STRUCTURE DETERMINATION OF A GEOMETRIC ISOMER OF 2-ACETYL-1,2,3,4-TETRAHYDRO-6,7-DIMETHOXY-1-(2-METHYLPROPYLIDENE)ISOQUINOLINE[†]

Tozo Fujii,[*,‡] Masashi Ohba,[‡] Naoko Fukui,[§] and Tadamasa Date[§]

[‡]*Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan*

[§]*Organic Chemistry Research Laboratory, Tanabe Seiyaku, Co., Ltd., Kawagishi-2-chome, Toda 335, Japan*

Abstract——A geometric isomer (mp 112–113°C) of 2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-methylpropylidene)isoquinoline (**4**), prepared previously from 3,4-dihydro-6,7-dimethoxy-1-(2-methylpropyl)isoquinoline (**3**) by acetylation with acetic anhydride and pyridine, has been shown to have the *E* configuration (**4a**) by means of ^{1}H nmr spectroscopic and X-ray crystallographic analyses.

One of the interesting chemical features of simple 1-alkyl-3,4-dihydroisoquinolines (type **1**) is that a tautomeric shift of the endocyclic C=N double bond to form the exocyclic C=C structure (type **2**) is possible under certain conditions. Our previous work[1] has confirmed that (1) the above bases and their protonated species have the corresponding endocyclic double bond structures (type **1**) under ordinary circumstances; (2) activation of the α-hydrogen(s) of the 1-alkyl group by quaternization of the nitrogen at the 2-position makes the exocyclic C=C structure (type **2**) possible under strongly basic conditions; and (3) the greatest stability of this exocyclic double bond structure (type **2**) is caused by a 1-substituent that can give extended conjugation and resonance stabilization by forming intramolecular hydrogen bonding with the secondary NH. Some ten years ago, we prepared a geometric isomer (mp 112–113°C) of 2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-methylpropylidene)isoquinoline (**4**),[1] a model for the exocyclic double bond structure, from the tertiary base (**3**)[2] by adaptation of the procedure[3] of Brossi *et al.* However, its configuration about the exocyclic double bond was not determined at

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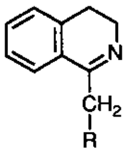
[†]Dedicated to Dr. Arnold Brossi on the occasion of his 70th birthday.



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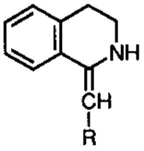

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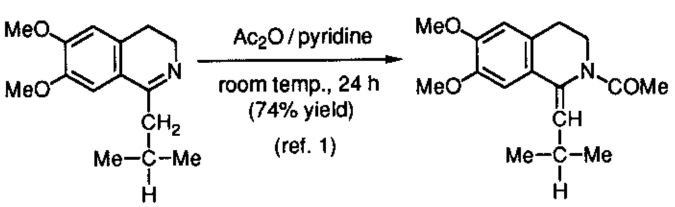
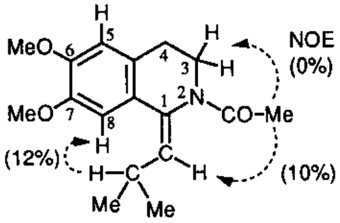


3

4
(mp 112–113°C)



4a
(mp 112–113°C)

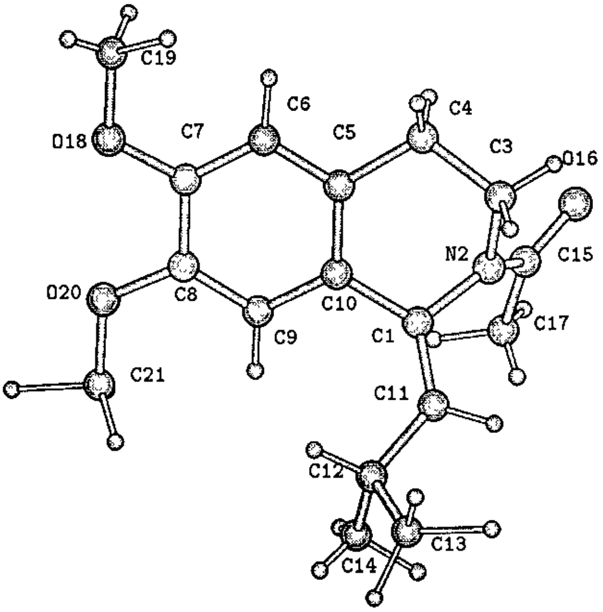


Figure 1. A Parallel View of the Molecular Structure of **4a** and the Numbering Scheme Employed for X-ray Crystallographic Data

that time. We now present ^1H nmr spectroscopic and X-ray crystallographic evidence that the double bond in the isomer has the *E* configuration, as shown in structure (**4a**).

The ^1H nmr spectrum of the isomer (mp 112–113°C) in $CDCl_3$ exhibited the following signals (δ values shown): (*a*) 1.14 (6H, d, *J* = 6.8 Hz, CH*Me*$_2$), (*b*) 2.14 [3H, s, N(2)-COMe], (*c*) 2.83 [2H, t, *J* = 6.6 Hz, C(4)-H's], (*d*) 2.90 (1H, m, C*H*Me$_2$), (*e*) 3.84 [2H, t, *J* = 6.6 Hz, C(3)-H's], (*f*) 3.89 and 3.90 (6H, s each, MeO's), (*g*) 5.34 (1H, d, *J* = 10.7 Hz, C=CH), (*h*) 6.69 [1H, s, C(5)-H], and (*i*) 6.92 [1H, s, C(8)-H]. On irradiation of the signal (*d*), a 12% nuclear Overhauser effect (NOE) was observed for the signal (*i*). On irradiation of the signal (*b*), a 10% NOE and a 0% NOE were observed for the signals (*g*) and (*e*), respectively. These NOE values clearly demonstrate the (*E*)-structure (4a) in which the C(8)-H and isopropyl-CH protons are in close proximity and so are the olefinic and N(2)-acetyl protons.

TABLE I. Final Atomic Coordinates and Equivalent Isotropic Thermal Parameters for Non-hydrogen Atoms of **4a** with Estimated SD in Parentheses

Atom	*x*	*y*	*z*	B_{eq} (Å^2)
C(1)	0.1947(3)	0.0927(2)	0.1313(2)	2.81(0)
N(2)	0.1441(2)	0.1987(2)	0.1010(2)	2.98(0)
C(3)	0.0333(3)	0.1927(3)	0.0203(3)	3.49(1)
C(4)	0.0690(3)	0.1439(2)	–0.0864(2)	3.54(0)
C(5)	0.1637(3)	0.0522(3)	–0.0691(3)	2.63(1)
C(6)	0.1900(3)	–0.0095(3)	–0.1596(3)	3.01(1)
C(7)	0.2786(3)	–0.0910(3)	–0.1504(3)	3.07(1)
C(8)	0.3469(3)	–0.1097(3)	–0.0488(3)	3.01(1)
C(9)	0.3207(3)	–0.0502(3)	0.0419(3)	2.86(1)
C(10)	0.2264(3)	0.0299(3)	0.0339(3)	2.49(1)
C(11)	0.1982(4)	0.0618(3)	0.2358(3)	3.27(1)
C(12)	0.2432(3)	–0.0436(3)	0.2890(3)	3.67(1)
C(13)	0.1520(3)	–0.0863(2)	0.3669(3)	4.98(1)
C(14)	0.3711(4)	–0.0257(3)	0.3534(3)	5.90(1)
C(15)	0.2091(4)	0.2937(4)	0.1149(3)	3.52(1)
O(16)	0.1690(4)	0.3778(3)	0.0711(3)	5.60(1)
C(17)	0.3299(4)	0.2913(3)	0.1885(3)	4.33(1)
O(18)	0.3073(4)	–0.1566(4)	–0.2353(4)	4.32(1)
C(19)	0.2267(5)	–0.1451(4)	–0.3357(3)	6.48(2)
O(20)	0.4369(5)	–0.1894(5)	–0.0472(4)	4.21(2)
C(21)	0.5157(5)	–0.2033(5)	0.0529(4)	4.37(2)

Final identification as the (*E*)-isomer (**4a**) was achieved by a single crystal X-ray diffraction analysis. Table I lists the final atomic positions and equivalent isotropic thermal parameters of the non-hydrogen atoms. The bond lengths and angles are given in Tables II and III, respectively, and a computer-generated drawing of the final X-ray model, together with the atomic numbering scheme employed for the X-ray crystallographic data, is presented in Figure 1. It may be seen that the exocyclic C(1)–C(11) bond is olefinic (bond length 1.329 Å) and the configuration of the isopropyl group at C(11) is *trans* with respect to the ring N(2) atom. Interestingly, the N(2)-COMe group exists in the *trans* form [with carbonyl oxygen *trans* to C(1)], locating C(17) far away from C(3). If **4a** is assumed to exist in the same *trans*-amide form even in $CDCl_3$, no NOE and the 10% NOE observed for the peaks (*e*) and (*g*) on irradiation of the signal (*b*) in the above nmr spectroscopic study are explainable.

In summary, the present results have thus established that the geometric isomer of **4** having mp 112–113°C has the *E* configuration (**4a**).

TABLE II. Selected Bond Lengths in **4a**

Bond	Length[a] (Å)	Bond	Length[a] (Å)
C(1)–N(2)	1.444(4)	C(7)–O(18)	1.372(6)
C(1)–C(10)	1.487(4)	C(8)–C(9)	1.380(5)
C(1)–C(11)	1.329(5)	C(8)–O(20)	1.375(6)
N(2)–C(3)	1.471(4)	C(9)–C(10)	1.408(5)
N(2)–C(15)	1.360(5)	C(11)–C(12)	1.506(6)
C(3)–C(4)	1.519(4)	C(12)–C(13)	1.525(5)
C(4)–C(5)	1.517(4)	C(12)–C(14)	1.530(5)
C(5)–C(6)	1.393(5)	C(15)–O(16)	1.222(6)
C(5)–C(10)	1.396(4)	C(15)–C(17)	1.504(5)
C(6)–C(7)	1.378(5)	O(18)–C(19)	1.438(7)
C(7)–C(8)	1.398(5)	O(20)–C(21)	1.429(7)

[a] Estimated SD's are given in parentheses for the least digits.

TABLE III. Selected Bond Angles in **4a**

Bond	Angle[a] (°)	Bond	Angle[a] (°)
N(2)–C(1)–C(10)	111.8(2)	C(7)–C(8)–O(20)	115.9(4)
N(2)–C(1)–C(11)	118.5(3)	C(9)–C(8)–O(20)	124.3(4)
C(10)–C(1)–C(11)	129.5(3)	C(8)–C(9)–C(10)	121.1(3)
C(1)–N(2)–C(3)	112.7(2)	C(1)–C(10)–C(5)	119.5(3)
C(1)–N(2)–C(15)	124.3(3)	C(1)–C(10)–C(9)	121.8(3)
C(3)–N(2)–C(15)	119.9(3)	C(5)–C(10)–C(9)	118.6(3)
N(2)–C(3)–C(4)	109.8(3)	C(1)–C(11)–C(12)	129.6(4)
C(3)–C(4)–C(5)	113.3(2)	C(11)–C(12)–C(13)	111.5(3)
C(4)–C(5)–C(6)	118.6(3)	C(11)–C(12)–C(14)	109.4(3)
C(4)–C(5)–C(10)	121.9(3)	C(13)–C(12)–C(14)	109.2(3)
C(6)–C(5)–C(10)	119.5(3)	N(2)–C(15)–O(16)	120.9(4)
C(5)–C(6)–C(7)	121.5(3)	N(2)–C(15)–C(17)	117.4(3)
C(6)–C(7)–C(8)	119.3(3)	O(16)–C(15)–C(17)	121.6(4)
C(6)–C(7)–O(18)	124.7(3)	C(7)–O(18)–C(19)	115.3(4)
C(8)–C(7)–O(18)	116.0(3)	C(8)–O(20)–C(21)	117.0(5)
C(7)–C(8)–C(9)	119.8(3)		

[a] Estimated SD's are given in parentheses for the least digits.

EXPERIMENTAL

^{1}H Nmr Measurements. The ^{1}H nmr spectrum of **4a** in $CDCl_3$ was taken in the usual manner on a JEOL JNM-GSX-500 (^{1}H 500 MHz) instrument. The results are given in the text, where chemical shifts are reported in δ values relative to Me_4Si, an internal standard, and the following abbreviations are used for the multiplicity of the signal: d = doublet, m = multiplet, s = singlet, t = triplet.

X-ray Analysis. Colorless transparent prisms of (*E*)-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-methylpropylidene)isoquinoline (**4a**) (mp 112–113°C)[1] were grown from acetone–diisopropyl ether. A crystal measuring 0.25 × 0.25 × 0.20 mm was selected from among them and used for all data collection. Unit cell constants and intensity data were obtained with a Rigaku AFC-5R automatic diffractometer using graphite-monochromated Cu $K\alpha$ radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular settings of 25 2θ-values in the range of 85–90°, giving the following crystal data: a = 10.748(2) Å; b = 12.268(2) Å; c = 12.230(2) Å; α = 90.00(0)°; β = 95.71(1)°; γ = 90.00(0)°; U = 1604.7(4) Å^3; space group $P2_1/c$; $Z = 4$; D_x = 1.198 g/cm^3; $F(000)$ = 624; μ(Cu $K\alpha$) = 0.665/mm. Out of 2382 unique reflections ($0° \le 2\theta \le 120°$) measured by using the $\omega/2\theta$ scan technique at a rate of 16°/min, 2049 without $|F_{obs}| = 0$ were considered unique and observed. No absorption corrections were applied.

Structure Determination and Refinement. The structure was solved by a direct method using the program SHELXS-86[4] and the difference Fourier method. Refinement of atomic parameters was carried out using the full-matrix least-squares method with anisotropic temperature factors. All hydrogen atoms were clearly located on difference Fourier maps and refined with isotropic temperature factors. Throughout the refinement, the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized, and the weight used during the final refinement stage was $\sqrt{w} = 1/\sigma(F_o)$; the final R value, 0.0720 (R_w = 0.0720). The atomic scattering factors were taken from the literature.[5] The final atomic positions and equivalent isotropic thermal parameters of the non-hydrogen atoms are listed in Table I. The bond lengths and angles are given in Tables II and III, respectively. A computer-generated,[6] parallel view of the structure of **4a** is presented in Figure 1.

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REFERENCES AND NOTES

1. T. Fujii, M. Ohba, O. Yonemitsu, and Y. Ban, *Chem. Pharm. Bull.*, 1982, **30**, 598.

2. (a) P. N. Craig, F. P. Nabenhauer, P. M. Williams, E. Macko, and J. Toner, *J. Am. Chem. Soc.*, 1952, **74**, 1316; (b) C. Djerassi, J. J. Beereboom, S. P. Marfey, and S. K. Figdor, *ibid.*, 1955, **77**, 484.
3. A. Brossi, M. Baumann, L. H. Chopard-dit-Jean, J. Würsch, F. Schneider, and O. Schnider, *Helv. Chim. Acta*, 1959, **42**, 772.
4. A program developed for crystal structure solution by G. M. Sheldrick (University of Göttingen, Germany) in 1986.
5. J. A. Ibers and W. C. Hamilton (eds.), 'International Tables for X-ray Crystallography,' Vol. IV, Kynoch Press, Birmingham, 1974.
6. A Sony NEWS-3860 computer was employed.

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