

## The Absolute Configuration of Halosaline

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Both the relative and absolute configuration of the two asymmetric centres in natural (–)-halosaline (II) have been determined by the combined use of ORD and CD. The results are in agreement with other physical and chemical evidence.

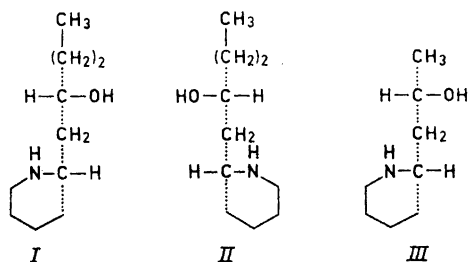
The alkaloid halosaline was isolated from *Haloxylon salicornicum*, and shown to consist of at least 95 % of one optically pure isomer.<sup>1</sup> From NMR spectra of the oxazine derivatives obtained by condensation with *p*-nitrobenzaldehyde halosaline was deduced to have the "threoid" configuration,<sup>1</sup> similar to that of the alkaloid sedridine.<sup>2,3</sup> The natural alkaloid must therefore have the absolute configuration I or II. The corresponding racemic form of halosaline was obtained by synthesis.<sup>1</sup>

Although halosaline had a low positive rotation in chloroform ( $[\alpha]_D + 3.3^\circ$ ,  $c=1$ ) it showed a stronger rotation of opposite sign in alcoholic solution ( $[\alpha]_D - 19.5^\circ$ ,  $c=0.6$ ). It is interesting that the closely related natural (+)-sedridine (III) has  $[\alpha]_D + 27.5^\circ$  ( $c$  0.3 in ethanol).

The absolute configuration of natural (–)-halosaline has now been determined by the ORD-CD method previously applied to the configuration of the sedridine and allosedridine alkaloids.<sup>4</sup>

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The ORD curve for (–)-halosaline (Fig. 1) shows a negative Cotton effect centred between 200 and 210  $\mu$ , which is due to the  $n \rightarrow \sigma^*$  transition of the non-bonding electrons of nitrogen and oxygen. The ORD curve ascends steeply below 210  $\mu$ . The hydrochloride of (–)-halosaline, however, gives a plain negative curve (Fig. 1) which is due to the  $n \rightarrow \sigma^*$  transition of oxygen,

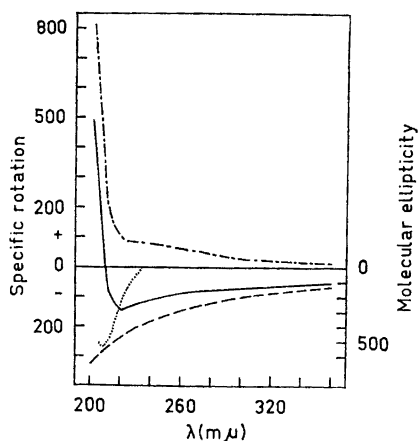


Fig. 1. (–)-Halosaline. ORD curves of base (—), hydrochloride (---), [base – hydrochloride] (-·-). CD curve of base (···).

since it is known that the  $n \rightarrow \sigma^*$  transit of amines disappears on protonation of the nitrogen. The curve of the hydrochloride therefore indicates the asymmetric centre in the side-chain to have the L-configuration, as found<sup>5</sup> for L-(–)-2-octanol and L-(–)-3-heptanol.

Subtraction of the curve for the hydrochloride from that of the base gives a plain positive ORD curve (Fig. 1) which indicates the asymmetric centre in the piperidine ring to have the D-configuration as in D-(+)-coniine.<sup>6</sup> This is confirmed by the CD curve for (–)-halosaline (Fig. 1) which shows a negative CD maximum at 204  $\mu$ , identical in wavelength, sign, and magnitude with that given by (+)-coniine<sup>7</sup> and by (–)-sedridine,<sup>4</sup> both of which are known to give R-(+)-pipecolic acid on oxidation, and thus to be members of the D-series for the asymmetric centre in the piperidine ring. As in the case of coniine or sedridine, no CD could be observed down to 195  $\mu$  after acidification,

showing that the CD maximum shown by the base is entirely due to the  $n \rightarrow \sigma^*$  transition of the nitrogen.

This assignment has now been confirmed by the identification of *R*-(+)-pipercolic acid,  $[\alpha]_D + 29^\circ$  ( $c=0.13$  in water) by chemical degradation of (-)-halosaline. The absolute configuration of (-)-halosaline is thus correctly given by (II), and is (2*R*)-1-[(2'*R*)-2'-piperidyl]-pentan-2-ol. In agreement with conclusion, the ORD and CD curves of (-)-halosaline are the mirror images of those obtained <sup>4</sup> for natural (+)-sedridine (III).

### EXPERIMENTAL

Optical rotatory dispersion and circular dichroism curves were measured with a JASCO spectropolarimeter in 95 % ethanol at 25° unless otherwise stated. CD curves were recorded in terms of molecular ellipticity units  $[\theta]$ .<sup>8</sup> Rotations are given below only for (a) the highest and lowest wavelengths measured (b) peaks and troughs.

(-)-*Halosaline*.  $[\alpha]_D - 19.5^\circ$  ( $c=0.60$  in 95 % EtOH). ( $c=0.60$  in 95 % EtOH)  $[\alpha]_{360} - 50^\circ$ ,  $[\alpha]_{222} - 142^\circ$  (tr),  $[\alpha]_{202} + 490^\circ$ . C.D.  $[\theta]_{235} 0$ ,  $[\theta]_{209} - 548$ ,  $[\theta]_{270} - 523$ .

*Halosaline hydrochloride*. R.D. ( $c=0.73$  in 95 % ethanolic 0.1 N HCl)  $[\alpha]_{360} - 65^\circ$ ,  $[\alpha]_{202} - 323^\circ$ .

*Oxidative degradation of halosaline to R-(+)-pipercolic acid*. Halosaline (0.05 g; m.p. 80–81°;  $[\alpha]_D - 19.5^\circ$ ,  $c=0.6$  in EtOH) was dissolved in a mixture of concentrated sulphuric acid (1 ml) and water (2 ml) and oxidized with chromium trioxide (0.15 g) in water (1.2 ml) according to the description by Beyerman *et al.*<sup>2</sup> to yield *R*-(+)-pipercolic acid (0.008 g; m.p. 268–272° decomp.;  $[\alpha]_D + 29^\circ$ ,  $c=0.13$  in water). The product was isolated from the reaction mixture by preparative TLC (cellulose "Maschery und Nagel", MN 300; propanol/H<sub>2</sub>O, 80/20;  $R_F$  0.4) and found to be identical (TLC, IR, m.p. and mixed m.p.) with an authentic sample. The TLC analyses were carried out with various systems: propanol/H<sub>2</sub>O (80/20),  $R_F$  (silica gel G) 0.25 and  $R_F$  (cellulose Maschery and Nagel, MN 300) 0.40; butanol/HOAc/H<sub>2</sub>O (80/20/20),  $R_F$  (silica gel G) 0.30 and  $R_F$  (cellulose) 0.45; isopropanol/H<sub>2</sub>O (80/20),  $R_F$  (silica gel G) 0.35 and  $R_F$  (cellulose) 0.45.

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