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OPTICAL ROTATORY DISPERSION AND ABSOLUTE CONFIGURATION—III

PYRROLIDINE, PIPERIDINE AND TETRAHYDROISOQUINOLINE ALKALOIDS[1]

J. CYMERMAN CRAIG and S. K. ROY
Department of Pharmaceutical Chemistry, University of California,
San Francisco 22, California

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Abstract—Optical rotatory dispersion measurements on pyrrolidine, piperidine, and tetrahydroisoquinoline alkaloids indicate that the absolute configuration of the α-asymmetric center may be assigned directly from the dispersion curve, provided *either* that the nitrogen atom is not protonated, *or* that the compound contains a chromophore absorbing above 200 mμ.

IN ORDER to test the general validity of assignment of absolute configuration to amines asymmetrically substituted in the α-position, by anomalous rotatory dispersion measurements in the 200 to 225 mμ region,[2] the dispersion curves of nicotine (I), anabasine (II), and (−)-cotinine (III; Fig. 1), were compared with those of L-proline and L-pipecolic acid[2] (Fig. 2).

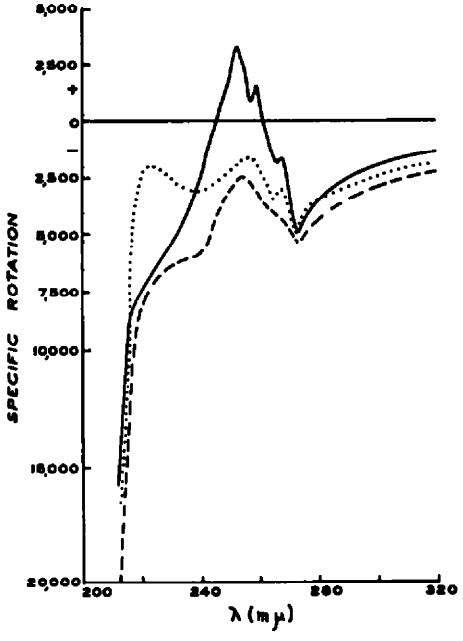


FIG. 1. Optical rotatory dispersion curves of S-(−)-nicotine (——), S-(−)-anabasine (– – –), and S-(−)-cotinine (· · · ·)

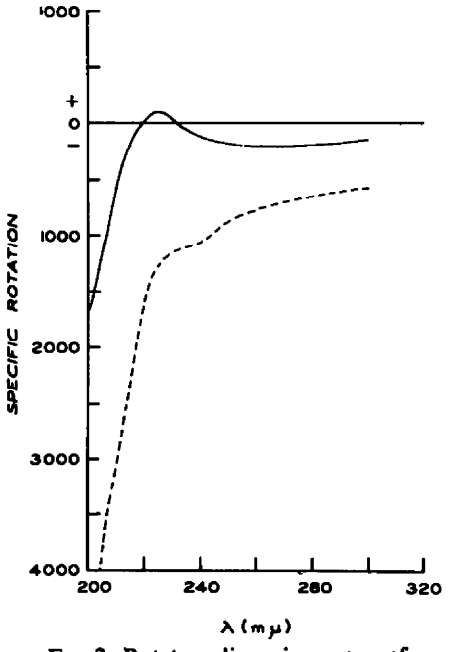


FIG. 2. Rotatory dispersion curves of L-proline (– – –) and L-pipecolic acid (——).

[1] Supported by research grant HE-5881 from the National Institutes of Health, U.S. Public Health Service.

[2] J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 393 (1965).

Nicotine has been assigned the S-configuration with reference to both L-proline[3] and L-serine;[4] anabasine has been related to L-pipecolic acid,[5] and (−)-cotinine has been reduced to (−)-nicotine[6] and therefore also has the S-configuration. The dispersion curves in Figs. 1 and 2 are clearly of the same general type, with the addition in the first group of the algebraic sum of the partial rotations associated with the strong absorption bands (ε 25,000) of the pyridine ring at 256, 263 and 270 mμ (as in 3-methylpyridine[7]), in place of the smaller Cotton effect due to the more weakly absorbing carboxyl group (λ_{max} 200–210 mμ, ε 40–70)[8] in the α-amino acids.

The extra shoulder in the dispersion curve of (−)-cotinine is the result of the partial rotation due to the lactam group associated with an additional absorption in the 200–220 mμ region,[8] such as that found at 205 mμ (log ε 3·46) in 1-methyl-2-pyrrolidone,[9] but not detectable in the UV spectrum in the present case due to intense end absorption. All compounds in Figs. 1 and 2 are configurationally identical, and all five show the marked steep descent of the rotatory dispersion below 220 mμ, previously reported[2] to be characteristic of the L-configuration in α-amino acids.

The effect of a chromophore other than the pyridine ring is shown in the dispersion curves of Fig. 3. In L-pelletierine sulfate[10] (IV) two Cotton effects, centered at 282 and 235 mμ, correspond to an UV maximum at 272 mμ (ε 53; C = O) and a shoulder at 230 mμ (ε 24), while in L-proline methyl ester hydrochloride the weak carbomethoxy chromophore,[8] though not discernible in the UV spectrum due to rising end absorption, is responsible for the Cotton effect centered at approx. 213 mμ. Again both dispersion curves of these L-compounds descend rapidly below 225 mμ.

In L-alaninol (2-amino-1-propanol, V; Fig. 4), the carboxyl function of alanine has been replaced by a primary alcohol group. The compound shows only rising end absorption in the UV, and exhibits a plain, steeply descending, rotatory dispersion curve, in agreement with its L-configuration.

D-Coniine (VI), a naturally occurring piperidine alkaloid, gave a plain dispersion curve (Fig. 4) showing a steep ascent below 225 mμ, similar in type to that of D-pipecolic acid, but lacking the Cotton effect of the amino acid. Resolution of 2-methylpiperidine was effected *via* the enantiomeric salts with D- and L-tartaric acid, respectively. The (+)-base (+)-bitartrate and (−)-base (−)-bitartrate both had m.p. 126°, and were dimorphic forms of the same compounds, m.p. 112°, reported in the literature.[11] It is interesting that their diastereoisomers,[11] the enantiomeric (+)-base (−)-bitartrate and the (−)-base (+)-bitartrate, also have m.p. 126°. The configuration of the (+)-base (+)-bitartrate and its enantiomer were confirmed by

[3] P. Karrer and R. Widmer, *Helv. Chim. Acta* **8**, 364 (1925).
[4] C. S. Hudson and A. Neuberger, *J. Org. Chem.* **15**, 24 (1950).
[5a] R. Lukes, A. A. Arojan, J. Kovar and K. Blaha, *Coll. Czech. Chem. Comm.* **27**, 751 (1962);
[5b] R. Lukes, J. Kloubek, K. Blaha and J. Kovar, *Ibid.* **22**, 286 (1957).
[6] H. McKennis, L. B. Turnbull, E. R. Bowman and E. Wada, *J. Amer. Chem. Soc.* **81**, 3951 (1959).
[7] H. V. Daeniker, *Helv. Chim. Acta* **35**, 1955 (1952).
[8a] J. W. Sidman, *Chem. Rev.* **58**, 689 (1958); [8b] H. H. Jaffé and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy*. J. Wiley, New York (1962); [8c] W. D. Closson and P. Haug, *J. Amer. Chem. Soc.* **86**, 2384 (1964).
[9] F. Korte and K. H. Lohmer, *Chem. Ber.* **91**, 1397 (1958).
[10] R. E. Gilman and L. Marion, *Bull. Soc. Chim. Fr.* 1993 (1961).
[11a] W. Marckwald, *Ber. Dtsch. Chem. Ges.* **29**, 43 (1896); [11b] A. Lipp, *Liebigs Ann.* **289**, 173 (1896); [11c] W. Leithe, *Monatsh.* **50**, 40 (1928).

conversion (ion exchange) into the known (—)- and (+)-hydrochlorides, respectively, and thence into the (+)- and (—)-bases. The dispersion curves of these were exact mirror images (Fig. 4), and that of the (+)-form agreed closely with the curve given by D-coniine.*

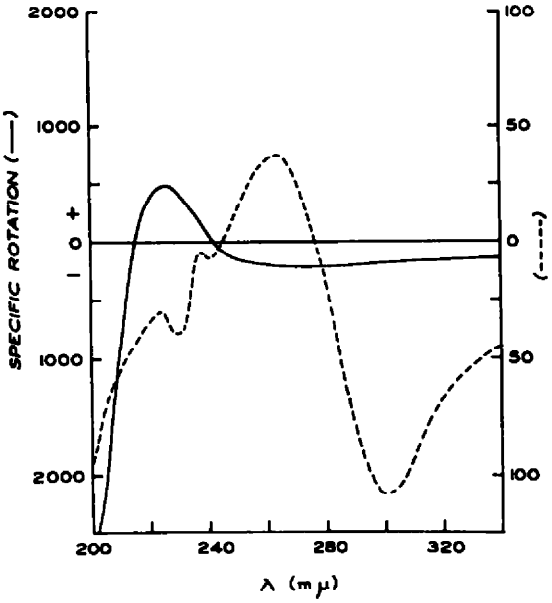


FIG. 3. Rotatory dispersion curves of L-pelletierine sulfate (- - -) and L-proline methyl ester hydrochloride (——).

Since coniine and 2-methylpiperidine show only rising end absorption in the UV, it may be concluded that the steep ascent or descent of their dispersion curves below 225 mμ is caused by a partial rotation associated with an absorption band located below 200 mμ. Saturated aliphatic and heterocyclic amines are, in fact, known[12] to show absorption maxima in the 200 mμ region, which must be due to excitation of the lone-pair (non-bonding) electrons of nitrogen since this absorption disappears in acid solution. In agreement with this finding, the rotatory dispersion curves of the *salts* of both coniine and 2-methylpiperidine no longer present the steep ascent or descent found below 225 mμ in the spectra of the free bases, but are flat and featureless.

We can, therefore, conclude that in any amine so far examined, possessing a

* A warning may be needed here to point out that the use of the Cahn-Ingold-Prelog convention[19] makes (+)-coniine a member of the S-series due to the operation of the sequence rule in which the n-butyl chain of the ring has priority over the n-propyl sidechain. In fact, it is however clear that D-coniine is related to D-pipecolic acid. It has already[20] been stressed that the sequence-rule symbol R or S refers only to the compound actually in question, since symbolism may be reversed on substitution on or near the chiral center, and does not correlate chemical or biogenetic families. To deduce absolute configuration from rotatory dispersion, the configurational comparison must therefore clearly be based on the D- or L-amino acids.

[12a] E. Tannenbaum, E. M. Coffin and A. J. Harrison, *J. Chem. Phys.* **21**, 311 (1953); [b] L. W. Pickett, M. E. Corning, G. M. Wieder, D. A. Semenov and J. M. Buckley, *J. Amer. Chem. Soc.* **75**, 1618 (1953).

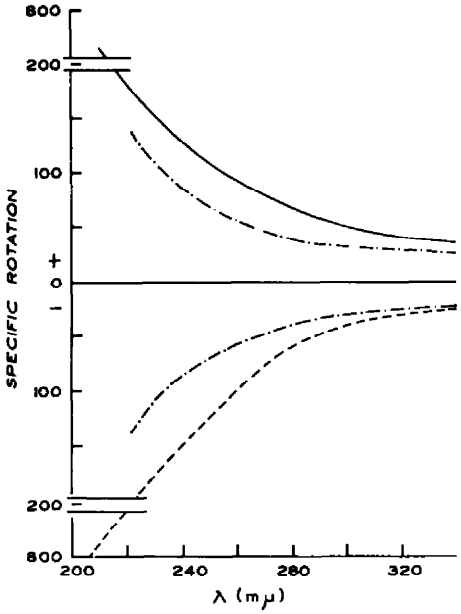


FIG. 4. Rotatory dispersion curves of D-coniine (——), 2-methylpiperidine (– · –), and L-alaninol (– – –).

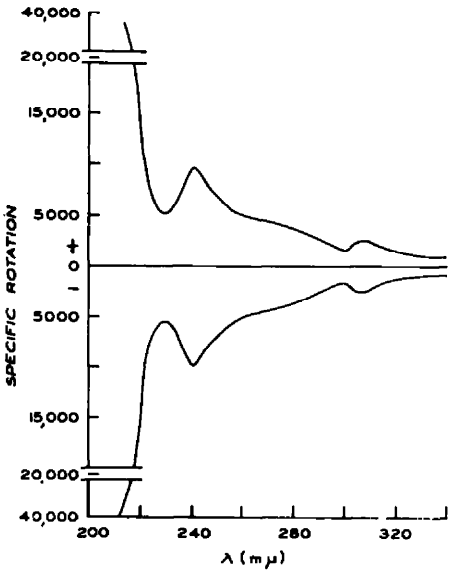


FIG. 5. Rotatory dispersion curves of tetrahydropalmatine enantiomers.

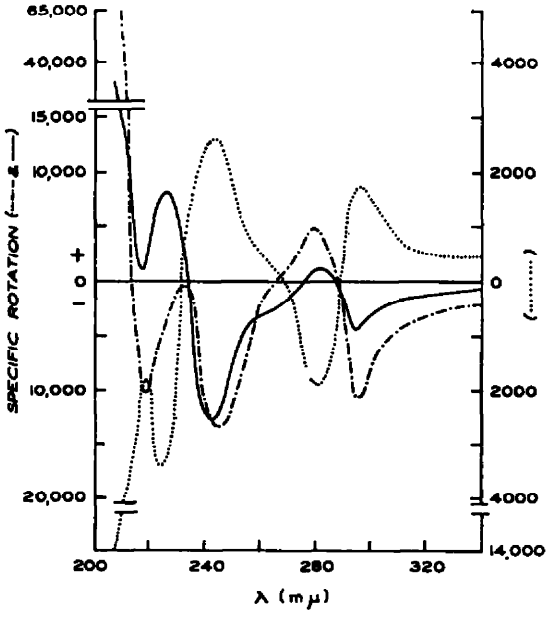
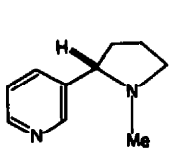


FIG. 6. Rotatory dispersion curves of D-laudanidine (– · –), D-armepavine (——), and L-norarmepavine (· · · ·).

single α-asymmetric center, its absolute configuration may be assigned from the direction of the dispersion curve between 200 and 225 mμ, provided that at least one of the following conditions is fulfilled: *either* that the amine is not protonated, *or* that the compound contains a chromophore absorbing above 200 mμ.

The ready applicability of the method to D- and L-tetrahydropalmatine (VII), a protoberberine alkaloid of known absolute configuration,[13] is shown in Fig. 5. The negative Cotton effect of (−)-tetrahydropalmatine at 300 mμ has also been correlated[14] with its absolute configuration by comparison with the plain curve of opposite sign given by (+)-1,2-diphenylethylamine at that wavelength.

In the benzylisoquinoline alkaloids, D-(−)-laudanidine (VIII) of known[13,15,16] configuration gives a dispersion curve (Fig. 6) with the anticipated positive (ascending) "tail" below 225 mμ. Although the closely related (−)-armepavine (IX)[16] and (−)-N-norarmepavine (X)[17] are both levo-rotatory, their dispersion curves (Fig. 6) show clearly that the latter possesses the L-configuration, while the former is a member of the D-series. This is in agreement with known chemical transformations which have established the correctness of these absolute configurations.[16,17]



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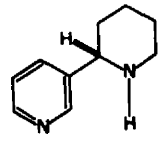

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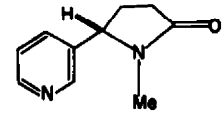

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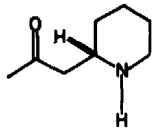

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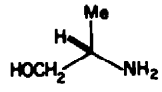
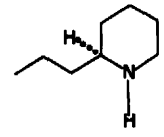
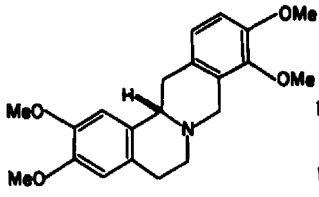


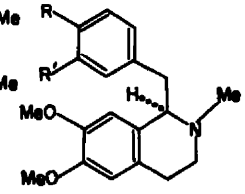
V



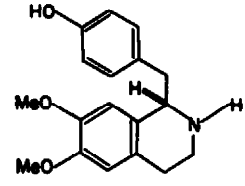
VI



VII



VIII R=OMe, R'=OH
IX R=OH, R'=H



X

[13] H. Corrodi and E. Hardegger, *Helv. Chim. Acta* **39**, 889 (1956).
[14] G. G. Lyle, *J. Org. Chem.* **25**, 1779 (1960).
[15] B. Frydman, R. Bendisch and V. Deulofeu, *Tetrahedron* **4**, 342 (1958).
[16] M. Tomita and J. Kunitomo, *J. Pharm. Soc. Japan* **82**, 734 (1962).
[17] S. M. Kupchan, B. Dasgupta, E. Fujita and M. L. King, *J. Pharm. Sci.* **51**, 599 (1962).

EXPERIMENTAL

Rotatory dispersion curves were determined with a Bendix model 460-C[18] or a Cary model 60 spectropolarimeter using 1 mm or 1 cm cells (*c* 0·01 to 0·3 in 95% ethanol) at 25°. Rotations are given below only for (1) the highest and lowest wavelengths measured, (2) peaks and troughs. Since dispersion curves of enantiomeric pairs agreed within 5%, only one isomer is described.

(−)-*Nicotine*. $[\alpha]_D$ −169°. R.D. (*c* 0·035 in 95% ethanol) $[\alpha]_{300}$ −1950°, $[\alpha]_{278}$ −4850° (trough), $[\alpha]_{269}$ −1500° (peak), $[\alpha]_{259}$ 1600° (peak), $[\alpha]_{253}$ 3230° (peak), $[\alpha]_{245}$ 0°, $[\alpha]_{215}$ −9560°.

(−)-*Anabasine*. $[\alpha]_D$ −84°. R.D. (*c* 0·043 in 95% EtOH) $[\alpha]_{300}$ −2800°, $[\alpha]_{278}$ −5420° (trough), $[\alpha]_{268}$ −4150° (peak), $[\alpha]_{254}$ −2500 (peak), $[\alpha]_{215}$ −14,400°.

(−)-*Cotinine*. $[\alpha]_D$ −19° (*c* 5·5 in MeOH). R.D. (*c* 0·038 in 95% ethanol) $[\alpha]_{300}$ −2480°, $[\alpha]_{278}$ −4800° (trough), $[\alpha]_{268}$ −3000° (peak), $[\alpha]_{256}$ −1676° (peak), $[\alpha]_{239}$ −2900° (trough), $[\alpha]_{222}$ −1840° (peak), $[\alpha]_{215}$ −10,240°.

(D)-(+)-*Coniine*. $[\alpha]_D$ 8° (*c* 4·0 in $CHCl_3$); R.D. (*c* 0·13 in 95% EtOH) $[\alpha]_{320}$ 44·5°, $[\alpha]_{310}$ 347·5°

Resolution of 2-*methylpiperidine*

(A) Treatment of the racemic base with (+)-tartaric acid gave the (+)-base (+)-bitartrate, m.p. 126–127° (Found: C, 48·32; H, 7·71; N, 5·46; Calc. C, 48·18; H, 7·68; N, 5·62%). [Lit.[11] gives m.p. 111–112°]. It was converted (ion exchange column) into the (−)-hydrochloride, m.p. 190–192°, $[\alpha]_D$ −3·5° (*c* 10·8 in 95% EtOH). [Lit.[11] m.p. 191°, $[\alpha]_D$ −4·2° (*c* 10 in EtOH).] The picrate had m.p. 116–117° [Lit.[11] m.p. 116–117°] and the (+)-base had $[\alpha]_D$ +11° (*c* 4·0 in $CHCl_3$).

(B) The racemic base similarly gave the (−)-base (−)-bitartrate, m.p. 126–128° (Found: C, 48·23; H, 7·65; N, 5·82%). [Lit.[11] gives m.p. 111–112°], and thence the (+)-hydrochloride, m.p. 190–191°, $[\alpha]_D$ +3·9° (*c* 10·3 in 95% EtOH), the picrate, m.p. 116–118°, and the (−)-base, $[\alpha]_D$ −11° (*c* 4·0 in $CHCl_3$). Mixed m.p. of the tartrates from (A) and (B) above was 105–115°, mixed m.p. of the two hydrochlorides was 208–210° (Lit.[11] m.p. of racemic salt 210–212°), and of the two picrates 132–134° (Lit.[11] m.p. of racemic salt 134–135°).

(C) The (+)-base was converted into the (+)-base (−)-bitartrate, m.p. 126–127° [Lit.[11] m.p. 126°].

(L)-(−)-2-*Methylpiperidine*. R.D. (*c* 0·22 in 95% EtOH) $[\alpha]_{345}$ −22·9°, $[\alpha]_{325}$ −147°.

(L)-(−)-*Proline methyl ester hydrochloride*. $[\alpha]_D$ −36·5° (*c* 4·0 in EtOH), R.D. (*c* 0·254 in 95% EtOH) $[\alpha]_{345}$ −118°, $[\alpha]_{270}$ −167° (trough), $[\alpha]_{225}$ 482° (peak), $[\alpha]_{200}$ −2755°.

(L)-(−)-*Pelletierine sulfate*. $[\alpha]_D$ −29·5° (*c* 1·05 in H_2O). R.D. (*c* 0·14 in 95% EtOH) $[\alpha]_{360}$ −36·1°, $[\alpha]_{300}$ −108·5° (trough), $[\alpha]_{263}$ 37·5° (peak), $[\alpha]_{236}$ −6·95° (peak), $[\alpha]_{224}$ −30·5° (peak), $[\alpha]_{200}$ −97·0°.

(L)-(+)-*Alaninol*. $[\alpha]_D$ 20° (*c* 8·0 in EtOH); R.D. (*c* 0·308 in 95% EtOH) $[\alpha]_{333}$ −29·2°, $[\alpha]_{308}$ −767°.

(L)-(−)-*Tetrahydropalmatine*. $[\alpha]_D$ −290° (*c* 1·0 in EtOH); R.D. (*c* 0·01 in 95% EtOH)$[\alpha]_{333}$ −1010°, $[\alpha]_{307}$ −2350° (trough), $[\alpha]_{298}$ −1500° (peak), $[\alpha]_{241}$ −9600° (trough), $[\alpha]_{229}$ −5160° (peak), $[\alpha]_{213}$ −35,650°.

(D)-(−)-*Laudanidine*. $[\alpha]_D$ −94° (*c* 2·0 in $CHCl_3$); R.D. (*c* 0·009 in 95% EtOH) $[\alpha]_{340}$ −2223°, $[\alpha]_{296}$ −12,670° (trough), $[\alpha]_{280}$ 4890° (peak), $[\alpha]_{245}$ −13,510° (trough), $[\alpha]_{232}$ −446° (peak), $[\alpha]_{219}$ −10,440° (trough), $[\alpha]_{209}$ 70,000°.

(D)-(−)-*Armepavine*. $[\alpha]_D$ −109° (*c* 2·0 in EtOH); R.D. (*c* 0·049 in 95% EtOH) $[\alpha]_{333}$ −855°, $[\alpha]_{294}$ −4305° (trough), $[\alpha]_{281·5}$ 1200° (peak), $[\alpha]_{243}$ −12,660° (trough), $[\alpha]_{226}$ 7880° (peak) $[\alpha]_{217}$ 1085° (trough), $[\alpha]_{208}$ 38,000°.

(L)-(−)-N-*Norarmepavine*. $[\alpha]_D^{25}$ −23° (*c* 1·33 in $CHCl_3$); R.D. (*c* 0·037 in 95% EtOH) $[\alpha]_{333}$ 406°, $[\alpha]_{296}$ 1728° (peak), $[\alpha]_{281·5}$ −1955° (trough), $[\alpha]_{244}$ 2700° (peak), $[\alpha]_{233·5}$ −5340° (trough), $[\alpha]_{217}$ −2155° (peak), $[\alpha]_{204}$ −14,200°.

Acknowledgment—The authors are grateful to the following who kindly provided the samples named: Dr. H. McKennis (cotinine), Dr. L. Marion (pelletierine), Dr. E. Gellert (tetrahydropalmatine), Dr. E. Brochmann-Hanssen (laudanidine), Dr. M. Tomita (armepavine), and Dr. J. Biel (nor-armepavine).

[18] A number of spectra were obtained on both instruments, and agreed within 5%.

[19] R. S. Cahn, C. K. Ingold and V. Prelog, *Experimentia* **12**, 81 (1956).

[20] R. S. Cahn, *J. Chem. Education* **41**, 116 (1964).