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Synthesis, Molecular Structure and Antibacterial Activity of Spiro[2,2']indane-1',3'-dione-3-(*o*-chloro)phenyl-4-nitro Pyrrolizidine

GUO-XIN SUN[1,*] and YAN-QING MIAO[2]

[1]Sports Physiology Biochemistry of Laboratory of Physical Education Department, Southwest Jiaotong University, Chengdu 611756, Sichuan, P.R. China
[2]Department of Pharmacology, Xi'an Medical University, Xi'an 710068, P.R. China

*Corresponding author: Tel/Fax: +86 28 88382693; E-mail: 53535600@qq.com

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Spiro[2,2']indane-1',3'-dione-3-(*o*-chloro)phenyl-4-nitro pyrrolizidine was synthesized by 1,3-dipolar cycloaddition reaction. It was characterized by NMR, MS and single-crystal X-ray diffraction. It crystallizes in the triclinic space group, P-1, with unit cell dimensions a = 7.6074(4) Å, b = 9.7454(5) Å and c = 12.6538(7) Å, α = 85.313(2)°, β = 84.217(2)°, γ = 86.571(2)° and Z = 2. It was screened for antibacterial activity against oilfield water-borne bacteria and it showed good to moderate activity against sulfate reducing bacteria.

Keywords: 1,3-Dipolar cycloaddition reaction, Spiro compound, Antibacterial.

INTRODUCTION

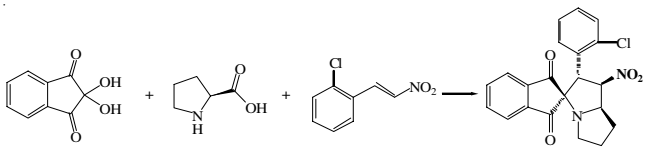
The 1,3-dipolar cycloaddition reaction is the reaction of a dipolarophile with a 1,3-dipolar compound that leads to 5-membered (hetero)cycles. Examples of dipolarophiles are alkenes and alkynes and molecules that possess related heteroatom functional groups (such as carbonyls and nitriles). 1,3-Dipolar compounds contain one or more heteroatoms and can be described as having at least one mesomeric structure that represents a charged dipole. The 1,3-dipolar cycloaddition reaction provides a simple and direct entry into a number of five-membered heterocyclic compounds such as pyrrolidines, pyrrolines and pyrroles[1-3]. In these reactions, the azomethine ylides firstly generate *in situ*, *via* decarboxylative condensation of aldehyde or ketone with α-amino acids, which can be trapped smoothly by trapping dipolarophiles forming five-membered heterocyclic compounds[4]. Almost all these reactions are in good yield with high regio- and stereoselectivity[1-4]. In this article, we synthesized spiro[2,2']indane-1',3'-dione-3- (*o*-chloro)phenyl-4-nitro pyrrolizidine (shown as **Scheme-I**) and determined the crystal structure by single-crystal X-ray diffraction for further research in regio- and stereoselectivity.

EXPERIMENTAL

All starting materials and solvents (A.R. grade) were commercially available and were used without further purification. NMR spectra were recorded in the stated solutions on a Bruker DPX 300 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C; δ values were reported in ppm and J values in hertz. Mass spectra were recorded on a Micromass PlatformIIspectrometer using the direct-inlet system operating in the electron impact (ESI) mode at 75 eV.

Synthesis of spiro[2,2']indane-1',3'-dione-3-(*o*-chloro)-phenyl-4-nitro pyrrolizidine (Scheme-I): A solution of ninhydrin (2 mmol), L-proline (2 mmol) and methyl methacrylate or (*E*)-β-2-chloro-phenyl-nitrostyrene (2.2 mmol) was stirred in 10 mL methanol at room temperature for 4 h. Completion of the reaction was evidenced by TLC analysis, the solvent was distilled off under reduced pressure and the residue was separated by column chromatography (silica gel, petroleum ether/ethyl acetate = 10: 1) to give the compounds. Yellow solid (82.3 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.91 (1H, m), 7.83 (1H, m), 7.75 (2H, m), 7.34 (1H, d, *J* = 6.4 Hz), 7.17 (1H, d, *J* = 6.4 Hz), 7.06 (1H, m), 7.0 (1H, m), 6.06 (1H, m), 5.46 (1H, d, *J* = 8.4 Hz), 4.66 (1H, m), 3.43 (1H, m), 2.82 (1H, m), 2.06 (2H, m), 1.77 (1H, m), 1.57 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 199.2, 195.4, 141.9, 140.8, 136.4, 136.2, 135.4, 130.3, 129.2, 129.1, 127.0, 123.7, 123.2, 92.6, 75.1, 65.9, 49.9, 47.0, 27.8, 25.7; ESI-MS, *m/z*: 397 (M + 1)

X-ray data collection and structure refinement: Intensity data for colourless crystals of spiro[2,2']indane-1',3'-dione-3-(o-chloro)-phenyl-4-nitro pyrrolizidine were collected at 150 K on a Bruker SMART 1000 CCD fitted with MoK_α radiation. The data sets were corrected for absorption based on multiple scans[5] and reduced using standard methods[6]. The structures was solved by direct-methods[7] and refined by a full-matrix leastsquares procedure on F^2 with anisotropic displacement parameters for non-hydrogen atoms, carbon- and nitrogen



Scheme-I: Synthesis of spiro[2,2']indane-1',3'-dione-3-(*o*-chloro)phenyl-4-nitro pyrrolizidine

bound hydrogen atoms in their calculated positions and a weighting scheme of the form w = $1/[\sigma^2(F_o^2) + (\alpha P)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3)$[8,9].

RESULTS AND DISCUSSION

A mixture of (*E*)-β-2-chloro-phenyl-nitrostyrene, ninhydrin and L-proline were refluxed in methanol and the title compound was obtained in high yields. The planar structure can be confirmed by the spectral data. The ^{1}H NMR spectra shows multiplet signals in the region δ 1.57-6.06 for the protons of hexahydro-pyrrolizine ring, in which a doublet at δ 4.69 (1H, d, *J* =12.8 Hz) indicates the presence of a benzylic proton, demonstrating the connection with C3 of the newly constructed pyrrolidine. The $CHNO_2$ proton exhibits a double doublet at δ 6.06 (1H, t, *J* = 8.0 Hz), which should correlate with C4 of the newly constructed pyrrolidine. The signals in the region δ 7.11-7.76 are for the protons of aryl groups.

Furthermore, the stereo structure of the title compound was corroborated by X-ray diffraction analysis. The main experimental data of the two compounds is displayed in Table-1 and the crystal informations are listed in Tables 2 and 3. The molecular structure is shown in Fig. 1 and the packing of the compounds are depicted in Fig. 3, which were drawn with DIAMOND[10]. The X-ray structural determination of the title compound confirmed the assignment of its structure from NMR and MS spectra data.

TABLE-1
EXPERIMENTAL DATA OF THE TITLE COMPOUND

Formula sum	$C_{21}H_{17}N_2O_4Cl$
Formula weight	396.82 (g/mol)
Crystal system	Triclinic
Space-group	P -1 (2)
Cell parameters	a = 7.6074(4) Å, b = 9.7454(5), Å c = 12.6538(7) Å α = 85.31(0)°, β = 84.22(0)°, γ = 86.57(0)°
Cell ratio	a/b = 0.7806, b/c = 0.7702, c/a = 1.6634
Cell volume	928.96(26) Å^3
Z	2
Calc. density	1.41856 (g/cm^3)

Geometric parameters of the title compound are in the usual ranges. It crystallizes in the triclinic space group, P-1, with unit cell dimensions a = 7.6074(4) Å, b = 9.7454(5) Å and c = 12.6538(7) Å. In the molecule structure, the indane-1',3'-dione and hexahydro-pyrrolizine parts join at the spiro-quaternary carbon (C2). The angle between the two planes of the phenyl and the indane parts is 64.819(64), as shown in Fig. 2. The relative configuration of this molecule could be determined as 3S, 4R, 5R. The indane-1',3'-dione moiety is nearly planar, with the C9-C14-C15-O1 torsion angle of -2.122(242)°. Effected by the asymmetric structure, the two carbonyl groups display different characters, the < C1-C15-

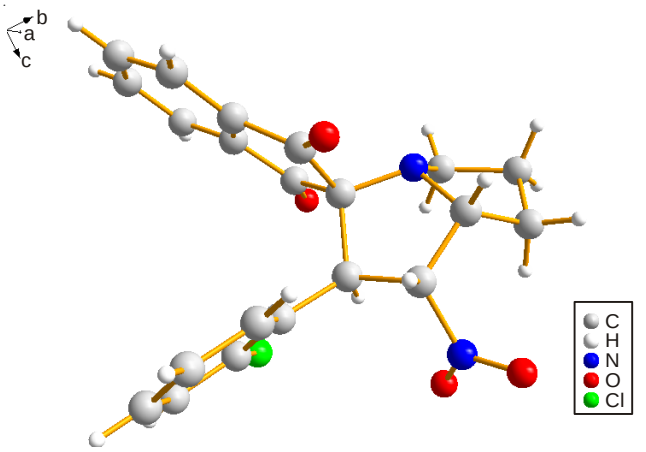


Fig. 1. Molecular structures and crystallographic numbering schemes of the title compound

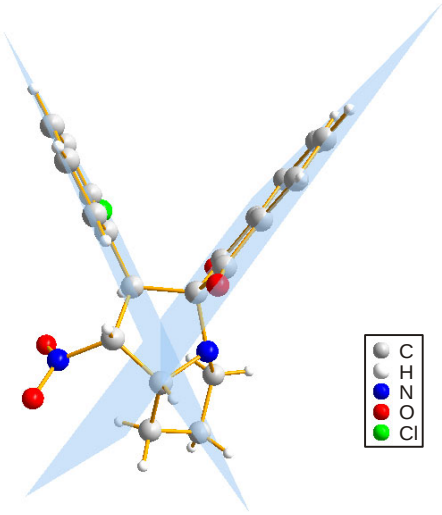


Fig. 2. Angle between the two planes

O1 is 124.301(190)° compared with 125.257(197)° of < C1-C8-O2 and < C3-N2-O3 is 119.503(258)° compared with 115.159(236)° of <C3-N2-O4. The dihedral angle between (*o*-chloro) phenyl plane and indane-1',3'-dione plane is 64.069(73)°, so the intramolecular π-π stacking interactions can be deduced.

There is no typical hydrogen bond in the two compound crystals for without hydrogen bond donor. Scarcely intermolecular π-π stacking interactions was found in the crystal of compound A as the dihedral angles are near to 90° between the neighbor planes (Fig. 3). The packing between hexahydro-pyrrolizine moieties is responsible for the crystal's frame work. Weak hydrogen bonds were fond in the crystal of the title compound, as shown in Table-3. The O3-H3A···O4 hydrogen bonds can be found between two molecules, which make the two connect to each other. The C2-H2A···Cl and O6-H6A···O1 (as shown in Fig. 3) hydrogen bonds keep the frame work extend in different way. These hydrogen bonds, as well as the π-π stacking interactions, are responsible for the crystal's 2-D supra-molecular structures.

Bioactivity: Microbiologically influenced corrosion (MIC) is metal deterioration as a result of the metabolic activity of various microorganisms. This corrosion is promoted or caused by microorganisms, typically chemoautotrophs. This type of

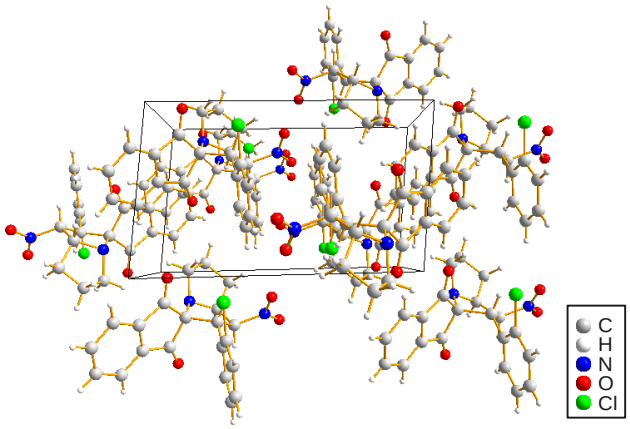


Fig. 3. Fragment of the title compound molecular packing in crystal

corrosion applies to non-metallic objects as well as metals. For instance, aerobic bacteria such as *Acidithiobacillus thioxidants* can cause significant corrosion as it serves as a factor in biogenic sulfide corrosion. MIC caused by growth of sulfate reducing bacteria (SRB), iron bacteria (IB) and total general bacteria (TGB) in oil pipelines, is considered a major problem for water treatment in the oil industry. MIC can result in different types of attack: pitting, crevices, dealloying and erosion in pipelines. Corrosion products produced by micro-organisms are production of hydrogen sulfide, molecular hydrogen, hydrogen ions and destabilization of metal oxide films. In addition, microbial degradation of crude oil can lead to increased acidity in the oil phase and oil containing acids is a problem concerning corrosion of pipelines. The reported results showed that the interaction of iron bacteria, sulfate reducing bacteria and total general bacteria accelerated the

TABLE-2
ATOMIC PARAMETERS

Atom	x/a	y/b	z/c	U (Å^2)
C11	0.6154(5)	0.0842(3)	-0.1121(2)	
H11A	0.63040	0.02000	-0.16320	0.0970
C10	0.7496(4)	0.0985(3)	-0.04932(18)	
H10A	0.85500	0.04520	-0.05710	0.0810
C12	0.4592(5)	0.1630(3)	-0.1008(2)	
H12A	0.37100	0.15070	-0.14440	0.0970
C9	0.7224(3)	0.1954(2)	0.02602(16)	
C13	0.4304(4)	0.2596(3)	-0.0265(2)	
H13A	0.32480	0.31280	-0.01960	0.0810
C14	0.5650(3)	0.2747(2)	0.03771(17)	
C19	0.3364(4)	-0.0233(3)	0.3887(2)	
H19A	0.25350	-0.08890	0.41010	0.0910
C18	0.5127(4)	-0.0629(3)	0.37342(19)	
H18A	0.54980	-0.15520	0.38480	0.0850
C20	0.2827(3)	0.1129(3)	0.3725(2)	
H20A	0.16320	0.13970	0.38290	0.0860
C17	0.6353(3)	0.0355(2)	0.34081(18)	
C21	0.4056(3)	0.2101(3)	0.34090(18)	
H21A	0.36700	0.30210	0.33040	0.0730
C16	0.5864(3)	0.1748(2)	0.32416(16)	
C2	0.7201(3)	0.2832(2)	0.29260(16)	
H2A	0.83500	0.24360	0.31210	0.0570
C1	0.7462(3)	0.3384(2)	0.17331(16)	
C3	0.6837(3)	0.4174(2)	0.34718(18)	
H3A	0.55580	0.43890	0.35450	0.0690
C4	0.7739(3)	0.5315(2)	0.2727(2)	
H4A	0.68670	0.60730	0.25850	0.0730
C5	0.9394(4)	0.5899(3)	0.3069(3)	
H5A	0.91270	0.68050	0.33280	0.1010
H5B	0.98860	0.52960	0.36250	0.1010
C6	1.0641(4)	0.5979(3)	0.2086(3)	
H6A	1.18580	0.59740	0.22530	0.1040
H6B	1.03810	0.67980	0.16270	0.1040
C7	1.0290(3)	0.4687(3)	0.1581(3)	
H7A	1.07330	0.47330	0.08330	0.0940
H7B	1.08240	0.38760	0.19440	0.0940
C15	0.5693(3)	0.3667(2)	0.12332(17)	
C8	0.8435(3)	0.2310(2)	0.10251(17)	
N1	0.8339(2)	0.46793(19)	0.17182(15)	
N2	0.7489(4)	0.4054(3)	0.4566(2)	
O1	0.4561(2)	0.45170(17)	0.15165(14)	
O2	0.9923(2)	0.18334(19)	0.11038(15)	
O3	0.8570(6)	0.3144(3)	0.4791(2)	
O4	0.7008(3)	0.5002(4)	0.5114(2)	
Cl1	0.85658(10)	-0.02166(7)	0.32378(7)	

TABLE-3
ANISOTROPIC DISPLACEMENT PARA0METERS (Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C11	0.123(3)	0.0694(17)	0.0524(14)	-0.0097(17)	-0.0158(15)	-0.0130(12)
C10	0.0910(18)	0.0574(15)	0.0520(13)	0.0015(13)	0.0011(12)	-0.0096(11)
C12	0.113(2)	0.0724(18)	0.0640(16)	-0.0152(17)	-0.0351(15)	-0.0043(14)
C9	0.0625(13)	0.0491(12)	0.0451(11)	-0.002(1)	0.0007(9)	-0.0035(9)
C13	0.0758(17)	0.0630(15)	0.0668(15)	-0.0053(12)	-0.0239(12)	0.0020(12)
C14	0.0594(13)	0.0459(12)	0.0494(11)	-0.0035(9)	-0.0083(9)	-0.0004(9)
C19	0.0816(19)	0.092(2)	0.0586(15)	-0.0372(16)	-0.0126(13)	-0.0001(14)
C18	0.096(2)	0.0618(16)	0.0584(14)	-0.0151(14)	-0.0204(13)	-0.0031(12)
C20	0.0573(15)	0.092(2)	0.0674(16)	-0.0180(14)	-0.0072(12)	-0.0061(14)
C17	0.0651(14)	0.0614(15)	0.0519(12)	-0.0029(11)	-0.0137(10)	-0.0096(10)
C21	0.0534(13)	0.0685(15)	0.0607(14)	-0.0065(11)	-0.0058(10)	-0.0091(11)
C16	0.0506(12)	0.0574(13)	0.0439(11)	-0.0033(9)	-0.0083(9)	-0.0106(9)
C2	0.0414(11)	0.0523(12)	0.0507(11)	0.0020(9)	-0.0063(8)	-0.0137(9)
C1	0.0406(10)	0.0475(12)	0.0542(12)	0.0061(8)	-0.0032(8)	-0.0131(9)
C3	0.0410(11)	0.0697(15)	0.0664(14)	-0.002(1)	-0.0022(10)	-0.0317(12)
C4	0.0568(13)	0.0467(13)	0.0807(16)	0.0103(10)	-0.0067(11)	-0.0178(11)
C5	0.089(2)	0.0678(17)	0.102(2)	-0.0292(15)	-0.0058(17)	-0.0252(15)
C6	0.0626(17)	0.0763(19)	0.122(3)	-0.0167(14)	0.0004(16)	-0.0191(17)
C7	0.0492(14)	0.0848(19)	0.103(2)	-0.0086(13)	0.0021(13)	-0.0275(16)
C15	0.0453(11)	0.0470(12)	0.0563(12)	0.0030(9)	-0.0049(9)	-0.0027(9)
C8	0.0489(12)	0.0525(13)	0.0550(12)	0.0059(10)	0.0027(9)	-0.0099(10)
N1	0.0464(10)	0.0517(11)	0.0675(12)	0.0004(8)	-0.0036(8)	-0.0111(9)
N2	0.0863(17)	0.116(2)	0.0717(15)	-0.0361(16)	-0.0014(13)	-0.0421(16)
O1	0.0500(9)	0.0686(11)	0.0868(12)	0.0171(8)	-0.0136(8)	-0.0194(9)
O2	0.0537(10)	0.0827(12)	0.0927(13)	0.0212(9)	-0.0050(9)	-0.0324(10)
O3	0.267(4)	0.0950(19)	0.111(2)	-0.017(2)	-0.107(2)	-0.0120(15)
O4	0.0941(17)	0.261(4)	0.123(2)	-0.028(2)	0.0110(14)	-0.134(2)
Cl1	0.0771(5)	0.0626(4)	0.1210(6)	0.0146(3)	-0.0144(4)	-0.0073(4)

corrosion rate and the corrosion in the mixture of iron bacteria, sulfate reducing bacteria and total general bacteria was more serious than in a single microbial system. If this is the case, different treatment system to inhibit corrosion should be considered, among which bactericide agent has received the greatest acceptance. Currently, oxidizer, aldehyde, quatemary ammonium salt and heterocyclic compounds has been used as bactericide agents and Cl_2, ClO_2, formaldehyde, pentane-1,5-dial and trichloroisocyanuric acid (TCCA), *etc*, but the toxicity tests have been conducted on a limited selection. The antifungal activity of the title compound against oilfield microorganism was tested under the concentration of 0.20 and 0.02 g/L and the results were summarized in Table-4. From the table, it can be found that spiro[2,2']indane-1',3'-dione-3-(*o*-chloro)-phenyl-4-nitro pyrrolizidine is antifungal active against sulfate reducing bacteria and iron bacteria, but less active against total general bacteria under both concentrations.

TABLE-4
ANTIFUNGAL ACTIVITY OF SPIRO[2,2']INDANE-1',3'-DIONE-3-(*o*-CHLORO)PHENYL-4-NITRO PYRROLIZIDINE AGAINST OILFIELD WATER-BORNE BACTERIA

Concentration	Microbiotic concentration (mL)		
	Sulfate reducing bacteria	Iron bacteria	Total general bacteria
–	110.0	110.0	110.0
0.20 g/L	0.0	0.0	50.0
0.02 g/L	0.0	1.3	25.0

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