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Crystal and Molecular Structure of Quinidine

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Received January 25, 1978, from the **Chemistry Department and Computer Science Center, University of Maryland, College Park, MD 20742,* and the ‡*Division of Drug Chemistry, Food and Drug Administration, Washington, DC 20204.* Accepted for publication April 27, 1978.

Abstract □ The structure of the free base quinidine was determined by single crystal X-ray diffraction. Quinidine crystallizes from absolute ethanol as the ethanolate, with the molecular formula $C_{20}H_{24}N_2O_2 \cdot C_2H_6O$ and molar mass 370.491 units. It crystallizes in the orthorhombic space group $P2_12_12_1$ with unit cell dimensions a = 1321.1(3), b = 989.3(2), and c = 1651.5(3) pm. The measured density was 1.15 g/cm^3; the density calculated for $Z = 4$ was 1.164 g/cm^3. The diffraction data were collected by using MoKα radiation. A final R value of 0.055 was obtained. Evidence for intermolecular hydrogen bonding was found. The crystal analysis is in agreement with the structure proposed by other methods. The absolute configuration is based on the published structure of 10-bromo-10,11-dihydroepiquinidine.

Keyphrases □ Quinidine—crystal and molecular structure, X-ray diffraction determination □ X-ray diffraction—determination, crystal and molecular structure of quinidine □ Cardiac depressants—quinidine, crystal and molecular structure determined by X-ray diffraction

The drug substance quinidine (I) contains several naturally occurring impurities (1). Commercial samples of I contain 3–22.1% of 10,11-dihydroquinidine (II). Compounds I and II are both potent antiarrhythmic agents, II being significantly more effective than I (2). Although structures for I and II have been determined by other techniques (3–7), no absolute configuration studies by single crystal X-ray diffraction have been reported. Because of the therapeutic significance of I and II, X-ray diffraction studies were undertaken.

One crystal study (8) was reported for 10-bromo-10,11-dihydroepiquinidine (III), a derivative of 10,11-dihydroepiquinidine (IV). Compounds II and IV differ only in the configuration about the carbon bearing the hydroxyl group. In the study of III, evidence was found for intramolecular hydrogen bonding between the hydroxyl group and the nitrogen in the quinuclidine ring. From models of II and IV, it was concluded that intramolecular hydrogen bonding in II and I is less favorable than in III and IV because of steric interactions of the quinoline and

Table I—Crystal Structure Analysis of Quinidine Ethanolate ($C_{20}H_{24}N_2O_2 \cdot C_2H_6O$)

Property	Analysis
Unit cell dimensions	a = 1321.1(3), b = 989.3(2), c = 1651.5(3) pm
Space group	$P2_12_12_1$
Density, g/cm^3	1.15 (measured), 1.164 ($Z = 4$) (calculated)
Radiation	MoKα
Number of observations	Total number of reflections = 1404, number of reflections less than 3σ above background = 586
Scattering factors	C,N,O (Ref. 11); H (Ref. 12)
Method of solution	Direct methods for partial structure, translation function, Fourier transform to complete
Method of refinement	Full-matrix least-squares
Weights	Unit
Programs used	XRAY76
Final R value ($\Sigma \Delta F/\Sigma\|F_0\|$)	0.055
Final difference synthesis	No significant peaks
Atomic coordinates	See Table II
Bond lengths	See Fig. 1
Bond angles	See Fig. 2
Hydrogen bonds between	O-12–H-12- - -N-1 O-9–H-91- - -N-1′

Distance from	Distance, pm
O-12–N-1	281(1)
H-12–N-1	160(8)
O-9–N-1′	279(1)
H-91–N-1′	243(8)

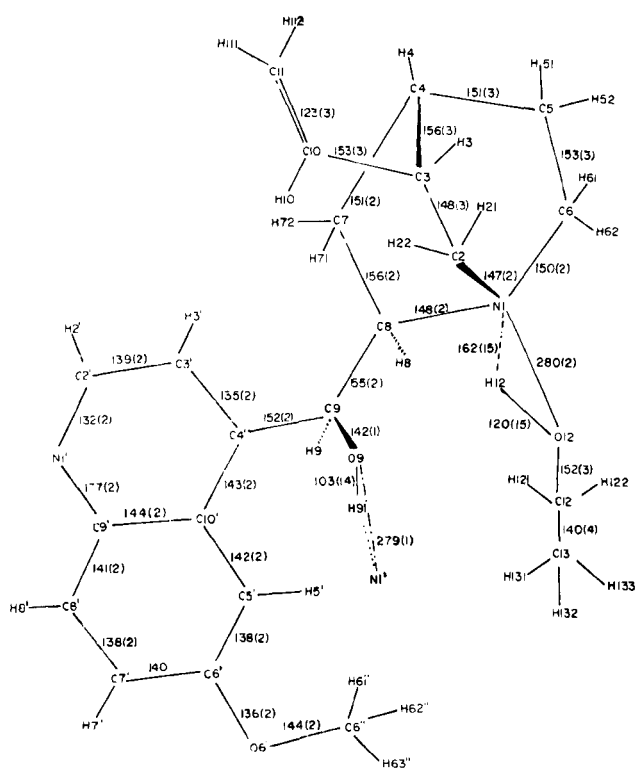

Figure 1—*Bond lengths (pm) for quinidine ethanolate.*

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Table II—Fractional Coordinates, Temperature Factors ($pm^2 \times 10^{-2}$), and Estimated Standard Deviations (in Parentheses)[a]

Atom	x	y	z	U_{11} or U	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C-6″	0.6924(12)	0.8118(15)	0.5846(11)	7.7(1.0)	5.7(0.9)	13.8(1.4)	−1.5(0.9)	−1.3(1.1)	1.6(1.0)
O-6′	0.6142(7)	0.8031(8)	0.5242(6)	7.5(0.7)	4.0(0.5)	10.2(0.7)	−1.5(0.5)	−0.3(0.6)	0.6(0.5)
N-1′	0.4388(8)	0.3084(12)	0.4433(7)	5.9(0.7)	5.6(0.7)	8.6(0.8)	−0.6(0.7)	−1.8(0.6)	−0.4(0.7)
C-2′	0.4765(11)	0.1882(14)	0.4714(9)	6.3(1.0)	4.9(0.9)	9.1(1.1)	−1.5(0.8)	−1.4(0.9)	−0.6(0.9)
C-3′	0.5597(11)	0.1811(14)	0.5231(9)	5.6(0.9)	4.9(0.8)	8.5(1.0)	−0.2(0.8)	−1.0(0.8)	0.1(0.8)
C-4′	0.6078(9)	0.2966(12)	0.5479(7)	5.0(0.7)	4.4(0.8)	5.4(0.8)	0.3(0.7)	0.7(0.7)	−0.1(0.7)
C-5′	0.6194(8)	0.5536(12)	0.5375(7)	3.5(0.8)	4.5(0.7)	6.6(0.9)	−0.2(0.7)	0.3(0.7)	−0.2(0.7)
C-6′	0.5791(10)	0.6741(14)	0.5071(8)	4.4(0.9)	6.2(1.0)	7.4(0.9)	−1.0(0.7)	0.0(0.7)	0.5(0.8)
C-7′	0.4964(11)	0.6735(14)	0.4544(9)	6.1(0.9)	5.4(0.9)	8.4(1.1)	0.8(0.8)	0.7(0.9)	1.4(0.8)
C-3′	0.4505(10)	0.5513(15)	0.4328(9)	5.2(0.8)	6.9(0.9)	6.3(0.9)	−0.1(0.8)	−0.9(0.7)	1.4(0.8)
C-9′	0.4862(10)	0.4254(13)	0.4645(8)	5.4(0.9)	5.5(0.8)	6.4(0.9)	0.3(0.7)	−0.2(0.7)	0.9(0.8)
C-10′	0.5735(10)	0.4225(12)	0.5169(8)	5.2(0.9)	4.7(0.8)	5.6(0.8)	−0.4(0.7)	0.0(0.7)	0.5(0.7)
C-9	0.6939(9)	0.2917(11)	0.6086(7)	4.5(0.7)	4.0(0.7)	6.3(0.8)	0.5(0.6)	−0.2(0.7)	−0.3(0.7)
O-9	0.7394(6)	0.1593(7)	0.6095(5)	5.2(0.5)	4.6(0.5)	7.9(0.6)	0.2(0.4)	−0.2(0.5)	0.4(0.5)
N-1	0.7290(9)	0.3725(11)	0.7506(6)	6.4(0.7)	6.9(0.7)	6.7(0.8)	0.0(0.6)	−0.5(0.7)	−0.4(0.6)
C-2	0.7806(13)	0.2542(18)	0.7875(10)	9.3(1.2)	10.9(1.3)	7.8(1.1)	2.8(1.1)	−1.7(1.0)	−0.5(1.0)
C-3	0.7126(18)	0.1678(19)	0.8374(10)	15.2(1.9)	9.0(1.3)	7.3(1.2)	2.6(1.4)	−0.3(1.2)	1.7(1.0)
C-4	0.6024(16)	0.2182(19)	0.8220(10)	15.0(1.8)	8.9(1.3)	9.0(1.3)	−1.9(1.4)	6.2(1.3)	−0.9(1.1)
C-5	0.5907(16)	0.3645(19)	0.8525(10)	13.3(1.6)	11.1(1.4)	7.9(1.1)	−0.5(1.3)	2.7(1.2)	−1.0(1.0)
C-6	0.6772(15)	0.4503(16)	0.8172(10)	12.0(1.4)	7.3(1.0)	8.7(1.2)	−0.2(1.1)	0.5(1.1)	−2.4(1.0)
C-7	0.5828(11)	0.2172(15)	0.7316(8)	8.0(1.1)	7.2(1.0)	7.1(0.9)	−1.6(0.9)	2.0(0.9)	0.2(0.9)
C-8	0.6500(9)	0.3317(13)	0.6921(8)	4.6(0.8)	5.1(0.7)	7.2(0.8)	0.5(0.7)	−0.5(0.7)	0.4(0.7)
C-10	0.7273(31)	0.0125(20)	0.8252(13)	40.0(4.8)[b]	8.4(1.4)	9.6(1.5)	3.3(2.2)	1.2(2.5)	2.6(1.2)
C-11	0.7034(32)	−0.0733(23)	0.8766(13)	50.1(5.6)[b]	9.7(1.5)	10.8(1.8)	−0.7(2.7)	8.6(2.8)	1.3(1.4)
C-12	0.9439(18)	0.5832(23)	0.7222(16)	11.9(1.7)	9.7(1.5)	18.5(2.2)	−1.2(1.4)	0.7(1.7)	3.1(1.7)
C-13	0.9077(25)	0.7034(31)	0.7587(17)	22.1(2.9)	16.0(2.2)	18.4(2.6)	−4.3(2.5)	−2.3(2.4)	6.4(2.3)
O-12	0.8572(9)	0.5497(13)	0.6646(7)	11.8(1.0)	12.2(1.0)	10.5(0.8)	−4.7(0.9)	−2.2(0.8)	0.5(0.8)
H-2′	0.44[c]	0.11	0.46	9.5[d]					
H-3′	0.59	0.09	0.54						
H-5′	0.68	0.55	0.57						
H-7′	0.47	0.76	0.44						
H-8′	0.38	0.55	0.40						
H-62″	0.67	0.77	0.64						
H-63″	0.71	0.91	0.60						
H-61″	0.75	0.76	0.56						
H-9	0.74	0.36	0.59						
H-91	0.81	0.17	0.59						
H-21	0.84	0.28	0.83						
H-22	0.80	0.20	0.74						
H-3	0.72	0.18	0.89						
H-4	0.55	0.16	0.84						
H-51	0.59	0.37	0.92						
H-52	0.53	0.40	0.83						
H-61	0.73	0.47	0.85						
H-62	0.65	0.54	0.80						
H-71	0.59	0.13	0.70						
H-72	0.51	0.24	0.71						
H-8	0.60	0.41	0.68						
H-10	0.74	0.00	0.79						
H-111	0.70	−0.17	0.86						
H-112	0.70	−0.05	0.92						
H-12	0.81	0.46	0.70						
H-121	1.00	0.60	0.68						
H-122	0.96	0.50	0.76						
H-131	0.85	0.67	0.79						
H-132	0.86	0.78	0.72						
H-133	0.96	0.73	0.79						

[a] The form of the anisotropic thermal parameters is $\exp[-2\pi^2(U_{11}h^2a^{*2} + \ldots + 2U_{23}klb^*c^*)]$. [b] There is evidence for disorder in the C-10–C-11 side chain. [c] All hydrogen values are ±1 in the last figure. [d] No attempt was made to refine the hydrogen thermal parameters. All were set to 9.5.

quinuclidine rings in II. These same interactions occur in I.

The crystal structure analysis for I is in agreement with the structure proposed by other methods. The structure of II was not determined since it would be a duplication of the work for I.

EXPERIMENTAL

Because of impurities (1), the commercial samples of I could not be used as received. Compound I was prepared free of natural II by the method of Smith *et al.* (1). Mercuric acetate was added to I; II was separated from this addition product, and I was regenerated by removal of the mercuric acetate. Compound I was recrystallized from absolute ethanol, mp 174°, as determined by differential thermal analysis[1] [lit. (1) mp 174–175°].

The crystal used for X-ray analysis was grown in 95% ethanol. Crystals similarly grown were heated in a thermal balance[2], and the weight loss of the crystal at 110° corresponded to a loss of one molecule of ethanol for each molecule of quinidine. The IR spectrum[3] bands at 910 and 990 cm^{-1} for the CH=CH (9) are in agreement with the proposed structure. For other tests performed, see Refs. 1 and 10.

Compounds I and II undergo photodecomposition under laboratory light (1). However, they were stable when kept refrigerated and in the dark. After standing for several days, the crystals of both I and II crumbled to powder, probably because of the loss of the ethanol of crystallization.

The X-ray crystallographic analysis[4,5] of I is summarized in Tables I and II. The bond lengths and angles are shown in Figs. 1 and 2. A view of the molecule and of a hydrogen-bonded fragment of a symmetrically

[1] DuPont thermal analyzer model 990.

[2] DuPont thermal gravimetric analyzer model 951.
[3] Perkin-Elmer model 621 recording IR spectrophotometer.
[4] Picker automated FACS I diffractometer.
[5] XRAY76 is part of the XRAY system of crystallographic programs, Technical Report TR-446 Computer Science Center, University of Maryland, Mar. 1976.

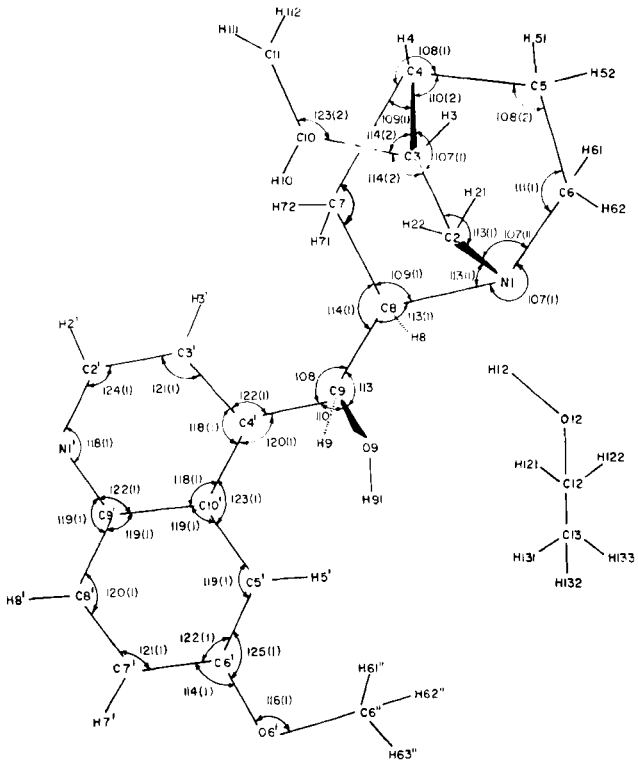

Figure 2—*Bond angles for quinidine ethanolate.*

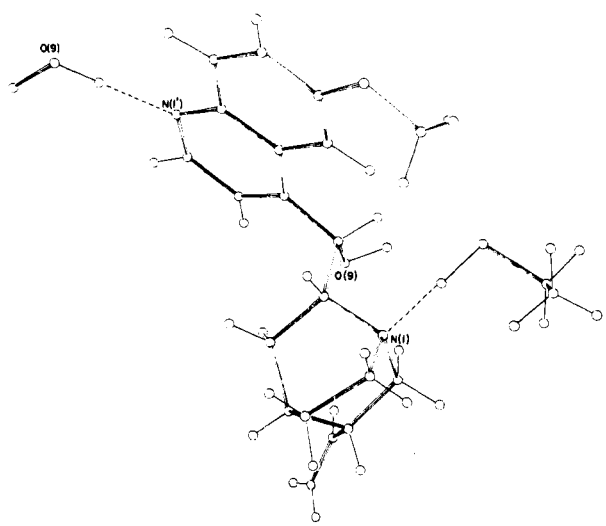

Figure 3—*Three-dimensional view of quinidine and ethanol molecules and a hydrogen-bonded fragment of a symmetrically related molecule.*

related molecule at $x - \frac{1}{2}, \frac{1}{2} - y$, and $-z$ is shown in Fig. 3. This plot was produced by ORTEP[6].

All other calculations were carried out by using the XRAY76 system[5]. The methods of solution and refinement were routine (Table I). The methods used in the calculations were found in a standard text on crystallographic analysis (13). The structure factor lists from which the values in Table II were obtained are available[7].

RESULTS AND DISCUSSION

Griffiths (14) previously reported the space group and cell dimensions

[6] See C. K. Johnson, "ORTEP," Report ORNL 5138 (3rd Rev. of ORNL 3794), UC-4-Chemistry, Oak Ridge National Laboratory (ORNL), Oak Ridge, Tenn.

[7] The structure factor lists are deposited with the Division of Drug Chemistry, Food and Drug Administration, Washington, DC 20204, and are available on request to the authors.

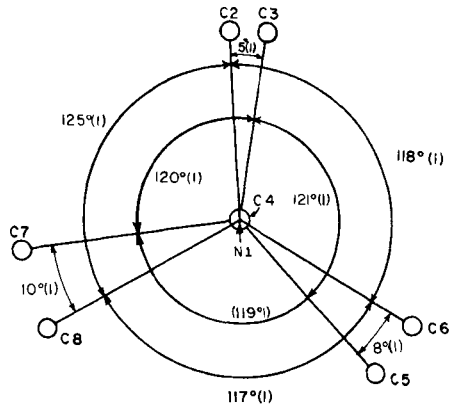

Figure 4—*Projection showing dihedral angles of the quinuclidine ring with special reference to the two bridgehead atoms, N-6 and C-4.*

of quinidine ethanolate to be $P2_12_12_1$ with a = 1310, b = 1660, and c = 960 pm. He reported a density of 1.18 g/cm^3 for $Z = 4$ under the conditions used. No structure was reported. The present study confirmed the assigned space group and approximate cell dimensions. The absolute configuration of I reported here (Fig. 3) is based on the published configuration of III (8). The relative configurations of I and epiquinidine (V) were established by chemical means (4), and the preparation of III from V does not affect the configurations about any of the asymmetric atoms in V. The difference between I and V is the configuration around C-9, so that I should have the same configurations as III around N-1, C-3, C-4, and C-8 and the opposite configuration around C-9. The absolute configuration reported for III (8) is 1*S*,3*S*,4*S*,8*S*,9*S*,10*S*. Therefore, the configuration for I is 1*S*,3*S*,4*S*,8*S*,9*R*.

The crystal structure of III (8) revealed strong intramolecular hydrogen bonding between the hydroxyl group and N-1. In the hydrogen-bonded conformation of III, the quinoline and quinuclidine rings are directed away from each other so there is no steric interaction between the rings. If I were to assume an analogous conformation, there would be a very strong steric interaction between the two rings. Thus, I does not exhibit intramolecular hydrogen bonding but crystallizes as the ethanolate in which N-1 is hydrogen bonded to the hydroxyl group of the molecule of ethanol.

A projection showing the dihedral angles of the quinuclidine ring with special reference to the two bridgehead atoms (N-1 and C-4) is given in Fig. 4.

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GI Absorption of β-Lactam Antibiotics I: Kinetic Assessment of Competing Absorption and Degradation in GI Tract

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Abstract □ An equation was derived for the simultaneous assessment of rate constants for absorption and nonenzymatic degradation of unstable drugs in *in situ* absorption experiments. The equation was substantiated by using a variety of β-lactam antibiotics in the recirculation technique through the rat small intestine. Plots of the apparent first-order rate constant for the disappearance of the drug from the gut lumen *versus* the reciprocal of the volume of recirculating solution yielded a straight line with a slope equal to the intrinsic absorption rate constant and with an intercept equal to the nonenzymatic degradation rate constant in the GI lumen. The kinetic method for evaluation of the absorption rate constant also was developed for a more complex situation in the GI lumen involving absorption, nonenzymatic degradation, and enzymatic metabolism. The proposed method was confirmed with carbenicillin indanyl, which was metabolized rapidly to carbenicillin by the action of nonspecific esterase in the intestine. In the absence of information on Michaelis–Menten kinetic parameters, the present method is advantageous for evaluation of the intrinsic absorption rate of all unstable drugs.

Keyphrases □ β-Lactam antibiotics—kinetics of GI absorption and nonenzymatic degradation in rats □ Absorption, GI—β-lactam antibiotics, kinetics in rats □ Degradation, nonenzymatic GI—β-lactam antibiotics, kinetics in rats □ Antibiotics, β-lactam—kinetics of GI absorption and nonenzymatic degradation in rats

Penicillins are susceptible, depending on the nature of the side chain, to acid degradation and attack by β-lactamase in the GI tract (1). Since such degradations and absorption processes compete at the absorption site, the GI absorption of penicillins is difficult to study. A great deal of information is now available concerning the serum levels after oral administration of a variety of penicillins to experimental animals and humans (1, 2). It is, however, not always easy to discuss the absorption rate and mechanism from serum level data only because of the complex kinetic processes for the degradation in the GI tract and distribution in and elimination from the body (3).

In situ animal techniques are suitable for the quantitative determination of absorption rates and the clarification of the transport mechanism of a drug from the GI walls. A single perfusion method (4), a recirculation method (4, 5), and the method of Doluisio *et al.* (6) were used to study drug absorption. The present investigation was undertaken to establish a kinetic method for the evaluation of chemically and enzymatically unstable drugs such as β-lactam antibiotics by use of the recirculation technique. This technique has advantages of accurate pH control and suitable change in the perfusion volume. In the accompanying paper (7), the techniques developed were applied to study the *in situ* absorption of penicillins.

EXPERIMENTAL

Materials—The following β-lactam antibiotics were used as supplied: carbenicillin indanyl sodium[1] (704 μg/mg as carbenicillin free acid), propicillin potassium[2] (993 μg/mg), penicillin V potassium[3] (1490 units/mg), penicillin G potassium[3] (1600 units/mg), carbenicillin disodium[1] (799 μg/mg), and cephalothin sodium[4] (930 μg/mg).

All other chemicals were analytical reagent grade. Imidazole was recrystallized from benzene, followed by a thorough washing with ether (8).

Test Animals—Male albino Wistar rats, 180 ± 45 g, were fasted 20 hr prior to the experiment. Water was given freely..

Rat *In Situ* Intestinal Absorption, Degradation, and Metabolism—The recirculation method was based on those of Schanker *et al.* (4) and Koizumi *et al.* (5). The rats were anesthetized with urethan, 1.3 g/kg ip, approximately 1 hr prior to surgery. A midline abdominal incision was made, and the small intestine was exposed. The glass tubings connected to silicone tubing were cannulated into both ends of the small intestine. The double ligations were made with a 000 silk thread, with care being taken not to interfere with blood flow. The bile duct was ligated to avoid any flow of fluid into the intestinal lumen during the absorption experiments. The intestine was replaced in the abdomen, the incision was closed with metal clips, and the cannula was connected to a microtube pump[5].

The small intestine was washed with 100 (at pH 4.0) or 50 (at pH 7.0) ml of a perfusion solution (6) maintained at 37°. Then the desired volume of the perfusion solution containing the antibiotic was recirculated from the duodenum to the ileum (~100 cm in length) at pH 4.0 or to the jejunum (~30 cm in length) at pH 7.0. The perfusion solution consisted of 1–2 mg/ml, unless otherwise stated, of a β-lactam antibiotic together with the following compounds per liter at pH 4.0: hydrochloric acid, 3.8 ml; citric acid, 12.6 g; sodium hydroxide, 1.8 g; and sodium chloride, 2.1 g (5). At pH 7.0, the compounds used were: dibasic sodium phosphate, 14.3 g; monobasic potassium phosphate, 3.6 g; and sodium chloride, 4.3 g (5).

The solution was maintained at 37° and perfused with a pump at 10 ml/min at pH 4.0 or at 2 ml/min at pH 7.0. The perfusion solution pH was kept constant at the desired value during the absorption experiments by a pH-stat[6]. The samples (0.1–0.2 ml, unless otherwise stated) were taken at suitable time intervals and analyzed.

At pH 4.0, the volume changes were almost negligible. For carbenicillin indanyl sodium, a 0.025-mg/ml drug solution was used because of its low

[1] Taito Pfizer Co., Tokyo, Japan.
[2] Takeda Chemical Industries, Osaka, Japan.
[3] Meiji Seika Kaisha, Tokyo, Japan.
[4] Shionogi and Co., Osaka, Japan.
[5] Tokyo Rika Kikai Co. or Mitsumi Scientific Industries, Tokyo, Japan.
[6] pH-Stat titrator assembly consisting of TTT2 titrator and ABU12b autoburet, Radiometer, Copenhagen, Denmark.

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