those in dimethyl sulfoxide and trichloroethanol included tris(acetylacetonato)chromium(III) (approximately 0.05 M) as a relaxation reagent. ^{15}N spectra in sulfur dioxide were obtained by the INEPT procedure.[6]

3,5-Dipyrrolidinophenol prepared as described previously was contaminated by a green oxidation product which could not be removed by crystallization or chromatography.[1,2] Pure material could be obtained by the careful exclusion of oxygen. Phloroglucinol (3.0 g) was charged into a bomb tube of approximately 100-mL capacity, which was swept with nitrogen while 5.0 mL of chilled pyrrolidine was added. The tube was sealed and heated to 150 °C for 90 min. After the tube was opened it was held under reduced pressure to remove excess pyrrolidine, flushed with nitrogen, charged with 50 mL of ethanol, flushed with nitrogen, and sealed. The mixture was heated to solution and allowed to cool. The tube was again opened and the supernatant removed by pipet, leaving 2.3 g of yellow crystals, mp 187.5–189 °C. On standing in air the crystals turned gray green. Spectrometric characteristics were identical with those previously reported.

3-*N*-Pyrrolidinyl-5-*N*-pyrrolidinio-1-hydroxy-3-cyclohexene Sulfonate (4). Solutions of 4 prepared for ^1H and ^{13}C NMR spectra were prepared by placing ca. 50 mg of 1 in a 5-mm NMR sample tube and chilling in a dry ice–acetone bath while 0.5 mL of sulfur dioxide was passed in. Water (0.004 mL) and a small amount of tetramethylsilane were then added before the tube was sealed. Conversion to 4 was prompt and complete. Samples for ^{15}N spectra were prepared similarly from 100 mg of 1 and 0.01 mL of water, with the substitution of 6 mg of nitromethane for the tetramethylsilane. Crystalline samples of 4 were prepared by allowing the sulfur dioxide to evaporate from the solution of 100 mg of 1 and 0.01 mL of water and crystallizing the residue from 1:1 dioxane–sulfur dioxide at −10 °C, mp 145–148 °C.

Registry No. 1, 16857-92-4; 2, 102869-96-5; 3, 102869-97-6; 4, 102869-98-7; SO_2, 7446-09-5; phloroglucinol, 108-73-6; pyrrolidine, 123-75-1.

(6) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101*, 760.

An Unusual Oxazolone from α-Bromopenicillin G

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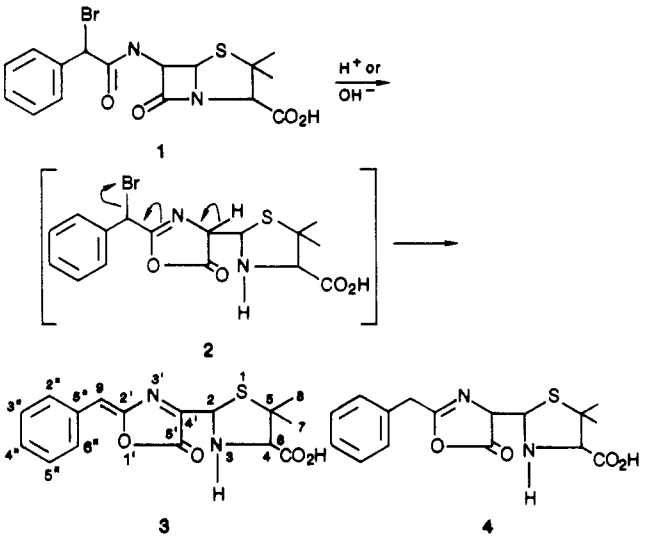
During an attempted preparation of a penicillin from 6-aminopenicillanic acid and α-bromophenylacetic acid, an unusual oxazolone–thiazolidine **3** was isolated. This oxazolone was very similar to the original azalactone formula proposed by early workers[1] and suggests that the acid degradation of a penicillin may proceed through a oxazolone–thiazolidine intermediate. Although the existence of the oxazolone–thiazolidine structure **4** has been proposed as early as 1942 by the Robinson group, numerous attempts to prepare this class of compounds proved to be elusive because of their inherent instability. Hitomi[2a] studied the decomposition of penicillin G under mild conditions and identified ten products. Johnson and Panetta[2b] studied the decomposition of methicillin in weakly acidic solutions and Dennen and Davis[2c] indicated

Scheme I



that penillic and penicilloic acids were the main products formed in a decomposition study of natural and semisynthetic penicillins. More recently Awang et al.[2d] investigated the degradation of penicillin in acidic media and proposed an oxazolone–thiazolidine intermediate as the mechanism for the degradation of a penicillin. None of the above investigators reported the isolation of any oxazolone with an intact thiazolidine ring. Therefore, we wish to describe the formation and characterization of **3**[3] which represents an example of this elusive oxazolone–thiazolidine.

When 6-aminopenicillanic acid was treated in aqueous sodium bicarbonate solution with α-bromophenylacetyl chloride, followed by an acid workup, a crystalline yellow amphoteric compound was isolated. The infrared spectrum showed a carbonyl absorption band at 1780 cm^{-1} consistent for a β-lactam carbonyl. However, the ^1H NMR spectrum was not consistent for the desired β-lactam because the β-lactam C_4' proton was missing and a new band appeared at 6.78 ppm. The mass spectrum showed no halogen. Combined evidence from the IR, ^{13}C NMR, ^1H NMR, MS, and microanalysis identified the compound as **3** shown in Scheme I.

Compound **3** shows ultraviolet maxima at 242, 359, and 377, reminiscent of a penicillenic acid, and its isolation offers credence to the rationalization that an oxazolone–thiozolidine intermediate is indeed the progenitor to the other reported degradation compounds. In the formation of **3** it is thought that the α-bromopenicillin **1** underwent dehydrohalogenation to the intermediate oxazolone **2** to form the stable isolatable compound **3**. Although in prior cases the oxazolone–thiazolidine system was readily degraded, the conjugation from C-9 to C-4′ in compound **3** stabilizes the two five-membered rings and permits isolation. The stereochemistry of carbon–carbon double bond at C2′ and C9 was not determined.

Experimental Section

General NMR spectra were recorded on a JEOL FY 90Q or a Bruker 360 spectrometer. Chemical shifts are reported in δ values relative to the tetramethylsilane as an internal standard. Infrared spectra were determined on a Nicolet 5DX FT-IR spectrophotometer. Mass spectra were recorded on a Dupont DP-102 Kratos MS-30 or Kratos MS-50 mass spectrometer. Melting point was taken on Fischer Johns melting point apparatus.

(1) Clarke, H. T.; Johnson, J. R.; Robinson, R. *The Chemistry of Penicillins*; Princeton University Press: Princeton, NJ, 1949; p 447, 730.

(2) (a) Hitomi, H. *Yakugaku Zasshi* **1959**, *79*, 1600; *Chem. Abstr.* **1959**, *54*, 10996g. (b) Johnson, D. A.; Panetta, C. A. *J. Org. Chem.* **1963**, *29*, 1826–1830. (c) Denner, D. W.; Davis, W. W. *Antimicrobial Agents Chemother.* **1961**, 531. (d) Awang, D. V. C.; Kindrac, D.; LeBelle, M. J.; Lauriault, G. 19th National Medicinal Symposium June 1984, Abstract #9, p 14.

(3) For convenience the numbering system used for the name does not coincide with the numbering system used for identification in the ^{13},c NMR and ^1H NMR.

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2-(5-Oxo-2-(phenylmethylene)-2*H*-oxazol-4-yl)-5,5-dimethyl-4-thiazolidinecarboxylic Acid. To a solution of 4.3 g (0.02 mol) of 6-aminopenicillanic acid dissolved in 100 mL of water by the addition of 4 g of $NaHCO_3$ was added at 5 °C dropwise 4.7 mL (0.02 mol) of α-bromophenylacetyl chloride in 30 mL of acetone. The mixture was stirred for 1 h and acidified to pH 2 with concentrated hydrochloric acid. A yellow solid was isolated and recrystallized from methanol–ether to yield 2.4 g (38%) of a mixed hydrobromide, hydrochloride salt. This was converted to the base by dissolving in sodium bicarbonate solution at pH 8.4 and adjusting to pH 5 with acetic acid to yield 1.5 g: mp 127 °C dec; IR (KBr) 3400, 2500–3000, 1780, 1740, 1655, 1230, 695 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.36 (s, 3 H, Me), 1.64 (s, 3 H, Me), 4.16 (s, 1 H, C-4H), 5.88 (s, 1 H, C-2H), 6.78 (s, 1 H, C-9H), 7.2–7.7 (m, 3 H, C-4″H, C-5″H, C-6″H), 7.7–8.1 (m, 2 H, C-1″H, C-6H); ^{13}C NMR ($CDCl_3$) δ 172.4 (C-6), 161.9 (C-5'), 156.6 (C-4'), 152.1 (C-2), 131.9 (C-1″), 131.0 (C-2″,C-6″), 130.1 (C-4″), 127.0 (C-3″, C-5″), 114.8 (C-9), 73.0 (C-4), 59.9 (C-2, C-5), 27.9 and 27.2 (C-7, C-8); mass spectrum, *m/z* (relative intensity) 333 (80), 332 M^+ (20), 289 (78), 263 (30), 257 (30, 136 (100); UV λ_{max}^{MeOH} 242 (ε7074), 359 (21494), 377 (18948). Anal. Calcd for $C_{16}H_{16}N_2O_4S \cdot H_2O$: C, 55.14; H, 4.63; N, 8.04. Found: C, 54.73; H, 4.75; N, 7.97; KF (H_2O) 3.81.

Acknowledgment. I thank Drs. T. Kaneko and R. B. Morin for helpful discussions and Dr. J. Medley and Mr. D. W. Whitehead for interpretations and recording spectra.

Registry No. 3, 102921-27-7; 6-aminopenicillanic acid, 551-16-6; α-bromophenylacetyl chloride, 19078-72-9.

Diagnosing Consecutive Reactions of Hypochlorite: pH and Oxidative Decarboxylation/Halogenation

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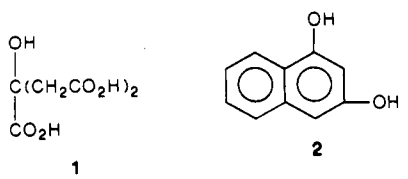
In addition to the classic "haloform" reaction of methyl ketones,[1] trihalomethanes result readily from hypohalous acid/hypohalite reactions of certain carboxylic acids[2] and amino acids,[3] as well as from activated β-diketones, meta-dihydroxylated aromatics, and quinones.[4-6] With some of these substrates, halogenation is but one component of a complex series of competitive and/or consecutive reactions.

A case in point is the reaction of citric acid (1), which over 100 years ago was discovered to yield CO_2, pentachloroacetone, and $CHCl_3$ on treatment with aqueous chlorine.[2a] On treatment with NaOCl/HOCl solutions, compound 1 gives a higher yield of $CHCl_3$ at pH 7 than at pH 9.[2b] In contrast, production of $CHCl_3$ from 1,3-dihydroxynaphthalene (2) has been found to be more facile at pH 11 than at pH 7.[6b] Therefore, it was important to discover that substantial increases in pH may occur during the course of hypochlorite reactions with either 1 or 2, reflecting production of multichlorinated products.



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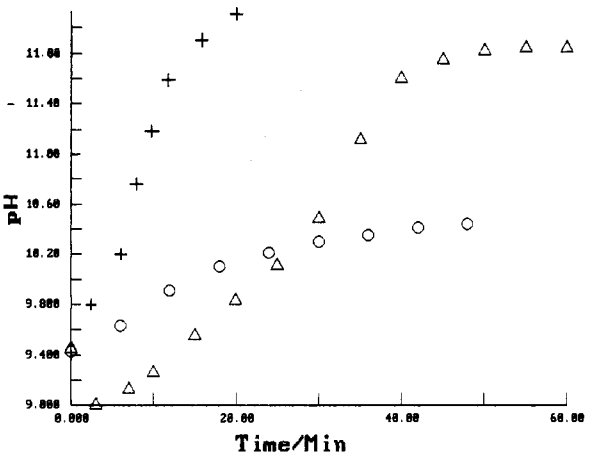

Figure 1. pH profiles of chloroform precursors with 10-fold excess of sodium hypochlorite at initial concentration = 0.68–0.74 M: + = acetone; ○ = citric acid; △ = 2-hydroxy-2-methylpropanoic acid.

Scheme I

$$R_2C(OH)CO_2H \xrightarrow{NaOCl} R_2C(O) + CO_2$$

1, R = CH_2CO_2H
3, R = CH_3
4, R = Ph
5, R = CH_2CH_3

For hypochlorite-induced oxidation of aromatic hydrocarbons, provision must be made to keep the pH from dropping during reactions, due to the acidic nature of products, CO_2, and benzenecarboxylic acids.[7] However, when the aromatic substrate 2 was subjected to reaction with hypochlorite at pH 9, a rapid increase (to pH >11.5 in less than 5 s) was observed. This occurred in spite of the fact that both CO_2 and phthalic acid were produced in significant yields.

This " pH jump" is a phenomenon which generally may be observed for reactions of hypochlorite with substrates that generate $CHCl_3$ by "haloform"-like reactions. Haloform test positive substrates such as acetone, 2-pentanone, acetophenone, and 5,5-dimethyl-1,3-cyclohexanedione show substantial pH jumps during hypochlorite reactions, whereas 3-pentanone, cyclohexanone, and 1-naphthol exhibit relatively stable pH behavior. The reaction–pH profile for acetone is shown in Figure 1.

When citric acid (1) was treated with hypochlorite under conditions similar to those used for acetone, the pH jump shown in Figure 1 also was observed. At fixed pH's, NMR studies revealed compound 1 to be more reactive with

(1) March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1977; p 574.
(2) (a) Plantamour, *Berzelius' Jaresber. 28*, 428. Stadeler, *Ann.* **1859**, *111*, 299. Cloez, S. *Ibid.* **1862**, *122*, 120. Grimaux, *Bull. Soc. Chim. Fr.* (2) 22, 26 as cited in *Beilstein (Hauptwerk)* **1921**, *3*, 560. (b) Larson, R. A.; Rockwell, A. L. *Environ. Sci. Technol.* **1979**, *13*, 325.
(3) Trehy, M. L.; Bieber, T. I. *Preprints of Papers, ACS Environmental Chemistry Division*, **1980**, *20*, 2.
(4) Booth, H.; Saunders, B. C. *Chem. Ind. (London)* **1950**, *69*, 824.
(5) Adachi, J. *Anal. Chem.* **1951**, *23*, 1491.
(6) (a) Rook, J. J. *J. Am. Water Works Assoc.* **1976**, *68*, 168. (b) Rook, J. J. *Environ. Sci. Technol.* **1977**, *11*, 478.
(7) (a) Landolt, R. G.; Davis, G. M.; Reilly, M. T.; Reinhold, D. S. *Chem. Ind. (London)* **1980**, 292. (b) Angert, J. L.; Gatton, S. L.; Reilly, M. T.; Landolt, R. G. *Fuel* **1977**, *56*, 224. (c) Landolt, R. G. *Fuel* **1975**, *54*, 299.

0022-3263/86/1951-3233$01.50/0