Compounds, based on the benzodiazepine skeleton are psychotherapeutic agents widely used for the treatment of anxiety and neurosis [1-4]. 1,5-Benzodiazepin-2-ones belong to a pharmacologically important subclass of benzodiazepines. A recent report from our research group [5] described the syntheses of a whole series of optically active 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-ones with one chiral centre at C-4 in the seven-membered ring. These compounds are analogues of the commercially available drug Lofendazam (7-chloro-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one) [6]. Although the CD spectra of these compounds were discussed in detail, it was neither possible to correlate the Cotton effects with the absolute configuration, nor to ascertain the conformations adopted by the seven-membered ring. Herein we describe the absolute configuration of this class of compounds with the help of X-ray crystallography.

The racemic 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (1) was synthesized, by the previously reported procedure [5]. The racemic mixture was resolved by the formation of the diastereoisomeric salt with D- (+)-3-bromocamphor-sulfonic acid in ethanol, which yielded pure (+) salt after two further fractional crystallizations as confirmed by 1H NMR spectroscopy in the presence of tris(3-heptafluorobutyryl)-(1R)-camphoratoeuropium [Eu(hfcb)]. After decomposition of this salt, enantiomerically pure 1 was obtained. It shows in its UV spectrum a first band at 298 (ε_{max} 3619), a medium strong one at 254 (ε_{max} 6657) and a very intense one at 222 nm (ε_{max} 32240), followed by a minimum around 202 nm. The CD spectrum shows negative and positive Cotton effects at 284 (Δε -1.40 ), 250 (Δε +0.39), 232 (Δε +3.38) and 217 nm (Δε -5.74), respectively. The 222 nm band in the UV spectrum does not coincide with the CD band, but is intermediate between bands located around 217 and 232 nm. The very strong β-absorption does, however, correspond to the intense Cotton effect in the same wavelength range, and there is one more Cotton effect visible at 217 nm (Δε -5.74). It was not possible to obtain good crystals either of 1 or its salts. Various derivatives were, therefore, synthesized from the enantiomerically pure starting material 1, but suitable crystals could only be obtained from 4,5-dimethyl-7-chloro-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (2). It was prepared from 1 by a 5-step reaction sequence without disturbing the chirality at C-4 [5]. The enantiomeric purity of 2 is confirmed by its 1H NMR spectrum with the previously described shift reagent [5]. The UV spectrum shows the first band at 304 (ε_{max} 4696), a moderate one at 268 (ε_{max} 7886), a very intense band at 233 (ε_{max} 34424) and an intense one at 195 nm (ε_{max} 15648). The CD spectrum shows six Cotton effects at 306 (Δε +1.76), 281 (Δε -1.30),
259 (sh., $\Delta \varepsilon$ +1.98), 241 ($\Delta \varepsilon$ +3.68), 231 ($\Delta \varepsilon$ -5.21) and 212 nm ($\Delta \varepsilon$ +3.80). Introduction of the chloro group at C-7 causes only bathochromic shifts of the individual Cotton effects [7], but some of the CD bands change their signs due to the methyl group at N-5 [5, 7]. It is well known from X-ray spectra of tetrahydroisoquinolines, substituted by an alkyl group at position 1, that this alkyl group adopts rather a quasiaxial conformation. On the other hand, this is not possible for 2, since such a methyl group pointing “into” a boat conformation is too overcrowded, and such a conformation is never adopted in similar systems [8]. The conformation of the heterocyclic ring of 2 must be different from that of 1, and, therefore, some of the Cotton effects change their signs. Conclusive evidence for the adopted conformation of 2 and the absolute configuration at C-4 of this series of compounds are now provided by X-ray crystallography. Suitable yellowish crystals were grown by slow evaporation of solvent from an ethanolic solution of 2 at room temperature.

The molecular structure of compound 2 is shown in Fig. 1 which clearly shows that configuration at C-4 of 2 and hence that of 1 is ‘R’.

![Fig. 1. Plot of the molecular structure of 2.](image)

**Experimental**

The details of the instruments used for the determination of melting points, optical rotations, and for recording of UV and CD spectra have already been provided in the previous communications [5, 7]. The compounds 1 and 2 were synthesized according to ref. [5]. For their identification, m.p. and rotational values are compared with those from the literature.

4 (R)-Methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (1)

M.p. 181 °C (ethanol). $[\alpha]_{D}^{20} = +1.3$ (c = 8, CHCl$_3$); ref. [5]: m.p. 182 °C (ethanol). $[\alpha]_{D}^{20} = +1.2$ (c = 16.2, CHCl$_3$).

7-Chloro-4 (R), 5-dimethyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (2)

M.p. 199.5 °C (ethanol). $[\alpha]_{D}^{20} = +39.5$ (c = 1.2, CHCl$_3$); ref. [5]: m.p. 199–200 °C (ethanol). $[\alpha]_{D}^{20} = +40.1$ (c = 1.52, CHCl$_3$).

**X-ray structure determination of 2**

C$_1$_H$_{13}$N$_2$OCl (224.68), yellowish crystal of size 0.45 x 0.28 x 0.20 mm, four circle diffractometer CAD4-T (Nonius, Delft), temperature 205(2) K, $\lambda$(MoK$\alpha$) = 71.073 pm, monoclinic, P2$_1$ (No.4), $a = 739.9(1)$, $b = 695.5(1)$, $c = 1150.6(1)$ pm, $\beta = 107.71(1)^\circ$, $V = 0.5640(1)$ mm$^3$, $Z = 2$, $\rho = 1.323$ g/cm$^3$, $\mu = 0.314$ mm$^{-1}$, F(000) = 236, $\theta = 3–27^\circ$, 0 $< h < 8$, -8 $< k < 8$, -14 $< l < 13$, 2298 observed reflections with $F > 4\sigma(F)$, 188 parameters, Goof = 1.084, $R_1 = 0.0263$, $wR_2 = 0.0659$, Flack parameter $\eta = 0.02(5)$. The refinement of the alternative S configuration led to worse values of $R_1 = 0.0282$, $wR_2 = 0.0731$ and Flack parameter $\eta = 1.02(1)$. Calculations were performed with SHELXTL[9], PLATON[10]. Further details of the x-ray structure determination are deposited at the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (Germany) and can be obtained by quoting the number CSD-404477, the authors and the citation.

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[9] Program package SHELXTL, version 5.03, Bruker AXS GmbH, Karlsruhe (Germany).