyclohexen-1-ones (1). General Procedure: a solution of methanesulfonyl chloride (4.8 mmol) in dry THF (2 ml) was added to the solution of 2-allyl-1,3-cyclohexanedione (4.0 mmol) and triethylamine (4.8 mmol) in dry THF (9 ml) at 0 °C and the reaction mixture was stirred for 1 h at room temperature. After filtering off the precipitates, the THF was evaporated to dryness. The residue was subjected to a short silica gel column chromatography(chloroform) to give the sulfonester in a quantitative yield. 2-Allyl-3-methanesulfonyloxy-2-cyclohexen-1-one: pale yellow oil; ir(NaCl)cm^{-1}: 1670(CO), 1350, 1180(SO_2); ^1H nmr δ : 1.9-2.2(m, 2H, 5-H), 2.50(br t, 2H, 6-H, J= 8 Hz), 2.92(br t, 2H, 4-H, J= 8 Hz), 3.12(br d, 2H, $-CH_2-$, J= 8 Hz), 3.23(s, 3H, $-CH_3$), 4.9-5.2(m, 2H, $=CH_2$), 5.6-6.0(m, 1H, =CH-). Sodium azide (5.2 mmol) was added portionwise to the solution of 2-allyl-3-methanesulfonyloxy-2-cyclohexen-1-one (4.0 mmol) in 20% aqueous methanol (12 ml) at 0 °C and the reaction mixture was stirred for 14 h at room temperature. The mixture was concentrated to a half volume and extracted with ether (5 x 30 ml). The ethereal layer was washed with brine and dried over anhydrous magnesium sulfate. The ether was evaporated to dryness. The residue was subjected to basic alumina column chromatography (ether/hexane=1/1) to give azide **1a** in 85% yield.

2-Allyl-3-azido-2-cyclohexen-1-one (**1a**): pale yellow oil; ir(NaCl) cm^{-1}: 2095(N_3), 1645(CO): ^1H nmr δ: 2.0-2.3(m, 2H, 5-H), 2.44(br t, 2H, 6-H, J= 9 Hz), 2.77(br t, 2H, 4-H, J= 9 Hz), 3.09(d, 2H, $-CH_2-$, J= 9 Hz), 4.9-5.2(overlapping, 2H, $=CH_2$), 5.6-6.1(m, 1H, =CH-); ms m/z: 177(M^+).

3-Azido-2-(trans-cinnamyl)-2-cyclohexen-1-one (**1b**): yellow oil; yield: 91% based on 2-(trans-cinnamyl)-1,3-cyclohexanedione; ir(NaCl) cm^{-1}: 2090(N_3), 1650(CO); ^1H nmr δ: 1.9-2.2(m, 2H, 5-H), 2.3-2.8(overlapping, 4H, 4- and 6-H), 3.15(br d, 2H, $-CH_2-$, J= 8 Hz), 5.9-6.5(overlapping, 2H, -CH=CH-), 7.2(m, 5H, phenyl); ms m/z: 253(M^+).

3-Azido-2-(trans-2-butenyl)-2-cyclohexen-1-one (**1c**): pale yellow oil; yield: 86% based on 2-(trans-2-butenyl)-1,3-cyclohexanedione; ir(NaCl) cm^{-1}: 2080(N_3), 1650(CO); ^1H nmr δ: 1.65(br d, 3H, $-CH_3$, J= 5 Hz), 1.9-2.3(m, 2H, 5-H), 2.44(t, 2H, 6-H, J= 8 Hz), 2.68(t, 2H, 4-H, J= 8 Hz), 3.0(br s, $-CH_2-$), 5.3-5.6(overlapping, 2H, -CH=CH-); ms m/z: 191(M^+).

3-Azido-2-(3-methyl-2-butenyl)-2-cyclohexen-1-one (**1d**): yellow oil; yield: 96% based on 2-(3-methyl-2-butenyl)-1,3-cyclohexanedione; ir(NaCl) cm^{-1}: 2095(N_3), 1655(CO); ^1H nmr δ: 1.73(s, 6H, CH_3), 1.9-2.3(m, 2H, 5-H), 2.4-2.7(overlapping, 4H, 4- and 6-H), 3.98(br d, 2H, $-CH_2-$, J= 8 Hz), 4.9-5.2(m, 1H, =CH-); ms m/z: 205(M^+).

3-Azido-2-(2-cyclohexenyl)-2-cyclohexen-1-one (**1e**): pale yellow oil; yield: 41% based on 2-(2-cyclohexenyl)-1,3-cyclohexanedione; ir(NaCl) cm^{-1}: 2090(N_3), 1650(CO); ^1H nmr δ: 1.2-2.1(ov, 6H, $-CH_2-$), 2.1-2.3(m, 2H, 5-H), 2.42(t, 2H, 6-H, J= 8 Hz), 2.70(t, 2H, 4-H, J= 8 Hz), 3.5-3.9(m, 1H, -CH), 5.3-5.9(overlapping, 2H, -CH=CH-); ms m/z: 217(M^+).

3-Azido-2-(2-methyl-2-propenyl)-2-cyclohexen-1-one (**1f**): pale yellow oil; yield: 72% based on 2-(2-methyl-2-propenyl)-1,3-cyclohexanedione; ir(NaCl) cm^{-1}: 2080(N_3), 1640(CO); ^1H nmr δ: 1.71(br s, 3H, CH_3), 1.9-2.2(m, 2H, 5-H), 2.41(t, 2H, 6-H, J= 8 Hz), 2.67(t, 2H, 4-H, J= 8 Hz), 2.97(s, 2H, $-CH_2-$), 4.52, 4.68(2 br s, 1H each, $=CH_2$); ms m/z: 191(M^+).

Thermolysis of 2-alkenyl-3-azido-2-cyclohexen-1-ones (1). General Procedure: a solution of 2-allyl-3-azido-2-cyclohexen-1-one (**1a**)(3.4 mmol) in dry toluene (30 ml) in the presence of molecular sieves 4A (5 g) was heated under reflux for 15 min. After filtering off the molecular sieves, the reaction mixture was concentrated to dryness. The residue was subjected to silica gel column chromatography to give **2a** (hexane/ethyl acetate=1/1) and **3a** (hexane/ethyl acetate=1/3).

2-Methyl-4-oxo-4,5,6,7-tetrahydroindole (**2a**): colorless prisms; mp 204-205 °C (lit.[4a] mp 204 °C); ^{13}C nmr δ: 12.8(CH_3), 22.8(7-C), 24.0(6-C), 37.8(5-C), 102.7(3-C), 120.7(2-C), 129.0(3a-C), 143.4(7a-C), 194.6(4-C).

3-Oxo-1a,2,3,4,5,6-hexahydro-1H-azirino[1,2-a]indole (**3a**): colorless oil, ir(NaCl) cm^{-1}: 1650(CO); ^1H nmr δ: 1.45(br d, 1H, 1-H*endo*, J= 2.5 Hz), 1.9-2.2(m, 2H, 5-H), 2.2-2.4(m, 2H, 4-H), 2.4-2.7(overlapping, 3H, 1-H*exo* and 6-H), 2.7-3.1(overlapping, 3H, 1a- and 2-H); ^{13}C nmr δ: 23.7, 26.0, 30.5, 37.0, 39.9, 41.5, 128.0(2a-C), 179.9(6a-C), 197.8(3-C); ms m/z: 149(M^+).

2-Benzyl-4-oxo-4,5,6,7-tetrahydroindole (**2b**): colorless prisms; mp 265-266 °C; ir(KBr) cm^{-1}: 3300(NH), 1625(CO); ^1H nmr δ: 2.1-2.2(m, 2H, 6-H), 2.21(s, 2H, $-CH_2-$), 2.46(t, 2H, 5-H, J= 6.2 Hz), 2.80(t, 2H, 7-H, J= 6.2 Hz), 7.24(br s, 1H, 3-H), 7.4(m, 5H, phenyl), 8.0-8.2(br s, 1H, NH);

^{13}C nmr($CDCl_3$+DMSO-d_6) δ: 11.2(CH_2), 22.9(6-C), 23.8(7-C), 39.0(5-C), 116.9(2-C), 118.8(3-C), 125.5, 125.9, 130.1, 135.2(phenyl), 127.2(3a-C), 143.0(7a-C), 193.0(4-C); ms m/z: 225(M^+). Found: C, 79.95; H, 6.77; N, 6.30. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22.

3-Oxo-1-phenyl-1a,2,3,4,5,6-hexahydro-1H-azirino[1,2-a]indole (**3b**): pale yellow crystals; mp 256-260 °C(dec); ir(KBr) cm^{-1}: 1650(CO); ^{1}H nmr δ: 1.9-2.2(m, 2H, 5-H), 2.3-2.4(m, 2H, 4-H), 2.4-2.7(overlapping, 3H, 1- and 6-H), 2.9-3.2(overlapping, 3H, 1a- and 2-H), 7.2-7.4(m, 5H, phenyl); ^{13}C nmr δ: 22.7(1-C), 26.2(1a-C), 30.9(5-C), 37.0(2-C), 50.1(6-C), 53.7(4-C), 126.2, 127.7, 128.5, 137.9(phenyl), 127.8(2a-C), 178.5(6a-C), 197.4(3-C); ms m/z: 225(M^+).

1-(exo-Methyl)-3-oxo-1a,2,3,4,5,6-hexahydro-1H-azirino[1,2-a]indole (**3c-exo**): colorless prisms; mp 77 °C; ir(KBr) cm^{-1}: 1650(CO); ^{1}H nmr δ: 1.32(d, 3H, CH_3, J= 5.9 Hz), 1.6-1.8(m, 1H, 1-H), 1.9-2.1(m, 2H, 5-H), 2.3-2.4(m, 2H, 4-H), 2.5-2.8(overlapping, 4H, 1a-, 2-H, and 6-H), 2.93(dd, 1H, 2-H, J= 14.3, 1.8 Hz); ^{13}C nmr δ: 18.0(CH_3), 22.6(1-C), 26.2(1a-C), 29.7(5-C), 36.9(2-C), 48.0(6-C), 49.0(4-C), 128.1(2a-C), 178.9(6a-C), 197.6(3-C); ms m/z: 163(M^+). Found: C, 73.70; H, 8.22; N, 8.48. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58.

The formation of **3c-endo** was confirmed by the ^{1}H and ^{13}C nmr spectra of reaction mixture; ^{1}H nmr δ: 1.08(d, CH_3, J= 6.2 Hz); ^{13}C nmr δ: 26.4(CH_3).

2-Isopropyl-4-oxo-4,5,6,7-tetrahydroindole (**2d**): yellow prisms; mp 173-174 °C; ir(KBr) cm^{-1}: 3200(NH), 1600(CO); ^{1}H nmr δ: 1.20(d, 6H, CH_3, J= 8 Hz), 2.1-2.3(m, 2H, 6-H), 2.50(br t, 2H, 5-H, J= 7.2 Hz), 2.6-2.9(overlapping, 3H, -CH and 7-H), 6.25(br s, 1H, =CH-), 8.9-9.4(br s, 1H, NH); ms m/z: 177(M^+). Found: C, 74.71; H, 8.70; N, 7.92. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90.

1,1-Dimethyl-3-oxo-1a,2,3,4,5,6-hexahydro-1H-azirino[1,2-a]indole (**3d**): colorless oil; ir(NaCl) cm^{-1}: 1650(CO), ^{1}H nmr δ: 1.09, 1.38(2s, 3H each, CH_3), 1.9-2.1(m, 2H, 5-H), 2.1-2.7(overlapping, 4H, 4-H and 6-H), 2.7-2.9(overlapping, 3H, 1a- and 2-H); ^{13}C nmr δ: 12.4(CH_3), 22.4(1-C), 26.9(1a-C), 27.4(CH_3), 27.5(5-C), 36.9(2-C), 48.8(6-C), 53.4(4-C), 131.3(2a-C), 174.4(6a-C), 196.7(3-C); ms m/z: 177(M^+).

4-Oxo-1,2,3,4,5,6,7,8-octahydrocarbazole (**2e**): colorless prisms; mp 226-227 °C; ir(KBr) cm^{-1}: 3240(NH), 1615(CO); ^{1}H nmr δ: 1.7-1.8(overlapping, 4H, 6- and 7-H), 2.0-2.2(m, 2H, 2-H), 2.43(t, 2H, 3-H, J= 6.5 Hz), 2.52(t, 2H, 5-H, J= 5.8 Hz), 2.7-2.8(overlapping, 4H, 1- and 8-H), 9.1-9.4(br s, 1H, NH); ^{13}C nmr δ:22.4, 22.6, 22.9, 23.0, 23.2, 24.2(1-, 2-, 5-, 6-, 7-, and 8-C), 38.5(3-C), 116.0(4b-C), 117.9(8a-C), 127.9(4a-C), 143.1(9a-C), 195.4(4-C); ms m/z:189(M^+). Found: C, 74.71; H, 8.70; N, 7.92. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90.

3-Methyl-5-oxo-5,6,7,8-tetrahydroquinoline (**5**): colorless prisms; mp 42-43 °C; ir(NaCl) cm^{-1}: 1690(CO); ^{1}H nmr δ: 2.1-2.2(m, 2H, 7-H), 2.37(s, 3H, CH_3), 2.68(t, 2H, 6-H, J= 6.2 Hz), 3.12(t, 2H, 8-H, J= 6.5 Hz), 8.08(d, 1H, 2-H, J= 2.2 Hz), 8.51(d, 1H, 4-H, J= 2.2 Hz); ^{13}C nmr δ:

18.0(CH_3), 22.0(8-C), 32.1(7-C), 38.6(6-C), 127.5(4a-C), 131.8(3-C), 135.0(4-C), 154.1(2-C), 160.8(8a-C), 198.4(5-C); ms m/z: 161(M^+). Found: C, 74.35; H, 7.08; N, 8.68. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69.

The products **3a**, **3b**, and **3d** did not gave satisfactory analytical data owing to the instability.

Photolysis of 2-allyl-3-azido-2-cyclohexen-1-one (1a). The deoxygenated benzene solution (10 ml) of **1a** (1.1 mmol) in Pyrex sealed tube was irradiated by high pressure mercury lamp (100 W) at room temperature for 48 h. The benzene was evaporated to dryness, which was subjected to silica gel column chromatography to give **2a**, **3a**, and **1a**.

REFERENCES AND NOTES

1. For recent reviews: C. Wentrup, Adv. Heterocycl. Chem., 1981, **28**, 231; E. F. Scriven, 'Reactive Intermediates', ed. by R. A. Abramovitch, Plenum, New York, 1982, Vol. 2, pp. 1-54; A. Padwa, '1,3-Dipolar Cycloaddition Chemistry', ed. by A. Padwa, Wiley, New York, 1984, Vol. 2, Chapter 12.
2. T. Hudlicky, J. O. Frazier, and L. D. Kwart, Tetrahedron Lett., 1985, **26**, 3523; W. H. Pearson, ibid., 1985, **26**, 3527; W. H. Pearson, J. E. Celebuski, Y. -F. Poon, B. R. Dixon, and J. H. Glans, ibid., 1986, **27**, 6301; T. Hudlicky, G. Seone, and T. C. Lovelace, J. Org. Chem., 1988, **53**, 2094.
3. P. Scheiner, J. Am. Chem. Soc., 1968, **90**, 988; idem, Tetrahedron, 1968, **24**, 2757.
4. a) Y. Tamura, Y. Yoshimura, T. Nishimura, S. Kato, and Y. Kita, Tetrahedron Lett., **1973**, 351; b) Y. Nomura, N. Hatanaka, and Y. Takeuchi, Chem. Lett., **1976**, 901; c) A. Padwa, A. Ku, H. Ku, and A. Mazzu, J. Org. Chem., 1978, **43**, 66; d) Y. Naruta, Y. Arita, N. Nagai, H. Uno, and K. Maruyama, Chem. Lett., **1982**, 1859; Y. Naruta, N. Nagai, Y. Arita, and K. Maruyama, J. Org. Chem., 1987, **52**, 3956.
5. a) G. L'abbe and A. Hassner, Angew. Chem., Int. Ed. Engl., 1971, **10**, 98; G. L'abbe and G. Mathys, J. Org. Chem., 1974, **39**, 1778; b) Y. Tamura, Y. Yoshimura, and Y. Kita, Chem. Pharm. Bull., 1971, **19**, 1068; idem, ibid., 1972, **20**, 871; Y. Tamura, S. Kato, Y. Yoshimura, T. Nishimura, and Y. Kita, ibid., 1974, **22**, 1291.
6. Probably, the ratio of products depended on the reaction temperature.
7. All melting points are uncorrected. The ir spectra were recorded on a JASCO IRA-1 spectrophotometer. The ^1H nmr spectra were measured on a JEOL-MH-100 and/or GSX-270 spectrometers and the ^{13}C nmr spectra were obtained by a JEOL GSX-270 spectrometer. The nmr spectra were taken in $CDCl_3$ with tetramethylsilane as an internal standard unless otherwise noted. The mass spectra were taken with a JEOL JMS-D mass spectrometer at an ionization energy of 75 eV.
8. K. -W. Rosemund and H. Bach, Chem. Ber., 1961, **94**, 2394.

Received, 24th July, 1989