STRUCTURE OF THE ISO FORM OF COLCHICINE. DEMETHYLISOTHIOCOLCHICINE

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SUMMARY

Demethylisothiocolchicine forms monoclinic crystals, space group $P2_1$, a = 11.906, b = 8.713, c = 10.004 Å; β = 89.44°; Z = 2. The crystal and molecular structure was determined from 1911 independent x-ray reflections and refined to R = 0.04. The molecule has the same overall shape as active colchicine derivatives but one methoxy group has a different conformation from that found in other compounds.

INTRODUCTION

Upon acid hydrolysis(1), colchicine(I) is converted to colchiceine(II), as shown in Figure 1. Addition of diazomethane converts II to I and to isocolchicine(III). Compounds in the "iso" form show little of the rather remarkable behavior of colchicine. Whereas colchicine is a powerful inhibitor of mitosis and has useful antiinflamatory properties, isocolchicine and its derivatives are essentially inactive(2). Colchicine is believed to act by binding to the microtubule protein, tubulin, preventing its polymerization into microtubules(3). It is likely that a benzenoid ring with one or more methoxy groups, as well as a carbonyl or OH group on Ring C, the troponoid ring, are involved in the colchicine-tubulin interaction(4-7). Crystal structures of colchicine derivatives(4,5) and of simpler troponoids(8) indicate that Ring C is not quite planar and shows a definite alternation in bond length, consistent with a system of π electrons only partially delocalized. This means that in iso compounds, Ring B will have a shorter

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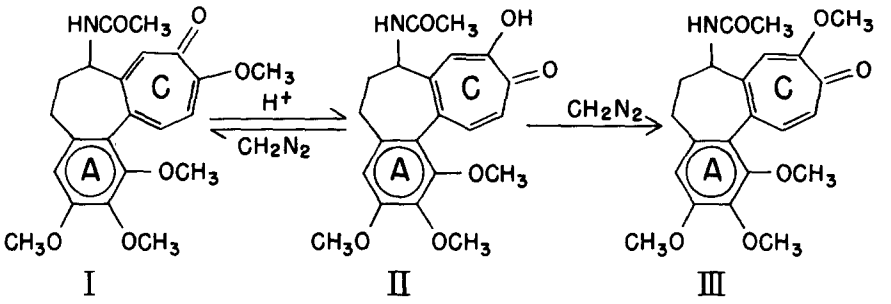

Figure 1. The conversion of colchicine (I) to isocolchicine (III) via colchiceine (II).

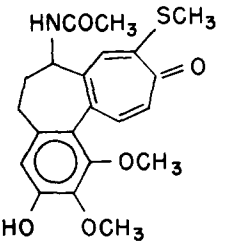

Figure 2. Structural formula of demethylisothiocolchicine (IV).

bond where it joins Ring C than in normal compounds. To find out what effect this has on the overall conformation of Ring B, I have carried out an X-ray diffraction study of an iso compound, demethylisothiocolchicine (IV, Fig. 2). This one of a series of compounds prepared at Roussel Chemical by Muller etal (9). In general, substitution of sulfur for oxygen in the troponoid methoxy does not diminish and indeed may enhance biological activity (3).

METHODS

Crystals of IV are monoclinic, space group $P2_1$, with a = 11.906, b = 8.713, c = 10.004 Å, β = 89.44°. There are 2 molecules of $C_{21}H_{23}NO_5S \cdot H_2O$ per unit cell. The structure was determined with the heavy atom method and refined by least squares to a final R factor of 0.040 for 1911 reflections measured on a Syntex diffractometer. Hydrogen atoms were located in a differ

Table 1

Atomic coordinates (estimated standard deviation in parentheses) for non-hydrogen atoms in demethylisothiocolchicine.*

Atom	x	y	z
S	0.47166 (8)	0	0.0678 (1)
N	0.4050 (2)	0.4664 (4)	0.3578 (3)
O1	0.2812 (2)	-0.0574 (4)	-0.0681 (3)
O3	-0.0438 (2)	0.2755 (3)	0.3493 (3)
O4	-0.1886 (2)	0.5207 (4)	0.4288 (3)
O5	-0.1391 (3)	0.8126 (4)	0.3421 (4)
O6	0.3407 (2)	0.3016 (5)	0.5130 (3)
OW	0.4056 (2)	0.1297 (5)	0.7401 (3)
C1	0.3500 (3)	0.1106 (5)	0.0940 (3)
C2	0.2581 (3)	0.0439 (4)	0.0161 (4)
C3	0.1435 (3)	0.0895 (5)	0.0368 (4)
C4	0.0981 (3)	0.2079 (5)	0.1088 (4)
C5	0.1477 (3)	0.3274 (4)	0.1840 (3)
C6	0.2619 (3)	0.3411 (4)	0.2107 (3)
C7	0.3485 (3)	0.2389 (5)	0.1708 (4)
C8	0.0699 (3)	0.4530 (4)	0.2281 (3)
C9	0.0931 (3)	0.6051 (4)	0.1888 (4)
C10	0.0201 (3)	0.7231 (5)	0.2261 (4)
C11	-0.0732 (3)	0.6934 (4)	0.3061 (4)
C12	-0.0962 (3)	0.5439 (4)	0.3974 (4)
C13	-0.0255 (3)	0.4229 (4)	0.3062 (4)
C14	0.1984 (3)	0.6379 (5)	0.1106 (4)
C15	0.3027 (3)	0.6249 (5)	0.2006 (4)
C16	0.2968 (2)	0.4825 (4)	0.2911 (3)
C17	0.4175 (3)	0.3794 (5)	0.4650 (4)
C18	-0.1527 (3)	0.2099 (6)	0.3246 (6)
C19	-0.1615 (3)	0.5012 (8)	0.5648 (4)
C21	0.5756 (3)	0.0911 (7)	0.1700 (5)
C22	0.5352 (3)	0.3737 (6)	0.5218 (5)

*O2 and C20 are not used in atomic numbering to be consistent with related compounds.

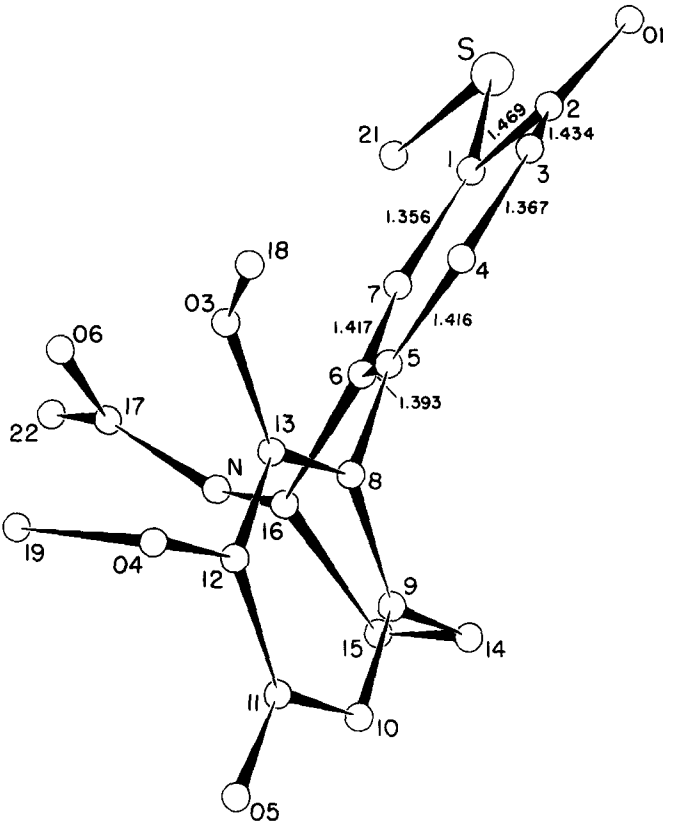

Figure 3. One molecule of demethylisothiocolchicine (IV) with selected bond lengths in Å. Unlabeled atoms are carbon, hydrogen atoms are omitted.

ence map and refined with isotropic temperature factors; all other atoms were refined anisotropically. Table I lists the positional parameters for the non-hydrogen atoms.

RESULTS AND DISCUSSION

Figure 3 shows a molecule of IV and the Ring C bond lengths. The troponoid ring (C) may be described as a shallow boat consisting of three planes.

plane 1	C4,C5,C6,C7
plane 2	C1,C3,C4,C7
plane 3	C1,C2,C3

Table 2. Torsion angles, τ, in Ring B of some colchicine derivatives

Atoms	Colcemid(4)	Deacetylthio-colchicine(5,10)	Thiocolchicine(10)	Demethyliso-thiocolchicine(this
C8-C5-C6-C16	-4.5	6.5	-3	-3.2
C5-C6-C16-C15	80.8	73.8	82	79.0
C6-C16-C15-C14	-48.3	-51.7	-50	-46.3
C16-C15-C14-C9	-41.3	-38.9	-39	-43.9
C15-C14-C9-C8	71.1	70.3	68	72.4
C14-C9-C8-C5	4.2	3.5	7	3.5
C9-C8-C5-C6	-53.9	-60.1	-55	-54.0

The dihedral angle between plane 1 and plane 2 is 4.0° and between plane 2 and plane 3 is 10.2°. These are larger than dihedral angles found in troponoid rings containing oxygen instead of sulfur and are consistent with a less delocalized system of π electrons. Ring C bond lengths show an alternation in accord with this view. The change in Ring C leads to only small changes in Ring B. In Table 2 torsion angles in Ring B are compared with those found in thiocolchicine, deacetylthiocolchicine, and colcemid, compounds with activity comparable to that of colchicine. It can be seen that these, and thus the shape of the molecule, are perhaps more sensitive to the charge on the nitrogen atom than to the change in Ring C, and resulting shortening of the bridging bond.

One difference between IV and the three active compounds is in the orientation of the O3 methoxy group. Methoxy groups on aromatic rings tend to have the methyl carbon coplanar (τ = 0°) or sticking out from the ring (τ = 90°). The torsion angle C12-C13-O3-C18 is 82°, 101° and 104° for I, II and III respectively while it is -56° for IV, i.e. pointed in the opposite direction. There are indications that the trimethoxy benzene portion of the

molecule interacts with tubulin, in which case orientation of $-O-CH_3$ group may influence that interaction and be involved in biological specificity. A pleasing aspect of the view is that it gives a role to the methoxy group, a group found in an unusually large number of drugs and biologically active molecules.

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