Atropisomerism in 4-(2-Thienyl)-4*H*-1,2,4-triazole Derivatives

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3-Aminomethyl-4-[3-(*o*-chlorobenzoyl)-5-ethylthiophen-2-yl]-5-methyl-4*H*-1,2,4-triazole (I), the hydrolytically ring-opened derivative of etizolam, which is one of the 1,4-diazepine antianxiety drugs, was investigated from the stereochemical point of view. In order to isolate atropisomers of compound I, its carbonyl group was reduced to a chiral secondary alcohol. The resulting compounds were resolved successfully into two components (IIa and IIb) by silica-gel column chromatography. The structures of atropisomeric IIa and IIb, possessing rotational differences about the single bond between the thiophene and triazole rings, were confirmed by X-ray crystallographic analysis. The interconversion behavior between them was also examined.

Keywords open-ring compound; etizolam; 1,4-diazepine; atropisomerism

The hydrolytic ring-opening reactions of 1,4-diazepine antianxiety drugs under acidic conditions have been communicated.[1,2] In these reactions the open-ring compounds are in equilibrium with the parent ones, and a rise in pH to neutrality readily permits ring closure. A similar phenomenon (Chart 1) has been found for etizolam, 4-(*o*-chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*]-*s*-triazolo-[4,3-*a*][1,4]diazepine.[3] The present work was focused on 3-aminomethyl-4-[3-(*o*-chlorobenzoyl)-5-ethylthiophen-2-yl]-5-methyl-4*H*-1,2,4-triazole (I), the hydrolytically ring-opened derivative of etizolam, from the stereochemical point of view. Thus, compound I was derived to an isolable form by reduction of the carbonyl group to a chiral secondary alcohol, and atropisomerism in the resulting compounds, caused by restricted rotation about the single bond between the thiophene and triazole rings, was investigated.

Experimental

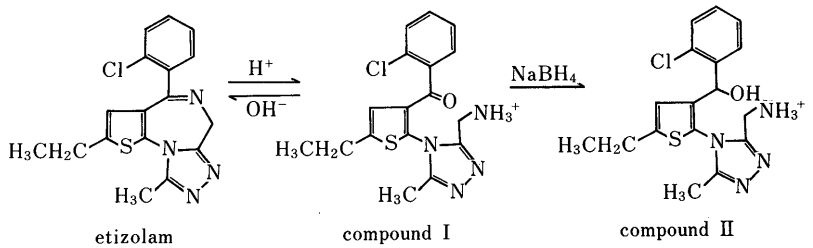
Apparatus and Procedure Reversed phase liquid chromatography (RPLC) was carried out using a Waters Model 510 equipped with a Model 484 ultraviolet (UV) monitor and a Data Module. A YMC-Pack A-312 (150×6 mm i.d. octadecylsilyl bonded silica-gel column) was obtained from Yamamura Chemical Lab. Co., Ltd. An Enraf-Nonius CAD4 diffractometer was employed for X-ray crystallographic analysis with graphite-monochromated Cu$K\alpha$ radiation. Intensity data collection was accomplished by the ω–2θ scan method. The structure was solved by the direct method with MULTAN 82,[4] and refined by block-diagonal least-squares and subsequent difference Fourier methods. The nuclear magnetic resonance (NMR) spectrum was recorded on a JEOL GSX-400 spectrometer. Chemical shifts were measured relative to internal tetramethylsilane.

Materials Etizolam was synthesized in our laboratory essentially according to a reported procedure.[5] Sodium borohydride was purchased from Wako Pure Chemicals. Other chemicals were of analytical grade and were used without further purification.

Reduction of Compound I Etizolam (2 g) was dissolved in 50 ml of 2.5 N hydrochloric acid and the solution was allowed to stand for 20 h at room temperature. Sodium borohydride (1 g) was added, and the mixture was allowed to react for 5 min. The crude product was extracted into chloroform, followed by vacuum drying after removal of the solvent. To complete the reduction, the obtained extract was similarly reduced once again. The resulting compounds were subjected to preparative column chromatography (25×2 cm i.d. silica-gel column) employing a nine-to-one mixture of chloroform and methanol as the mobile phase: flow rate, 1.0 ml/min, fraction volume, 10—15 ml. The single crystals of IIa and IIb employed for X-ray analysis were recrystallized from methanol and a mixture of equal portions of dichloromethane and diethylether, respectively. Compounds IIa and IIb (about 50 mg each) were separated. Compound IIa: colorless prisms, mp 162—163 °C. *Anal.* Calcd for $C_{17}H_{19}ClN_4OS$: C, 56.27; H, 5.28; N, 15.44. Found: C, 56.20; H, 5.23; N, 15.59. EI-MS: *m/z* 362 $[M]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.00 (1H, s), 5.98 (1H, s), 4.18 (2H, d, J=13.8 Hz), 3.62 (2H, d, J=13.8 Hz), 2.86 (2H, q, J=8.0 Hz), 1.58 (3H, s), 1.36 (3H, t, J=8.0 Hz). Compound IIb: colorless needles, mp 154—155 °C. *Anal.* Calcd for $C_{17}H_{19}ClN_4OS$: C, 56.27; H, 5.28; N, 15.44. Found: C, 55.70; H, 5.22; N, 15.28. EI-MS: *m/z* 362 $[M]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.31 (1H, s), 5.65 (1H, s), 4.30

TABLE I. Crystallographic Data for Compounds IIa and IIb

	IIa	IIb
Cell dimensions		
a (Å)	10.129 (2)	11.253 (5)
b (Å)	10.890 (2)	11.629 (3)
c (Å)	8.610 (1)	7.156 (1)
α (°)	93.61 (1)	92.16 (2)
β (°)	110.40 (1)	94.54 (2)
γ (°)	91.38 (1)	75.46 (3)
V (Å^3)	887.3 (2)	903.5 (5)
Space group	$P\bar{1}$	$P\bar{1}$
Z	2	2
D_m (gcm^{-3})	1.358	1.333
F (000)	380	380
μ (mm^{-1})	3.10	3.04
Max θ (°)	60	55
Number of unique reflections	2415	1648
R factor	0.043	0.072



etizolam compound I compound II

Chart 1. Reversible Ring-Opening of Etizolam and Derivatization of Compound I to II

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(2H, d, J=13.0 Hz), 3.60 (2H, d, J=13.0 Hz), 2.74 (2H, q, J=8.0 Hz), 2.47 (3H, s), 1.24 (3H, t, J=8.0 Hz).

Interconversion Behavior between IIa and IIb Compound IIa or IIb was dissolved in a given volume of methanol or chloroform. An aliquot of the solution was withdrawn at appropriate time intervals and analyzed by RPLC. The proportions of IIa and IIb were calculated from the ratio of peak area using a Data Module.

Results and Discussion

The atropisomerism due to restricted rotation about a single bond (pivot bond) is well known in compounds with six-membered aromatic rings, such as biphenyl derivatives with large substituents in the *ortho* positions.[6] However, so far as we know, there has been no report about atropisomerism in five-membered heterocyclic ring compounds involving a thiophene ring. Direct isolation of compound I is hardly possible because of the ready ring closure. We attempted the chromatographic resolu-

TABLE II. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors for Non-hydrogen Atoms of Compounds IIa and IIb with Their Estimated Standard Deviations in Parentheses

Compound	Atom	x	y	z	B_{eq} (Å^2)
IIa	Cl	6726 (1)	4860 (1)	4605 (1)	4.79 (2)
	S	4731 (1)	8516 (1)	1176 (1)	5.16 (3)
	O	9390 (2)	8141 (2)	4518 (2)	3.89 (6)
	N1	7193 (2)	8065 (2)	716 (3)	3.27 (7)
	N2	8455 (3)	8722 (3)	−691 (3)	4.90 (9)
	N3	7857 (3)	7552 (3)	−1384 (3)	4.84 (9)
	N4	9919 (3)	10261 (3)	2741 (3)	4.31 (8)
	C1	6436 (3)	8041 (3)	1833 (4)	3.55 (9)
	C2	6889 (3)	7684 (3)	3418 (3)	3.52 (8)
	C3	5778 (4)	7814 (3)	4096 (4)	4.39 (10)
	C4	4576 (4)	8225 (4)	3065 (5)	5.52 (13)
	C5	8320 (3)	7239 (3)	4373 (3)	3.15 (8)
	C6	8615 (3)	6041 (3)	3559 (3)	3.23 (8)
	C7	7937 (3)	4938 (3)	3569 (4)	3.76 (9)
	C8	8182 (4)	3836 (3)	2813 (4)	4.92 (11)
	C9	9175 (4)	3863 (3)	2046 (4)	5.22 (12)
	C10	9887 (4)	4939 (4)	2034 (4)	4.85 (11)
	C11	9612 (3)	6037 (3)	2778 (4)	3.98 (9)
	C12	8038 (3)	9008 (3)	559 (4)	3.68 (9)
	C13	7110 (3)	7166 (3)	−535 (4)	3.83 (9)
	C14	8458 (4)	10162 (3)	1665 (4)	4.45 (10)
	C15	6306 (4)	5989 (4)	−809 (4)	5.28 (12)
	C16	3177 (5)	8434 (6)	3297 (6)	9.16 (21)
	C17	3305 (5)	8664 (5)	5038 (7)	8.16 (20)
IIb	Cl	7725 (2)	180 (2)	6891 (3)	5.82 (6)
	S	5070 (2)	3666 (2)	3592 (3)	4.03 (4)
	O	9007 (4)	1702 (4)	2013 (6)	3.84 (13)
	N1	7266 (4)	3810 (4)	5357 (6)	2.76 (13)
	N2	8346 (5)	5097 (5)	6278 (7)	3.71 (16)
	N3	8030 (5)	4601 (5)	7867 (7)	3.67 (15)
	N4	9094 (5)	4124 (5)	2053 (7)	3.76 (16)
	C1	6609 (6)	3131 (5)	4200 (8)	2.89 (17)
	C2	7085 (5)	2033 (5)	3396 (8)	2.84 (16)
	C3	6151 (6)	1646 (6)	2303 (9)	3.53 (18)
	C4	5024 (6)	2399 (6)	2258 (10)	4.09 (20)
	C5	8436 (5)	1387 (5)	3548 (8)	2.74 (16)
	C6	8639 (5)	54 (5)	3488 (8)	2.93 (17)
	C7	8386 (6)	−588 (6)	4919 (8)	3.55 (19)
	C8	8659 (6)	−1814 (6)	4944 (11)	4.26 (21)
	C9	9194 (7)	−2439 (6)	3429 (12)	4.65 (23)
	C10	9433 (6)	−1848 (6)	1960 (10)	4.44 (22)
	C11	9161 (6)	−624 (6)	1935 (9)	3.79 (19)
	C12	7874 (6)	4603 (5)	4813 (8)	2.91 (17)
	C13	7392 (6)	3868 (6)	7283 (8)	3.22 (17)
	C14	7976 (7)	4894 (6)	2806 (8)	3.74 (20)
	C15	6828 (8)	3169 (7)	8493 (9)	4.98 (24)
	C16	3844 (7)	2299 (8)	1210 (14)	6.51 (29)
	C17	3962 (10)	1772 (13)	−619 (19)	11.87 (55)

TABLE III. Selected Bond Distances, Bond Angles, Torsion Angles and Hydrogen Bonding Distances of Compounds IIa and IIb with Their Estimated Standard Deviations in Parentheses

	IIa	IIb
Bond distance (Å)		
S–C1	1.723 (3)	1.728 (6)
S–C4	1.735 (5)	1.735 (7)
O–C5	1.412 (4)	1.422 (8)
N1–C1	1.425 (5)	1.418 (8)
N1–C12	1.364 (4)	1.367 (9)
N1–C13	1.388 (4)	1.376 (7)
N2–C12	1.309 (5)	1.318 (8)
N2–N3	1.400 (4)	1.404 (8)
N3–C13	1.302 (5)	1.298 (9)
N4–C14	1.444 (4)	1.485 (8)
C1–C2	1.365 (4)	1.379 (8)
C2–C3	1.435 (5)	1.422 (9)
C2–C5	1.512 (4)	1.527 (8)
C3–C4	1.339 (5)	1.355 (8)
C4–C16	1.519 (7)	1.511 (11)
C5–C6	1.528 (4)	1.509 (9)
C12–C14	1.486 (5)	1.508 (9)
C13–C15	1.462 (5)	1.491 (11)
C16–C17	1.464 (8)	1.426 (17)
Bond angle (°)		
C1–S–C4	91.2 (2)	91.8 (3)
C1–N1–C12	127.4 (3)	127.9 (5)
C1–N1–C13	126.1 (3)	128.3 (6)
C12–N1–C13	106.3 (3)	103.8 (5)
N3–N2–C12	107.6 (3)	106.3 (6)
N2–N3–C13	108.2 (3)	107.3 (5)
S–C1–N1	118.5 (2)	121.2 (4)
S–C1–C2	113.0 (3)	112.5 (5)
N1–C1–C2	128.5 (3)	126.3 (5)
C1–C2–C3	109.9 (3)	109.9 (5)
C1–C2–C5	126.4 (3)	124.3 (6)
C3–C2–C5	123.6 (3)	125.6 (5)
C2–C3–C4	115.1 (3)	115.9 (6)
S–C4–C3	110.8 (3)	109.8 (5)
S–C4–C16	118.6 (3)	119.8 (5)
C3–C4–C16	130.6 (4)	130.3 (7)
O–C5–C2	111.0 (2)	109.2 (5)
O–C5–C6	109.2 (3)	107.4 (5)
C2–C5–C6	111.8 (2)	112.5 (6)
N1–C12–N2	109.3 (3)	111.1 (5)
N1–C12–C14	125.4 (3)	124.7 (6)
N2–C12–C14	125.3 (3)	124.2 (6)
N1–C13–N3	108.6 (3)	111.5 (6)
N1–C13–C15	124.2 (3)	122.7 (6)
N3–C13–C15	127.2 (3)	125.8 (6)
N4–C14–C12	114.6 (3)	111.1 (5)
C4–C16–C17	113.5 (4)	115.3 (8)
Torsion angle (°)[a]		
(1)–(2)–(3)–(4)		
C12–N1–C1–S	91.0 (3)	−90.6 (7)
C12–N1–C1–C2	−88.9 (4)	87.3 (8)
C13–N1–C1–S	−82.7 (3)	86.0 (7)
C13–N1–C1–C2	97.4 (4)	−96.2 (8)
Hydrogen bonding distance (Å)		
Donor Acceptor		
N4 O(x, y, z)[b]	2.986 (3)	—
O N4(x, y, z)[b]	—	2.842 (7)
O N4(2−x, 2−y, 1−z)[b]	2.713 (3)	—
N4 N2(2−x, 1−y, −z)[b]	3.040 (5)	—

a) The clockwise rotation of bond (3)–(4) with reference to bond (2)–(1) is given. *b*) Represents equivalent position of hydrogen acceptor.

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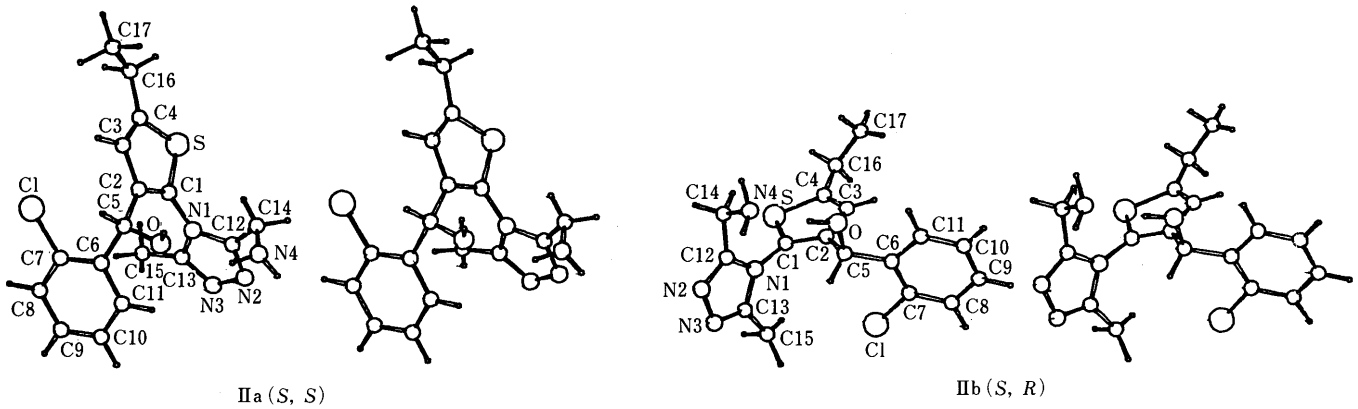

Fig. 1. Molecular Structures of IIa and IIb in the Crystalline State

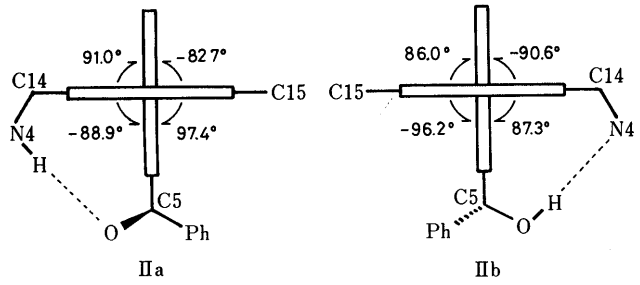

Fig. 2. Schematic Drawing of Interplanar Geometry between Thiophene and Triazole Rings

The broken lines indicate intramolecular hydrogen bonding.

tion of atropisomers under acidic conditions at ambient temperature, but without success. Thus, an alternative method to resolve atropisomers was designed; the carbonyl group on compound I was reduced to a chiral secondary alcohol with sodium borohydride in an acidic medium. It is thought that the reduction leads to the production of diastereomeric atropisomers. When the resulting compounds were subjected to silica-gel column chromatography, two easily resolvable components (IIa and IIb) were obtained. Subsequently compounds IIa and IIb were submitted to X-ray crystallographic analysis. Their crystallographic data and atomic parameters for non-hydrogen atoms are summarized in Tables I and II, respectively. Stereoscopic molecular views of compounds IIa and IIb with their atomic labeling are depicted in Fig. 1. Compounds IIa and IIb were present similarly in the centric unit cell (space group: triclinic $P\bar{1}$). As can be seen from the relatively high temperature factors for C16 and C17, partial disordered structures were found at the ethyl group on the thiophene ring in both crystals. Table III gives selected bond distances, bond angles, torsion angles and hydrogen bonding distances of compounds IIa and IIb. These was no distinctive difference in either bond distances or bond angles between these compounds. A comparison of torsion angles between compounds IIa and IIb demonstrates the evident rotational difference about the pivot bond between the thiophene and triazole rings (the interplanar geometry is drawn in Fig. 2). Thus, *S,S*- and *R,R*-enantiomers and the corresponding diastereomers were found in the crystals of compounds IIa and IIb, respectively. The ^{1}H-NMR data given in Experimental also supported the view that compound IIa is diastereomeric with IIb. Intramolecular hydrogen

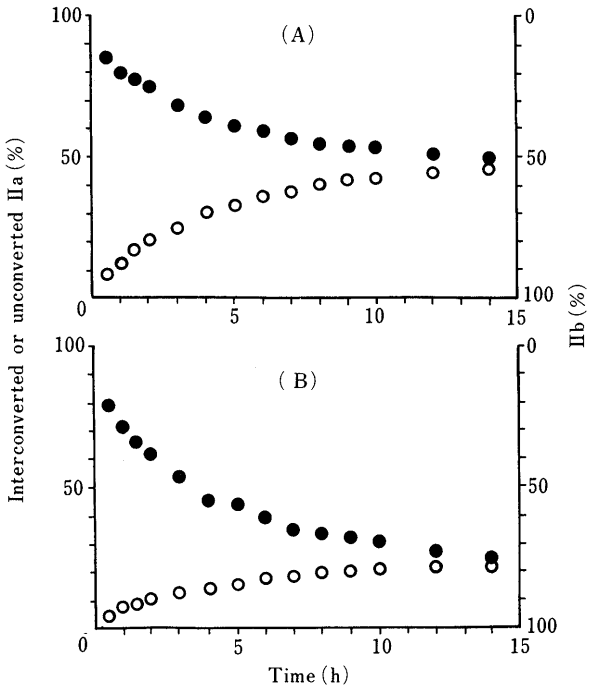

Fig. 3. Interconversion Behavior between Compounds IIa and IIb in Methanol (A) and Chloroform (B) at Ambient Temperature

●, IIa to IIb; ○, IIb to IIa. Chromatographic conditions: mobile phase, 0.05 M perchlorate buffer (pH 2.5)–acetonitrile (6 : 4); column, YMC-Pack A-312; flow rate, 1.0 ml/min; detection, 254 nm.

bonding between O and N4 (broken line in Fig. 2) was observed in compound IIa, in which O and N4 acted as hydrogen acceptor and donor, respectively. This intramolecular contact would make a contribution toward stabilization of the atropisomers in the crystalline state. A similar interaction was also detected in compound IIb. However, the orientation of hydrogen atoms attached to O and N4, that is, the mode of intramolecular hydrogen bonding, was different from that of compound IIa, and the distance between O and N4 was shorter. On the other hand, intermolecular hydrogen bonding among O, N2 and N4 was formed only in compound IIa. The presence or absence of such interaction can be ascribed to the difference in geometry between compounds IIa and IIb.

To examine further the character of IIa and IIb, the interconversion behavior between them in methanol and chloroform was followed as a function of time by using

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RPLC. As is shown in Fig. 3, IIa interconverted gradually to IIb, or *vice versa* and equilibrium was reached in approximately 10 h. It is considered that such behavior is due to atropisomerization between IIa and IIb. The rotational barrier about the pivot bond in compound II would be higher than that in compound I due to an increase in the bulkiness of the substituent on the thiophene ring (conversion of $=O$ to $-OH$). The population of compounds IIa and IIb in methanol at equilibrium was almost equal, but that in chloroform lay towards compound IIb, although no marked difference was observed in time required to reach equilibrium. The difference in the mode of intramolecular hydrogen bonding, which was observed in X-ray crystallographic analysis, may be one of the factors affecting this behavior.

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