Thermal and Photochemical Behavior of Sterically Hindered *N*-Vinyliminopyridinium Ylides

Akikazu Kakehi,* Suketaka Ito, Takahisa Funahashi, and Yoshio Ota

Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan

Received November 25, 1975

Thermolyses of sterically hindered *N*-vinylimino-2,6-lutidinium ylides (**3a** and **3b**) afforded 2,6-lutidine, indoles (**5a** and **5b**), oxazoles (**6a** and **6b**), phenylacetates (**7a** and **7b**), and phenylcyanoacetates (**8a** and **8b**) in fairly good yields, while their photolyses gave 2,6-lutidine, a six-membered mesoionic compound (**9**), isonitriles (**10a** and **10b**), and an azirine (**11a**). The reactions of the *N*-ylides (**3a** and **3b**) with ethyl propiolate afforded the rearranged vinylpyridine derivatives (**4a** and **4b**) in 40 and 51% yields, respectively. Structural elucidation of these products was mainly accomplished by their chemical conversions and by comparisons with authentic samples. Some mechanisms for these reactions are also discussed.

Various types of pyridinium *N*-ylides have been synthesized in recent years, and their dipolar[1] and nucleophilic reactivities[1j,2] are well documented. In some reactions of these *N*-ylides, ylidic bond fissions were often observed, and products derived from the resulting reactive species such as carbenes and nitrenes were detected.[3] However, such decomposition of the pyridinium *N*-ylides has been an undesirable side reaction in most cases. Recent interest in azirine chemistry[4] prompted us to investigate the possibility of obtaining vinylnitrene intermediates by this process. In this paper, we wish to report the preparation of *N*-vinyliminopyridinium ylides designed for this purpose and their thermal and photochemical behavior.

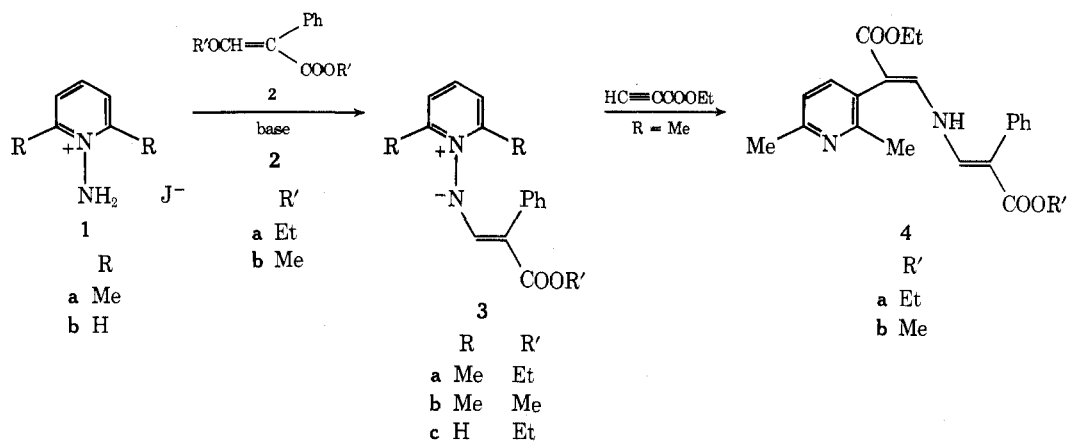
Results and Discussion

Preparation of Pyridinium *N*-Ylides (3a–c). *N*-(3-Alkoxycarbonyl-3-phenylvinylimino)-2,6-lutidinium ylides (**3a** and **3b**) were prepared from the reactions of 2,6-lutidinium *N*-imine hydriodide (**1a**) with ethyl ethoxy- (**2a**) and methyl methoxymethylenephenylacetate (**2b**). These compounds were selected as models, because the ylide bond might be weakened by steric hindrance of 2 and 6 substituents on the pyridine ring[3b] and the generated vinylnitrene would be trapped intramolecularly by the phenyl and/or the alkoxycarbonyl groups in the N substituent.[3e,5] *N*-Vinyliminopyridinium ylide (**3c**) was similarly prepared from pyridinium *N*-imine hydriodide (**1b**) and ethoxymethylene compound (**2a**) for comparison of its reactivity with those of 2,6-lutidinium ylides (**3a** and **3b**). In order to determine the stereochemistry on the vinyl group in the *N*-ylides **3a–c**, we carried out the reactions of the *N*-ylides **3a** and **3b** with ethyl propiolate and obtained the expected rearranged products (**4a** and **4b**)[6] in 40 and 51% yields, respectively. Since no hydrogen bonding between the amino and the two ester carbonyl groups of the rearranged compounds (**4a** and **4b**) was observed in their ir and NMR spectra (see Experimental Section), the configuration of these groups in the divinylamine moiety was concluded to be both trans. From this, the cis configuration of the iminopyridinium and phenyl groups in the parent *N*-ylides (**3a** and **3b**) was deduced, since this kind of rearrangement of *N*-vinyliminopyridinium ylide has been proposed to proceed with retention of the configuration of the exocyclic *N*-vinyl group.[6a] These results are shown in Scheme I.

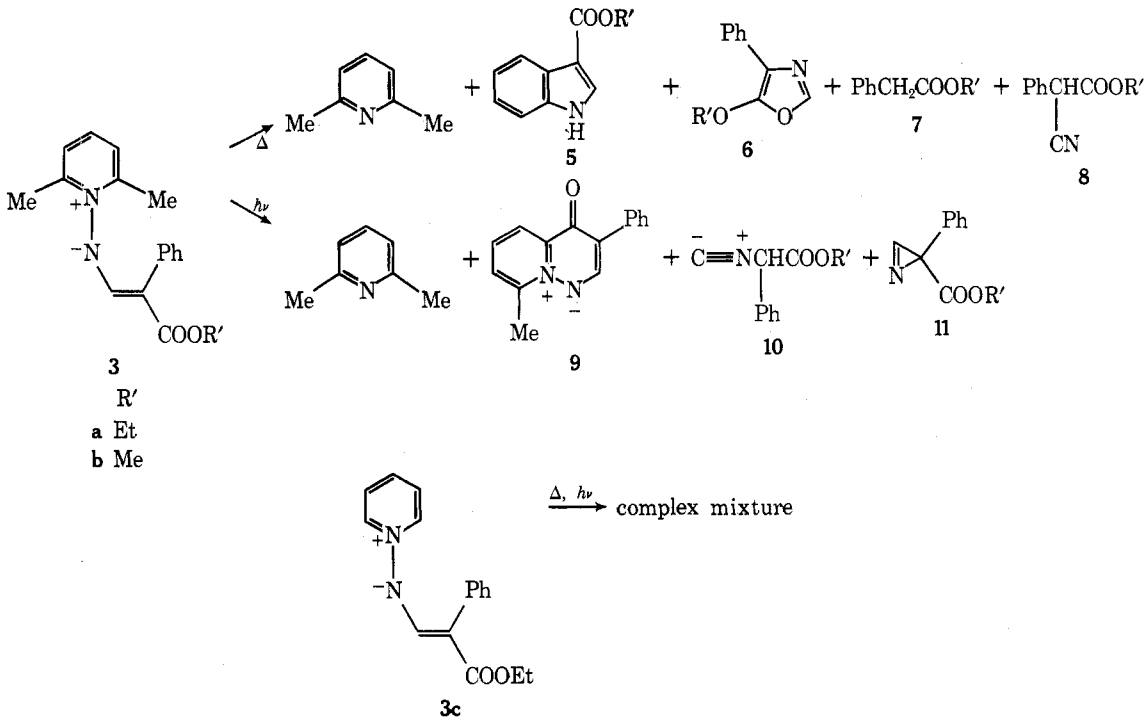
The stereochemical assignment was also supported by the consideration of thermal behavior of these *N*-ylides as will be indicated below.

Thermolysis and Photolysis of *N*-Ylides 3a–c. When *N*-ylides **3a** and **3b** were thermolyzed in refluxing xylene, the smooth generation of expected 2,6-lutidine with disappearance of the *N*-ylides was observed by thin layer chromatography. After evaporation of xylene and 2,6-lutidine from the reaction mixture, separation of the residue gave three types of products, a crystalline compound (**5a**, mp 122–124 °C, 10%, and **5b**, mp 147–148 °C, 7%), and two oily compounds (**6a**, 31% and **7a**, 30%, and **6b**, 32% and **7b**, 2%), respectively (Scheme II). Furthermore, another product (**8a** and **8b**) was detected from the reaction mixture by gas chromatography, but the yields were exceedingly small. On the other hand, photolysis of *N*-ylide **3a** in benzene afforded a crystalline compound (**9**, mp 226–228 °C, 15%), and an oily mixture (**10a** and **11a**, 44%), and that of *N*-ylide **3b** gave only oily product (**10b**, 37%) together with trace amount of compound **9**, except the formation of considerable amounts of 2,6-lutidine. When the *N*-ylides **3a** and **3b** were irradiated in benzene in the presence of a sensitizer such as benzophenone, compounds **10a** and **10b** were obtained exclusively with decreased irradiation time.[3c]

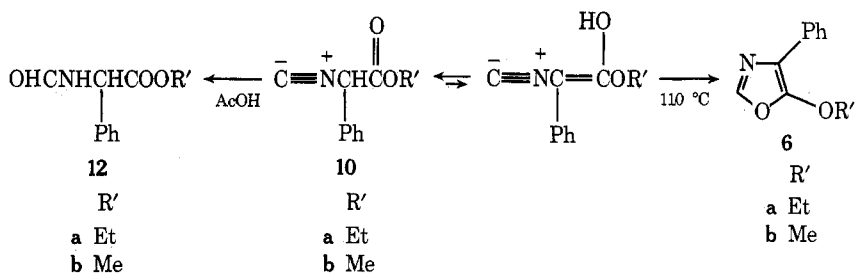
Scheme I



Scheme II



Scheme III



In contrast with *N*-ylides **3a** and **3b**, *N*-ylide **3c**, thermally and photochemically, gave only complex mixtures and isolation of significant product from them was unsuccessful.

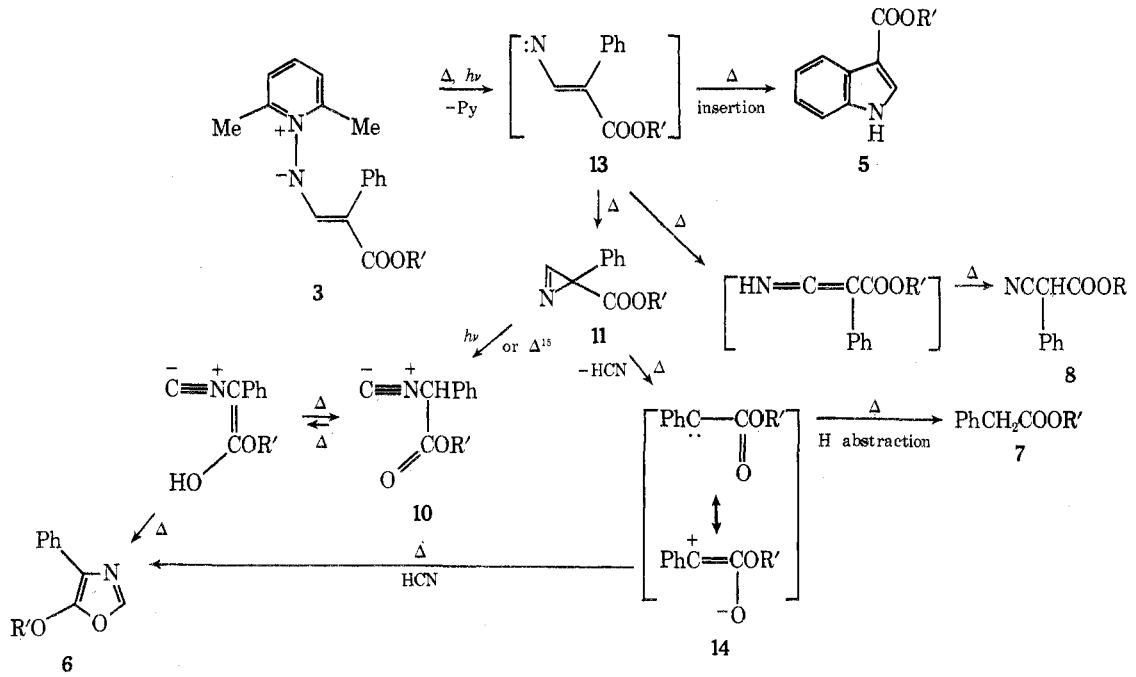
The structures of these compounds (**5, 6, 9–11**) were determined by their elemental and spectral analyses and by comparisons with authentic samples, and those of compounds **7** and **8** by gas chromatographic identification. Compound **5a**, for example, was assigned to be 3-ethoxycarbonylindole, because the ir spectrum exhibited a secondary amino absorption at 3210 cm^{-1} and a strong carbonyl absorption at 1655 cm^{-1}, and the NMR spectrum showed signals at δ 7.27 (3 H, m), 7.84 (1 H, d), 8.18 (1 H, m), and 9.26 (1 H, br s, NH) attributable to the indole skeleton. The melting points of the products (**5a** and **5b**) were, of course, well coincident with those reported by Peterson et al.[7] Compounds **6a** and **6b** were determined to be 5-alkoxy-4-phenyloxazole derivatives, but not the isomeric isoxazoles, by comparisons with samples prepared in very good yields by isomerization[8] of the corresponding isonitriles (**10a** and **10b**), which were photochemically generated from *N*-ylides **3a** and **3b**. The spectral data of compounds **6a** and **6b** were also completely in accord with those reported in the literature.[9] Compounds **10a** and **10b** showed each one characteristic isonitrile absorption at 2170 cm^{-1} in the ir spectra, and respective singlet signal at δ 5.30 (**10a**) and 5.32 (**10b**) due to exchangeable methine proton by keto–enol tautomerization in the NMR spectra. In addition, conversion of these compounds (**10a** and **10b**) to oxazoles **6a** and **6b** on thermolysis and to formamide derivatives **12a** and **12b** by treatment with acetic acid supported the assignments as ethyl (**10a**) and methyl phenylisocyanoacetate (**10b**) (Scheme III).

Crystalline compound **9** showed a largely shifted carbonyl absorption at 1560 cm^{-1} in the ir spectrum, and only aromatic proton multiplets in the range of δ 7.23–7.98 (9 H) and one methyl proton singlet at δ 2.81 in the NMR spectrum. The presence of the methyl group derived from the 2,6-lutidine moiety exhibited that compound **9** is not a product from ylidic bond fission. Further information for this structure was obtained by its uv spectral inspection: this compound (**9**) has two maximum absorptions in ethanol at 282 (ϵ 4.63 × 10^4) and 332 nm (ϵ 1.29 × 10^4). The former absorption at 282 nm is the same as that at 282 nm (ϵ 2.39 × 10^4) of the *N*-ylide **3a** and also those at 275–290 nm characteristics of various *N*-vinyliminopyridinium ylide structures.[1h,6a] From these results, compound **9** was assigned to be a six-membered mesoionic compound possessing a diazanaphthalene skeleton.[10] Compound **11a** exhibited a singlet signal at δ 9.81 characteristic of the 2-methine proton in the 1-azirine derivative,[11] but several attempts to isolate it were unsuccessful.

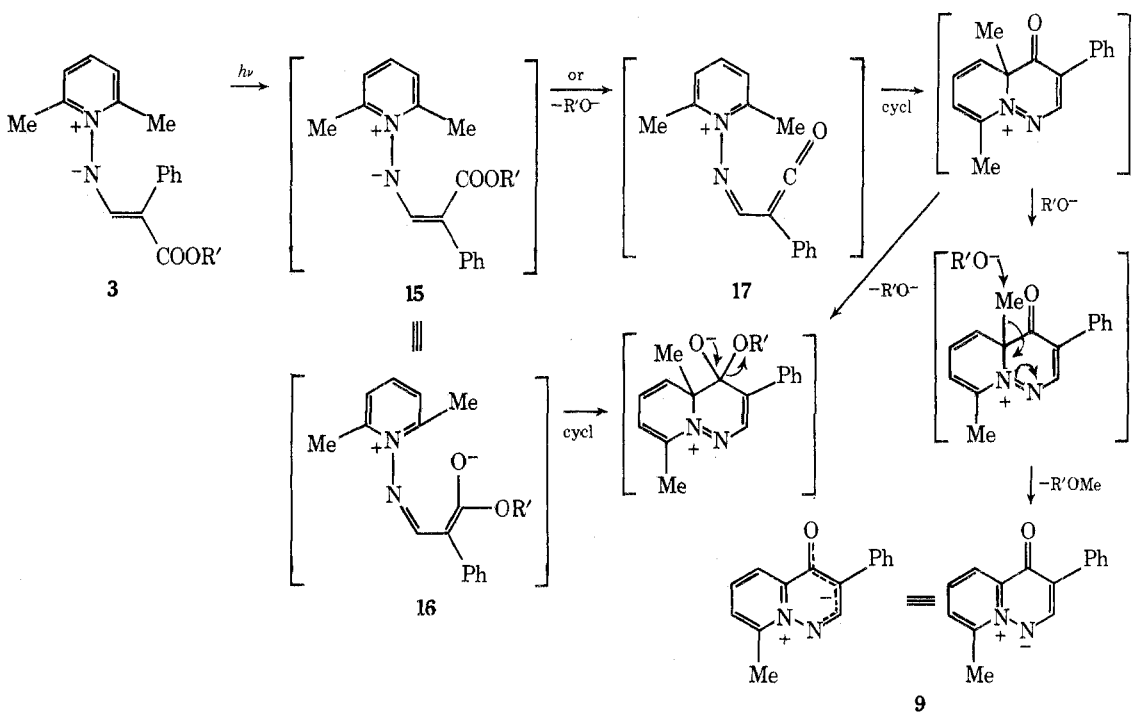
Mechanism. Possible mechanisms for these reactions are summarized in Schemes IV and V.

Except mesoionic compound **9**, all of the products (**5–8, 10,** and **11**) may be formed via vinylnitrene intermediates (**13**) from ylidic bond fission of the *N*-ylides **3a** and **3b**. Indoles **5a** and **5b** should be formed by direct insertion of the nitrenes **13a** and **13b** to the cis-faced aromatic carbon–hydrogen bond rather than ring enlargement of the azirine intermediates **11a**

Scheme IV



Scheme V



and **11b**,[4] because other possible products, isoxazoles, could not be detected in the reaction mixture. Oxazoles **6a** and **6b** seem to be produced via 1,3-dipolar cycloaddition between hydrogen cyanide and alkoxycarbonylphenylcarbenes (**14a** and **14b**), both which were generated by thermal fragmentation of the azirines **11a** and **11b**. Such a fragmentation of 2-unsubstituted 1-azirine[12] and similar cycloadditions of acylcarbenes with nitriles[13] were reported, while thermal preparation of oxazoles via vinylnitrenes and 1-azirines was not. In addition, the isolation of phenylacetates **7a** add **7b** seems to be clear proof of intervention of the carbenes **14**. The formation of nitriles such as compounds **8a** and **8b** has been observed usually in thermal decomposition of vinyl azides possessing an acyl group.[14] The photochemical path of azirine to isonitrile was already established by Hafner et al.[12,15] and facile thermal isomerization of various acyl-substituted isonitriles to oxazoles[8] has been also well known. On the other hand, possible paths of *N*-ylide to mesoionic compound (**9**) may be initiated by photochemical cis–trans isomerization[1h] of the vinyl group of *N*-ylide **3**, and proceeds via cyclization of diazahexatriene component (**16** or **17**) with elimination. Similar mechanisms were proposed for some reactions.[16]

Experimental Section

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer. The NMR spectra were determined with a JEOL JNM-4H-100 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values. The ir and uv spectra were taken with a JASCO DS-301 and a Hitachi EPS-2A spectrophotometer.

Preparation of *N*-Vinyliminopyridinium Ylides (3a–c). Gen-

eral Procedure. A mixture of alkoxyatropate (**2a** or **2b**) and small excess of pyridinium *N*-imine hydriodide (**1a** or **1b**) was stirred with potassium carbonate in ethanol or methanol at room temperature for 2 days. The insoluble substances were removed from the reaction mixture by filtration and the filtrate was concentrated in vacuo. After the separation of the residue by column chromatography (alumina) recrystallization from dichloromethane–ether–*n*-hexane gave pure *N*-ylides **3a–c.**

N-(3-Ethoxycarbonyl-3-phenylvinylimino)-2,6-lutidinium ylide (**3a**): orange prisms, 73%, mp 107–109 °C; ν (KBr) 1640 and 1525 cm^{-1}; δ ($CDCl_3$) 1.22 (3 H, t, J = 7.0 Hz), 2.64 (6 H, s), 4.11 (2 H, q, J = 7.0 Hz), 6.8–7.7 (8 H, m), and 7.94 (1 H, s); λ_{max} (EtOH) 282 nm (ϵ 2.39 × 10^4).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.95; H, 6.71; N, 9.50.

N-(3-Methoxycarbonyl-3-phenylvinylimino)-2,6-lutidinium ylide (**3b**): orange prisms, 70%, mp 131–133 °C; ν (KBr) 1630 and 1500 cm^{-1}; δ ($CDCl_3$) 2.60 (6 H, s), 3.60 (3 H, s), 6.8–7.7 (8 H, m), and 7.82 (1 H, s).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.34; H, 6.52; N, 9.86.

N-(3-Ethoxycarbonyl-3-phenylvinylimino)pyridinium ylide (**3c**): red prisms, 97%, mp 119–121 °C; ν (KBr) 1640 and 1520 cm^{-1}; δ ($CDCl_3$) 1.27 (3 H, t, J = 7.0 Hz), 4.16 (2 H, q, J = 7.0 Hz), 6.9–7.6 (8 H, m), 8.1–8.3 (2 H, m), and 8.40 (1 H, s).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.54; H, 5.97; N, 10.60.

Reactions of *N*-Ylides 3a and 3b with Ethyl Propiolate. General Procedure. A mixture of the *N*-ylide (1.5 mmol) and ethyl propiolate (147 mg, 1.5 mmol) was stirred in benzene (25 ml) at room temperature for 2 days. After evaporation of the solvent from the reaction mixture the residue was separated by preparative thin layer chromatography (Merck Kieselgel GF_{254}). Recrystallization of the crude product from dichloromethane–ether–*n*-hexane gave pale yellow plates.

4a: 235 mg (40%); mp 104–106 °C; ν (KBr) 3310, 1680, and 1605 cm^{-1}; δ ($CDCl_3$) 1.22 (6 H, t, J = 7.0 Hz), 2.27 (3 H, s), 2.46 (3 H, s), 4.20 (4 H, q, J = 7.0 Hz), 6.34 (1 H, br t, J = 12.0 Hz, NH), 6.8–7.4 (7 H, m), 7.20 (1 H, d, J = 12.0 Hz), and 7.24 (1 H, d, J = 12.0 Hz).

Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.01; H, 6.82; N, 7.03.

4b: 290 mg (51%); mp 144–145 °C; ν (KBr) 3310, 1680, and 1610 cm^{-1}; δ ($CDCl_3$) 1.19 (3 H, t, J = 7.0 Hz), 2.26 (3 H, s), 2.45 (3 H, s), 3.69 (3 H, s), 4.18 (2 H, q, J = 7.0 Hz), 6.32 (1 H, br t, J = 12.0 Hz, NH), 6.8–7.4 (7 H, m), 7.73 (1 H, d, J = 12.0 Hz), and 7.75 (1 H, d, J = 12.0 Hz).

Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.41; H, 6.40; N, 7.19.

Thermolysis of *N*-Ylides 3a and 3b. *N*-Ylide (1.5 mmol) was thermolyzed in refluxing xylene solution (25 ml) for 30 min and then the reaction mixture was concentrated in vacuo. The separation of the residue by preparative thin layer chromatography afforded the following compounds.

From **3a,** 3-ethoxycarbonylindole (**5a**), 10%, mp 122–124 °C (lit.[7] 119–123 °C), ν (KBr) 3210 and 1655 cm^{-1}, δ ($CDCl_3$) 1.40 (3 H, t, J = 7.0 Hz), 4.37 (2 H, q, J = 7.0 Hz), 7.27 (3 H, m), 7.84 (1 H, d, J = 3.0 Hz), 8.18 (1 H, m), and 9.26 (1 H, br s, NH); 5-ethoxy-4-phenyloxazole (**6a**), 31%, colorless oil, ν (neat) 1645 cm^{-1}, δ ($CDCl_3$) 1.42 (3 H, t, J = 7.0 Hz), 4.29 (2 H, q, J = 7.0 Hz), 7.38 (1 H, s), and 7.1–7.8 (5 H, m); ethyl phenylacetate (**7a**), 30%; and ethyl phenylcyanoacetate (**8a**), trace.

From **3b:** 3-methoxycarbonylindole (**5b**), 7%, mp 147–148 °C (lit.[7] 144–145.6 °C), ν (KBr) 3200 and 1655 cm^{-1}; 5-methoxy-4-phenyloxazole (**6b**), 32%, colorless oil, ν (neat) 1640 cm^{-1}, δ ($CDCl_3$) 4.02 (3 H, s), 7.45 (1 H, s), and 7.2–7.9 (5 H, m); methyl phenylacetate (**7b**), 2%; and methyl phenylcyanoacetate (**8b**), trace.

The structures of these compounds (**5–6**) were determined by comparisons with physical and spectral data of authentic samples and those of compounds **7–8** by gas chromatographic identification.

When *N*-ylide **3c** was treated under the same condition, only a complex mixture was obtained.

Photolysis of *N*-Ylides 3a and 3b. A benzene solution (100 ml) of *N*-ylide (1 mmol) was irradiated under a nitrogen atmosphere with a high-pressure mercury lamp through a Pyrex filter for 2–3 h. The reaction mixture was concentrated in vacuo and then the residue was separated by preparative thin layer chromatography.

From **3a:** diazanaphthalene (**9**), 15%, mp 226–228 °C (from dichloromethane–ether–*n*-hexane), ν (KBr) 1560 cm^{-1}, λ_{max} (EtOH) 282 (ϵ 4.63 × 10^4) and 332 nm (ϵ 1.29 × 10^4), δ ($CDCl_3$) 2.81 (3 H, s), 7.66 (1 H, s), and 7.2–8.0 (8 H, m) (Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.13; H, 5.28; N, 11.78); ethyl phenylisocyanoacetate (**10a**), ca. 34%, colorless oil, ν (neat) 2170 and 1745 cm^{-1}, δ ($CDCl_3$) 1.20 (3 H, t, J = 7.0 Hz), 4.16 (2 H, q, J = 7.0 Hz), 5.30 (1 H, s), and 7.36 (5 H, m) (Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.42; H, 5.91; N, 7.20); 3-ethoxycarbonyl-3-phenyl-1-azirine (**11a**), ca. 10%, pale yellow oil, δ ($CDCl_3$) 1.20 (3 H, t, J = 7.0 Hz), 4.16 (2 H, q, J = 7.0 Hz), 7.36 (5 H, m), and 9.81 (1 H, s).[17]

From **3b: 9;** trace, methyl phenylisocyanoacetate (**10b**), 37%, colorless oil, ν (neat) 2170 and 1750 cm^{-1}, δ ($CDCl_3$) 3.73 (3 H, s), 5.32 (1 H, s), and 7.38 (5 H, m).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.22; H, 5.23; N, 7.74.

When the *N*-ylides **3a** and **3b** were irradiated in benzene in the presence of benzophenone (twofold moles), isonitriles (**10a,** 36%, and **10b,** 37%) were obtained exclusively with decrease of irradiation time (ca. 15 min).

In contrast with *N*-ylides **3a** and **3b,** *N*-ylide **3c** gave only a complex mixture on its irradiation.

Thermolysis of Isonitriles 10a and 10b. When isonitriles **10a** and **10b** were heated in refluxing toluene for ca. 5 h, they rearranged to the corresponding oxazoles (**6a** and **6b**) in 89 and 94% yields, respectively. These compounds were identical with those (**6a** and **6b**) prepared by the thermolysis of *N*-ylides **3a** and **3b.**

Hydrolysis of Isonitriles 10a and 10b. Treatment of isonitriles **10a** and **10b** with 99% acetic acid for 1 day afforded the corresponding formamide derivatives (**12a** and **12b**) in 78 and 85% yields.

N-Formylphenylglycine ethyl ester (**12a**): colorless oil; ν (neat) 3240, 1735, and 1670 cm^{-1}; δ ($CDCl_3$) 1.14 (3 H, t, J = 7.0 Hz), 4.14 (2 H, q, J = 7.0 Hz), 5.60 (1 H, d, J = 7.5 Hz), 7.25 (1 H, br, NH), 7.28 (5 H, s), and 8.10 (1 H, d, J = 1.0 Hz).

N-Formylphenylglycine methyl ester (**12b**): colorless needles (from dichloromethane–*n*-hexane); mp 84–85 °C; ν (KBr) 3320, 1730, and 1670 cm^{-1}; δ ($CDCl_3$) 3.64 (3 H, s), 5.58 (1 H, d, J = 7.0 Hz), 7.25 (1 H, br, NH), 7.26 (5 H, s), and 8.09 (1 H, d, J = 1.0 Hz).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.04; H, 5.76; N, 6.92.

Registry No.—**1a,** 36012-28-9; **1b,** 6295-87-0; **2a,** 15937-27-6; **2b,** 6460-86-2; **3a,** 58298-83-2; **3b,** 58298-84-3; **3c,** 58298-85-4; **4a,** 58298-86-5; **4b,** 58298-87-6; **5a,** 776-41-0; **5b,** 942-24-5; **9,** 58298-88-7; **10a,** 39533-31-8; **10b,** 39533-32-9; **11a,** 58298-89-8; **12a,** 34641-48-0; **12b,** 58298-90-1; ethyl propiolate, 623-47-2.

References and Notes

(1) (a) R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Lett.*, 387 (1962); (b) T. Okamoto, M. Hirobe, and Y. Tamai, *Chem. Pharm. Bull.*, **11,** 1089 (1963); **14,** 506, 512, 523 (1966); (c) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **33,** 2062 (1968); (d) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc. C,* 481 (1970); (e) Y. Kobayashi, T. Kutsuma, and Y. Sekine, *Tetrahedron Lett.*, 3325 (1972); (f) E. Pojara, *ibid.*, 2585 (1972); (g) Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, *Tetrahedron,* **28,** 21 (1972); (h) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **37,** 3106 (1972); (i) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Bull. Chem. Soc. Jpn.*, **45,** 2050 (1972); (j) *Tetrahedron,* **28,** 4947 (1972); (k) A. Kakehi and S. Ito, *Bull. Chem. Soc. Jpn.*, **47,** 938 (1974).

(2) (a) T. Eicher and A. Hansen, *Tetrahedron Lett.*, 1169 (1967); (b) T. Eicher, E. von Angerer, and A.-M. Hansen, *Justus Liebigs Ann. Chem.*, **746,** 102 (1971); (c) T. Eicher and E. von Angerer, *ibid.*, **746,** 120 (1971); (d) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **36,** 2451 (1971); (e) *Tetrahedron,* **28,** 1469 (1972); (f) J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **50,** 584 (1972); (g) C. W. Rees and E. von Angerer, *J. Chem. Soc., Chem. Commun.*, 420 (1972); (h) Y. Sugimura, N. Soma, and Y. Kisida, *Bull. Chem. Soc. Jpn.*, **45,** 3174 (1972); (i) A. Kakehi and S. Ito, *J. Org. Chem.*, **39,** 1542 (1974); (j) A. Kakehi, S. Ito, and T. Manabe, *ibid.*, **40,** 544 (1975).

(3) (a) J. Streith, A. Blind, J.-M. Cassal, and C. Sigwalt, *Bull. Soc. Chim. Fr.*, 948 (1969); (b) T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.*, **35,** 426 (1970); (c) J. Streith, J. P. Luttringer, and M. Nastasi, *J. Org. Chem.*, **36,** 2962 (1971); (d) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *J. Chem. Soc., Perkin Trans. 1,* 2089 (1973); (e) Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *ibid.*, 2580 (1973).

(4) There are several reviews about them. See below. (a) F. W. Fowler, *Adv. Heterocycl. Chem.*, **13,** 45 (1971); (b) H. Taniguchi and K. Isomura, *Yuki Gosei Kagaku,* **30,** 280 (1972); (c) J. Anderson and A. Hassner, *Synthesis,* 483 (1975).

(5) (a) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Am. Chem. Soc.*, **89,** 2077 (1967); (b) D. Knittel, H. Hemetsberger, R. Leipert, and H. Weidmann, *Tetrahedron Lett.*, 1459 (1970); (c) H. Hemetsberger, D. Knittel, and H. Weidemann, *Monatsh. Chem.*, **101,** 161 (1970); (d) H. Hemetsberger and D. Knittel, *ibid.*, **103,** 194, 205 (1972); (e) K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 3499 (1968); (f) G. Smolinsky and C. A. Pryde, *J. Org. Chem.*, **33,** 2411 (1968).

(6) (a) T. Sasaki, T. Kanematsu, and A. Kakehi, *Tetrahedron Lett.*, 5245 (1972); (b) *J. Org. Chem.*, **36,** 2978 (1971); (c) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Bull. Chem. Soc. Jpn.*, **45,** 2050 (1972).

(7) P. E. Peterson, J. P. Wolf, III, and C. Niemann, *J. Org. Chem.*, **23**, 303 (1958).
(8) Formation of oxazole from the corresponding acyl-substituted isonitrile has been well investigated. See I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
(9) T. Miki and T. Matsuo, *Yakugaku Zasshi*, **91**, 1030 (1971).
(10) The benzo analogues of the compound (**9**) were prepared recently by pyrolysis of 2-(2-azidobenzoyl)pyridines. See R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Heterocycl. Chem.*, **11**, 125 (1974).
(11) The chemical shift of the 2-methine proton in 1-azirine derivatives is in the range of δ 9.6–10.2. See ref 4b and 5e.
(12) W. Bauer and K. Hafner, *Angew. Chem.*, **81**, 787 (1969).
(13) (a) R. Huisgen, H. Konig, G. Binsch, and H. J. Sturm, *Angew. Chem.*, **73**, 368 (1961); (b) R. Huisgen, *ibid.*, **75**, 604 (1963).
(14) D. Knittel, H. Hemetsberger, R. Leipert, and H. Weidmann, *Tetrahedron Lett.*, 1459 (1970).
(15) However, thermal process of 2-unsubstituted azirine to the corresponding isonitrile was also proposed in the isomerization of indoxazene to benzoxazole. See J. P. Ferris and F. R. Antonucci, *J. Am. Chem. Soc.*, **96**, 2014 (1974).
(16) (a) R. C. Shah and M. B. Ichaporia, *J. Chem. Soc.*, 431 (1936); (b) H. M. Blatter and H. Lukaszewski, *Tetrahedron Lett.*, 855 (1964).
(17) Contaminated with isonitrile **10a**.

Synthesis of C_7 Alkylated 7-Deaminocephalosporin Derivates

J. S. Wiering and Hans Wynberg*

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

Received November 24, 1975

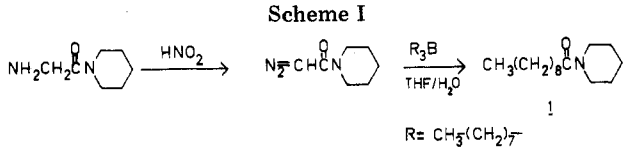
Several 7-alkyl cephalosporins lacking the 7-amino function have been prepared by treatment of the 7-diazo derivatives of cephalosporanic acid *tert*-butyl esters with a variety of trialkylboranes and a dialkylborane. Mixtures of α- and β-substituted cephalosporin *tert*-butyl esters were formed. These were hydrolyzed to the free acids. Biological screening of the free acids (as α and β mixtures) showed little or no antimicrobal activity except for the 7-methyleneadamantyldeacetoxycephalosporanic acid. A new, very mild method of oxidation of the sulfur atom in the cephalosporins was discovered. Sulfoxides were isolated from the alkylation reaction.

In recent years intensive research has been carried out in order to obtain modified cephalosporins with improved properties.[1] Several groups have attempted modifications at the C_7 positions of cephalosporins.[1b,2] As far as we know no cephalosporins[3] are known in which the 7-amino function has been replaced by an alkyl or functionalized alkyl group.[3] By introducing such alkyl groups the lipophilic character of the molecule, and consequently its penetrating ability[4] into the cell wall, changes. The purpose of the research reported here was to synthesize alkylated cephalosporins lacking the amino function at the β-lactam C_7 carbon, and to determine the effect of this change on biological activity.

Results and Discussion

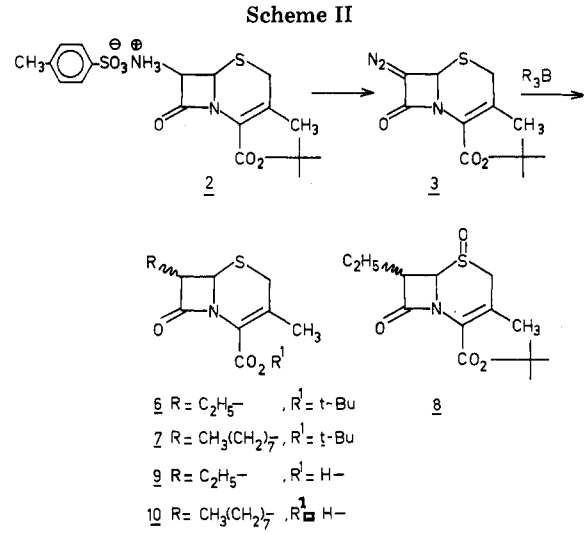
In order to introduce an alkyl side chain at C_7, in fact the replacement of an amino by a methylene group, we made use of the reaction of trialkylboranes with diazo esters,[5a] a reaction which we found to be applicable to diazo amides also. For example, the reaction of trioctylborane with 1-(α-diazoglycyl)piperidine in aqueous tetrahydrofuran gave the amide 1 in almost quantitative yield[6] (Scheme I).

Scheme I



The diazotization of the *p*-toluenesulfonic acid salt of 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester (**2**, Scheme II) and 7-aminocephalosporanic acid *tert*-butyl ester (**4**, Scheme IV) was carried out in a mixture of methylene chloride and water.[8] It was possible to isolate the diazo cephem **3** in 80% and **5** in 60–80% yield. Both compounds are yellow, crystalline solids, of which **5** could be obtained analytically pure. The alkylation of **3** with triethyl- and trioctylborane was only successful within a temperature range from −40 to −80 °C (Scheme II). At temperatures higher than −40 °C, no products with intact β-lactam ring were formed. The amount of water was of crucial importance to the course of the reaction.[5] With more than 30 equiv of water, based on diazo cephem **3**, no β-lactam containing products could be isolated. With 20–30 equiv of water, sulfoxide **8** was formed. It could be shown that the latter was not produced during oxidative work-up.

Scheme II



Using minor amounts of water (5–20 equiv) a mixture of **6** and **8** was formed, while alkylation in the presence of 1–5 equiv of water gave the cephem ester **6** as the sole product. The alkylated cephem esters **6** and **7** are both relatively unstable liquids and difficult to purify. Treatment of **6** and **7** with trifluoroacetic acid afforded the acids **9** and **10**, which are stable for a few days at −20 °C.

Diborane reacts with alkenes containing bulky groups to the dialkylborane stage only.[7] Since dialkylmonochloroboranes with bulky alkyl groups react rapidly with diazo esters,[9] we used monochloroborane as reagent to transform methyleneadamantane into the dimethyleneadamantylmonochloroborane **11**. Alkylation of **3** with **11** gave two products **12** and **14**, in the statistical ratio 2:1[10] (Scheme III). The products were separated by repeated chromatography.