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Synthesis and Crystal Structure of 1,7,8,9-Tetrachloro-*N*-ethyl-10,10-dimethoxy-4-azatricyclo(5,2,1,$0^{2,6}$)dec-8-ene-3,5-dione

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1,7,8,9-Tetrachloro-*N*-ethyl-10,10-dimethoxy-4-azatricyclo(5,2,1,$0^{2,6}$)dec-8-ene-3,5-dione was obtained by Diels-Alder reaction between *N*-ethylmaleimide with 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene in toluene. Its structure was characterized by elemental analysis, ^{1}H NMR, MS and X-ray single-crystal diffraction techniques. The title compounds comprise a polycyclic fused pyrrolidine ring system. Two methoxyl groups lied in symmetry axis on the top of "chair" cycloheptane structure.

Keywords: Polycyclic fused pyrrolidine ring, Diels-Alder reaction, Crystal structure.

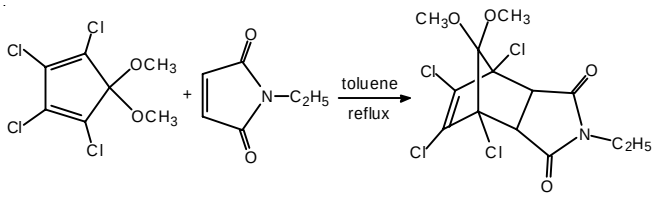
INTRODUCTION

Cyclic imides and their derivatives, such as succinimides, maleimides, glutarimides, phthalimides, possess structural features, bearing potential biological activity and pharmaceutical use. The fused pyrrolidine ring systems compounds, such as X-azatricyclo[m.n.0.0^{a,b}]alkanes, are frequently encountered structural unit in many synthetically challenging and biologically active alkaloids [1-3]. As a consequence, the construction of polycyclic fused pyrrolidine ring system has emerged as an important and challenging synthetic endeavor. The Diels-Alder reactions between N-substituted maleimide with cyclodiene compounds is identified as one of the most attractive strategy for the construction of isolated as well as fused pyrrolidine ring systems. Taking the advantage of the intramolecular [3+2]-cycloadditions, compounds possessing complex molecular framework such as bicyclic and polycyclic1 fused pyrrolidine ring systems were obtained. We envisaged the construction of 4-azatricyclo(5,2,1,$0^{2,6}$)alkanes, a important azatricyclic structural entities, by the intramolecular [3+2]-dipolar cycloaddition reaction of *N*-substituted maleimide with cydopentadiene. The interest of constructing skeletons of this type 7 was further enlightened by the recent report of Kozio *et al.* [4,5] that the rigid arylcyclo analogues having azatricyclo ring systems show anti-HIV-1 activity, anticancer, antiviral and antibacterial activities [6].

Recently, we synthesized a series of fused pyrrolidine ring compounds *N*-substituted 1,7,8,9-tetrachloro-10,10-dimethoxy-4-azatricyclo(5,2,1,02,6)dec-8-ene-3,5-dione as a kind of potent anticancer reagent [7,8]. The biological tests suggest that the title compound displays more effective inhibitory activity on the growth of cancer cell lines.

EXPERIMENTAL

All reagents were commercially available and used without further purification or purified by standard methods prior to use. Melting points were determined using a RY-1 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on JNM-ECA-400 400 MHz instrument in the solvent indicated below. Chemical shift values are reported in parts per million (ppm) relative to those for tetramethylsilane used as an internal reference standard. Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. Elemental analysis was carried at the CarloErba-1106. *N*-ethylmaleimide was synthesized as similar method described in the literature [9]. The synthetic pathway for the title compound is outlined in **Scheme-I**.



Scheme-I: Synthesis of the title compound

N-Ethylmaleimide (1.88 g, 15 mmol) and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (3.96 g, 15 mmol) were dissolved in anhydrous toluene (200 mL). Then the solution

was refluxed for 8 h. After the solvent was removed under reduced pressure, the residue was dissolved in ether (300 mL), washed with water and brine, dried over anhydrous sodium sulfate and concentrated to dryness. The product was purified by flash-chromatography (petroleum ether/ethyl acetate, 6:1) and the title compound was isolated as a white solid (4.55 g, 78 %). m.p.: 104-106 °C. ^{1}H NMR (ppm, $CDCl_3$, 25 °C) δ: 3.78 (2H, s), 3.69 (s, 3H), 3.61 (2H, m), 3.58 (s, 3H), 1.35 (3H, m). ESI-MS: 390.5(M^{+1}). Anal. calcd. (%) For $C_{13}H_{13}NO_4Cl_4$: C, 40.13; H, 3.37; N, 3.60. Found (%): C, 40.85; H, 3.31; N, 3.52.

Crystallographic study: A colourless crystal of the title compound with dimensions of 0.25 mm × 0.20 mm × 0.15 mm was mounted on a glass fiber in a random orientation. The data were collected by a Bruker CCD-1000 diffractometer with a graphite-monochromated MoK_α radiation (λ = 0.71073 Å) by using an ω scan mode in the range of $3.10 \le \theta \le 27.48°$ at 293(2) K. The structure was solved by direct methods and all data were corrected by using SHELXL-97 program [10]. Unit cell dimensions were obtained with least-squares refinements. A total of 30978 reflections were collected with 7573 unique ones (R_{int} = 0.0620), of which 398 with $I > 2\sigma(I)$ were considered as observed and used in the succeeding refinements. All the other non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was carried out by full-matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. The hydrogen atoms were added theoretically and allowed to ride on the concerned atoms and refined with fixed thermal factors. The final refinement gave R = 0.0481 and wR = 0.1214 for 398 observed reflections ($w = 1/[\sigma^2(F_o)^2 + (0.0750\,P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$), S = 0.998, $(\Delta/\sigma)_{max}$ = 0.092, $(\Delta\rho)_{max}$ = 0.276 and $(\Delta\rho)_{min}$ = -0.278 e/Å^3.

RESULTS AND DISCUSSION

The title compound was obtained by the Diels-Alder reaction between *N*-ethylmaleimide with 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene in toluene. Crystals of the title compound suitable for X-ray structure determination were obtained from the filtrate by slow evaporation of the Et_2O solution.

The ^{1}H NMR, MS and elemental analysis for the product are in good agreement with the title compound. Crystallographic data and experimental details for structural analyses are summarized in Table-1. The selected bond distances and angles are listed in Table-2. Fig. 1 shows the molecular structure of the title compound.

The X-ray ORTEP structure of the title compound with atomic labeling is shown in Fig. 1. X-ray structure analytical data show that the title compound is composed of a polycyclic fused pyrrolidine ring system. Three symmetric fused five-membered rings structure was formed by the Diels-Alder reaction between *N*-ethylmaleimide with 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene. The bond angle of C(2)-C(1)-C(7)(99.8(2)°) and C(6)-C(1)-C(7)(100.46(19)°), C(5)-C(4)-C(7)(100.14(519)°) and C(7)-C(4)-C(3) (99.41(19)°) are very closed. Two methoxyl groups lied in the symmetry axis, on the top of "chair" cycloheptane structure. The distance of C(2)-C(3) is 1.325(4) Å indicated that is a double bond, it is shorter than the normal C-C bonds. The maleimide ring is adapted a quasi-plane. The distance of C(11)-O(3)and C(10)-O(4) are 1.206(3) Å and 1.197(3) Å respectively, which is very shorten than C(8)-O(1)(1.439(4) Å) single bond in the methoxyl group indicated that they are two carbonyl double bonds. The imide part in the maleimide ring is involved in a similar conjugated system which consists of two peptide units: N(1)-C(11)=O(3)and N(1)-C(10)=O(4), causing the shortening of C-N distance around the O atom. (N(1)-C(10)(1.390(3) Å) and N(1)-C(11)(1.373(3) Å). The imide moiety is symmetric having equal respective bond lengths within the (O(3))C(11)-

TABLE-1
CRYSTALLOGRAPHIC DATA AND STRUCTURE REFINEMENT SUMMARY FOR THE TITLE COMPOUND

CCDC deposit No.	1059964
Empirical formula	$C_{13}H_{13}NO_4Cl_4$
Molecular weight	389.05
Measured temperature	23(2) K
Crystal size (mm^3)	0.25 × 0.20 × 0.15
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 12.824(3) Å b = 8.1512(16) Å c = 32.111(6) Å β = 99.41(3)°
Volume V (Å^3)	3311.4(11)
Z	4
D_{calcd} (g cm^{-3})	1.561
μ (mm^{-1})	0.729
F (000)	1584
θ range (°)	3.10-27.48°
Completeness to θ	99.6 %
h/k/l	-16/16, -10/10, -41/41
Reflection unique	7573
Parameters refined	398
R(int)	0.0620
Final R indices [$I \ge 2\sigma(I)$]	R1 = 0. 0481, wR2 = 0.1214
Goodness of fit	0.998
Residual electron densities (e Å^{-3})	0.276 and -0.278

TABLE-2
SELECTED BOND LENGTHS (Å) AND BOND ANGLES (°)

Bond	Dist.	Angle	(°)
O1-C7	1.389(3)	C10-N1-C11	113.9(2)
O2-C9	1.433(3)	C2-C1-C6	109.0(2)
N1-C10	1.390(3)	C3-C2-C1	108.0(2)
C1-Cl3	1.753(3)	C3-C4-C5	107.3(2)
C1-C6	1.546(4)	O2-C7-C1	108.12(19)
C3-C4	1.508(4)	O3-C11-N1	124.4(3)
C5-C10	1.518(4)	O4-C10-N1	124.8(3)
O1-C8	1.439(4)	C11-N1-C12	122.7(2)
O3-C11	1.206(3)	C2-C1-C7	99.8(2)
N1-C11	1.373(3)	C2-C3-C4	107.6(2)
C2-Cl1	1.694(3)	C7-C4-C5	100.14(19)
C1-C7	1.573(3)	O1-C7-C1	115.8(2)
C4-C7	1.573(4)	O3-C11-C6	127.3(3)
C5-C6	1.531(3)	O4-C109-C5	127.6(3)
O2-C7	1.377(3)	C12-N1-C10	123.3(2)
O4-C10	1.197(3)	C6-C1-C7	100.46(19)
N1-C12	1.468(4)	C3-C4-C7	99.41(19)
C1-C2	1.507(4)	O2-C7-C4	118.8(2)
C2-C3	1.325(4)	C4-C7-C1	91.16(18)
C4-C5	1.558(3)	N1-C11-C6	108.3(2)
C6-C11	1.506(4)	N1-C10-C5	107.7(2))

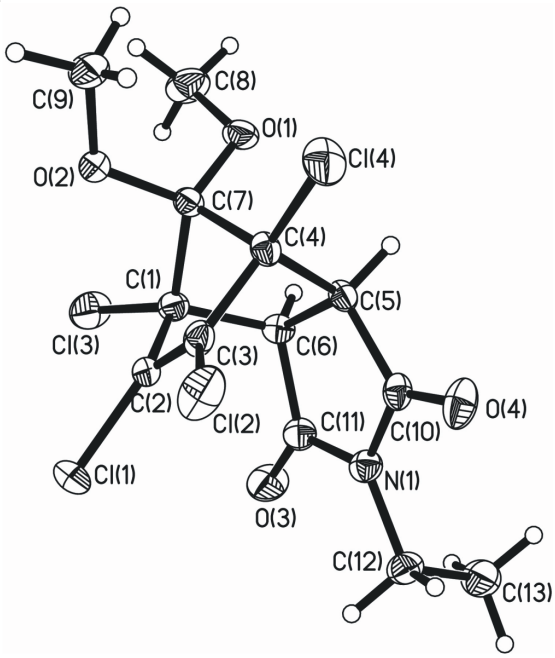


Fig. 1. Molecular structure of the title compound with 20 % probability of thermal ellipsoids

N1-C(10)(O(4)) fragment, indicating the hydrocarbon skeleton is rigid.

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