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Crystal and Molecular Structure of Chelidonine

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The crystal and molecular structure of benzophenantridine alkaloid chelidonine, $C_{20}H_{19}NO_5$ (M = 353.37) was solved by direct methods and refined by the least-squares technique to a conventional *R* index of 0.117 for 1888 unique reflections. The crystals are monoclinic, space group *P*2$_1$. Both, B and C rings have half chair conformation and are in *cis* junction. The *N*-methyl and C14-hydroxyl groups are in equatorial and axial positions, respectively. The OH-group forms intramolecular hydrogen bond with N atom. Conformation of the molecule is quite different from that found in chelidonine-*p*-brombenzoate[1](CBB).

INTRODUCTION

In the course of our studies of natural products we investigated the crystal and molecular structure of benzophenantridine alkaloid chelidonine isolated from *Chelidonium majus L. (Papaveraceae).* In Europe and in Asia it has been used from time immemorial as medicinal plant. The aerial parts of the plant were collected at a locality of Fruška Gora in the flowering phase. Chelidonine was isolated as a dominant alkaloid. The plant material was extracted with methanol[2] and the alkaloids were separated by column chromatography[3]. Chelidonine has physiological effects similar to papaverin because it affects spasmodically the path of billious acids and bronchi.[4] The relative configuration of chelidonine was determined by Šantovy *et al.*[5] while its total synthesis was performed by Oppolzer and Keller.[10]. Chelidonine has been applied in the homeopat treatment of hepatitic diseases.[11]

EXPERIMENTAL

Crystal Data

From single crystal diffractometry: $a=0.8964(3)$, $b=0.9115(3)$, $c=1.0622(3)$ nm, $\beta=93.32(3)°$, $V=0.866$ nm^3, $Z=2$, $D_x=1.354$ Mgm^{-3}, space group $P2_1$, F(000)=372, $\mu(MoK\alpha)=0.91$ cm^{-1}, $\lambda=0.07107$ nm, crystal size: 0.219×0.219×0.292 mm.

Intensity Data, Structure Determination and Refinement

Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer (Berne) equipped with graphite monochromator using ω-2Θ scan in the range 2Θ<53.9°. Cell constants were determined by least-squares from setting angles of 20 reflections collected in the range of 4.4°<Θ<8.4° scanned by $MoK\alpha$ radiation. The systematic absences are $k=2n+1$ in OkO. $h_{max}=11$, $k_{max}=11$, $l_{max}=13$. A standard reflection ($\bar{2}$ $\bar{2}$ 0) was monitored every 200 min. but no intensity variations were recorded. Of the 2007 measured reflections, 1888 with $F_o>3\sigma(F_o)$ were taken as observed. No correction for absorption was applied.

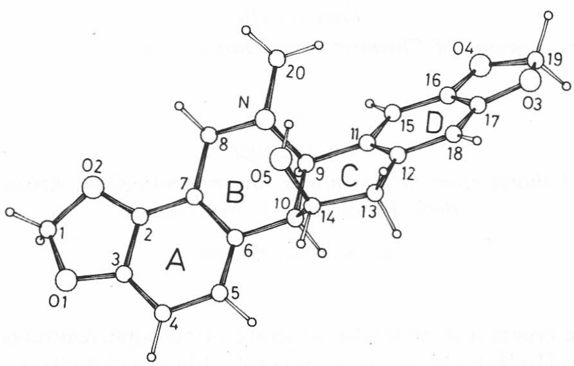

Figure 1. A perspective view of the molecule with the numbering sheme. Numbers refer to C atoms unless otherwise indicated.

The structure was solved by direct methods using the SHELX86 program.[6] An E-map computed by using the phase set for 291 normalized structure factors having $E>1.20$ revealed all 26 non-hydrogen atoms ($R=0.240$). Refinement was performed using the SHELX76 program[7] by the least-squares procedure, minimizing $\Sigma w(|F_o|-|F_c|)^2$ for 235 parameters, assuming unit weights for all reflections. Hydrogen atoms were generated from assumed geometry. They were not refined but included in the structure factor calculations. Final R is 0.117 for the 1888 reflections observed. The high R-value is due to the poor quality of the crystal. In the final stage, the maximum ratio of shift to error was 0.09. Max. and min. heights in the final difference Fourier synthesis are 425 e/nm^3 and -363 e/nm^3, respectively. Scattering factors were taken from SHELX76. All calculations* were carried out on a PC AT computer.

* Lists of the observed and calculated structure factors and anisotropic thermal parameters are obtainable from the authors on request.

DESCRIPTION OF THE STRUCTURE AND DISCUSSION

Figure 1 shows a perspective view of the molecule of the title compound computed from the fractional atomic coordinates given in Table I and II. Figure 2 shows a packing of the molecules. Bond distances and bond angles are listed in Table III.

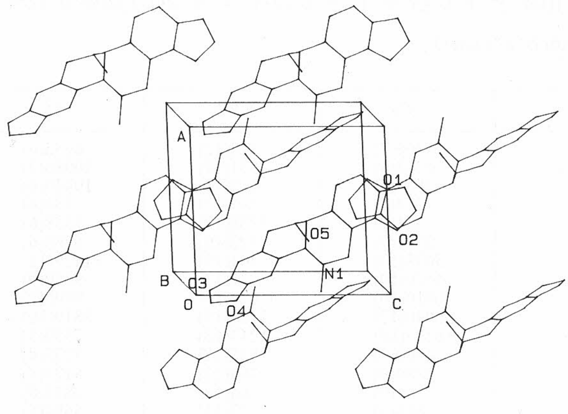

Figure 2. Packing of the molecules.

In the five-membered rings, the C-O single bonds are of two types: the first type involves the C-atom of an aromatic ring and varies in length between 0.137 and 0,138 nm, and the second type involves the C-atom of a CH_2 group and ranges from 0.143

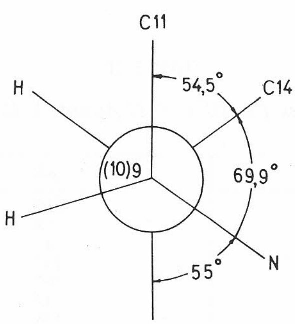

Figure 3. Newman projection perpendicular to C9-C10 bond.

to 0.146 nm. The mean value of three C-N-C angles (111°)indicates sp^3 hybridization of N-atom. The dihedral angle between A and D benzene rings is 47.9(3)°. The corresponding angles in two symmetrically independent CBB molecules are 84° and 90°.

TABLE I

Atomic Coordinates ($\times 10^4$) of non-H Atoms and Equivalent Isotropic Thermal Parameters (pm^2) with Estimated Standard Deviation in Parentheses.

$$U_{eq} = \frac{1}{3} \mid U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2(U_{12}aba^*b^*cos\gamma + U_{13}aca^*c^*cos\beta + U_{23}bcb^*c^*cos\alpha) \mid$$

	x/a	y/b	z/c	U_{eq}
N	1766(7)	440(12)	6632(6)	330(10)
01	6283(9)	534(14)	10988(7)	620(20)
02	3857(8)	-172(13)	10440(6)	520(20)
03	217(8)	387(12)	734(6)	490(20)
04	-54(9)	-1788(12)	1858(6)	480(20)
05	2754(7)	3226(0)	6260(6)	370(10)
C1	5038(13)	-304(19)	11429(11)	640(30)
C2	4526(10)	271(13)	9379(9)	370(20)
C3	6010(10)	679(15)	9706(9)	420(20)
C4	6940(12)	1168(15)	8819(10)	500(30)
C5	6303(10)	1243(13)	7559(9)	360(20)
C6	4860(9)	835(12)	7233(8)	300(20)
C7	3889(9)	369(12)	8173(8)	310(20)
C8	2291(9)	-66(14)	7877(8)	360(20)
C9	2813(9)	27(11)	5694(8)	270(20)
C10	4241(10)	984(12)	5910(8)	310(20)
C11	2163(9)	190(13)	4339(8)	310(20)
C12	2405(10)	1483(13)	3651(9)	360(20)
C13	3420(11)	2691(13)	4142(9)	390(20)
C14	3889(10)	2608(12)	5538(9)	340(20)
C15	1334(10)	-972(13)	3789(8)	320(20)
C16	770(10)	-775(13)	2567(9)	350(20)
C17	953(10)	477(15)	1894(9)	380(20)
C18	1752(11)	1644(15)	2422(9)	400(20)
C19	-299(13)	-1093(16)	625(11)	520(20)
C20	202(9)	-108(15)	6394(9)	430(20)

TABLE II

Atomic Coordinates ($\times 10^3$) of H-Atoms | $U = 510(70)\ pm^2$

	x/a	y/b	z/c
H	184	269	610
H1A	468	18	1229
H1B	160	42	856
H4	809	147	905
H5	698	162	682
H8A	160	42	856
H8B	219	-125	791
H9	305	-112	586
H10	506	59	529
H13A	443	265	362
H13B	286	372	396
H14	488	325	577
H15	114	-197	431
H18	188	265	189
H19A	29	-168	-8
H19B	-148	-109	36
H20A	-23	24	547
H20B	-48	34	710
H20C	18	-129	645

TABLE III

Interatomic Distances (nm) and Angles (°) with Estimated Standard Deviation in Parentheses

C1-01	0.1452(14)	C10-C14	0.1560(12)
C1-02	0.1453(13)	C11-C12	0.1410(13)
C2-02	0.1368(11)	C11-C15	0.1402(12)
C2-C3	0.1405(13)	C12-C13	0.1502(13)
C2-C7	0.1374(12)	C12-C18	0.1408(13)
C3-01	0.1377(12)	C13-C14	0.1519(13)
C3-C4	0.1368(15)	C14-05	0.1426(11)
C4-C5	0.1425(14)	C15-C16	0.1377(13)
C5-C6	0.1371(12)	C16-04	0.1379(11)
C6-C7	0.1427(11)	C16-C17	0.1362(14)
C6-C10	0,1487(12)	C17-03	0.1366(11)
C7-C8	0.1502(11)	C17-C18	0.1382(15)
C8-N	0.1453(11)	C19-03	0.1429(15)
C9-N	0.1457(11)	C19-04	0.1460(13)
C9-C10	0.1555(11)	C20-N	0.1496(11)
C9-C11	0.1528(11)		
02-C1-01	105.4(9)	C9-C11-C15	118.9(8)
C1-01-C3	105.8(8)	C10-C6-C7	118.7(7)
01-C3-C2	109.3(9)	C10-C9-C11	110.5(7)
C3-C2-02	109.2(8)	C10-C14-05	112.3(7)
C1-02-C2	106.5(7)	C10-C14-C13	109.6(7)
C2-C3-C4	121.5(9)	C11-C12-C13	122.7(8)
01-C3-C4	129.2(9)	C11-C15-C16	116.8(8)
C3-C2-C7	123.3(8)	C11-C9-N	113.2(6)
02-C2-C7	127.5(8)	C11-C12-C18	120.0(9)
C3-C4-C5	115.8(9)	C12-C13-C14	115.5(7)
C4-C5-C6	123.0(9)	C12-C11-C15	120.6(8)
C5-C6-C7	120.6(8)	C12-C18-C17	118.3(9)
C5-C6-C10	120.6(8)	C13-C12-C18	117.2(9)
C6-C7-C2	115.7(8)	C13-C14-05	109.8(8)
C2-C7-C8	121.2(7)	C14-C10-C6	112.6(7)
C6-C7-C8	123.0(7)	C15-C16-C17	123.7(9)
C7-C8-N	111.2(7)	C15-C16-04	125.7(9)
C8-N-C9	110.7(6)	C16-C17-C18	120.5(8)
C8-N-C20	107.4(7)	C16-C17-03	110.9(9)
N-C9-C10	108.1(7)	C16-04-C19	104.3(8)
C9-N-C20	115.6(7)	C17-C16-04	110.6(8)
C9-C10-C6	110.3(7)	C17-03-C19	105.5(8)
C9-C10-C14	110.0(7)	C18-C17-03	128.6(10)
C9-C11-C12	120.5(8)	03-C19-04	107.8(8)

Both, B and C rings have half-chair conformation and are fused by *cis*-junction. Puckering parameters of Cremer and Pople[8] are: Q=0.054(1) nm, $\varnothing$=218(2)°, Θ=48(1)° for ring B and Q=0.051(1)nm, $\varnothing$=346(2)°, Θ=46(1)° for ring C. Contrary to the CBB, the N-methyl group is in equatorial position. In accordance with the antiperiplanar[9] torsion angle, C6-C10-C9-C11=179.4(8)° (Figure 3). (in CBB molecules they are synclinal, 74°, 81°), the C14-hydroxyl group assumes axial position, whereas the bromobenzoyl moiety in CBB is in equatorial position. The OH group is bent over ring B donating only an intramolecular hydrogen bond to N-atom with the parameters O5-H: 0.096 nm, N...H: 0.213 nm, O5...N: 0.273 nm, ∡O5-H...N: 119°. The molecules are linked together by van der Waals interactions.

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SAŽETAK

Kristalna i molekulska struktura helidonina

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Kristalna i molekulska struktura helidonina, $C_{20}H_{19}NO_5$, određena je direktnim metodama i utačnjena do R = 0.117 za 1888 refleksa. Kristali pripadaju monoklinskom sistemu, a prostorna grupa je $P2_1$. Prstenovi B i C poseduju polustoličastu konformaciju, *N*-metilna grupa je u ekvatorijalnom, C14-hidroksilna grupa u aksijalnom položaju. OH grupa gradi intramolekulsku vodoničnu vezu sa *N*-atomom. Konformacija molekula bitno se razlikuje od one u helidonin-*p*-brombenzoatu.