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DETERMINATION OF THE ABSOLUTE CONFIGURATION OF 4-PHENYL-1,2,3,4-TETRAHYDROISOQUINOLINES UTILIZING ORD AND CD SPECTROSCOPY

V. Toome, J. F. Blount, G. Grethe and M. Uskoković
Chemical Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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In connection with the structure elucidation of cherylline (1), we have determined the absolute configuration at C-4 of various optically active 4-phenyl-1,2,3,4-tetrahydroisoquinolines by the use of ord and cd spectroscopy.

The pertinent data are tabulated in Table I and graphic illustrations for compounds **1** and **11** are given in Figures 1 and 2. In conjunction with the X-ray analysis of **11** (see below), it is clearly demonstrated that all 4(*S*)-compounds exhibit a negative and their enantiomers a positive first Cotton effect in the 270-290mμ region (2) corresponding to the uv absorption band of the more substituted aromatic ring A (3). The second observed Cotton effect in compounds **1**-**6** with typical vibrational structure of the ^1L_b band (4) is located in the 240-260mμ region. It is caused by the nonsubstituted 4-phenyl chromophore and it bears an opposite sign to that of the first Cotton effect. The third Cotton effect having the same sign as the first one occurs in the 230mμ region and can be ascribed to the optically active ^1L_a band (4,5) of ring A. Overlap with a Cotton effect of opposite sign occurs in this region when the substituent in 4-position is methoxyphenyl, and identification of the origin of the transitions is almost impossible with the evidence on hand.

As illustrated in Figures 1 and 2 for compounds **1** and **11** [both 4(*S*)] the cd curves are better resolved than the ord spectra. The latter show also a strong background rotation in several cases due to the tertiary amine moiety [$n\rightarrow\sigma^*$ transition of the nonbonding electron pair of nitrogen (6)] which disappears in methanolic HCl solution. Whether this is due to the protonation of the nitrogen atom or to the solvent effect is a subject of a future investigation.

The tabulated data indicate that upon substitution the Cotton effects are shifted to longer wavelength, as expected (3). In the case where only ring A carries a methoxy group [compounds **3**-**6**] and the 4-phenyl group is not substituted, the resolution of the spectra is especially clear. Although the first Cotton effects were used in all cases for the configurational assignments, one has to be careful in interpretating the ord and cd spectra when the 4-phenyl group bears more than one substituent. It should again be mentioned that in such cases the Cotton effects might coincide and the results would not be conclusive.

For the X-ray diffraction analysis compound **7** was transformed into the N-*p*-bromobenzoyl derivative **11**. The crystals of **11** are monoclinic, space group $P2_1$, with a = 15.704, b = 5.902, c = 12.969, Å, β = 110.59°, D_m = 1.45 g.cm^{-3}, Z = 2, D_c = 1.43 g.cm^{-3}. The intensities of 3041 reflections (1907 unobservedly weak) of the hemisphere with $h \geqslant 0$ were measured with a Hilger-Watts four-circle diffractometer, Cu K_α radiation; the data were corrected for Lorentz-polarization and absorption effects. The structure was determined by the usual Patterson and Fourier methods. Refinement was carried out by full-matrix least squares with allowance for the anomalous dispersion of the bromine atom. Anisotropic thermal parameters were used for the bromine atom, and individual isotropic thermal parameters were used for the lighter atoms. The absolute configuration was established by taking into account the relative intensities of $hk\ell$ and $h\bar{k}\ell$ pairs of reflections (7). The final reliability index, R, is 0.082 for the observed reflections. The absolute stereochemistry of **11** is shown in Figure 3.

References

(1) A. Brossi, G. Grethe, S. Teitel, W. C. Wildmann, and D. T. Bailey, *J. Org. Chem.*, **35**, 0000 (1970).

(2) Similar results were obtained in the Lignane series. P. Crabbé in "Advances in Stereochemistry", Vol. I, N. J. Allinger and E. L. Eliel, Ed., p.144 (1967) and references therein.

(3) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", p. 89-97, Pergamon Press, The Macmillan Co., New York (1964).

(4) In the Platt notation: J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949).

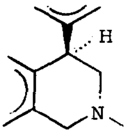
(5) L. Verbit and Yuzo Inouye, *J. Am. Chem. Soc.*, **89**, 5717 (1967).

(6) E. Tannenbaum, E. M. Coffin, and A. J. Harrison, *J. Chem. Phys.*, **21**, 311 (1953).

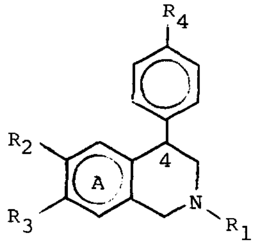
(7) A. F. Peerdeman, A. J. van Brommel, J. M. Bijvoet, *Proc. k. Ned. Acad. Wetenschap.*, **54**, B, 16 (1951).

(8) All compounds are new and gave satisfactory elemental analyses. The spectra (ir, uv, nmr, and ms) were in agreement with the assigned structures.

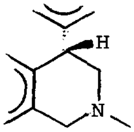
TABLE I. - First Cotton Effects of ORD and CD Spectra of 4-Phenyl-1,2,3,4-tetrahydroisoquinolines[a] (8)



R



1 - 11



S

							ORD		CD	
Cpd.	Confg.	R_1	R_2	R_3	R_4	[α]D[b]	λ(mμ)	[φ]	λ(mμ)	[θ]
1	S	CH_3	H	H	H	+18.4°	276	- 1,250°tr[c]	275	- 2,890
1(HCl)	S	CH_3	H	H	H	+ 1.9°	274	- 1,160°tr	274	- 1,400
1(HCl)	S	(in methanolic 0.1 N HCl)				-13.8°[d]	274	- 630°tr	273	- 600
2(HCl)	R	CH_3	H	H	H	- 2.2°	274	+ 920°pk	273	+ 700
2(HCl)	R	(in methanolic 0.1 N HCl)				+15.4°[d]	273	+ 450°pk	273	+ 550
3	S	H	H	OCH_3	H	- 9.8°	292	- 6,800°tr	280	-10,250
4	R	H	H	OCH_3	H	+10.1°	291	+ 6,200°pk	280	+ 9,240
5	S	CH_3	H	OCH_3	H	+ 7.2°[d]	290	- 7,020°tr	280	- 4,180
5	S	(in methanolic 0.1 N HCl)				- 9.4°[d]	289	- 4,230°tr	276	- 5,300
5(HCl)	S	CH_3	H	OCH_3	H	-11.8°	289	- 5,670°tr	279	- 2,920
6	R	CH_3	H	OCH_3	H	- 7.1°[d]	291	+ 7,800°pk	279	+ 4,180
6	R	(in methanolic 0.1 N HCl)				+12.2°[d]	288	+ 3,970°pk	277	+ 5,620
6(HCl)	R	CH_3	H	OCH_3	H	+11.5°	289	+ 4,820°pk	280	+ 3,110
7	S	H	OCH_3	OCH_3	OCH_3	-38.2°	293	-11.070°tr	289	-22,020
8	R	H	OCH_3	OCH_3	OCH_3	+38.4°	293	+10,250°pk	288	+21,680
9	S	CH_3	OCH_3	OCH_3	OCH_3	-21.7°	294	-12,400°tr	288	-23,670
10	R	CH_3	OCH_3	OCH_3	OCH_3	+21.6°	294	+12,400°tr	288	+23,660
11	S	p-bromo-benzoyl	OCH_3	OCH_3	OCH_3	+120°	291	+ 6,000°tr	288	-13,200

(a) Ord and cd spectra were recorded in methanol unless stated otherwise on a JASCO Spectropolarimeter, Model ORD/CD/UV-5 at 23°C. Concentrations were in the average of 0.2 - 0.5%.

(b) Optical rotations were measured on a Perkin Elmer Polarimeter Model 141 at 23-25° using methanol as solvent.

(c) tr = trough; pk = peak.

(d) Calculated from the ord spectra.

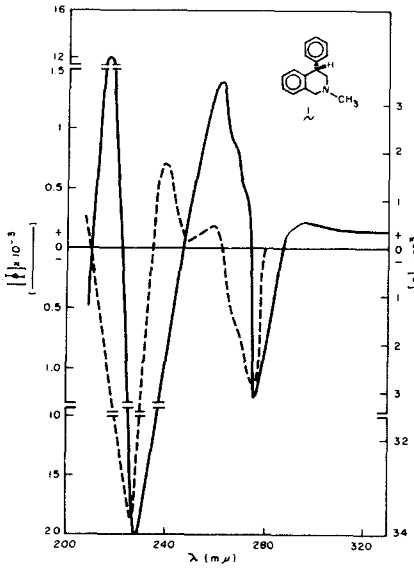


Figure I - ORD (—) AND CD (---) SPECTRA OF I (CH$_3$OH)

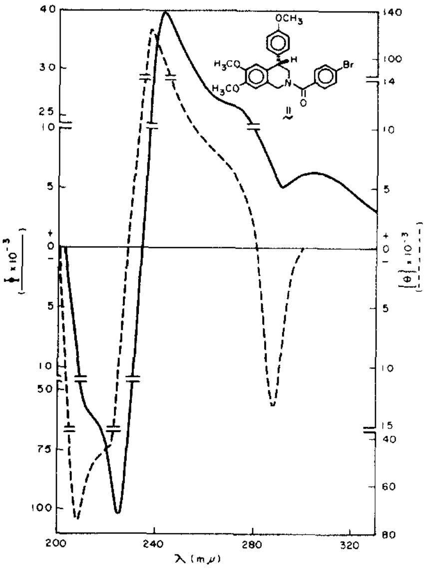


Figure 2 - ORD (–) AND CD (---) SPECTRA OF II (CH$_3$OH)

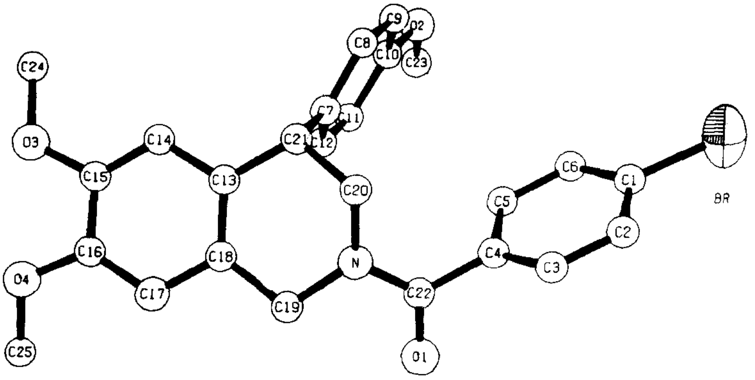


Figure 3.- View showing the absolute configuration of 11.