Notes

Chem. Pharm. Bull.
30(8)2986—2990(1982)

The Crystal Structures of 5-Hydroxy-3,4-dihydro-2-quinolone and 5-Hydroxy-1-methyl-3,4-dihydro-2-quinolone

MASARU KIDO* and KAZUYUKI NAKAGAWA

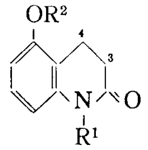
Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd.,
Kawauchi-cho, Tokushima 771-01, Japan

(Received November 2, 1981)

The crystal structures of 5-hydroxy-3,4-dihydro-2-quinolone (**2**) and 5-hydroxy-1-methyl-3,4-dihydro-2-quinolone (**3**) were determined by X-ray analysis. The C(3)—C(4) bond distance of **2**, 1.430(9) Å, is slightly shorter than a single bond distance. On the other hand, those of the two independent molecules of **3** found in an asymmetric unit, 1.474(6) Å and 1.516(6) Å, are normal with usual thermal parameters for the C(3) atom, probably because of the restriction of the ring puckering by compact crystal packing.

Keywords——5-hydroxy-3,4-dihydro-2-quinolone; 5-hydroxy-1-methyl-3,4-dihydro-2-quinolone; X-ray analysis; MULTAN method; crystal structure

The 3,4-dihydro-2-quinolone ring is the main skeleton of carteolol (**1**), a novel, potent β-blocker.[1,2] The C(3)–C(4) bond distance of **1** was found to be significantly shorter than the normal C–C single bond distance by X-ray analysis.[2] It is thought that such shortening of the C(3)–C(4) bond is a result of thermal vibration and/or some sort of conformational disorder at the C(3) atom. Furthermore, as shown in our previous paper, irradiation of carteolol in HCl solution with a tungsten lamp yields a product which exhibits a new fluorescence spectrum due to the formation of the C(3)–C(4) double bond.[3] Therefore, it is of great



1: $R^1=H$, $R^2=CH_2\overset{OH}{C}HCH_2NHC(CH_3)_3$
2: $R^1=H$, $R^2=H$
3: $R^1=CH_3$, $R^2=H$

Chart 1

TABLE I. Atomic Coordinates ($\times 10^4$) and Thermal Parameters for Non-hydrogen Atoms of **2**, with Their e.s.d.'s in Parentheses

	x	y	z	B_{eq}[a]
O(1)	9488(7)	3844(3)	5858(3)	3.8
O(2)	650(8)	2120(3)	2873(3)	4.6
N(1)	7408(9)	4228(4)	4241(4)	3.3
C(2)	7769(11)	3657(4)	5190(5)	3.3
C(3)	5865(14)	2840(6)	5403(5)	7.4
C(4)	4533(13)	2375(5)	4467(4)	4.7
C(5)	2066(11)	3006(4)	2741(4)	3.3
C(6)	1647(12)	3752(5)	1895(5)	4.2
C(7)	3149(13)	4623(5)	1808(5)	4.7
C(8)	5102(13)	4798(5)	2548(5)	3.8
C(9)	3968(11)	3168(4)	3522(4)	2.8
C (10)	5450(11)	4060(5)	3432(4)	3.0

[a] Equivalent isotropic thermal parameters were calculated from the refined anisotropic thermal parameters.

interest to clarify whether only carteolol possesses such a labile bond, or whether the 2-quinolone ring itself has such character.

Therefore, we carried out X-ray analyses of two compounds having the same skeleton as carteolol, 5-hydroxy-3,4-dihydro-2-quinolone (**2**) and 5-hydroxy-1-methyl-3,4-dihydro-2-quinolone (**3**).

The final atomic coordinates and thermal parameters and the molecular structures of **2** and **3** are shown in Tables I and II, and Figs. 1 and 2, respectively. Bond distances and angles are listed in Table III.4) No abnormal distance or angle was found in the structure of **2** except for the C(3)–C(4) bond, 1.430(9) Å, which is slightly shorter than the normal single bond distance. The equivalent isotropic thermal parameter of the C(3) atom is rather large as compared with those of the other constituent atoms of the ring. The large thermal vibration of the C(3) atom perpendicular to the ring plane, as well as of the C(3) atom of **1**, may contribute to the shortening of the C(3)–C(4) bond. However, the accuracy of the structure refinement is not high, and at this stage it is difficult to decide whether the shortening is due to thermal anisotropy or some sort of conformational disorder. On the other hand, the bond distances and angles of both molecules in **3**, molecules A and B, are similar to each other and the C(3)–C(4) distances show normal single bond character (1.474(6) Å and 1.516(6) Å). The thermal parameters of the C(3) atoms are also normal, probably because of packing restriction of the ring by reasonable van der Waals interactions as well as stacking interactoins in the crystal as shown in Fig. 3.

TABLE II. Atomic Coordinates ($\times 10^4$) and Thermal Parameters for Non-hydrogen Atoms of **3**, with Their e.s.d.'s in Parentheses

	x	y	z	B_{eq} a)
Molecule A				
O(1)	4880(2)	1496(4)	1493(2)	6.4
O(2)	1334(2)	4822(4)	1067(2)	5.3
N(1)	3539(2)	624(4)	1198(2)	4.0
C(2)	4147(2)	1864(6)	1469(3)	4.4
C(3)	3902(3)	3641(6)	1775(3)	5.3
C(4)	3043(2)	4241(5)	1269(3)	4.5
C(5)	1567(2)	3054(5)	1057(2)	3.7
C(6)	997(2)	1669(6)	946(3)	4.2
C(7)	1266(2)	−83(5)	939(3)	4.3
C(8)	2112(2)	−462(5)	1036(3)	4.0
C(9)	2410(2)	2745(5)	1162(2)	3.3
C(10)	2670(2)	977(5)	1140(2)	3.3
C(11)	3779(3)	−1207(6)	970(3)	5.8
Molecule B				
O(1)	9878(2)	−4339(4)	1428(2)	5.3
O(2)	6442(2)	−7702(4)	1498(2)	5.8
N(1)	8576(2)	−3442(4)	1435(2)	3.4
C(2)	9151(2)	−4721(5)	1376(3)	3.9
C(3)	8832(2)	−6637(6)	1228(3)	4.5
C(4)	8134(2)	−7035(5)	1684(3)	4.3
C(5)	6629(2)	−5966(5)	1334(3)	3.9
C(6)	6028(2)	−4628(6)	1082(3)	4.6
C(7)	6271(2)	−2908(6)	954(3)	4.7
C(8)	7114(2)	−2483(5)	1080(3)	3.8
C(9)	7480(2)	−5596(5)	1437(2)	3.3
C(10)	7710(2)	−3837(5)	1312(2)	3.1
C(11)	8860(3)	−1580(5)	1555(3)	4.4

a) Equivalent isotropic thermal parameters were calculated from the refined anisotropic thermal parameters.

Table III. The Bond Distances (Å) and Angles (°) of **2** and **3** for Non-hydrogen Atoms, with Their e.d.s.'s in Parentheses

	2	**3**	
		Molecule A	Molecule B
N(1)-C(2)	1.336(7)	1.337(5)	1.362(5)
N(1)-C(10)	1.428(7)	1.438(5)	1.421(5)
C(2)-C(3)	1.472(10)	1.483(6)	1.509(6)
C(3)-C(4)	1.430(9)	1.474(6)	1.516(6)
C(4)-C(9)	1.515(8)	1.502(6)	1.489(5)
C(5)-C(6)	1.378(8)	1.372(6)	1.378(6)
C(5)-C(9)	1.384(8)	1.377(5)	1.399(5)
C(6)-C(7)	1.362(9)	1.373(6)	1.365(6)
C(7)-C(8)	1.376(9)	1.394(6)	1.388(6)
C(8)-C(10)	1.399(8)	1.390(5)	1.380(5)
C(9)-C(10)	1.377(8)	1.383(5)	1.385(5)
C(2)-O(1)	1.231(7)	1.232(5)	1.217(5)
C(5)-O(2)	1.355(7)	1.366(5)	1.360(5)
N(1)-C(11)		1.479(5)	1.452(5)
C(2)-N(1)-C(10)	125.2(5)	123.2(3)	123.0(3)
O(1)-C(2)-N(1)	122.1(5)	120.5(4)	121.9(4)
O(1)-C(2)-C(3)	123.1(5)	122.5(4)	121.8(4)
N(1)-C(2)-C(3)	114.7(5)	116.9(4)	116.3(3)
C(2)-C(3)-C(4)	119.8(6)	115.0(4)	113.5(3)
C(3)-C(4)-C(9)	113.1(5)	112.0(3)	110.2(3)
C(6)-C(5)-C(9)	119.6(5)	121.9(4)	121.0(4)
C(5)-C(6)-C(7)	120.1(6)	119.6(4)	119.3(4)
C(6)-C(7)-C(8)	122.1(6)	120.5(4)	121.1(4)
C(7)-C(8)-C(10)	117.4(6)	118.2(4)	119.2(4)
C(4)-C(9)-C(5)	122.1(5)	122.8(3)	121.7(3)
C(4)-C(9)-C(10)	118.2(5)	119.3(3)	119.9(3)
C(5)-C(9)-C(10)	119.6(5)	117.9(3)	118.4(3)
N(1)-C(10)-C(8)	119.3(5)	119.2(3)	120.4(3)
N(1)-C(10)-C(9)	119.6(5)	118.9(3)	118.8(3)
C(8)-C(10)-C(9)	121.2(5)	121.8(3)	120.8(3)
O(2)-C(5)-C(6)	123.2(5)	122.2(3)	123.0(4)
O(2)-C(5)-C(9)	117.3(5)	115.9(3)	116.0(3)
C(2)-N(1)-C(11)		118.0(3)	117.5(3)
C(10)-N(1)-C(11)		118.8(3)	119.3(3)

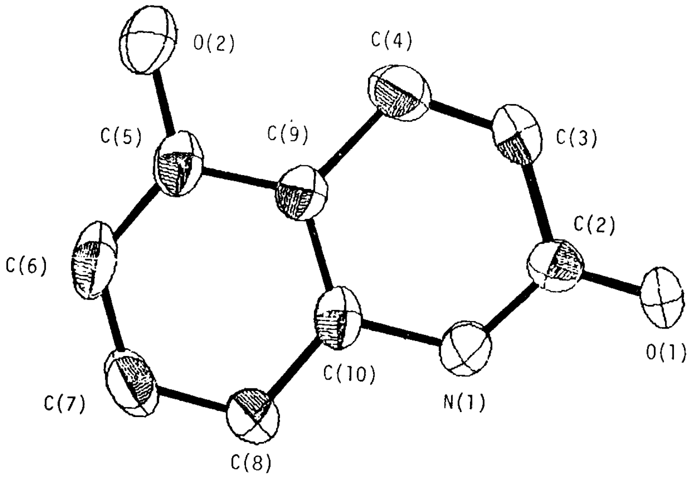


Fig. 1. The Molecular Structure of **2** together with Atomic Numbering

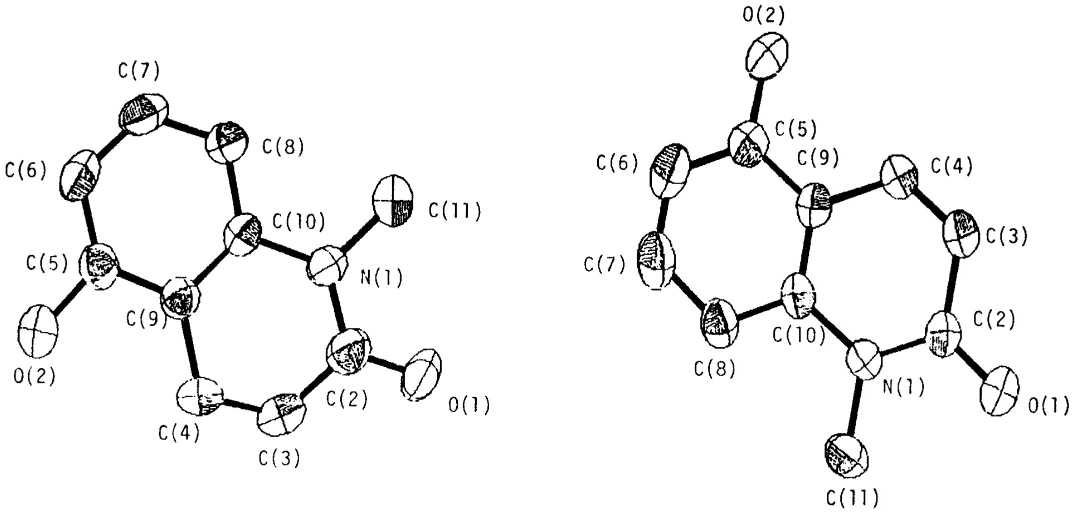


Fig. 2. The Molecular Structure of 3 together with Atomic Numbering

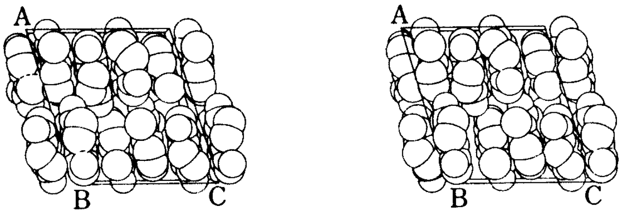


Fig. 3. A Stereoview of the Crystal Packing of 3

The amide group in 2 forms a dimer structure through the N(1)–H···O(1) hydrogen bonds (2.937(6) Å) with the neighboring molecule related by a center of symmetry, whereas the phenolic O(2) atom is linked to the neighboring O(1) atom by the O(2)–H···O(1) hydrogen bond (2.722(5) Å). The hydrogen bonding in crystalline 3, however, is different. The phenolic O(2) atom of molecule A forms a hydrogen bond with the amide O (1) atom of molecule B and *vice versa*. [The O(2)A–H···O(1)B and O(2)B–H···O(1)A distances are 2.679(4) and 2.648(4) Å, respectively.]

Experimental

Intensity data were collected on a Syntex R3 four-circle diffractometer with graphite-monochromated M_oK_α radiation using the ω scan mode. All the computations were made on a NOVA-3 computer coupled to the diffractometer, using the Syntex XTL programs.

Crystal Data for 2——Chemical formula $C_9H_9NO_2$, M.W.=163.18, monoclinic, space group $P2_1/c$, $a=5.398(6)$, $b=12.494(8)$, $c=11.743(8)$ Å, $\beta=90.67(7)°$, $Z=4$, $Dx=1.37$ g/cm³, $\mu(M_oK_\alpha)=1.1$ cm^{-1}. A total of 2719 independent reflections was collected within 2θ less tha 60°, among which 806 reflections [$I>1.96\sigma(I)$] were used as observed.

Crystal Data for 3——Chemical formula $C_{10}H_{11}NO_2$, M.W.=177.21, monoclinic, space group $P2_1/c$, $a=16.532(7)$, $b=7.411(4)$, $c=14.624(6)$ Å, $\beta=106.40(3)°$, $Z=8$, $Dx=1.37$ g/cm³, $\mu(M_oK_\alpha)=1.0$ cm^{-1}. A total of 3020 independent reflections was collected within 2θ less than 50°, among which 2148 reflections [$I>1.96\sigma(I)$] were used as observed.

Structure Determination and Refinement for 2——The structure of 2 was solved by the direct method using the MULTAN program.[5] The resulting E map revealed the positions of all non-hydrogen atoms. All the hydrogen atoms except for those attached to the C(3) atom were found on a difference Fourier map. The refinement of atomic parameters was carried out by a block-diagonal least-squares method. Thermal parameters were refined anisotropically for all the non-hydrogen atoms, but the atomic parameters of hydrogen atoms were fixed. The final R-value was 0.110.[4]

Structure Determination and Refinement for 3——The structure of **3** was determined by the direct method using the MULTAN program⁵⁾ and refined by the least-squares method as described in the preceding section. The final R-value was 0.073.⁴⁾

Acknowledgement The authors wish to thank Professor Ken-ichi Tomita and Dr. Takaji Fujiwara of Osaka University for helpful discussions.

References and Notes

1) K. Nakagawa, N. Murakami, S. Yoshizaki, M. Tominaga, H. Mori, Y. Yabuuchi, and S. Shintani, *J. Med. Chem.*, **17**, 529 (1974).
2) M. Kido, K. Nakagawa, T. Fujiwara, and K. Tomita, *Chem. Pharm. Bull.*, **29**, 2109 (1981).
3) M. Kido, H. Mori, S. Masuda, H. Kohri, and K. Nakagawa, *Yakugaku Zasshi*, **97**, 1 (1977).
4) Tables of the observed and calculated structure factors, anisotropic temperature factors, the coordinates of the hydrogen atoms, and bond distances and angles, including the hydrogen atoms of **2** and **3**, are available from the authors on request.
5) G. Germain, P. Main, and H.H. Woolfson, *Acta Crystallogr.*, Sect., **A27**, 368 (1971).