117523-53-2; 19·oxalate, 118142-59-9; 20, 117523-72-5; 20·oxalate, 118142-60-2; 21, 117523-73-6; 21·oxalate, 118142-61-3; 22, 117523-62-3; 22·oxalate, 118142-62-4; 23, 117523-63-4; 23·oxalate, 118142-63-5; 24, 117523-48-5; 24·oxalate, 118142-64-6; 25, 117523-64-5; 25·oxalate, 118142-65-7; 26, 117523-65-6; 26·oxalate, 118142-66-8; 27, 117624-38-1; 27·oxalate, 118142-67-9; 28, 117523-45-2; 28·oxalate, 118142-68-0; 29, 117523-66-7; 29·oxalate, 118142-69-1; 30, 117523-52-1; 30·oxalate, 118142-70-4; 31, 117523-67-8; 31·oxalate, 118142-71-5; 32, 117523-47-4; 32·oxalate, 118142-72-6; 33, 117523-68-9; 33·oxalate, 118142-73-7; 34, 117523-69-0; 34·oxalate, 118142-74-8; 35, 117523-50-9; 35·oxalate, 118142-75-9; 36, 117523-70-3; 36·oxalate, 118142-76-0; 37, 117523-71-4; 37·oxalate, 118142-77-1; 38, 117523-51-0; 38·oxalate, 118170-20-0; 39, 117523-74-7; 39·oxalate, 118142-78-2; 40, 117523-75-8; 40·oxalate, 118142-79-3; 41, 117523-76-9; 41·oxalate, 118142-80-6; 42, 117523-77-0; 42·oxalate, 118142-81-7; 43, 117523-78-1; 43·oxalate, 118142-82-8; 44, 117523-79-2; 44·oxalate, 118142-83-9; 45, 117523-80-5; 45·oxalate, 118142-84-0; 46, 117523-81-6; 46·oxalate, 118170-21-1; 47, 117523-82-7; 47·oxalate, 118142-85-1; 48, 117523-83-8; 48·oxalate, 118142-86-2; 49, 117523-46-3; 49·oxalate, 118142-87-3; 50, 117523-84-9; 50·oxalate, 118142-88-4; 51a, 118142-37-3; 51b, 118142-38-4; 52, 51448-56-7; 53, 465-65-6; 1-piperidinylamine, 2213-43-6; 4-morpholinylamine, 4319-49-7; 3-pyridinylamine, 462-08-8; 4-pyridinylamine, 504-24-5; 2-chloro-3-pyridinylamine, 6298-19-7; 2-chloro-5-pyridinylamine, 5350-93-6; 5-indolylamine, 5192-03-0; 5-indazolylamine, 19335-11-6; 3-quinolinylamine, 580-17-6; 2,1,3-benzothiadiazol-4-ylamine, 767-64-6; 2-pyrazinyl chloride, 14508-49-7; 2-chloro-4-pyrimidinyl chloride, 7461-50-9; 4-chloro-6-pyrimidinyl chloride, 5305-59-9; 2-pyrimidinyl chloride, 109-12-6; 2-benzothiazolyl chloride, 136-95-8; 2-benzoxazolyl chloride, 4570-41-6; 2-chloro-4-methylpyridine, 3678-62-4; 3-furoic acid, 488-93-7; 2-furoyl chloride, 527-69-5; 3-furoyl chloride, 26214-65-3; methoxymethyl acid chloride, 38870-89-2.

Studies on Prodrugs. 11. Synthesis and Antimicrobial Activity of *N*-[(4-Methyl-5-methylene-2-oxo-1,3-dioxolan-4-yl)oxy]norfloxacin

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Received May 2, 1988

The chemical oxidation of *N*-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]norfloxacin (2) was carried out to afford *N*-[(4-methyl-5-methylene-2-oxo-1,3-dioxolan-4-yl)oxy]norfloxacin (4). In vitro, 4 exhibited lower activity than that of norfloxacin (NFLX, 1) for both Gram-positive and Gram-negative bacteria. However, in vivo the activity of 4 was higher than that of NFLX. Bioavailability studies in mice showed that 4 liberated a higher concentration of NFLX in plasma than NFLX itself when administered orally. From these data, 4 obtained by the chemical oxidation of 2 functioned as a prodrug of NFLX as well as did 2. The mechanism of the formation of 4 is interpreted in terms of [2,3]-sigmatropic rearrangement.

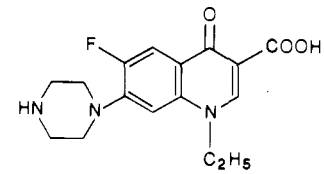
Norfloxacin (NFLX, 1) is a new quinolone which has been shown to be a clinically effective antibacterial agent.[1] On the basis of pharmacokinetic studies in animals,[2] we have applied the prodrug technique to NFLX.[3-5] Recently, we have reported on the N-masked NFLX prodrug 2[3] which is transformed into 1 in vivo by the cleavage of the C–N bond.

Various biological N-dealkylations are oxidatively catalyzed by cytochrome P-450.[6] For the purpose of understanding the metabolic mechanism of conversion of 2 to 1 in vivo, we first decided to examine chemical models for the oxidation of 2.

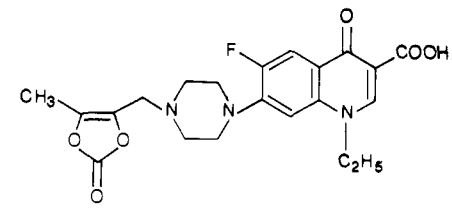
We observed that the nonbiological oxidation of N-masked NFLX (2) with *m*-chloroperbenzoic acid (MCPBA) at low temperatures (<5 °C) afforded allylic *N*-oxide 3. This allylic *N*-oxide (3) rearranged at approximately 50 °C to give the corresponding *O*-allylhydroxylamine 4.

This paper describes the synthesis and the mechanism of the formation of 4 and its antibacterial activity both in vitro and in vivo.

Chart I



1



2

Chemistry

N-[(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl]norfloxacin (2) was synthesized according to our previous report.[3]

The oxidation of 2 with MCPBA in dry chloroform at 50 °C under an argon atmosphere afforded 4 (Scheme I). This new compound was characterized by NMR analyses (^{1}H, ^{13}C), IR spectroscopy, and mass spectrometry. In particular, the methyl protons of the 2-oxo-1,3-dioxolane moiety in 4 were observed at higher field (δ 1.76) than the methyl protons of the 2-oxo-1,3-dioxole in 2 (δ 2.15). In addition, two doublets due to the exocyclic methylene of 4 were recorded at 4.95 and 5.10 ppm (J = 4.0 Hz). The IR spectra of 2 and 4 showed characteristic five-membered ring carbonyl bands at 1815 and 1845 cm^{-1}, respectively. The ^{13}C NMR spectrum of 4 was completely consistent with the proposed structure, the most pertinent points of

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(4) Kondo, H.; Sakamoto, F.; Kodera, Y.; Tsukamoto, G. *J. Med. Chem.* 1986, *29*, 2020.
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(6) (a) Guengerich, F. P.; Macdonald, T. L. *Acc. Chem. Res.* 1984, *17*, 9. (b) Ullrich, V. *Top. Curr. Chem.* 1979, *83*, 67. (c) White, R. E.; Coon, M. J. *Annu. Rev. Biochem.* 1980, *49*, 3154.

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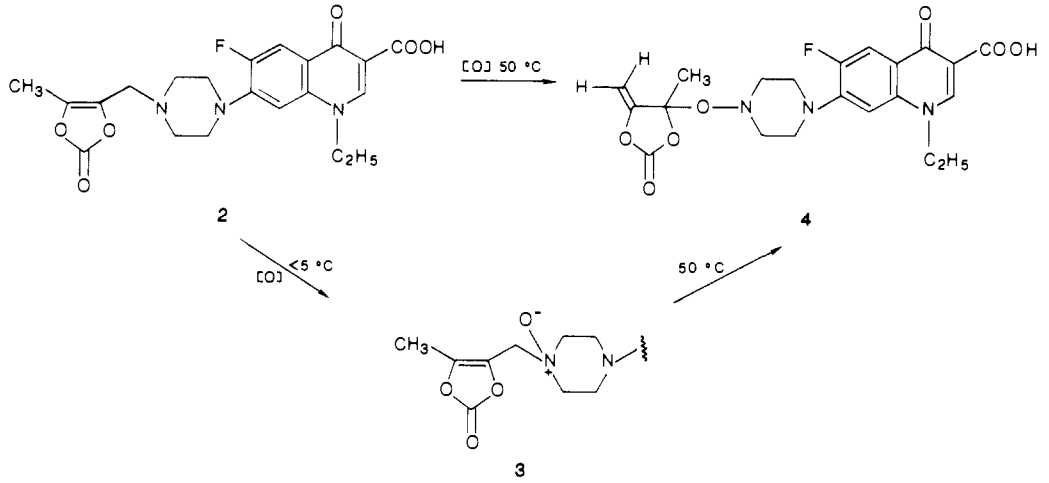
Scheme I



Scheme II

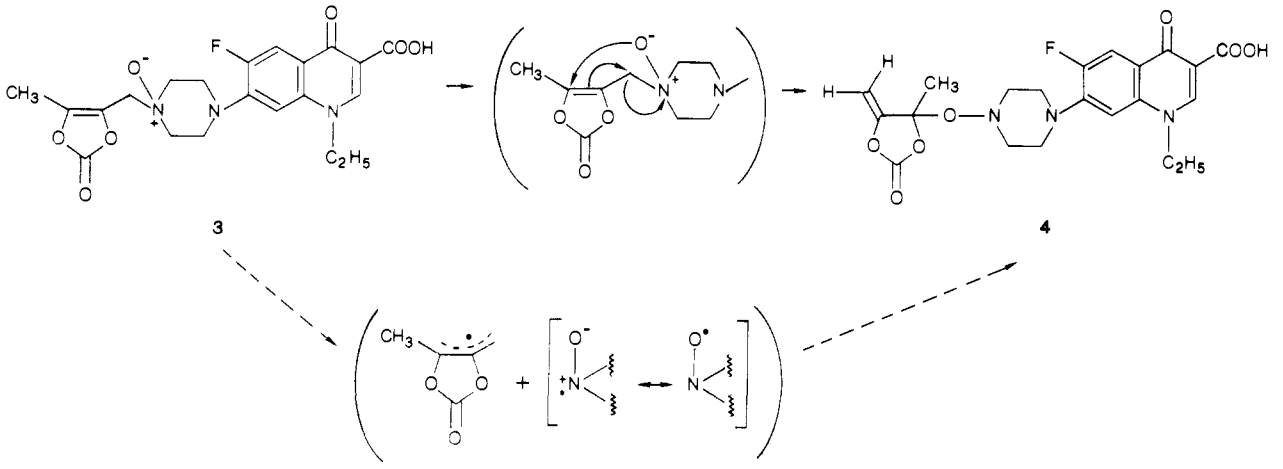
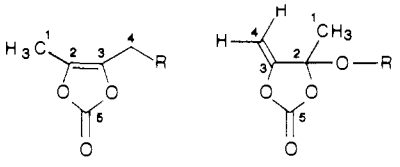
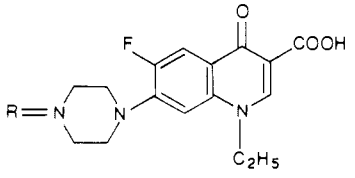


Table I. ^{13}C NMR Spectral Data[a] of Compounds 2 and 4





no.	C_1	C_2	C_3	C_4	C_5
2	9.6	134.8	140.7	49.0	154.4
4	21.6	108.7	149.9	89.1	155.3

[a] All spectra were determined in DMSO-d_6 and the shifts are given in parts per million from TMS as an internal standard.

which were the large upfield shift of C_2 and downfield shifts of C_1, C_3, C_4 of 4 as compared to the signals in 2 (Table I).

When the oxidation of 2 with MCPBA at low temperature (<5 °C) was carried out according to the method of Craig,[7] an *N*-oxide 3 was isolated. The mass spectra clearly showed that 3 contained a *N*-oxide moiety.[8] The *N*-oxide 3, thus prepared, was heated to 50 °C where it readily rearranged to 4 (Scheme I).

Table II. Yields of 4 by the Rearrangement of *N*-Oxide 3 in the Presence of Varying Concentrations of 1-Butanethiol

ratio (1-butanethiol/3)	yield,[a,b] %	
	3	4
0	-	97.5
1	-	93
1.5	-	87
2	-	82
5	-	79.6

[a] Isolation yield. [b] Reaction condition: see the Experimental Section.

Thermal conversion of a tertiary amine oxide to a substituted hydroxylamine is known as the Meisenheimer rearrangement.[9] There have been some reports on the mechanism of the rearrangement of allylic *N*-oxides, and both a nonradical route[10] and a radical process[11] have been

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Table III. Antibacterial Activity of Compounds 1, 2, and 4

compd	microorganism[a]							ED_{50}[b] (*E. coli* KC-14), mg/kg oral
	Sa	Bs	Ec	Kp	Sm	Pv	Pa	
1	0.19	0.19	0.10	0.05	0.19	0.05	0.39	3.13 (1.87–5.31)
2	0.39	0.19	0.20	0.10	0.39	0.10	1.56	1.93 (1.56–2.40)
4	0.78	0.19	1.56	0.10	3.12	0.05	6.25	1.31 (1.02–1.70)

[a] Microorganism: Sa, *Staphylococcus aureus* FDA207PJC-1; Bs, *Bacillus subtilis* ATCC6633; Ec, *Escherichia coli* KC-14; Kp, *Klebsiella pneumoniae* PCI602; Sm, *Serratia marcescens* IAM 1184; Pv, *Proteus vulgaris* OX-19; Pa, *Pseudomonas aeruginosa* E-2. [b] 95% confidence limit.

Table IV. Serum Concentrations of 1, 2, and 4 after Oral Administration in Mice (50 mg/kg)[a]

compd		time after administration, h						AUC[b]
		0.25	0.5	1.0	2.0	3.0	4.0	
1	1	0.64	1.48	0.66	0.26	0.07	0.21	1.8
2	1	3.95	3.50	2.44	0.90	0.47	0.81	5.7
	2	nd[c]	nd	nd	nd	nd	nd	
4	1	1.75	2.58	2.54	1.04	0.71	0.68	5.4
	4	nd	nd	nd	nd	nd	nd	

[a] A dose equivalent to 50 mg/kg of NFLX. [b] In μg/mL per h. [c] Not detected.

Table V. Oral Efficacy on Systemic Infections of 1, 2, and 4

compd	ED_{50}, mg/kg, po (95% confidence limit)				LD_{50},[e] mg/kg, po
	Sa[a]	Ec[b]	Pa[c]	Ec[d]	
1	225 (100–503)	3.15 (1.87–5.31)	77.1 (43.9–135)	NT[f]	>4000
2	93.3 (60.2–145)	1.93 (1.56–2.40)	20.3 (15.4–26.8)	6.16 (4.67–8.12)	>4000
4	70.7 (47.8–105)	1.31 (1.02–1.70)	17.7 (11.9–26.2)	2.68 (1.91–3.76)	>4000

[a] Sa, *Staphylococcus aureus* IID803. [b] Ec, *Escherichia coli* KC-14. [c] Pa, *Pseudomonas aeruginosa* E-2. [d] On systemic infection due to *E. coli* KC-14 in rat. [e] A suspension of each compound in 0.5% CMC was administered, and the number of dead animals within 1 week was counted, the LD_{50} values being calculated by the method of weil. [f] NT = not tested.

postulated. To clarify the mechanism of the formation of **4**, the thermolysis of **3** was examined in the presence of a strong radical scavenger. When a 1 mM solution of **3** in dry chloroform was heated at 50 °C in the presence of an equimolar amount of 1-butanethiol, **4** was obtained in 93% yield in a short time. The thermolysis of **3** was also tried to investigate the effect of the concentration of 1-butanethiol on the yield of **4**. As shown in Table II, the formation of **4** was not much decreased by much higher ratios of 1-butanethiol. If this rearrangement were a radical process, very little **4** would be formed after the addition of 1-butanethiol. The mechanism of the formation of **4** is therefore suggested to be a [2,3]-sigmatropic rearrangement as shown in Scheme II.

Biological Results and Discussion

Compounds **1**, **2**, and **4** were tested for in vitro antibacterial activity against Gram-positive and Gram-negative bacteria. The available results are summarized in Table III. N-Masked NFLXs **2** and **4** showed lower activity against all bacteria than NFLX.

Compounds **1**, **2**, and **4** were then tested, with oral administration, on systemic infection due to *Escherichia coli* KC-14 in mice. Both **2** and **4** exhibited higher activity than that of NFLX. The enhancement of the activity of **2** in vivo was explicable, as stated in our previous report,[3] by an increase in oral absorption and the liberation of a high concentration of NFLX in vivo. A similar explanation was considered to account for the in vivo activity of **4**. To clarify this point, blood levels and biological transformation of **4** were studied. First, the stability of **2** and **4** at pH 6.8 and 37 °C was determined by high-performance liquid chromatography (HPLC), which indicated half-lives of 8.5 and 7.0 h, respectively. The serum specimens were collected at regular time intervals, 0.25, 0.5, 1.0, 2.0, 3.0, and 4.0 h, and the concentrations of compounds **1**, **2**, and **4** in serum were measured by HPLC (Table IV). As was expected, **4** liberated a high concentration of NFLX in vivo. Both **2** and **4** were undetected in serum. Serum levels and areas under the curve (AUC) of liberated NFLX after oral administration of **4** were higher than those of NFLX itself. Indeed the AUC of **4** was 3.0 times more than that of NFLX itself and was comparable to that of **2**. This corresponds to the in vivo activity outlined in Table V. From these results, compound **4**, which was the rearrangement product obtained by the chemical oxidation of **2**, functioned as a prodrug of NFLX as well as did **2**.

It is well known that dealkylation of an alkylamine is initiated by oxidation of the α-carbon atom to the nitrogen atom or the nitrogen atom itself.[12] However, the mechanism for conversion of **2** to NFLX has not yet been ascertained. We observed that the nonbiological oxidation of the N-masked NFLX **2** with MCPBA at low temperature (<5 °C) gives allylic *N*-oxide **3** and **3** rearranges at approximately 50 °C to give the corresponding *O*-allylhydroxylamine **4**, which has not been seen in the biological metabolism of **2** as shown in Table IV. The metabolic mechanism of conversion of **4** to NFLX in vivo has not been elucidated in the present study.

In summary, the rearrangement of **2** to **4** is a useful observation in the context of the application of **2** as a prodrug.

Experimental Section

Melting points were determined on a Yamato capillary melting point apparatus, Model MP-21, and all melting points are uncorrected. ^1H NMR spectra were determined at 100 MHz on a Nihon Denshi PS-100 NMR spectrometer using TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 75.47 MHz. IR spectra were recorded

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with a Hitachi IR 270-50 machine. Mass spectra were measured with a Hitachi M-80B mass spectrometer, a 0101 control system, and a M8061 SIMS apparatus. All compounds were analyzed for C, H, N, and values were within ±0.4% of theoretical values.

In Vitro Antibacterial Activity. According to the method of Goto et al.,[13] the MICs of compounds tested in this study were determined by the serial 2-fold dilution technique, using Mueller-Hinton agar. The inoculum size was approximately 10^6 cfu/mL. The concentrations of compounds in the plates ranged from 0.006 to 100 μg/mL. MIC was defined as the lowest concentration of a compound that prevented visible growth of bacteria after incubation at 37 °C for 18 h.

In Vivo Efficacy on Systemic Infections. In vivo assays were carried out according to the general method already published.[14] Groups of five male ddY mice (20 ± 2 g) were infected with bacteria. A 0.5-mL volume of a bacterial dilution, corresponding to 10 or 100 times the 50% lethal dose, was inoculated intraperitoneally. The test compounds were suspended in 0.5% sodium (carboxymethyl)cellulose and administered orally at 1 h postinfection. Survival rates were evaluated after 1 week.

Oral Absorbability Test. The serum concentration of NFLX in mice treated with compounds **2**, 4, and NFLX itself was determined by HPLC. Test compounds were suspended in 0.5% sodium (carboxymethyl)cellulose and administered orally at a dose of 50 mg/kg. After 0.25, 0.5, 1.0, 2.0, 3.0, and 4.0 h, the mice were killed by bleeding. The collected blood was centrifuged, and the test serum was adjusted. A HPLC machine was equipped with a Model 6000A pump, a Model U6K universal injector, a Shimadzu Model SPD-2A spectrophotometric detector (at 280 nm), and a YMC A-312 column. The mobile phase consisted of 5% acetic acid–methanol (80:20 v/v), and a flow rate was 2.0 mL/min.

(A) *N*-[(4-Methyl-5-methylene-2-oxo-1,3-dioxolan-4-yl)oxy]norfloxacin (4). To a solution of *N*-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]norfloxacin (**2**)[3] (1.0 g, 2.3 mmol) in $CHCl_3$ was added MCPBA (400 mg, 2.3 mmol) in small portions, and the mixture was heated at 50 °C under an argon atmosphere for 10 min. After the mixture cooled, the solvent was removed under reduced pressure. The residue was washed with ether to give 4 (730 mg, 70%) as a white powder: mp 162–168 °C dec; IR (KBr) cm^{-1} 1845 (five-membered carbonyl); ^1H NMR (DMSO-d_6) δ 1.42 (3 H, t, J = 7.0 Hz), 1.76 (3 H, s), 2.80–3.90 (8 H, m), 4.60 (2 H, q, J = 7.0 Hz), 4.98 (1 H, d, J = 4.0 Hz), 5.10 (1 H, d, J = 4.0 Hz), 7.18 (1 H, d, J = 8.0 Hz), 7.84 (1 H, d, J = 14 Hz), 8.86 (1 H, s), 15.06 (1 H, s); MS, m/e 448 (MH^+, 30), 336 (21), 317 (26), 201 (81), 130 (83), 106 (100). Anal. ($C_{21}H_{22}N_3O_7F$) C, H, N.

Preparation of the *N*-Oxide of Compound 2 (3). According to the method of Craig et al.,[7] to an ice-cooled, stirred solution of *N*-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]norfloxacin (**2**)[3] (500 mg, 1.15 mmol) in $CHCl_3$ was added MCPBA (200 mg, 1.15 mmol) in small portions at 0–5 °C. The mixture was stirred for 2.5 h at 0–5 °C and the resulting precipitate was separated. The crude solid was purified by washing with cold $CHCl_3$ to give **3** (460 mg, 88%) as a white powder: mp 138–144 °C dec; ^1H NMR (DMSO-d_6) δ 1.42 (3 H, t, J = 7.2 Hz), 2.13 (3 H, s), 3.5–3.96 (8 H, m), 4.57 (2 H, q, J = 7.2 Hz), 4.62 (2 H, s), 7.30 (1 H, d, J = 7.0 Hz), 8.0 (1 H, d, J = 13 Hz), 8.98 (1 H, s); MS m/e 448 (MH^+, 27), 432 (MH − 16, 10), 414 (25), 335 (44), 318 (72), 245 (80), 130 (100).

Procedure for the Rearrangement of the *N*-Oxide. A suspension of the amine oxide **3** (400 mg) in dry $CHCl_3$ was heated at 50 °C under an argon atmosphere for 20 min. After the mixture cooled, the solvent was removed under reduced pressure. The residue was washed with ether to give 4 (390 mg, 97.5%) as a white powder.

General Procedure for the Thermolysis of *N*-Oxide in the Presence of 1-Butanethiol. A suspension of the amine oxide and varying concentrations of 1-butanethiol in dry $CHCl_3$ was stirred at 5 °C for 5 min, followed by heating at 50 °C for 20 min. After the mixture cooled, the solvent was removed under reduced pressure, and the residue was washed with ether. The results are shown in Table II.

Registry No. 1, 70458-96-7; **2**, 85195-76-2; **3**, 118376-55-9; 4, 117458-86-3; 1-butanethiol, 109-79-5.

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In Vitro Metabolic Transformations of Vinblastine: Oxidations Catalyzed by Peroxidase

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Vinblastine is converted to a single major metabolite during in vitro enzymatic oxidations catalyzed by horseradish peroxidase in the presence of hydrogen peroxide. Preparative-scale enzyme incubations permitted the isolation of sufficient amount of the transformation product for complete structural identification and biological evaluation. The metabolite was identified as catharinine (also known as vinamidine) by ^1H and ^{13}C NMR and by mass spectrometry. Incubations conducted in $H_2{}^{18}O$-enriched water gave catharinine in which a single atom of ^{18}O was incorporated into the metabolite structure. The labeling experiment provided evidence for an unusual ring-fission pathway by which peroxidase transforms vinblastine to catharinine. Catharinine is 77 times less active than vinblastine when tested in vitro against the human T-cell leukemic cell line (CRFF-CEM).

The dimeric Vinca alkaloids vinblastine (VLB) (1) and vincristine (VCR) have been used extensively in the treatment of human cancers for nearly three decades.[1] Structural analogues vindesine,[2] vizolidine,[3] and navelbine[4] have been developed in the hope of reducing the dose-limiting neurotoxicities and myelosuppressive effects exhibited by VCR[5,6] and VLB,[2] respectively. Clinically observed differences in neurotoxicities among Vinca alkaloids may be due to differences in compartmentalization as the drugs are distributed after administration, differences in

* To whom requests for reprints should be addressed.

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