Nitrosaminoaldehyde **5** was not detected. Spectral data for **7** are given in the text.

Reaction of *N*-Methyl-Δ^1-pyrrolinium Chloride (26) with $NaNO_2$. *N*-Methyl-Δ^1-pyrrolinium chloride (**26**) was prepared by the lithium aluminum hydride reduction of *N*-methyl-2-pyrrolidone (**28**), followed by dehydration as previously reported.[30] The NMR spectrum ($CDCl_3$) showed the following absorptions: 12.91 (br s, 1 H, $CH{=}N^+$), 3.78 (t, 2 H, CH_2N^+), 3.14 (s, 3 H, N^+CH_3), 3.02 (m, 2 H, $CH_2C{=}N^+$), and 2.31 ppm (m, 2 H, ring CCH_2C), indicating the absence of **28**. The pyrrolinium salt **26** (1.6 g, 0.023 mol) thus obtained was dissolved in 20 mL of H_2O and allowed to react with $NaNO_2$ (1.6 g, 0.023 mol) in 20 mL of H_2O at reflux for 10 min. The aqueous solution was extracted with $CHCl_3$ (3 × 20 mL), and the $CHCl_3$ extract was dried ($MgSO_4$) and concentrated to give a residue which was chromatographed on silica gel with elution by hexane/Et_2O/CH_2Cl_2 (1:2:2); 4-(*N*-methyl-*N*-nitrosamino)butanal (**27**) was obtained pure in 5% yield. The nitrosamine **27** showed spectral characteristics which were identical with those of a reference sample synthesized independently.[18] The major product (50%) was eluted from the column with acetone and identified as *N*-methyl-2-pyrrolidone (**28**). The nitrosation of pyrrolinium salt **26** was also done in refluxing 95% EtOH, in pH 6 buffer under reflux, and at 20 °C, under N_2, in 95% EtOH. Similar results were obtained.

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Registry No.—**3**, 16543-55-8; **4**, 64091-91-4; **5**, 64091-90-3; *anti*-**6**, 64091-89-0; *syn*-**6**, 64091-88-9; **7**, 64091-87-8; **26**, 18028-53-0; isopropyl nitrite, 541-42-4; nicotine, 54-11-5; $NaNO_2$, 7632-00-0.

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Thermal Decomposition of 2-Azidoquinoxaline *N*-Oxides

John P. Dirlam,* Berkeley W. Cue, Jr.,* and Kerry J. Gombatz

Department of Agricultural Organic Chemistry, Pfizer Central Research, Groton, Connecticut 06340

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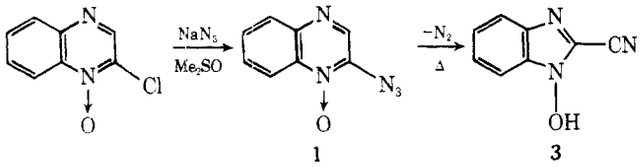
The thermolysis of some 2-azidoquinoxaline 1-oxides and 1,4-dioxides has been studied. When these are unsubstituted in the 3 position, 2-cyano-1-hydroxy-1*H*-benzimidazoles are obtained in high yield. The thermolysis of 2-azido-3-methylquinoxaline 1,4-dioxide, on the other hand, resulted in the formation of 2-cyano-2-methyl-2*H*-benzimidazole 1,3-dioxide, which underwent further intramolecular rearrangement to afford a novel 3*H*-2,1,4-benzoxadiazine 4-oxide. A mechanistic interpretation of these observations, as well as a discussion of ^{13}C NMR spectra of the thermolysis products, is presented.

In the course of work on the chemistry of quinoxalines, 2-azidoquinoxaline 1-oxide (**1**) and 2-azidoquinoxaline 1,4-dioxide (**2**) were synthesized and their thermal chemistry was studied. The thermolysis of **1** to give 2-cyano-1-hydroxy-1*H*-benzimidazole (**3**) has been described.[1] We now wish to report our observations concerning the modes of reaction of several such azides.



1 **3**

2-Azidoquinoxaline 1-oxide (**1**) was prepared by sodium azide displacement of 2-chloroquinoxaline 1-oxide[2] in Me_2SO at room temperature. Prolonging the reaction time resulted in loss of nitrogen from **1** and formation of 2-cyano-1-hydroxy-1*H*-benzimidazole (**3**). The benzimidazole **3** was more efficiently prepared by the thermolysis of **1** at 90 °C in benzene solution. The structural assignment of **3** was based on its spectral properties (NMR, IR, UV, mass spectrum), combustion analysis, and an unambiguous synthesis from 2-nitroanilinoacetonitrile according to a literature procedure.[3]

Extension of this reaction to 2-azidoquinoxaline 1,4-dioxide (**2**) was accomplished in the following manner. 2-Methylsulfonylquinoxaline 1,4-dioxide[4] (**4**) was allowed to react with

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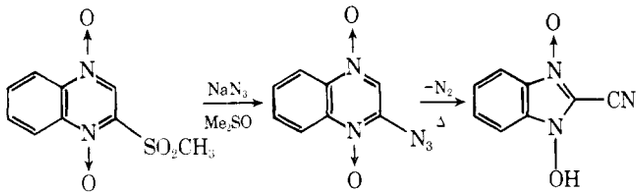
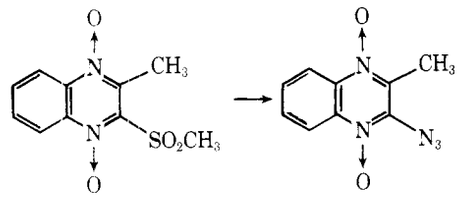


4 2 5

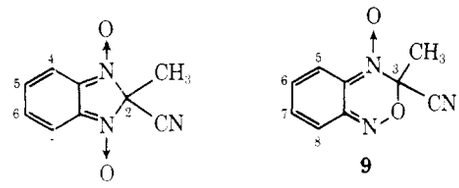
sodium azide to afford **2**. Thermolysis of **2** in refluxing benzene gave 2-cyano-1-hydroxy-1*H*-benzimidazole 3-oxide (**5**) in good yield.

We then turned our attention to a study of 2-azido-3-methylquinoxaline 1,4-dioxide (**7**), which was prepared by the reaction of 2-methylsulfonyl-3-methylquinoxaline 1,4-dioxide[5] and tetramethylguanidinium azide in methylene chloride at room temperature.[6] These are the conditions of choice for preparing such azides, owing to the absence of side products and decomposition which were noted when sodium azide in polar solvents was employed.



7

From a consideration of the behavior of 2-azido-3-methylpyridine 1-oxide on thermolysis in benzene[7] we expected the formation of 2-cyano-2-methyl-2*H*-benzimidazole 1,3-dioxide (**8**) as the major (if not exclusive) product of **7** when decomposed. Heating **7** in toluene at 90 °C for 30 min gave a 94% yield of an amber oil after column chromatography. NMR analysis of this compound revealed a complex pattern of aromatic protons which appeared at δ 6.76–7.35 in a ratio of 3:1 and a three-proton singlet at δ 2.20. The unsymmetrical nature of the aromatic proton resonances was inconsistent with the AA′BB′ pattern predicted[8,9] for **8**. The infrared spectrum of the oil showed a weak absorption at 2240 cm^{-1} (C≡N). The mass spectrum of the oil showed a molecular ion at *m/e* 189 with principal fragments at *m/e* 173 ($M^+ - O$) and 159 ($M^+ - NO$). These spectral data were consistent[10] with the novel 3*H*-2,1,4-benzoxadiazine 4-oxide **9** and not **8**.

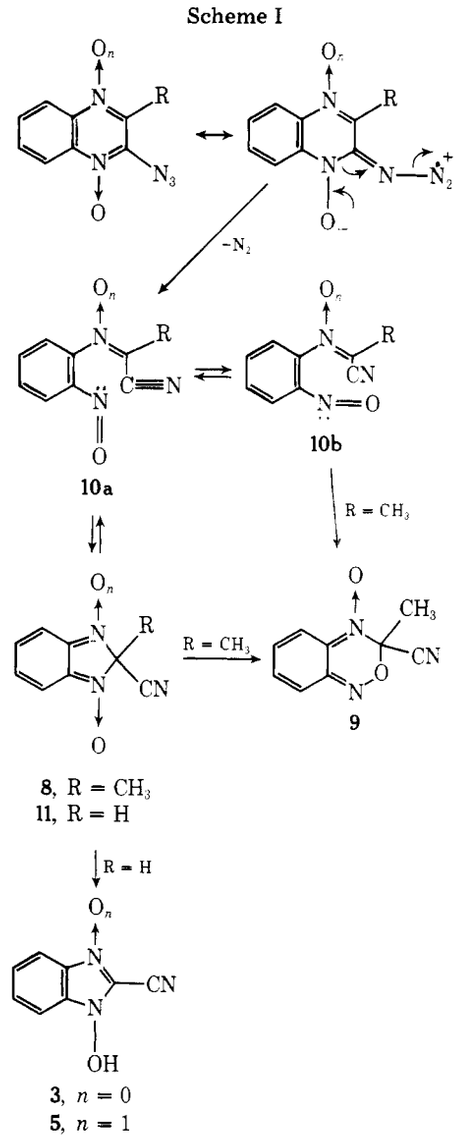


8 9

When the thermolysis of **7** was carried out in refluxing benzene for 10 min followed by careful column chromatography on silica gel, a violet solid (mp 111–112 °C) was obtained in 45% yield along with **9** in 41% yield. This new product was tentatively characterized as the expected 2*H*-benzimidazole 1,3-dioxide **8** based on the following spectral properties. The NMR spectrum of **8** in $CDCl_3$ exhibited an AA′BB′ pattern centered at δ 7.07 along with a singlet at δ 2.16 in the ratio of 4:3. The UV spectrum of **8** [λ_{max} (methanol) 247 (ϵ 16 550), 531 nm (4840)] compared very favorably with the reported UV spectra of similar 2*H*-benzimidazole 1,3-dioxides.[8,9]

A determination of the ^{13}C NMR spectra (proton decoupled) of both products **8** and **9** enabled us to confidently characterize the amber oil as 3-cyano-3-methyl-3*H*-2,1,4-benzoxadiazine 4-oxide (**9**) and the violet crystalline solid as 2-cyano-2-methyl-2*H*-benzimidazole 1,3-dioxide (**8**). A

Scheme I

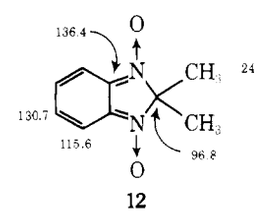


8, R = CH_3
11, R = H

3, *n* = 0
5, *n* = 1

nine-line spectrum was observed for **9**. The cyano carbon resonance appeared at 113.5 ppm.[7] The spectrum also indicated the presence of six aromatic carbon atoms (four bearing a hydrogen atom, 130.6, 130.1, 123.5, and 117.3 ppm; and two that were not, 150.8 and 129.1 ppm). This further illustrates that **9** is unsymmetrical. The resonance for C-3 appeared at 86.1 ppm and the methyl carbon resonance was found at 19.1 ppm.

In contrast, the symmetrical nature of **8** was revealed by its ^{13}C spectrum. Thus two resonances were observed for the aromatic carbons bearing hydrogens at 132.1 and 115.5 ppm for C-4, C-7 and C-5, C-6, respectively. A weak signal appeared at 137.7 ppm for the ring-fused quaternary carbons. The cyano carbon resonance was found at 116.4 ppm. The resonance for C-2 appeared at 85.7 ppm, and the methyl carbon resonance was observed at 24.0 ppm. These values compare favorably with those reported in the literature[9b] for a similar 2*H*-benzimidazole 1,3-dioxide **12**.



12

A plausible mechanism which accounts for our observations is depicted in Scheme I. Loss of nitrogen from the azides accompanied by ring opening[1,7] would give the *o*-nitrosophenylnitrone **10a**, which can undergo intramolecular cyclization[1,7,8] to give **8** or **11**. If R = H, aromatization of **11** would give the observed 2-cyano-1-hydroxy-1*H*-benzimidazoles **3** and **5**.[1,8,9] Alternatively, **10b** could cyclize to a 2,1,4-benzoxadiazine 4-oxide **9**. Mechanistic analogy for this mode of cyclization exists in the chemistry of 2-azido-3-halopyridine 1-oxides, which afford 6,6-disubstituted-1,2-oxazines.[6] A more likely course of events is that **8** is formed initially, but undergoes a further rearrangement to give **9**, either via **10a** ⇌ **10b** or by a direct ring expansion. Support for this hypothesis was obtained from the following experiment. Azide **7** was heated under reflux for 5 min, which resulted in the formation of **8** and unreacted **7** in a ratio of 2:1, respectively, based on NMR analysis of the crude product mixture. When this mixture was resubjected to the reaction conditions (refluxing benzene) for 0.5 h neither **7** nor **8** could be detected, and **9** was isolated in 76% yield. The rearrangement of **8** to **9** appears to be unusual, since heating 2,2-dimethyl-2*H*-benzimidazole 1,3-dioxide (**12**) in toluene at 90 °C for 0.5 h led to no observable decomposition.[14]

Experimental Section

General. Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. Proton NMR spectra were recorded on Varian T-60 and Varian XL-100-15 spectrometers with Me_4Si as the external standard. The ^{13}C NMR were obtained in the FFT mode on a Varian XL-100-15 (25 MHz) spectrometer equipped with a Nicolet Technology 1080 data system. Complete proton decoupling was provided by square wave modulation[11] of the Varian gyrocode heteronuclear decoupler. Deuterated chloroform solvent resonance (76.9 ppm) was used as an internal standard adjusted relative to Me_4Si to provide chemical shift value. IR spectra were determined with Perkin-Elmer Model 21 and 237 B spectrophotometers. Mass spectra were obtained with Perkin-Elmer RMU-6E and AEI MS-30 mass spectrometers. Combustion analyses were performed by the Pfizer Physical Measurements Department.

2-Azidoquinoxaline 1-Oxide (1). Sodium azide (0.71 g, 11 mmol) was added to a solution of 2-chloroquinoxaline 1-oxide[2] (2.00 g, 11 mmol) in Me_2SO (25 mL) at room temperature. The solution was stirred for 6 h and then it was diluted with water (50 mL), causing a precipitate to form. The tan solid was filtered and washed with cold water to give 1.08 g (52%) of **1**: mp 81–83 °C dec; NMR (Me_2SO-d_6) δ 7.60–8.50 (4, m, H-5, H-8), 8.60 (1, s, H-3); IR (KBr) 2150 cm^{-1} (N_3); UV λ_{max} (MeOH) 225 (ϵ 18 100), 265 (29 300), 335 nm (5300); mass spectrum *m/e* 187 $[M]^+$, 159 $[M - N_2]^+$. Elemental analysis (C, H, N) of **1** was consistent with the presence of ~10% of **3**. Further purification attempts were unsuccessful due to the thermal instability of this compound.

2-Cyano-1-hydroxy-1*H*-benzimidazole (3). A suspension of 2-azidoquinoxaline 1-oxide (1.50 g, 8.1 mmol) in benzene (25 mL) was heated under reflux until the evolution of gas ceased (~0.5 h). The reaction mixture was allowed to cool to room temperature and a light brown solid was filtered and washed with benzene to afford 1.17 g (92%) of **3**: mp 249–250 °C dec; NMR (Me_2SO-d_6) δ 7.20–8.00 (m, H-4, H-7); IR (KBr) 2222 cm^{-1} (CN); UV λ_{max} (MeOH) 225 (ϵ 19 400), 286 nm (13 000); mass spectrum *m/e* 159 $[M]^+$. Anal. Calcd for $C_8H_5N_3O$: C, 60.43; H, 3.17; N, 26.43. Found: C, 60.29; H, 3.31; N, 26.69. This material was identical with **3** prepared by a literature[3] procedure via a base-catalyzed cyclization of 2-nitroanilinoacetonitrile.[12]

2-Azidoquinoxaline 1,4-Dioxide (2). To a solution of 2-methylsulfonylquinoxaline 1,4-dioxide[5] (1.00 g, 4.2 mmol) in Me_2SO (15 mL) was added sodium azide (0.27 g, 4.2 mmol). The mixture was stirred for 15 h at room temperature and then it was diluted with water (75 mL) and extracted with chloroform (3 × 20 mL). The combined chloroform extracts were dried over anhydrous magnesium sulfate and evaporated under vacuum to yield **2** as a yellow solid (0.50 g, 60%): mp 117–118 °C dec; NMR (Me_2SO-d_6) δ 8.00 (2, m, H-6, H-7), 8.50 (2, m, H-5, H-8), 8.60 (1, s, H-3); IR (KBr) 2140 cm^{-1} (N_3); UV λ_{max} (MeOH) 238 (ϵ 19 000), 283 (25 200), 395 nm (6000); mass spectrum *m/e* 203 $[M]^+$, 159 $[M - N_2O]^+$. An attempt to prepare an analytical sample of **2** was unsuccessful due to the thermal instability of this compound.

2-Cyano-1-hydroxy-1*H*-benzimidazole 3-Oxide (5). 2-Azidoquinoxaline 1,4-dioxide (200 mg, 1.0 mmol) was suspended in benzene (5 mL) and heated under reflux until the evolution of gas ceased (~0.5 h). The reaction mixture was allowed to cool to room temperature and a tan solid was filtered and washed with benzene to give 105 mg (61%) of **5**: mp 165–166 °C dec; NMR (CF_3CO_2D) δ 7.50 (m, H-4, H-7); IR (KBr) 2222 cm^{-1} (CN); UV λ_{max} (MeOH) 235 (ϵ 23 400), 303 (9200), 369 nm (4500); mass spectrum *m/e* 175 $[M]^+$, 159 $[M - O]^+$. Anal. Calcd for $C_8H_5N_3O_2$: C, 54.91; H, 2.88; N, 24.01. Found: C, 54.53; H, 2.96; N, 23.74.

2-Azido-3-methylquinoxaline 1,4-Dioxide (7). To a cooled solution of 2-methyl-3-methylsulfonylquinoxaline 1,4-dioxide[2] (4.00 g, 15.7 mmol) in chloroform (60 mL) was added dropwise tetramethylguanidinium azide (2.48 g, 15.7 mmol) in chloroform (20 mL). The solution was stirred for 1.5 h at room temperature and then it was washed with water, dried ($MgSO_4$), and evaporated to give a solid. The solid was triturated with water and then ether, which afforded a yellow solid as **7** (2.25 g, 66%): mp 106–107 °C dec; NMR (Me_2SO-d_6) δ 2.60 (s, 3, CH_3), 7.75 (m, 2, H-6, H-7), 8.41 (m, 2, H-5, H-8); IR (KBr) 2128 cm^{-1} (N_3); UV λ_{max} (MeOH) 237 (ϵ 23 340), 280 (30 200), 380 nm (7850); mass spectrum *m/e* 217.0600 (M^+; $C_9H_7N_5O_2$ requires 217.0600), 189 ($M - N_2$). An attempt to prepare an analytical sample of **7** was unsuccessful due to the thermal instability of this compound. The sample darkened at room temperature within 24 h; however, the NMR spectrum was unchanged.

2-Cyano-2-methyl-2*H*-benzimidazole 1,3-Dioxide (8). 2-Azido-3-methylquinoxaline 1,4-dioxide (200 mg, 0.92 mmol) was dissolved in benzene (7 mL) and heated under reflux for 10 min. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under vacuum to afford a purple oil, which was purified by column chromatography on silica gel. Elution with chloroform gave **9** (72 mg, 41%), which was followed by removal of **8** from the column as violet crystals (81 mg, 46%): mp 111–112 °C dec; NMR ($CDCl_3$) δ 2.16 (s, 3, CH_3), 6.90–7.24 (m, AA'BB', 4, H-4, H-7); IR ($CHCl_3$) no C≡N band observed;[13] UV λ_{max} (MeOH) 247 (ϵ 16 550), 531 nm (4840); mass spectrum *m/e* 189.0523 (M^+; $C_9H_7N_3O_2$ requires 189.0539), 173 ($M^+ - O$), 157 ($M^+ - O_2$). Attempted purification of this sample was unsuccessful owing to the thermal instability of this compound. A shorter reaction time (solution was heated for ~5 min in benzene under reflux) resulted in the formation of **8** and starting material (**7**) in a ratio of 2:1, respectively, based on NMR analysis. When this mixture was resubjected to the reaction conditions for 0.5 h neither **7** nor **8** was detected, and **9** was isolated in 76% yield.

3-Cyano-3-methyl-3*H*-2,1,4-benzoxadiazine 4-Oxide (9). 2-Azido-3-methylquinoxaline 1,4-dioxide (400 mg, 1.84 mmol) was dissolved in toluene (15 mL) and heated at 90 °C until the evolution of gas ceased (~0.5 h). The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under vacuum to afford a brown oil, which was purified by column chromatography on silica gel. Elution with chloroform gave 228 mg (94%) of **9** as an amber oil: NMR ($CDCl_3$) δ 2.20 (s, 3, CH_3), 6.76–7.16 (m, 3, H-3, H-4, H-5), 7.16–7.35 (m, 1, H-6); IR ($CHCl_3$) 2240 cm^{-1} (C≡N); UV λ_{max} (MeOH) 228 (ϵ 17 000), 405 nm (3620); mass spectrum *m/e* 189.0532 (M^+; $C_9H_7N_3O_2$ requires 189.0539), 173 ($M^+ - O$), 159 ($M^+ - NO$). Anal. Calcd for $C_9H_7N_3O_2$: C, 57.20; H, 3.73; N, 22.23. Found: C, 57.40; H, 3.79; N, 21.88. Samples of **9** darkened at room temperature within a few hours, although no change in the sample composition could be detected by NMR or UV after 24 h at room temperature. In another experiment **9** was obtained in 72% yield when benzene was used as solvent instead of toluene.

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Registry No.—**1**, 51796-69-1; **2**, 64010-67-9; **3**, 40159-90-8; **4**, 50473-31-9; **5**, 64010-77-1; **7**, 64010-76-0; **8**, 64010-79-3; **9**, 64010-78-2; sodium azide, 26628-22-8; 2-chloroquinoxaline 1-oxide, 5227-57-6; 2-methyl-3-methylsulfonylquinoxaline 1,4-dioxide, 39576-77-7; tetramethylguanidinium azide, 56899-56-0.

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Chlorination of the Cephem Dihydrothiazine Ring. Factors Influencing Carbon-2 Substitution vs. Degradation to Isothiazoles[1]

W. H. Koster,* J. E. Dolfini, and B. Toeplitz

The Squibb Institute for Medical Research, Princeton, New Jersey 08540

J. Z. Gougoutas

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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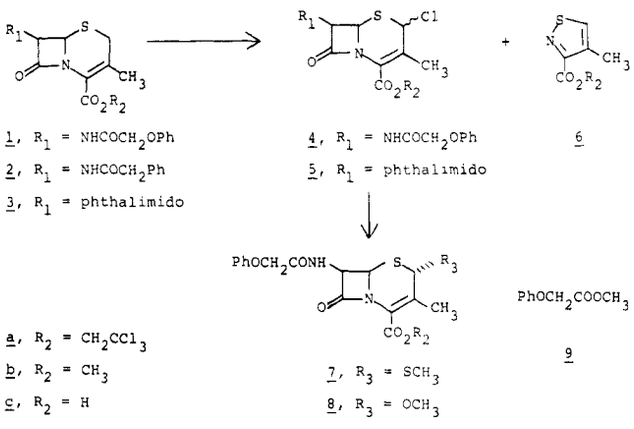
The reaction of Δ^3-cephalosporin esters with *N*-chlorosuccinimide (NCS) is described. When a 7-phenoxyacetamido- or a 7-phthalimido-Δ^3-cephem (**1a** or **3a**) is reacted with NCS, the unstable 2-chloro-Δ^3-cephem (**4a** or **5a**, respectively) can be observed in solution by NMR. Nucleophilic displacement of chloride ion in the 2-chloro derivative **4a** by methanethiol or methanol yields the 2α-methylthio- and 2α-methoxy-Δ^3-cephems **7a** and **8a**, respectively. Chlorination of 7-phenylacetamido-Δ^3-cephems **2a** and **2b** gives the isothiazoles **6a** and **6b** exclusively; **6a** is also a minor product in the chlorination of **1a**. The structure of the degradation product **6** is proven by x-ray analysis of 4-hydroxyisothiazole-3-carboxylic acid (**12**), derived from the chlorination of methyl 7-(*N*-phenylacetamido)cephalosporanate (**10**), followed by saponification.

The synthesis of 2-halo-Δ^3-cephems was undertaken to prepare a versatile intermediate for C-2 substituted cephalosporins. Methods for the introduction of alkoxy and acyloxy residues at C-2[2] involving the oxidation of sulfur in the dihydrothiazine ring cannot be used with nucleophiles susceptible to the oxidative conditions. Therefore, a substrate capable of undergoing nucleophilic substitution at C-2 was desired. Investigations by others in this area have led to the isolation and methanolysis of a 2-bromo-Δ^3-cephem and 2,3-dibromocephams, prepared by the bromination of a cephalosporin lactone[3] and Δ^2-cephems,[4] respectively. We have studied the chlorination of Δ^3-cephalosporin esters using *N*-chlorosuccinimide (NCS) and now report on the factors influencing this reaction following the initial halogenation of sulfur.

Scheme I



Results

A solution of **1a**, containing 1 equiv of NCS in deuteriochloroform, was monitored by NMR. Within 15 min the simultaneous disappearance of the NCS singlet (δ 2.94) and the AB quartet of the cephem C-2 protons (δ 3.43) was observed. The formation of an unstable C-2 substituted Δ^3-cephem, presumed to be the 2-chloro derivative **4a**, was indicated by the appearance of the resonances shown in Table I.[5] Simultaneously, a non-β-lactam component was formed having an aromatic methyl singlet (δ 2.63) and a low-field singlet (δ 8.42). After 1.5 h at ambient temperature the 2-chlorocephem **4a** had completely decomposed while the non-β-lactam component was stable to these conditions. To prove the intermediacy of a 2-chlorocephem, methanethiol was added to the reaction mixture after the NCS was consumed and gave the 2α-methylthio derivative **7a** in 33% yield[6] (Scheme I). The C-2 configuration was assigned based on long-range ^5J coupling (<1 Hz) between H-2β and H-7α and a nuclear Overhauser effect (15%) between H-2β and CH_3.[2b,8] Methanolysis of **4a** gave the 2α-methoxy derivative **8a** (identical with a sample prepared by a modification of Spry's procedure[2b] using NCS in methanol), plus equimolar amounts of the non-β-lactam compound and methyl phenoxyacetate (**9**). Cleavage of the trichloroethyl ester gave the free acid **8c**,[2b,4] which had less antimicrobial activity than the parent C-2 unsubstituted compound.

When 1 equiv of NCS was mixed with the trichloroethyl ester **2a** indeuteriochloroform, all the NCS reacted rapidly, yielding a mixture of starting material and the same non-β-lactam product observed in the reaction of **1a**. However, the desired 2-chlorocephem was not detected. The phthalimido analogue **3a** reacted slowly over a 3-h period yielding a solution of the 2-chlorocephem **5a** (Table I). None of the non-β-lactam product, formed in the chlorination of **1a** and **2a**, was observed in this reaction.

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