

THE CRYSTAL STRUCTURE OF COCLAURINE HYDROBROMIDE MONOHYDRATE AND THE ABSOLUTE CONFIGURATION OF COCLAURINE

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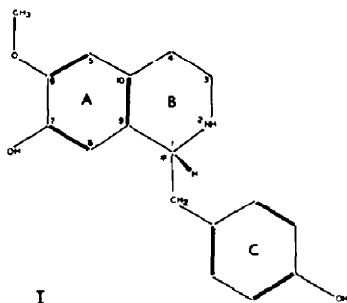
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Abstract—The structure and absolute configuration of coclaurine has been determined by X-ray analysis of its hydrobromide monohydrate. The (+)-enantiomer has the D-configuration. The chirality of the molecular structure is correlated with circular dichroism measurements.

ANALYSIS was initiated with the alkaloid isolated from *Alseodaphne archboldiana* (Allen) Kost., a New Guinea tree of the family *Lauraceae*. Chemical and mass-spectrometric investigations established it as a simple benzyltetrahydroisoquinoline, either coclaurine or isococlaurine. X-ray structure analysis of the alkaloid hydrobromide was carried out to determine conformational details of the ring systems in the crystalline state and establish the absolute configuration of the molecule to allow correlation with its circular dichroic spectrum.

The molecular skeleton derived from the X-ray data had a MeO group at position 6 (conventional isoquinoline numbering), an OH group at 7 and a *p*-hydroxybenzyl group at 1. The base investigated was therefore coclaurine (I) — $C_{17}H_{19}O_3N$.



The molecular conformation in the crystal is evident in Figs 1(a) and (b) which show the disposition of the molecules in the unit cell, viewed along the *a* and *c*-axes respectively. In Fig. 1(b), only two of the four molecules are shown to avoid confusion due to overlap. Ring B is in a distorted half-chair form with 3(C9) and 2(N) out of the mean plane of the AB ring system by ca. 0.2 and 0.4 Å respectively while atoms 1(C7) and 4(C10) of this ring also deviate from the mean plane by ± 0.15 Å, Fig. 2.* An

* The atom designation in brackets corresponds to that in Table 2 and Fig. 3.

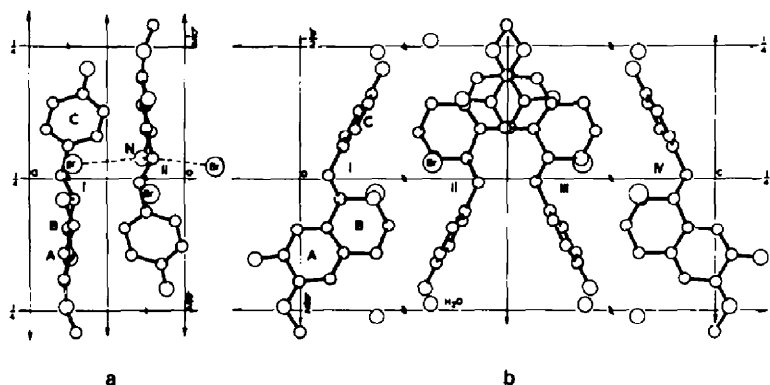


FIG. 1. Projection of the crystal structure (a) down the a axis and (b) down the c axis. In (b), only two of the four molecules are shown, to avoid overlap.

apparent associated distortion of the aromatic ring A is also evident, Fig. 2. The mobile methoxycarbon (C22) is out of plane by ca. 0.6 Å in the direction opposite to N and pointing away from the hydroxyl oxygen (O18) at 7. The plane of the hydroxybenzyl ring C is nearly perpendicular to the mean plane of the isoquinoline ring system

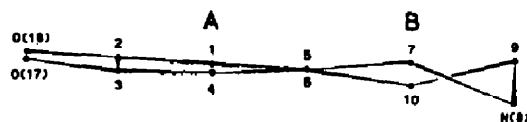


FIG. 2. View of the AB ring system to show deviations of atoms from the mean plane.

and its main axis is approximately parallel to bond 7–8 (Fig. 1). Around bond (C7)–(C21), the conformation is staggered, with bonds (C11)–(C21) and (C7)–(C6) virtually parallel in space, Fig. 1. Molecular bond lengths and angles are detailed in Fig. 3.

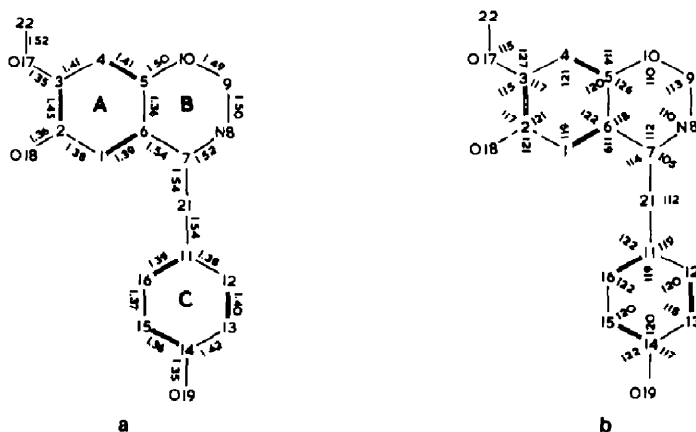


FIG. 3. (a) Bond lengths and (b) bond angles in the molecule.

The molecules in the crystal are arranged roughly in sheets parallel to the *ac*-plane. They are held together in the region of the ring A by van der Waals' forces with approach distances of 3.5–4.0 Å while the protonated nitrogen is held between Br ions, Fig. 1(b). The ring C region is stabilized by hydrogen bonds between the hydroxyl oxygen and the water oxygen (2.72 and 2.80 Å), Fig. 1(a). The Br[−] ions stabilize the structure not only through ionic association with the >NH_2^+ ion but apparently also by association with the aromatic ring C. The Br atom is located almost normal to the centre of the hydroxybenzyl ring, a disposition somewhat similar to that noted in the adduct compound, benzene-Br₂,¹ although the ring centre—Br distance, ~4 Å, is rather large to be considered as involving electron transfer bonding.

Determination of absolute configuration

The coclaurine, isolated from *Alseodaphne*, from which the derivative used in the analysis was originally prepared, had a specific rotation $[\alpha]_D +22^\circ$ whereas material isolated previously from other sources has usually been the racemic form.^{2,3} The absolute configuration of the *Alseodaphne* coclaurine was determined from the anomalous dispersion of Br with CuK radiation by Bijvoet's method⁴ on a *specific* single crystal and, for this crystal, proved to correspond to the L-configuration^{5,7} (amino-acid convention).

In the meantime, coclaurine of higher optical activity was isolated⁶ from another species, *Xylopiapapuana* Diels. This material had $[\alpha]_D +47^\circ$ and gave, on N-methylation, (−)-N-methylcoclaurine with $[\alpha]_D -115^\circ$ in close agreement with other literature values for this derivative.⁸ Assuming this material to be pure (+)-coclaurine, the earlier sample from *Alseodaphne* was necessarily regarded as a mixture of the (+) and (−)-forms in the approximate ratio of 3:1.

There was therefore a 1 in 4 probability that the specific crystal selected from the *Alseodaphne* coclaurine batch was of the minor component, i.e. the (−)-form. Accordingly a batch of crystals of the hydrobromide of the coclaurine from *Xylopiapapuana*

TABLE 1. REFLECTIONS USED IN DETERMINING THE ABSOLUTE CONFIGURATION

<i>hkl</i>	$(F_{hkl}^2 - F_{\bar{h}\bar{k}\bar{l}}^2) \text{ calc}$	$I_{hkl} - I_{\bar{h}\bar{k}\bar{l}}$	
		Alseodaphne derivative	(+)-coclaurine
112	+	−	+
116	−	+	−
117	−	+	−
119	+	−	+
217	−	+	−
227	+	−	+
2,2,10	−	+	−
316	−	+	−
318	+	−	+
319	+	−	−

papuana was prepared. From this, a crystal was selected and was confirmed as being essentially identical with the first product in respect of the diffraction pattern. The absolute configuration of this crystal was as given in I, i.e. (+)-cocclaurine has the D-configuration. The alternative configuration determined from the first crystal obviously must correspond to (–)-cocclaurine with the L-configuration, in agreement with the results reported by Barton *et al.*³ The reflexions used to define the absolute configuration in both crystals are listed in Table 1.

The steps taken to ensure the correct absolute configuration of (+)-cocclaurine by the X-ray technique have been given here at some length to stress the care necessary in the application of this technique to individual crystals of natural product derivatives where the sample could contain an appreciable proportion of the other enantiomer. Such a situation is more liable to be troublesome in structures with only one centre of asymmetry—as is the case for cocclaurine.

Subsequent measurement of the circular dichroism of (+)-cocclaurine hydrobromide (in methanol) showed a pronounced negative Cotton effect, peaking at 276 mμ and, although due to high absorption the measurements were not extended to shorter wavelengths, the negative peak recorded for (+)-cocclaurine is in accord with the conclusions of Craig *et al.*^{7,*}

EXPERIMENTAL

Crystals of the hydrobromide of the *Alseodaphne* alkaloid are orthorhombic with parameters, $a = 7.25$, $b = 12.27$, $c = 19.42$ Å, determined from Weissenberg photographs calibrated with a powdered Si standard. The space group is $P2_12_1$ (non-standard setting of $P2_12_12$, No. 18) with 4 molecules in the unit cell. Data were collected from room-temp. equi-inclination Weissenberg photographs of 6 layers around the a -axis and

TABLE 2. ATOMIC PARAMETERS, REFERRED TO A RIGHT-HANDED SET OF AXES FOR (+)-COCLAUURINE

Atom	x	y	z	Atom	x	y	z
C(1)	0.260	0.193	0.008	C(15)	0.026	0.259	0.361
C(2)	0.260	0.294	0.039	C(16)	0.068	0.164	0.393
C(3)	0.223	0.393	0.000	C(21)	0.298	0.018	0.435
C(4)	0.778	0.383	0.072	C(22)	0.813	0.416	0.500
C(5)	0.755	0.280	0.103				
C(6)	0.743	0.189	0.064	O(17)	0.232	0.486	0.038
C(7)	0.709	0.081	0.101	O(18)	0.261	0.303	0.109
C(9)	0.719	0.179	0.212	O(19)	0.130	0.418	0.303
C(10)	0.782	0.283	0.181	O(20)(H ₂ O)	0.772	0.481	0.315
C(11)	0.248	0.127	0.399				
C(12)	0.387	0.186	0.368	N(8)	0.784	0.080	0.174
C(13)	0.348	0.288	0.338				
C(14)	0.162	0.319	0.331	Br	0.229	0.062	0.182

3 layers around the c -axis (total of ca. 1200 reflexions), using CuK_α radiation. Intensities were estimated visually, using an intensity scale of timed exposures of a typical reflexion.

The position of the Br atom was determined from Harker sections, $H(\frac{1}{2}, v, w)$, $H(u, 0, w)$ and $H(u, v, \frac{1}{2})$ of unsharpened and sharpened (point atoms) 3-dimensional Patterson distributions while the approximate

* A weak positive Cotton effect appears as a shoulder at ca. 270 mμ, a feature which is also evident on some of the curves recorded in Ref. 7.

disposition of rings AB and ring C were deduced from 3-dimensional Fourier syntheses, phased on Br. Subsequently two Fourier syntheses and two cycles of least-squares refinements (individual isotropic temp. factors) allowed side groups to be positioned, the C, N and O atoms to be differentiated and the presence of a water molecule to be established. Atomic parameters are given in Table 2. Overall agreement as assessed by $R(\sum |F_o - F_c|/\sum |F_o|)$ was 0.18. The condition of the crystals, as evidenced in the diffraction photographs, did not warrant refinement beyond this stage.

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REFERENCES

- ¹ O. Hassel and K. O. Strømme, *Acta Chem. Scand.* **12**, 1146 (1958).
- ² ^a A. Kondo and J. Kondo, *Yakagaku Zasshi* **48**, 1156 (1928).
^b M. Tomita, T-H. Yang, K. M. Gaid and S. K. Gaveja, *Ibid.* **83**, 218 (1963).
- ³ ^a R. R. Arndt, *J. Chem. Soc.* 2547 (1963).
^b L. J. Haynes, K. L. Stuart, D. H. R. Barton, D. S. Bhakuni and G. W. Kirby, *Chem. Comm.* 141 (1965).
- ⁴ J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature, Lond.*, **168**, 271 (1951).
- ⁵ A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P. M. Scopes and M. J. Vernago, *J. Chem. Soc.* 2239 (1965).
- ⁶ S. R. Johns, J. A. Lamberton and A. A. Sioumis, *Austral. J. Chem.* **20**, 1729 (1967).
- ⁷ ^a J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 401 (1965).
^b J. C. Craig, M. Martin-Smith, S. K. Roy and J. B. Stenlake, *Ibid.* **22**, 1335 (1966).
- ⁸ ^a C. Ferrari and V. Deulofeu, *Ibid.* **18**, 419 (1962).
^b M. Tomita and J.-I. Kunimoto, *J. Pharm. Soc. Japan* **82**, 734 (1962).