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OPTICAL ROTATORY DISPERSION AND ABSOLUTE CONFIGURATION—VIII

PETALINE AND OTHER BENZYLTETRAHYDROISOQUINOLINE ALKALOIDS[1]

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Abstract—The ORD of benzyltetrahydroisoquinoline alkaloids shows three Cotton effects which have been correlated with the UV absorption, CD and absolute configuration of these compounds. The application of this method shows petaline to have the D(=R) configuration.

Evidence was recently presented[2] that the quaternary alkaloid (-)-petaline (I) from *Leontice leontopetalum* L. is the first simple benzylisoquinoline alkaloid having a 7,8-dioxygenation pattern. The determination of its absolute configuration was therefore of considerable interest in view of its close resemblance to the 7,8-dioxygenated structure (II) which has been suggested[3] as a biogenetic precursor, by the removal of two hydrogens, for the formation of cularine (III), the parent of the only known group of benzylisoquinoline, or benzylisoquinoline-derived, alkaloids which is not 6,7-dioxygenated.

The ORD curves of three benzylisoquinoline alkaloids have been briefly recorded[4] and it was shown that it is possible to deduce the absolute configuration of the asymmetric center from these curves. Although the rotation of the compounds at the D-line is no criterion of their absolute configuration (e.g. D-armepavine and L-norarmepavine are both levo-rotatory), the rotatory dispersion curves of the L (or S)[5] series show three positive [and their D-(or R)[5] enantiomers three negative] Cotton effects in the 200–320 mμ region which has recently become accessible with improved instrumentation.

We now wish to present the further application of this method to the determination of the absolute configuration of petaline, and to report our detailed findings on the relation between UV absorption and ORD of benzylisoquinoline alkaloids, since our conclusions differ in some small, but fundamental, respects from those reached in a recent publication[6] describing the ORD curves of a series of bisbenzylisoquinoline alkaloids and also of some benzylisoquinolines.

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[1] Supported in part by research grant MH-4582 from the National Institutes of Health, U.S. Public Health Service.

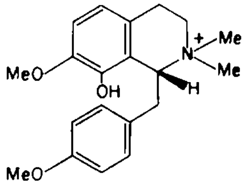
[2] N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith and J. B. Stenlake, *Tetrahedron Letters* No. 51, 3841 (1964).

[3] R. H. F. Manske, *J. Amer. Chem. Soc.* 72, 55 (1950); cf. M. F. Grundon, in *Progress in Organic Chemistry* Vol. 6, p. 38. Butterworths, Washington (1964); and D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll* p. 117. Birkhäuser, Basel (1957).

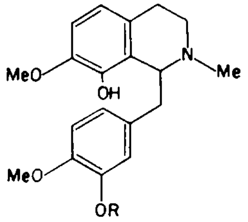
[4] J. C. Craig and S. K. Roy, *Tetrahedron* 21, 401 (1965).

[5] Using the Sequence Rule: R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* 12, 81 (1956).

[6] A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P. M. Scopes and M. J. Vernengo, *J. Chem. Soc.* 2239 (1965).



I



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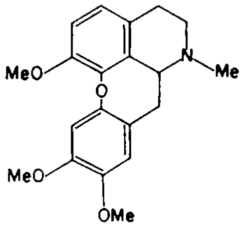

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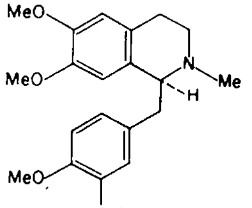

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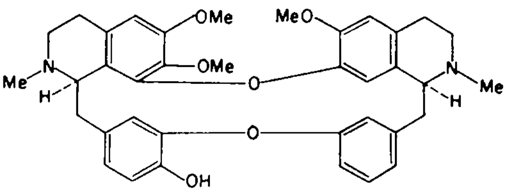

V

The UV spectrum of 1,2,3,4-tetrahydroisoquinoline (Table 1) is shifted in the expected manner on the introduction of the 6,7-dimethoxy substituents, and these compounds (e.g. calycotomine, Table 1) show the simple aromatic spectrum of a 4,5-dialkylcatechol dimethyl ether[7] in which the benzene transitions at 184, 203·5 and 254 mμ (log ε 4·78, 3·87 and 2·31) have been displaced to 204, 232 and 284 mμ (log ε 4·67, 3·89 and 3·56). However, while the 184 mμ (local excitation)[7] band of benzene now appears at ca. 205 mμ (log ε 4·5–5·0), the second local excitation band of benzene at 203·5 mμ is now at 235–245 mμ, where it is masked by the intense absorption at 228–235 mμ (log ε 3·9–4·3) due to the p → π electron transfer transition of the catechol system, which also further displaces and intensifies the (often not resolved) local excitation bands[7] in the 280–285 mμ region.

The introduction of the mono- or di-oxygenated 1-benzyl substituent results in a final spectrum (Table 1) which can be regarded as the superposition of that of a 3,4-dimethoxytoluene on the absorption of the 4,5-dialkyl catechol dimethyl ether, with the expected[7] increase in the intensity of the absorption bands, particularly that in the 228–235 mμ region.

The ORD spectrum (Fig. 1) of L-(+)-laudanosine (IV) is in full agreement with this conclusion, and shows three positive Cotton effects ascribable to the absorption bands at 282, 232 and 207 mμ respectively. The presence of three positive CD maxima at the expected positions affords final conclusive proof (Fig. 1). Only the first two Cotton effects were reported in the work cited.[6] No CD curves have, to our knowledge, been reported for any benzylisoquinoline alkaloids. Since the absorption of alkoxy-diphenyl ethers also occurs at 230 and 270–280 mμ,[8] the UV spectra of the bisbenzyl-tetrahydroisoquinolines would not be expected to differ markedly from those of the simple benzyltetrahydro-compounds, and this is seen to be the case for (+)-berbamine (V) (Table 1) which again shows three absorption bands, and also exhibits three Cotton effects in its ORD spectrum (Fig. 2). The second Cotton effect is clearly

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[7] cf. A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products* pp. 90–94. Pergamon Press, The Macmillan Co., New York (1964).

[8] H. E. Ungnade, E. E. Pickett, L. Rubin and E. Youse, *J. Org. Chem.* **16**, 1318 (1951).

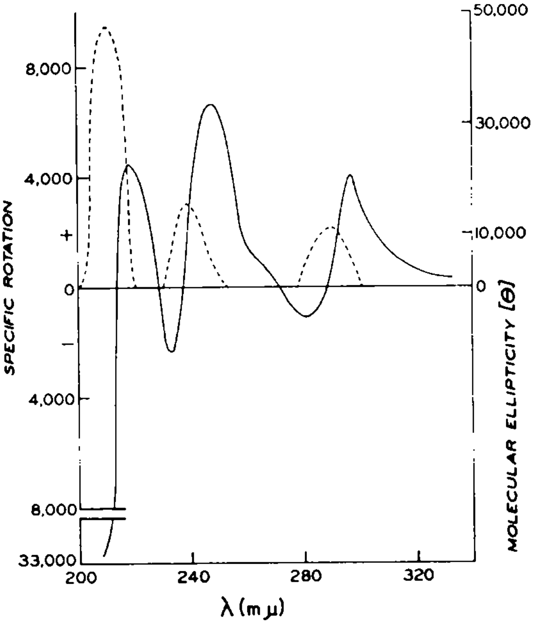

Fig. 1. Rotatory dispersion (——) and circular dichroism (- - -) curves of L-(+)-laudanosine.

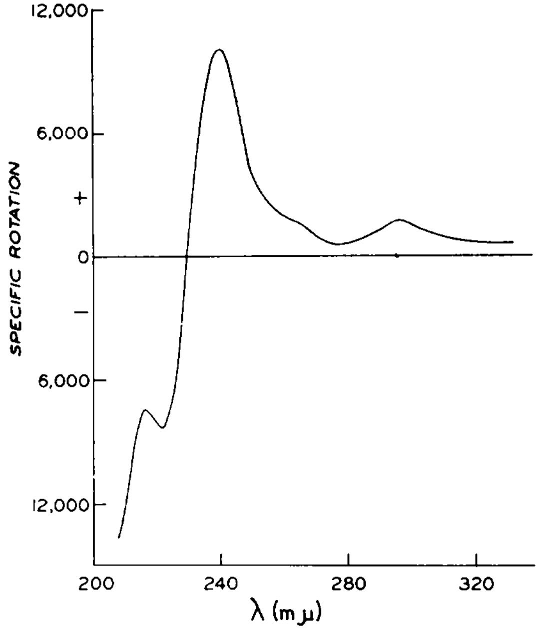

Fig. 2. Optical rotatory dispersion curve of berbamine.

associated with the UV absorption at 237 mμ, rather than with the intense 207 mμ band, as has been stated.[6] These authors did not report the short-wavelength Cotton effect.

It was of interest to examine if protonation of the nitrogen in the benzyltetrahydroisoquinolines affected the ORD curve. Both the UV spectrum (Table 1) and the rotatory dispersion (Experimental) of L-laudanosine hydrochloride closely resembled those of the parent base. The same was true for L-laudanosine methiodide

TABLE 1. UV ABSORPTION OF TETRAHYDROISOQUINOLINES

Substituent at position					Compound	λ_{max} mμ (log ε)					Ref.
6	7	8	2	1							
—	—	—	H	—	1,2,3,4-Tetrahydroisoquinoline			240 min	266 (2·61)	273 (2·61)	9
OMe	OMe	—	Me	—	6,7-Dimethoxy-2-methyl-tetrahydroisoquinoline		235 sh (3·83)	255 min (3·10)		285 (3·59)	10
OMe	OMe	—	Me	isoBu	Locopherine methyl ether			254 min (2·75)		285 (3·59)	11
OMe	OMe	—	H	CH_2OH	Calycotomine hydrochloride	204 sh (4·67)	232 (3·89)	252 min (2·47)	280 (3·47)	284 (3·56) 290 (3·48)	—
—	OMe	OH	Me_2	4′-OMe-benzyl	Petaline iodide	206 sh (4·87)	233 sh (4·35)	255 min (2·97)	278 (3·59)	284 (3·59)	—
OMe	OMe	—	Me	4′-OH-benzyl	Armepavine		228 (4·37)	254 min (2·92)		282 (3·82)	—
OMe	OMe	—	H	4′-OH-benzyl	Nor-Armepavine	207 sh (4·75)	228 (4·23)	253 min (2·95)	282 (3·75)	286 (3·74)	—
OMe	OMe	—	Me	3′-OH-4′-OMe-benzyl	Laudanidine		230 sh (4·15)	254 min (2·88)		283 (3·83)	—
OMe	OMe	—	Me	3′,4′-di-OMe-benzyl	Laudanosine	207 sh (4·89)	232 (4·17)	256 min (2·97)		282 (3·77)	—
OMe	OMe	—	Me	3′,4′-di-OMe-benzyl	Laudanosine hydrochloride	207 sh (5·03)	232 (4·30)	256 min (3·20)		281 (3·80)	—
OMe	OMe	—	Me_2	3′,4′-di-OMe-benzyl	Laudanosine methiodide	207 sh (4·95)	232 (4·30)	256 min (3·02)		281 (3·76)	—
OMe	$PhCH_2O$	—	H	3′,4′-di-OMe-benzyl	7-Benzyloxy-6-Methoxy-1-(3′4′-dimethoxybenzyl)-tetrahydroisoquinoline		233 sh (4·35)	258 min (3·15)		285 (3·85)	12
					Berbamine hydrochloride	207 sh (5·01)	237 sh (4·27)	258 min (3·30)		282 (3·74)	—

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[9] A. J. Birch and D. Nasipuri, *Tetrahedron* **6**, 148 (1959).

[10] J. Knabe, *Arch. Pharm.* **292**, 652 (1959).

[11] C. Djerassi, J. J. Beereboom, S. P. Marfey and S. K. Figdor, *J. Amer. Chem. Soc.* **77**, 484 (1955).

[12] N. Arumugam, T. R. Govindachari, K. Nagarajan and U. R. Rao, *Chem. Ber.* **91**, 40 (1958).

(Fig. 3). The absolute configuration of a benzyltetrahydroisoquinoline alkaloid may thus be assigned from the ORD curve of either the base, a salt or the quaternary derivative. The ORD curve of (-)-petaline iodide (Fig. 3) is seen to be the mirror image of that of L-laudanosine methiodide, so that petaline can be assigned the D-(= R) configuration.

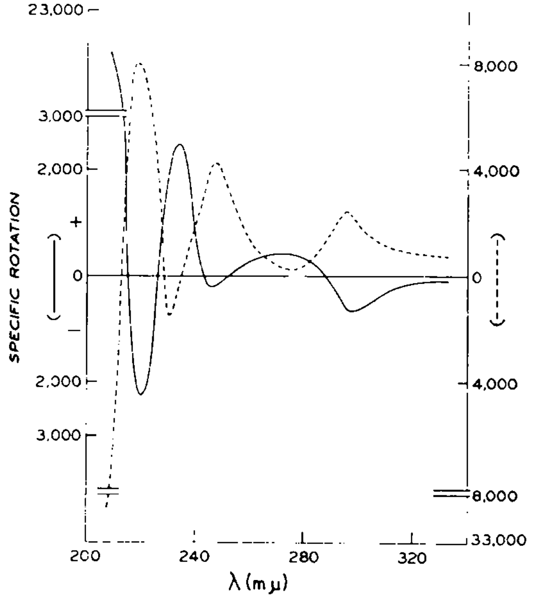

FIG. 3. Rotatory dispersion curves of L-laudanosine methiodide (- - -) and D-petaline iodide (——).

EXPERIMENTAL

ORD curves were determined as described previously.[4] CD was measured on a Jasco ORD/CD-5 instrument, and is recorded in molecular ellipticity units [θ].[18]

L-(+)-*Laudanosine*. $[\alpha]_D$ +107° (*c* 1·2, EtOH). ORD (*c* 0·041 in 95% EtOH) $[\alpha]_{333}$ 395°, $[\alpha]_{296.5}$ 4083° (peak), $[\alpha]_{281}$ −1112° (trough), $[\alpha]_{246}$ 6650° (pk), $[\alpha]_{233.5}$ −2385° (tr), $[\alpha]_{218}$ 4505° (pk), $[\alpha]_{208}$ −31400°. CD $[\theta]_{300}$ 0, $[\theta]_{289}$ +7200, $[\theta]_{278}$ 0; $[\theta]_{252}$ 0, $[\theta]_{238}$ +15,280, $[\theta]_{230}$ 0; $[\theta]_{220}$ 0, $[\theta]_{210}$ +47,130, $[\theta]_{200}$ 0.

L-*Laudanosine hydrochloride*. ORD (*c* 0·041 in 95% ethanolic N–HCl) $[\alpha]_{333}$ 175·2°, $[\alpha]_{298.5}$ 3575° (pk), $[\alpha]_{280}$ −1792° (tr), $[\alpha]_{246}$ 6152° (pk), $[\alpha]_{233.5}$ −4950° (tr), $[\alpha]_{216.5}$ 5400° (pk), $[\alpha]_{208}$ −34,900°.

L-*Laudanosine methiodide*. This compound crystallized from alcohol as plates, m.p. 221–221·5°. (Found: C, 52·73; H, 6·22; N, 2·76; Calc. for $C_{22}H_{30}INO_4$: C, 52·92; H, 6·01; N, 2·80%.) ORD (*c* 0·05 in 95% EtOH) $[\alpha]_{333}$ 803°, $[\alpha]_{298}$ 2400° (pk), $[\alpha]_{275.5}$ 288° (tr), $[\alpha]_{246.5}$ 4352° (pk), $[\alpha]_{229.5}$ −1588° (tr), $[\alpha]_{218}$ 8854° (pk), $[\alpha]_{208}$ −16,200.

(+)-*Berbamine dihydrochloride*. M.p. 255–257°, $[\alpha]_D$ +60° (*c* 1·5, H_2O). ORD (*c* 0·063 in 95% EtOH) $[\alpha]_{333}$ 665°, $[\alpha]_{297}$ 1772° (pk), $[\alpha]_{276}$ 635° (tr), $[\alpha]_{240}$ 10,100° (pk), $[\alpha]_{222}$ −8335° (tr), $[\alpha]_{216.5}$ −7530° (pk), $[\alpha]_{208}$ −13620°.

(−)-*Petaline iodide*. $[\alpha]_D$ −3·1° (*c* 7·35 in $CHCl_3$); ORD (*c* 0·224 in 95% EtOH) $[\alpha]_{333}$ −107°, $[\alpha]_{296.5}$ −656° (tr), $[\alpha]_{274}$ 456° (pk), $[\alpha]_{245}$ −205° (tr), $[\alpha]_{232.5}$ 2470° (pk), $[\alpha]_{219.5}$ −2295° (tr), $[\alpha]_{208}$ 15,120°.

Acknowledgement—The authors are grateful to Professor A. R. Battersby for a sample of calycotomine.

[18] C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.* 299 (1963).