399. *Optical Rotatory Dispersion. Part XIV.* Bisbenzyltetrahydroisoquinoline Alkaloids*

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The optical rotatory dispersion curves of some 1-substituted (including 1-benzyl) tetrahydroisoquinolines have been measured. The curves for an extensive series of bisbenzyltetrahydroisoquinoline alkaloids of different structural and stereochemical types with two diphenyl ether linkages have also been measured and related to the stereochemistry and to the ultraviolet absorption of the compounds.

THE bisbenzyltetrahydroisoquinoline alkaloids containing two diphenyl ether linkages present many stereochemical problems. One of their most interesting features is that the physical and chemical properties of each compound are dependent partly on the *configurations* around the two asymmetric centres, and partly on the *conformations* around the four mobile linkages between the cyclic systems (*i.e.*, around the two ether bridges and the two methylene bridges).

The absolute configurations of certain key-compounds in the (mono)benzyltetrahydroisoquinoline series (I) have been determined,[1] and the configurations of the two asymmetric centres in each bis-compound can usually be determined by cleavage of the ether linkages with alkali metals in liquid ammonia, to give the two components. The absolute stereochemistry at the asymmetric centre of each (mono)benzyltetrahydroisoquinoline has usually been designated as (+) or (—) according to the sign of rotation at the D-line, and the bis-bases have been described as (++), (+—), etc., according to the signs of rotation of the component units. Using the serine convention and the Sequence Rule, (+) = L = *S*, and (—) = D = *R*.

The conformations around the four mobile linkages in each alkaloid could be determined for the solid state by *X*-ray studies, but circumstantial evidence about the conformation in solution can also be obtained by modern physical techniques such as nuclear magnetic resonance (discussed previously [2]) and optical rotatory dispersion.

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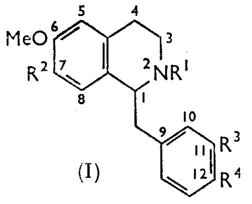
* Part XIII, C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, 1965, **21**, 163.

[1] H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, 1956, **39**, 889; A. R. Battersby and D. M. Foulkes, unpublished work; A. R. Battersby and J. H. Clements, unpublished work.

[2] I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Vernengo, *J.*, 1961, 1896.

In this Paper we present the results obtained from rotatory dispersion measurements on a series of bisbenzylisoquinoline alkaloids and some related simple 1-alkyl- and 1-benzylisoquinolines of known absolute configuration. Our present theoretical knowledge permits us to offer only empirical correlation between dispersion curves and configuration for compounds of known structure, but these may help in allotting configurations to newly discovered compounds.



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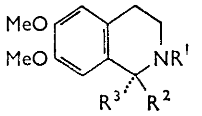

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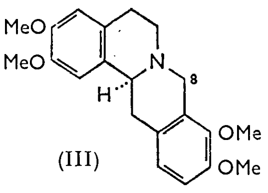

(III)

Optical Rotation Comparisons (*Monochromatic*).—Much work has been done in the past on comparisons of optical rotations at the D-line, in attempts to rationalise the behaviour of the bis-bases. Studies of the bases in a variety of solvents have been summarised.[3] (For a general survey of monochromatic rotation studies, see ref. 4.)

von Bruchhausen *et al.*[5,6] attempted to interpret the stereochemistry of the bisbenzyltetrahydroisoquinoline bases on the assumption that their optical rotations followed an additive rule, *i.e.*, that the rotation of each bis-base was the sum of those of the two monobenzyltetrahydroisoquinoline components.[5] Subsequent degradative work has shown that the rotations of isotetrandrine and tetrandrine are in accordance with an additive rule, but that repandine and oxyacanthine are exceptions. For the last two compounds, (+—) and (++) formulations, respectively, had been expected from rotational evidence, but instead 1-benzyltetrahydroisoquinoline fragments corresponding to (++) and (+—) formulations were obtained.[7]

Attempts [8] to explain this anomaly by postulating a Walden inversion during cleavage were unfruitful (cf. ref. 9). It was later suggested [10] that an exaltation of the optical rotation caused by molecular asymmetry was responsible for the anomalies in the case of repandine and oxyacanthine, and that (with allowance for this molecular exaltation) the additive rule still held.[10] The absolute configurations of the two centres in these compounds are now known as a result of cleavage experiments and work on the mono-bases; [11,12] it may therefore be possible to use the rotations of the bis-bases to gain an insight into the asymmetry of the whole molecule, *i.e.*, to study the conformations about the mobile linkages.

Optical Rotatory Dispersion Measurements.—(a) 1-*Benzyl and other simple* 1-*substituted tetrahydroisoquinolines.* The aromatic chromophore in different stereochemical environments can give rise to different types of dispersion curve, and in the region of the 283 mμ absorption band of the aromatic nucleus Cotton effects may be expected.[13] Negative

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[3] P. S. Clezy, Ph.D. Thesis, University of Tasmania.

[4] W. Klyne in " Determination of Organic Structures by Physical Methods," ed. E. A. Braude and F. C. Nachod, Academic Press, New York, 1955, p. 78.

[5] F. von Bruchhausen, H. Oberembt, and A. Feldhaus, *Annalen*, 1933, **507**, 144.

[6] F. von Bruchhausen, *Arch. Pharm.*, 1961, **294**, 373.

[7] M. Tomita, *Fortschr. Chem. org. Naturstoffe*, 1952, **9**, 184.

[8] M. Tomita, E. Fujita, and F. Murai, *J. Pharm. Soc. Japan*, 1951, **71**, 1035, 1039; M. Tomita and E. Fujita, *ibid.*, 1952, **72**, 213, 217; E. Fujita and T. Saijoh, *ibid.*, 1952, **72**, 1232; F. von Bruchhausen, *Arch. Pharm.*, 1950, **283**, 44; M. Tomita, Y. Inubushi, and E. Fujita, *Pharm. Bull.* (*Japan*), 1955, **3**, 97.

[9] I. R. C. Bick and A. R. Todd, *J.*, 1948, 2170.

[10] M. Tomita and E. Fujita, *Chem. and Pharm. Bull.* (*Japan*), 1953, **1**, 101.

[11] M. Tomita and Juni-ichi-Kunitomo, *J. Pharm. Soc. Japan*, 1962, **82**, 734, 741, 981.

[12] C. Ferrari and V. Deulofeu, *Tetrahedron*, 1962, **18**, 419.

[13] C. Djerassi, " Optical Rotatory Dispersion: Applications in Organic Chemistry," McGraw-Hill, New York, 1959; C. Djerassi, K. Mislow, and M. Shamma, *Experientia*, 1962, **18**, 53.

Cotton effects attributed to this aromatic absorption band have been observed for morphine, codeine, and dihydrocodeine.[14] There is also a report [15] on the optical rotatory dispersion of (—)-tetrahydropalmatine (III), one of the protoberberine alkaloids. Here, the " berberine bridge " at C-8 makes the structure much more rigid; this base cannot therefore be considered as a suitable model compound for studies of the bisbenzyltetrahydroisoquinoline alkaloids.

The 1-substituted tetrahydroisoquinolines (II) have an aromatic ring attached to an asymmetric centre, and even with simple alkyl substituents [16] at C-1 good Cotton effects occur between about 290 and 270 mμ (see Table 1). The results for a series of 1-benzyltetrahydroisoquinolines are in Table 2. The rotatory dispersion curves of all these compounds show a clear aromatic Cotton effect at about 290—270 mμ and also the first extremum of a second Cotton effect at about 240 mμ. The absolute configurations of these compounds are known, and all members of the *S*-series have two positive Cotton effects, while the enantiomeric *R*-compounds have double negative curves. The amplitudes for the compounds with 1-benzyl substituents are considerably greater than those for the simpler compounds with small 1-alkyl substituents.

TABLE 1

Optical rotatory dispersion of simple 1-substituted tetrahydroisoquinolines

a is the amplitude for the first Cotton effect at *ca.* 290—270 mμ

Formula	R^1	R^2	R^3	[ϕ]	λ (mμ)	*a*
(II)	MeCO	$CH_2{\cdot}OH$	H	+2670	286	+22
				+485	270	
(II)	MeCO	H	$CH_2{\cdot}OH$	−6740	290	−36
				−3085	266	
(II)	$SO_2{\cdot}C_6H_4Me$	Me	H	+6050	288	+52
				+830	260	
(II)	SO_2Me	H	$CH_2{\cdot}O{\cdot}SO_2Me$	−4060	286	−13
				−2740	268	

TABLE 2

Optical rotatory dispersion of 1-benzyltetrahydroisoquinolines

First Cotton effect; *a* is amplitude at *ca.* 290—270 mμ.
Second Cotton effect; [ϕ] × 10^{-2} is value for first extremum at *ca.* 240 mμ; *i.e.*, it is approximately a "half-amplitude."

						1st Cotton effect *a*		2nd Cotton effect [ϕ] × 10^{-2}	
Compound		R^1	R^2	R^3	R^4	*S*(+)	*R*(−)	*S*(+)	*R*(−)
N-Acetyltetrahydropapaverine	(I)	MeCO	MeO	MeO	MeO	+78	−104	+92!	−110
N-Benzovltetrahydropapaverine	(I)	PhCO	MeO	MeO	MeO	+142	−135		
Reticuline hydrochloride	(I)	MeH^+Cl^-	HO	HO	MeO	+83	−94	+168	−148
Orientaline hydrochoride	(I)	MeH^+Cl^-	HO	MeO	HO	+48	−85	+156	−136
OO'-Dibenzylreticuline	(I)	Me	$PhCH_2{\cdot}O$	$PhCH_2{\cdot}O$	MeO	+84	−141	+195	−260
OO'-Dibenzylorientaline	(I)	Me	$PhCH_2{\cdot}O$	MeO	$PhCH_2{\cdot}O$	+93	−129	+203!	−266
Armepavine	(I)	Me	MeO	MeO	H	+113		+297	

[*Note added in Proof* (27th January, 1965).—L. C. Craig and S. K. Roy (*Tetrahedron*, 1965, **21**, 401) have recently described optical rotatory dispersion curves of armepavine, *N*-norarmepavine, and laudanidine which agree essentially with those for armepavine and related compounds given in Table 2 of this Paper.

Other related optical rotatory dispersion work is that of A. Rheiner, jun., and A. Brossi (*Experientia*, 1964, **22**, 488) on tetrahydro-*N*-methyl-1-(2-phenylethyl)isoquinolines and of

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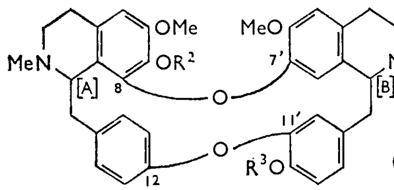
[14] J. M. Bobbit, U. Weiss, and D. D. Hanessian, *J. Org. Chem.*, 1959, **24**, 1582.

[15] G. G. Lyle, *J. Org. Chem.*, 1960, **25**, 1779.

[16] A. R. Battersby and T. P. Edwards, *J.*, 1960, 1214; A. R. Battersby, R. Binks, and T. P. Edwards, *J.*, 1960, 3474.

Z. Horii, M. Ikedo, Y. Yamawaki, Y. Tamura, S. Saito, and K. Kodera (*Tetrahedron*, 1963, **19**, 2101) on 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (as II; $R^2 = H$; R^1 and $R^3 = [CH_2]_4$). This latter compound is a " rigidified " 1-alkyltetrahydroisoquinoline; the *R* compound has a negative Cotton effect curve like the simpler compounds of type II (*R*) described here.]

(b) *Bisbenzyltetrahydroisoquinolines.* The optical rotatory dispersion curves of the bisbenzyltetrahydroisoquinolines are complex in the region 300—220 mμ, with 3—5 extrema in most cases. Most of these compounds have extrema at about 290 and 270 mμ, and a further very large extremum at about 235 mμ. Other peaks and troughs with smaller molecular rotation values may occur at about 250 mμ. The ultraviolet spectra were measured for six compounds representing the main structural types of alkaloid (Table 3); each spectrum exhibited two bands, the first of moderate intensity (ε 6000—11,000) at 282 mμ, and the second an intense band (ε 80,000—130,000) at 206 mμ, with a shoulder at 225—238 mμ. The first Cotton effect may clearly be ascribed to the 282 mμ aromatic absorption band, as in the simple asymmetric tetrahydroisoquinolines; the second Cotton effect, of which only the first extremum is reached, must be due to the intense 206 mμ band.



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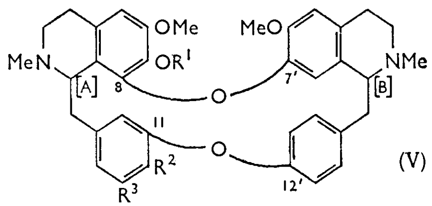

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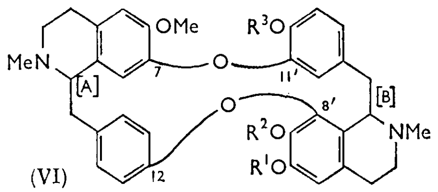

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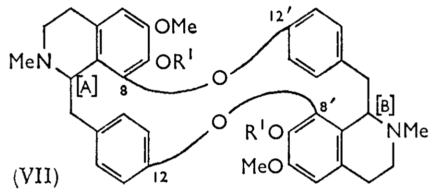

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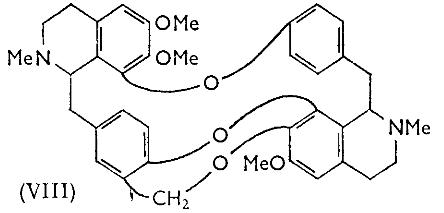

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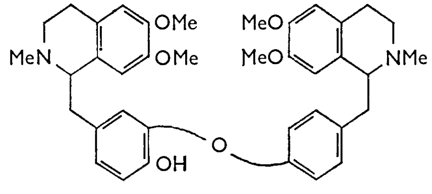


(IX)

It is convenient to consider the alkaloids in four groups according to the method of linkage of the benzyltetrahydroisoquinoline units; within those groups further subdivision may be made according to the absolute stereochemistry (where known) of the asymmetric centres. The four structural types are represented in formulæ (IV)—(VII).

In order to correlate the optical rotatory dispersion data with the stereochemistry of these compounds, use may be made of two roughly quantitative measurements, *viz.*, the amplitude (difference in molecular rotation between first and second extrema × 10^{-2}) for the first Cotton effect, and the molecular rotation at the first extremum × 10^{-2} for the second Cotton effect. (The latter quantity may be considered very approximately as a " half-amplitude.") These two values for the alkaloids are shown in Table 4.

Type 1 (8,7′ : 11′,12-coupling; formula IV). The compounds of this type may be further sub-divided according to absolute configuration into (*SR*; +—) and (*SS*; ++) types. The (*SR*)-compounds have rotatory dispersion curves with two positive Cotton effects,

TABLE 3

Ultraviolet spectra (in methanol) of bisbenzyltetrahydroisoquinoline alkaloids

Compound	Type	Confign.	$\lambda_{max.}$ (mμ)	(ε_{max})	Compound	Type	Confign.	$\lambda_{max.}$ (mμ)	($\varepsilon_{max.}$)
O-Methylrepandine	1	*SS*(++)	282	(6500)	Phæanthine	2	*RR*(−−)	282	(8100)
			233sh	(45,000)				236sh	(27,500)
			206	(128,000)				206	(95,000)
Oxyacanthine	1	*SR*(+−)	282	(8400)	Curine	3	*RR*(−−)	282	(9650)
			238sh	(28,300)				225sh	(41,200)
			206	(87,500)				206	(89,500)
O-Methylberbamine	2	*RS*(−+)	282	(7050)					
			238sh	(23,900)					
			206	(92,500)					

TABLE 4

Optical rotatory dispersion of bisbenzyltetrahydroisoquinolines

First Cotton effect; *a* is amplitude at *ca.* 290—270 mμ.

Second Cotton effect; $[\phi] \times 10^{-2}$ is value for first extremum at *ca.* 240 mμ; *i.e.*, it is approximately a " half-amplitude."

Compound	R^1	R^2	R^3	1st Cotton effect *a*	2nd Cotton effect $[\phi] \times 10^{-2}$	Configuration (from fission)
Type 1 (IV)						
Repandine	Me	Me	H	+103	+580	(*S*,*S*) (++)
O-Methylrepandine	Me	Me	Me	+94	+711	(*S*,*S*) (++)
Oxyacanthine	Me	Me	H	+59	+794	(*S*,*R*) (+−)
O-Methyloxyacanthine	Me	Me	Me	+54	+634	(*S*,*R*) (+−)
Daphnoline	H	H	H	+231	+961	(*S*,*R*) (+−)
Daphnandrine	H	H	Me	+399	+1158!	(*S*,*R*) (+−)
Cepharanthine	Me	*	Me	+179	+718!	(*S*,*R*) (+−)
		* O·CH$_2$·O at 6, 7.				
Type 2 (V)						
Berbamine	Me	OH	H	+260	+700!	(*R*,*S*) (−+)
O-Methylberbamine (isotetrandrine)	Me	OMe	H	+282	+123	(*R*,*S*) (−+)
(+)-Tetrandrine	Me	OMe	H	+111	+1490!	(*S*,*S*) (++)
(−)-Tetrandrine (Phæanthine)	Me	OMe	H	−170	−1350	(*R*,*R*) (−−)
Pycnamine	Me	OH	H	−107	−609	(*R*,*R*) (−−)
(+)-Tenuipine	Me	O·CH$_2$·O			+1284	(*S*,*S*) (++)
(−)-Tenuipine	Me	O·CH$_2$·O			−1040	(*R*,*R*) (−−)
(+)-Nortenuipine	H	O·CH$_2$·O			+915	(*S*,*S*) (++)
Hernandezine	Me	OMe	H †	+254	+1490	
		† Additional MeO at 8′.				
Type 3 (VI)						
Curine	Me	H	H	−240	−965	(*R*,*R*) (−−)
OO′-Dimethylcurine	Me	Me	Me	−174	−935	(*R*,*R*) (−−)
Chondrocurine	H	Me	H	+89	+494	(*S*,*R*) (+−)
*OO′*Dimethylchondrocurine	Me	Me	Me	+70	+622	(*S*,*R*) (+−)

In each case the first sign refers to the left half of the molecule as drawn (centre A) and the second sign to the right half (centre B).

the rotation at the second peak being three or four times as great as the amplitude of the first Cotton effect (Figure, a). The (*SS*)-compounds also have two positive Cotton effects; the first of these is on a negative background, between a shoulder at about 290 mμ and a trough about 277 mμ; some minor peaks and troughs occur between about 270 and 250 mμ, and the first extremum of the second large Cotton effect is at 240 mμ (Figure, b). Daphnoline and daphnandrine have larger amplitides than other members of the group; this may be due to the absence of a substituent on nitrogen in one tetrahydroisoquinoline unit.

Type 2 (8,7′ : 12′,11-coupling; formula V). Three groups of alkaloids of this general type have been examined, *viz.*, two (*RS*)-compounds and seven (*RR*)- and (*SS*)-compounds, including two pairs of enantiomers, the (*SS*; ++)- and (*RR*; −−)-tenuipines and -tetrandrines. These alkaloids give rotatory dispersion curves which in their general pattern are the converse of those of Type 1 alkaloids. The (*SS*)- and (*RR*)-compounds, with two similar asymmetric centres, have curves each with two Cotton effects of the same sign (both positive and both negative, respectively); the second peak is about eight to ten times

TABLE 5

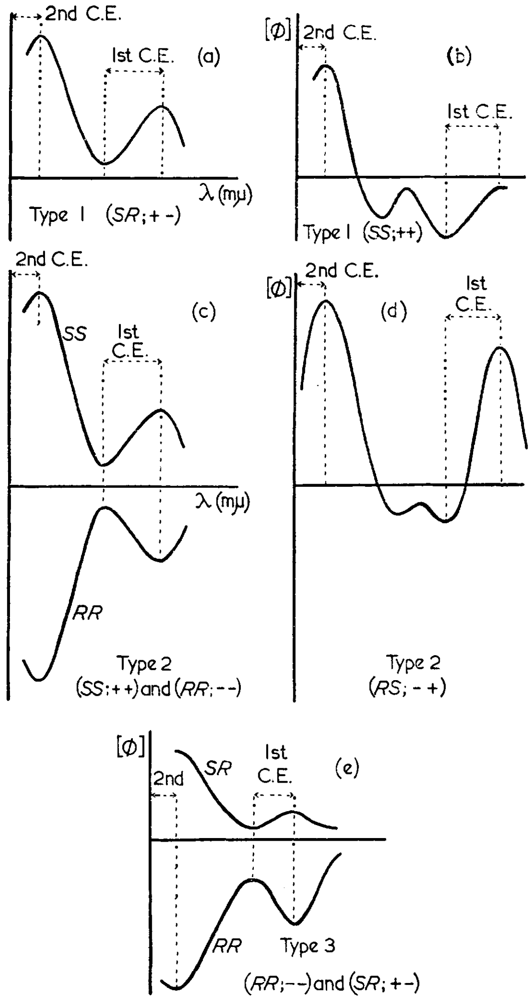
Molecular rotations and Cotton effects (pk = peak; tr = trough; sh = shoulder; ! = lowest wavelength measured)

Compound	Formula	$[\phi]$	λ (mμ)	**a** (1st C.E.)
(+)-*N*-Acetyltetrahydropapaverine	(II) (*S*)	+6370 −1470 +9200!	290pk 272tr 241!	+78
(−)-*N*-Acetyltetrahydropapaverine	(II) (*R*)	−10,420 0 −11,040	292tr 273pk 244tr	−104
(+)-*N*-Benzoyltetrahydropapaverine	(II) (*S*)	+9250 −4980 0	291pk 272tr 244pk	+142
(−)-*N*-Benzoyltetrahydropapaverine	(II) (*R*)	−12,100 +1425 −6400	292tr 274pk 248!	−135
(+)-Reticuline hydrochloride	(II) (*S*)	+7760 −545 +16,830	292pk 275tr 238pk	+83
(−)-Reticuline hydrochloride	(II) (*R*)	−10,710 −1320 −14,760	292tr 272pk 238tr	−94
(+)-Orientaline hydrochloride	(II) (*S*)	+5300 +530 +15,570	289pk 272tr 236pk	+48
(−)-Orientaline hydrochloride	(II) (*R*)	−7950 +540 −13,600	292tr 275pk 241tr	−85
(+)-*OO′*-Dibenzylreticuline	(II) (*S*)	+9350 +975 +19,480	292pk 274tr 243pk	+84
(−)-*OO′*-Dibenzylreticuline	(II) (*R*)	−14,600 −485 −25 950	292tr 278pk 245tr	−141
(+)-*OO′*-Dibenzylorientaline	(II) (*S*)	+9300 0 +20,330	293pk 276tr 242!	+93
(−)-*OO′*-Dibenzylorientaline	(II) (*R*)	−12,870 0 −26,600	294tr 280pk 244tr	−129
Armepavine	(II) (*S*)	+7280 −4020 +29,700	292pk 278tr 240pk	+113
Repandine	(IV) (*S*,*S*)	−13,600 −23,900 −4640 +58,000 −136,000!	292sh 279tr 258pk 236pk 217	+103
O-Methylrepandine	(IV) *S*,*S*	−7160 −16,600 −2890 −11,300 +71,100 −10,500!	289sh 276tr 260pk 247tr 234pk 226	+94
Oxyacanthine	(IV) (*S*,*R*)	+18,750 +12,900 +79,400 +2560!	295pk 287tr 242pk 233	+59
O-Methyloxyacanthine	(IV) (*S*,*R*)	+13,550 +8110 +63,400 +7910!	294pk 285tr 246pk 227	+54
Daphnoline	(IV) (*S*,*R*)	+33,100 +9970 +96,100	295pk 280tr 234pk	+231

TABLE 5 (*Continued*)

Compound	Formula	[ϕ]	λ (mμ)	*a* (1st C.E.)
Daphnandrine	(IV) (*S*,*R*)	+46,350	297pk	+399
		+6500	280tr	
		+115,800	233!	
Cepharanthine	(IV) (*S*,*R*)	+31,230	294pk	+179
		+13,320	283tr	
		+71,800	248pk	
Berbamine	(V) (*R*,*S*)	+5990	294pk	+190
		−13,000	271tr	
		−7860	261pk	
		−13,000	250tr	
		+30,100!	240	
O-Methylberbamine (Isotetrandrine)	(V) (*R*,*S*)	+15,100	290pk	+282
		−13,100	274tr	
		−4090	258pk	
		−6940	251tr	
		+12,260	235pk	
(+)-Tetrandrine	(V) (*S*,*S*)	+24,900	289pk	+111
		+13,800	272tr	
		+149,000!	235	
(−)-Tetrandrine (Phæanthine)	(V) (*R*,*R*)	−25,700	290tr	−170
		−8700	268pk	
		−135,000	236tr	
		−81,000!	228	
Pycnamine	(V) (*R*,*R*)	−19,000	290tr	−107
		−8310	267pk	
		−60,900	235tr	
		−40,650!	227	
(+)-Tenuipine	(V) (*S*,*S*)	+87,800	244	
		+128,400	238pk	
		−82,300!	228	
(−)-Tenuipine	(V) (*R*,*R*)	−45,000	253sh	
		−104,000	239tr	
		−70,300!	232	
Nortenuipine *	(V) (*S*,*S*)	+14,630	281?pk	
		+13,180	262?tr	
		+91,500	236pk	
Hernandezine	(V)	+23,500	292pk	+254
		−1880	275tr	
		+149,000	235pk	
		+135,700!	229	
Curine	(VI) (*R*,*R*)	−31,900	292tr	−240
		−7890	280pk	
		−96,500	239tr	
		−7100!	231	
OO'-Dimethylcurine	(VI) (*R*,*R*)	−26,100	292tr	−174
		−8700	278pk	
		−93,500	240tr	
		−80,000!	236	
Chondrocurine	(VI) (*S*,*R*)	+16,500	292pk	+89
		+7600	283tr	
		+49,400	240pk	
OO'-Dimethylchondrocurine	(VI) (*S*,*R*)	+15,380	292pk	+70
		+8410	272tr	
		+62,200	240pk	
		+58,500!	233	
Isochondrodendrine †	(VII) (*R*,*R*)	+7090	284pk	+39
		+3185	259tr	
		+10,260	243pk	
		+8150!	238	
OO'-Dimethylisochondrodendrine	(VII) (*R*,*R*)	+19,000	283pk	+285
		−9500	264tr	
		+12,150	254pk	
		−108,000!	237	
Insularine	(VIII)	+10,450	280pk	
		−123,500	237tr	
		−107,200!	213	
Dauricine	(IX)	−20,600	289tr	−148
		−5820	272pk	
		−52,000	240tr	
		−29,900!	235	

* I. R. C. Bick, J. Harley-Mason, and M. J. Vernengo, *Anales Asoc. quim. argentina*, 1963, **51**, 135. † J. A. D. Jeffreys, *J.*, 1956, 4451.



Optical rotatory dispersion curves

as great as the first (Figure, c). In contrast, the (*RS*)-compounds with dissimilar asymmetric centres have curves which show minor extrema, between the two main Cotton effects (Figure, d), though these are both of the same sign. Hernandezine[17] differs from tetrandrine only in having one additional methoxyl group at position 8′, and as its dispersion curve closely parallels that of (*SS*; ++)-tetrandrine, it may also be allotted the (*SS*) configuration.

Type 3 (7,11′ : 8′,12-coupling; formula VI). These compounds have more symmetrical molecules than Types 1 and 2, and four examples have been examined. It has been shown on chemical evidence that curine and *OO*′-dimethylcurine have the (*RR*; ——) configuration while chondrocurine and *OO*′-dimethylchondrocurine belong to the (*SR*; +—) stereochemical group.[18] This has been confirmed by nuclear magnetic resonance studies.[2] Curine and its dimethyl ether have similar negative rotatory dispersion curves, with the second Cotton effect three or four times as great as the first. Chondrocurine and *OO*′-dimethylchondrocurine give similar positive curves but the magnitudes of the Cotton effects are not as great as for the (*RR*)-compounds (Figure, e).

[17] J. Padilla and J. Herran, *Tetrahedron*, 1962, **18**, 427.

[18] I. R. C. Bick and P. S. Clezy, *J.*, 1953, 3893; T. A. Henry, " The Plant Alkaloids," Churchill, London, 1949, pp. 374—377.

Type 4 (8,12′ : 8′,12-coupling; formula VII). These compounds have formulæ which are more symmetrical than those of the other bisbenzyltetrahydroisoquinoline alkaloids. We have examined two compounds of this type; both have given two positive Cotton effects.

General Comparisons.—A comparison of the results obtained for these alkaloids shows that, for type 2, those structures with two similar asymmetric centres (either both *R* or both *S*) have relatively simple curves with two Cotton effects of the same sign (*e.g.*, Figure, c) while compounds with two dissimilar centres have other extrema between the main peaks and troughs (*e.g.*, Figure, d). This is as would be expected if the contributions of the two centres to the rotation of the molecule as a whole are additive. However, the magnitude of rotation of the second (low wavelength, 240 mμ) Cotton effect is much more than twice that for the simple monobenzyltetrahydroisoquinolines (cf. Tables 2 and 4); this enhanced rotation is presumably due to conformational effects.

The compounds of Type 1 are exceptions to this pattern of behaviour; the members of this group with dissimilar centres give two Cotton effects only (Figure, a) whereas those with two similar centres have more complicated curves (Figure, b). The (*SR*)-bases of Type 3 are also exceptional in that their dispersion curves, although smaller in magnitude, are of the shape generally expected for the (*SS*)-compounds with no minor extrema between the main Cotton effects. In these cases, therefore, it appears that the overall molecular shape (which is determined not only by the *configurations* of the asymmetric centres but also by the *conformations* of the ether linkages) is a major factor in determining the form of the dispersion curves. If the rotatory dispersion method is to be used for the determination of the absolute configuration of biscoclaurine alkaloids, compounds of the same chemical type must be used for comparison.

The results appear to imply that the conformational peculiarities of the type 1 and 3 linkage result in strong optical rotational effects which outweigh the contributions of the individual units, but that in Type 2, although the contributions of units are not strictly additive, the curves of the bis-bases could be predicted very approximately from the curves of the units.

Other Related Alkaloids.—The experimental results for a number of other related alkaloids are included here, although our present knowledge does not permit us to offer any detailed explanation of their optical rotatory dispersion behaviour.

Experimental.—Optical rotatory dispersion curves were measured in methanol on a Bellingham and Stanley/Bendix-Ericsson automatic recording spectropolarimeter " Polarmatic 62 " ($l = 0{\cdot}1$ dm.; $t = 20$—$25°$; $c = 1$ mg./ml. or less). Molecular rotations are listed in Table 5. Ultraviolet spectra were measured in methanol on a Unicam S.P. 700 spectrophotometer (path-length = 1 cm.; $c = 1$ mg./ml. or less).

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