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X-RAY STRUCTURAL INVESTIGATION OF THE ALKALOID SPECIOSINE

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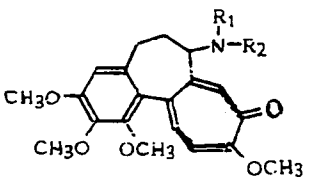
The molecular and crystalline structures of a tropolone alkaloid of the colchicine series — speciosine — have been determined by x-ray structural analysis. It has been established that the presence of an ortho-*hydroxyphenyl group does not lead to appreciable changes of the colchicine skeleton in the speciosine molecule. In the crystals, the speciosine molecules are linked into zigzag chains through O6—H···O1 intermolecular H-bonds.*

Speciosine ($C_{28}H_{31}NO_6$) is one of the minor components in the total alkaloids of the tuberous roots of the showy autumn crocus (*Colchicum speciosum* Stev.) [1, 2]. In the production of the main alkaloids of the plant — colchicine (**1**) and colchamine (**2**) — speciosine (**3**) accumulates in considerable amounts and, being a potential antimitotic agent, may have independent practical interest [3]. However, no method for its isolation has been adequately developed and its chemical transformations and fine structure have remained little studied. With the aim of elucidating the fine details of its molecular and crystalline structures, we have made a complete x-ray analysis of the alkaloid speciosine.



1. R_1=H, R_2=$COCH_3$
2. R_1=H, R_2=CH_3
3. R_1=CH_3, R_2=$CH_2C_6H_5OH$

The skeleton of the speciosine molecule consists of three condensed rings with various functional groups: a six-membered aromatic ring (ring *A*) with three methoxy groups, a cycloheptadiene ring (ring *B*) with an (*ortho*-hydroxyphenyl)methylamino group, and a seven-membered aromatic ring (the tropolone ring *C*) with carbonyl and methoxy groups (Fig. 1).

The six-membered aromatic ring *A* is planar with a maximum deviation of the atoms from the plane of 0.004 Å. One of the methoxy groups, O5—C20, lies in the plane of ring *A* (dihedral angle 8.9°) and the O5—C20 bond is directed toward the cycloheptadiene ring *B*. The other two methoxy groups, O3—C18 and O4—C19, which may have a different arrangement in colchicine and colchamine crystals [4-7], are *cis*-oriented in relation to the plane of ring *A* in speciosine. The dihedral angles between the plane of the aromatic ring *A* and the O4—C19 and O3—C18 methoxy groups are equal, at 56.5°.

The cycloheptadiene ring *B* has a distorted boat conformation formed by three planes: C14,C9,C8,C5 — plane I (with an accuracy of 0.013 Å): C14,C15,C5,C6 — plane II (with an accuracy of 0.14 Å); and C15,C16,C6 — plane III. The dihedral angle between planes I and II is 54°, between II and III, 55°; and between I and III, 72°.

The tropolone ring *C* is roughly planar (to within 0.03 Å). It shows a clear alternation of short and long bonds. The O2—C21 methoxy group is arranged almost parallel to the plane of the ring (dihedral angle 2.7°). The dihedral angle between rings *A* and *C* is 52.4°.

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TABLE 1. Interatomic Distance (r, Å) and Valence Angles (ω, deg)

Distance	r	Distance	r	Angle	ω	Angle	ω
C1-C2	1.485(9)	C1-C7	1.42(2)	C2-C1-C7	122.3(7)	C2-C1-O1	119.0(7)
C1-O1	1.25(2)	C2-C3	1.35(2)	C7-C1-O1	118.7(7)	C1-C2-C3	128.2(7)
C2-O2	1.34(2)	C3-C4	1.40(2)	C1-C2-O2	109.8(6)	C3-C2-O2	122.0(7)
C4-C5	1.37(1)	C5-C6	1.44(1)	C2-C3-C4	129.7(7)	C3-C4-C5	131.4(7)
C5-C8	1.49(2)	C6-C7	1.34(2)	C4-C5-C6	124.7(7)	C4-C5-C8	117.5(6)
C6-C16	1.55(1)	C8-C9	1.417(9)	C6-C5-C8	117.7(6)	C5-C6-C7	127.9(7)
C8-C13	1.39(2)	C9-C10	1.39(2)	C5-C6-C16	114.8(6)	C7-C6-C16	117.1(6)
C9-C14	1.49(2)	C10-C11	1.40(2)	C1-C7-C6	133.7(7)	C5-C8-C9	119.8(6)
C11-C12	1.41(1)	C11-O5	1.35(2)	C5-C8-C13	121.5(6)	C9-C8-C13	118.6(6)
C12-C13	1.39(2)	C12-O4	1.35(2)	C8-C9-C10	120.0(7)	C8-C9-C14	120.0(6)
C13-O3	1.387(9)	C14-C15	1.56(1)	C10-C9-C14	119.9(6)	C9-C10-C11	120.8(7)
C15-C16	1.548(9)	C16-N1	1.50(1)	C10-C11-C12	119.2(7)	C10-C11-O5	125.5(7)
C17-C22	1.50(1)	C17-N1	1.48(1)	C12-C11-O5	115.4(7)	C11-C12-C13	120.1(7)
C18-O3	1.45(1)	C19-O4	1.44(2)	C11-C12-O4	122.2(6)	C13-C12-O4	117.6(6)
C20-O5	1.41(1)	C21-O2	1.433(8)	C8-C13-C12	120.9(6)	C8-C13-O3	120.7(6)
C22-C23	1.40(1)	C22-C27	1.36(2)	C12-C13-O3	118.4(6)	C9-C14-C15	109.9(6)
C23-C24	1.40(1)	C23-O6	1.34(2)	C14-C15-C16	112.7(6)	C6-C16-C15	109.9(6)
C24-C25	1.35(2)	C25-C26	1.40(2)	C6-C16-N1	114.7(6)	C15-C16-N1	108.8(6)
C26-C27	1.39(1)	C28-N1	1.464(9)	C22-C17-N1	114.2(7)	C22-C17-O6	123.9(8)
				N1-C17-O6	121.9(8)	C16-N1-C17	121.3(6)
				C2-O2-C21	123.0(6)	C13-O3-C18	110.8(5)
				C12-O4-C19	116.2(6)	C11-O5-C20	118.4(6)

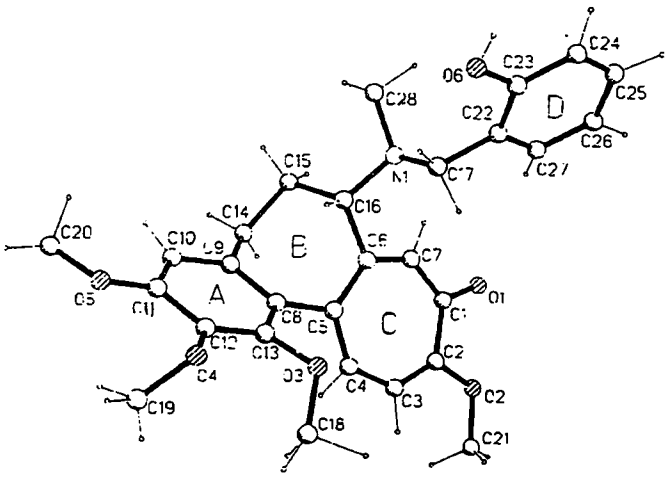

Fig. 1. Numbering of the atom in the speciosine molecule and its conformation.

The nitrogen atom has a pyramidal configuration and departs from the plane of the substituents by 0.5 Å. The phenyl ring *D* makes angles of 81.7° and 133.9°, respectively, with rings *A* and *C*. No intramolecular hydrogen bonds are observed in the speciosine molecule.

On the whole, the conformation of the speciosine molecule that we have studied differs insignificantly from the conformation of the molecules of the colchicine alkaloids [4-7]. The interatomic distances and valence angles for the speciosine molecule are given in Table 1.

In the crystals, the speciosine molecules are linked into zigzag chains in the [001] direction through O6–H···O1 intermolecular hydrogen bonds (length 2.69 Å and angle 166°) (Fig. 2). In the chains the phenyl radicals are directed inwards, which is possibly the reason for the weakening of the phenolic properties of speciosine.

The crystal structure of speciosine is formed in the packing of these zigzag chains by transformation through a fourth-order screw axis. The interaction between the chains is purely of the van der Waals type.

TABLE 2. Coordinates ($\times 10^4$) and Temperature Factors ($\times 10^3$) of the Nonhydrogen Atom of Speciosine

Atom	x	y	z	U
C1	7655(4)	1723(4)	750(12)	42(2)
C2	8720(4)	1749(4)	548(12)	40(2)
C3	9159(4)	2048(4)	-335(12)	40(2)
C4	8774(4)	2377(4)	-1282(12)	48(2)
C5	7839(4)	2452(4)	-1651(13)	41(2)
C6	6957(4)	2205(4)	-1036(12)	41(2)
C7	6957(4)	1926(4)	-40(12)	36(2)
C8	7711(4)	2875(4)	-2703(12)	45(2)
C9	7098(5)	3698(5)	-2822(12)	52(2)
C10	7004(5)	4135(5)	-3788(13)	64(3)
C11	7494(6)	3764(6)	-4654(12)	66(3)
C12	8098(6)	2935(6)	-4544(13)	60(3)
C13	8188(5)	2508(5)	-3574(13)	54(2)
C14	6555(5)	4073(5)	-1908(13)	57(2)
C15	5695(4)	3399(5)	-1581(12)	53(2)
C16	6017(4)	2318(4)	-1614(12)	45(2)
C17	5518(5)	651(5)	-1545(12)	52(2)
C18	9689(5)	1593(6)	-3768(13)	84(3)
C19	9116(8)	3044(8)	-6043(14)	20(5)
C20	6860(9)	4974(8)	-5765(13)	120(5)
C21	0249(5)	1466(6)	1383(13)	77(3)
C22	4975(4)	-143(4)	-999(13)	44(2)
C23	4309(4)	-722(5)	-1547(12)	48(2)
C24	3826(5)	-1479(5)	-1026(13)	55(3)
C25	4024(6)	-1665(5)	-21(13)	68(3)
C26	4699(6)	-1098(6)	533(13)	69(3)
C27	5166(5)	-346(5)	15(12)	58(3)
C28	4271(4)	1878(5)	-1434(13)	63(3)
N1	5278(3)	1642(4)	-1159(12)	46(2)
O1	7386(3)	1493(3)	1641(12)	58(2)
O2	9205(3)	1457(3)	1398(12)	57(2)
O3	8676(3)	1629(4)	-3462(12)	61(2)
O4	8482(4)	2489(4)	-5381(12)	81(2)
O5	7380(5)	4099(5)	-5628(12)	97(3)
O6	4143(3)	-525(4)	-2548(12)	68(2)

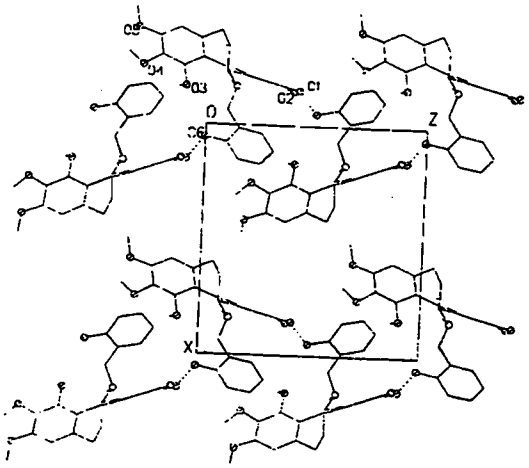

Fig. 2. Crystal structure of speciosine.

EXPERIMENTAL

Single crystals of speciosine were grown from solution in alcohol at room temperature. The unit cell parameters and the space group were determined and refined on a Syntex-P2 automatic four-circle diffractometer. To measure the intensities

of the reflections from the speciosine crystal, we used CuK_α radiation monochromatized by reflection from a graphite crystal with $\theta/2\theta$ scanning to an angle $2\theta < 116°$ at a variable rate between 4.8 and 12.2 degrees/min. The experimental group was corrected for polarization and Lorentz factors, but absorption was not taken into account in view of the absence of heavy atoms from the structure. The group consisted of 1777 reflections of which 1616 having $I > 2\sigma(I)$ were used in the calculations.

The crystal structure was interpreted by direct methods using the SHELX-86 program [8] and was refined by a program of the SHELXL-93 group [9], first in the isotropic and then in the anisotropic approximation. The hydrogen atoms were found by electron density difference syntheses. The final R-factor was 0.046. Atomic coordinates corresponding to this value of the discrepancy factor are given in Table 1.

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