Nitrogen Bridgehead Compounds. Part 71 [1]. Chiroptical Properties of 9-Halo Derivatives of 6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 3-Carboxy Derivative

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Earlier assignments [2] relating to the CD bands of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were utilized to explain the chiroptical properties of their 9-halogenated derivatives. The signs of the most characteristic CD bands proved to be determined by the axial substituents in the benzylic position to the inherently achiral pyrimidinone chromophore.

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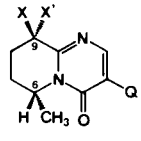
We previously reported on the circular dichroism of chiral derivatives of different types of tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [2]. That analysis was based on the comparison of the experimental CD spectra of a series of structurally related compounds, and on theoretical calculations of the optical activities of simple models. The good correlation between theory and experiment allowed us to explain the origins of the optical activity of the different bands found in the CD spectra. In order to check the validity of our assignments, we have extended our experimental studies to a further series of models, the 9,9-dihalo derivatives of **1a** and its 3-carboxy derivative **1b** (**2a**, **3a** and **2b**, **3b**, respectively) [3]. The 9-monobromo derivative of **1b**, which has been prepared [3] in a stereochemically pure state, has also been investigated. In the present paper we describe and analyse the results of these newer studies.



	Q	X	X'
1a	H	H	H
2a	H	Cl	Cl
3a	H	Br	Br
1b	COOH	H	H
2b	COOH	Cl	Cl
3b	COOH	Br	Br
4b	COOH	Br	H

The data on the uv and CD spectra measured in ethanol are presented in Table 1. (The previously published [2] data on **1a** and **1b** are also given for comparison). The CD spectra of **1a** and **1b** and their halo derivatives are shown in Figures 1 and 2, respectively.

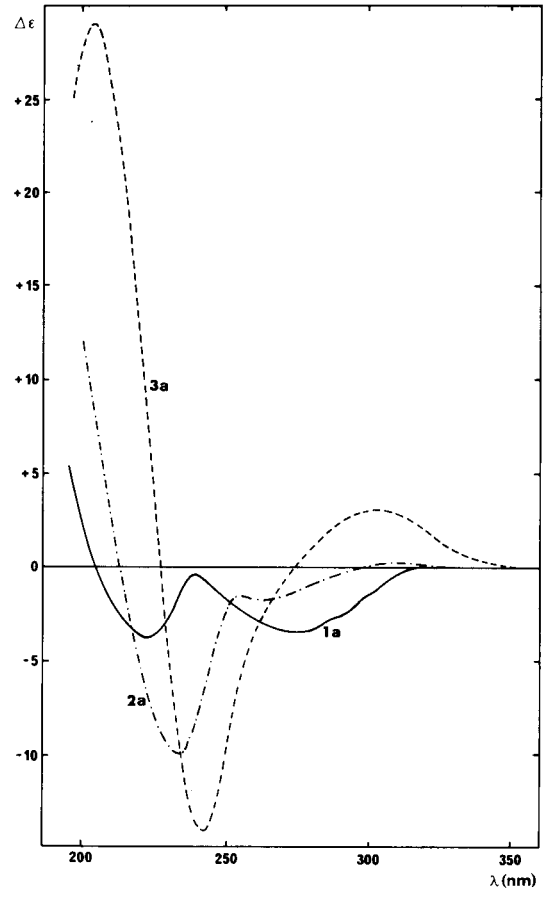


Figure 1. CD spectra of **1a-3a** in ethanol.

The most striking feature of all the CD spectra is the pair of bands with opposite signs at the short-wavelength end. The sing of the first, at around 230-240 nm, is negative, while that of the shorter-wavelength band is

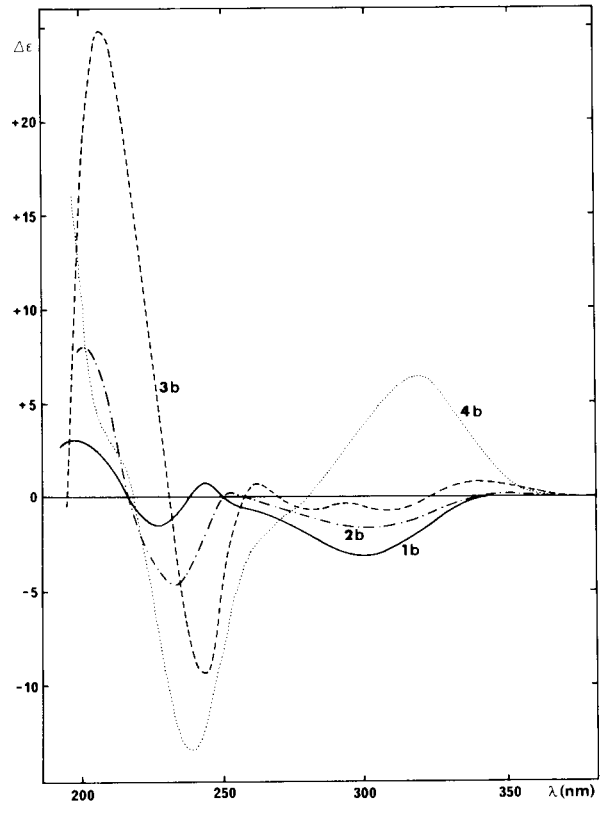


Figure 2. CD spectra of **1b-4b** in ethanol.

positive for all compounds with 6*R* configuration. The positions of these bands are slightly shifted to the red on going from the 9-unsubstituted parent compounds **1a** and **1b** to their dichloro **2a, 2b** and dibromo **3a, 3b** derivatives. The counterpart of the negative CD band in the uv spectrum is a well-separated band for **2a, 3a** and **4b** or a shoulder for **2b** and **3b** of medium and almost constant intensity for all the compounds studied (ϵ = 4000-5000). The maximum of the shortest-wavelength uv band lies below 200 nm in most of the spectra, and therefore could not be measured for all compounds. The end absorbance at 200 nm is rather high (ϵ = 14000 for the dichloro and 18000-19000 for the dibromo derivatives). The fairly high intensity of these uv bands indicates that they originate from electronically allowed transitions of mostly $\pi \rightarrow \pi^*$ type.

On the basis of our previous quantum-chemical calculations [2] on **1a**, the 230 nm uv band can be assigned to a $\pi \rightarrow \pi^*$ transition of the pyrimidinone chromophore. However, in contrast with the lower-lying (280 nm), optically inactive $\pi \rightarrow \pi^*$ transition of this inherently achiral, heteroaromatic chromophore (see below), this second $\pi \rightarrow \pi^*$ transition is associated with a non-negligible rotational strength with negative sign for the 6*R* configuration. This indicates that the molecular orbitals taking part in the excited state due to this transition are delocalized to a significant extent, over the chiral surroundings of the chromophore. The CD band at 230-240 nm can therefore be expected to be especially sensitive to the stereochemistry of the chiral part, *i.e.* the substituted tetrahydropyridine ring of the molecules.

The nmr investigations of the halo derivatives [4] have shown that the conformations with an axial 6-methyl group are strongly favored. Even for the *trans* 9-monobromo derivative **4b**, the conformation with both the 6-methyl and the 9-bromo substituents in axial positions is

Table 1

UV and CD Spectral Data on **1a-4b** in Ethanol [a]

1a	UV	279 (5000),				227 (6750)	
	CD	277 (−3.49),				224 (−3.83),	194 (+5.3)
2a	UV	291.5 (4460),				234.5 (4110),	200 ! (13900)
	CD	313 (+0.17), 262 (−1.80),				234 (−9.90),	200 ! (+12.1)
3a	UV	300 (4760),				236 (4850),	200 ! (18200)
	CD	303 (+3.15),				243 (−14.1),	205 (+29.1)
1b	UV	303 (8230),				230 (5510),	207 (5510)
	CD	300 (−3.03),			243 (+0.73),	230 (−1.43),	195 (+3.0)
2b	UV	309.5 (7600),				230 sh (4300),	201.5 (12400)
	CD	355 (+0.03), 299 (−1.51),			253 (+0.09),	235 (−4.58),	203 (+7.8)
3b	UV	320.5 (8080),				238 sh (4120),	200 ! (18900)
	CD	340 (+0.71),	304 (−0.68),	281 (−0.56),	263 (+0.82),	244 (−9.32),	209 (+24.8)
4b	UV	317.5 (8250),				233.5 (4705),	201 (17500)
	CD	317 (+6.02), 270 sh (−1.15),				239 (−13.6),	203 ! (+11.3)

[a] The uv and CD data are given in λ, nm (ϵ) and λ, nm ($\Delta\epsilon$), respectively; sh means shoulder; ! means end absorbance.

predominant in solution. This means that the helicity of the chiral second sphere is unaffected by the mono- or dihalo substitution at position 9. The similarity of the low-wavelength part of the CD spectra of the halo derivatives and of their parent compounds lends support to the earlier assignment [2] of the corresponding CD bands.

The small bathochromic shift and the increased intensity of the 230 nm band in the CD spectra of the halo derivatives with respect to those of their parent compounds, however, clearly show that the halo substituents at position 9 (primarily the axial one; *cf.* the highest intensity of this band in the CD spectrum of **4b**) contribute very strongly to the optical activity of this transition. An axial *C*-halogen bond in the benzylic position to the heteroaromatic pyrimidinone chromophore is hyperconjugated (or $\sigma\pi$ homoconjugated) with the π-system of the latter. Accordingly, the "chromophore" itself, which is assigned to this delocalized $\pi \rightarrow \pi^*$ transition, must also be extended to the benzylic axial *C*-halogen bond at least, and can therefore be considered to be inherently chiral [5].

From the very strong isotropic absorption at the low-wavelength end of the uv spectra, it can be concluded that the CD band at around 200 nm must also originate from a $\pi \rightarrow \pi$ transition. (This transition was not considered in our previous calculations [2]). It is very likely, however, that the $\sigma \rightarrow \sigma^*$ transition of the *C*-halogen bond also contributes to this highest-energy CD band. The pair of CD bands with opposite signs between 200 and 250 nm might be considered an exciton couplet originating from the interaction of a $\pi \rightarrow \pi^*$ transition of the heteroaromatic ring and a $\sigma \rightarrow \sigma^*$ transition of the axial benzylic *C*-halogen bond (*cf.* [6]). Whatever the exact theoretical assignment of these bands, an empirical rule can be deduced for their signs. The plane of the pyrimidinone ring must be a nodal plane for all transitions. The signs of the two highest-energy CD bands are the same for **1b**, which has a single axial benzylic methyl group at position 6, and for **4b**, which contains an additional axial bromine atom at C-9 in the *trans* position to the methyl group, *i.e.* at the other face of the plane of the ring. This fact indicates that at least one other nodal plane is required, which is perpendicular to the first one and bisects it "longitudinally", somewhere between carbon atoms 6 and 9. Hence, the following "experimental" sector rules can be suggested for the signs of the two short-wavelength CD bands at 200-220 and 220-240 nm.

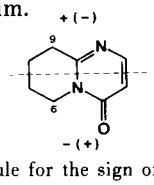


Figure 3. Simple sector rule for the sign of the CD band due to the $\pi \rightarrow \pi^*$ transition at around 230 nm. Signs in parentheses refer to sectors below the plane of the paper. With inverted signs, the rule refers to the highest-energy $\pi \rightarrow \pi^*$ transition at about 200 nm.

These rules imply that, for these transitions, it is not the helicity of the second sphere, *i.e.* the tetrahydropyridine ring itself, which determines the sign of the CD: the decisive role is played by the axial substituents in the benzylic positions (6 and 9), which belong to the third sphere of the chromophore. This explanation indicates that, even for the 9-unsubstituted parent compounds, the most significant perturbational effect on the highest-energy transitions is exerted by the axial 6-methyl group and not by the chiral ring.

The longer-wavelength halves (between 250 and 350 nm) of the CD spectra exhibit a higher degree of variety, whereas in the uv spectra only one well-separated band can be found in this wavelength region. The intensity of this band is about the same for the parent compounds and their halo derivatives (ϵ = 5000 for series **a** and 8000 for series **b**), but its position is shifted to the red in the sequence H→Cl→Br at position 9.

Our theoretical calculations relating to **1a** [2] have shown that this band (or rather band system, the asymmetric shape of which is apparent even in the CD spectra of **1a** and **1b**) is composed of one $\pi \rightarrow \pi^*$ and two $n \rightarrow \pi^*$ transitions. The rather strong isotropic absorbance of the uv band is due to the optically almost inactive $\pi \rightarrow \pi^*$ transition of the achiral pyrimidinone chromophore, whereas the CD band in the same wavelength range originates from the two nearly degenerate $n \rightarrow \pi^*$ transitions with rotational strengths of the same sign. Though both of these transitions are of mixed type, that of lower energy can be considered to be mostly a $p_x \rightarrow p_z^*$ transition of the carbonyl oxygen bound to the ring, and the second one, at somewhat higher energy, a $p_y \rightarrow p_z^*$ transition localized at nitrogen atom 1.

The composite character of the CD at higher wavelengths becomes apparent in the spectra of the halo derivatives, which exhibit several bands with different signs in this spectral region. The experimental data permit the following conclusions.

An axial halogen substituent with *R* configuration at C-9 results in a positive CD band above 300 nm. This means that the sign of the rotational strength of the $n_o \rightarrow \pi^*$ transition of the parent compound is inverted by the presence of an axial halogen at C-9. The sign of the second $n \rightarrow \pi^*$ band, below 300 nm, remains the same as that of the corresponding band of the parent compound, *i.e.* negative for the 6*R* configuration. The effect of bromine is much stronger than that of chlorine. Thus, in the CD spectrum of **2a** or **2b**, the first, positive band is weak and the second, negative one is rather strong (but weaker than in the parent compounds), whereas for **3a** only a strong positive band can be found, and even in the spectrum of **3b** the positive band is stronger than the two negative ones.

The positive contribution to the $n_o \rightarrow \pi^*$ transition of an axial bromine at C-9 is most convincingly evidenced by the CD spectrum of **4b**, which contains this single halogen substituent. In this spectrum the second (negative) $n_N \rightarrow \pi^*$ band appears only as a shoulder. In contrast to **4b**, the spectrum of **3b**, which contains an additional equatorial bromine atom, exhibits a weak positive band at 340 nm and two negative ones at shorter wavelengths. In can be argued that the equatorial bromine lying at the other face of the nodal plane of the chromophore partly compensates the effect of the axial one. It seems likely that the orientations of the two bromine atoms at C-9 do not differ too much from each other, and thus the geometry around C-9 is nearly planar. On this supposition, which is in agreement with the nmr results [4], the compensating effect of the two halogens at C-9 might easily be explained. Such an interpretation is suggested especially by the CD spectrum of **2b**, which hardly differs from that of the parent **1b**. The weak positive band at the long-wavelength end, however, is present in the spectrum of **2b**, too [7].

In a comparison of the CD spectra of the respective members of the **a** and **b** series, differing in the carboxy substituent at C-3, the most striking difference can be found between those of **3a** and **3b**. The carboxyl group in position 3 does not produce any chiral effect, but influences the transition moments of the $n \rightarrow \pi^*$ transitions (*cf.* [8]). Though no calculation taking into account the effect of the C-3 substituent has been performed, the experimental spectra indicate that the presence of the 3-carboxyl group has a strengthening effect on the negative contribution of the $nN \rightarrow \pi^*$ transition, and thereby results in an effective compensation of the contributions of the two $n \rightarrow \pi^*$ transitions with opposite signs in the CD spectrum of **3b**.

Without new theoretical calculations, it is not possible to give a deeper interpretation of the chiroptical effect on the $n_o \rightarrow \pi^*$ transition of the 9-axial halogen substituent. However, since this transition has been shown [2] to be localized mostly on the oxygen atom, it does not seem unreasonable to try to apply the octant rule for ketones to it. On this basis, an axial halogen substituent with *R* configuration at C-9 must indeed give a positive CD effect.

In conclusion, we may state that the basic lines of our earlier interpretation of the chiroptical properties of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones proved applicable for the explanation of the CD spectra of their 9-halo derivatives as well.

EXPERIMENTAL

Melting points are uncorrected. Yields were not optimized. The uv and CD spectra were recorded on a SPECORD spectrometer (C. Zeiss, Jena) and on a Roussel-Jouan Dichrograph Mark III (Jobin-Yvon), respectively, in quartz cells at ambient temperature.

(−)-(6*R*)-9,9-Dichloro-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2a**).

A solution of (−)-(6*R*)-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one **1a** [2] ($[\alpha]_D^{20} = -120°$; c 1, methanol) (0.5 g, 3.04 mmoles) and *N*-chlorosuccinimide (0.9 g, 6.7 mmoles) in glacial acetic acid (5 ml) was refluxed for 1.5 hours. The reaction mixture was evaporated *in vacuo* to dryness. The residue was suspended in hot water (20 ml). The crystals were filtered off, washed with hot water, dried, and recrystallized from 50% aqueous ethanol giving 0.4 g (57%) of dichloro derivative **2a**, mp 145-146°, $[\alpha]_D^{20} = -17.5°$ (c 1, methanol).

Anal. Calcd. for $C_9H_{10}Cl_2N_2O$: C, 46.38; H, 4.32; N, 12.02. Found: C, 46.51; H, 4.28; N, 11.97.

(+)-(6*R*)-9,9-Dibromo-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**3a**).

A solution of (−)-(6*R*)-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one **1a** [2] ($[\alpha]_D^{20} = -120°$; c 1, methanol) (0.5 g, 3.04 mmoles) and *N*-bromosuccinimide (1.19 g, 6.70 mmoles) in glacial acetic acid (5 ml) was refluxed for 2 hours. The reaction mixture was diluted with water (20 ml). The precipitated white crystals were filtered off, washed with water, dried, and recrystallized from methanol giving 0.5 g (51%) of dibromo derivative **3a**, mp 160-161°, $[\alpha]_D^{20} = +72.5°$ (c 1, methanol).

Anal. Calcd. for $C_9H_{10}Br_2N_2O$: C, 33.57; H, 3.13; N, 8.70. Found: C, 33.28; H, 3.15; N, 8.79.

(−)-(6*R*)-9,9-Dichloro-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxylic Acid (**2b**).

A mixture of (−)-(6*R*)-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxylic acid (**1b**) [2] ($[\alpha]_D^{20} = -113.7°$; c 2, methanol) (4.16 g, 20 mmoles) and *N*-chlorosuccinimide (5.32 g, 40 mmoles) in chloroform (20 ml) was refluxed for 6 hours. The reaction mixture was shaken with water (3 x 20 ml). The dried (sodium sulfate) chloroform solution was evaporated to dryness *in vacuo* and the residue was crystallized from methanol (twice) giving 2.22 g (40%) of the dichloro acid **2b**, mp 128-129°, $[\alpha]_D^{20} = -42°$ (c 1, methanol).

Anal. Calcd. for $C_{10}H_{10}Cl_2N_2O_3$: C, 40.78; H, 3.80; N, 10.57. Found: C, 40.87; H, 3.62; N, 10.49.

(+)-(6*R*)-9,9-Dibromo-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxylic Acid (**3b**).

A mixture of (−)-(6*R*)-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxylic acid **1b** [2] ($[\alpha]_D^{20} = -113.7°$; c 2, methanol) (1.04 g, 5 mmoles) and *N*-bromosuccinimide (0.91 g, 5.5 mmoles) in chloroform (20 ml) was refluxed for 6 hours. The reaction mixture was shaken with water (3 x 10 ml) and the dried (sodium sulfate) organic solvent was evaporated to dryness *in vacuo*. The residue was recrystallized from methanol (twice) giving 0.5 g (27%) of dibromo acid **3b**, mp 160-161° dec; $[\alpha]_D^{20} = +47.7°$ (c 1, methanol).

Anal. Calcd. for $C_{10}H_{10}Br_2N_2O_3$: C, 30.54; H, 2.85; N, 7.91. Found: C, 30.68; H, 2.81; N, 7.90.

(+)-(6*R*,9*R*)-9$_{ax}$-Bromo-6$_{ax}$-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxylic Acid (**4b**).

To a solution of (−)-(6*R*)-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxylic acid **1b** [2] ($[\alpha]_D^{20} = -113.7°$; c 2, methanol) (2.08 g, 10 mmoles) in glacial acetic acid (10 ml) bromine (1.59 g, 10 mmoles) in glacial acetic acid (2 ml) was added dropwise at ambient temperature. Then the reaction mixture was stirred at 40-45° for 1 hour. The cooled reaction mixture was diluted with water (10 ml) and the *p*H of the solution was adjusted to 3 with 20% aqueous sodium hydroxide solution. The aqueous reaction mixture was extracted with chloroform (3 x 10 ml). The combined, dried (sodium sulfate) organic layer was evaporated to dryness *in vacuo*. The residue was recrystallized from methanol (twice) to give 0.9 g (31%) of 9-bromo acid **4b**, mp 158-160° dec; $[\alpha]_D^{20} = +47.5°$ (c 1, methanol). According to ^{1}H nmr the product is pure *trans* isomer.

Anal. Calcd. for $C_{10}H_{11}BrN_2O_3$: C, 39.29; H, 4.03; N, 10.18. Found: C, 39.07; H, 3.98; N, 10.31.

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[5] The situation is similar to that of axial allylic chirality considered for olefins and dienes; *cf.* A. Yogev, D. Amar and Y. Mazur, *J. Chem. Soc., Chem. Commun.*, 339 (1967); A. W. Burgstahler and R. C. Barkhurst, *J. Am. Chem. Soc.*, **92**, 7601 (1970); A. W. Burgstahler, L. O. Weigel and J. K. Gawronski, *J. Am. Chem. Soc.*, **98**, 3015 (1976).

[6] G. Snatzke, in "Optical Activity and Chiral Discrimination", S. F. Mason, ed, Reidel, Dodrecht, 1979, p 43.

[7] In the CD spectrum of **2a** in chloroform, the intensity of the first, positive band at 310 nm is somewhat higher ($\Delta\epsilon = +0.54$) and that of the second, negative one at 266 nm is somewhat lower ($\Delta\epsilon = -1.44$) than in ethanol. This is in accordance with expectations.

[8] I. Hermecz, M. Kajtár, K. Simon, T. Breining, P. R. Surján, G. Tóth and Z. Mészáros, *J. Org. Chem.*, **50**, 2918 (1985).