THE CONFIGURATION AND CONFORMATION OF CULARINE¹

N. S. BHACCA,^a J. CYMERMAN CRAIG,^b R. H. F. MANSKE,^c S. K. Roy,^b M. SHAMMA^d and W. A. SLUSARCHYK^d

Joint contribution from ^a Instrument Division, Varian Associates, Palo Alto, California; Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94122;
^c Dominion Rubber Research Laboratory, Guelph, Ontario, Canada; and ^a Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802.

(Received 7 September 1965; in revised form 5 November)

Abstract—The absolute configuration of cularine has been shown to be D(=R) from the ORD of its hydrogenolysis product (VIII). The hydrochloride, methiodide and O-acetate of VIII showed a complete reversal of the long-wavelength Cotton effect and CD maximum at 290 m μ , while the short-wavelength Cotton effects at 226 and 210 m μ remained unaffected. This reversal is attributed to steric hindrance to rotation of the 2'-substituted benzyl moiety. NMR spectra at 100 mc/s permit the assignment of one of the 3 possible bent conformations to cularine.

THE cularine alkaloids² form a unique group of benzylisoquinoline compounds, occurring only in the genera *Dicentra* and *Corydalis*, and possessing a seven-membered heterocyclic ring system containing an oxygen in a diphenyl ether linkage. They are, moreover, anomalous in their oxygen substitution pattern. Cularine (I) is 7,8-dioxy-genated, while all other benzylisoquinoline or benzylisoquinoline-derived alkaloids contain oxygen functions in the 6- and 7-positions.

Cularine could arise^{3.3} by radical-oxidation (and subsequent O-methylation) of either of the diphenols II or III, or³ from oxidative coupling of a precursor of structure IV, with subsequent removal of the unwanted C-6 substituent.

It is of interest that the protoberberine alkaloid capaurine (V), which has the same oxygen substitution pattern as IV, occurs in *Corydalis* species.⁴ The formation of cularine may thus require the simultaneous presence of hydroxyl groups in both the 8- and 3'-positions (as in II and IV). Recent advances in our knowledge of free radical coupling suggest⁵ that the formation of I from II may involve *p*-coupling *via* the intermediate quinonoid biradical (VI).

It is therefore of particular interest that the recently isolated quaternary alkaloid

- ¹ Supported by research grants MH-4582 from the National Institutes of Health, U.S. Public Health Service to J. C. C., and GP-1941 from the National Science Foundation to M. S. One of us, W. A. S., was the recipient of National Institutes of Health predoctoral fellowship 5-FI-GM-20, 691-02. This paper can be considered as paper IX in the series Optical Rotatory Dispersion and Absolute Configuration.
- ³ R. H. F. Manske, in R. H. F. Manske and H. L. Holmes, *The Alkaloids—Chemistry and Physiology* Vol. 4, p. 1. Academic Press, New York (1954).
- ³ K. W. Bentley, The Isoquinoline Alkaloids p. 61. Pergamon Press, Oxford (1965).
- ⁴ R. H. F. Manske, Canad. J. Research 9, 436 (1933); 17B, 57 (1939); 18B, 80 (1940); 20B, 49 (1942).
- ⁵ M. F. Grundon, in Progress in Organic Chemistry Vol. 6, p. 38. Butterworths, Washington (1964).



petaline⁶ (VII) is the first simple benzylisoquinoline alkaloid having a 7,8-dioxygenation pattern, and has now been shown⁷ to possess the D-configuration from the observation that the ORD curve of petaline iodide is the mirror image of that of L-(+)-laudanosine methiodide. Since the presence of the diphenyl ether bridge in cularine (I) confers molecular dissymmetry upon the molecule, a simple correlation of its ORD curve (Fig. 1) with those of the benzyltetrahydroisoquinoline alkaloids^{7.8} is not possible. Fission of the ether bridge by hydrogenolysis with sodium in liquid ammonia⁹ gave the phenolic base (VIII) in agreement with the predictable direction of ether-fission based on the *ortho*-effect.⁵ The main mass spectral peaks for the phenolic base (VIII) were at m/e 343 (molecular ion), 176 (base), 167 and 161, in accord with the cleavages shown on p. 1469

The ORD curve of VIII (Fig. 2) showed three negative Cotton effects centered at 292, 226 and 210 m μ , characteristic of benzyltetrahydroisoquinolines possessing the D(=R) configuration^{7.8} (e.g. D-laudanidine and D-armepavine). Since the liquid ammonia reduction does not involve the asymmetric center at C-1, this result also permits the assignment of the D-configuration to cularine and hence to the cularine group of alkaloids² (as all of these could be converted into the parent compound).

- ⁷ J. C. Craig, M. Martin-Smith, S. K. Roy and J. B. Stenlake, Tetrahedron 22, 1335 (1966).
- ⁸ J. C. Craig and S. K. Roy, Tetrahedron 21, 401 (1965).
- * R. H. F. Manske, J. Amer. Chem. Soc. 72, 55 (1950).

[•] N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith and J. B. Stenlake, *Tetrahedron Letters* No. 51, 3841 (1964).



It was recently shown⁷ that both the UV absorption and the ORD of benzyltetrahydroisoquinolines remain unchanged on conversion of the base to the hydrochloride or the methiodide. It was therefore unexpected to find that acidification of VIII was accompanied by a drastic change in the specific rotation from $[\alpha]_D -152^\circ$ to $[\alpha]_D$ +66.4°. The ORD curve (Fig. 2) similarly showed a remarkable change, the longwavelength Cotton effect now being *positive*, with the appearance of a further positive



FIG. 1. Rotatory dispersion curve of Cularine (I).

Cotton effect centered at 240 m μ , where there had been only a characteristic inflexion⁸ in the curve of the neutral substance. On addition of ammonia to pH 7, the ORD curve reverted to the original, once again exhibiting three negative Cotton effects. The two short-wavelength Cotton effects remained unaffected by changes in pH.

The correctness of this interpretation was fully confirmed by CD measurements, which showed three negative maxima at the expected positions for the neutral solution (Fig. 3), while addition of acid resulted in a complete reversal of the 290 m μ CD



FIG. 2. Rotatory dispersion curves of 1-(4',5'-Dimethoxy-2'-hydroxybenzyl)-7-methoxy-2-methyltetrahydroisoquinoline VIII (-----) and its hydrochloride (----).

maximum, and the emergence of a new positive dichroism peak at 240 m μ . The UV spectra (Fig. 3) showed a less marked difference, with increased absorption in the 230-300 m μ region for the hydrochloride.

Such drastic changes in specific rotation, ORD and CD are indicative of deepseated alterations in the shape, and hence in the dipole moment, of the molecule. The appearance of the two positive Cotton effects at 290 and 240 m μ on acidification, and the concurrent reduction in the amplitude of the negative Cotton effects centered at 226 and 210 m μ , indicates the destruction of a preferred conformation. Examination of space-filling models reveals that the protonation of VIII, resulting in the conversion of the pyramidal nitrogen to the tetrahedral conformation, causes restricted rotation of the 2'-substituted benzyl moiety (even with the N-methyl group occupying the favored equatorial position), and forces the molecule to undergo a change in conformation. The change in the CD in acid solution may thus be regarded as due to the change in the spatial orientation of the 2-hydroxy-4,5-dimethoxytoluene moiety, in agreement with the known intense absorption at 240 m μ due to the p $\rightarrow \pi$ electron transfer transition of this system, and also with its intensifying effect on the local excitation bands in the 280-290 m μ region.¹⁰

These conclusions were supported by the preparation of the methiodide of VIII and the observation that its ORD curve (Fig. 4) was essentially the same as that of the hydrochloride, concomitant with the enhanced steric hindrance to rotation offered by the doubly methylated tetrahedral nitrogen atom.

¹⁰ A. I. Scott, Interpretation of the Ultraviolet Spectra of Natural Products p. 90. Pergamon Press, New York (1964).





FIG. 4. Rotatory dispersion curves of 1-(4',5'-Dimethoxy-2'-hydroxybenzyl)-7-methoxy-2,2-dimethyltetrahydroisoquinolinium iodide (---) and 1-(2'-Acetoxy-4',5'-dimethoxybenzyl)-7-methoxy-2-methyltetrahydroisoquinoline IX (----).

N. S. BHACCA et al.

Finally, preparation of the acetoxy derivative of VIII was undertaken in order to demonstrate that steric restriction could equally originate from a bulky substituent at the 1'-position. This was verified by the ORD curve of the acetoxy-base IX (Fig. 4) showing the same Cotton effects as the methiodide and hydrochloride down to 230 m μ (below this wavelength, the additional Cotton effects due to the acetoxy group invalidate further comparison). Both the methiodide and the acetoxy-base exhibited a positive CD maximum at 288 m μ , in agreement with the ORD data, and showed very similar UV spectra (Table 1).

Compound			$\lambda_{\max} m\mu \ (\log \varepsilon)$			
1-(4',5'-Dimethoxy-2'-hydroxybenzyl)-7-methoxy-		228 sh	257 min	278 sh	288	300 sh
2-methyl tetrahydroisoquinoline (VIII)		(4·12)	(3·01)	(3·70)	(3·85)	(3·64)
Hydrochloride of VIII		228	256 min	278 sh	288	297 sh
		(4·17)	(3·52)	(3·80)	(3·90)	(3·75)
Methiodide of VIII		220 (4·33)	256 min (3·20)	278 (3·71)	288 (3·76)	297 sh (3·61)
1-(2'-Acetoxy-4',5'-dimethoxybenzyl)-7-methoxy-		228 sh	257 min	282	288 sh	
2-methyltetrahydroisoquinoline (IX)		(4·16)	(3·08)	(3·72)	(3·71)	
Laudanidine		230 sh (4·15)	254 min (2·88)		283 (3·83)	
Cularine (I)	206 sh	229 sh	256 min	274	283	295 sh
	(5·21)	(4·12)	(3·13)	(3·63)	(3·79)	(3·48)

TABLE	1.	U٧	SPECTRA
-------	----	----	---------

Although the absolute configuration of the asymmetric center of cularine is now established as D (R on the Cahn-Ingold-Prelog¹¹ convention), the presence of the oxygen bridge in cularine confers dissymmetry upon the molecule. R-Cularine may therefore exist in the bent conformations R-1, R-2, or R-3. The models of R-1 and R-2 can be interconverted by simultaneously rotating the bonds C-8-O-C-2' and C-1-C-9-C-1'. The two conformations differ in only one important respect. If the two hydrogens at C-9 are designated as H_A and H_B and that at C-1 as H_X , Newman projections X and XI reveal that in form R-1 the dihedral angle between H_X and H_B is approximately 180°, while that between H_x and H_A is nearly 60°. Thus the coupling constant J_{AX} will be between 3 to 4 c/s, while J_{BX} will have a larger magnitude of between 8 and 14 c/s. In the case of form R-2, however, H_X bisects the 120° angle between H_A and H_B , so that each dihedral angle will be about 60°, and the resulting coupling constants J_{AX} and J_{BX} will both be between 3 to 4 c/s. The third conformation, R-3 may be obtained either from R-2 by twisting at C-9 while keeping the oxygen bridge stationary, or from R-1 by rotating the C-8-O-C-2' bond while keeping C-9 stationary. The Newman projection X of R-3 is identical with that of R-1. The 100 mc spectrum of cularine¹² (Fig. 5) exhibits a pair of doublets representing

¹¹ R. S. Cahn, C. K. Ingold, and V. Prelog Experientia 12, 81 (1956).

1472

¹³ NMR spectra were determined in CDCl_s solution using a Varian HA-100 spectrometer. Chemical shifts (δ) are given in ppm downfield from an internal tetramethylsilane standard.





a single proton at $\delta = 4.44$. When this absorption is irradiated with a strong radiofrequency H₂ while operating the spectrometer in the frequency sweep mode, the complex pattern at $\delta = 3.24$ and 2.98 changes into a pair of AB doublets with coupling constants $J_{AB} = 16$ c/s. This indicates that proton H_x is spin coupled to H_A and H_B with a spin coupling constant of $J_{AX} = 4$ and $J_{BX} = 12$ c/s respectively, and that cularine possesses conformation R-1 or R-3, but not R-2.

In the 100 mc spectrum of the aporphine glaucine, the ABX pattern is upfield and is mixed with the resonances of the other aliphatic protons at C-3 and C-4 in the molecule. The downfield shift of the signals due to the proton at C-1 in cularine is therefore directly attributable to the electrostatic effect of the oxygen bridge present between rings A and D. Comparison of molecular models of forms R-1 and R-3 shows that in R-1 the oxygen atom is adjacent to H_B but well removed from H_x whereas in form R-3 the oxygen is close to H_x and would thus account for the marked downfield shift of this hydrogen. Moreover in form R-1 there is steric overlap between the N-methyl group and the equatorial hydrogen at C-9 (H_A), while in form R-3 the N-methyl group is free to rotate. The NMR results thus point to conformation R-3 as that most likely for cularine.

The tall peaks at $\delta = 2.60$, 3.79, 3.84 and 3.87 are assigned to the one N-methyl and three methoxy groups respectively. Assignments may also be made for the four aromatic protons. The signal at $\delta = 6.51$ is attributed to $H_3'^{13}$; the broadness of the H_3' resonance can be attributed to spin coupling between the two *para* protons H_3' and H_6' . The two AB quartets at $\delta = 6.76$ and 6.87 with a coupling constant of 8.5 c/s correspond to H_6 and H_5 respectively. The doublet at $\delta = 6.87$ is somewhat broadened since H_5 is slightly coupled to the benzylic hydrogens at C-4, and the signal superimposed on the taller line (685 c/s) of the H_5 doublet is assigned to H_6' .



¹⁹ N. S. Bhacca, D. P. Hollis, L. F. Johnson and E. Pier, NMR Spectra Catalog Vol. 2, No. 678. Varian Associates, Palo Alto, Calif. (1963).

EXPERIMENTAL

ORD curves were determined with a Cary model 60 spectropolarimeter in 95% EtOH at 25°. Rotations are given below only for (1) the highest and lowest wavelengths measured, (2) peaks and troughs. CD was measured at 25° on a Jasco ORD/CD-5 instrument, and is recorded in molecular ellipticity units [θ].¹⁴

Cularine. $[\alpha]_{D} + 285^{\circ}$ (c 0.8, MeOH). ORD (c 0.075) $[\alpha]_{sss} + 1276^{\circ}$, $[\alpha]_{ss7} + 1844^{\circ}$ (pk), $[\alpha]_{ss3} + 36.9^{\circ}$ (tr), $[\alpha]_{s13} + 41,500^{\circ}$ (pk), $[\alpha]_{ss0} - 92,400^{\circ}$.

1-(4',5'-Dimethoxy-2'-hydroxybenzyl)-7-methoxy-2-methyl-tetrahydroisoquinoline (VIII). A sample of cularine in ether was treated with Na in liquid ammonia according to the procedure of Manske¹⁰ to give yellow, oily VIII. Preparative TLC on Adsorbosil-1 (silica gel) using ether-MeOH (9:1) as developer gave a pure sample of oily VIII which was used for all measurements. The IR spectrum of VIII (CHCl₃ solution) exhibited broad bands at $3\cdot8-4\cdot3 \mu$ and $5\cdot5-6\cdot0 \mu$ and no peak in the region $2\cdot9-3\cdot0 \mu$.

 $[\alpha]_{D} - 152^{\circ} (c \ 0.2, \text{EtOH}). \text{ ORD } (c \ 0.082) [\alpha]_{3333} - 1220^{\circ}, [\alpha]_{300} - 2866^{\circ} (\text{tr}), [\alpha]_{334} + 219 \cdot 5, [\alpha]_{333} - 10,070^{\circ} (\text{tr}), [\alpha]_{313} - 1098^{\circ} (pk), [\alpha]_{313} - 10,070^{\circ} (\text{tr}), [\alpha]_{205} + 28,050^{\circ}. \text{ CD } [\theta]_{310} 0, [\theta]_{305} - 5300, [\theta]_{319} 0; [\theta]_{333} - 28,300, [\theta]_{319} - 15,220, [\theta]_{310} - 73,500, [\theta]_{304} 0.$

Hydrochloride of VIII. $[\alpha]_{D} + 66.4^{\circ}$ (c 0.2, 95% ethanolic 0.1 N-HCl). ORD (c 0.082 in 95% alcoholic 0.1 N-HCl) $[\alpha]_{325} + 854^{\circ}$, $[\alpha]_{325} + 2316^{\circ}$ (pk), $[\alpha]_{372} - 610^{\circ}$ (tr), $[\alpha]_{351} + 244^{\circ}$ (pk), $[\alpha]_{325} - 4270^{\circ}$ (tr), $[\alpha]_{325} - 1830^{\circ}$ (pk), $[\alpha]_{310} - 6405^{\circ}$ (tr), $[\alpha]_{305} + 12,200^{\circ}$. CD $[\theta]_{210} 0$, $[\theta]_{200} + 4600$, $[\theta]_{270} 0$; $[\theta]_{200} 0$, $[\theta]_{240} + 11500$, $[\theta]_{320} 0$, $[\theta]_{324} - 19,600$, $[\theta]_{317} - 5670$, $[\theta]_{310} - 45400$, $[\theta]_{300} 0$.

Methiodide of VIII. ORD ($c \ 0.040$) [α]₃₅₀ +325°, [α]₃₅₇₋₅ +1000° (pk), [α]₃₇₇ -750° (tr), [α]₃₅₈₋₅ +625° (pk), [α]₃₅₈ -1200° (tr), [α]₃₅₇ -800° (pk), [α]₃₁₁ -1500° (tr), [α]₃₆₅ +3500°.

1-(2'-Acetoxy-4',5'-dimethoxybenzyl)-7-methoxy-2-methyltetrahydroisoquinoline (IX). A solution of 34 mg VIII, 1 ml dry pyridine and 0.4 ml acetic anhydride was left stoppered at room temp for 2 days. Ether was added and the mixture washed repeatedly with water. The ether layer was dried over MgSO₄, and evaporated under red. press. to 20 mg. (75%) of pale yellow oily acetate exhibiting an IR peak at 5.75 μ , no peaks in the regions 2.9-3.0 μ and 3.8-4.3 μ , and no broad band in the area 5.5-6.0 μ . The mass spectrum showed peaks at m/e 385 (molecular ion), 209 (very weak), and 176 (base peak). ORD (c 0.040) [α]₃₈₀ +625°, [α]_{881.5} +1750° (pk), [α]₃₈₅ -406° (tr), [α]₃₆₆ +1312° (pk), [α]₃₈₈ -2250° (tr), [α]₃₈₀ -1375° (pk), [α]₃₈₂ -2875° (tr), [α]₃₁₃ -500° (pk), [α]₃₂₆ -2815°.

¹⁴ C. Djerassi and E. Bunnenberg, Proc. Chem. Soc. 299 (1963).