367. *Structural Correlations in the Nuclear Magnetic Resonance Spectra of Bisbenzylisoquinoline and Aporphine Alkaloids.*

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The hydrogen nuclear magnetic resonance spectra of a range of bisbenzylisoquinoline alkaloids, and of a few aporphine alkaloids, have revealed a number of useful correlations between the resonance positions of methoxyl and *N*-methyl groups and the chemical and stereochemical structures of these molecules. These correlations have been used to make predictions about the structures of the incompletely characterised alkaloids tenuipine, nortenuipine, and chondrofoline.

We have examined the hydrogen (proton) nuclear magnetic resonance spectra of several series of alkaloids, mostly of the bisbenzylisoquinoline type, and have found that some useful correlations may be made between the chemical shifts of certain functional groups and their structural and stereochemical locations. The stereochemical variations within this class of alkaloid are of considerable complexity, owing to the presence of two asymmetric centres adjacent to the nitrogen atoms, and to the possible relative locations of the two ether linkages. The correlations recorded here are mostly concerned with the strong and sharp methyl resonances of the methoxyl and methylimino-groups, but a few other regularities are also recorded. The data so obtained have been of assistance in assigning structures to three incompletely characterised alkaloids.

Goodwin, Shoolery, and Johnson,[1] on the basis of experimental data from three aporphine alkaloids, previously suggested that the resonances of methoxyl and aromatic CH groups might give rise to useful correlations in the alkaloid field.

EXPERIMENTAL.—Except where otherwise specified, the substances concerned were examined in approximately saturated solutions in chloroform. The chemical shifts are quoted in parts per million on the τ scale [2,3] relative to the resonance of tetramethylsilane as an internal standard at $\tau = +10{\cdot}00$. The measurements were made at 40 Mc. sec.$^{-1}$ with a Varian Associates 12″ electromagnet, and a V-4300 B spectrometer, with tubes of 5 mm. outside diameter, sample spinning, and flux stabilisation. Calibration of the peaks was made by using side bands generated by a Muirhead-Wigan D 695 A decade oscillator. During the early part of this work the positions of the peaks were measured relative to the solvent (chloroform) resonance and these have been calculated to the τ scale by assuming $\tau = +2{\cdot}75$ for chloroform. Subsequent measurements were made directly against tetramethylsilane used as an internal standard in the chloroform solutions. As the latter values are likely to be somewhat more accurate the names of the appropriate compounds are indicated by asterisks in Tables 1—3. Errors due to the earlier procedure are unlikely to exceed $\pm 0{\cdot}05$.

DISCUSSION

Resonances of OMe *and* NMe *Groups.*—(a) *Factors affecting the chemical shifts of such groups.* A methoxyl group attached to a benzene ring has a normal chemical shift of *ca.* 6·2 on the τ scale (anisole in chloroform gives 6·17). This chemical shift is an average value taken over the various orientations of the methoxyl group with respect to the benzene ring reached by rotation about the aromatic C–O bond. Benzene rings are magnetically very anisotropic because applied magnetic fields readily generate currents in the π-electron system.[4] The sense of this anisotropy is such that the hydrogen nuclei of a methoxyl group lying in the plane of the ring will have a somewhat lower chemical shift than those of a methoxyl group above or below the ring, *i.e.*, lying so that the plane of the C–O–C atoms is perpendicular to that of the ring.[4,5] The presence of bulky substituents near such a group will tend to force it out of the aromatic plane, *i.e.*, to favour higher τ values by a few hundredths of a unit. More pronounced shifts to higher τ values by several tenths of a unit are found when a methoxyl group can take up configurations so that its hydrogen atoms fall more directly over the top of a second adjacent benzene ring.[5,6] This is the predominant cause of the marked spread of methoxyl resonances (6·05—6·98) observed with these alkaloids. The methylimino-resonances also exhibit a range of values (7·35—7·75) for the same reasons.

(b) *The repandine–oxyacanthine* (I) *and berbamine–tetrandrine* (II) *series.* Table 1 summarises chemical shift data for a number of alkaloids of each of these two series, and for the related compound cepharanthine (III). In addition to the strong and sharp resonances of methoxyl and methylimino-groups, we also list the position of the maxima of the broader collective resonances of the ring methylene groups. Some typical spectra are shown in Fig. 1. Many of the chemical-shift regularities shown in Table 1 speak for themselves; we shall only point out the salient features.

Methoxyl groups at position 4″ have a chemical shift (6·05—6·13) that is slightly lower than the normal value of ~6·2, whereas the same group at position 7 has a very high value (6·80—6·98). An examination of molecular models showed that the 7-methoxy-group can, and in many of its orientations must, pass closely over the top of the adjacent aromatic ring B; this is certainly the cause of the high chemical shift. The purely

[1] Goodwin, Shoolery, and Johnson, *Proc. Chem. Soc.*, 1958, 306.
[2] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.
[3] Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, London, 1959.
[4] Bernstein, Schneider, and Pople, *Proc. Roy. Soc.*, 1956, *A*, **236**, 515.
[5] Bovey and Johnson, *J. Chem. Phys.*, 1958, **29**, 1012.
[6] Fessenden and Waugh, *J. Amer. Chem. Soc.*, 1957, **79**, 846.

empirical evidence does not allow a clear-cut assignment of the chemical shifts at *ca.* 6·25 and 6·35—6·7 to methoxyl groups at positions 6 and 6′. However, the series of peaks of lower chemical shift have been provisionally assigned to 6-methoxyl on the grounds that

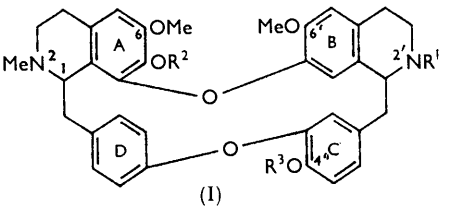
TABLE 1. *Chemical shift data (τ values) for alkaloids of the repandine–oxyacanthine–berbamine–tetrandrine–pheanthine series.*‡

Name	Formula	R¹	R²	R³	OMe 4″	OMe 6	OMe 6′	OMe 7	Ring CH_2	NMe 2′	NMe 2
Repandine	I(++)	Me	Me	H	—	6·27	6·62	6·98	7·20	7·50	7·50
O-Methylrepandine	I(++)	Me	Me	Me	6·05	6·25	6·60	6·95	7·22	7·45	7·45
Oxyacanthine *	I(+−)	Me	Me	H	—	6·27	6·44	6·85	7·12	7·52	7·52
O-Methyloxyacanthine *	I(+−)	Me	Me	Me	6·10	6·21	6·40	6·80	7·05	7·35	7·45
Daphnandrine	I(+−)	H	H	Me	6·12	6·25	6·40	—	7·12	—	7·50
Aromoline §	I(+−)	Me	H	H	—	6·23	6·44	—	—	7·51	7·51
Daphnoline †	I(+−)	H	H	H	—	6·17	6·35	—	—	—	+
Cepharanthine	III(+−)	—	—	—	6·10	—	6·30	—	7·05	7·35	7·42
Berbamine *	II(−+)	H	Me	—	—	6·18	6·35	6·85	7·1	7·35	7·75
Isotetrandrine *	II(−+)	Me	Me	—	6·05	6·22	6·37	6·82	7·07	7·40	7·72
Tetrandrine	II(++)	Me	Me	—	6·10	6·27	6·65	6·82	7·00	7·41	7·70
Fangchinoline	II(++)	Me	H	—	6·03	6·23	6·60	—	6·94	7·38	7·62
Pheanthine *	II(−−)	Me	Me	—	6·13	6·28	6·68	6·80	6·92	7·40	7·70
Pycnamine *	II(−−)	H	Me	—	—	6·27	6·82	6·82	—	7·37	7·65

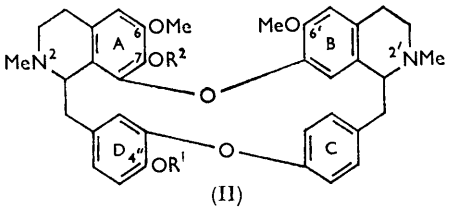
* Data for these molecules are somewhat more accurate (see Experimental section). § Weak spectrum owing to limited solubility in chloroform. † Solution in formic acid; weak spectrum. ‡ Chemical evidence for the structures of most of these alkaloids is summarised by Kulka, " The Alkaloids," ed. Manske and Holmes, Academic Press, New York, Vol. IV, p. 199, and Vol. VII, p. 439; the structures of daphnandrine, aromoline, and daphnoline have been reported by Bick, Clezy, and Vernengo (*J.*, 1960, 4928) and that of pycnamine by von Bruchhausen *et al.* (personal communication; *Arch. Pharm.*, 1960, **293**, 785).

the group at position 6′ occupies a position more closely analogous to that of 7. Molecular models confirm that the 6′-methoxyl group approaches the top of the aromatic ring A.

A potentially very useful regularity is that when the asymmetric carbon centres are paired (+−) or (−+) the 6′-methoxyl resonance, as assigned above, has a chemical shift



(I)



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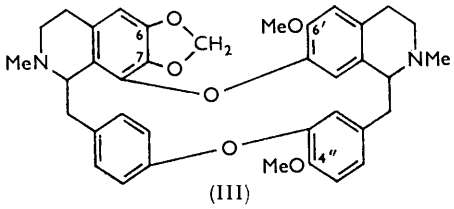

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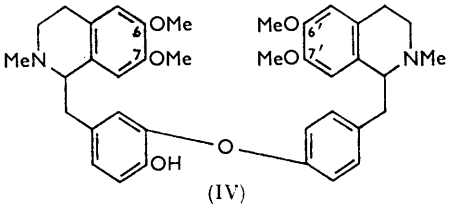


(IV)

near 6·4, whereas the pairing (++) or (−−) gives a value near 6·65. Models show that in the latter case the methyl-hydrogen atoms are less free to move away from the adjacent aromatic ring. The 6′-methoxyl resonance of cepharanthine has an abnormally low value.

For alkaloids of the repandine type both methylimino-resonances occur near 7·45, whereas for the berbamine series they give well separated peaks near 7·4 and 7·7. Monobenzylisoquinoline alkaloids normally have their methylimino-resonances between 7·45

and 7·5 (Table 3). However molecular models show that the *N*-methyl group at position 2 in the alkaloids in the berbamine series approaches the top of aromatic ring D, and therefore we have assigned the *ca.* 7·7 chemical shift to the methylimino-group at this position.

Dauricine (IV) has a simpler spectrum than those discussed above, as would be expected from the fact that the two tetrahydroisoquinoline rings are no longer joined by an ether bridge. There are two methoxy-resonances at 6·20 and 6·45, each of which corresponds to two groups, probably at positions 6 and 6′ and 7 and 7′ respectively. As there is no ether

FIG. 1. *Nuclear magnetic resonance spectra of*: 1, *repandine*; 2, O-*methyloxyacanthine*; 3, *isotetrandrine*; 4, *tetrandrine*; 5, *pheanthine*.

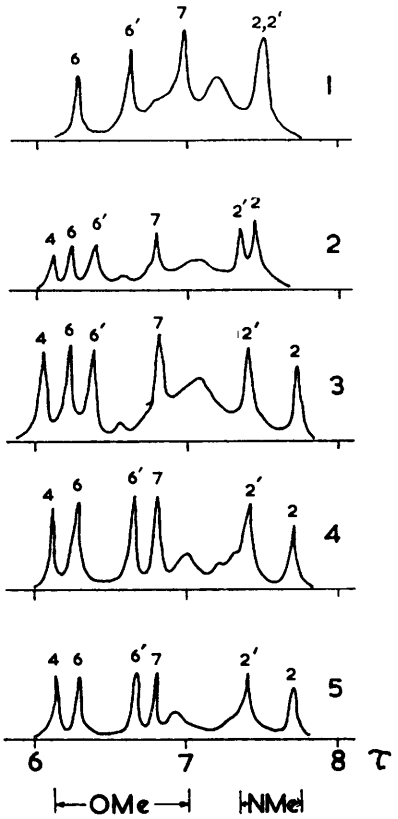
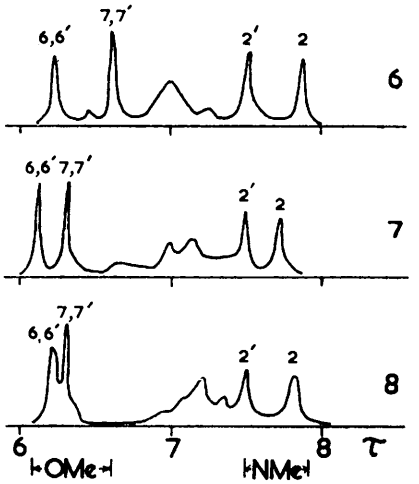


FIG. 2. *Nuclear magnetic resonance spectra of*: 6, OO′-*dimethylisochondrodendrine*; 7, OO′-*dimethylcurine*; 8, OO′-*dimethylchondrocurine*.

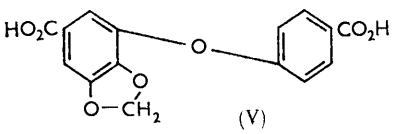


bridge to cause the 7-methoxy-group to be held close to an adjacent aromatic ring the chemical shift value has returned much closer to the normal value although its resonance is still separate and distinguishable from that of the 6-methoxyl groups, presumably because of the effect of the adjacent benzyl aromatic ring. The methylimino-peaks overlap at 7·50 and the broad ring CH_2 resonance occurs at 7·23.

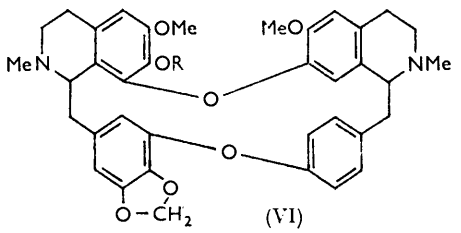
The correlations set out above have been used to make tentative structural assignments for the incompletely characterised alkaloids tenuipine and nortenuipine (previously described as de-*N*-methyltenuipine [7]). The former compound has methoxyl peaks at 6·25, 6·65, and 6·82, a pair of methylimino-peaks at 7·40 and 7·65, and a peak at 4·02 to be attributed to the methylenedioxy-group. The three methoxy-resonances may clearly be

[7] Bick, Taylor, and Todd, *J.*, 1953, 695.

assigned to positions 6, 6′, and 7 respectively (see Table 1), and the absence of a peak near 6·1 suggests that there is no methoxyl attached to the benzyl residue. This has been confirmed by the isolation of repandulinic acid (V) by oxidation,[8] and thus position 4 is taken up by one end of the methylenedioxy-ring as in (VI; R = Me). The presence of



(V)



(VI)

two *N*-methyl peaks indicates that the alkaloid is of the berbamine–tetrandrine type, and the high value of the 6′-resonance suggests that the pair of asymmetric centres are (++) or (−−). The nuclear magnetic resonance evidence has hence greatly narrowed the structural possibilities for tenuipine, and degradations are being carried out to test this evidence. Nortenuipine has methoxyl peaks at 6·22 and 6·67, two methylimino-peaks at

TABLE 2. *Chemical shift data (τ values) for alkaloids of the isochondrodendrine–curine and chondrocurine series.*‡

					OMe				Ring	NMe	
Name	Formula	R^1	R^2	R^3	6	6′	7	7′	CH_2	2′§	2§
Isochondrodendrine *	VII(−−)	H	H	—	6·13	6·13	—	—	7·12	7·47	7·73
O-Methylisochondrodendrine †*	VII(−−)	Me	H	—	6·23	6·23	6·59	—	7·02	7·51	7·65
OO′-Dimethylisochondrodendrine *...	VII(−−)	Me	Me	—	6·22	6·22	6·62	6·62	7·00	7·50	7·87
Insularine *	VIII(−−)	—	—	—	6·18	6·25	6·70	—	6·99	7·46	7·52
					6	6′	7	4″			
Curine	IX(−−)	Me	H	H	6·07	6·07	—	—	7·12	7·53	7·70
OO′-Dimethylcurine *	IX(−−)	Me	Me	Me	6·12	6·12	6·32	6·32	7·12	7·48	7·70
Chondrocurine *	IX(+−)	H	Me	H	—	6·12	6·18	—	7·10	7·55	7·75
OO′-Dimethylchondrocurine	IX(+−)	Me	Me	Me	6·20	6·20	6·30	6·30	7·20	7·50	7·82

* Chemical shift data for these compounds are slightly more accurate (see experimental section).
† Very weak spectrum. ‡ Chemical evidence for the structures of these alkaloids is summarised by Wintersteiner in "Curare and Curare-like Agents," Elsevier, Amsterdam, 1959, p. 153.
§ Assigned tentatively on the basis of molecular models (see text).

7·37 and 7·68, and a broad ring CH_2 resonance at 7·00. These and the properties of nortenuipine indicate that 7-methoxyl is replaced by a hydroxyl group, but that otherwise the structure is closely related to that of tenuipine, *i.e.*, (VI; R = H).

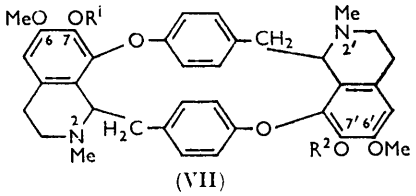
(c) *The* Curare *series.* In these series of bisbenzylisoquinoline alkaloids the two halves of the molecule are joined by head-to-tail linkages instead of the head-to-head, tail-to-tail links of the alkaloids discussed in Section (b). Molecules of the isochondrodendrine series are the more symmetrical, but even in isochondrodendrine itself (VII; $R^1 = R^2 = H$) the molecule as a whole lacks a centre of symmetry because of the (−−) configurations at the two asymmetric centres. Insularine (VIII) is closely related to this series. Curine (IX; $R^1 = Me$, $R^2 = R^3 = H$) and chondrocurine (IX; $R^2 = Me$, $R^1 = R^3 = H$) differ from the isochondrodendrine series in the location of one of the ether bridges.

The nuclear magnetic resonance data for these compounds are collected in Table 2 and some typical spectra are shown in Fig. 2.

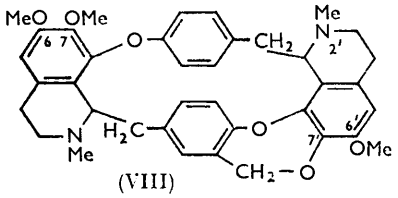
[8] Bick, Doebel, Taylor, and Todd, *J.*, 1953, 692, and unpublished results.

Considering first the methoxyl resonances we see that for all these compounds the 6- or 6′-substituents give rise to relatively normal chemical shifts (6·07—6·25). The somewhat higher values for 6′-methoxyl as observed in the repandine–berbamine series no longer occur, because the more extended structures of these molecules do not bring the 6′-methoxy-group in close proximity to an adjacent benzene ring. The 7,7′-methoxy-groups in the isochondrodendrine series have somewhat higher values (~6·65), but in the curine–chondrocurine series they too are only slightly higher than normal (6·18—6·32).

Table 2 also shows that all the compounds of the two main series have one normal *N*-Me resonance at ~7·5 and a higher peak at 7·75. Insularine (VIII) is an exception to



(VII)



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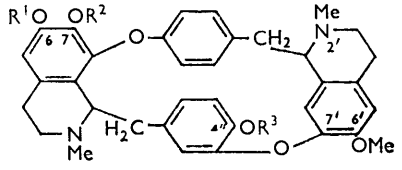

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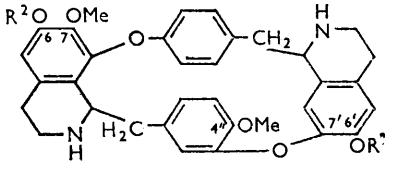


(X)

this generalisation but its structure is more rigid because of the formation of the additional ring.

Molecular models for these classes of alkaloid show considerably more flexibility than for the repandine–berbamine classes, and for this reason detailed interpretations are more difficult here. In all cases molecular conformations can be found which can account for the regularities in the spectral data of Table 2, but it is not immediately obvious why these conformations are more probable than others which would be expected to give different results. Conversely, the spectroscopic data may be of use in the future in providing evidence for the most probable conformations of these molecules. However, it does appear from the models that for chondrocurine a high value of a methylimino-resonance is likely to go with a low 7-methoxyl value on the same ring and therefore in Table 2 we tentatively assign the higher *N*-Me resonance to position 2.

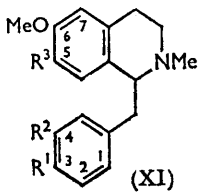
Chondrofoline is an alkaloid of the curine group whose detailed structure is uncertain although King [9] has provisionally formulated it as (X; R^1 = Me or H, and *vice-versa* for R^2) on the basis of degradations and colour reactions. However, the spectrum clearly shows the presence of two methylimino-groups (7·47 and 7·71) and this confirms more recent analytical results.[10] Further, the three methoxyl groups give a pair of resonances close to 6·15 and one at 6·26, suggesting that both R^1 and R^2 may be methyl groups and that the hydroxyl group may be at position 7 or 4″. However, this does not accord with King's location of the hydroxyl group from the Millon test; further work may enable a decision to be made between these possible structures, but in the meantime it may be noted that fangchinoline,[11] an alkaloid of the tetrandrine series, responds exceptionally to the test.

(d) *Some benzylisoquinoline and aporphine alkaloids.* In Table 3 we compare chemical shift data for several examples of each of these two classes of alkaloid.

[9] King, *J.*, 1940, 737; cf. Bick and Clezy, *J.*, 1960, 2404.
[10] Bick, unpublished results.
[11] Hsing Chi-Yi and Chang Ching-Hsiang, *Acta Chim. Sinica*, 1957, **23**, 405.

Results for dicentrine, *O*-methylbulbocapnine, and glaucine have been published recently by Goodwin, Shoolery, and Johnson;[1] their results, when approximately converted to the present units, agree with ours to within less than 0·1 τ unit. The data on isocorydine methochloride are taken from a paper by Katritzky, Jones, and Bhatnagar.[12]

It is seen that for both classes of alkaloid the chemical shifts of methoxyl groups



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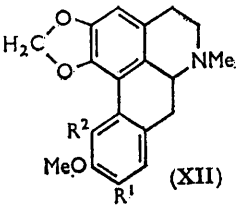

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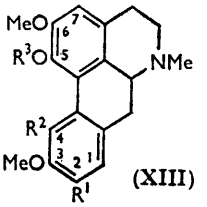

(XIII)

adjacent to two benzene rings at positions 5 have consistently higher chemical shifts (6·37—6·58) than those at 2, 3, or 6 (6·11—6·28). Those at position 4 have intermediate chemical shifts (6·28—6·35) for the aporphine alkaloids; only one example is available for a benzylisoquinoline alkaloid. All methylimino-resonances lie between 7·45 and 7·65.

Resonances of Methylenedioxy-groups.—Goodwin, Shoolery, and Johnson [1] showed that the methylenedioxy-ring joining positions 5 and 6 of aporphine alkaloids (XII) gives rise to a quartet of lines corresponding to a small chemical shift between the two hydrogen atoms. They attributed the chemical non-equivalence of the two hydrogen atoms to a

TABLE 3. *Chemical shift data (τ values) for alkaloids of the benzylisoquinoline and aporphine series.* ‡

Name	Formula				OCH₃				NCH₃	OCH₂O
	R¹	R²	R³	2Δ	3Δ	4	5	6Δ		
±) -Laudanosine.....	XI	OMe	OMe	OMe	—	6·18	6·22	6·45	6·18	7·48	—
O-Methylarmepavine ...	XI	OMe	H	OMe	—	6·20	—	6·58	6·28	7·45	—
(+)-*O*-Ethyl-*N*-methyl-coclaurine	XI	OH	H	OEt	—	—	—	—	6·20	7·48	—
Dicentrine *	XII	OMe	H	—	6·20	6·20	—	—	—	7·62	4·05, 4·20 (doublets)
Bulbocapnine *	XII	H	OH	—	—	6·20	—	—	—	7·65	3·97, 4·15 (doublets)
O-Methylbulbocapnine	XII	H	OMe	—	—	6·18	6·28	—	—	7·50	3·95, 4·15 (doublets)
Corydine *	XIII	H	OMe	H	—	6·18	6·35	—	6·18	7·55	—
O-Methylcorydine *.....	XIII	H	OMe	Me	—	6·18	6·32	6·37	6·18	7·50	—
Glaucine *.....	XIII	OMe	H	Me	6·20	6·25	—	6·45	6·20	7·57	—
Isocorydine metho-chloride §	XIII	H	OH	Me	—	6·11	—	6·46	6·16	—	—

* These data are somewhat more accurate (see experimental section). ‡ Chemical evidence for the structures of these alkaloids is summarised by Manske in "The Alkaloids," ed. Manske and Holmes, Academic Press, New York, Vol. IV, p. 119 and Vol. VII, p. 423. § Data from ref. 12. Δ Assignments of resonance to these positions may be interchanged.

non-planarity of the linked biphenyl ring system. Sasaki [13] has made a particular study of the resonances of methylenedioxy-groups attached to benzene rings (including some alkaloids), and his data, when recalculated into our units with the help of his values for cepharanthine and isotetrandrine, show that such groups usually have their resonance between 3·7 and 4·6. This accords with our values of 4·42, 4·02, and 4·00 for cepharanthine, tenuipine, and nortenuipine respectively, and with the values listed in Table 3 for the dicentrine-type alkaloids. In agreement with the ideas expressed by Goodwin *et al.*[1] the resonances are single except for those from aporphine alkaloids, although in the case of cepharanthine the line is broad, suggesing incipient splitting caused by a small chemical shift between the two methylenedioxy-hydrogen atoms.

Aromatic CH *Resonances.*—Goodwin, Shoolery, and Johnson [1] have pointed out that

[12] Katritzky, Jones, and Bhatnagar, *J.*, 1960, 1950.
[13] Sasaki, *J. Pharm. Soc. Japan*, 1960, **80**, 241.

the pattern of lines caused by aromatic CH groups of the aporphine alkaloids can often be used effectively to check the positions of substituents around the benzene rings. Although we have also made use of such data in a number of simple cases, we have not yet attempted a detailed analysis of this region of the spectrum for the present compounds, partly because chloroform as a solvent somewhat obscures the resonances, and partly because the four benzene rings of the bisbenzylisoquinoline alkaloids give overlapping, and therefore complex spectra. Nevertheless, some interesting regularities have been observed in the overall patterns of bands in this region; for example, the two curine spectra are similar in appearance but differ from those of the chondrocurines, while chondrofoline has a similar spectrum to that of the curines. We hope that a further study of this region of the spectrum will give more detailed information on a number of points of structure and conformation.

We gratefully acknowledge the award of Research Grants from the Consejo Nacional de Investigaciones Científicas y Técnicas of Argentina (to M. J. V.), and of a Royal Society and Nuffield Foundation Commonwealth Bursary (to I. R. C. B.). Generous gifts of material were received from Professor Masao Tomita (cepharanthine, insularine, and *O*-methylarmepavine); Professor F. von Bruchhausen (pycnamine); Dr. J. D. Dutcher (curine, chondrocurine, and isochondrodendrine); Dr. J. Walker (chondrofoline); Dr. J. R. Price (pheanthine); Dr. J. A. D. Jeffries (*O*-ethyl-*N*-methylcoclaurine); Dr. R. H. F. Manske (glaucine and dauricine); Dr. T. Kikuchi (*O*-methylisochondrodendrine); and Professor S. Kupchan (fangchinoline).

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[*Received, August 22nd,* 1960.]