of a deep purple solid identified as quinone **28**: 360-MHz NMR ($CDCl_3$) $\delta$ 2.30 (s, 3 H), 3.80 (t, $J$ = 6 Hz, 2 H), 5.20 (s, 1 H), 5.24–5.34 (m, 2 H), 5.78–5.92 (m, 1 H), 6.15 (br s, 1 H), 6.63 (s, 1 H), 9.23 (br s, 1 H); MS (EI) 216, 199, 187, 175, 159, 154, 108.

The more polar fraction was isolated as 3.8 mg of off-white solid and identified as spirocyclopropane **1b** by direct spectral comparison (NMR, IR) with an authentic sample.[23]

**Photolysis of Diazoindolone 2b with Detection of 29.** A sample of **2b** was dissolved in $CDCl_3$ in an NMR tube to afford an orange-brown solution, and a 360-MHz NMR spectrum was recorded. The solution was photolyzed for 15 min with aqueous $CuSO_4$ and $NaNO_2$ solutions as filters. After the photolysis, the solution was bright red. The major product at this point was **29** identified by its NMR spectrum: 360-MHz NMR ($CDCl_3$) $\delta$ 2.33 (s, 3 H), 2.93 (s, 1 H), 3.73–3.83 (m, 2 H), 4.53–4.63 (m, 1 H), 5.21–5.30 (m, 2 H), 5.73 (s, 1 H), 5.69–5.88 (br m, 1 H), 6.77 (br s, 1 H), 9.68 (br s, 1 H), 9.89 (br s, 1 H). If the photo product was subjected to flash chromatography prior to hydrolytic workup, **29** could be isolated.

**Thermal Decomposition of Diazoindolone 2b.** A suspension of diazoindolone **2b** (8.3 mg, 0.027 mmol) in 2 mL of toluene was heated to 110 °C for 0.5 h. Upon cooling and concentration in vacuo, the crude product mixture was subjected to flash chromatography and yielded 4 mg (68%) of quinone **28** and 2.3 mg (30%) of cyclopropane **1b**.

**Catalyzed Decomposition of Diazoindolone 2b.** The diazoindolone (0.05–0.1 mmol) with the solvent and catalyst were heated at the temperature and time specified in Table I. The solvent was then evaporated, and the residue was separated by flash chromatography and identified by NMR. The yields are given in Table I.

**Photolysis of Diazoindolone 22.** The diazoindolone (10 mg, 0.013 mmol) was dissolved in dry $CH_2Cl_2$ under nitrogen in a Pyrex tube. The reaction mixture was photolyzed for 30 min with a 450-W Hanovia lamp with $CuSO_4$ and $NaNO_2$ solutions as filters. The reaction mixture was washed with saturated $NaHCO_3$, dried, and evaporated. The crude reaction mixture was purified by flash column chromatography (hexane–dichloromethane–ether, 1:1:1) to yield 4.5 mg (55%) of a purple solid identified as quinone **31**: 360-MHz NMR ($CDCl_3$) $\delta$ 2.33 (s, 3 H), 3.70 (t, 2 H), 5.15 (s, 1 H), 5.20–5.27 (m, 2 H), 5.75–5.85 (m, 1 H), 7.47 (s, 1 H), 7.51–7.67 (m, 3 H), 8.11 (d, 2 H); MS (CI) 357, 217, 143. The second fraction yielded 1.0 mg (10%) of bright orange solid identified as sulfinamide **32**: 360-MHz NMR ($CDCl_3$) $\delta$ 2.35 (s, 3 H), 2.88 (s, 3 H), 3.70 (d of m, $J_{gem}$ = 16 Hz, 1 H), 4.50 (d of m, $J_{gem}$ = 16 Hz, 1 H), 5.20 (m, 2 H), 5.67 (m, 1 H), 5.68 (s, 1 H), 7.55 (m, 3 H), 7.66 (m, 1 H), 8.13 (d, $J$ = 9 Hz); MS (CI) 419, 357, 64. The final fractions yielded 2.0 mg (20%) of the spirocyclopropane **30**.

**Thermolysis of Diazoindolone 22.** Diazoindolone **22** (14 mg) was dissolved in 3 mL of toluene. The reaction mixture was refluxed for 0.5 h. The solvent was evaporated and the residue was separated by flash chromatography (hexane–ethyl acetate (3:1) → ethyl acetate) to yield 1.2 mg (11%) of quinone **31**, 1.0 mg (8%) of sulfinamide **32**, and 4.0 mg (30%) of the spirocyclopropane **30**. Recrystallization from ethyl acetate–hexane afforded an analytical sample of **30**: mp 208–210 °C dec; 300-MHz NMR ($CDCl_3$) $\delta$ 1.40 (t, $J$ = 4.9 Hz, 1 H), 1.94–2.04 (m, 1 H), 2.02 (s, 3 H) 2.95–3.02 (m, 1 H), 2.97 (s, 3 H), 3.92 (q, $J$ = 5.5 Hz, 1 H), 4.08 (d, $J$ = 10.1 Hz, 1 H), 6.16 (s, 1 H), 7.47–7.62 (m, 4 H), 8.07 (d, $J$ = 9.0 Hz, 2 H); MS (CI) 419, 279, 143, 89. Anal. Calcd for $C_{19}H_{18}N_2O_5S_2$: C, 54.53; H, 4.34; N, 6.69. Found: C, 54.57; H, 4.35; N, 6.65.

**Catalyzed Decomposition of Diazoindolone 22.** The diazoindolone **22** (0.05–0.1 mmol) with the solvent and catalyst was heated as specified in Table I. The solvent was evaporated, and the residue was separated by flash chromatography and identified by NMR.

**Acknowledgment.** This research was supported by Grant GM-34047 by the National Institutes of Health.

# A Selective Cleavage of the Oxazole Moiety in Noviosylcoumarin Antibiotics: A New Process to Key Intermediates for Coumermycin Analogue Synthesis

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*Received March 21, 1988*

The oxazole moiety of the noviosylcoumarinooxazole **6** was found to be cleaved selectively under mild acidic conditions to produce 3-amino-4-hydroxycoumarins **3** without destruction of the glycosidic bond. By use of this selective oxazole cleavage reaction, a new process to key intermediates for the synthesis of coumermycin analogues PNC-amine[1] **3a** and 2′-acetyl PNC-amine **3b** has been developed by starting from coumermycin $A_1$ (**1**). This process was also applied to the novobiocin series, establishing the first chemical transformation of novobiocin (**2**) to novenamine (**8a**).

Coumermycin $A_1$ (**1**) is an antibiotic, isolated from fermentation broths of several different species of streptomyces almost 20 years ago.[2] Coumermycin $A_1$ (**1**) and the structurally related coumarin antibiotic novobiocin (**2**)[3] have recently been receiving much attention because of their potent antibacterial activity against methicillin-resistant strains of Staphylococci species, which have become clinically important pathogens over the last several years.[4] Coumermycin $A_1$ (**1**) and novobiocin (**2**) have also been

(1) PNC-amine stands for 3-amino-4-hydroxy-8-methyl-7-[[3-*O*-[(5-methyl-2-pyrrolyl)carbonyl]novisoyl]oxy]coumarin (**3a**). The coumermycin subunits are referred to as P, 5-methylpyrrole; N, noviose; and C, 4-hydroxy-8-methylcoumarin, see ref 6.

(2) (a) Kawaguchi, H.; Tsukiura, H.; Okanishi, M.; Miyaki, T.; Ohmori, T.; Fujisawa, K.; Koshiyama, H. *J. Antibiot., Ser. A* **1965**, *18*, 1. (b) Kawaguchi, H.; Naito, T.; Tsukiura, H. *J. Antibiot., Ser A* **1965**, *18*, 11. (c) Berger, J.; Schocher, A. J.; Batcho, A. D.; Pecherer, B.; Keller, O.; Marics, J.; Karr, A. E.; Vaterlans, B. P.; Furlenmeier, A.; Spiegelberg, H. *Antimicrob. Agents Chemother.* **1966**, 778.

(3) For review on coumarin-glycoside antibiotics, see: Berger, J.; Batcho, A. D. In *Antibiotics: Isolation, Separation and Purification*; (*J. Chromatography Library 15*); Weinstein, M. J., Wagmen, G. H., Eds.; Elsevier: London, 1978; p 101.

(4) (a) Wenzel, R. P. *Ann. Intern. Med.* **1982**, *97*, 440. (b) Meyers, B. R.; Srulevitch, E. S.; Hirschman, S. Z. *Antimicrob. Agents Chemother.* **1985**, 706. (c) Rahal, J. J. In *Antimicrobial Agents Annual/1*; Peterson, P. K., Verhoof, J., Eds. Elsevier: New York, 1986; Chapter 44, p 489.

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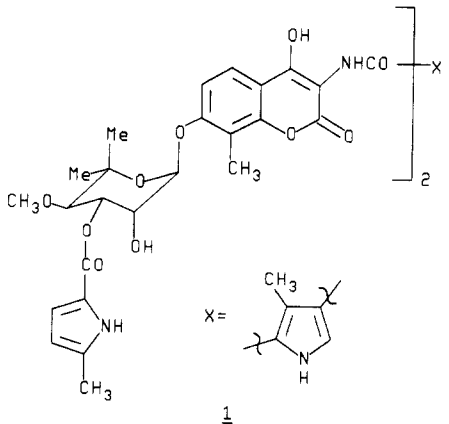
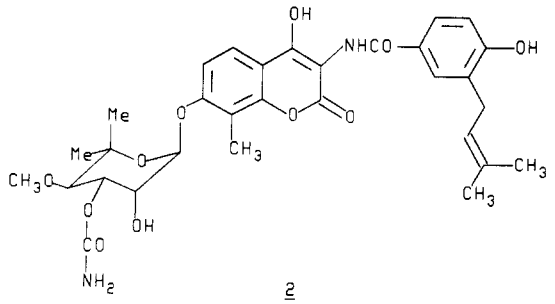
known to exhibit a unique mechanism of action as compared to other antibiotics such as β-lactams and macrolides by inhibiting bacterial DNA gyrase.[5]



1

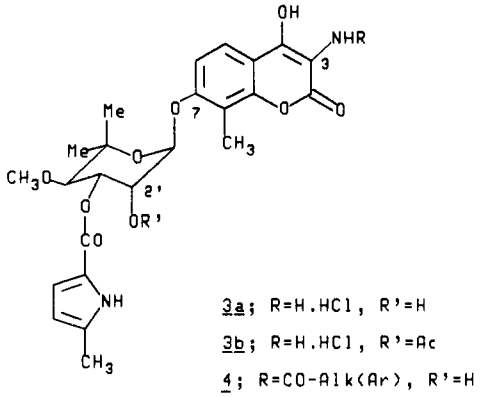


2

Chemical modification of coumermycin $A_1$ (1) has been extensively studied.[6] It has been recognized that 3-aminocoumarin derivative, PNC-amine hydrochloride **3a**, is a key intermediate for the preparation of semisynthetic coumermycin analogues containing carboxamide moieties at the C-3 position, **4**. Some of these analogues exhibited potent antibacterial activities. The reported process to PNC-amine hydrochloride **3a** involved a transacylation of coumermycin $A_1$ (1) with benzyl chloroformate to the benzyloxycarbonyl derivative **5** followed by catalytic hydrogenation.[7] However, this process suffered from low yield, the first step being reported to give a 7% yield of **5**. In our hands, the yield was less than 4%.

In order to synthesize and evaluate the antibacterial activity of coumermycin analogues having a variety of carboxamides at the C-3 position, a better process for PNC-amine hydrochloride **3a**, or its equivalent 2′-acetyl PNC-amine hydrochloride **3b**, from coumermycin $A_1$ (1) was required. Here we report a new process that involves conversion of oxazolocoumarins **6** to 3-aminonoviosylcoumarins **3** by selective, acid-mediated cleavage of the oxazole moiety.

It has been recognized that direct conversion of coumermcyin $A_1$ (1) to PNC-amine **3** by chemical means[8] such as hydrolysis of the amide linkage is difficult because of

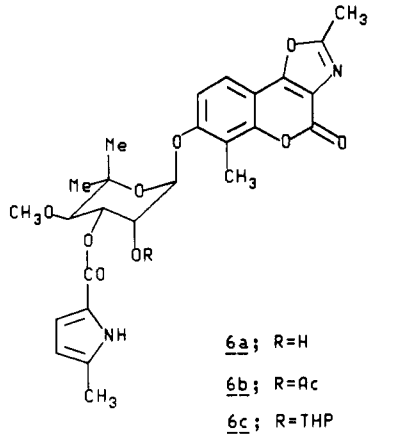


**3a**; R=H.HCl, R'=H

**3b**; R=H.HCl, R'=Ac

**4**; R=CO-Alk(Ar), R'=H

**5**; R=$CO_2CH_2Ph$, R'=H



**6a**; R=H

**6b**; R=Ac

**6c**; R=THP

the presence of the more labile functionalities in the molecule (e.g. ester, coumarin lactone, and glycosidic bond).[6] However, it is also well known that the amide bond in novobiocin (**2**) can be selectively cleaved to oxazolocoumarin **7b** by treatment with acetic anhydride in refluxing pyridine.[10] This same process was also applied to coumermycin $A_1$ to produce oxazolocoumarin **6b**.[6] The cleavage of the oxazole moiety in **7** or **6** to 3-amino-4-hydroxycoumarins **8** or **3** without destruction of other groups has been a long standing concern.[6,9,10] For example, alkaline treatment of **6c** caused hydrolysis of the ester group and ring opening of the coumarin ring with the oxazole moiety intact.[6a] In contrast, treatment of **7b** with excess of mineral acid lead to cleavage of the glycosidic bond;[10] however, this latter treatment also effected the cleavage of the oxazole moiety to 3-amino-4-hydroxycoumarin **9**.[10,11] Although this process served successfully for the degradation studies and the structural determination of novobiocin[10] and coumermycins,[2b] the conditions used in this acid treatment seemed unreasonably harsh for the selective cleavage of the oxazole moiety in **6** or **7** to 3-aminonoviosylcoumarins **3** or **8**. Therefore, we decided to investigate milder acidic conditions[12] to cleave the ox-

(5) (a) Gellert, M.; O'Dea, M. H.; Itoh, T.; Tomizawa, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4474. (b) Hooper, D. C.; Wolfson, J. S.; McHugh, G. L.; Winters, M. B.; Swartz, M. N. *Antimicrob. Agents Chemother.* **1982**, 662.

(6) (a) Keil, J. G.; Godfrey, J. C.; Cron, M. J.; Hooper, I. R.; Nettleton, D. E.; Price, K. E.; Schmitz, H. *Pure Appl. Chem.* **1971**, *28*, 571. (b) Godfrey, J. C.; Price, K. E. *Adv. Appl. Microbiol.* **1972**, *15*, 231.

(7) Keil, J. G.; Hooper, I. R.; Schreiber, R. H.; Swanson, C. L.; Godfrey, J. C. *Antimicrob. Agents Chemother.* **1969**, 200.

(8) Although enzymic cleavage of novobiocin (**2**) to novenamine (**8a**) has been reported,[9] application of this process to the coumermycin series has not been described. Chemical transformation of novobiocin (**8a**) has not been successful.[9]

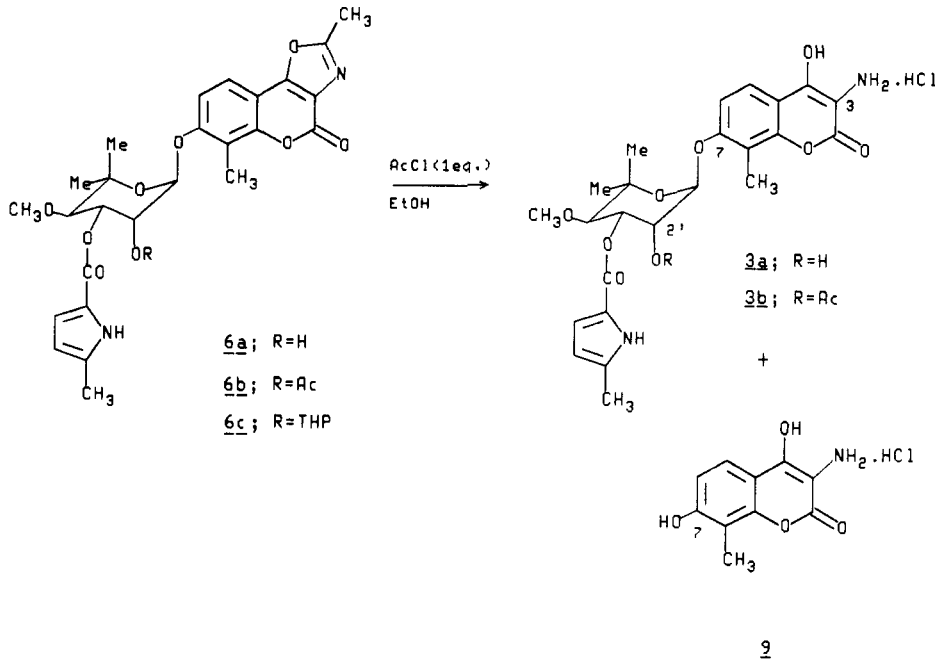
(9) Sebek, O. K.; Hoeksema, H. *J. Antibiot.* **1972**, *25*, 434.

(10) Hinman, J. W.; Caron, E. L.; Hoeksema, H. *J. Am. Chem. Soc.* **1957**, *79*, 3789.

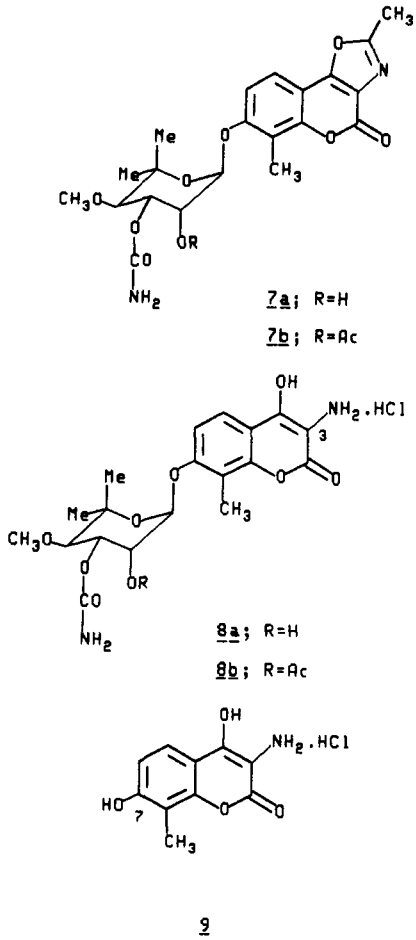
(11) Although alkyl- and aryloxazoles are generally stable toward ring cleavage by acids, 5-alkoxyoxazoles, 5-aminooxazoles, and oxazole-4-carboxylates are reported to undergo ready hydrolysis with mineral acids. For recent reviews on oxazoles, see: (a) Boyd, G. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 6, p 177. (b) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. See also Clerin, D.; Kille, G.; Fleury, J. P. *Tetrahedron* **1974**, *30*, 469.

(12) A milder condition, treatment with 1 equiv of acetyl chloride in refluxing EtOH, was applied to novobiocin (**2**), producing 7-hydroxycoumarin derivative and ethyl novioside.[10] Therefore, it was believed that the glycosidic linkage of noviosylcoumarins, such as novobiocin (**2**), would not survive even under these mild conditions.[9]

**Scheme I**




azole moiety of **6** or **7** selectively without losing the noviose group.

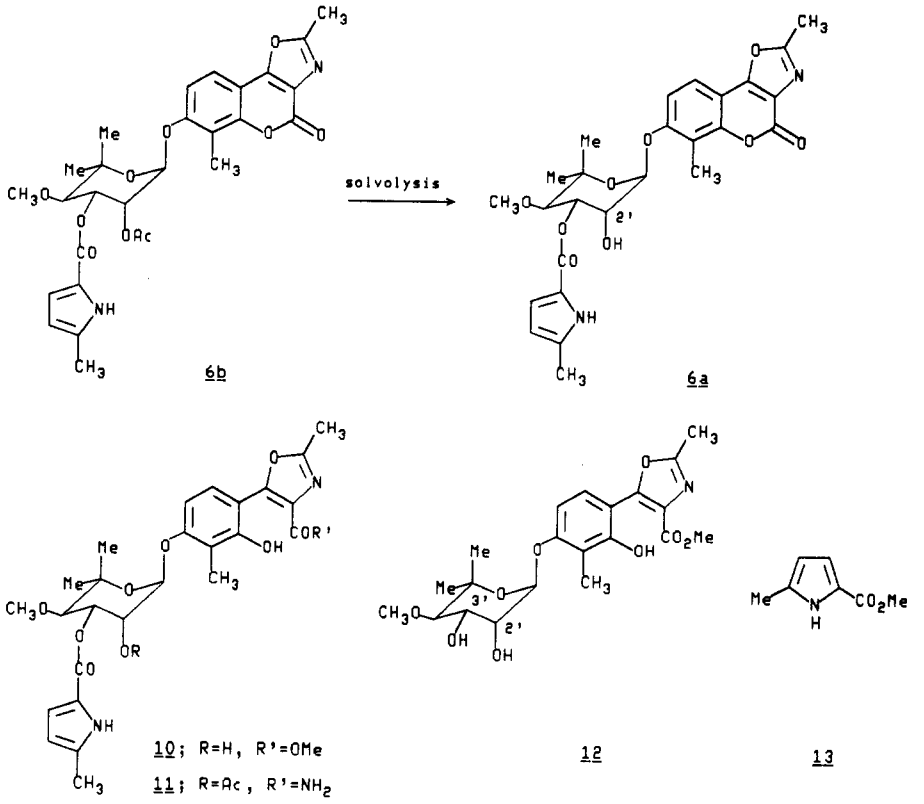



When the oxazole **6b**, which was prepared from coumermycin $A_1$ (1) in 48% yield, was treated with 1 equiv of acetyl chloride in refluxing EtOH, the oxazole group was smoothly cleaved, producing 2′-acetyl PNC-amine hydrochloride **3b** as a major product (Scheme I). The $^1H$ NMR analysis of the product, isolated as a yellowish powder in 86% yield, indicated loss of the oxazolyl methyl group and presence of the pyrrolylnoviose moiety, and it also revealed that under these conditions only a small amount of byproduct **9** was produced (ratio of **9**/**3b** ≤ 1/9). This success is presumably due to the more facile cleavage of this particular oxazole[11] than the acidic solvolysis of the glycosidic bond. Additionally, the hydrochloric acid generated from acetyl chloride is trapped as the amine hydrochloride, leaving no excess acid for further cleavage of the sugar linkage. Use of an excess of acetyl chloride or a prolonged reaction time caused more glycosidic bond cleavage, producing more of phenolic byproduct **9**. Although 2′-acetyl PNC-amine hydrochloride **3b** could be purified by column chromatography, more conveniently this crude product was acylated to a carboxamide and purified at this stage.

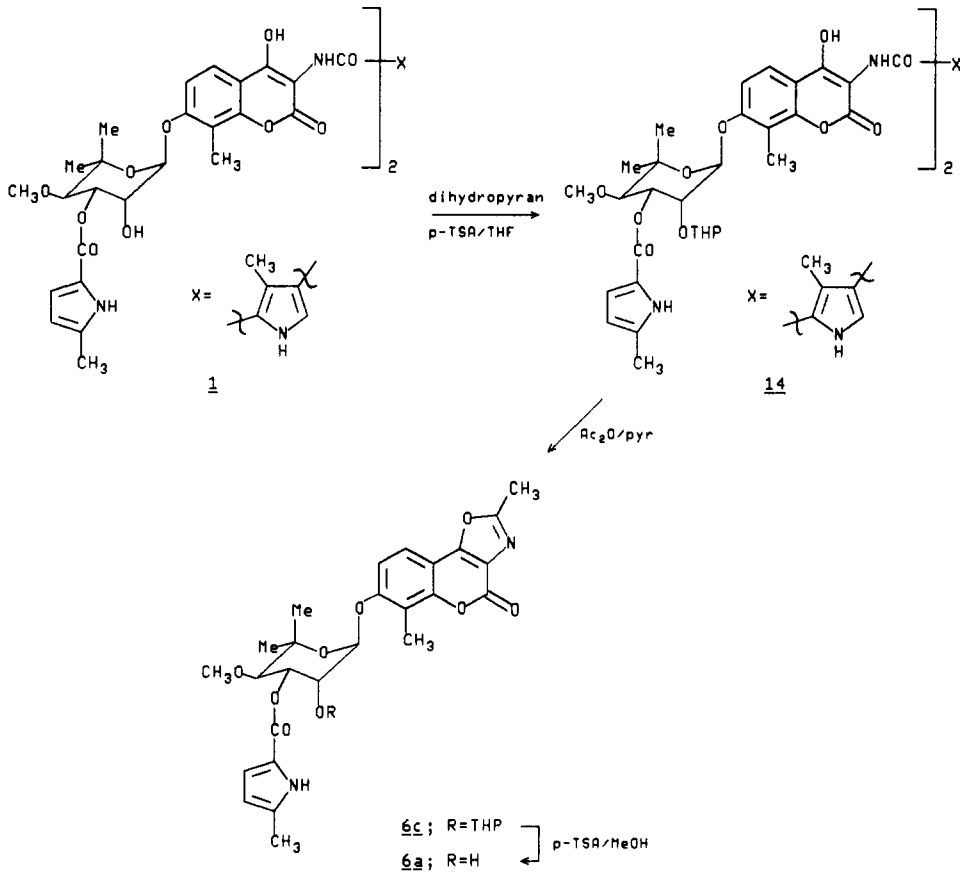
We then turned to the preparation of PNC-amine hydrochloride **3a** by using the oxazole-process described above. We first investigated the preparation of the requisite intermediate 2′-hydroxyoxazole **6a** by two approaches. One approach was a simple solvolysis of the corresponding acetate **6b** (Scheme II). We found this solvolysis was not as straightforward as we originally thought. Alkaline hydrolysis (1 equiv of NaOH, $Na_2CO_3$, or $NaHCO_3$ in aqueous MeOH) of the acetate **6b** at room temperature slowly produced not only the desired 2′-hydroxyoxazole **6a** but also a significant amount of coumarin-opened material **10**. When liquid ammonia was used as a base in a mixture of $CH_2Cl_2$ and MeOH, **6b** produced only the coumarin-opened amide **11** and the 2′-acetoxy group was untouched. After several attempts we found, however, tht a solvolysis without the addition of a base, that is, refluxing **6b** in MeOH, slowly produced the desired hydroxy compound **6a** without opening the coumarin ring. After several hours of reflux, the product **6a** crystallized out on cooling. A catalytic amount (ca. 5 mol %) of NaOMe facilitated this transformation,[13] yielding 72% of

(13) Use of NaOMe as a base is reported for the deacetylation of the 2′-acetoxyoxazole **7b** to **7a** without description of the amount.[10]

**Scheme II**




**Scheme III**




**6a** in 2.5 h. When 1 equiv of NaOMe was used, coumarin-opened ester **10** was quickly generated, which was further converted to 2′,3′-dihydroxy compound **12** and methyl 5-methylpyrrole-2-carboxylate (**13**).

The other approach to 2′-hydroxyoxazole **6a**, which we investigated, involved protection of the 2′-hydroxy group with the tetrahydropyranyl group as shown in Scheme III.[6a] Coumermycin $A_1$ (**1**) was treated with dihydropyran in

THF to produce bis(tetrahydropyranyl) derivative **14**[14] in 87% yield. In this reaction, the order of mixing as described in the Experimental Section is important to secure the best results. This bis(tetrahydropyranyl) coumermycin $A_1$ **14** was treated with acetic anhydride in refluxing pyridine[10] to produce the oxazole **6c** in 23% yield after column chromatographic separation. The cleavage of the tetrahydropyranyl (THP) group was effected by a catalytic amount of *p*-toluenesulfonic acid in MeOH[14] to give the 2′-hydroxyoxazole **6a** in 49% yield. This material was identical with that obtained by solvolysis of 2′-acetoxyoxazole **6b**. This approach required three steps from coumermycin $A_1$ (1), and the overall yield (10%) was less than the first two-step process, which had 35% overall yield.

Having established the processes to prepare 2′-hydroxyoxazole **6a**, this oxazole was subjected to the acid-mediated cleavage reaction to produce PNC-amine hydrochloride **3a**. When **6a** was treated under the conditions described eralier, that is, refluxing with 1 equiv of acetyl chloride in EtOH, in contrast to the earlier case, it produced mainly the byproduct **9** and a small amount (less than 20%) of the desired PNC-amine hydrochloride **3a** (Scheme I). It was found, however, that when **6a** was heated at a lower temperature (60 °C), the reaction proceeded smoothly and afforded, after 20 h, PNC-amine hydrochloride **3a** in 80% yield, contaminated with about 20% of the 7-hydroxyaminocoumarin **9**. Although the PNC-amine hydrochloride **3a** could be purified by column chromatography, the crude material was found to be sufficiently pure for the preparation of 3-carboxamido derivatives **4**.

Later we found that 2′-tetrahydropyranyloxazole **6c** could also be directly subjected to the oxazole-cleavage reaction, producing PNC-amine hydrochloride **3a** with concomitant removal of the tetrahydropyranyl group (Scheme I). However, for practical purposes and also to ensure the quality of PNC-amine **3a**, we preferred to go through the 2′-hydroxyoxazole **6a**, which was readily purified by crystallization.

This newly found, mild oxazole-cleavage procedure was also applied to the novobiocin series, specifically compounds **7a** and **7b**. The resulting conversion of **7a** and **7b** to **8a** and **8b**, respectively, establishes the first reported chemical transformation of novobiocin (**2**) to novenamine (**8a**).[9]

The use of PNC-amine and 2′-acetyl PNC-amine hydrochlorides **3** as key intermediates for synthesis of novel semisynthetic coumermycins will be the subject of a forthcoming publication.

In summry, we have developed a new procedure that allows selective cleavage of the oxazole moiety in noviosyl coumarin antibiotics to the important synthetic intermediates, PNC-amine **3a** and novenamine **8a** for the preparation of a variety of semisynthetic coumermycin and novobiocin analogues.

## Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Infrared spectra were recorded on a Perkin-Elmer Model 1800 FTIR spectrophotometer. The UV spectra were obtained with a Hewlett-Packard 8452A diode array spectrophotometer. The $^1$H NMR spectra were taken with a Bruker WM 360 (360 MHz), when unspecified, or a Bruker AM 300 (300 MHz), or a Varian VXR-200 (200 MHz) NMR spectrometer. Tetramethylsilane or residual protonated solvents were used as internal references. Splitting patterns: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet; br, broad. Mass spectra were obtained on either a Kratos MS25RFA 4500 (FAB) or a Finnigan E1-C1 mass spectrometer. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Freshly opened anhydrous diethyl ether (Aldrich) was used without further treatment. Pyridine was distilled from $CaH_2$ and stored over NaOH. Analytical thin-layer chromatography (TLC) was performed by using precoated plates (silica gel 60A, MK6F Whatman). The plates were visualized by UV light. Flash column chromatography was performed by the method of Still[15] by using silica gel 60 (230–400 mesh, E. Merck). All other column chromatography was run on open columns of silica gel 60 (70–230 mesh, E. Merck).

**1-[(2,6-Dimethyl-4-oxo-4*H*-[1]benzopyrano[3,4-*d*]oxazol-7-yl)oxy]-2-acetoxy-4-methoxy-5,5-dimethyl-3-tetrahydropyranyl 5-Methyl-1*H*-pyrrole-2-carboxylate (6b).** A solution of coumermycin $A_1$ (1) (11.1 g, 10 mmol) in pyridine (60 mL) was mixed with acetic anhydride (18.9 mL, 200 mmol), and the mixture was heated under reflux for 24 h. The dark solution was cooled and poured slowly into a mixture of 12 N HCl (65 mL) and ice (100 mL). The brown precipitate was filtered, washed, and dried in vacuo to obtain 11.93 g of crude solid. This was dissolved in hot $CH_2Cl_2$ and placed on a pad consisting of a layer of Celite over a layer of silica gel (50 g). This pad was eluted with 20% EtOAc/$CH_2Cl_2$ (1 L). The filtrate and eluent were combined, concentrated, and purified by column chromatography ($SiO_2$, 500 g), eluting with 10–20% EtOAc/$CH_2Cl_2$ to obtain 5.15 g (9.29 mmol, yield 46.3%) of the title compound **6b** as pale yellow solid. An analytical sample was obtained by crystallization from MeOH: mp 167 °C dec; $[\alpha]_D$ −104.9° (*c* 1.0, $CHCl_3$); IR (KBr disk) $\nu_{max}$ 3370, 1760, 1705, 1650, and 1610 cm$^{-1}$; UV (EtOH) $\lambda_{max}$ 282 ($\epsilon$ 2.87 × 10$^4$) and 314 nm ($\epsilon$ 1.96 × 10$^4$); $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (3 H, s, 5′-Me), 1.40 (3 H, s, 5′-Me), 2.15 (3 H, s, 2′-OAc), 2.31 (3 H, s, 5-Me), 2.39 (3 H, s, 6″-Me), 2.65 (3 H, s, 2-Me), 3.55 (3 H, s, 4′-OMe), 3.58 (1 H, d, *J* = 9.9 Hz, 4′-H), 5.53 (1 H, t, *J* = 3 Hz, 2′-H), 5.59 (1 H, d, *J* = 3 Hz, 1′-H), 5.76 (1 H, dd, *J* = 3, 9.8 Hz, 3′-H), 5.95 (1 H, t, *J* = 3.0 Hz, 4-H), 6.77 (1 H, t, *J* = 3.0 Hz, 3-H), 7.20 (1 H, d, *J* = 8.8 Hz, 8″-H), 7.57 (1 H, d, *J* = 8.8 Hz, 9″-H), and 9.17 (1 H, br s, 1-H); MS (FAB), *m/e* 555 (M + H), 324 (base), 232. Anal. Calcd for $C_{28}H_{30}N_2O_{10}\cdot{}^1/_2H_2O$: C, 59.68; H, 5.55; N, 4.98. Found: C, 59.55; H, 5.33; N, 4.89.

**3-Amino-4-hydroxy-8-methyl-7-[[3-*O*-[(5-methyl-2-pyrrolyl)carbonyl]-2-*O*-acetylnoviosyl]oxy]coumarin Hydrochloride (3b).** To a suspension of oxazole **6b** (3.32 g, 6.00 mmol) in absolute EtOH (125 mL) was added acetyl chloride (438 μL, 6.0 mmol), and the mixture was heated at reflux for 3 h under an atmosphere of nitrogen. The solvent was evaporated to dryness, and the residual foam was triturated with dry $Et_2O$ (80 mL × 3) to obtain 2.90 g (5.12 mmol, yield 85.3%) of the title compound **3b** as light yellow solid. The $^1$H NMR spectrum (DMSO-$d_6$) indicated contamination of about 10% of 4,7-dihydroxy-3-amino-8-methylcoumarin (**9**) [$\delta$ 7.68 (d, *J* = 8 Hz, 5-H) and 6.86 (d, *J* = 9 Hz, 6-H)]. An analytical sample was obtained by flash column chromatography ($SiO_2$), eluting with c-$NH_4OH$/MeOH/$CH_2Cl_2$, 2:18:80, followed by treatment with concentrated HCl (1 equiv) in cold absolute EtOH: mp 200 °C dec; $[\alpha]_D$ −67.22° (*c* 0.18, MeOH); IR (KBr disk) $\nu_{max}$ 3400, 1730, 1710, and 1610 cm$^{-1}$; UV (EtOH) $\lambda_{max}$ 234 ($\epsilon$ 1.44 × 10$^4$) and 282 nm ($\epsilon$ 2.84 × 10$^4$); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 1.15 (3 H, s, 5′-Me), 1.36 (3 H, s, 5′-Me), 2.09 (3 H, s, 2′-OAc), 2.20, 2.22 (2 × 3 H, 2 s, Ar-Me, pyrr-Me), 3.48 (3 H, s, 4′-OMe), 3.53 (1 H, d, *J* = 9.2 Hz, 4′-H), 5.38 (1 H, t, *J* = 3.0 Hz, 2′-H), 5.57 (1 H, dd, *J* = 3, 9 Hz, 3′-H), 5.73 (1 H, d, *J* = 3 Hz, 1′-H), 5.90 (1 H, s, 4″-H), 6.72 (1 H, t, *J* = 3.0 Hz, 3″-H), 7.07 (1 H, d, *J* = 9.0 Hz, Ar H), 7.75 (1 H, d, *J* = 9.0 Hz, Ar H), 7.00, 7.17, 7.34 (3 s, exchanged with $D_2O$), and 11.68 (1 H, s, NH); MS (methane DCI), *m/e* 531 (M + H), 324, 208, 108. Anal. Calcd for $C_{26}H_{30}N_2O_{10}\cdot HCl\cdot 2H_2O$: C, 51.79; H, 5.86; N, 4.65. Found: C, 51.86; H, 5.80; N, 4.89.

**1-[(2,6-Dimethyl-4-oxo-4*H*-[1]benzopyrano[3,4-*d*]oxazol-7-yl)oxy]-2-hydroxy-4-methoxy-5,5-dimethyl-3-tetrahydro-**

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**pyranyl 5-Methyl-1*H*-pyrrole-2-carboxylate (6a). (1) From 2′-Acetate 6b.** A suspension of the acetate **6b** (8.90 g, 16.1 mmol) in MeOH (720 mL, dried over molecular sieves 3A) was heated to dissolve, and to this solution was added 1 N NaOMe/MeOH (0.8 mL), and the mixture was heated at reflux for 2.5 h by which time TLC (50% EtOAc/$CH_2Cl_2$) indicated that the reaction was complete. The solvent was evaporated in vacuo to the volume of about 200 mL, and this was cooled in an ice bath to obtain 5.87 g (11.4 mmol, yield 71.7% from two crops) of the title compound **6a** as white crystals: mp 226–8 °C dec; $[\alpha]_D$ –67.91° (*c* 1.0, $CH_2Cl_2$); IR (KBr disk) $\nu_{max}$ 3400, 1745, 1705, 1650, and 1610 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 280 ($\epsilon$ 2.84 × $10^4$) and 314 nm ($\epsilon$ 2.03 × $10^4$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.19 (3 H, s, 5′-Me), 1.39 (3 H, s, 5′-Me), 2.31 (3 H, s, 5-Me), 2.36 (3 H, s, 6″-Me), 2.55 (1 H, d, *J* = 4 Hz, 2′-OH, exchanged with $D_2O$), 2.65 (3 H, s, 2″-Me), 3.53 (3 H, s 4′-OMe), 3.64 (1 H, d, *J* = 9.4 Hz, 4′-H), 4.42 (1 H, q, *J* = 3 Hz, 2′-H), 5.63 (1 H, d, *J* = 2.6 Hz, 1′-H), 5.67 (1 H, dd, *J* = 3, 9.7 Hz, 3′-H), 5.96 (1 H, t, *J* = 3 Hz, 4-H), 6.86 (1 H, t, *J* = 3 Hz, 3-H), 7.23 (1 H, *J* = 9 Hz, 9-H), 7.55 (1 H, d, *J* = 9 Hz, 8-H), and 9.04 (1 H, br s, 1-H); MS (methane DCI), *m/e* 513 (M + H), 282, 232 (base), 108. Anal. Calcd for $C_{26}H_{28}N_2O_9 \cdot H_2O$: C, 58.87; H, 5.71; N, 5.29. Found: C, 58.92; H, 5.79; N, 5.18.

The title compound was also obtained in 48% yield by refluxing in MeOH for 8–24 h without NaOMe, but the reaction was much slower and it was useful only for a small-scale preparation.

**(2) From 6c.** To a solution of **6c** (2.79 g, 4.68 mmol; see below) in MeOH (78 mL) was added *p*-toluenesulfonic acid monohydrate (180 mg, 0.94 mmol), and the mixture was stirred at room temperature for 7.5 h. The mixture was diluted with $CH_2Cl_2$, washed with diluted brine, dried ($Na_2SO_4$), and evaporated to yield a crude solid. This was purified by column chromatography ($SiO_2$, 50% EtOAc/$CH_2Cl_2$) to yield 1.18 g (2.30 mmol, yield 49.2%) of white solid, which was identical with the material obtained above (TLC and $^1H$ NMR).

**Solvolysis of the Acetate 6b. (1) NaOH/MeOH.** To a solution of the acetate **6b** (28 mg, 0.05 mmol) in MeOH (2 mL) was injected 1 N NaOH/$H_2O$ (50 $\mu$L, 0.05 mmol), and the mixture was stirred at room temperature for 2.5 h by which time TLC indicated that the reaction was complete. This was diluted with EtOAc, washed with diluted brine, dried ($Na_2SO_4$), and evaporated to 26 mg of yellowish solid, which was purified by preparative TLC ($SiO_2$, 50% EtOAc/$CH_2Cl_2$) to obtain 5 mg (0.01 mmol, yield 20%) of **6a** and 13 mg (0.024 mmol, yield 48%) of the coumarin-opened material **10** as off-white solid: mp 126–170 °C dec; IR (film) $\nu_{max}$ 3300, 1690, and 1610 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 224 ($\epsilon$ 1.72 × $10^4$) and 280 nm ($\epsilon$ 2.73 × $10^4$); $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.25 (3 H, s, 5′-Me), 1.39 (3 H, s, 5′-Me), 2.26 (3 H, s, 5-Me), 2.34 (3 H, s, Ar-Me), 2.56 (3 H, s, oxazole-Me), 3.55 (3 H, s, 4′-OMe), 3.65 (1 H, d, *J* = 9.6 Hz, 4′-H), 4.01 (3 H, s, $CO_2Me$), 4.40 (1 H, t, *J* = 2.5 Hz, 2′-H), 5.61 (1 H, d, *J* = 2.5 Hz, 1′-H), 5.72 (1 H, dd, *J* = 3, 10 Hz, 3′-H), 6.00 (1 H, t, *J* = 3 Hz, 4-H), 6.89 (1 H, t, *J* = 3 Hz, 3-H), 6.95 (1 H, d, *J* = 9 Hz, Ar H), 7.35 (1 H, d, *J* = 9 Hz, Ar H), and 9.06 (1 H, br s, NH); MS (FAB), *m/e* 545 (M + H), 282, 264, 232, 108 (base).

The solvolysis with aqueous $NaHCO_3$ was much slower, producing a mixture of **6a** and **10**.

**(2) One Equivalent of NaOMe/MeOH.** A suspension of the acetate **6b** (554 mg, 1 mmol) in MeOH (15 mL) was heated at reflux with 1 N NaOMe/MeOH (1.0 mL, 1 mmol) for 45 min. The same workup as described above gave a crude foam, which was purified by column chromatography ($SiO_2$, 50% EtOAc/$CH_2Cl_2$) to obtain 103 mg (0.74 mmol, yield 74%) of methyl 5-methylpyrrole-2-carboxylate (**13**) [IR (film) $\nu_{max}$ 3310 and 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.31 (3 H, s, 5-Me), 3.83 (3 H, s, $CO_2Me$), 5.95 (1 H, t, *J* = 3 Hz, 4-H), 6.81 (1 H, t, *J* = 3 Hz, 3-H), and 9.0 (1 H, br, NH); MS (methane DCI) *m/e* 140 (M + H, base), 108], 40 mg (0.074 mmol, yield 7.4%) of the ring-opened ester **10**, and 81 mg (0.19 mmol, yield 19%) of diol **12** as white foam [IR (film) $\nu_{max}$ 3400, 1730, 1685, and 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.16 (3 H, s, 5′-Me), 1.37 (3 H, s, 5′-Me), 2.18 (3 H, s, Ar-Me), 2.55 (3 H, s, oxazole-Me), 3.37 (1 H, d, *J* = 9 Hz, 4′-H), 3.61 (3 H, s, 4′-OMe), 4.00 (3 H, s, $CO_2Me$), 4.24 (1 H, br s, 2′-H), 4.26 (1 H, m, 3′-H), 5.60 (1 H, br s, 1′-H), 6.94 (1 H, d, *J* = 9 Hz, Ar H), and 7.34 (1 H, d, *J* = 9 Hz, Ar H); MS (FAB), *m/e* 438 (M + H), 264, 232 (base)].

After the reaction mixture was refluxed for 15 min, TLC (50% EtOAc/$CH_2Cl_2$) of the reaction mixture indicated that the major product was **10**; no formation of **12** or **13** was observed.

**(3) Liquid $NH_3$/MeOH–$CH_2Cl_2$.** To a solution of the acetate **6b** (12 mg, 0.022 mmol) in $CH_2Cl_2$ (5 mL) was added liquid $NH_3$ (ca. 5 mL) at –30 °C, and the mixture stirred at –30 °C for 5 h. The cooling bath was removed, and the volatile material was evaporated by purging dry nitrogen at room temperature overnight (ca. 20 h). TLC (50% EtOAc/$CH_2Cl_2$) indicated that the reaction was incomplete but produced a slow moving product. The crude mixture was crystallized from $CH_2Cl_2$–$Et_2O$ to yield 8 mg (0.014 mmol, yield 64%) of the amide **11** as white solid: IR (KBr disk) $\nu_{max}$ 3420, 3060, 1730, 1670, and 1590 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 282 nm; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.16 (3 H, s, 5′-Me), 1.35 (3 H, s, 5′-Me), 2.10 (6 H, s, OAc, 5-Me), 2.22 (3 H, s, Ar-Me), 2.48 (3 H, s, oxazole-Me), 3.48 (3 H, s, 4′-OMe), 3.52 (1 H, d, *J* = 9.4 Hz, 4′-H), 5.37 (1 H, t, *J* = 3 Hz, 2′-H), 5.57 (1 H, dd, *J* = 3.0, 9.4 Hz, 3′-H), 5.68 (1 H, d, *J* = 2.5 Hz, 1′-H), 5.91 (1 H, d, *J* = 2 Hz, 4-H), 6.72 (1 H, t, *J* = 2 Hz, 3-H), 6.82 (1 H, d, *J* = 9 Hz, Ar H), 7.34 (1 H, d, *J* = 9 Hz, Ar H), 8.32 (1 H, s, CONH, slowly exchanged with $D_2O$), 8.36 (1 H, s, CONH, slowly exchanged with $D_2O$), 11.23 (1 H, s, Ar-OH, exchanged with $D_2O$), and 11.7 (1 H, s, 1-H); MS (FAB), *m/e* 572 (M + H), 324, 232, 108 (base).

**2′-*O*-Bis(tetrahydropyranyl)coumermycin $A_1$ (14).** To a suspension of coumermycin $A_1$ (**1**) (30 g, 27 mmol) in dihydropyran (300 mL, Aldrich) was added *p*-toluenesulfonic acid monohydrate (84 mg, 0.44 mmol), and this was stirred for 0.5 h. To this mixture THF (300 mL) was added and stirred at room temperature under an atmosphere of nitrogen for 20 h. The solvents were evaporated in vacuo to dryness, and the residue was triturated with anhydrous $Et_2O$ (350 mL × 2) to yield 29.9 g (23.4 mmol, yield 86.7%) of the title compound **14** as yellowish powder: mp >150 °C dec; IR (KBr disk) $\nu_{max}$ 3380, 1700, 1640, and 1610 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 276 ($\epsilon$ 5.24 × $10^4$) and 336 nm ($\epsilon$ 4.23 × $10^4$); $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.11 (6 H, s, 5′-Me), 1.32, 1.35 (6 H, 2s, 5′-Me), 1.4–1.8 (6 H, m, $CH_2$), 2.23 (6 H, s, 5″-Me), 2.27 (6 H, s, 8-Me), 2.62 (3 H, s, 5‴-Me), 3.3–3.6 (2 H, m, $OCH_2$), 3.47, 3.49 (6 H, 2 s, 4′-OMe), 3.56, 3.58 (2 H, 2 d, *J* = 9 Hz, 4′-H), 3.82 (2 H, m, $OCH_2$), 4.23 (2 H, m, 2′-H), 4.68, 4.97 (2 H, 2 s, OCHO), 5.61 (2 H, d, *J* = 10 Hz, 3′-H), 5.75, 5.86 (2 H, 2 s, 1′-H), 5.92 (2 H, m, 4″-H), 6.75 (2 H, t, *J* = 5 Hz, 3″-H), 7.22, 7.24 (2 H, 2 d, *J* = 9 Hz, Ar H), 7.76, 7.77 (2 H, 2 d, *J* = 9 Hz, Ar H), 7.82 (1 H, s, 5‴-H), 8.68, 8.99 (2 H, 2 s, NHCO), 11.69, 11.72, 11.92 (3 H, 3 s, NH), and 12.35 (br, 4-OH); MS (FAB), *m/e* 1110 (M – 168), 622, 366, 282, 108, 85 (base). Anal. Calcd for $C_{65}H_{75}N_5O_{22} \cdot H_2O$: C, 60.24; H, 5.99; N, 5.40. Found: C, 60.33; H, 5.87; N, 5.38.

**1-[(2,6-Dimethyl-4-oxo-4*H*-[1]benzopyrano[3,4-*d*]oxazol-7-yl)oxy]-2-[(tetrahydro-2-pyranyl)oxy]-4-methoxy-5,5-dimethyl-3-tetrahydropyranyl 5-Methyl-1*H*-pyrrole-2-carboxylate (6c).** A solution of **14** (6.40 g, 5.00 mmol) in pyridine (30 mL) was mixed with acetic anhydride (9.44 mL, 100 mmol), and the mixture was heated at 100 °C under a nitrogen atmosphere for 16 h. The same workup as described for the preparation of **6b** gave 1.35 g (2.27 mmol, yield 22.7%) of the title compound **6c** as yellowish solid: mp >150 °C dec; IR (KBr disk) $\nu_{max}$ 3360, 1770, 1710, 1650, and 1610 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 280 ($\epsilon$ 2.83 × $10^4$) and 314 nm ($\epsilon$ 2.06 × $10^4$); $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 1.10 (3 H, s, 5′-Me), 1.34 (3 H, s, 5′-Me), 1.3–1.8 (6 H, m, $CH_2$), 2.23 (3 H, s, 5-Me), 2.30 (3 H, s, 6″-Me), 2.64 (3 H, s, 2″-Me), 3.25 (1 H, m, 5‴-H), 3.48 (3 H, s, 4′-OMe), 3.56 (1 H, d, *J* = 9 Hz, 4′-H), 3.83 (1 H, m, 5‴-H), 4.22 (1 H, t, *J* = 3 Hz, 2′-H), 4.69 ($^1/_4$ H, br s, 1‴-H), 4.97 ($^3/_4$ H, br s, 1‴-H), 5.60 (1 H, dd, *J* = 3, 9 Hz, 3′-H), 5.75 ($^1/_4$ H, d, *J* = 3 Hz, 1′-H), 5.88 ($^3/_4$ H, d, *J* = 3 Hz, 1′-H), 5.91 (1 H, br s, 4-H), 6.75 (1 H, t, *J* = 3 Hz, 3-H), 7.30 (1 H, d, *J* = 9 Hz, 8″-H), 7.77 (1 H, d, *J* = 9 Hz, 9″-H), and 11.70, 11.72 (1 H, 2 s, 1-NH); MS (methane DCI), *m/e* 597 (M + H), 514 (base), 365, 281, 232, 108, 85. Anal. Calcd for $C_{31}H_{36}N_2O_{10}$: C, 62.41; H, 6.09; N, 4.70. Found: C, 62.15; H, 6.36; N, 4.34.

**3-Amino-4-hydroxy-8-methyl-7-[[3-*O*-[(5-methyl-2-pyrrolyl)carbonyl]noviosyl]oxy]coumarin Hydrochloride (3a).** A suspension of **6a** (961 mg, 1.88 mmol) in absolute EtOH (83 mL) was mixed with a solution of acetyl chloride (137 $\mu$L, 1.88 mmol) in absolute EtOH (10 mL), and this mixture was heated at 60 °C under a nitrogen atmosphere for 20 h. The solvent was evaporated to dryness and triturated with anhydrous $Et_2O$ (×3) to obtain 790 mg (1.50 mmol, 80.0%) of the title compound **3a** as yellowish solid, which was contaminated with about 20% of

7-(hydroxyamino)coumarin **9**. An analytical sample was obtained by the method used for **3b**: mp >280 °C dec; $[\alpha]_D$ −56.97° (c 0.25, MeOH); IR (KBr disk $\nu_{max}$ 3200, 3070, 1700, and 1610 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 234 ($\epsilon$ 1.72 × $10^4$) and 282 nm ($\epsilon$ 3.09 × $10^4$); $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 1.08 (3 H, s, 5′-Me), 1.28 (3 H, s, 5′-Me), 2.21 (3 H, s, Me), 2.24 (3 H, s, Me), 3.46 (3 H, s, 4′-OMe), 3.63 (1 H, d, $J$ = 10 Hz, 4′-H), 4.13 (1 H, t, $J$ = 2.5 Hz, 2′-H), 5.46 (1 H, dd, $J$ = 3, 10 Hz, 3′-H), 5.54 (1 H, d, $J$ = 2.5 Hz, 1′-H), 5.91 (1 H, t, $J$ = 3 Hz, 4″-H), 6.76 (1 H, t, $J$ = 3 Hz, 3″-H), 7.02, 7.19, 7.36 (3 s, $D_2O$ exchangeable), 7.07 (1 H, d, $J$ = 9 Hz, 6-H), 7.74 (1 H, d, $J$ = 9 Hz, 5-H), and 11.65 (1 H, s, NH, $D_2O$ exchangeable); MS (FAB), $m/e$ 489 (M + H), 282, 208, 108 (base). Anal. (free base) Calcd for $C_{24}H_{28}N_2O_9 \cdot H_2O$: C, 56.92; H, 5.98; N, 5.54. Found: C, 56.79; H, 5.66; N, 5.47.

**3-Amino-4-hydroxy-8-methyl-7-[(3-*O*-carbamyl-2-*O*-acetylnoviosyl)oxy]coumarin Hydrochloride (8b).** The title compound **8b** was prepared from oxazole **7b**[10] by the method described for **3b** in 97% yield. This crude material was contaminated with about 25% of 7-hydroxy-3-aminocoumarin **9**. The pure sample was obtained as a free base after column chromatography ($SiO_2$, c-$NH_4OH$/MeOH/$CH_2Cl_2$, 3:27:70) in 45% yield: mp 195–215 °C dec; IR (KBr disk) $\nu_{max}$ 3400, 1740, 1670, and 1610 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 236 ($\epsilon$ 1.22 × $10^4$) and 298 nm ($\epsilon$ 1.28 × $10^4$); $^1H$ NMR ($CD_3OD$) $\delta$ 1.19 (3 H, s, 5′-Me), 1.37 (3 H, s, 5′-Me), 2.15 (3 H, s, 2′-OAc), 2.30 (3 H, s, Ar-Me), 3.49 (1 H, d, $J$ = 9 Hz, 4′-H), 3.61 (3 H, s, 4′-OMe), 5.44 (2 H, m, 2′-H and 3′-H), 5.61 (1 H, s, 1′-H), 7.12 (1 H, d, $J$ = 8.8 Hz, Ar H), and 7.77 (1 H, d, $J$ = 8.8 Hz, Ar H).

**3-Amino-4-hydroxy-8-methyl-7-[(3-*O*-carbamylnoviosyl)oxy]coumarin Hydrochloride (Novenamine Hydrochloride) (8a).** The title compound **8a** was prepared from oxazole **7a**[10] by the procedure described for **3a** in 41% yield. The low yield was due to the incompletion of the reaction. The pure material was obtained as a free base (novenamine) after column chromatography ($SiO_2$, c-$NH_4OH$/MeOH/$CH_2Cl_2$, 3:27:70) in 21% yield: mp 215–235 °C dec (lit.[9] mp >220 °C dec); IR (KBr disk) $\nu_{max}$: 3400, 3200, 1720, 1670, and 1610 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 236 ($\epsilon$ 1.14 × $10^4$) and 298 nm ($\epsilon$ 1.15 × $10^4$); $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.05 (3 H, s, 5′-Me), 1.24 (3 H, s, 5′-Me), 2.15 (3 H, s, Ar-Me), 3.45 (3 H, s, 4′-OMe), 3.47 (1 H, d, $J$ = 10 Hz, 4′-H), 4.03 (1 H, t, $J$ = 2.5 Hz, 2′-H), 5.14 (1 H, dd, $J$ = 3, 10 Hz, 3′-H), 5.43 (1 H, d, $J$ = 2.5 Hz, 1′-H), 6.6 (br, CONH, exchanged with $D_2O$), 6.98 (1 H, d, $J$ = 9 Hz, Ar H), 7.2 (br, CONH, exchanged with $D_2O$), and 7.64 (1 H, d, $J$ = 9 Hz, Ar H).

**Acknowledgment.** We would like to thank the Analytical Research Department for the elemental analyses and the spectroscopic data.

# Exploratory, Mechanistic, and Synthetic Aspects of Silylarene–Iminium Salt SET Photochemistry. Studies of Diradical Cyclization Processes and Applications to Protoberberine Alkaloid Synthesis

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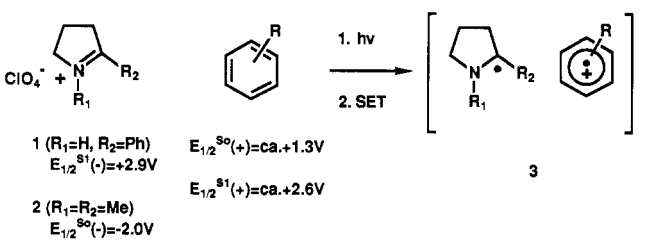
*Received April 29, 1988*

The photochemistry of a number of 2- and 1-(*o*-((trimethylsilyl)methyl)benzyl)-substituted 3,4-dihydroisoquinolinium perchlorates has been studied as part of efforts to probe the application of diradical cyclization methodologies to protoberberine and spirobenzyl isoquinoline alkaloid synthesis. Routes for preparation of the 2-(silylxylyl)-3,4-dihydroisoquinolinium salts have been developed based upon silver perchlorate induced, N-alkylation reactions between appropriate 3,4-dihydroisoquinolines and *o*-((trimethylsilyl)methyl)benzyl halides. Irradiation of these salts leads to efficient production of cyclization products having the tetracyclic protoberberine skeleton via pathways involving sequential single-electron transfer–desilylation and diradical coupling. This strategy has been employed to synthesize two representative protoberberines, xylopinine and stylopine, both of which contain alkoxy substitution patterns in the aromatic A and D rings characteristic of members of this alkaloid family. Studies of 1-(silylxylyl)-3,4-dihydroisoquinolinium perchlorate photochemistry have demonstrated that cyclization of the diradical intermediate, formed by sequential single-electron transfer–desilylation pathways, is competitive with a 1,4-H-shift process. The latter route leads to eventual production of desilylated dihydroisoquinolinium salts. The operation of this reaction pathway has been probed by deuterium-labeling methods. Finally, the viability of dipolar cyclization routes, initiated by fluoride-induced desilylation of the 1-(silylxylyl)-3,4-dihydroisoquinolinium perchlorates, has been investigated. Protoberberines are produced in these processes. However, the cyclization yields are lower than those in the photoinduced reactions owing to competitive formation of reduced tetrahydroisoquinolines and dihydroisoquinolones.

## Introduction

Single-electron transfer (SET) in the excited states of donor (D)–acceptor (A) systems is a process that has attracted increasing attention in recent years owing to several interesting features of this chemistry.[1] Perhaps the most important aspect of this process for those who are seeking to develop new reactions is that excited-state SET in A–D pairs occurs with predictable rates[2] and that it results in the generation of ion radical pairs (intermolecular) or ion diradicals (intramolecular).[3] In general, the rate constants for SET are known to approach those of diffusion (ca. 1 × $10^{10}$ $M^{-1}$ $s^{-1}$) when the free energy for SET ($\Delta G_{SET}$) is negative.[2] Importantly, $\Delta G_{SET}$ can be readily calculated on the basis of oxidation and reduction potentials of the respective donor and acceptor and the energy of the par-

**Scheme I**

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