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The Absolute Configuration of Cularine: A Chemical Correlation to L(*S*)-Laudanosine

Alkaloids of the cularine group[1] isolated from the genera *Dicentra* and *Corydalis* (Papaveraceae) have the unique structural feature of the diphenyl ether linkage forming a seven-membered heterocycle in their molecules.

The absolute stereochemistry of cularine (I) has been assigned by optical rotatory dispersion (ORD) measurement of its sodium-liquid ammonia reduction product (II) that it has D(*R*)-configuration.[2] We describe here our results on the determination of the absolute configuration of this group of alkaloids by chemical correlation to L(*S*)-romneine (III),[3,4] of which configuration has previously been correlated to L(*S*)-laudanosine (IV).[5]

Bromination of L(*S*)-romneine (III)[4b] gave a monobromo derivative (V), mp 101.5—102°, $[\alpha]_D$+49.0° (EtOH). This was characterized as L(*S*)-6′-bromoromneine (V) by nuclear magnetic resonance (NMR) measurement and by spectral (infrared (IR), NMR, ultraviolet (UV)) and thin-layer chromatography (TLC) comparisons with *dl*-6′-bromoromneine[6] obtained *via* standard Bischler-Napieralski synthesis starting from 6-bromohomoveratric acid and homo piperonylamine. V and guaiacol were submitted to Ullmann condensation in pyridine in presence of cupric oxide[7] and potassium carbonate to afford L(*S*)-6′-(2-methoxyphenoxy)-romneine (VI) as an oily product, $[\alpha]_D$+70.0° (EtOH). Sodium-liquid ammonia reduction of VI resulted in concomitant fission of both methylenedioxy group and diphenyl ether linkage to afford a mixture of two species of diphenolic bases (VII) and (VIII) in agreement with the prediction[8] of the direction of ether fission. Without separation this mixture was treated with ethereal diazomethane for 24 hours, and a monomethylated derivative (IX) was isolated from the reaction mixture as an alkali-insoluble fraction, colorless oil, $[\alpha]_D$ −26.8° (EtOH), NMR ($CDCl_3$) τ: 7.41 (3H, s, NCH_3), 6.29, 6.24, 6.20 (3×3H, s, 3×OCH_3), 3.65—2.83 (5H, arom. H). Being soluble in Claisen's alkali,[9] this base (IX) was found to

1) R.H.F. Manske, "The Alkaloids," (ed. R.H.F. Manske, H.L. Holmes) IV, 1954, p. 249: X, 1968, p. 463; Academic Press, New York; T. Kametani, "The Chemistry of Isoquinoline Alkaloids," Hirokawa Publishing Co., Tokyo, 1968, p. 74.
2) N.S. Bhacca, J.C. Craig, R.H.F. Manske, S.K. Roy, M. Shamma, and W.A. Slusarchyk, *Tetrahedron*, **22**, 1467 (1966).
3) F.R. Stermitz, L. Chen, and J.I. White, *Tetrahedron*, **22**, 1095 (1966).
4) *a*) F.R. Stermitz and L.C. Teng, *Tetrahedron Letters*, **1967**, 1601; *b*) J. Kunitomo, E. Yuge, Y. Nagai, and K. Fujitani, *Chem. Pharm. Bull.* (Tokyo), **16**, 364 (1968).
5) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **39**, 889 (1956).
6) Details of the synthesis will be reported elsewhere.
7) M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. Pharm. Bull.* (Tokyo), **13**, 1341 (1965).
8) P.A. Sartoretto and F.J. Sowa, *J. Am. Chem. Soc.*, **59**, 603 (1937); M. Tomita, Y. Inubushi, and H. Niwa, *Yakugaku Zasshi*, **72**, 206 (1952); H. Furukawa, *ibid.*, **85**, 850 (1965).
9) L. Claisen, *Ann.*, **418**, 96 (1919); L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, New York, 1967, p. 153.

be cryptophenolic and its structure was confirmed by spectral (IR, NMR, UV) and TLC comparisons with racemic IX[6] prepared by an unambiguous route starting from *m*-methoxyphenethylamine and 6-bromohomoveratric acid.

Alkali-soluble fraction of the above methylation reaction product was further submitted to prolonged treatment with ethereal diazomethane to give another cryptophenolic monomethylated product (II) as colorless oil, $[\alpha]_D$—89.6° (EtOH); optical rotatory dispersion (ORD) (EtOH): $[\alpha]_{304}$—2132° (tr), $[\alpha]_{284}$+723° (pk), $[\alpha]_{244}$—3974° (tr), $[\alpha]_{236}$—2565° (pk) (Fig. 1); NMR ($CDCl_3$) τ: 7.43 (3H, s, NCH_3), 6.32, 6.29, 6.20 (3×3H, s, 3×OCH_3), 3.63—2.91 (5H, arom. H); UV λ_{max}^{EtOH} mμ (log ε): 228 (sh, 4.00), 278 (sh, 3.57), 288 (3.69), 300 (sh, 3.47); mass spectrum *m/e*: 343 (M^+), 176 (base peak), 167, 161. The fragmentation pattern indicates the presence of the 2-hydroxy-4,5-dimethoxybenzyl moiety and was found to be very similar to that of racemic IX.

Thus, the structure of this monomethylated base (II) was confirmed unequivocally as L(*S*)-1-(2-hydroxy-4,5-dimethoxybenzyl)-2-methyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline; reported data[2] including ORD curve of the cularine hydrogenolysis product (II) are in good accordance with the data obtained above of our synthetic product (II).

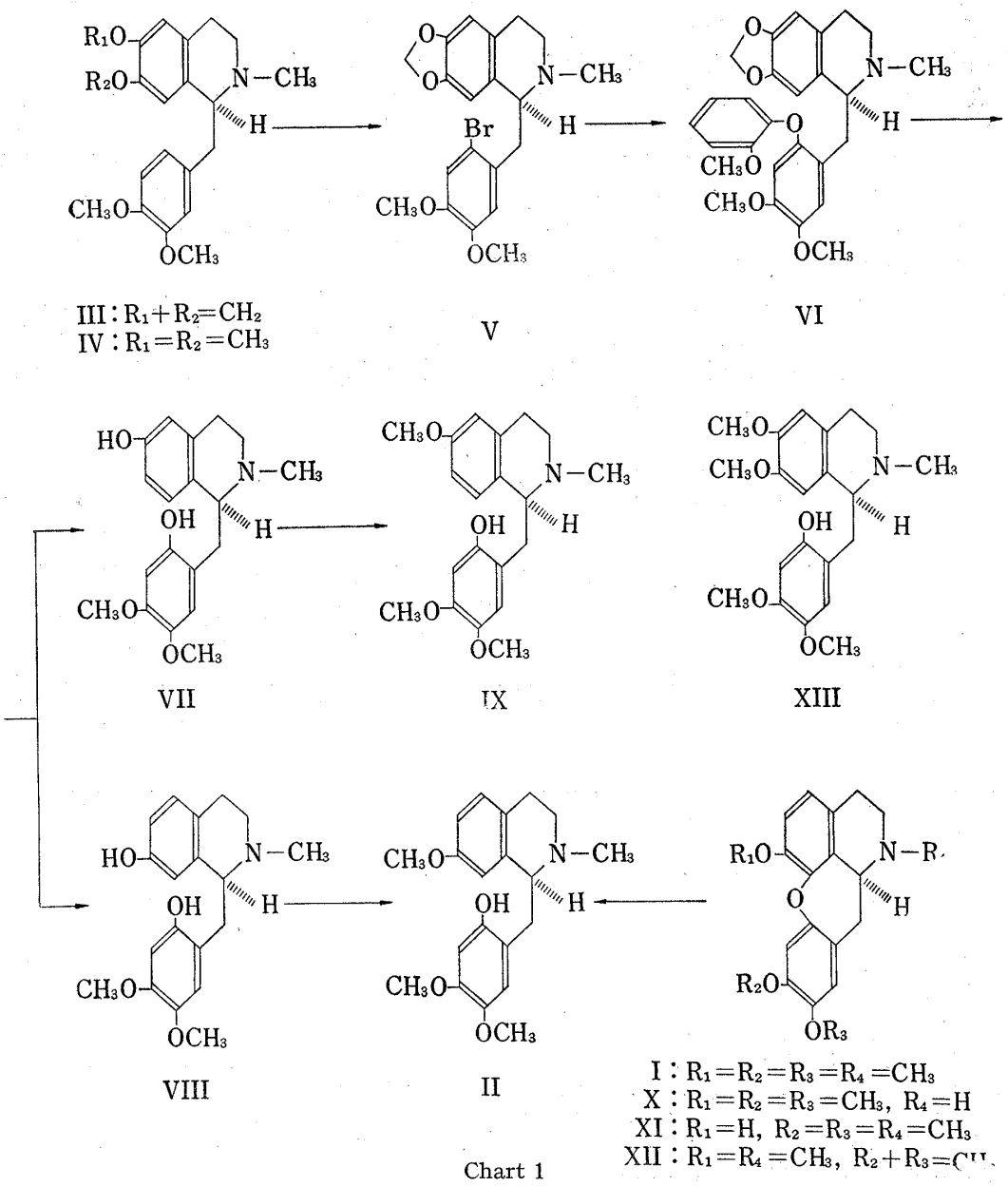

Chart 1

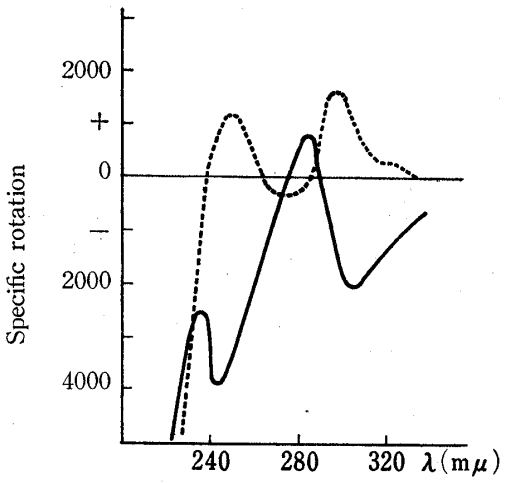

Fig. 1. Rotatory Dispersion Curves

(−)-1-(2-hydroxy-4,5-dimethoxybenzyl)-2-methyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (II) (——) and its hydrochloride (------)

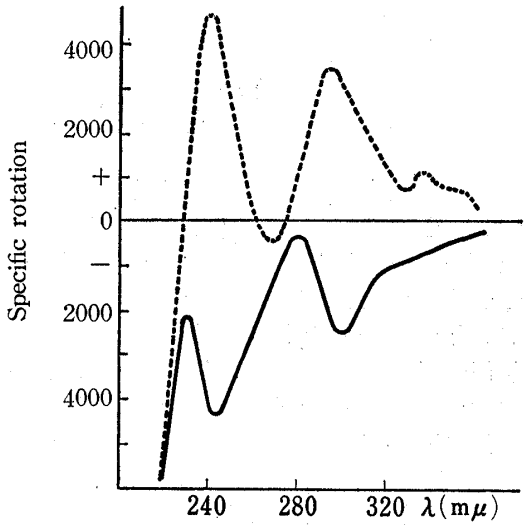

Fig. 2. Rotatory Dispersion Curves

L(*S*)-6′-hydroxylaudanosine (XIII) (——) and its hydrochloride (------)

As the reaction sequence from III to II does not involve the chiral center at C-1, the chemical correlation of configuration between L(*S*)-laudanosine (IV) and (+)-cularine has thus been established, and the alkaloids of cularine group [cularine (I), cularimine (X),[10] cularidine (XI)[11] and cularicine (XII)[12]] have been shown to have L(*S*)-configuration.

The conclusion of the chemical correlation seems to contradict earlier assignment by ORD, and led us examine ORD (Fig. 2) of a compound of closely related structure to (II) with known configuration, L(*S*)-1-(2-hydroxy-4,5-dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [L(*S*)-6′-hydroxylaudanosine] (XIII).[13] The ORD of II and XIII are compared and both compounds showed the same three negative Cotton effects,[2] and the reversal of the sign of long wavelength Cotton effect on acidification was commonly observed. Thus, L(*S*)-laudanosine (IV)[14] and L(*S*)-6′-hydroxylaudanosine (XIII) were found to show opposite Cotton effects in ORD in spite of the same configuration.

These ORD findings together with the chemical correlation show that earlier ORD assignment[2] of D(*R*)-configuration to cularine hydrogenolysis product (II) should be revised to L(*S*)-configuration. Interpretation of the ORD anomalies found with the 6′-hydroxylated benzyltetrahydroisoquinolines will be discussed elsewhere in a full account of this work.

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10) R.H.F. Manske, *Can. J. Research*, **16B**, 81 (1938).
11) R.H.F. Manske, *Can. J. Chem.*, **44**, 561 (1966).
12) R.H.F. Manske, *Can. J. Chem.*, **43**, 989 (1965).
13) M. Tomita, H. Furukawa, S-T.Lu, and S.M. Kupchan, *Chem. Pharm. Bull.* (Tokyo), **15**, 959 (1967).
14) J.C. Craig, M. Martin-Smith, S.K. Roy, and J.B. Stenlake, *Tetrahedron*, **22**, 1335 (1966).