Heteroatom Chemistry
Volume 6, Number 5, 1995

Crystal and Molecular Structure of Novel 10-Membered Ring Compound: 10-Chloro-1,7-ditosyl-8-phenyl-4,1,7-benzoxadiazecine

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Received 31 January 1995

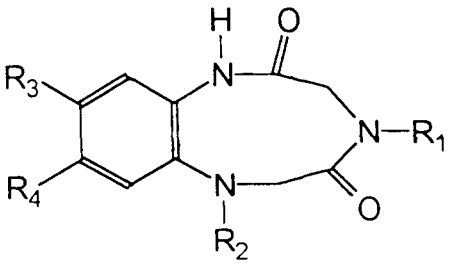
ABSTRACT

10-Chloro-1,7-ditosyl-8-phenyl-4,1,7-benzoxadiazecine is obtained by reacting the sodium salt of N,N'-*ditosyl-2-amino-5-chlorobenzhydrylamine with the ditosylate of bis(hydroxyethyl) ether in DMF. The structure of the title compound was established by X-ray crystal structure analysis. The 10-membered ring that is the core of the molecule is asymmetric and considerably folded.* © *1995 John Wiley & Sons, Inc.*

INTRODUCTION

Vast efforts have been invested in recent years into the synthesis of new, multimembered, heterocyclic systems. Upon introduction of pharmacophoric substituents suitable for a desired activity into those systems, it is expected that derivatives will be obtained exhibiting numerous favorable properties such as: analeptic activity, possible anticancer and anti-HIV activities, ability to form complexes with iron and magnesium, and forming potential radiopharmaceuticals. Seven- to 10-membered *hetero* rings are expected to participate in ion transport across cell membranes and to possess catalytic properties comparable with the activity of enzymes, as observed by Hanson and Jakubke [1], Ivanov [2], and Pedersen and Frensdorf [3]. The possibility of linking metal ions to form stable complexes allows utilization of macroheterocyclic systems for modeling the cation receptors in proteins, as reported by Ovchinnikov [4] and Müller [5]. Many macrocyclic systems are also useful in environmental protection, in medical therapies using complexones, and in the treatment of poisoning with heavy and radioactive metals, as reported by Bandot and Jacque [6] and Num et al. [7]. Within this area of research, a series of derivatives have been obtained aimed at containing the postulated 1,4,7-benzotriazonine nine-membered ring (I) (Mikiciuk-Olasik et al. [8] and Szadowska et al. [9]).

Formula of (**I**)



The supposed 2,3,4,5,6,7-tetrahydro-1*H*-1,4,7-

Dedicated to Professor Zdzisław Galdecki on the occasion of his seventieth birthday.

*Authors to whom correspondence should be addressed: structural aspects (T.J.B.), synthetic and pharmacological aspects (B.K.).

1042-7163/95/050495-04

TABLE 1 Crystal Data and Structure Refinement for **1**

Identification code	ACT3M1
Empirical formula	$C_{31}H_{31}ClN_2O_5S_2$
Formula weight	611.15
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P2(1)/*n*
Unit cell dimensions	*a* = 9.452(2) Å, α = 90° *b* = 13.032(3) Å, β = 92.54(3)° *c* = 24.049(5) Å, γ = 90°
Volume	2959.4(11) Å^3
Z	4
Density (calculated)	1.372 Mg/m^3
Absorption coefficient	0.314 mm^{-1}
F(000)	1280
Crystal size	0.40 × 0.31 × 0.28 mm
θ range for data collection	1.70 to 27.05°
Index ranges	$-12 \le h \le 12$, $0 \le k \le 16$, $0 \le l \le 30$
Reflections collected	6040
Independent reflections	5904 (R_{int} = 0.0320)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5853/0/402
Goodness of fit on F^2	1.146
Final *R* indices ($I > 2\sigma(I)$)	*R*1 = 0.0744, *wR*2 = 0.2039
R indices (all data)	*R*1 = 0.1456, *wR*2 = 0.2988
Extinction coefficient	0.033(4)
Largest diffraction peak and hole	0.648 and −0.586 eÅ^{-3}

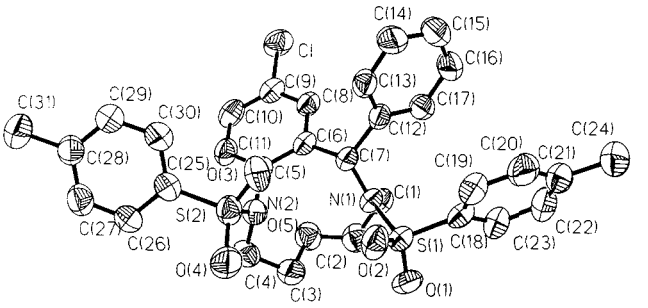


FIGURE 1 The molecular conformation of **1** with atom numbering. The thermal ellipsoids are scaled at 50% probability [12].

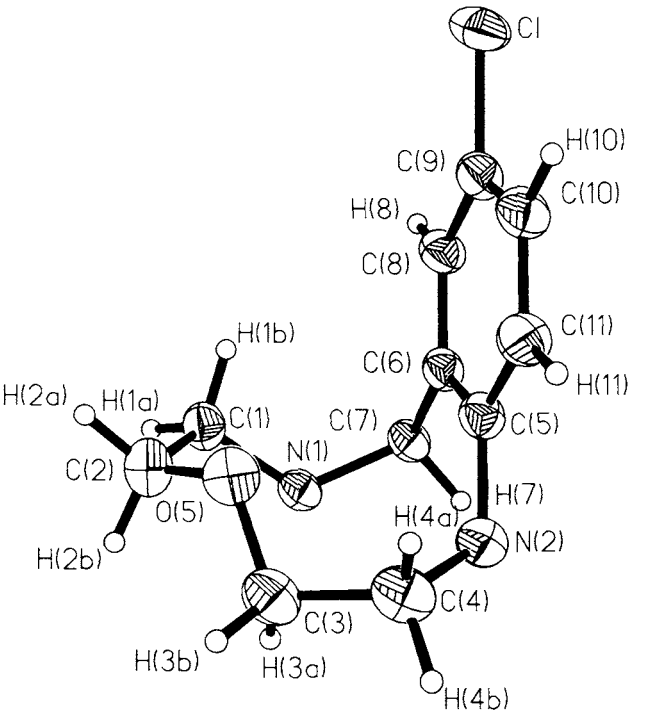


FIGURE 2 The fragment of the molecule of **1** showing the conformation of the 10-membered ring.

benzotriazonine-2,5-dione showed psychotropic activity according to a report by Szadowska et al. [9]. The compound was subjected to X-ray crystal structure analysis that showed it to be in fact 4-[2-acetyl-2- (4-ethoxyphenyl) amino-1-oxoethyl]-1,2,-3,4-tetrahydro-2-quinoxalinone [10]. Molecular formulas of both compounds are identical; 4-acyl-quinoxalin-2-ones are potential peripheral benzodiazepine receptor ligands with expected anti-HIV activity. Two derivatives were evaluated by the National Cancer Institute (Bethesda, MD) for in vitro anti-HIV activity but were found to be inactive [11]. In this work, we report the synthesis and X-ray crystal structure analysis of a derivative of the new, 4,1,7-benzoxadiazecine system: 10-chloro-1,7-ditosyl-8-phenyl-4,1,7-benzoxadiazecine (ACT3M1, **1**).

SYNTHESIS

A 5.4 g (10 mmol) amount of **N**,**N**′-ditosyl-2-amino-5-chloro benzhydrylamine was dissolved in 100 mL of hot, dry 1-butanol (solution I). Elemental sodium (0.5 g) was dissolved in 50 mL of 1-butanol contained in a 250 mL flask, and the solution was heated to 90–100°C. Then, the hot solution I was added and the contents of the flask were heated and stirred for 1 h. After evaporation in vacuo, the sodium salt obtained was dissolved in 100 mL of freshly distilled **N**,**N**-dimethylformamide (DMF). To the resulting solution at 100°C, a solution of 4.1 g (10 mmol) of the ditosylate of bis(hydroxyethyl)-ether in 40 mL of DMF was added dropwise during 3 h. The mixture was heated for 30 min, 25 mL of water was added, and the solution was left to cool. The crystals were filtered off the next day, m.p. 216–218°C.

X-RAY CRYSTALLOGRAPHY

Full details concerning the crystal structure analysis and refinement of **1** are given in Table 1. Fig-

TABLE 2 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters (Å $\times$ 10^3) for **1**

	x	y	z	$U_{(eq)}$[a]
N(1)	7979(3)	5103(3)	2202(2)	50(1)
C(1)	8283(5)	6198(4)	2115(2)	57(1)
C(2)	8624(6)	6440(5)	1521(2)	71(1)
O(5)	7552(4)	6087(3)	1133(1)	67(1)
C(3)	7908(6)	5171(5)	853(2)	68(1)
C(4)	6566(6)	4596(5)	691(2)	66(1)
N(2)	5849(4)	4243(3)	1189(2)	54(1)
C(5)	5024(4)	5002(4)	1467(2)	48(1)
C(6)	5367(4)	5276(3)	2017(2)	45(1)
C(7)	6559(4)	4760(4)	2365(2)	48(1)
C(8)	4549(4)	6047(4)	2252(2)	52(1)
C(9)	3438(4)	6488(4)	1958(2)	56(1)
C(10)	3090(5)	6210(4)	1418(2)	64(1)
C(11)	3890(5)	5458(4)	1177(2)	60(1)
Cl	2431(1)	7414(1)	2273(1)	76(1)
C(12)	6298(4)	4824(3)	2979(2)	48(1)
C(13)	5309(5)	4155(4)	3186(2)	56(1)
C(14)	4973(6)	4180(5)	3733(2)	69(1)
C(15)	5646(6)	4865(5)	4093(2)	74(2)
C(16)	6626(6)	5530(5)	3896(2)	69(1)
C(17)	6953(5)	5515(4)	3344(2)	56(1)
S(1)	9306(1)	4301(1)	2295(1)	57(1)
O(1)	10403(3)	4670(4)	1960(2)	78(1)
O(2)	758(4)	3288(3)	2208(2)	75(1)
C(18)	9951(4)	4385(4)	2988(2)	54(1)
C(19)	9517(5)	3689(5)	3380(2)	69(1)
C(20)	10055(6)	3737(6)	3923(3)	82(2)
C(21)	11030(6)	4476(6)	4087(2)	76(2)
C(22)	11446(6)	5166(5)	3694(3)	77(2)
C(23)	10924(5)	5128(5)	3150(2)	69(1)
C(24)	11651(9)	4528(9)	4682(3)	113(3)
S(2)	5311(1)	3037(1)	1219(1)	58(1)
O(3)	5115(4)	2823(3)	1789(1)	67(1)
O(4)	6293(4)	2464(3)	910(2)	78(1)
C(25)	3634(5)	2951(4)	867(2)	55(1)
C(26)	3538(6)	2736(4)	312(2)	62(1)
C(27)	2212(6)	2658(5)	43(2)	71(1)
C(28)	998(6)	2785(4)	326(2)	65(1)
C(29)	1108(6)	2990(5)	887(2)	71(1)
C(30)	2423(6)	3080(4)	1163(2)	67(1)
C(31)	−436(7)	2702(7)	20(3)	99(2)

TABLE 3 Selected Bond Lengths (Å) and Angles (°) for **1**

N(1)–C(1)	1.472(6)	N(1)–C(7)	1.484(5)
C(1)–C(2)	1.512(7)	C(2)–O(5)	1.423(6)
O(5)–C(3)	1.419(7)	C(3)–C(4)	1.510(8)
C(4)–N(2)	1.476(6)	N(2)–C(5)	1.442(6)
C(5)–C(6)	1.395(6)	C(6)–C(7)	1.528(5)
C(1)–N(1)–C(7)	120.9(3)	N(1)–C(1)–C(2)	112.8(4)
O(5)–C(2)–C(1)	112.1(4)	C(3)–O(5)–C(2)	114.0(4)
O(5)–C(3)–C(4)	109.0(4)	N(2)–C(4)–C(3)	110.9(4)
C(5)–N(2)–C(4)	116.0(4)	C(6)–C(5)–N(2)	120.4(4)
C(5)–C(6)–C(7)	122.8(4)	N(1)–C(7)–C(6)	112.2(3)

TABLE 4 Selected Torsion Angles (°) for the Atoms Belonging to 10-membered Core **1**

(N1)–C(1)–C(2)–O(5)	53.9(6)
C(1)–C(2)–O(5)–C(3)	−102.6(5)
C(2)–O(5)–C(3)–C(4)	152.0(4)
O(5)–C(3)–C(4)–N(2)	65.5(6)
C(3)–C(4)–N(2)–C(5)	79.7(5)
C(4)–N(2)–C(5)–C(6)	118.8(5)
N(2)–C(5)–C(6)–C(7)	3.3(6)
C(5)–C(6)–C(7)–N(1)	74.9(5)
C(6)–C(7)–N(1)–C(1)	45.8(5)
C(7)–N(1)–C(1)–C(2)	116.0(5)

ure 1 shows the molecule of **1** with the numbering scheme, whereas Figure 2 exhibits the conformation of the 10-membered ring. Fractional atomic coordinates are given in Table 2. Selected bond lengths and angles are listed in Table 3. A Siemens *P*3 single-crystal automatic diffractometer was used for data collection, SHELXTL [12] and SHELXL92 [13] programs being used for structure solution and refinements, respectively, on a personal computer compatible with an IBM PC. Full crystallographic details have been deposited with CCDC, United Kingdom [14].

DISCUSSION

The conformation of the reference structure in the solid state, that of cyclodecane and its derivatives, is fairly well understood largely due to X-ray crystallographic analyses by Dunitz and his co-workers [15,16,17]. The cyclodecane ring has C_{2h} symmetry, the torsion angles around the ring being approximately staggered and the C–C–C bond angles being opened to an average value of ca. 117°. Conformational biasing can be achieved by the introduction of small heteroatoms into the ring. The "normal" cyclodecane conformation can be disrupted by the special requirements of heteroatoms. Indeed, this is the case with the structure being described in this work. The 10-membered ring, which is the core of the molecule of **1**, exhibits an asymmetric conformation (Figure 2), as best shown by the torsion angles (Table 4). This breaking down of the ring symmetry is caused by the introduction of the aromatic bond C(5)–C(6) and by the presence of small heteroatoms: the trigonal N(1) and N(2) nitrogen atoms, and the oxygen O(5) in the 10-membered ring. The asymmetric conformations of 10-membered rings in 1,2,5,8-dithiadiazecine-6,7-diones, as detected by X-ray crystallography in the solid state and by NMR spectroscopy in solution, were reported by Yamaguchi et al. [18].

ACKNOWLEDGMENTS

This work was supported financially by Grant 3 0302 91 01 from the State Committee for Scientific Research, Warsaw, Poland.

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[14] Full lists of bond lengths and angles (Table 4), anisotropic thermal parameters (Table 5), hydrogen atom parameters (Table 6), and structure factors (Table 7) have been deposited with the Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom.

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