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Dichroism and dispersion studies of the optically active aromatic chromophore

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DICHROISM AND DISPERSION STUDIES OF THE OPTICALLY ACTIVE AROMATIC CHROMOPHORE

by

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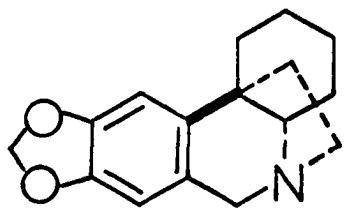
I. INTRODUCTION

The Amaryllidaceae alkaloids have been very intensively studied by a number of groups in different countries, and the results of these investigations have been published in recent monographs (1, 2, 3, 4). At the present time eight basic ring systems have been found in the Amaryllis (1). One of the most thoroughly studied has been that one containing the 5, 10b-ethanophenanthridine structure. These investigations include structure proof (5), biosynthesis (6, 7, 8), and relative stereochemistry (9, 10). Since almost all of the compounds in the 5, 10b-ethanophenanthridine series, as well as those in the tazettine and lycorine groups possess an allylic hydroxyl or methoxyl function, Mill's rule (11) has been used to assign their absolute stereochemistry (12, 13, 14). It has not been established that Mill's rule is applicable to systems other than steroids and terpenes, where the only strong end absorption prevailing is that due to the allylic hydroxyl or methoxyl system. The validity of applying Mill's rule to systems having strong end absorption caused by chromophores above that of the allylic system is questionable. There has been no degradation of any alkaloid to a simple compound of known absolute configuration in the family and X-ray data has been presented only for the galanthamine series supporting these assignments (15).

It has been shown that the 5, 10b-ethanophenanthridine ring alkaloids can occur in both antipodal forms in the Amaryllidaceae. Nerine

bowdenii contains alkaloids based on both the (+) and (-) crinane nucleus I and II respectively (16). The bulbs of Crinum moorei contain



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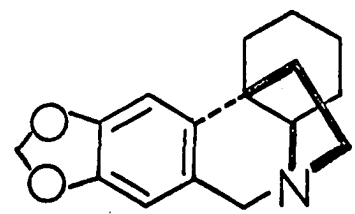

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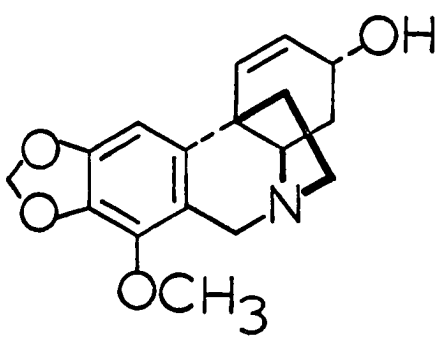
the alkaloid powelline (17), which has been shown to have structure (III) (18). The structures of crinine (IV) (19) and powelline have been rigorously proven by both degradative and chemical methods. The structural and stereochemical relationships between the two compounds was established by the conversion of powelline to dihydroepicrinine (V).

Rotational data for the crinine-powelline series and their derivatives demonstrated that these compounds were indeed quite similar (20). A comparison of the molecular rotational differences, ΔM afforded results which were in accord with the suspected similarities of these two compounds (21). However, as a better understanding of optical rotatory dispersion evolved, the results obtained at 589 mu were questioned. Dihydropowelline and powellane afforded positive optical rotatory dispersion (ORD) spectra and dihydrocrinine and crinane negative ones (22).

The difference in sign of the ORD curves seem to indicate that (-) crinane and (+) powellane possess enantiomorphic ring systems. However

this seemed highly unlikely from the chemical degradations utilized. This dichotomy seemed worthy of investigation. The modern instruments available permit measurements of rotatory power to be made between 700 and 215 mu. This thesis describes the results of the first thorough investigation of an asymmetric center adjacent to an aromatic chromophore. Using the techniques of ORD and circular dichroism (CD) it is possible to study the effects of the asymmetric center on the sign of the Cotton effects associated with the aromatic ring. This study placed primary emphasis on aromatic natural products in general, and aromatic alkaloids in particular. The ramifications of this work extend into the fields of the relative and absolute stereochemistry of structurally rigid molecules possessing a chromophore other than the carbonyl group.



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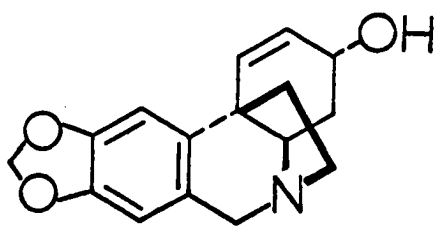

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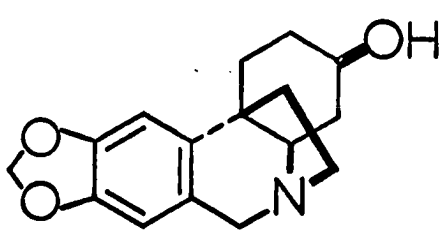

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II. HISTORICAL

Few properties of matter can rival optical rotatory power as a means of gaining valuable information about the more subtle aspects of molecular structure. Optical rotation is a phenomenon which has long interested both physicists and chemists. Optically active compounds in nature give it fundamental importance in the fields of biochemistry, chemistry and biology (23). It has been suggested that the occurrence of small quantities of the "wrong" antipode in proteins may be responsible for the decrease in efficiency of some fundamental life processes (24).

Wilhelmy's use of the polarimeter to measure the rotations of sugar solutions opened the door for intensive investigations on the field of optical activity (25, 26). The monumental works of Biot and Pasteur (27, 28, 29, 30) and the former's contributions to the theory of optical rotatory power are well known. Biot was also the first to measure the change of optical rotation with a change in wave length. This advance was checked however by the invention of the Bunsen burner, a convenient source of monochromatic light which set back the progress of polarimetry by fifty years (31). From this time onward the progress of experimental polarimetry advanced rapidly due to the work of such men as Arago (32), Fresnel (33) and Cotton (34). The details of this early work can be found in the excellent reviews of Heller (35), Lyle (25), Mitchell (36) and Levene and Rothen (37).

The relationships between ultraviolet spectroscopy (UV), optical rotatory dispersion (ORD) and circular dichroism (CD) were first demonstrated by Cotton (38). Except for Cotton and his group very little was done in this field until 1914 when Tschugaeff and Rupe did their pioneering work (39, 40, 41). In 1928 Rosenfeld (42) advanced his quantum mechanical theory of rotatory power. This work served as the cornerstone for a number of complex mathematical treatises dealing with the phenomenon of optical activity. The most important of these were developed by Condon, Altar and Erying (43), Kauzmann (44), Kirkwood (45) and Kuhn (46). Recent contributions to the theoretical aspects of optical activity have been forwarded by Moffit (47, 48), Moscowitz (49) and Tinoco (50). All of these models lead to approximately the same expressions for rotatory power, and those of Rosenfeld might be applied with satisfactory compromise between tractibility and accuracy (51).

It is common knowledge that the true test of any theoretical considerations come in the laboratory. Largely through the efforts of Werner Kuhn, a man far ahead of his time in the field of rotatory dispersion, these theories were tested. T. M. Lowry was active in the field at the same time and he, together with Kuhn, was the first to use CD to study the stereochemistry of organic molecules (52, 53, 54). All of this work was done before the photoelectric spectropolarimeter was introduced by Rudolph in 1952 (55).

The correlation of the stereostructures of molecules with their absolute and relative configurations advanced rapidly after the introduction of Rudolf's polarimeter. This was for the most part due to the dynamic groups of Djerassi, Klyne and Ourisson, who studied the ORD spectra of steroid and terpene molecules containing the carbonyl chromophore in an asymmetric environment (56, 57, 58). These measurements were taken in the 50's when instrumentation had not reached the level of sophistication that it has today. The choice of the carbonyl group, with its large ratio of rotation to absorption was a fortunate one. Two very important empirical rules, useful in predicting absolute stereochemistry grew out of this early work. These were the axial halo-ketone rule (59) and the well known octant rule (60). It is impossible to cite the voluminous amount of ORD data accumulated for these systems; references to them can be found in the bibliography (61-72).

In 1960 Grosjean and LeGrand of the Rousell-Uclaf Company in Paris introduced the first commercially available dichrograph (73). Circular dichroism studies were confined for the most part to the easily accessible carbonyl chromophore. The superiority of CD over ORD in many cases was amply demonstrated by the studies of Djerassi, Mislow and Bunnenberg (74-82).

Reports of ORD data obtained for the aromatic chromophore have appeared in the literature from 1957 to the present. These data concern the aromatic chromophore in a variety of environments (83, 84, 85).

However the spectra present only "partial" dispersion curves and as such supplied only a limited amount of useful data about the compounds studied (69).

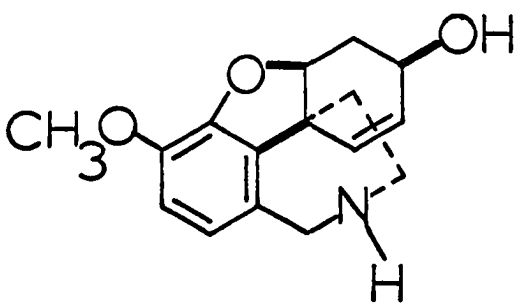
The aromatic ring is found in a wide variety of natural product molecules. The application of rotatory dispersion to alkaloids containing one or several aromatic rings has so far been limited to a relatively small number of compounds (86, 87). The list of these compounds is short enough to cite here. It includes the narcotines (88), hydrastines, garryfoline, cuauchichine and their dihydro derivatives (86), yohimbane, and related compounds (88), jervine (86), and isojervine (89), rubijervine (90), tetrahydropalmitine (84), seredone (87), haemanthamine, buphanisine (91), (-)demethylgalanthamine, (+) demethyldihydrogalanthamine (92), emetine, isoemetine (93), lysergic acid (94) and its derivatives and benzylisoquinoline alkaloids (95), as well as various alkaloids belonging to the morphine series (96). Unfortunately most of these curves were obtained when instrumentation did not allow a complete evaluation of their Cotton effects (69).

From the above list it can be seen that the Amaryllidaceae alkaloids have been studied but very little. Several unpublished ORD curves of the Amaryllis are available, but these are plain curves recorded from 700 to 300 mu (97, 22).

The first published CD curves of the aromatic chromophore appeared in the literature in December of 1965 (98). These curves were recorded

for the relatively simple compounds estradiol and 9-epiestradiol.

Narcissamine (VI) has been found to be a mixture of (-) demethylgalanthamine (VII) and (+) demethyldihydrogalanthamine (VIII) (92). Optical rotatory dispersion played an important role in this structure elucidation, as it provided an early clue to the quasi racemic nature of the alkaloid. The only other alkaloids of the Amaryllis for which ORD spectra have been recorded are desoxydihydrohaemanthidine (99), buphanisine and haemanthamine. As stated previously the amount of ORD data accumulated for alkaloids is but a fraction of that for steroids and terpenes. The most recent textbook on rotatory dispersion surveys all of the spectral data published for these compounds in ten pages (69). This lack of information about a rather large group of natural products, coupled with the crinane-powellane anomaly discussed previously was further incentive to undertake the present study.



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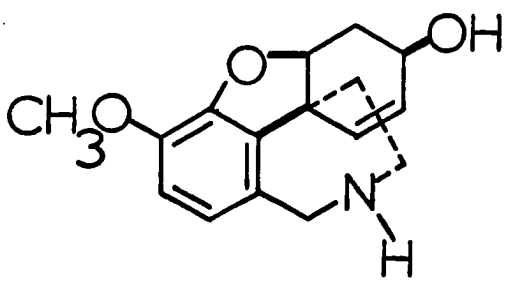

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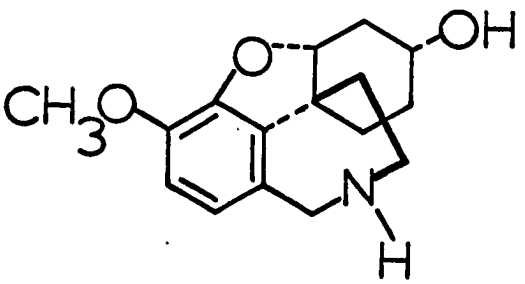


VIII

It is easy to see why workers in the field could not study the aromatic chromophore in greater detail. The ratio of the rotation to absorption of a chromophore (α/E) is one of the most important practical factors in carrying out ORD measurements. In the case of a typical carbonyl compound this ratio is quite large. An average value for ketones is 500, whereas in the aromatic chromophore this ratio approaches unity. Only because of the improvements in electronics and optics in the present day instruments is it possible to measure the dispersions in compounds having ratios as low as these. The limiting factor in the dichroism measurements has always been the ratio of the differential absorption of right and left handed light to the absorbance of a given chromophore, ($\Delta E/E$). In the commercial dichrographs presently available this places the maximum value at 1×10^{-4}. Aromatic compounds in general give rise to a ratio of 1×10^{-4}, and it is quite obvious that one would be making measurements at the absolute limits of the machine's capabilities. The modified Jouan dichrograph available to us had 1×10^{-5} as its limiting ratio.

Whereas the spectral range previously available extended from 700 mu to 300 mu it was now possible to make measurements as low as 215 mu with this instrument and to confirm many stereochemical assignments made previously. It has also been possible to show beyond a reasonable doubt that the aromatic chromophore can be optically active (100-103).

III. RESULTS AND DISCUSSION

A. Methylenedioxy Benzene Alkaloids

The first member of the 5, 10b-ethanophenanthridine system to be studied was crinine (Fig. 1). Most of the Amaryllidaceae alkaloids containing the methylenedioxy chromophore give rise to UV spectra very similar to crinine and therefore the spectra in Figure 2 may be taken as representative of this group of compounds. The 296 mu aromatic absorption maximum gives rise to a negative dispersion which reaches a maximum at 303 mu in the ORD spectrum of crinine. It is not possible to tell where the 240 mu benzene band begins, but its presence in the spectrum is indicated by the crossover point at 240 mu. The crossover point at 296 mu corresponds to the first benzene band at 296 mu. The CD negative maximum at 294 mu and the positive one at 240 mu correspond to the aromatic absorption in the ultraviolet, and bear out the assignments made from the ORD spectrum. It will become obvious as this discussion continues that by far the most valuable information concerning the optically active benzene ring is obtained from the CD measurements. In most of the compounds studied two bands are found, one plus and the other minus. With only rotatory dispersion measurements available these two bands can only be tentatively assigned as plus and then minus or visa versa. When a sign change occurs as in the case of powellane it is not possible to unambiguously assign this to a change in sign of

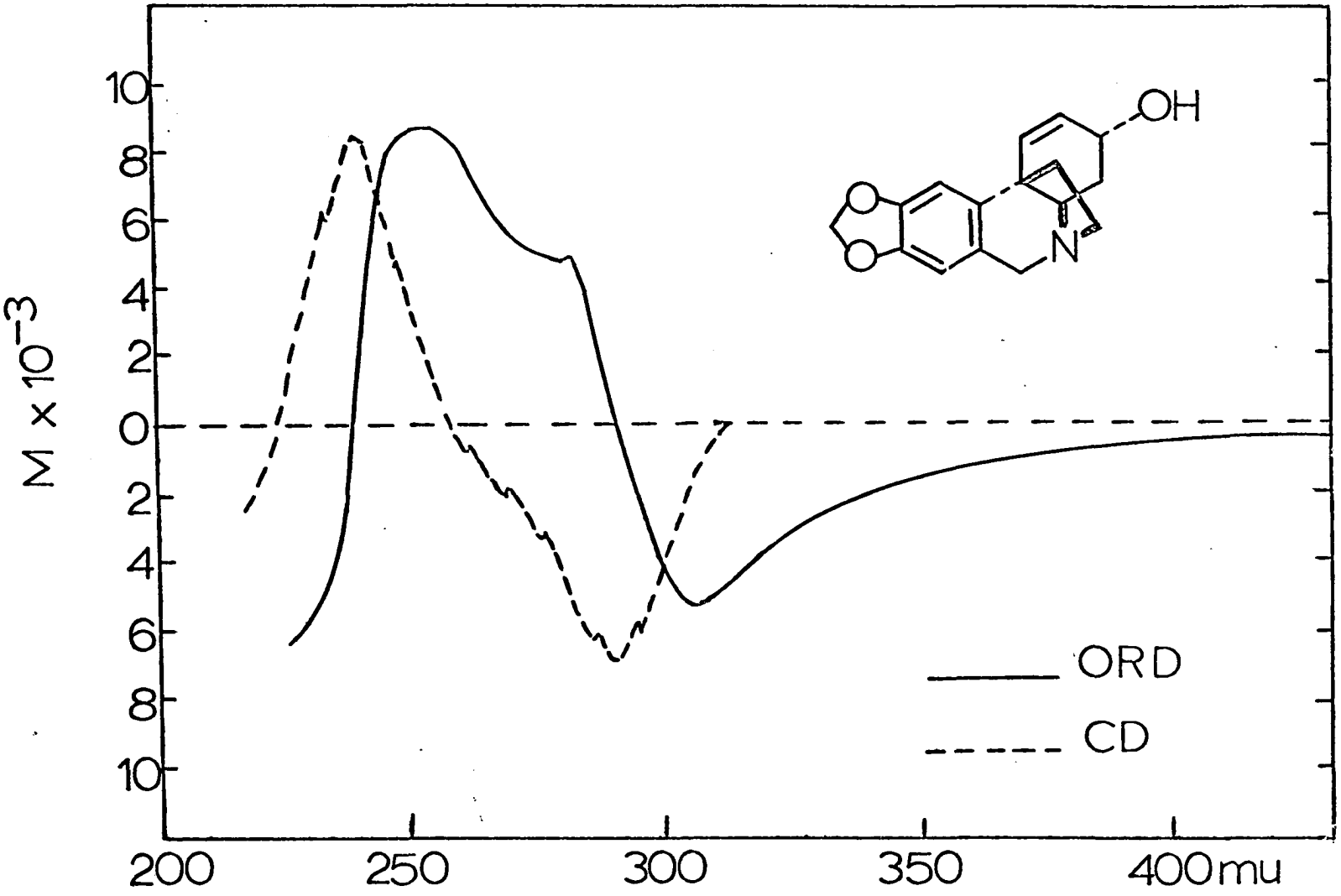


Fig.1

ORD and CD of CRININE

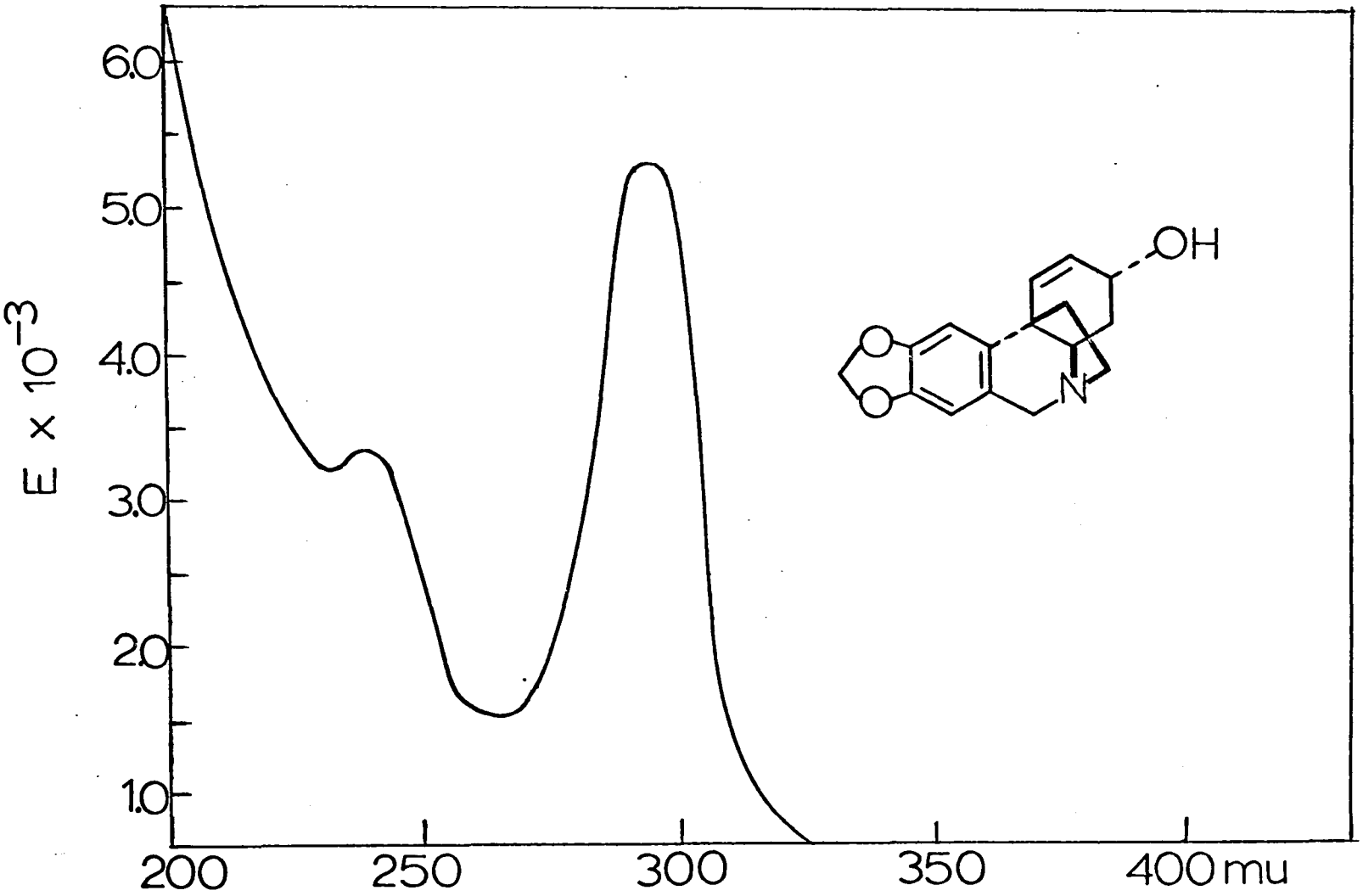


Fig. 2

UV SPECTRUM of CRININE

the aromatic Cotton effect or to a change of some other chromophore. The CD maxima occur at the same wave length as the UV maxima and can answer questions such as these with a minimum of uncertainty. The CD spectra in which the aromatic maxima are of opposite sign shall hereafter be referred to as "normal".

The amplitude of the benzene chromophore decreases rapidly in going from crinine to dihydrocrinine (Fig. 3). This could be rationalized in the ORD spectrum by removal of the allylic dispersion. However this cannot account for the decrease in the CD maxima, as it is well known that the dichroism of the aromatic ring at 295 mu is not effected by a chromophore in the 210 mu region (31, 69). (-) Crinane (Fig. 4) represents the parent compound in the 5, 10b-ethanophenanthridine series and contains neither the hydroxyl group nor the double bond. (-) Crinane shows normal dichroism and dispersion curves with a similar decrease in the amplitudes relative to crinine. Since crinine, dihydrocrinine and (-) crinane serve as model systems for the methylenedioxy group of 5, 10b-ethanophenanthridine alkaloids a more detailed study of the origins of the spectra was undertaken.

In crinine there are asymmetric centers at positions 3, 5 and 10b. Absorptions at positions 5 and 10b are not observed in the usual type of UV spectrophotometer, while the allylic hydroxyl absorption can be seen only with difficulty. We have observed that the benzene chromophore gives rise to two dispersions and ellipticities in a readily accessible

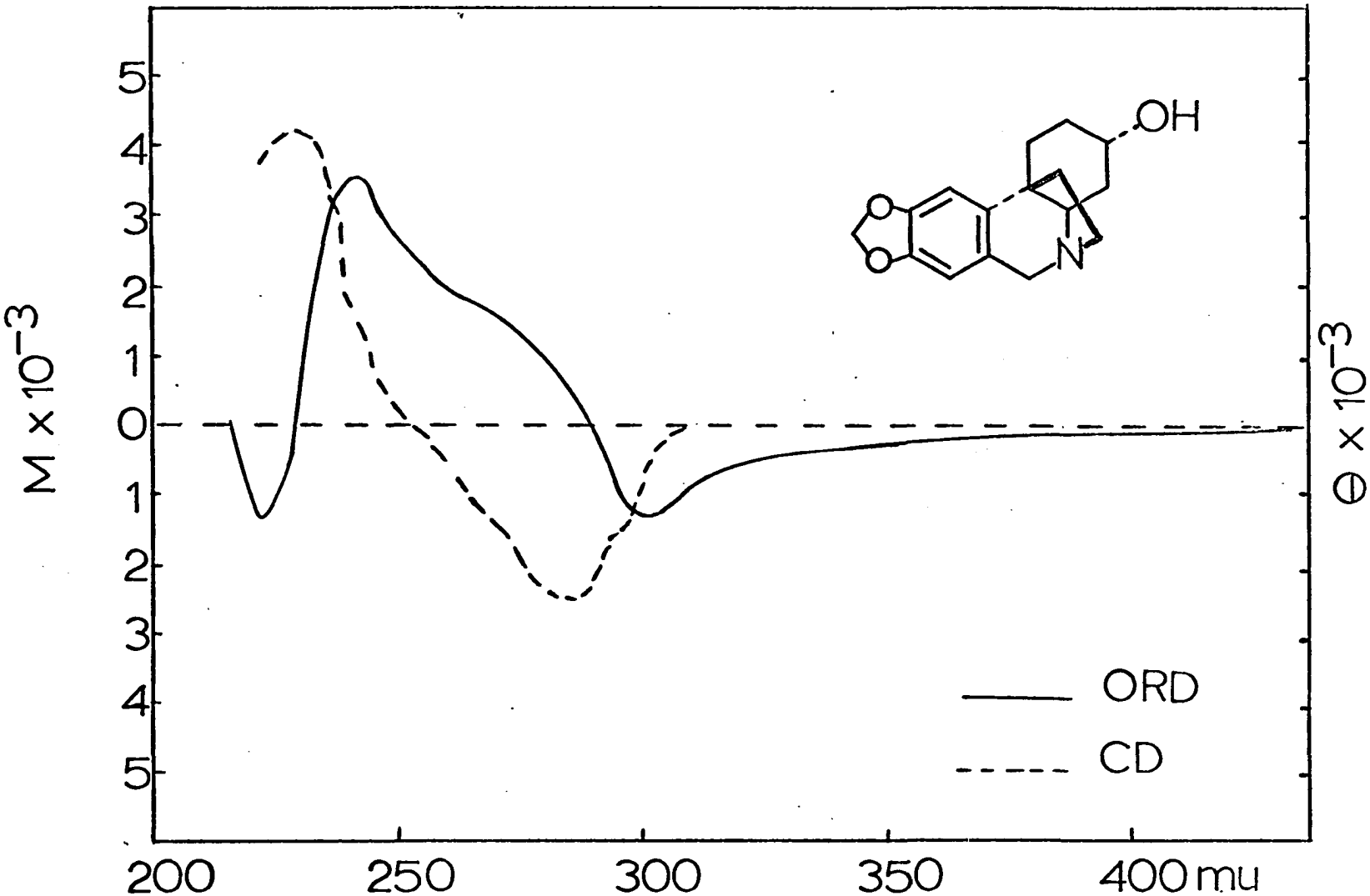


Fig. 3

ORD and CD of DIHYDROCRININE

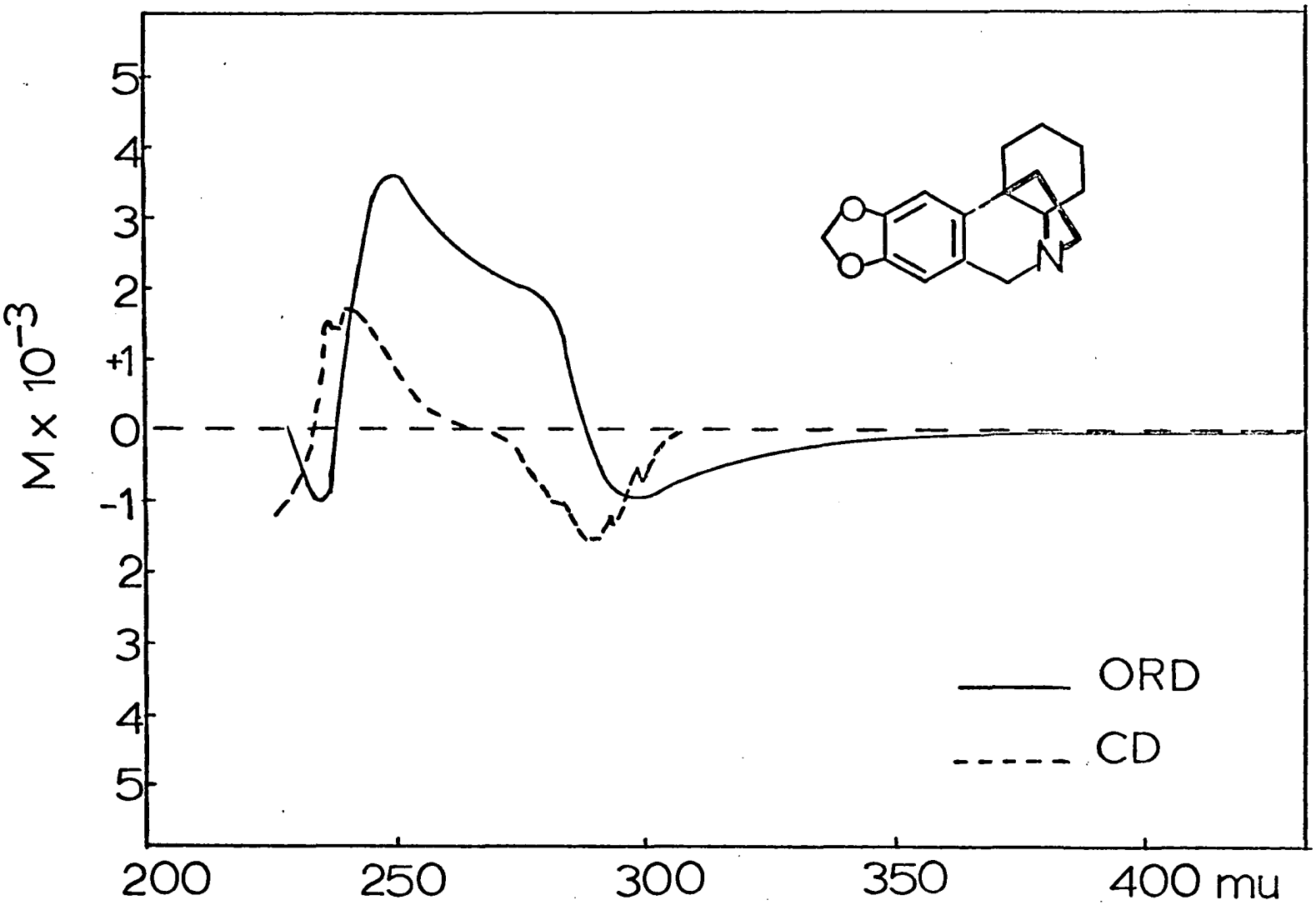
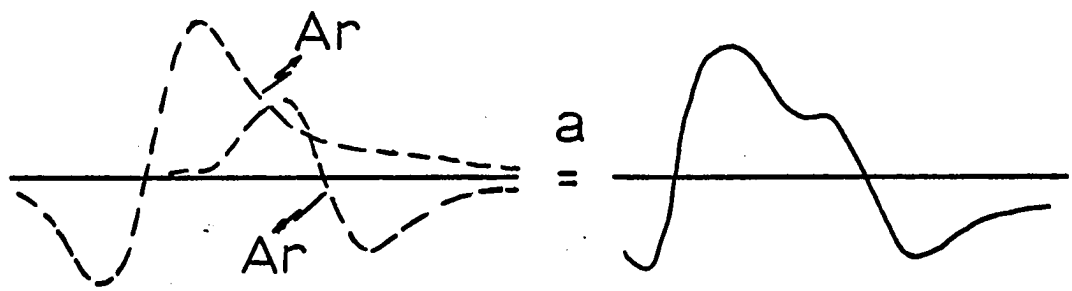
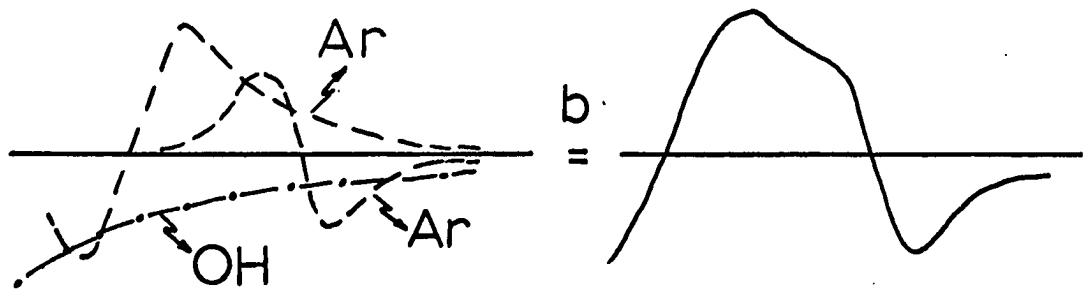


Fig.4
ORD and CD of CRINANE

portion of the spectrum. The two optically active benzene bands and the band due to the alcohol function provide the dispersions necessary to construct plausible theoretical ORD curves for these compounds. From chemical evidence cited previously it is known that the benzene ring and the alcohol group are cis to each other. If one assumes that the first (296 mu) benzene dispersion in (-) crinane and the hydroxyl group dispersion of crinine are of the same sign, the ORD curve of crinine may be constructed by simply superimposing the large hydroxyl dispersion upon those due to the benzene bands. This procedure has been carried out for crinane and crinine and is shown in a and b below.



Theoretical Observed



240 295 mu 240 295 mu

The composite curves agree well with the experimental ones. The assignment of a negative sign to an α-OH is in accord with similar ones made in the steroid field. These assignments were made both for secondary and allylic alcohols (104, 105).

Careful scrutiny of the ORD curve of crinane reveals two pertinent facts. The shape of the curve is quite similar to that of crinine between 375 and 225 mu, which would tend to corroborate the statement that the Cotton effects arising from the two optically active benzene bands are the primary contributors to the dispersion curves in this region. The peak at 250 mu is much more pronounced in crinane than in crinine. This suggests that in crinane the main shape if the curve is derived from the two S-shaped dispersions of benzene as shown above. The decrease in amplitude of crinane relative to crinine is most likely due to removing the double bonds and hydroxyl group. This same decrease is apparent in analogous compounds of the morphine series (69). The dichroism curve of crinane is well defined and needs no additional comment.

Kuhn (106) and Moscowitz (107, 108) have developed equations from which it is possible to calculate a number of properties of optically active molecules. If the absorption and rotatory dispersion spectra are known for a given compound, an anisotropy factor (g) can be calculated for compounds with homogenous (isolated) absorption bands. The compound which Kuhn used as a model for his calculations was azido-

propionic-dimethylamide [$CH_3CHN_3CON(CH_3)_2$]. This molecule possesses absorption bands at 290 mu and ca. 205 mu. Kuhn calculated the contribution of the azide function to the total observed ORD curve from equation 1.

$$1.\quad M = 3723\, g_o E_{max} \frac{f}{f_o}\left[e^{-(f_o-f/\Theta)^2} \int_o^{\frac{f_o-f}{\Theta}} e^{x^2} dx - \frac{\Theta}{2(f_o-f)}\right]$$

where:

M = molecular rotation

g_o = anisotropy factor at f_o

f_o = frequency at the center of the absorption band

E_{max} = value of the molecular absorption coefficient corresponding to the center or the absorption band

E = absorption coefficient of racemic substance for ordinary light

f = frequency at which rotatory contribution (ORD) is a maximum

Φ = maximum rotatory contribution at

Θ = parameter related to the half width of an absorption band by f" = 1.665

f" = half width of an absorption band

$E_l - E_r = \Delta E$ = circular dichroism.

Kuhn defines the anisotropy factor, g_o, as shown in equations 2 and 3.

$$2.\quad g_o = \frac{\Phi}{2014(E_{max})} \qquad 3.\ g_o = \frac{E_l - E_r}{E} = \frac{\Delta E}{E}$$

4. $$E = E_{max}\, e^{-(f_o - f/\theta)^2}$$

It can be seen that the anisotropy factor is nothing more than the ratio of the differential absorption of right and left handed light to the extinction coefficient, which was shown previously to be one of the limiting factors in making dichroism measurements. Therefore g_o has no special significance and shall be used only as a convenient term.

The Amaryllis alkaloids, having absorption bands at 295 mu and 240 mu, should prove amenable to the same treatment which Kuhn used with azidopropionic-dimethylamide. The following calculations have been carried out for crinine and crinane. Both of these compounds have a well defined 296 mu absorption band and both, as do all of the alkaloids of this ring system, have rigid structures. This latter fact is important as it eliminates any conformational and rotational changes which would otherwise have to be considered. Equation 2 was used to calculate g_o for crinine and crinane. This was then substituted into equation 3 ($E = E_{max}$ for the Amaryllis) and a CD maxima was calculated for each compound at f_o. In order to check the validity of such calculations eight other compounds were examined. The results are shown in Table 1.

If the individual dispersions of the benzene bands were completely separated, good agreement between the calculated and observed CD maxima would be expected. The disagreement between the calculated and the

Table 1. Calculated CD maxima for selected alkaloids

Compound	Calculated CD	Observed CD	% Error
Crinine	- 9,250	- 7,300	+ 20
Crinane	- 1,120	- 1,500	- 25
Powelline	- 1,800	- 1,620	+ 5
Powellane	+ 1,230	+ 850	+ 30
Vittatine	+ 9,300	+ 7,900	+ 20
Crinamine	+ 14,700	+ 12,000	+ 22
6-Hydroxycrinamine	+ 10,700	+ 9,600	+ 10
Haemanthidine	+ 7,800	+ 9,600	- 20
Haemanthamine	+ 9,600	+ 11,900	- 20
Buphanidrine	- 1,430	- 1,200	+ 7

observed values for (-) crinane indicate that the aromatic dispersions overlap by about the same amount as the calculated and observed CD maxima are in error, i.e., 25%. From this and the knowledge that the two bands are opposite in sign (antipodal) it becomes apparent that the observed CD for crinane must be larger than the calculated. In the CD spectrum the problem of overlapping bands is less serious and a much better reflection of the actual shape of the curve can be obtained. The data for crinine shows that the calculated value is 20% larger than the observed. This is in accord with assigning a negative sign to the hydroxyl dispersion in this compound.

Before these calculations were made it was postulated that crinamine (Fig. 20) would have a much larger dispersion at 304 mu than crinine if the allylic methoxyl group at C_3 and the secondary hydroxyl group at C_{11}

had dispersions of the same sign, were adding to the 296 mu benzene dispersion. The data in Table 1 show that this is the case. Haemanthamine has a much smaller dispersion than crinamine at 304 mu, and this may be accounted for by the fact that these compounds are epimeric at C_3. In haemanthamine (Fig. 19) the allylic methoxyl group subtracts from the aromatic dispersion as is evident from Table 1. It should also be noticed that the observed CD for both compounds are very similar, emphasizing the fact that the dichroic ellipticities are not subject to the effects of "tailing" due to the allylic hydroxyl or methoxyl groups.

The next calculations carried out derived the shape and amplitude of the 296 mu aromatic absorption band when separated from dispersions of other chromophores. Equation 1 was used to do this, and the results are shown for crinine and crinane in Figures 5 and 6. The results are compared with the actual experimental data in Tables 2 and 3. In these calculations the value for g was taken from CD data, and f" from the equation $f'' = 1.665\Theta(109)$.

It is obvious from the table that the results are not as good as expected in the region of maximum dispersion, i.e., 300 mu to 320 mu. The constant 3723, which Kuhn used in the azidopropionic-dimethylamide calculations, should be most correct for this compound. Since it is more than likely that the electronic structures of the chromophores giving rise to the dispersions in Kuhn's compound are different than in the Amaryllis alkaloids, it was decided to derive a constant which

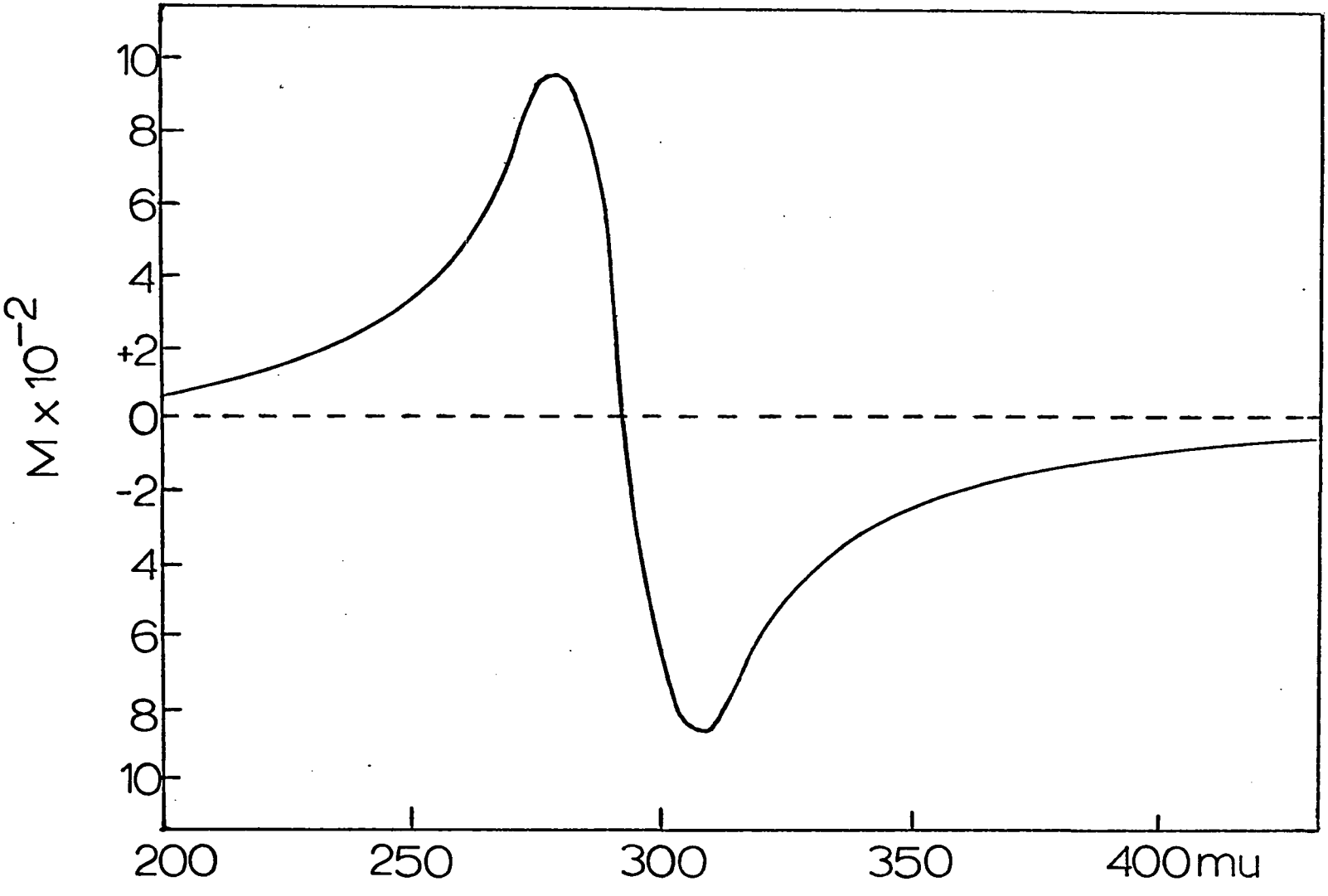


Fig. 5

CALCULATED DISPERSION of CRINANE

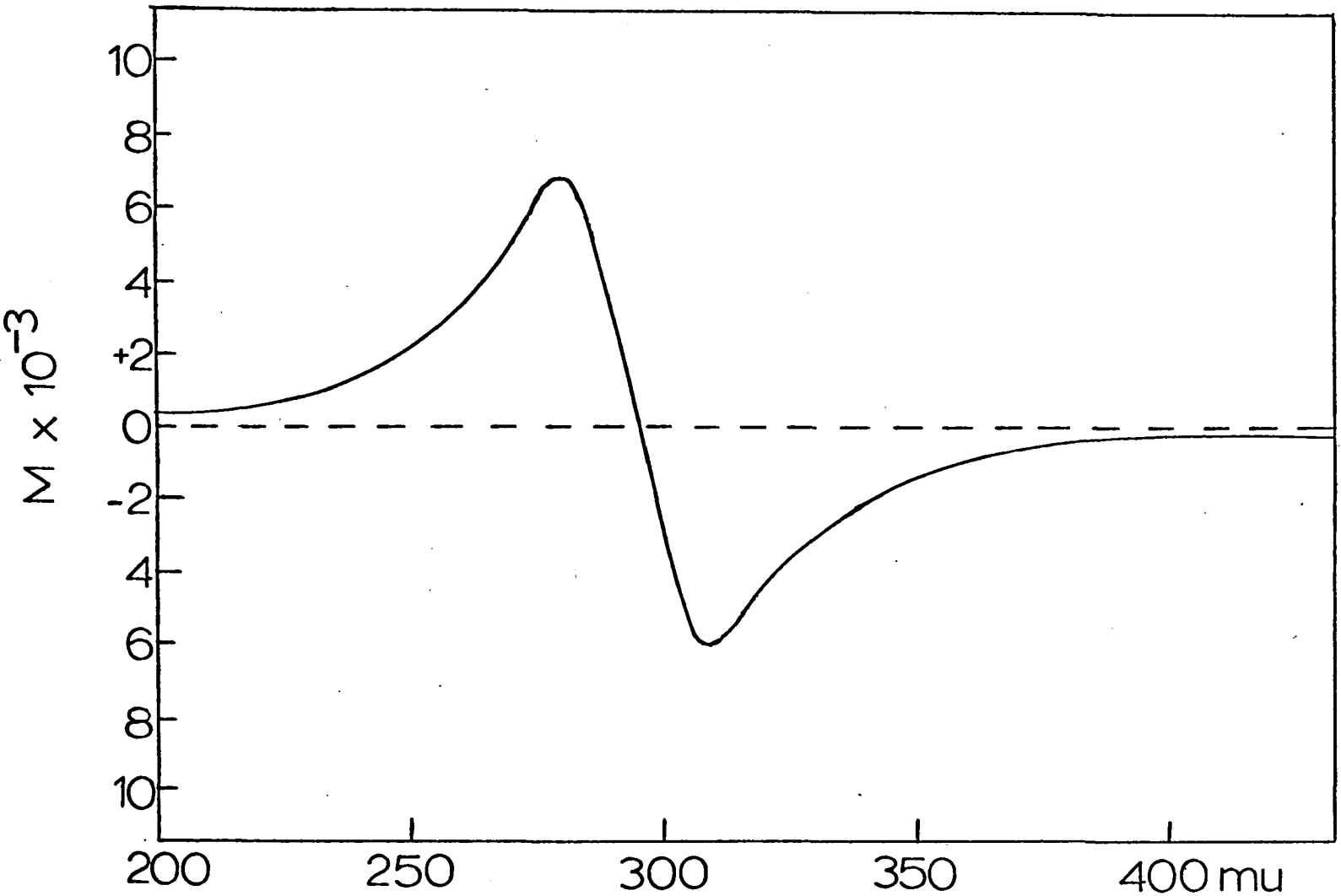


Fig.6

CALCULATED DISPERSION of CRININE

Table 2. Calculated rotatory dispersions for crinane at 296 mu of Kuhn's method

Wave length (mu)	Calculated value of M	Observed value of M
350	- 240	- 140
340	- 300	- 165
330	- 430	- 220
320	- 640	- 440
310	- 870	- 890
300	- 650	- 680
290	+ 450	+ 130
280	+ 970	+ 1770
270	+ 720	+ 2170
260	+ 440	+ 2800
250	+ 310	+ 4200

Table 3. Calculated rotatory dispersions for crinine at 296 mu of Kuhn's method

Wave length (mu)	Calculated value of M	Observed value of M
350	- 1820	- 650
340	- 2360	- 810
330	- 3400	- 1220
320	- 4970	- 1700
310	- 6000	- 3900
300	- 2870	- 5600
290	+ 3800	- 3400
280	+ 6600	+ 8130
270	+ 4780	+ 8900
260	+ 3000	+ 9300
250	+ 1950	+10500

would be more meaningful in the alkaloidal series. In order to do this, it becomes necessary to use the data compiled in the calculations of the CD maxima done previously. The per cent error found in the calculated versus the observed values of the CD maxima reflect the effect of the 240 mu benzene band on the 296 mu band in crinane. In compounds possessing chromophores other than aromatic the per cent error reflects these adding to or subtracting from this same 296 mu band. In order to include these factors in any new constant which would be general for the 5, 10b-ethanophenanthridine alkaloids the following equation was used; (Eq. 5)

$$5.\quad M_{max} = M_{obs} \pm M_{obs}(n) = K g_o E_{max} \frac{f}{f_o}\left[e^{-q^2}\int_o^q e^{x^2}dx - \frac{\Theta}{2(f_o+f)}\right]$$

M_{max} is equal to the observed value of the first dispersion in a given compound plus or minus this observed value times the per cent error. This is shown in Equation 6.

$$6.\quad \text{where:}\quad M_{max} = M_{observed} \pm M_{observed}(n)$$

n = per cent error.

Since this calculation is based on the maximum value of the dispersion in the compound under scrutiny, the integral term can be set at its maximum value. This value, obtained from National Bureau of Standards Table Number 55, is 0.54. An average value of the term $\Theta/2(f_o+f)$ was

found to be 0.01. Actually the final answers would be changed very little if this last term were neglected. The constant (K) calculated in the above way, should represent the value found for a completely isolated absorption band which reaches its maximum rotational value at some frequency f and where M = 0 at f_o. Experimentally M ≠ 0 at f_o and f is not at Kuhn's f_*. Both are displaced according to the degree of band overlap. This displacement is small in crinane, but becomes larger in more substituted compounds. Constants were calculated for four compounds and these plus an average value with its average deviation are shown in Table 4.

Table 4. Calculated constant for dispersion equation

Compound	Calculated constant
Crinane	4850
Crinine	3950
Crinamine	3730
6-OH crinamine	4780
	Average 4325 ± 490

The error in these values is 11%, which is of the same order of magnitude found experimentally and as good as can be expected for calculations done by hand. It should be possible to refine these calculations by feeding the parameters to a computer and thereby obtain the best possible result. However, at this time it would be difficult to justify

the expenditure of time and money involved in this type of approach. As will be shown, the constant obtained affords plausible results.

Moscowitz (109) has used a slightly different approach in developing equations which can be used to calculate partial dispersions. The final equations which Moscowitz arrives at are shown in 7 and 8.

$$7.\ [\phi]^{\circ}_{k} = \frac{2[\theta^{\circ}_{k}]}{\sqrt{\pi}}\left[e^{-(\lambda-\lambda^{\circ}_{k}/\Delta^{\circ}k)^{2}}\int_{o}^{\lambda-\lambda^{\circ}_{k}/\Delta k} e^{x^{2}}dx - \frac{\Delta^{\circ}k}{2(\lambda\ \lambda^{\circ}_{k})}\right]$$

$$8.\ [\phi]_{k} = \frac{R_{k}}{0.696\times10^{-42}}\ \frac{\lambda^{\circ}_{k}}{\Delta^{\circ}_{k}}\frac{2}{\pi}\left[e^{-(\lambda-\lambda^{\circ}_{k}/\Delta^{\circ}k)^{2}}\int_{o}^{\lambda-\lambda^{\circ}_{k}} e^{x^{2}}dx - \frac{\Delta^{\circ}k}{2(\lambda+\lambda^{\circ}_{k})}\right]$$

where:

$[\theta^{\circ}_{k}]$ = dichroism at λ_{max}

λ = wave length where calculation being made

λ°_{k} = wave length at center of absorption band

$\Delta^{\circ}k$ = half width of absorption band at half height

$[\phi]^{\circ}_{k}$ = dispersion (molecular rotation) at wave length where calculation being made

R_{k} = rotational strength $\equiv 0.696 \times 10^{-42} \sqrt{\pi}\, O^{\circ}_{k}\, \frac{\Delta^{\circ}k}{\lambda^{\circ}_{k}}$

Either one of these can be used to calculate the partial dispersion of the 296 mu benzene band. Equation 8 was chosen in the present work as it involved the calculation of R_{k}, the rotational strength. The rotational strength simply guages the intensity of a particular dichroism

and says nothing more than the dichroism of a given band is equal to its molar extinction coefficient times some constant. It was of interest to compare the rotational strengths calculated for these aromatic chromophores with those calculated for a number of ketone chromophores. Since the values of the rotational strengths are very small, reduced rotational strengths [R] are tabulated in Table 5. The reduced rotational strength is related to the rotational strength as shown in Equation 9.

$$9. \qquad [R] = (100/u_o u_d) R_K \cong 1.08 \times 10^{40} \cdot R_K$$

where: u_o = magnetic dipole moment in Bohr magnetrons

u_d = electric dipole moment in Debyes.

Table 5. Calculated reduced rotational strengths

[R] (aromatic)			[R] (carbonyl)	
Crinine	-	11.2	2,2,5 trimethylcyclohexanone	+ 6.7
Crinane	-	1.18	2,2 dimethylcyclohexanone	+ 1.8
Powelline	-	2.07	trans-9-methyl-3-decalone	- 3.6
Powellane	+	1.25	cis-9-methyl-6-decalone	+ 0.73

In general it seems that the rotational strengths of the aromatic and carbonyl chromophores are comparable. When applied to the 296 mu benzene band, Equation 8 gives results which are in good agreement with those obtained using the constant derived for the Amaryllis and used in

Kuhn's equation. A comparison of these results is made in Tables 6 and 7, and the curves from the calculated constant are shown in Figures 7 and 8. It should be noted from the tables that the maximum rotational values for crinane come at the same wave lengths for both the calculated and observed cases. This is not the case in the crinine calculations. This discrepancy is due probably to a shift in the crossover point of the experimental ORD curve caused by the additional hydroxyl dispersion. These calculations support the hypothesis that the 296 mu dispersion is decreased in the actual ORD spectra of the 5, 10b-ethanophenanthridine alkaloids because of its proximity to an oppositely signed ca. 240 mu benzene band.

Table 6. Calculated dispersions of crinane at 296 mu of Moscowitz's method

Wave length (mu)	Calc. const. (4325)	Moscowitz	Observed
350	M = - 280	M = - 310	M = - 140
340	- 340	- 380	- 165
330	- 500	- 520	- 220
320	- 740	- 770	- 440
310	- 1020	- 1040	- 890
300	- 650	- 635	- 680
290	+ 525	+ 500	+ 130
280	+ 1120	+ 1020	+ 1770
270	+ 835	+ 730	+ 2170
260	+ 510	+ 430	+ 2800
250	+ 350	+ 390	+ 4200

Table 7. Calculated dispersions of crinine at 296 mu of Moscowitz's method

Wave length (mu)	Calc. const. (4325)	Moscowitz	Observed
350	M = - 2140	M = - 1810	M = - 650
340	- 2800	- 2300	- 810
330	- 4050	- 3380	- 1220
320	- 5900	- 5400	- 1700
310	- 7100	- 7400	- 3900
300	- 3400	- 3060	- 5600
290	+ 4470	+ 4470	- 3400
280	+ 7850	+ 7000	+ 8130
270	+ 5650	+ 4800	+ 8900
260	+ 3500	+ 3000	+ 9300
250	+ 2300	+ 2100	+10500

The agreement between Kuhn's and Moscowitz's equations is good in crinine and fair in crinane. The agreement between the values obtained from the constant calculated for the Amaryllis and Moscowitz's equation is good in crinane and fair in crinine. In effect all three methods give tenable results in view of the approximations used and the errors inherent in the method. It may be argued that, since the calculated constant was derived from parameters specific for the Amaryllis, these results should be more meaningful. Both approaches use the concept of rotational strength but Moscowitz's equations use directly the value of experimental CD measurements. Since these measurements are free from the interferences which arise in the ORD spectra, the numbers obtained from this method are probably better than those obtained from Kuhn's equations. This does not mean that these are correct in the absolute

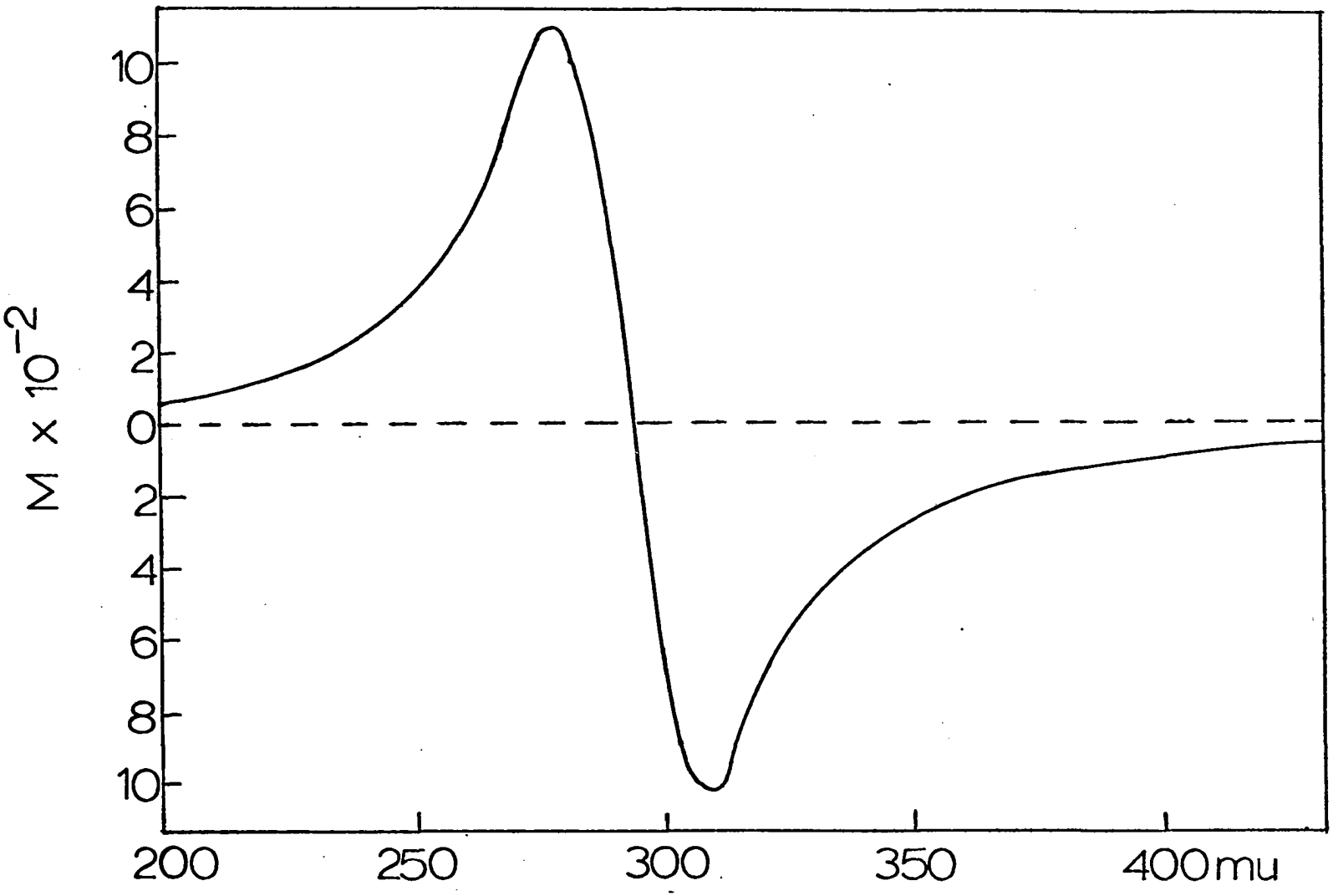


Fig. 7

CALCULATED DISPERSION of CRINANE

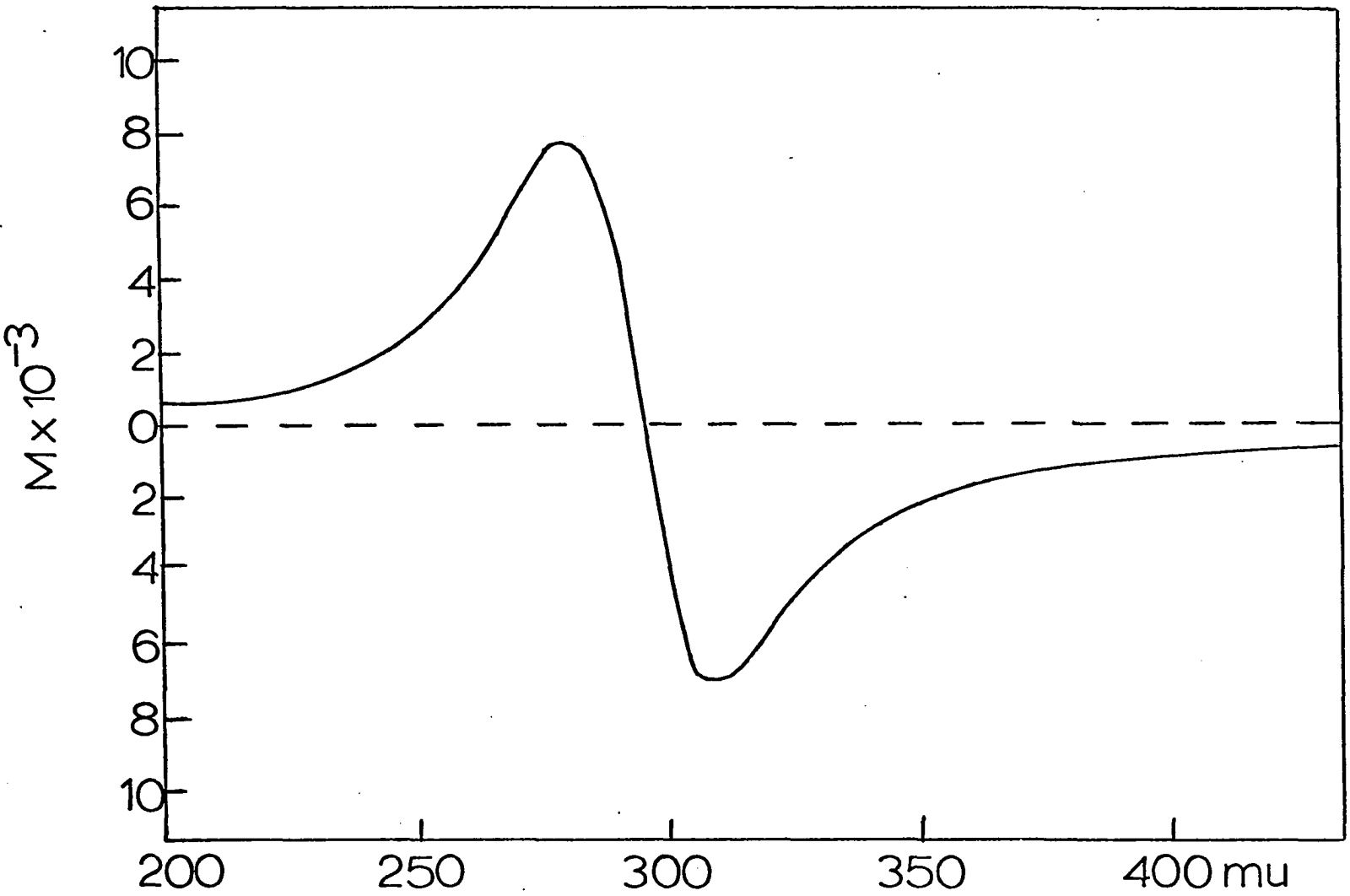


Fig. 8

CALCULATED DISPERSION of CRININE

sense. What the above calculations attempt to do is set up a standard whereby the amount of tail overlap in the ORD can be measured. If this can be determined, it should then be possible to calculate the dispersions of chromophores which cannot be measured directly. The standard chosen is crinane. Since the dispersion of the 296 mu band is now known, that of the 240 mu band can be calculated. A method for doing this is shown in Equation 10 and the results are shown in Figure 9.

10. $$[M]_{obs} = [M]_{296} + [M]_{240} + [M]_{B}$$

where:

M_{obs} = observed ORD spectra

M_{296} = dispersion of the 296 mu benzene band

M_{240} = dispersion of the 240 mu benzene band

M_{B} = background curve.

Included in the background term is the carbon at position 5 and the dispersion arising from the molecule as a dissymmetric chromophore. The background term does not include any functional groups, these are represented by individual terms such as $[M]_{AA}$ for the allylic alcohol group. This is given below for crinine.

$$[M]_{obs} = [M]_{296} + [M]_{240} + [M]_{AA} + [M]_{B}$$

Since the first two right hand terms are known and the background cancels for any two equations, subtraction of the equation for crinane from the above gives the dispersion of the allylic alcohol chromophore. This is shown graphically in Figure 10.

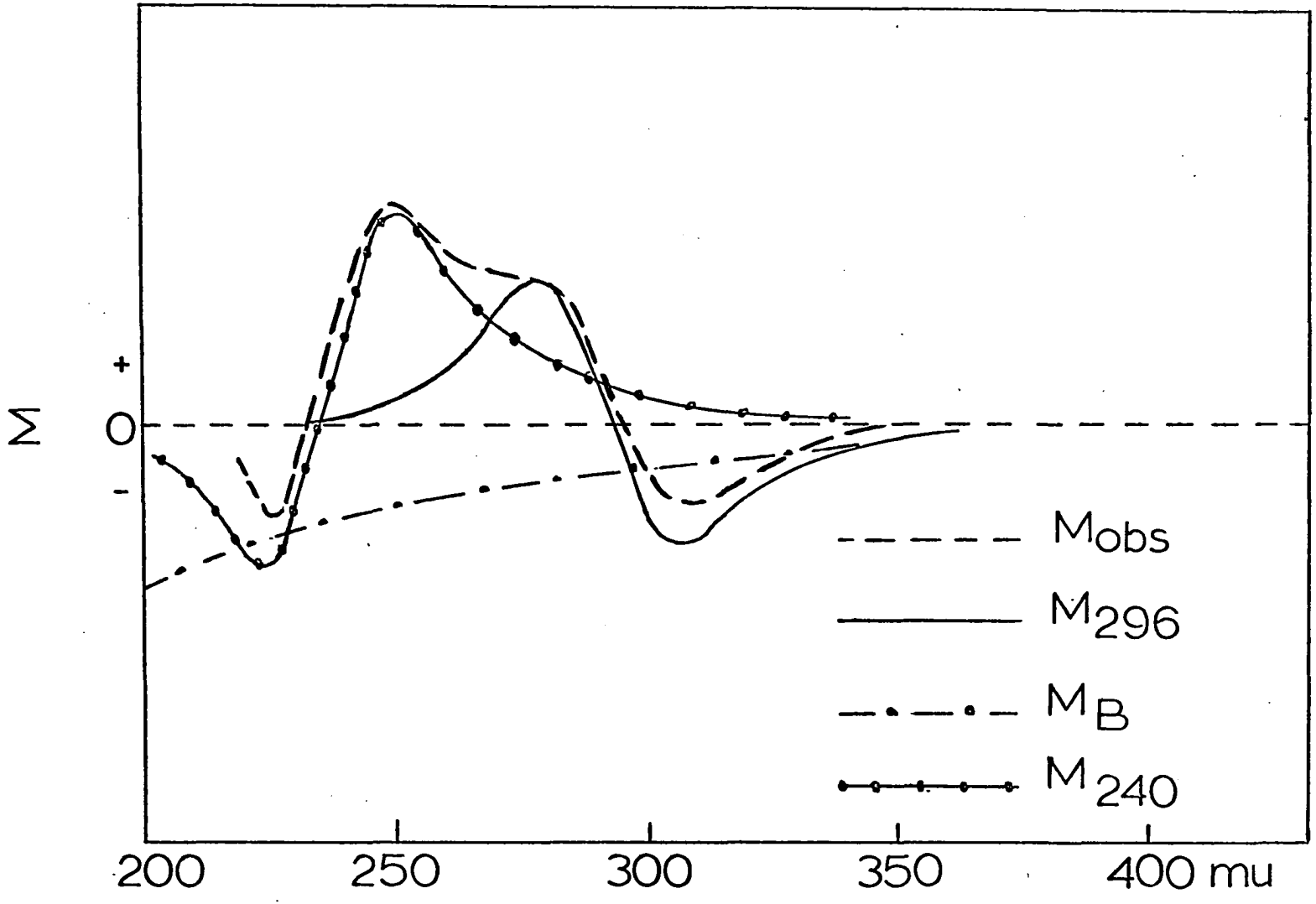


Fig.9

CONSTRUCTED ORD of CRINANE

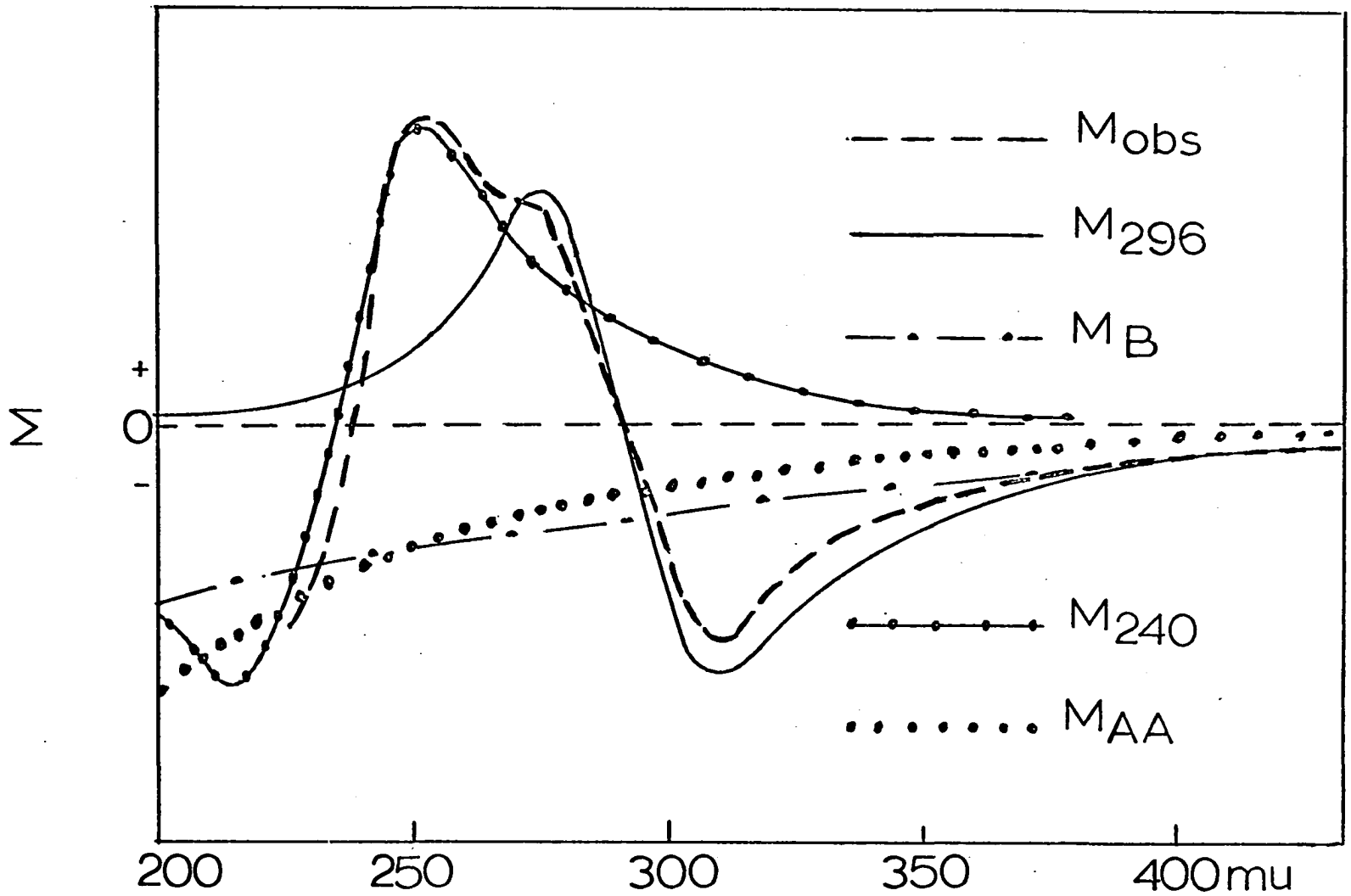


Fig.10

CONSTRUCTED ORD of CRININE

The size of the dispersions should not vary from compound to compound. Their apparent size varies depending upon the degree of substitution in the molecule, but the ratio of the two benzene bands remains constant for simple molecules. The dichroism of the isolated bands in crinane are equal to those in crinine times some constant. Once the relative sizes of the benzene dispersions are known it becomes possible in principle to know what contributions to the total dispersion curve are made by the various functional groups in any particular molecule. Examples of this were given previously for crinamine and haemanthamine.

The concept of deriving the dispersion of one compound from the known dispersion of another more simple molecule is not a new one. Klyne (61) describes a similar operation performed for keto steroids. In these cases however the curve of the entire keto compound was subtracted from that of the deoxo compound to obtain the keto group dispersion in an asymmetric environment. While this method provides much useful information about the general shape of the dispersion curve, it provides no insights into where one dispersion ends and another begins. It should be possible with the help of a computer to use both approaches and thereby learn more about optically active absorption bands in complex aromatic molecules. Moscowitz has carried out calculations of this type on some keto steroids.

The calculations outlined above can be used to obtain CD maxima from ORD data as was done in this case, or the reverse calculations can

be carried out. The former were attempted here since the number of instruments capable of measuring CD spectra directly is small. These calculations provide a practical way of obtaining an approximate CD spectra when no instrument is available. In theory ORD data obtained from CD curves would be much more reliable.

The ORD and CD spectra of (-) epicrinine and (-) dihydroepicrinine are shown in Figures 11 and 12. The trough at 304 mu in (-) epicrinine has a more slightly negative value than crinine, but the size of the dispersion in the 250 mu region of the spectrum is smaller than crinine by approximately 7000°. It is difficult to rationalize this phenomenon in any other way than to assign the β - OH in the allylic position a more negative dispersion than the α -OH in crinine. Examples of epimeric allylic alcohols having the same sign dispersion are known (69). This assignment agrees with that made previously by applying Mill's rule, however it is necessary to point out that this assignment is made from the differences in molecular rotations at 250 mu, not 589 mu. The rotational differences at 304 mu are small in these compounds and at 589 mu they would be even smaller. The fact that Mill's rule seems to work in these compounds most likely arises from the fact that the benzene dispersion is of the same sign as the -OH dispersion.

It has been shown that vittatine and crinine are complete enantiomers (110). The spectra of vittatine and its dihydro derivative shown in Figures 13 and 14 are antipodal to those of crinine and its dihydro

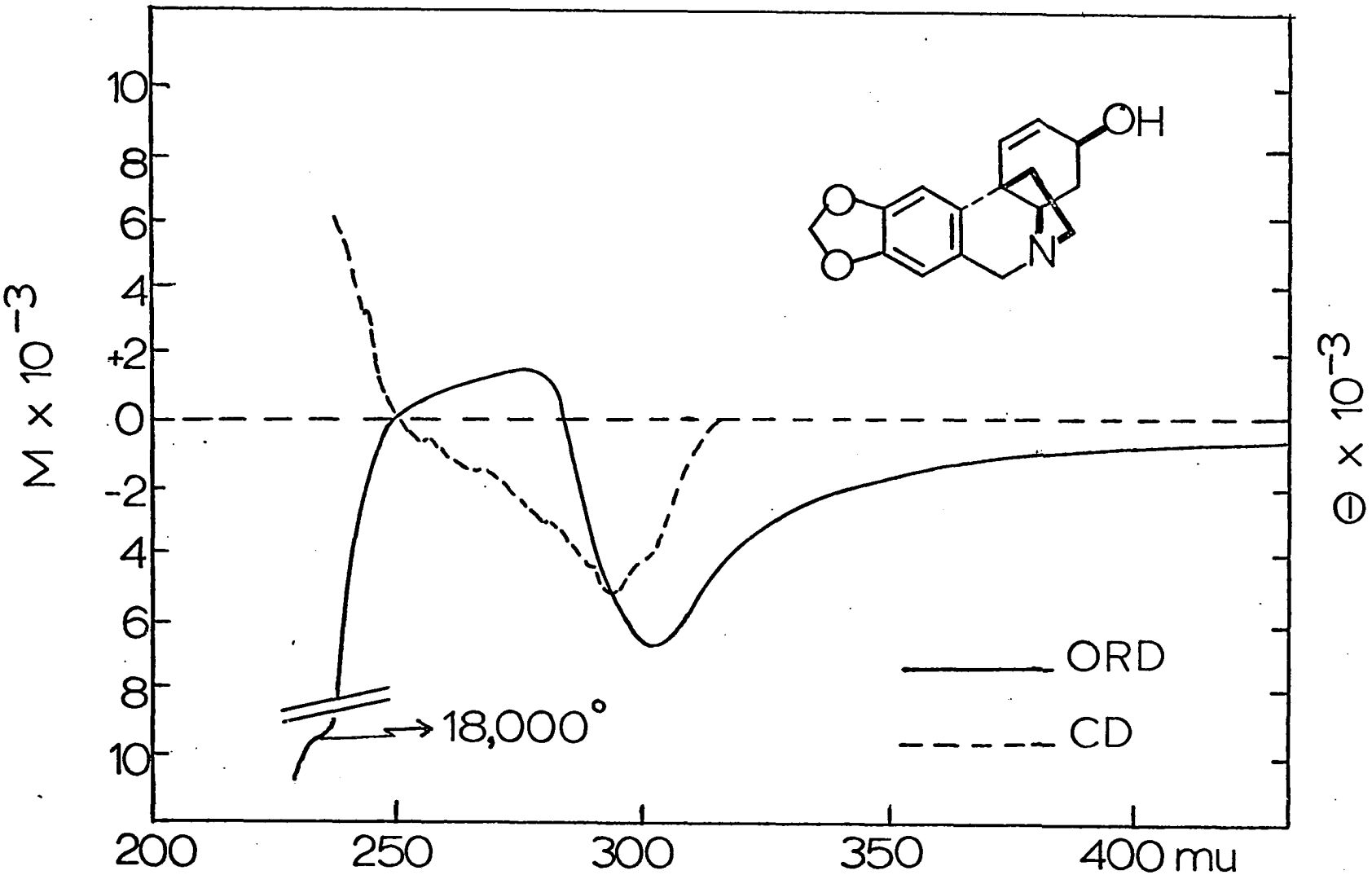


Fig.11

ORD and CD of EPICRININE

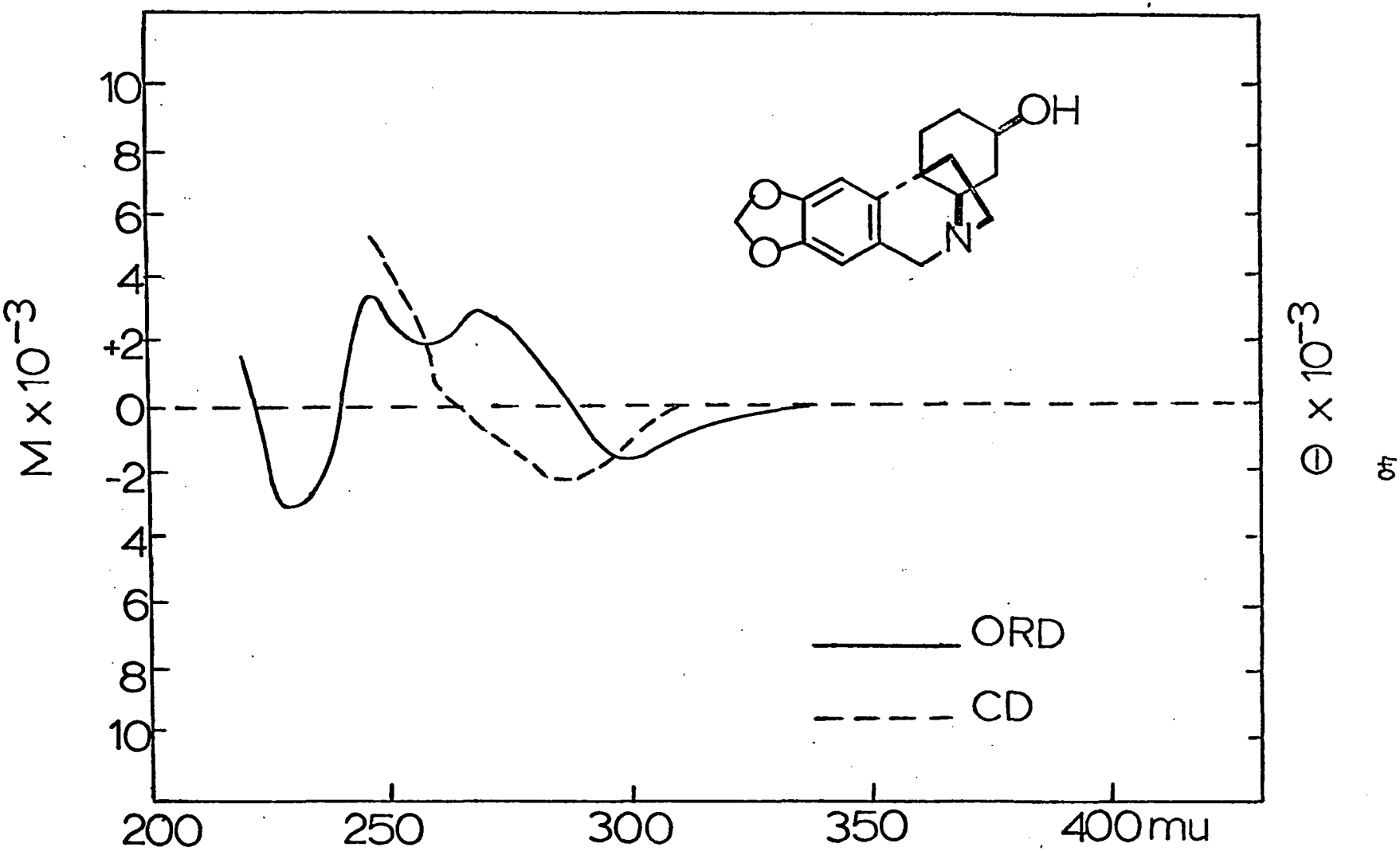


Fig. 12

ORD and CD of DIHYDROEPICRININE

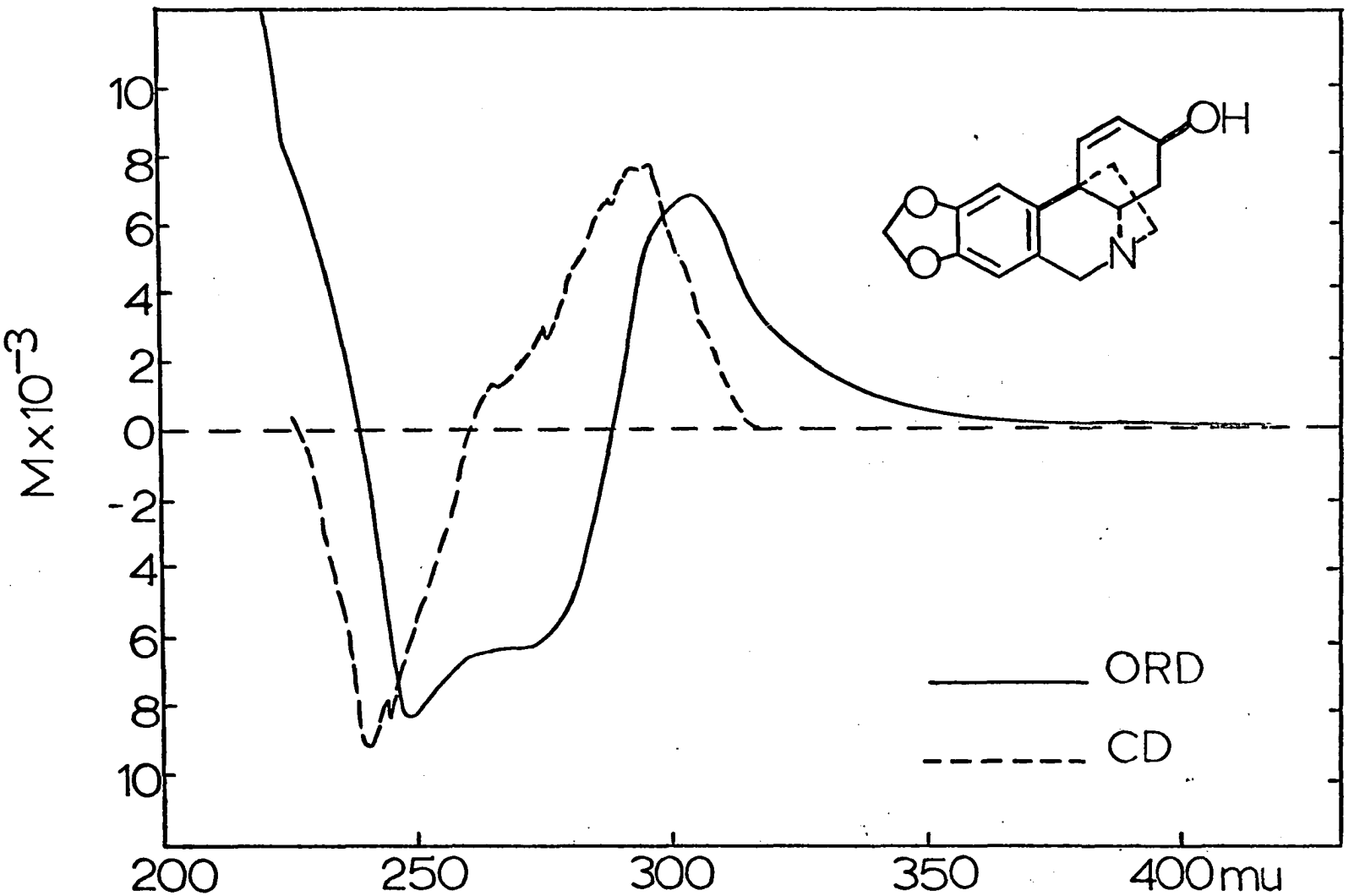


Fig.13

ORD and CD of VITTATINE

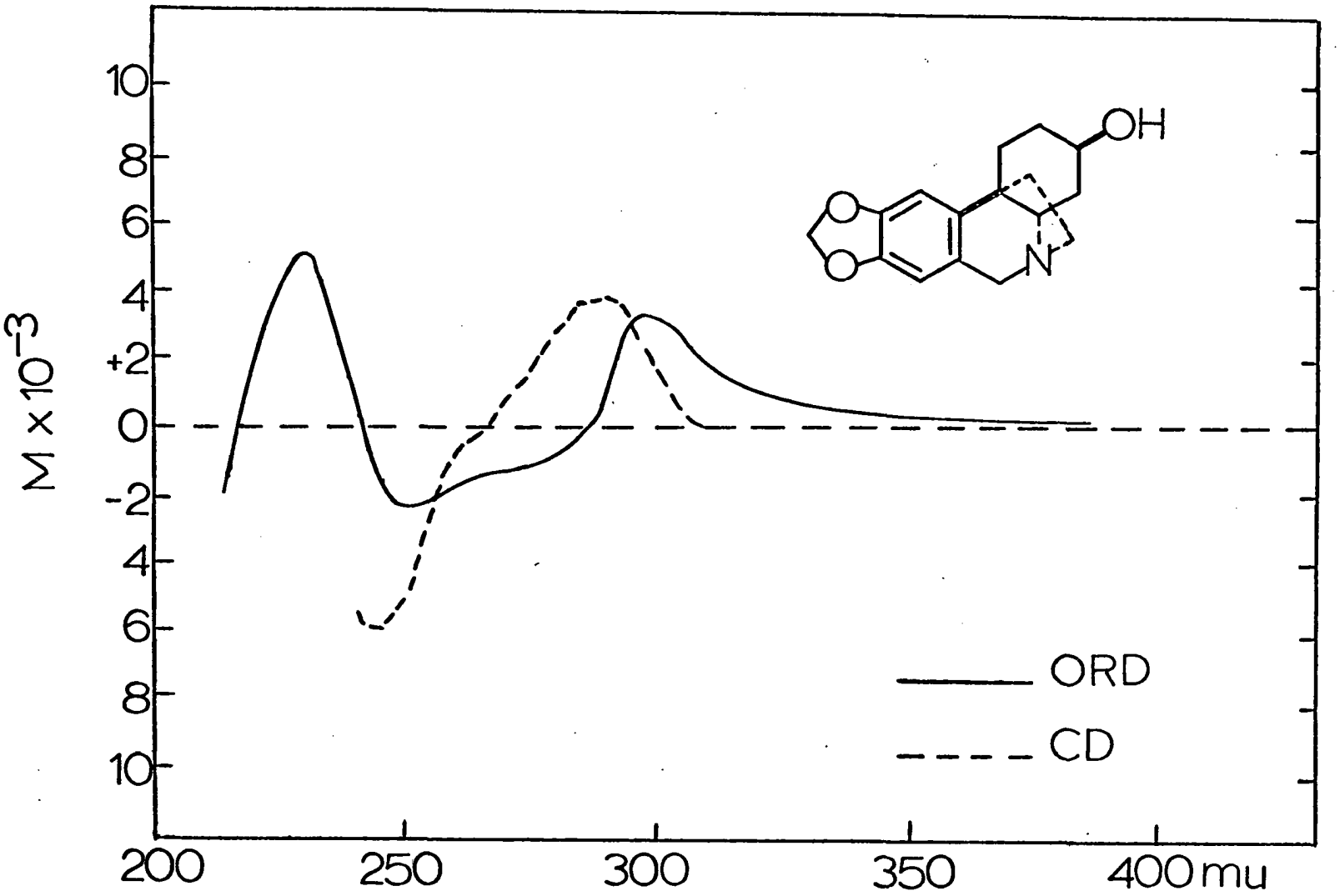


Fig.14

ORD and CD of DIHYDROVITTATINE

derivatives. A mixture of equal weights of vittatine and crinine afforded no dispersion between 450 and 215 mu. This demonstrates that the observed dispersions are not due to stray light or solvent effects, but to the optically active benzene chromophore (111, 112). During the course of this investigation an alkaloid, named alkaloid 16, was discovered in Pancratium maritimum L (113). Chemical investigations proved the gross structure to be as shown in Figure 15. The CD and ORD spectra suggested that alkaloid 16 and vittatine were very similar stereochemically. The positive maximum at 304 mu in the ORD spectrum has the same rotation and overall shape as vittatine. The rest of the entire spectrum is very similar to vittatine. The normal CD curve verifies that the main contribution to the curve is from the benzoid bands. Nuclear magnetic resonance data has shown that the substitution on the aromatic ring is dimethoxy rather than methylenedioxy (113). It has been postulated that ORD measurements can help to differentiate between these substitution patterns (114). Since the methylenedioxy group introduces a strain (69) in the benzene ring it can be anticipated that the dichroisms of aromatic rings so substituted will be larger than those containing methoxyl groups (115). A comparison of the maximum ellipticities of vittatine and alkaloid 16 support this postulate. This difference is not as evident in the ORD measurements because of the interfering tail dispersions.

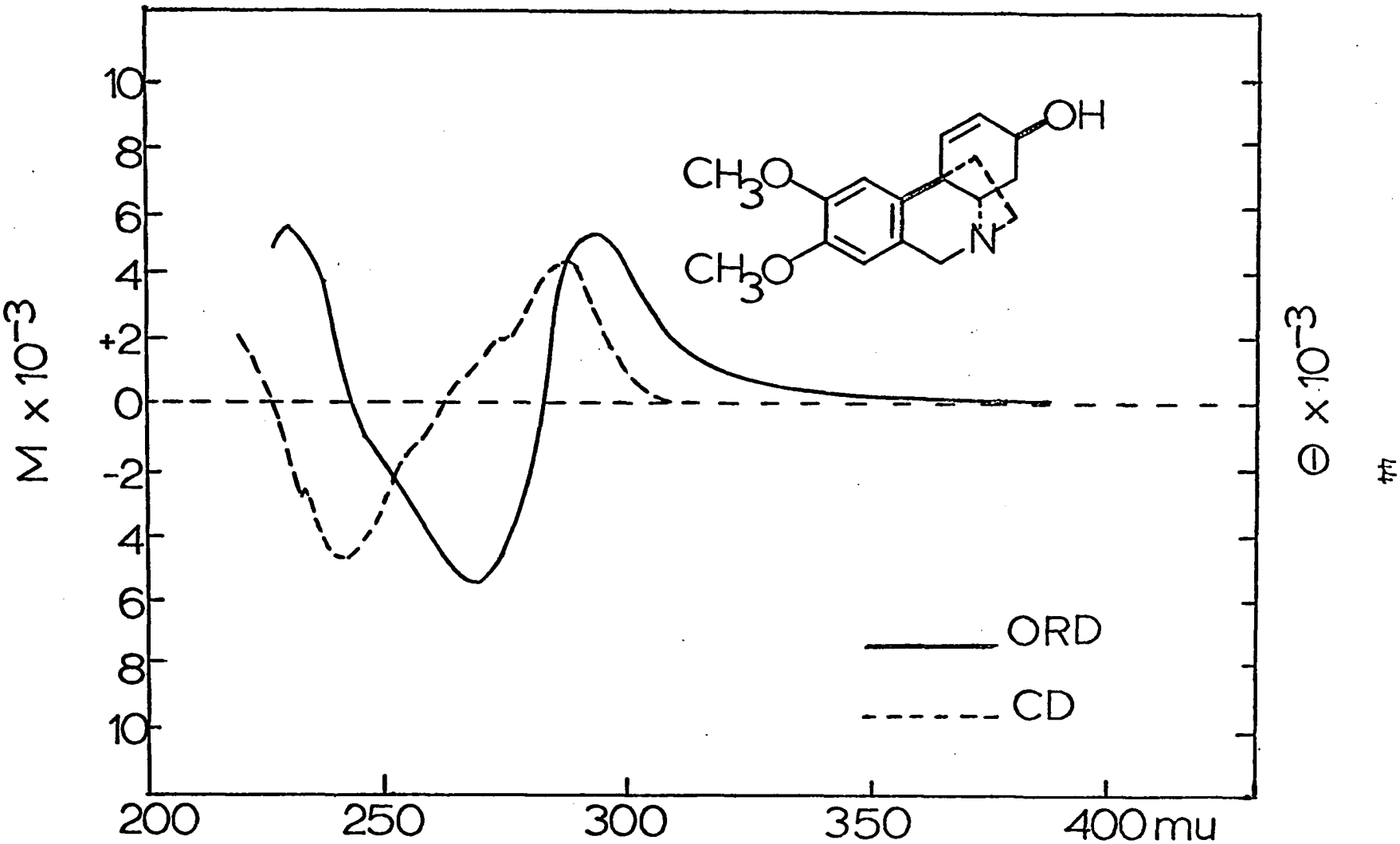


Fig 15

ORD and CD of ALKALOID 16

(+) Epicrinine (epivittatine) (Fig. 17) bears the same relationship to vittatine as epicrinine does to crinine. Arguements similar to those used to assign the relative stereochemistry of the allylic hydroxyl group in epicrinine can be used in epivittatine if the latter is assigned the more positive rotation.

Buphanisine (Fig. 18) is the methyl ether of crinine. Both the CD and ORD spectra of buphanisine are almost superimposable on those of crinine. The replacement of a hydrogen by a methyl group does not effect the amplitude of the dispersion curve. The contribution of the methoxyl to the overall electronic environment of the benzene chromophore is of the same order of magnitude as the hydroxyl group (116).

Haemanthamine (Fig. 19) differs from vittatine in the presence of a hydroxyl group at C_{11} in the former. The configuration of the hydroxyl has been assigned on the basis of a strong hydrogen bond to the pi-electrons of the double bond (117). As in vittatine, the allylic functional group at C_3 is <u>cis</u> to the phenyl group, and haemanthamine should give rise to a very similar dispersion. Comparison of the ORD spectra of vittatine and haemanthamine show that they are very similar in shape but slightly different in amplitude. The molecular rotation of vittatine at 304 mu is 6800°, while that of haemanthamine is 6350°. This difference is within experimental error and the presence of an 11-hydroxyl group does not give rise to a dispersion large enough to effect the spectrum of haemanthamine in this region. Comparison of the rota-

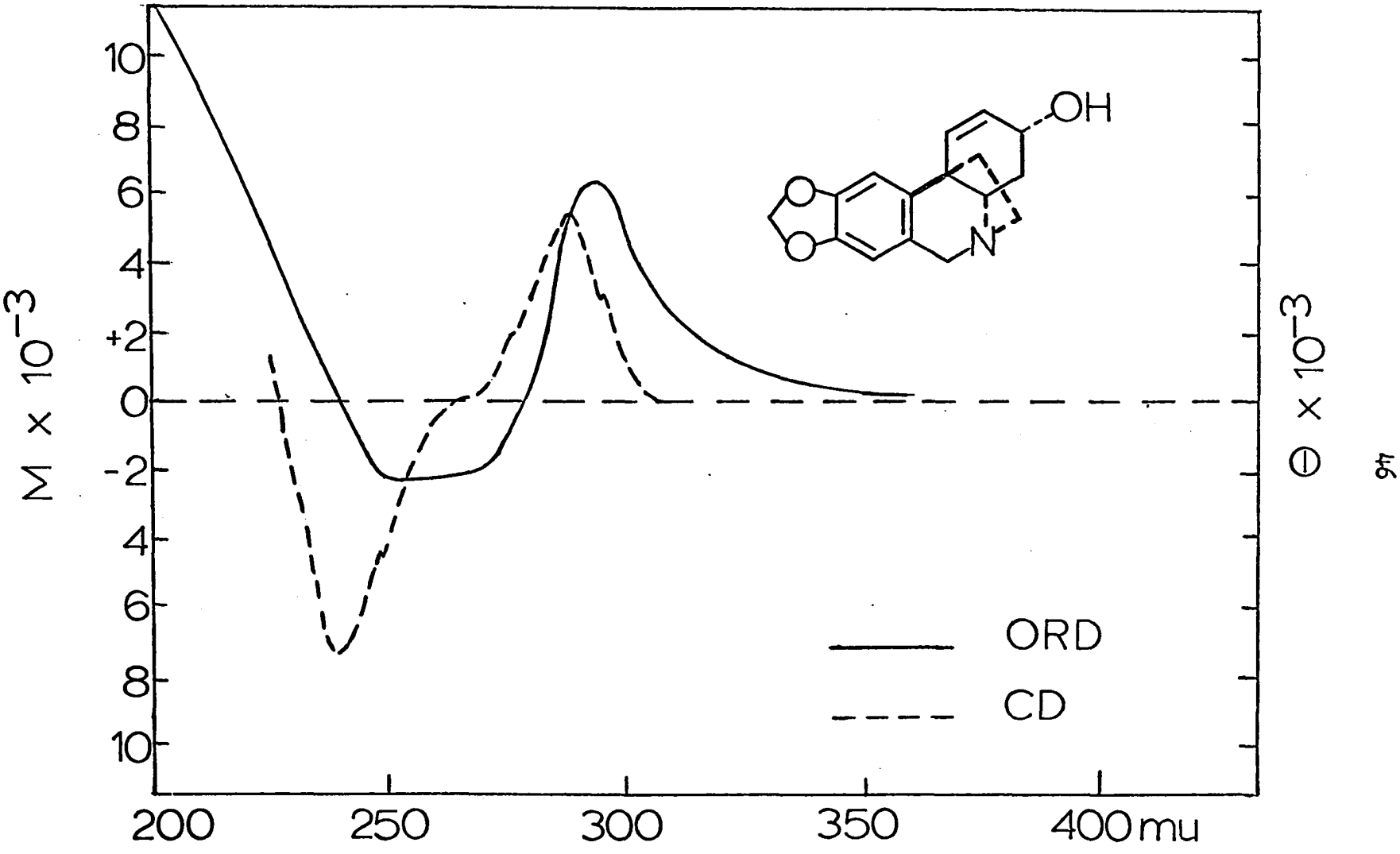


Fig.16-17

ORD and CD of EPIVITATTINE

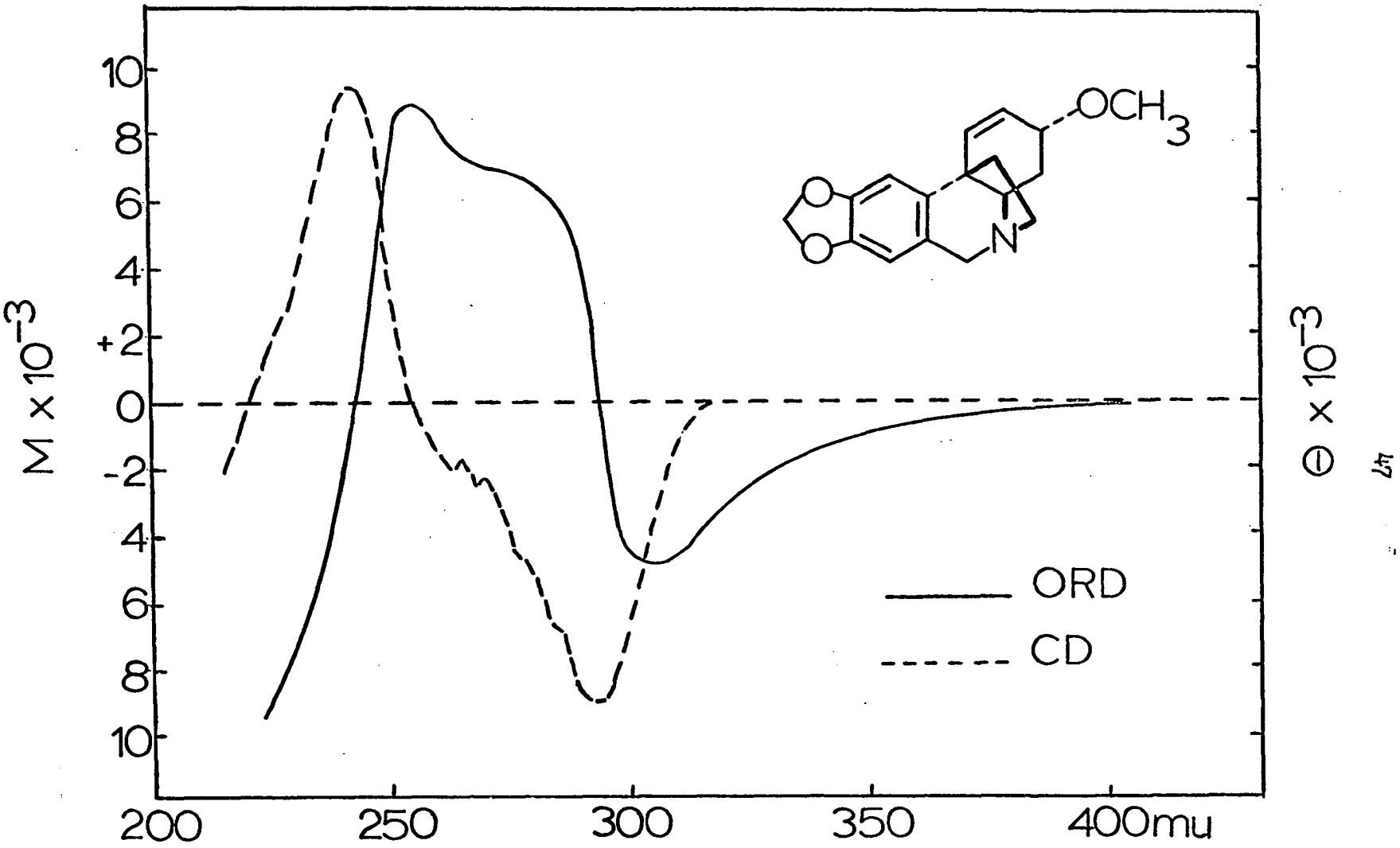


Fig.18

ORD and CD of BUPHANISINE

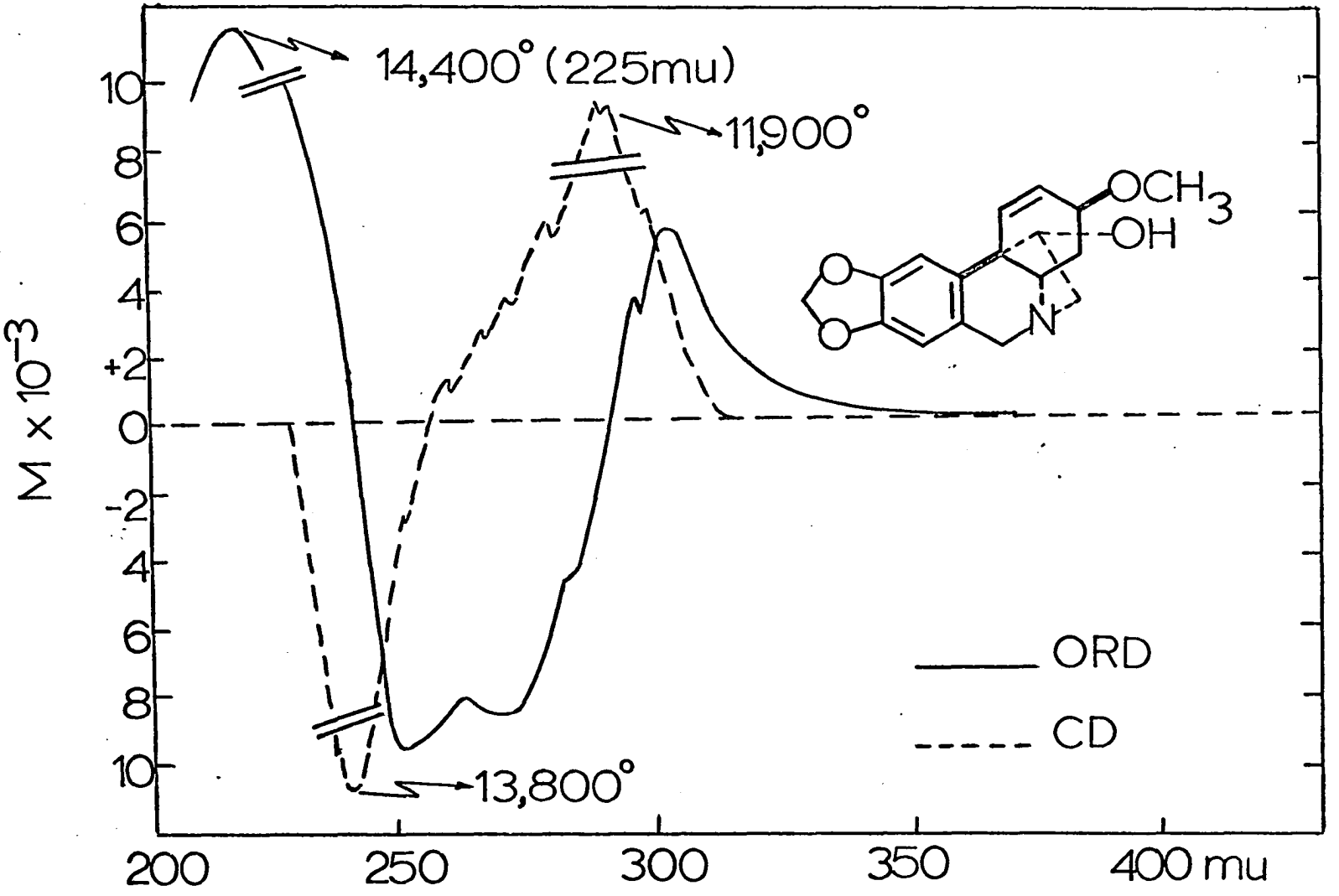
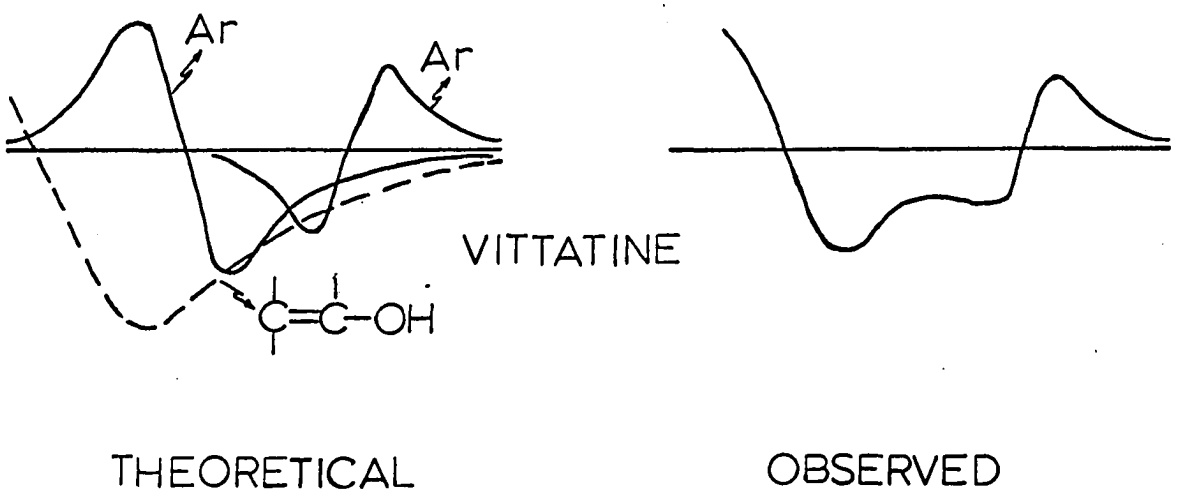
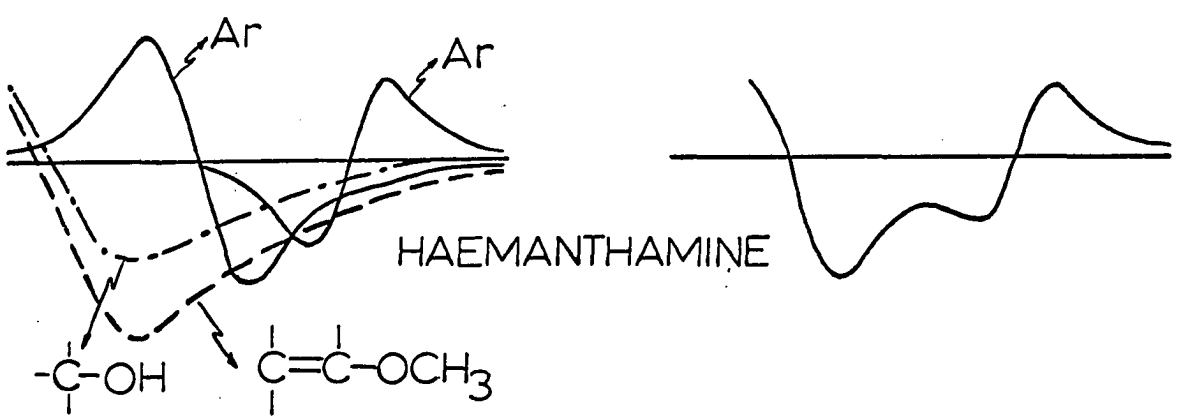


Fig 19

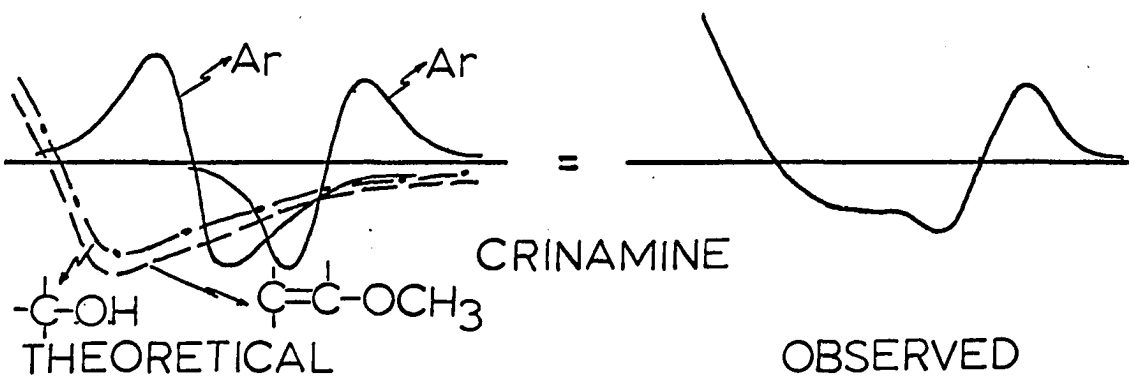
ORD and CD of HAEMANTHAMINE

tions at 250 mu affords a difference which is large enough (1100°) to be outside of the experimental limits, and can be used to assign a relative sign to the 11-hydroxyl dispersion. Addition of a negative dispersion to the total curve of vittatine results in the theoretical curve of haemanthamine shown below.





Crinamine (Fig. 20) has been shown to be the C_3 epimer of haemanthamine (117, 118). Comparison of the ORD spectra of crinamine, haemanthamine and vittatine demonstrate that the use of rotatory dispersion techniques can easily differentiate between allylic methoxyl groups either cis of trans to the phenyl group. The molecular rotation of crinamine at 304 mu is 8500°, while those of vittatine and haemanthamine are close to 6500°. The rotations at 250 mu are 9300°, 7200° and 2400° for haemanthamine, vittatine and crinamine respectively. Since the only difference between crinamine and haemanthamine is the configuration at C_3, the large molecular rotation difference can be attributed to a less negative dispersion of the allylic methoxyl group of crinamine than in haemanthamine. This is in agreement with Mill's rule for allylic alcohols. A theoretical spectra for crinamine can be constructed by adding a small negative dispersion to the dispersions in vittatine. The result is a spectra which agrees well with the experimentally determined one.



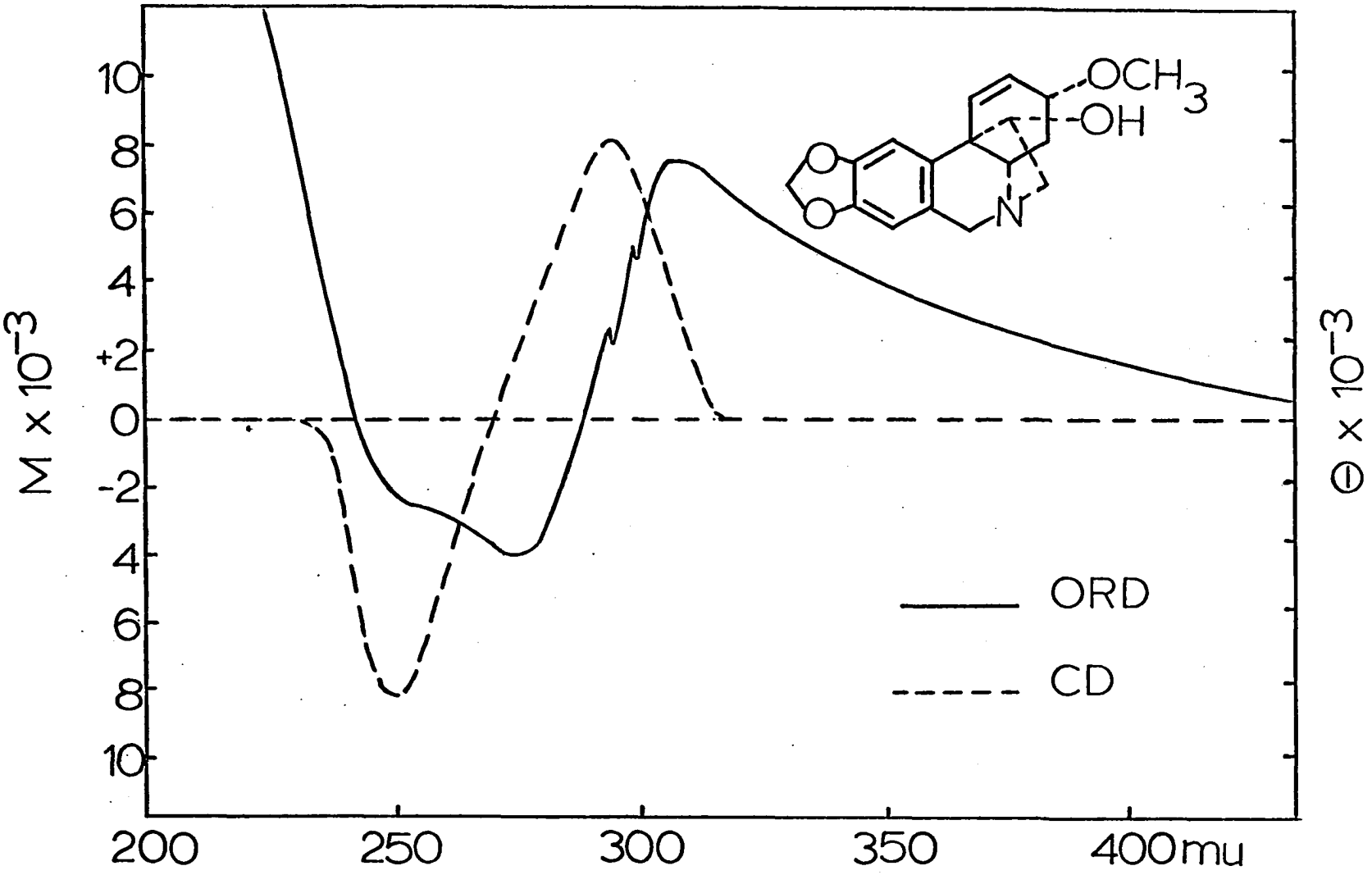


Fig.20

ORD and CD of CRINAMINE

Van Tamelen has used similar addition of rotatory dispersions to determine the stereochemistry of the alkaloid, emetine (93).

The CD spectra of crinamine, haemanthamine and vittatine are given with the ORD spectra and are normal in that all three compounds afford antipodal ellipticities at the proper wave lengths. The CD maxima of crinamine and vittatine are, within experimental error, identical. This is surprising since one would have anticipated that the added hydroxyl group at C_{11} would increase the electric field around the benzene ring, thereby increasing the ellipticity. The ellipticity of haemanthamine is larger than in either crinamine or vittatine, which again is unexpected, since the electronic environment at the benzene ring should not be drastically different in crinamine and haemanthamine. Possibly the cis relationship of the methoxyl and phenyl ring are responsible for this difference. There is not enough known about these subtle effects on the CD intensities of the aromatic chromophore to make any generalizations at this time.

The CD and ORD of dihydrocrinamine are shown in Figure 21. As was observed in crinine and vittatine, hydrogenation results in an overall decrease in the amplitude of the ORD and CD spectra. The change in shape of the ORD curve can best be accounted for by the known difference in the position of the saturated methoxyl vs the allylic methoxyl absorption band (119). A less likely cause of the change in shape of the curve might be removal of the double bond, thereby removing the hydrogen

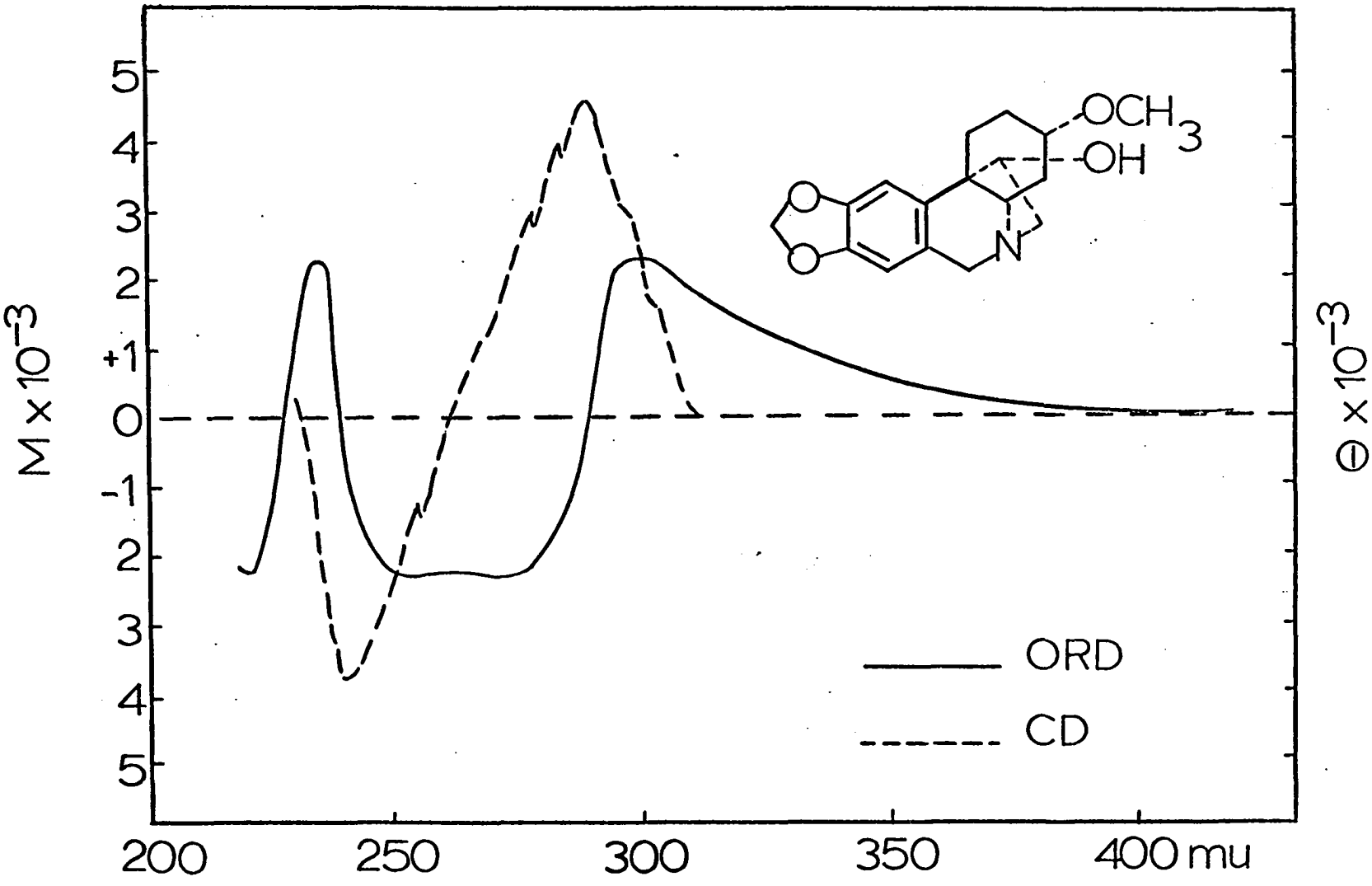


Fig. 21

ORD and CD of DIHYDROCRINAMINE

bond to the hydroxyl. This could conceivably either change the sign, or decrease the amplitude of the hydroxyl dispersion (120, 121).

In addition to alkaloid 16 there was isolated from Pancratium maritimum L. another alkaloid which was named alkaloid 13 (113). The structure has been proven to be very similar to haemanthamine, and is shown in Figure 22. The rotatory dispersion curve of alkaloid 13 is almost superimposable upon that of haemanthamine. This is especially true in the 250 mu region of the spectrum where the troughs in haemanthamine and alkaloid 13 are 5.2 times as large as the trough in crinamine. The differences in the molecular rotations at 304 mu are not large enough for any meaningful comparisons to be made. The CD spectra of alkaloid 13 and haemanthamine do not afford any information as to the relative stereochemistries of the functional groups in these two molecules, but they do show that the stereochemistry of both compounds at the asymmetric benzylic position is the same.

Substitution of a hydroxyl for one of the benzylic protons at the 6 position of crinamine affords the alkaloid 6-hydroxycrinamine. Both the ORD and the CD spectra of this compound are very similar to crinamine. Except for the fact that the slope of the dispersion curve of 6-hydroxycrinamine (Fig. 23) at ca. 310 to 320 mu increases more rapidly than that of crinamine in the same region, the spectra are virtually superimposable. The introduction of the 6 hydroxyl group produces a new asymmetric center and it is surprising that the spectrum does not

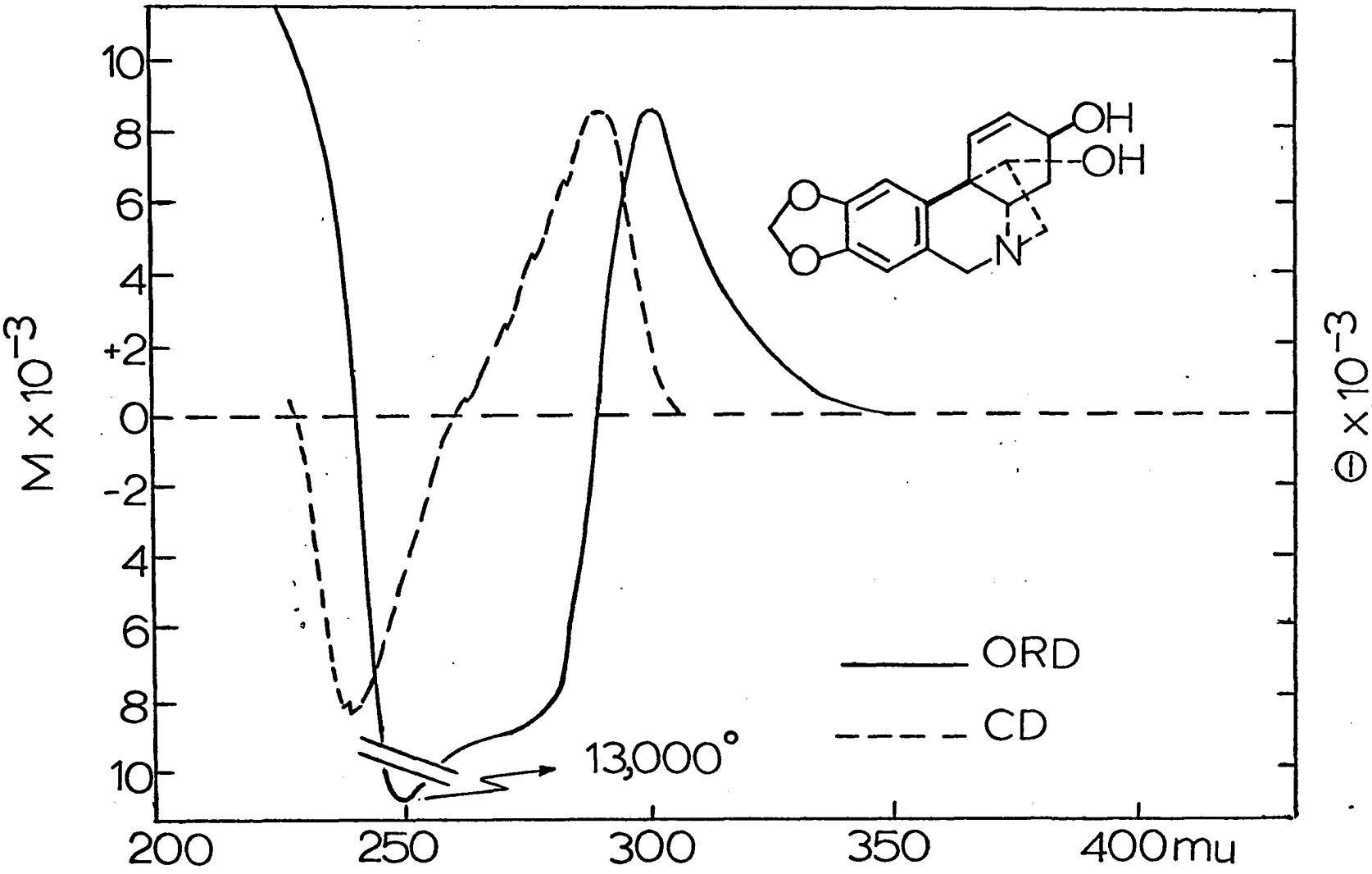


Fig. 22

ORD and CD of ALKALOID -13

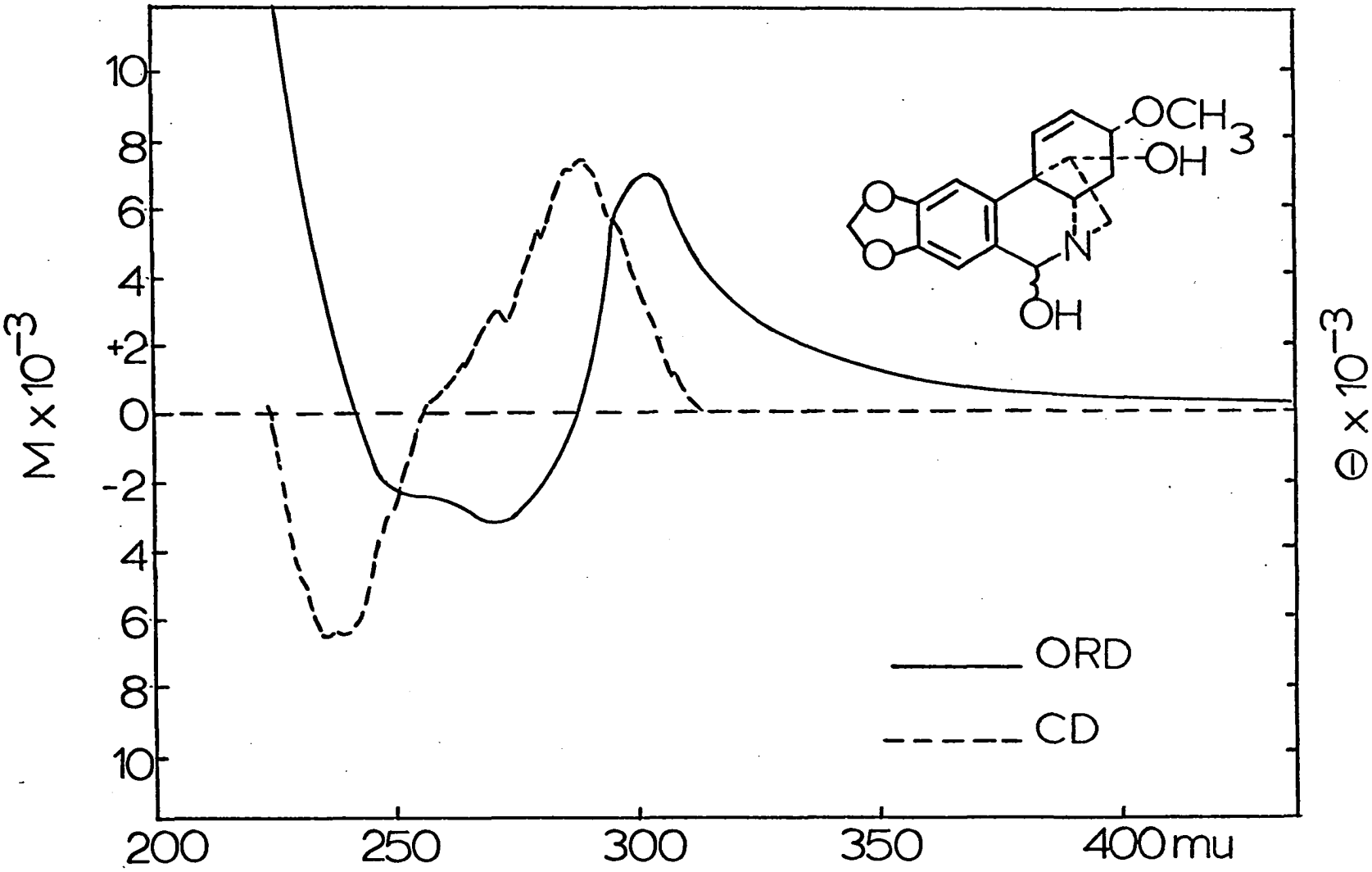
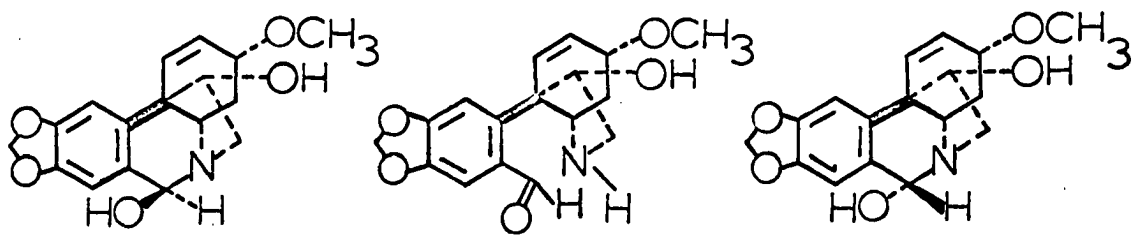


Fig.23

ORD and CD of 6-HYDROXYCRINAMINE

reflect this. It has been shown that 6-hydroxycrinamine does not exist as shown in Figure 23, but is a mixture of two C_6 epimers (122). It has been postulated that the aldehyde (IX) shown below is the common intermediate which gives rise to the C_6 epimers. From NMR evidence 6-hydroxycrinamine exists in solution as a 50-50 mixture of compounds (X) and (XI). The fact that it is impossible to demonstrate the creation of a new asymmetric center in this molecule corroborates NMR findings.



X IX XI

The spectra of dihydro-6-hydroxycrinamine (Fig. 24) is similar to that of dihydrocrinamine and needs no further comment. If 6-hydroxycrinamine does exist in the epimeric forms as indicated, it should be possible to verify this by examination of the 11-acetyl and 6, 11-diacetyl 6-hydroxy-crinamines. 11-acetyl-6-hydroxycrinamine exists as a mixture of epimers as shown by NMR data, whereas the 6, 11-acetyl-6-hydroxycrinamine has been shown to exist primarily as only one epimer (122). The CD spectra of 11-acetyl-6-hydroxycrinamine shows (Fig. 25) in addition to the two normal benzene dichroisms the beginning of a third band which is usually

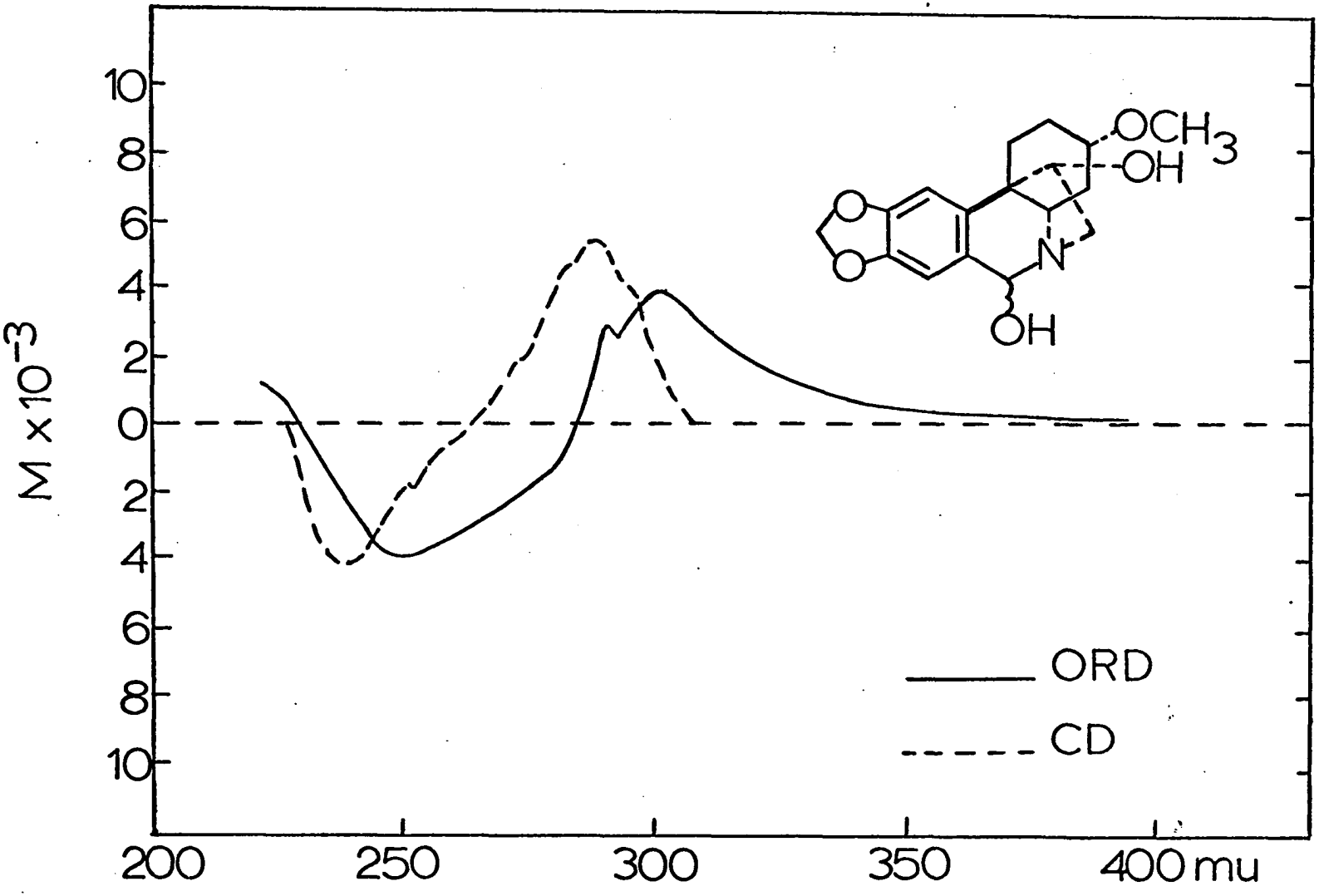


Fig. 24

ORD and CD of DIHYDRO-6-HYDROXYCRINAMINE

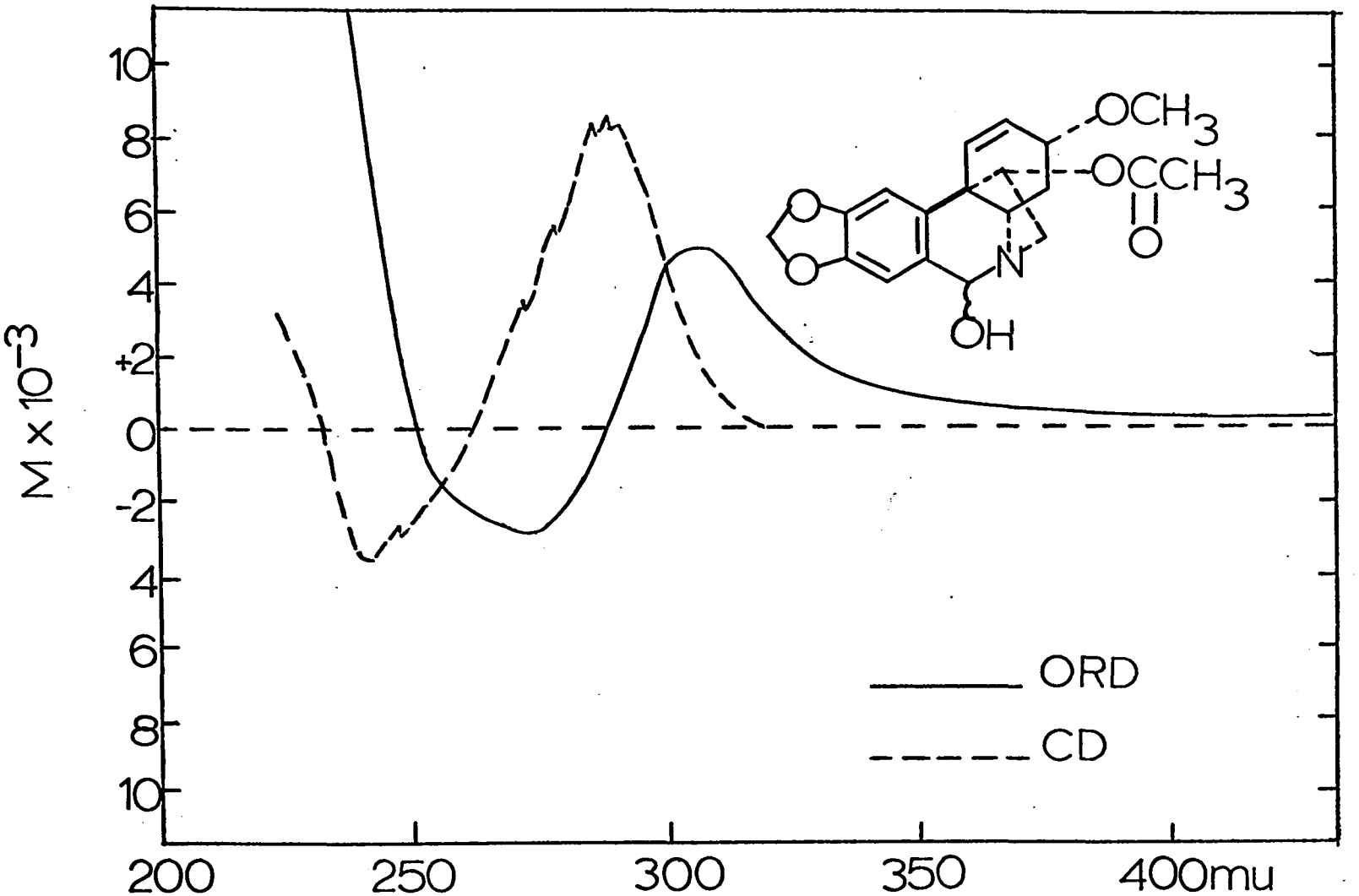


Fig. 25

ORD and CD of 11-ACETYL-6-HYDROXYCRINAMINE

quite difficult to observe. This may be the beginning of the dichroism of the optically active acetyl group which should absorb at ca. 225 mu (119). The ORD spectrum of this compound is quite similar to that of crinamine and affords no information about the acetyl and hydroxyl functions.

The CD and ORD spectra of 6, 11-diacetyl-6-hydroxycrinamine are given in Figure 26. The peak at 300 mu is similar to that found in crinamine and contributes no additional information concerning the introduction of the second acetyl function. The sharp increase in the slope of the curve at 285 mu is indicative of a new chromophore however. The CD spectra is particularly helpful here as it shows that the sign of the Cotton effect at 260 mu is positive instead of negative as it has been in all previous spectra of this series. It has been found in all of the compounds investigated that the second benzene band at ca. 240 mu is always of constant sign for analogous alkaloids of the same absolute configuration. This shall be commented on in greater detail in a latter section. The beginning of the positive dichroism is therefore not assigned to a benzene band but to the optically active acetyl group at C_6. This data can be taken as excellent supporting evidence that the diacetyl derivative of 6-hydroxycrinamine exists primarily in only one of its possible epimeric forms. The ORD and CD spectra of dihydro 6, 11-diacetyl 6-hydroxycrinamine is given in Figure 27 and is in complete agreement with the above statements. In this

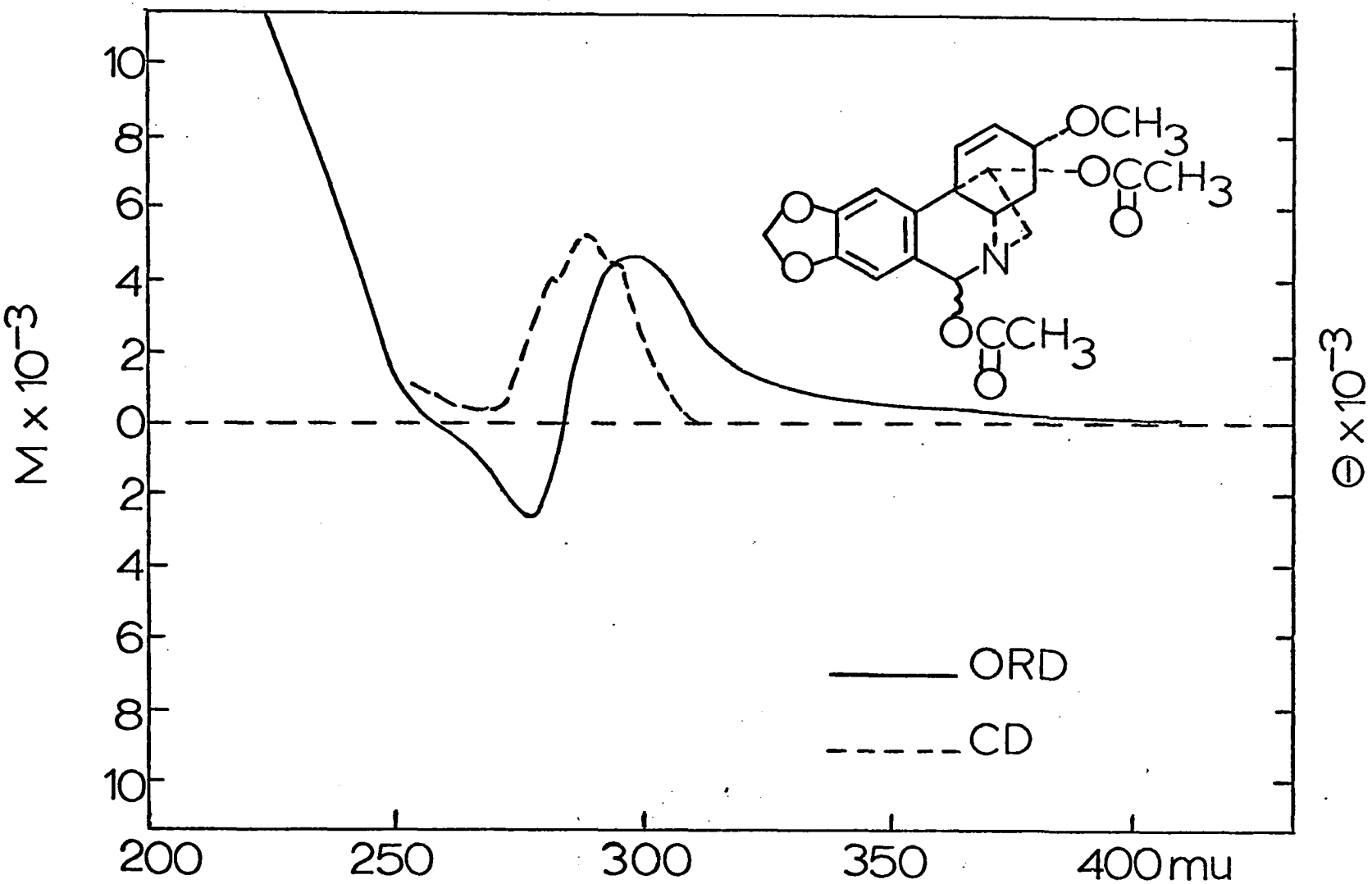


Fig. 26

ORD and CD of 6,11-DIACETYL-6-HYDROXYCRINAMINE

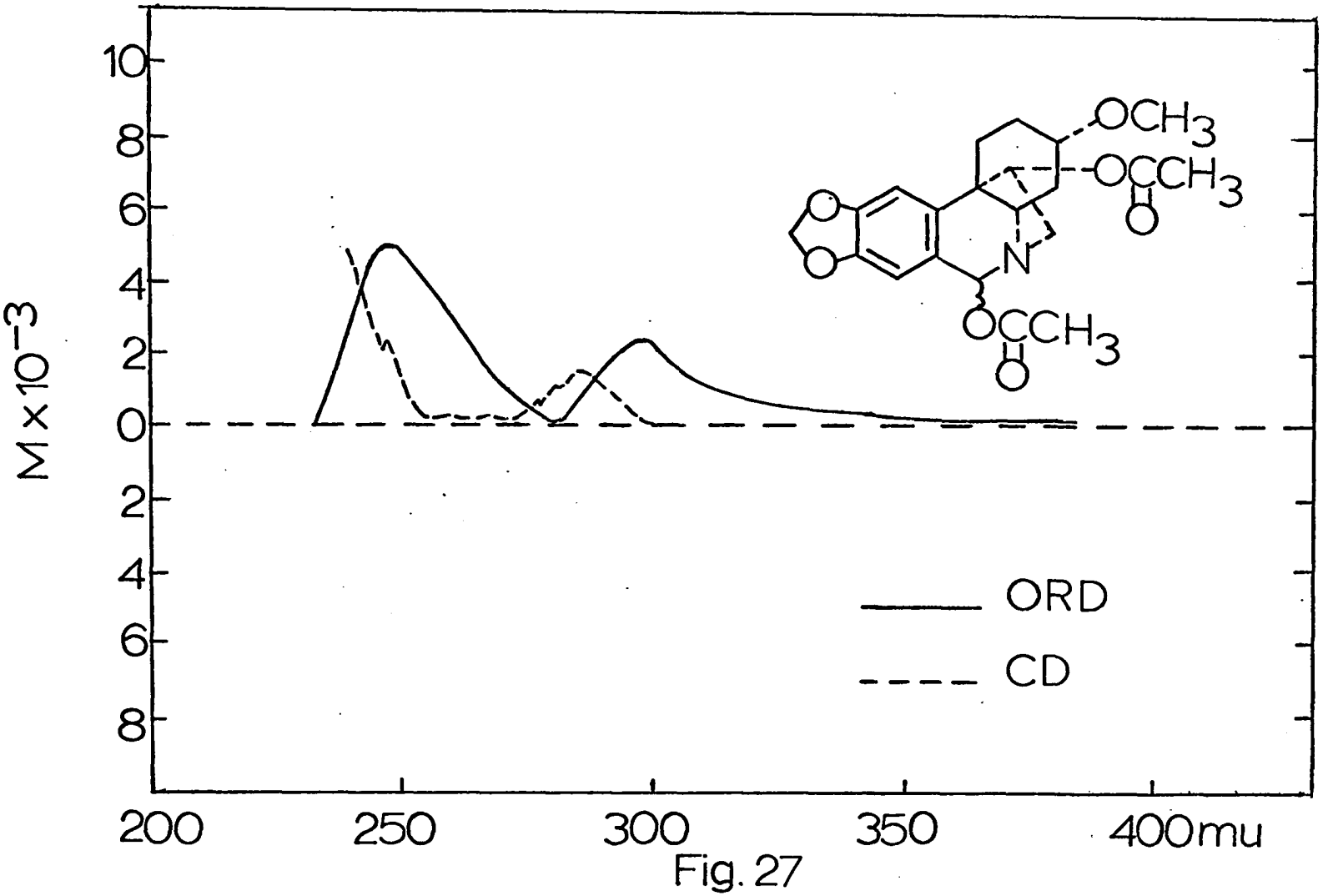


Fig. 27

ORD and CD of DIHYDRO 6,11-DIACETYL 6-HYDROXYCRINAMINE

compound the allylic methoxyl dispersion and absorption move to shorter wave lengths and the dispersion and ellipticity of the 6-acetyl group becomes more evident.

It should be noted that as the hydroxyl groups in 6-hydroxycrinamine are progressively acetylated the benzene dichroism decreases upon introduction of each new acetyl group. Theoretically the dichroism of a particular chromophore should not be overly effected by chromophores far removed from the one under observation. This decrease in the benzene dichroism upon acetylation indicates that the amplitude of the benzene chromophore is highly dependent upon its electronic environment. These effects are analogous to the vicinal effects proposed by Kuhn (123). A second less important effect may be the electric field produced by the acetyl and hydroxyl groups in the region of the benzene chromophore. This second effect is postulated according to the one electron theory of optical activity of Erying and Condon (124).

Haemanthidine (Fig. 28) is epimeric with 6-hydroxycrinamine and differs only in the configuration at C_3. It may be referred to as 6-hydroxyhaemanthamine. The molecular rotation of crinamine at 304 mu is 2000° larger than in haemanthidine while at 250 mu the molecular rotation of haemanthidine is 7200° more negative. These differences demand that the stereochemistry of haemanthidine be the same as haemanthamine. These comparisons are analogous with those made previously for crinamine and haemanthamine. The CD spectrum of haemanthi-

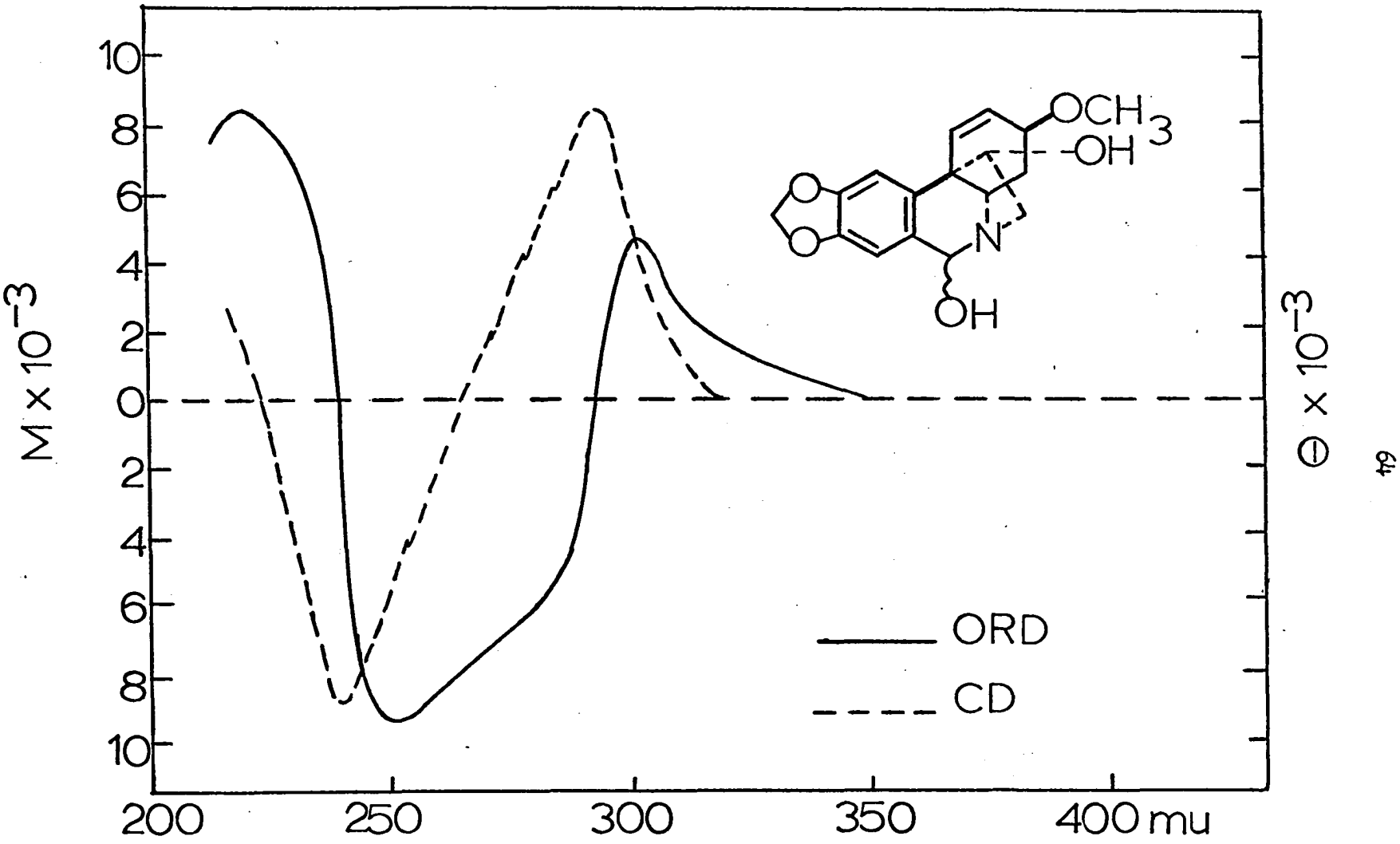


Fig. 28

ORD and CD of HAEMANTHIDINE

dine is given in Figure 28, and comparison of the ellipticities with those of crinamine shows them to be the same. It should be noted that the calculated CD maximum at 293 mu is 7800° and the observed value is 8300°. This is an error of 7%, which again points to a contribution to the benzene chromophore from the functional group dispersions.

A multiple Cotton effect spectrum was obtained from 6-hydroxy-crinamine lactam (Fig. 29). The ultraviolet spectrum has maximum absorptions at 310 mu (logE=3.76), 270 mu (logE=3.76) and 230 mu (logE=4.48) whereas the CD spectrum has maximua at 325 mu, 295 mu, 270 mu and 230 mu. The UV band at 310 mu is not symmetrical and is probably a composite band consisting of a smaller band on the long wave length side which can be assigned to the n-pi* transition of the carbonyl group. This assignment would place the main component of the 310 mu band at approximately 304 mu (125), which can be assigned to one of the electron transfer bands of benzene while the CD maximum at 295 mu is assigned to a second electron transfer (E. T.) benzene band. The 270 mu CD maximum corresponds to the 270 mu absorption band and can also be designated an E. T. band (119). The CD and UV bands at 230 mu are aromatic absorptions (119). In 6-hydroxycrinamine lactam the combination of the benzene ring and the carbonyl group represents a new chromophore. This results in drastic changes in both the UV and CD spectra. This new chromophore is simply an extension of the original benzene one and as such should reflect the stereochemistry at position 10b. If the CD

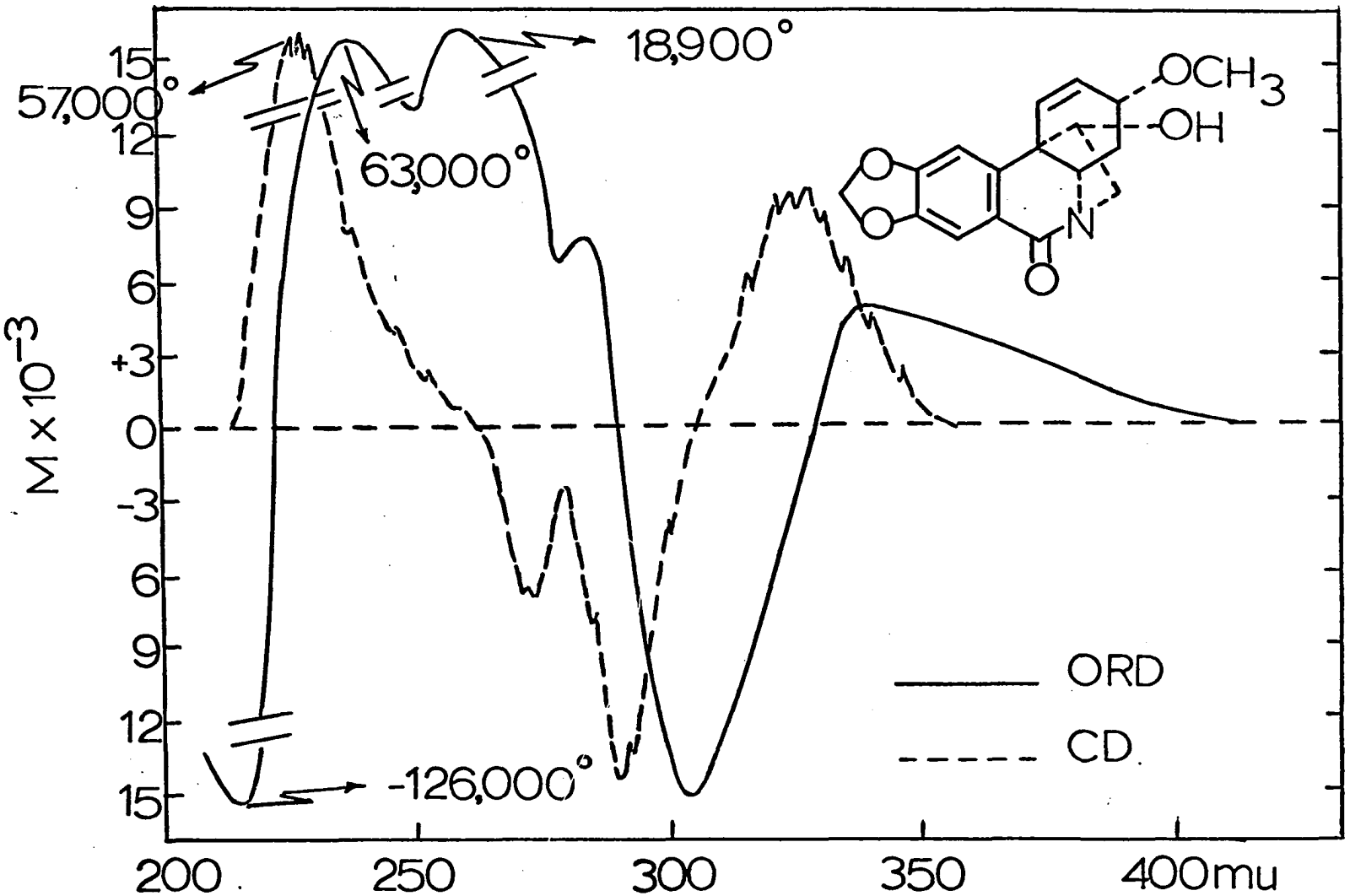


Fig. 29

ORD and CD of 6-HYDROXYCRINAMINE LACTAM

maximum of the absorption band at 304 mu is positive as are all of the first benzene bands in methylenedioxybenzene alkaloids of this absolute configuration and smaller than that one attributed to the n-pi* transition it would be under the latter and impossible to observe. The CD maximum at 270 mu corresponds to the absorption at 270 mu as is the second benzene band in all of the crinamine derivatives. The conclusion drawn is that it seems possible to use the E. T. bands of the aromatic lactones to determine the relative stereochemistry at position 10b. Further evidence that this hypothesis is correct shall be presented in the section of this thesis dealing with the absolute stereochemistry of the aromatic lactonal alkaloids homolycorine and albomaculine.

B. Methylenedioxymethoxy Benzene Alkaloids

The second group of 5, 10b-ethanophenanthridine alkaloids which were studied were those containing the methylenedioxymethoxy chromophore, of which powellane (Fig. 30) may be considered the parent compound. The methoxyl group at position 7 is responsible for a hypsochromic shift in the aromatic absorption band of 8 mu relative to crinane. (288 mu vs. 296 mu). This shift is evident in the ORD and CD spectra of these compounds.

The absolute configuration of powellane is the same as crinane. However the ORD spectra recorded between 700 mu and 300 mu for crinane and powellane showed that the sign of the curve for powellane was opposite from that expected for a compound of the same absolute config-

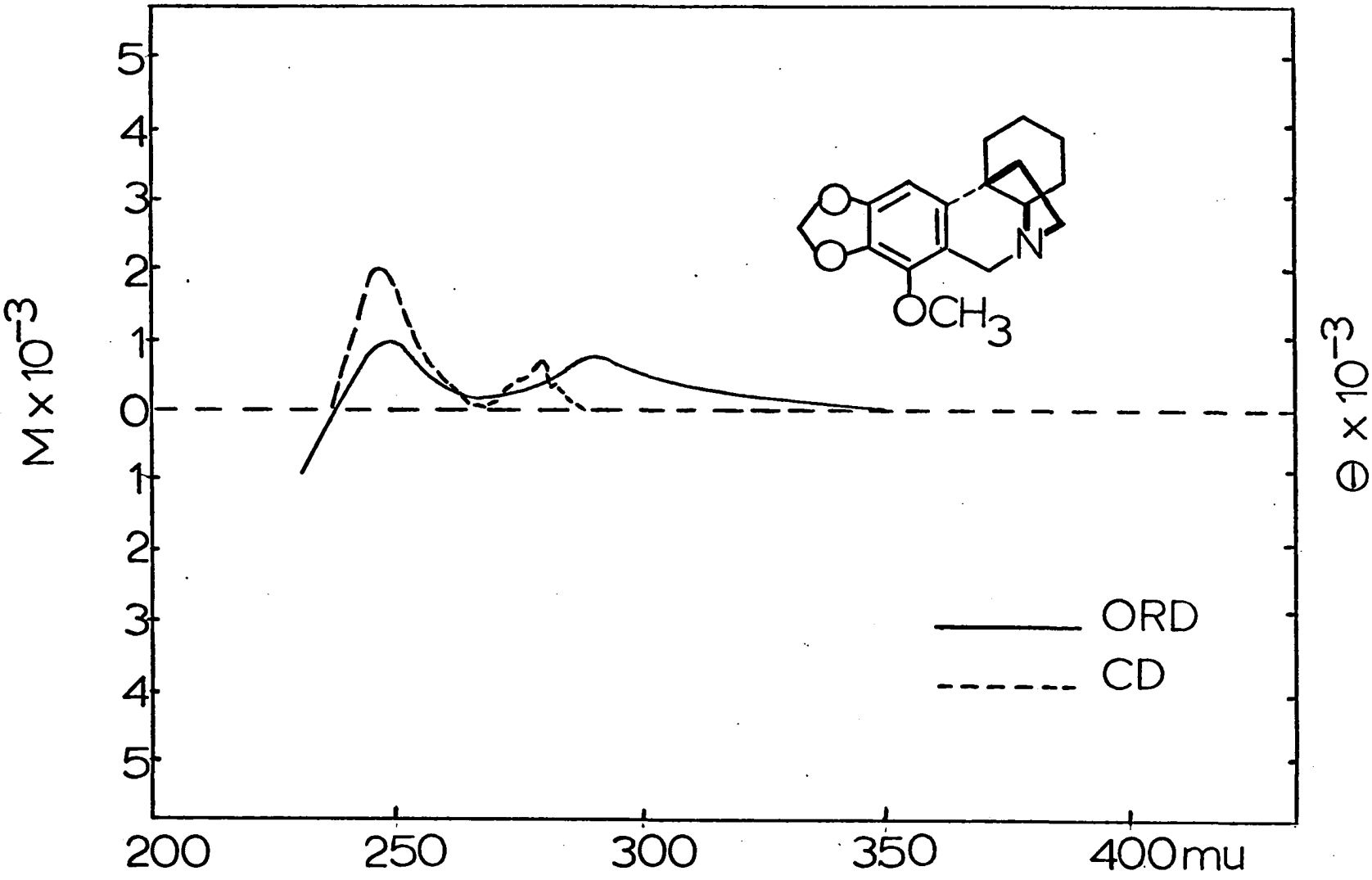


Fig.30

ORD and CD of POWELLANE

uration. It was this anomaly, the mirror image spectra of two compounds proven to be of the same stereochemistry, which initiated the present investigation.

Powelline (Fig. 31) (19) has been shown to be the 7-methoxy analog of crinine. The molecular rotations of powelline are of the same sign, but significantly smaller than those in crinine. The rotation of powelline at 304 mu is only 16% that of crinine. Examination of Dreiding models shows that the introduction of the methoxyl group does not change any of the bond angles in the molecules. The C_7 methoxyl group is too far removed from the asymmetric center to be directly involved in any steric interaction which could effect the rotatory dispersion spectrum. The CD spectrum is unusual in that the band centered at 290 mu is smaller than anticipated from previous data for these alkaloids, while the band at 240 mu is within experimental error of that of crinine.

Dihydropowelline (Fig. 32) is shown to have a positive Cotton effect associated with the 286 mu band. This is unexpected since upon hydrogenation there has been no change in the stereochemistry of the asymmetric center adjacent to the benzene ring. The CD spectra of dihydropowelline also gave an unusual amount of data. It shows a "double hump" curve with a negative maximum at 300 mu and positive maxima at 286 and 245 mu. The UV spectra of this compound has maxima at 286 mu and 240 mu. An absorption band at 300 mu is not observed in dihydropowelline, but it may be of low extinction and hidden under the

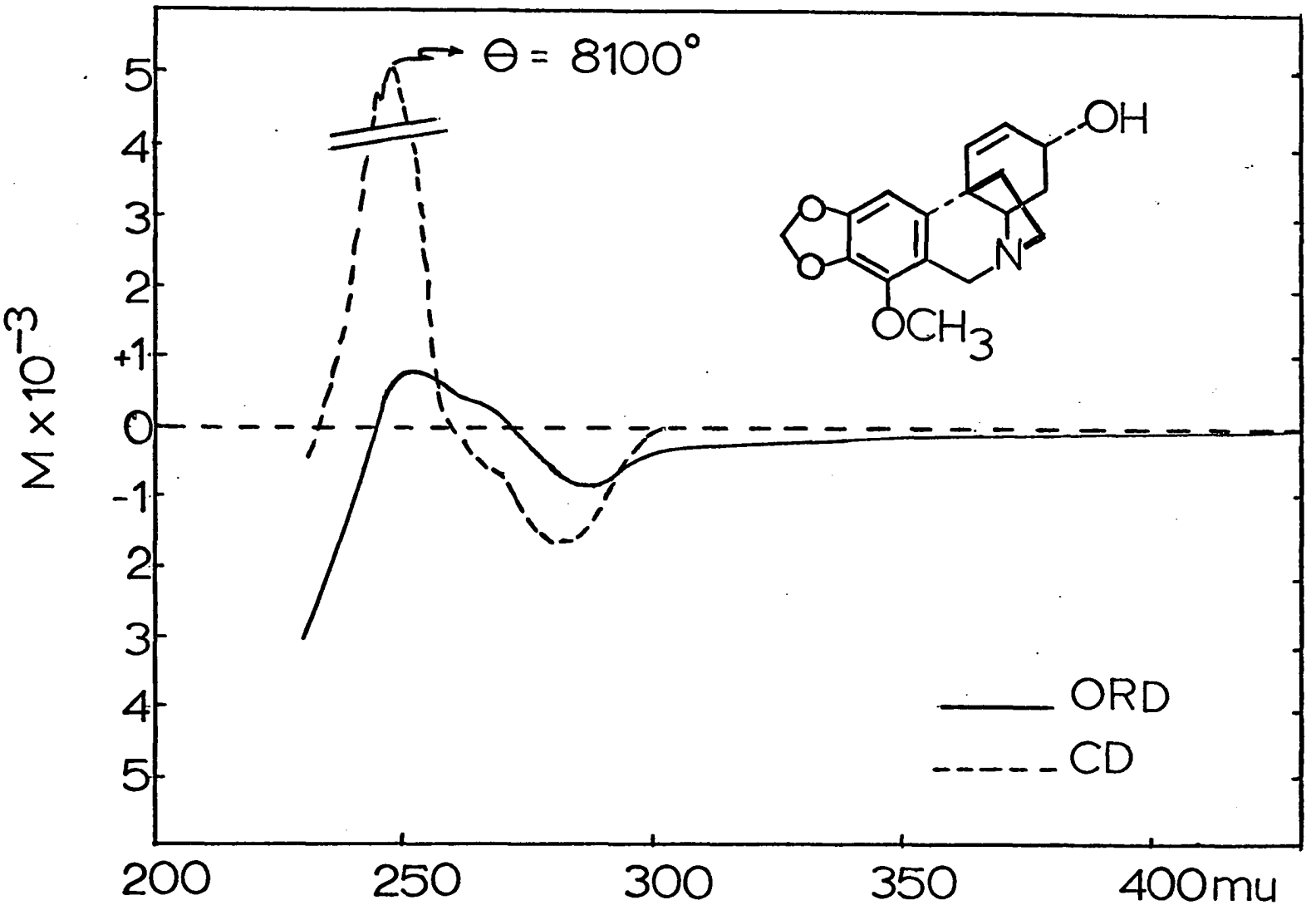


Fig.31

ORD and CD of POWELLINE

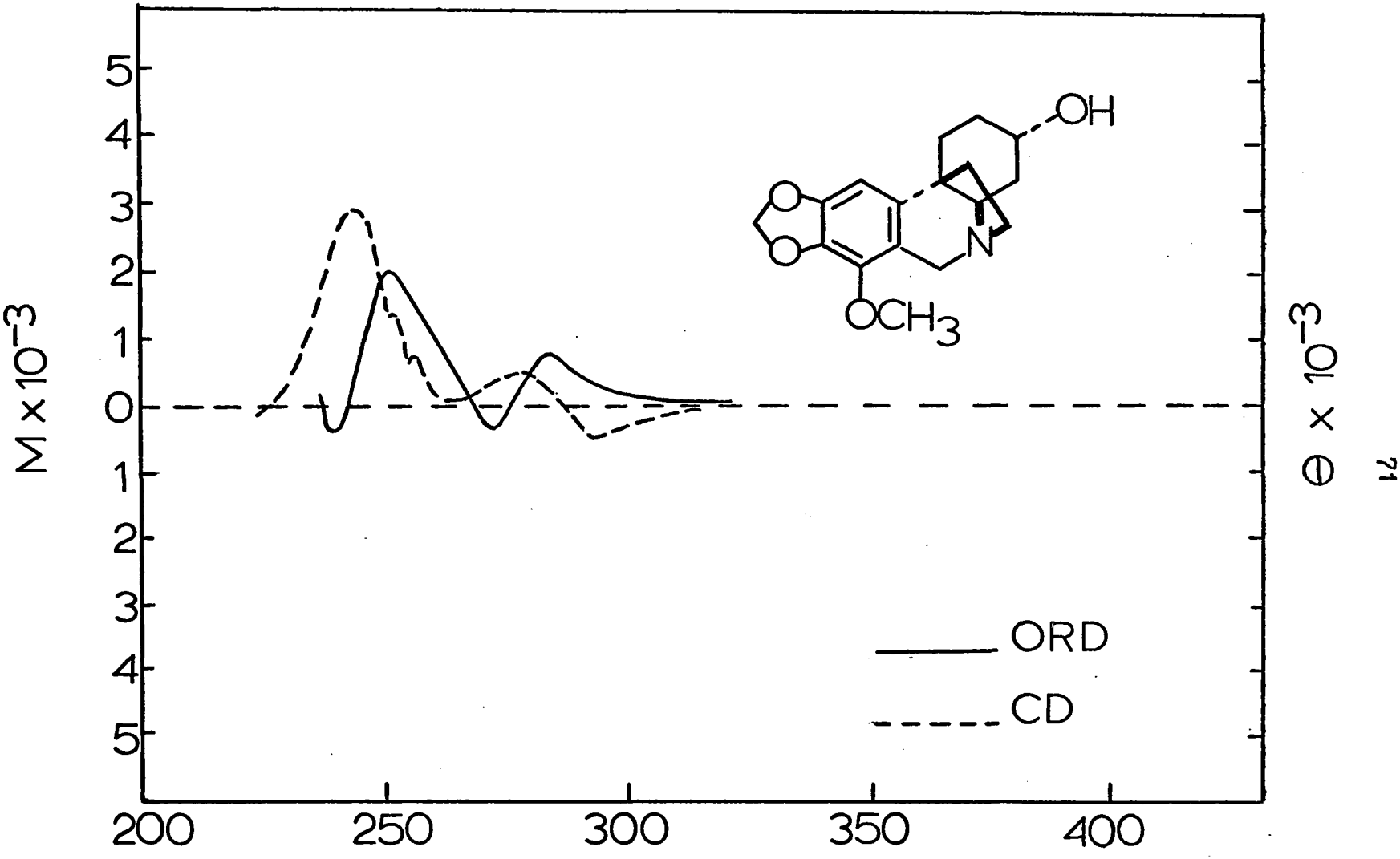


Fig. 32

ORD and CD of DIHYDROPOWELLINE

tail of the 286 mu band. The existence of this band was verified by running the CD spectrum of this compound several times under different experimental conditions, and the same "double humped" spectrum was always observed. This is an excellent example of the superiority of CD over ORD and UV for investigating absorption phenomenon. Investigation of a number of compounds in acid and neutral solution has shown that the band at 286 mu in the powelline series and the band at 296 mu in the crinine series each consist of two bands separated by only 5 to 7 mu. Vibrational bands of the benzene chromophore usually have the same sign in the CD. The spectrum of dihydropowelline seems to be an exception to this generalization. It is entirely possible that this compound represents an extremely fortuitous case where the electronic factors which govern the sign of the transitions of the benzene ring are such that the sign of one of the vibrational bands has changed. However this may be one of the few compounds in which the vibrational bands are of opposite sign. In any case it is obvious that the sign of the 288 mu band has changed. The fact that the band in the longest wave length portion of the spectrum is negative helps account for the negative sign of the rotation at 589 mu.

The spectrum of powellane is shown in Figure 30 and it can be seen that the sign of the 288 mu band has changed from negative to positive. The entire ORD spectrum of powellane is positive which accounts for the positive rotation observed at the sodium D line. The CD spectrum

verifies this sign change at 288 and also indicated that the 240 mu band is still positive. It was possible to run a second spectrum of powellane and get through the entire band at 240 mu since enough sample was made available for a second run under different conditions.

Buphanidrine (126) is the methyl ether of powelline, and its ORD and CD spectra are given in Figure 33. The rotatory dispersion curve is well defined and is identical in shape with the curve of powelline. The molecular rotation of buphanidrine at 288 mu is (-) 750° whereas that of powelline is (-) 1100°. This may be taken as qualitative evidence that methylation of the hydroxyl decreases the rotatory power of this chromophore, however this hypothesis must be taken as tentative since the differences in molecular rotations found previously between crinine and buphanisine are small enough to be within experimental error. The CD spectrum of buphanidrine shows a negative dichroism at 285 mu and a positive maximum at 240 mu. This curve is normal in every respect and needs no additional comment. It should be noted that the spectrum of buphanidrine perchlorate was run and this was quite different from the spectrum of the free base. The trough at 285 mu in the free base is not readily evident in the spectrum of the perchlorate. In an effort to determine whether this is a general phenomenon the hydrochlorides of crinine, powelline, dihydropowelline, powellane, lycorine and dihydrolycorine were made and the CD spectra run. In all cases there were changes in the spectra. The usual differences were in decreased amplitudes. In powellane the peak at 288 mu was split into

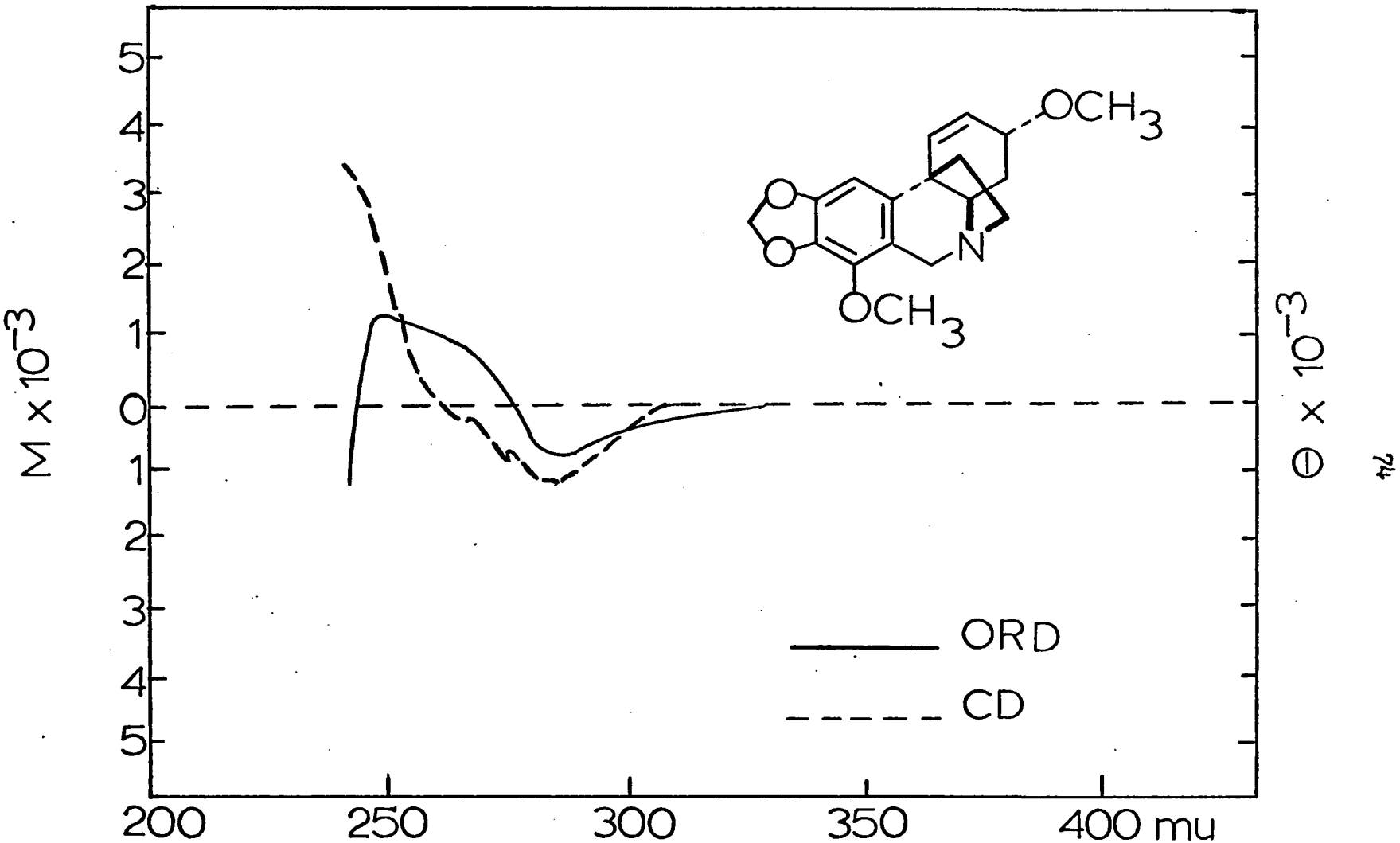


Fig. 33

ORD and CD of BUPHANIDRINE

two distinct peaks which corresponded to maxima at the same wave lengths in the UV spectrum. It should therefore be emphasized again that the spectra of two compounds should only be compared under the same set of conditions.

The circular dichroism spectrum of epipowelline (Fig. 34) is very similar to powelline in both magnitude and position of maximum ellipticities, and is normal in having two antipodal bands of the proper sign relative to the absolute stereochemistry assigned. The ORD curve is unusual because it bears no resemblance to the spectra of any Amaryllidaceae alkaloids. This alkaloid is known to be the C_3 epimer of powelline. The large negative dispersion spectrum can be explained on the same basis as powelline if the hydroxyl group in epipowelline is assigned a more negative value than the hydroxyl of powelline. This would explain the more negative value of the dispersion in the 300 to 400 mu region, but cannot account for the curve below 300 mu. Probably the best explanation of the spectrum in this region is the drastically reduced size of the dispersions of the two benzene bands. In epicrinine the rotatory dispersion curve is positive in the 250 mu region, but in epipowelline it is negative. A large negative dispersion due to the hydroxyl group would completely cancel a small positive dispersion due to the benzene ring. The small dichroism of the 240 mu band supports this explanation. It would probably not be possible to come to this conclusion on the basis of the rotatory dispersion data alone.

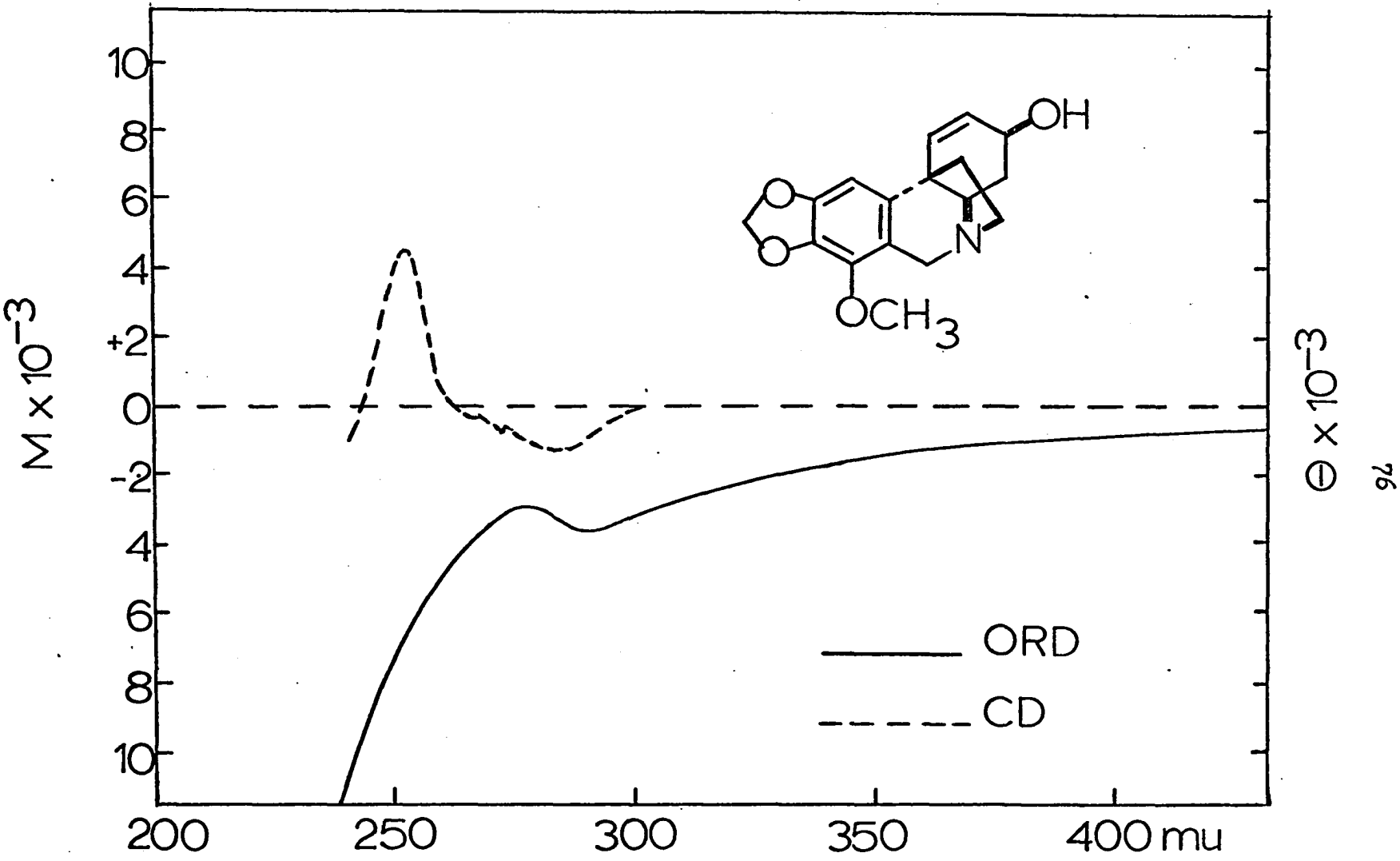


Fig. 34

ORD and CD of EPIPOWELLINE

The spectrum of dihydroepipowelline (Fig. 35) exhibits the same sign change as was evident in powellane and dihydropowelline. Removal of the allylic hydroxyl dispersion results in shifting the hydroxyl dispersion farther into the UV and the benzene bands have become more evident. It is possible to construct this curve by simply drawing two positive S-shaped dispersions at the proper wave lengths, and superimposing upon this the negative tail of the hydroxyl dispersion. The CD spectrum provided proof that this change in sign of the benzene bands is real and not an artifact.

At this point it should be pointed out that the sign of the 288 mu aromatic band has changed in all of the methylenedioxymethoxy benzene alkaloids upon hydrogenation. This phenomenon is not exclusive with powelline and dihydropowelline.

A number of other methylenedioxymethoxy alkaloids were studied, all of which resulted in rather unusual spectra. Ambelline (Fig. 36) is the 11-hydroxy analog of powelline (127), but this relationship is not evident from a comparison of the ORD spectra of these compounds. The rotation at 589 mu of ambelline is (+) 63.5° and this positive trend continues until 305 mu is reached. At this point there is a decrease in the rotation which reaches the zero axis but which never succeeds in crossing it; after this there is a peak and then a steady decrease in rotation, which finally crosses the axis at 260 mu. The CD spectrum provides an explanation of the ORD curve. It can be seen that

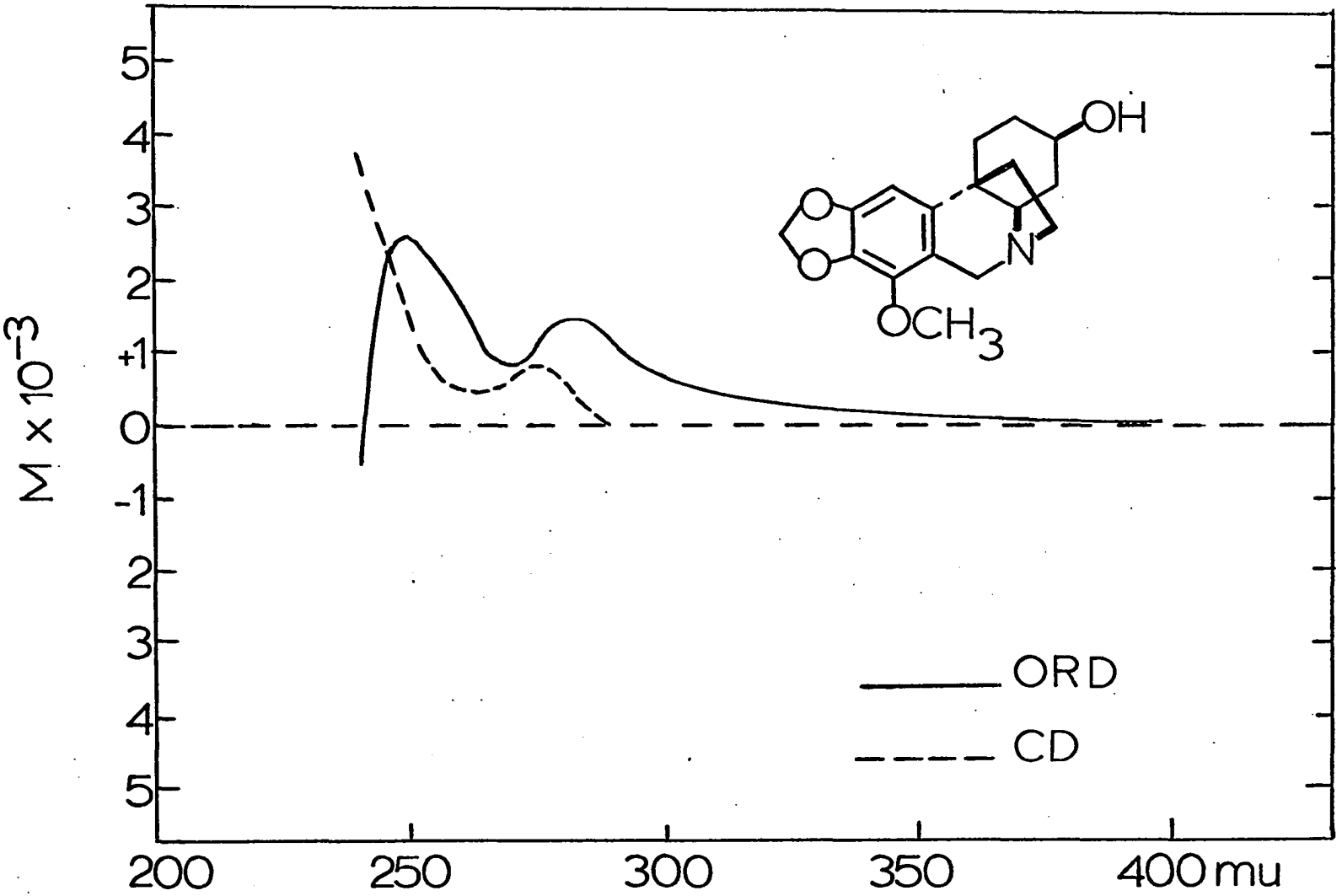


Fig. 35

ORD and CD of DIHYDROEPIPOWELLINE

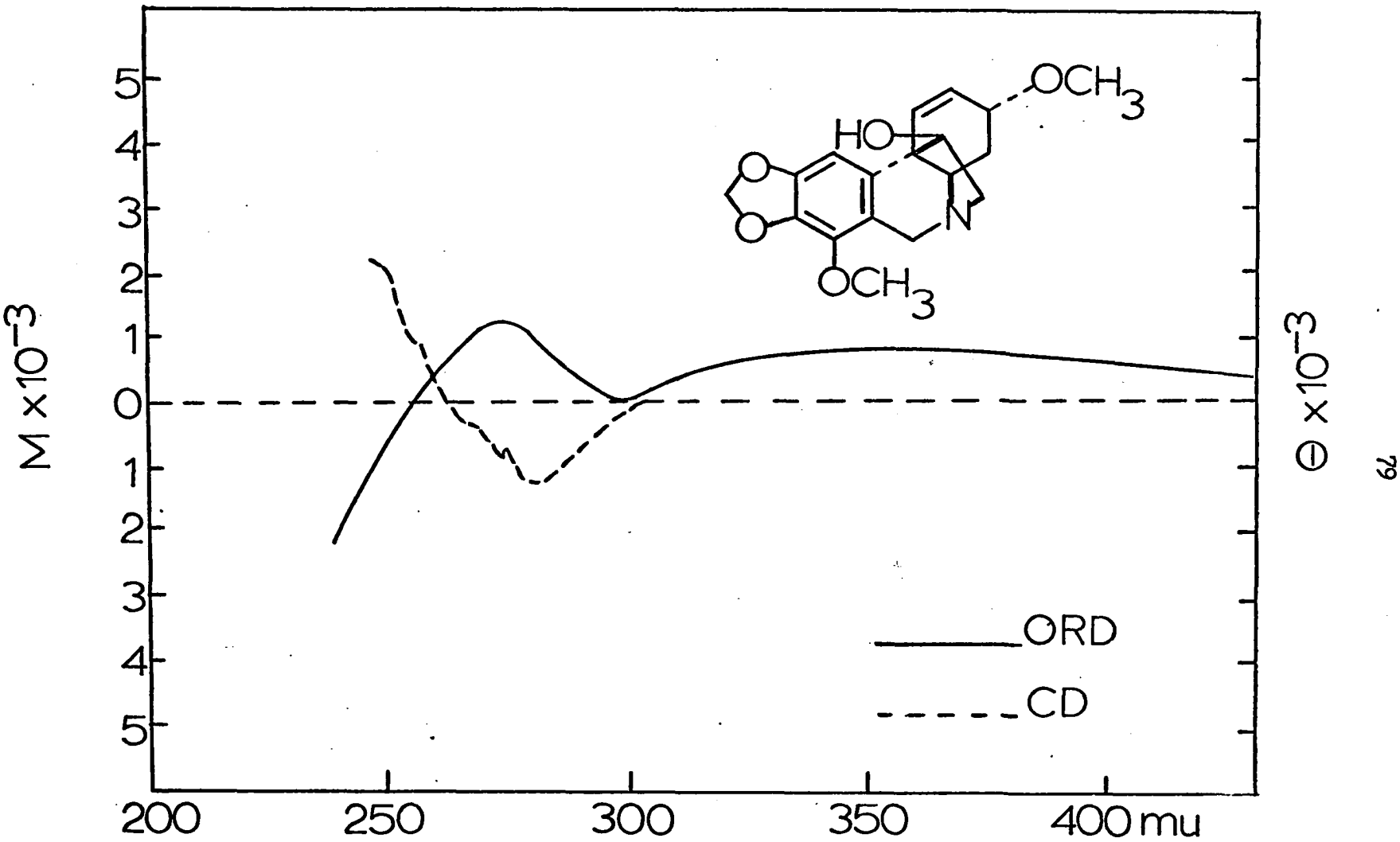


Fig. 36

ORD and CD of AMBELLINE

the dichroism displayed by ambelline is very similar to that of powelline and other alkaloids of this type, and is of the correct sign for the relative stereochemistry assigned to this compound. The CD spectrum is made up of the usual negative and positive components at 288 and 240 mu respectively. This leaves the contributions of the methoxyl and hydroxyl groups to be accounted for in the observed spectrum. The methoxyl group may be dismissed from consideration as it has been present in a number of previously studied compounds and has never resulted in any irregularities. In ambelline the C_{11} hydroxyl function has been found to be hydrogen bonded to the pi cloud of the benzene ring, while in crinamine the hydroxyl is hydrogen bonded to the double bond. It is known that hydrogen bonding can give rise to enhanced dispersion spectra (121), and it is possible that this can account for the unusual shape of the ORD spectra of ambelline. We have shown that the C_{11} hydroxyl group of crinamine gives rise to a negative dispersion, and is feasible that the hydroxyl in ambelline, having the opposite configuration at C_{11}, gives rise to a dispersion of opposite sign. Either one or both of the above reasons can account for the observed rotatory dispersion spectra of ambelline.

The spectrum of dihydroambelline (Fig. 37) is completely different from that of ambelline, as the entire curve is negative and approximately twice as intense. This is the only spectrum in which the amplitudes have increased upon hydrogenation. The CD spectrum provided a clue

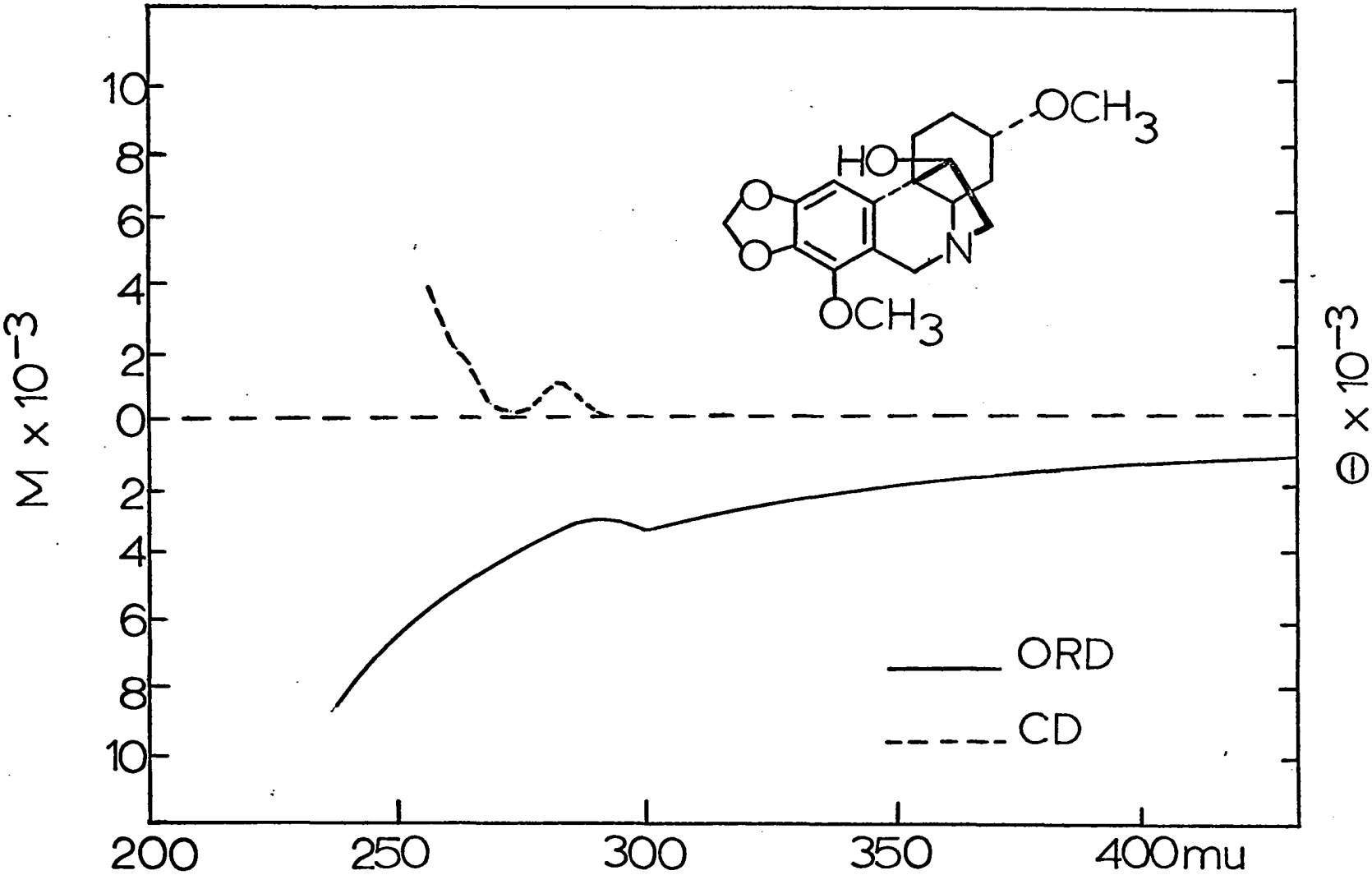


Fig.37

ORD and CD of DIHYDROAMBELLINE

which accounts for this apparent discrepancy. The sign of the 288 mu band has changed while the sign at 240 mu has remained constant. The 288 mu benzene dichroism is unusually small in dihydroambelline, and as the methoxyl and hydroxyl dispersions are relatively large and probably negative, the shape of the ORD spectrum can be accounted for. This is especially true as a negative hydroxyl dispersion enhanced by hydrogen bonding to the benzene ring would be large enough to cancel the effects of a small aromatic ellipticity.

Buphanamine (128) (Fig. 38) is a rather interesting compound in which the hydroxyl group at C_1 has been shown to be hydrogen bonded to the aromatic ring (118). This results in a very large negative hydroxyl dispersion which completely hides the aromatic dispersions. As in dihydroambelline it is possible that the hydroxyl dispersion is probably much larger than the benzene one due to strong hydrogen bonding. The CD spectrum of buphanamine points out that the dichroism associated with the 288 mu absorption band is positive. There are two obvious interpretations of this positive sign. The first is that the stereochemistry at position 10b is different from that in crinane and powellane, or secondly that some phenomenon not directly associated with the stereochemistry has caused the sign of this first benzene band to change. Buphanamine has been interrelated chemically to powellane (132) which eliminates the former explanation for the positive dichroism. This leaves only the second alternative as an explanation. The sign of the

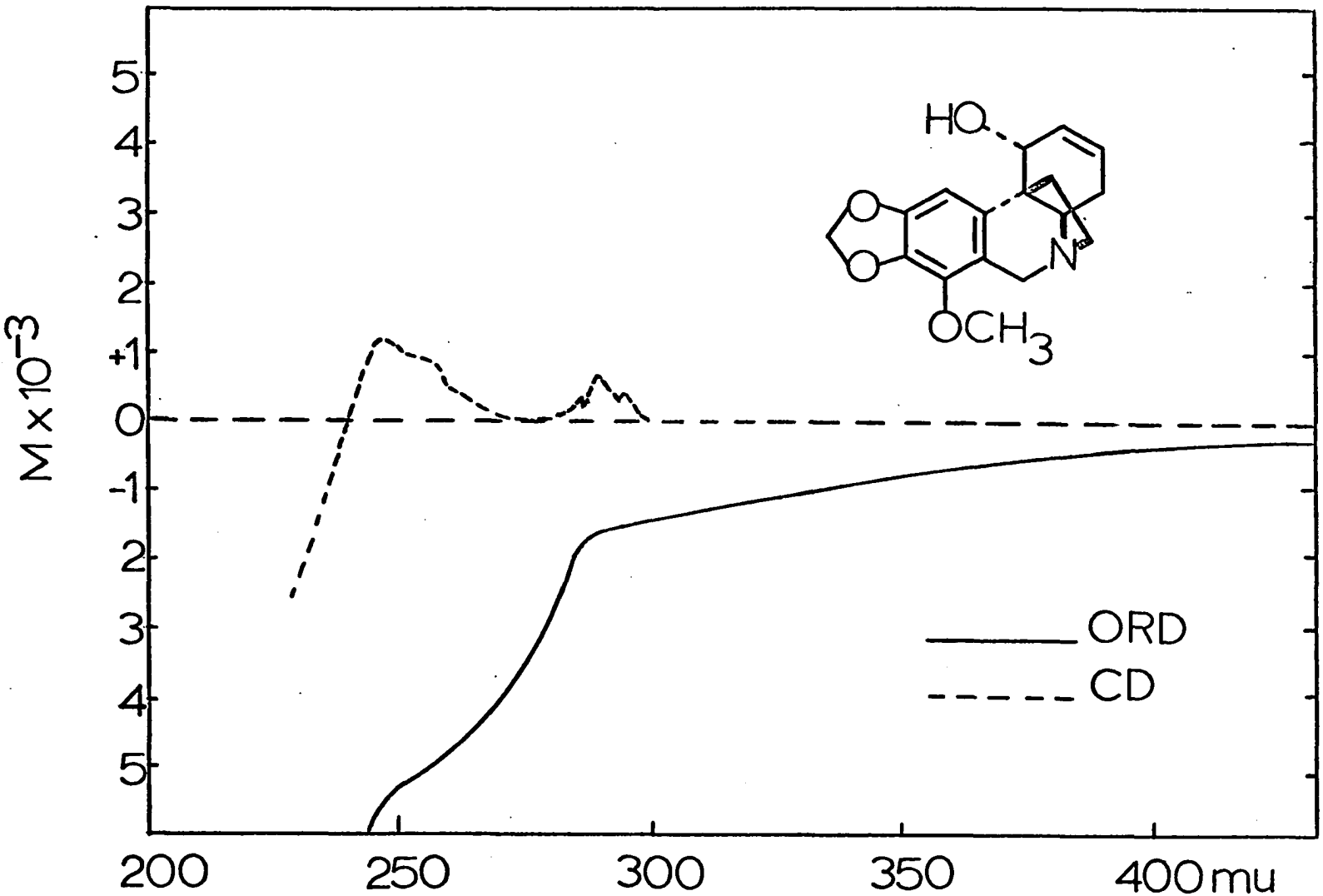


Fig. 38
ORD and CD of BUPHANAMINE

Cotton effect is known to be effected by stereoelectronic effects when the molecules exist in conformations which allow homoconjugation between the carbonyl and benzene pi-electrons (129-132). Interpretation of the CD spectra of a number of compounds has been made on the basis of a strong interaction of the type mentioned above. In order to see if this hypothesis would provide similar information in our compounds, oxobuphanamine was studied. The CD and ORD spectra of this compound is shown in Figure 39. The very large dichroism centered at 348 mu can be readily assigned to the carbonyl chromophore, while the negative maxima at 290 mu is assigned to the benzene chromophore. Since it was impossible to get through the entire band which begins to display a positive maximum at 260 mu it is difficult to determine whether this is the second benzene dichroism or the K band of the α,β unsaturated ketone. However it is clear that the sign of the first benzene dichroism has changed. In oxobuphanamine the carbonyl group and the benzene ring are within the distances required for homoconjugation to occur. From a study of molecular models it was found that ring C can exist only in a quasi-boat conformation, which results in almost complete coplanarity of the benzene and carbonyl pi systems. Upon reduction of the carbonyl function this strong interaction is removed and the sign of the Cotton effect changes. The rotatory dispersion spectrum does not afford meaningful data in the case of oxobuphanamine, since if one were not aware of the change in sign of the benzene Cotton effect, it

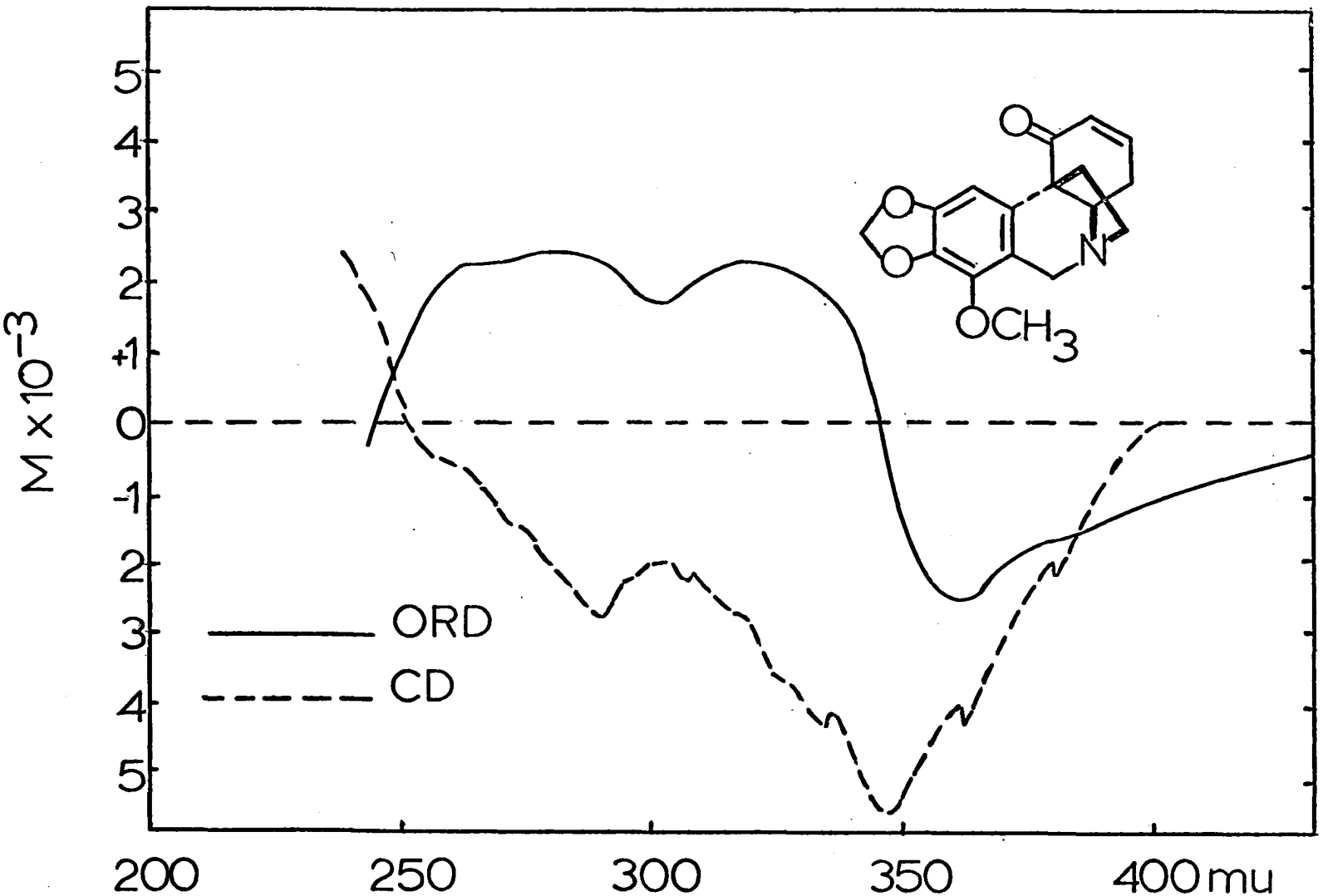
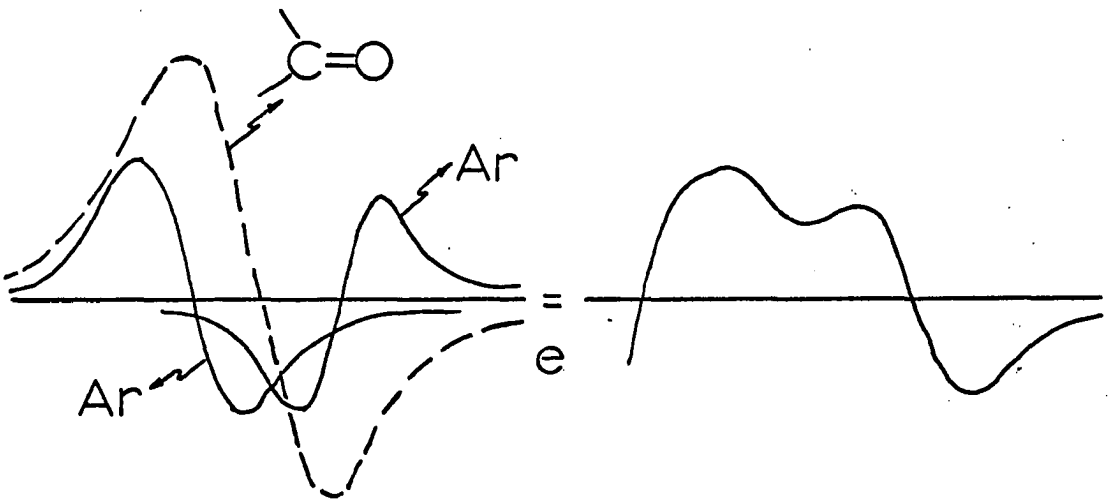
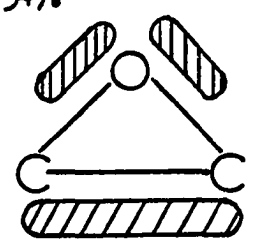


Fig. 39
ORD and CD of OXOBUPHANAMINE

would seem necessary to assign a positive sign to the dispersion expected at 304 mu. With the CD data in hand and an awareness that the carbonyl dispersion is quite large it is possible to construct the observed ORD curve as shown in e below.



Epoxypowelline (133) (Fig. 40) has the same stereochemistry as powelline and this is evident from the CD spectra. As has been shown the sign of the Cotton effect of the longest wave length band changes sign upon hydrogenation of the C_1-C_2 double bond. In this case the hybridization goes from sp^2 to sp^3 in carbon atoms two and three. The suggestion has been forwarded that the electronic structure of an epoxide is as shown below (134).



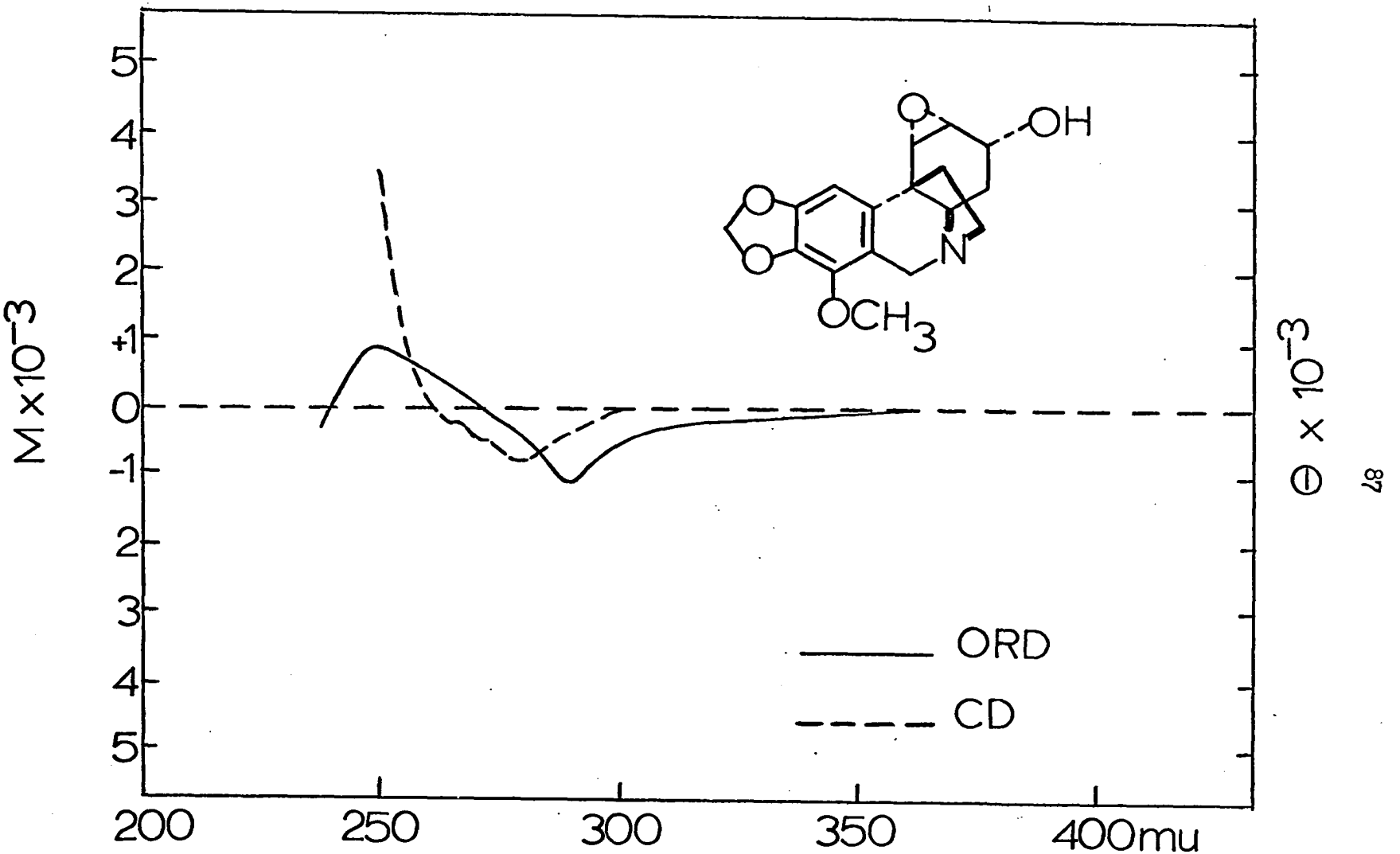


Fig.40

ORD and CD of EPOXYPOWELLINE

Where:  are π electrons

This presentation states that in effect the oxide ring exists as an $sp^{2.n}$ hybrid, where n represents some degree of hybridization between sp^2 and sp^3. On the basis of this hypothesis one would expect the magnitude of the benzene dichroism, which reflects the electronic environment of the aromatic ring, to be less negative than powelline, but more negative than dihydropowelline. Inspection of the CD spectra of these three compounds shows this to be the case. The maximum ellipticity of powelline at 288 mu is (-) 1800°, that of epoxypowelline is (-) 800°, and dihydropowelline has a positive CD at 288 mu of (+) 500°. These values are well out of the range of experimental error and are probably true reflections of the electronic changes taking place in these molecules.

Crinamidine has been found to be the β-epoxy analog of powelline (135). The ORD and CD spectra of this compound are shown in Figure 41. The CD spectrum demonstrates that the dichroism attributed to the first benzene band is negative followed by the normal second band of opposite sign. This was rather surprising since the ORD spectrum was positive

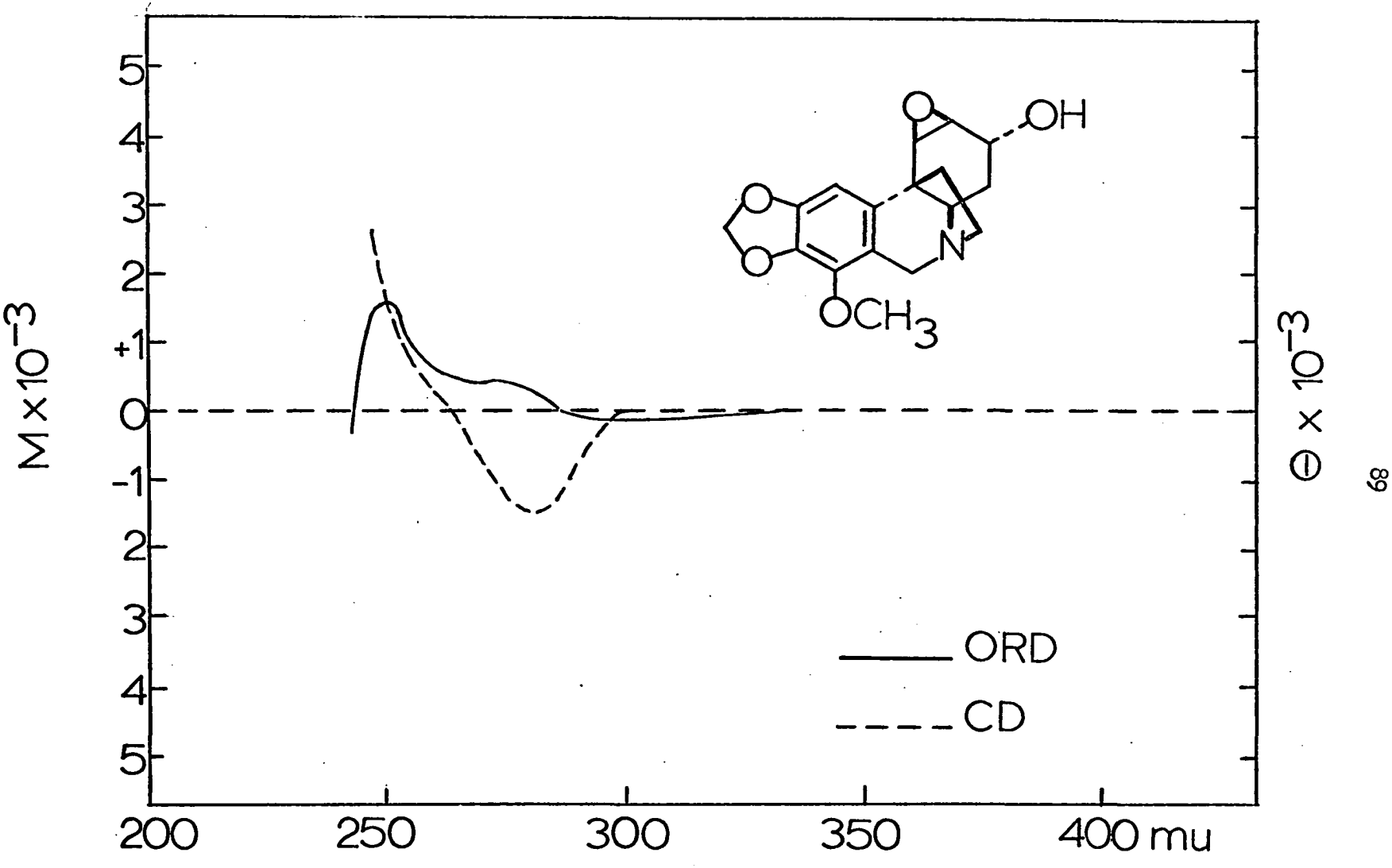


Fig. 41

ORD and CD of CRINAMIDINE

in the 280 mu region of the curve. A comparison of the spectra of crinamidine and undulatine provides similar results, i.e., a negative trough followed by two positive peaks.

Undulatine (135) (Fig. 42) is the methyl ether of crinamidine. The CD spectra of the two compounds are very similar. The rotations of the two compounds are comparable in the 300 mu region of the spectra, but are very different at 250 mu. The oxide ring in undulatine is in the β-configuration, whereas the configuration in epoxypowelline is α. The large rotational differences at 250 mu (4400°) between these two compounds may reflect this difference in configuration. The three compounds, epoxypowelline, crinamidine and undulatine represent the two possible configurations of the oxirane ring. The ORD spectra of both compounds with the β-configuration display curves very similar in shape while epoxypowelline differs from these two. The CD spectra verify that the relative stereochemistry at the 10b carbon atom is the same and that the same electronic environment exists for the most part near the aromatic ring. The differences must therefore be attributed to the signs and amplitudes of the β- and α-epoxides. From the foregoing data it seems that the β-configuration can be assigned the most positive dispersion, and the α-configuration a less positive or negative one. However since these assignments are made for data on only three compounds, empirical correlations of the stereochemistry of the oxirane ring should be made with great caution until more data on structures of

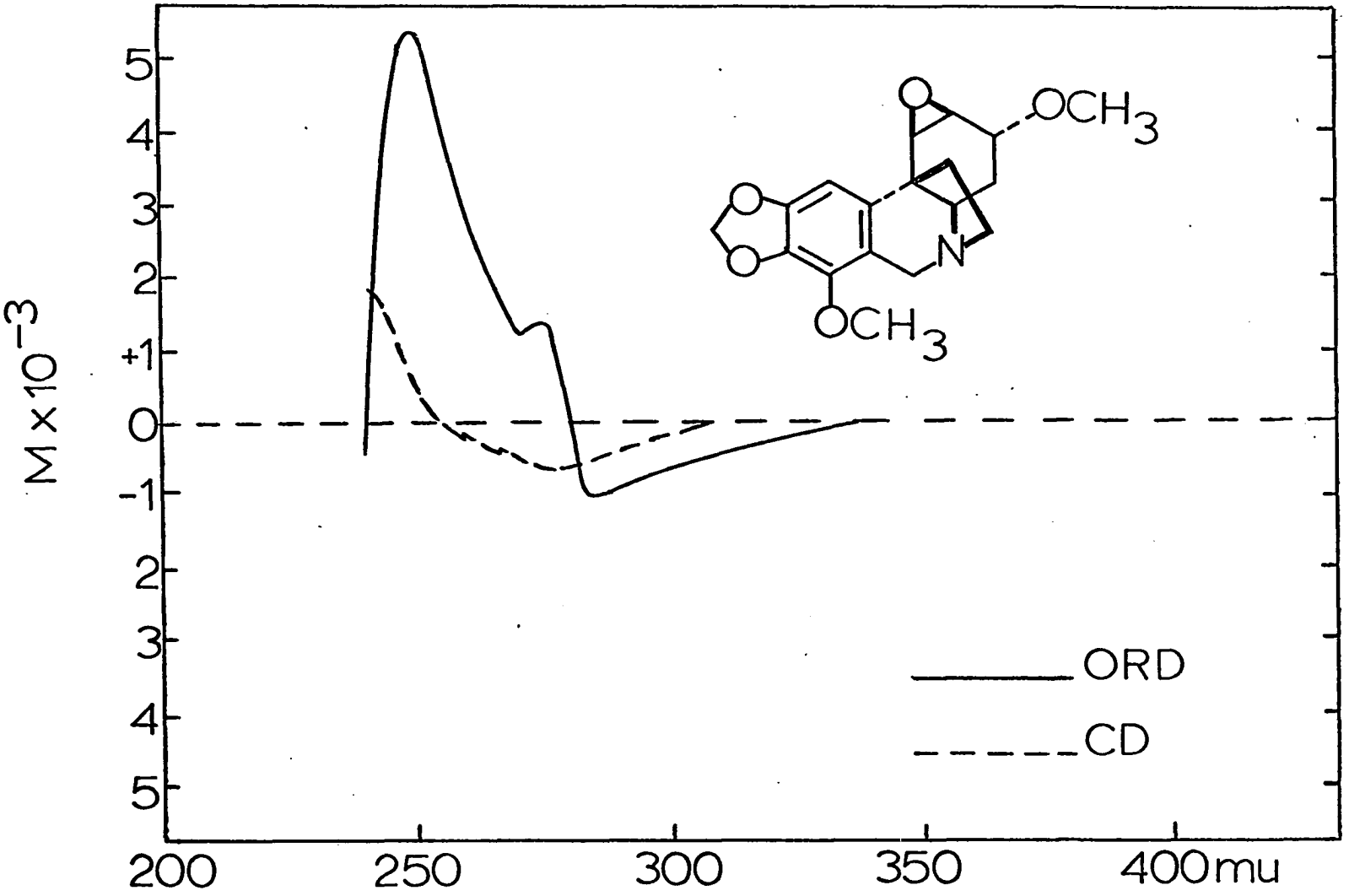


Fig.42

ORD and CD of UNDULATINE

this type are available.

Dihydroundulatine (Fig. 43) differs from other dihydro derivatives that have been studied thus far. Removal of the epoxide ring destroys one asymmetric center, but there still remains one asymmetric center at C_2 which is not present in any other dihydro compounds for which spectral data have been recorded. Because of this the ORD spectra cannot be interpreted on the same basis as previously. Since the configurations of the hydroxyl and methoxyl groups are opposite, and neither would be expected to have a significantly larger dispersion, they would expect to cancel each other to a large extent. Possibly the large decrease in rotation of 3000° at 255 mu reflects this. It is evident from the CD spectrum that the sign of the Cotton effect at 288 mu has changed. In the conversion of an unsaturated alkaloid to its dihydro derivative the change in hybridization has been sp^2 to sp^3. In dihydroundulatine it has been $sp^{2.n}$ to sp^3. The end result of this process is a completely saturated carbon at C_1. It seems at this point that one of the prerequisites for a change in sign of the long wave length band in the methylenedioxymethoxy alkaloids is a completely saturated carbon at C_1. This shall be commented upon in greater detail in Section IV of this thesis.

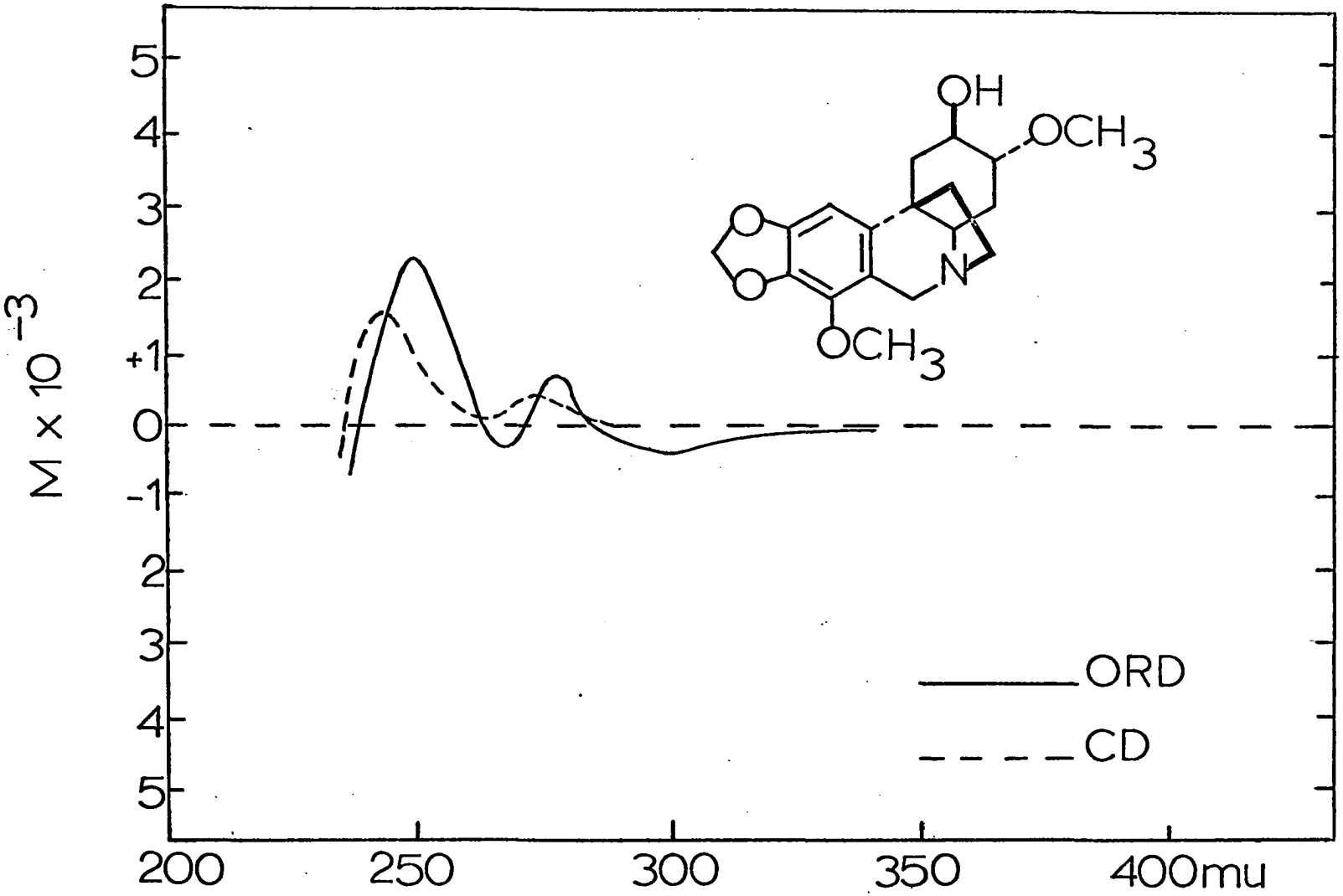


Fig.43

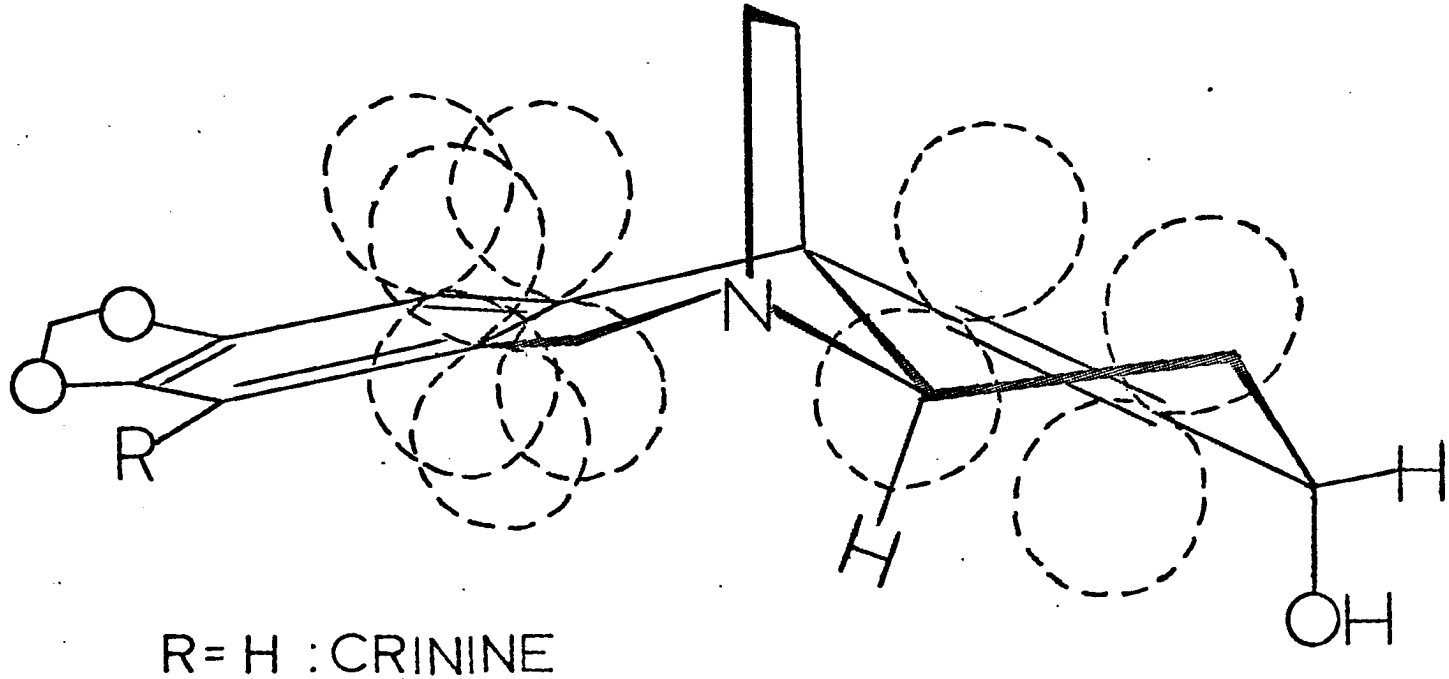
ORD and CD of DIHYDROUNDULATINE

IV. THEORETICAL INTERPRETATION OF RESULTS

The large amount of data presented in the previous section emphasized that there are some subtle structural differences which cause the ORD and CD spectra of crinine and powelline type alkaloids to be decidedly different. It has become evident that while the ORD spectra can be quite useful as a fingerprinting technique for any given class of compounds it is inferior to CD as a method of examining any particular transition. This is because in the rotatory dispersion spectra the overlapping of the tails of individual dispersions becomes quite serious. Even when it is possible to do the necessary calculations of the dispersions of isolated absorption bands the problem is only simplified, not solved. This problem usually does not arise in the CD spectra. It is quite an easy matter to know when the dichroism spectrum will become troublesome, as one must only look at the absorption spectrum of the compound under scrutiny. If the absorption bands are closer than 25 mu, it usually is not possible to differentiate between them in the CD curve unless they are of opposite sign and then only under the best possible conditions. For the reasons cited above this discussion shall for the most part rely on CD data and NMR data where applicable to explain the spectral anomalies found.

The dichroism at 296 mu in crinine is large and negative and at 240 mu large and positive. Hydrogenation of the C_1-C_2 double bond results in dihydrocrinine which affords a CD spectrum of the same signs

but of greatly reduced amplitude. It is easy to rationalize this change in the ORD spectra as due to the loss of the allylic chromophore, however this explanation cannot apply to the dichroism spectra. The first explanation of the CD curve which seems tenable is that the decrease is caused by a change in conformation of ring C. A careful examination of Dreiding models has shown that the bond angles at carbon atoms 1, 2, 3 and 4 change upon hydrogenation, but that the bond angles at the bridgehead carbon and at carbon 5 change very little or not at all. Since the Cotton effect arising from the benzene ring is intimately associated with the asymmetric center, one would conclude that any changes in this Cotton effect due to conformational changes, would be associated with changes at the bridgehead position. The conformation of ring C does not change in going from dihydrocrinine to crinane, but the molecular ellipticity has decreased 800° (32%). This data demands that effects other than conformational ones be used for any complete explanation of these results. As stated previously hydrogenation results in a change in hybridization at the C_1 position. A trigonally bound hydrogen atom is replaced by two which are bonded tetrahedrally. This change brings the two hydrogen atoms at C_1 within the normal 1-3 nonbonded interaction distance (2.8 A) from the pi cloud of the benzene ring. This is shown in Figures 44 and 45. The possibility that this increased stereoelectronic interaction could alter the amplitude and even the sign of the Cotton effect of the benzene chromophore is not unprecedented in rotatory



R= H : CRININE

R= OCH_3 : POWELLINE

Fig. 44

PI ORBITALS in CRININE TYPE ALKALOIDS

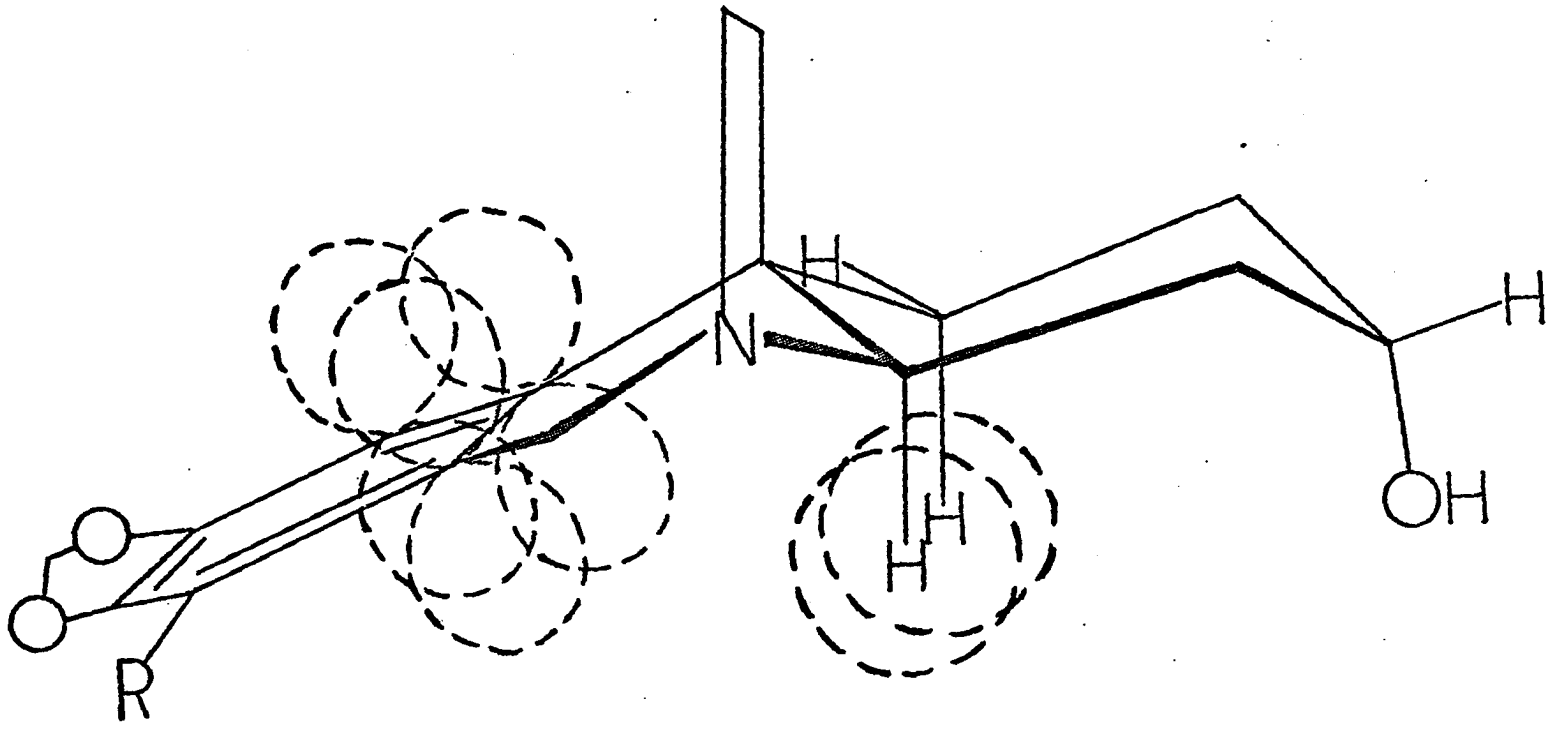


Fig.45

PI ORBITALS in CRININE TYPE ALKALOIDS

phenomenon (136). This effect has been investigated only slightly by optical rotatory dispersion techniques and not at all using circular dichroism until the present investigation was made. If the hypothesis advanced above is correct, one should expect to see an even more striking change in amplitude when progressing from powelline to powellane.

The methylenedioxymethoxy aromatic system may be treated as an odd-alternate system in which the methoxyl group at position seven donates electrons to a non-bonding orbital rather than to an antibonding one. This information was obtained using a simplified alternate orbital, molecular orbital treatment. By this method it can be shown that the positions ortho and para to the methoxyl group at C_7 have electron densities about 0.2 of an electron greater than the meta positions.* The same conclusion can be reached using the simple ortho-para directing ability of a methoxy group as a guide. If these statements reflect the electronic structure of the aromatic ring, it should be possible to find differences in the nuclear magnetic resonance spectra (NMR) which could be attributed to the added electron density at C_{10} in powelline. The NMR spectra of crinine, crinane, powelline and powellane are shown in Figures 46 to 49. The relevant chemical shift data for these compounds and their oxo derivatives is given in Table 9 (137).

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*The author would like to thank Dr. Klaus Rudenberg for his interest and helpful comments. Dr. Rudenberg performed the above calculations.

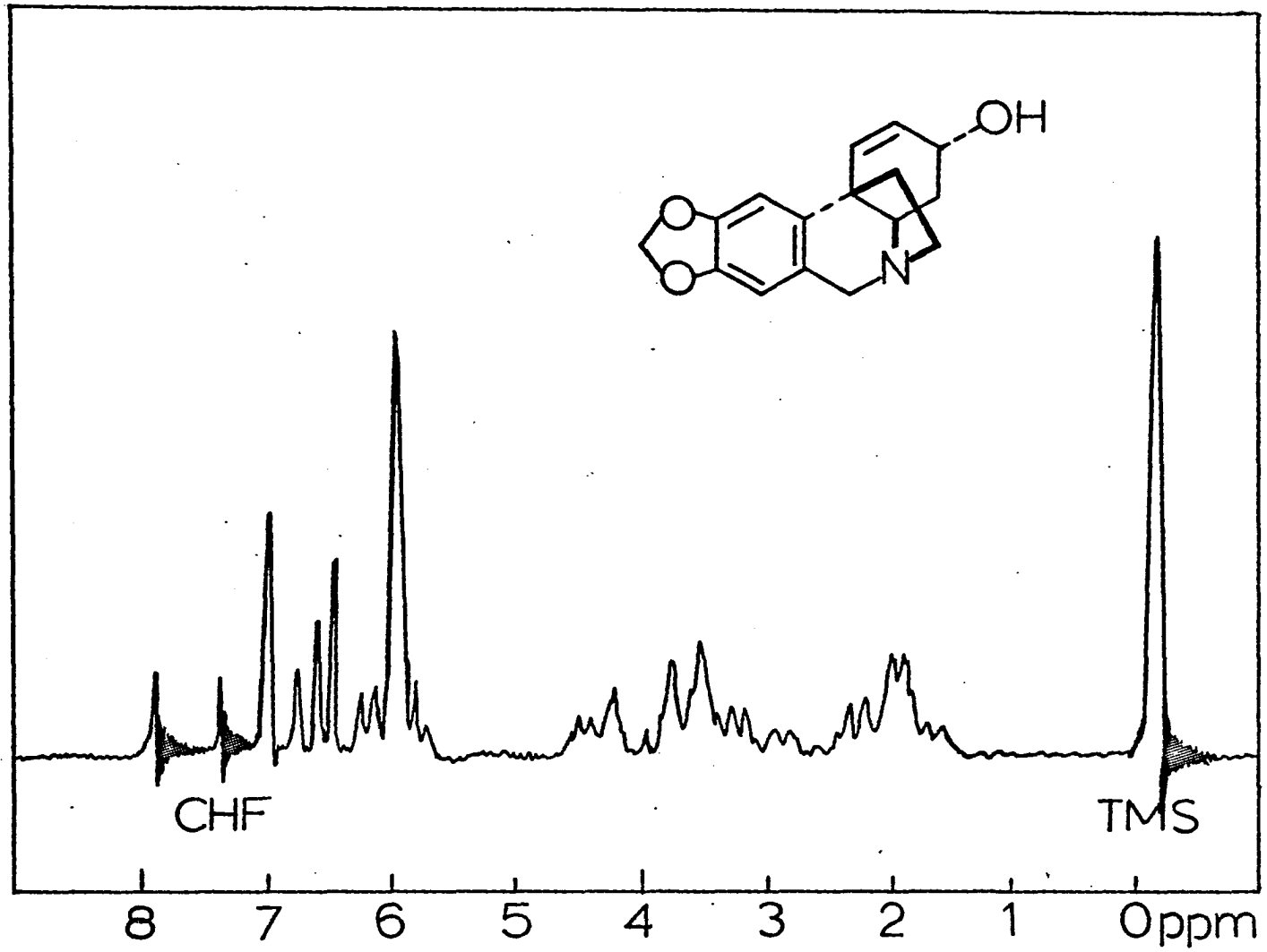

Fig.46

NMR SPECTRUM of CRININE

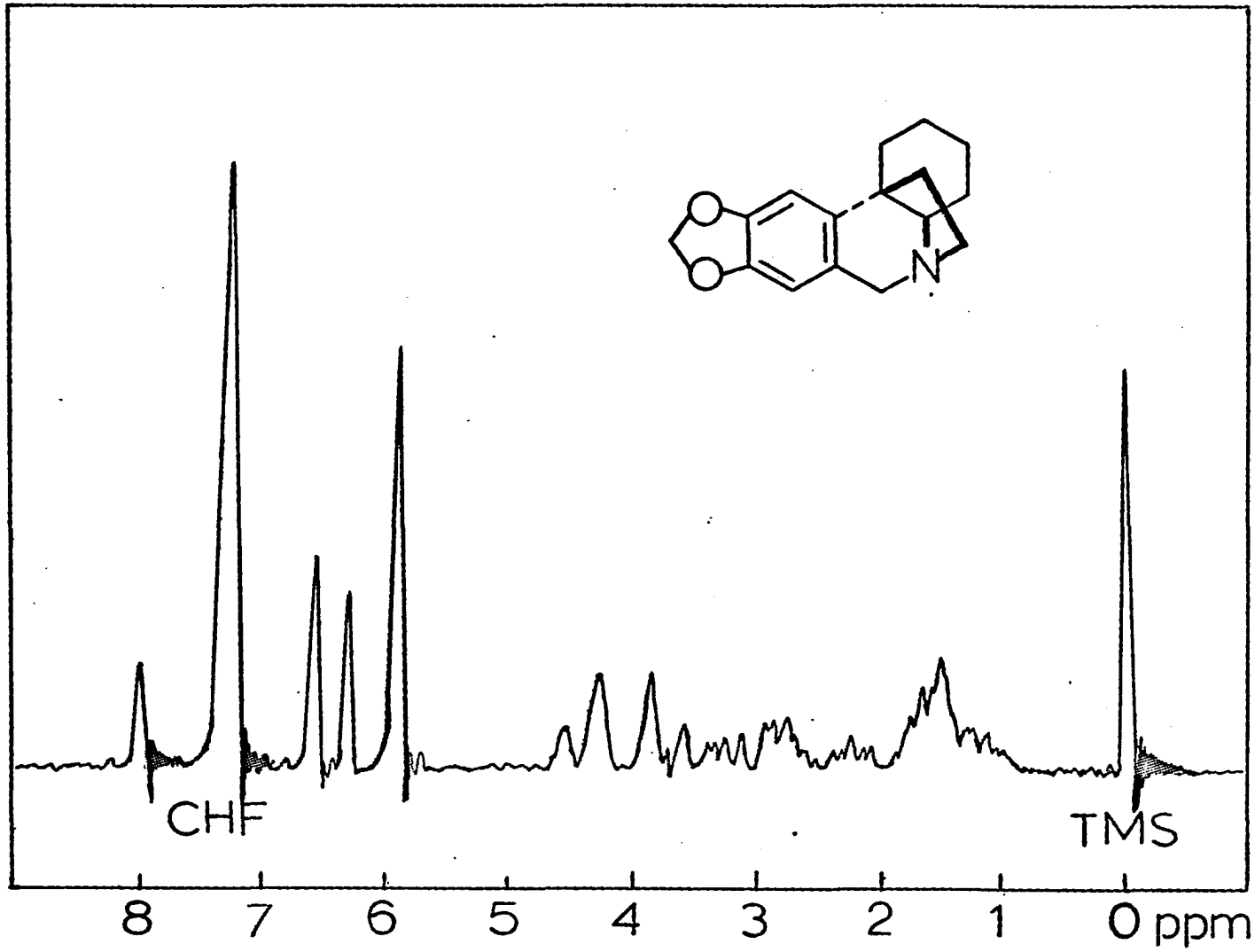

Fig.47

NMR SPECTRUM of CRINANE

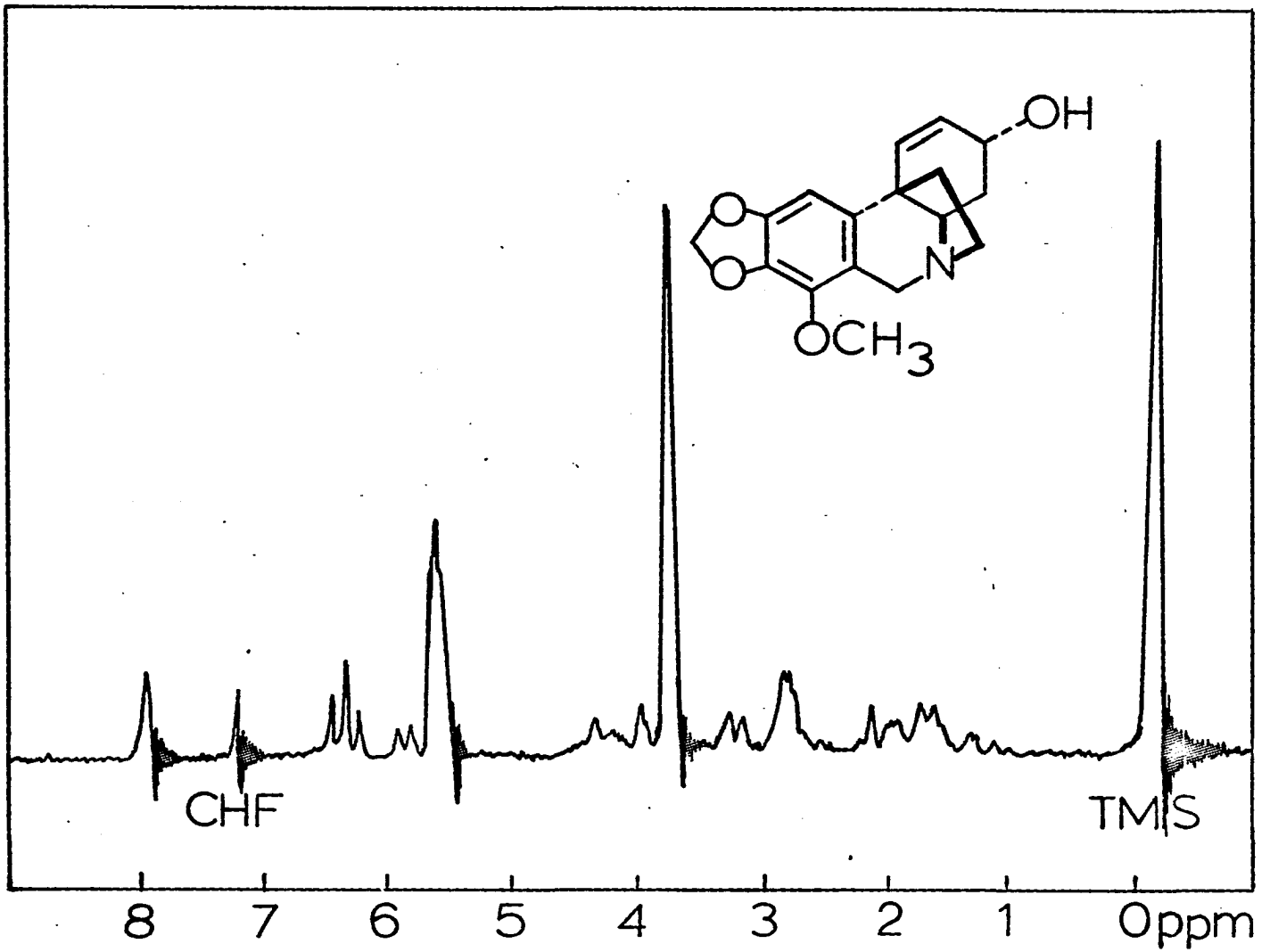

Fig. 48

NMR SPECTRUM of POWELLINE

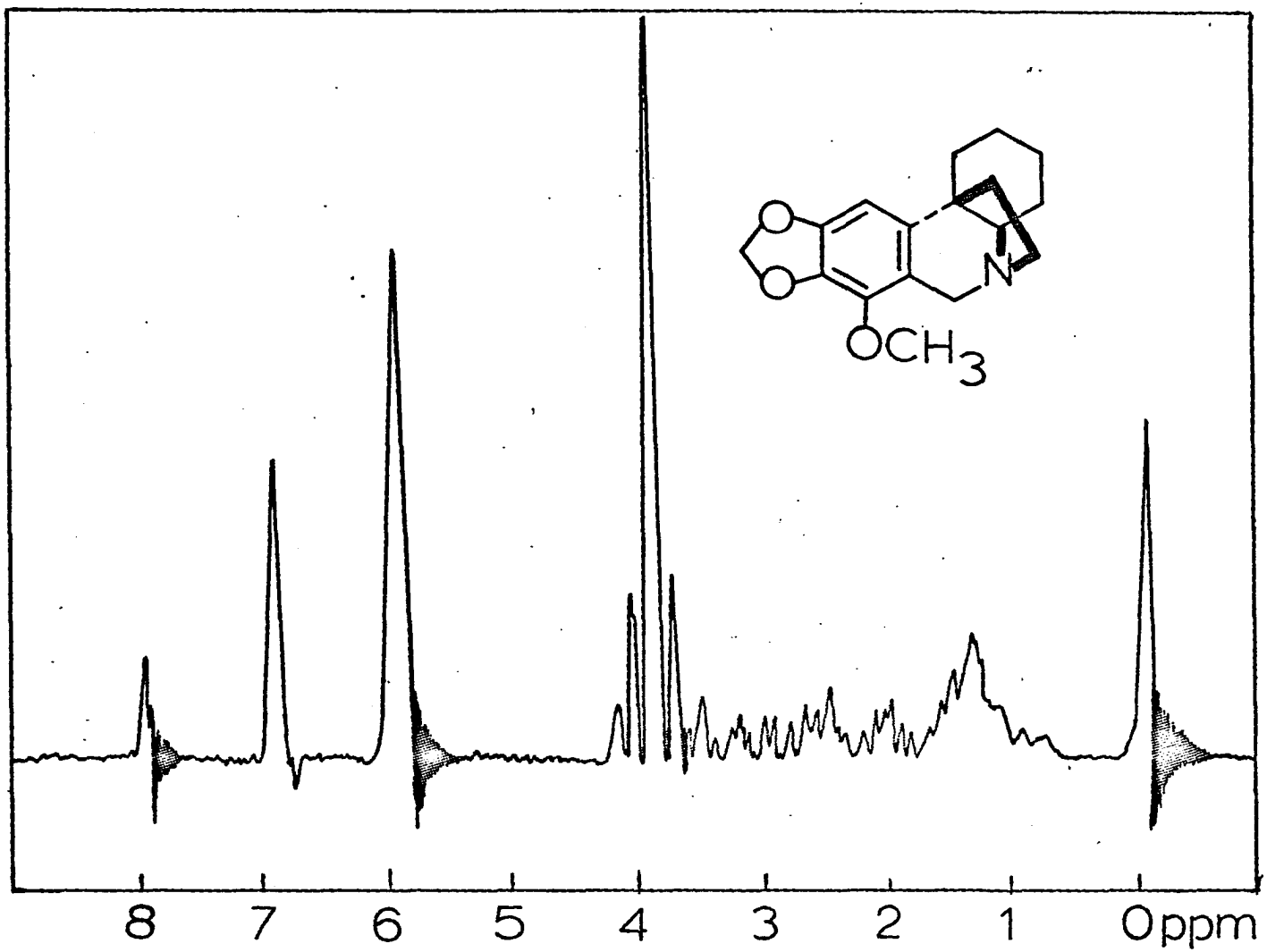

Fig. 49

NMR SPECTRUM of POWELLANE

Table 9. Nuclear magnetic resonance data of Amaryllis alkaloids

	Aromatic proton (C_{10})	Olefinic proton (C_1)
Crinine	407.7 cps	396.8 cps
Crinane	402.0 cps	
Powelline	395.0 cps	390.5 cps
Powellane	387.8 cps	
Oxocrinine	465.0 cps	510.6 cps
Oxopowelline	450.0 cps	508.2 cps

The C_{10} aromatic proton undergoes a 12.7 cps diamagnetic shift from powelline to crinine. This is to be expected on the basis of the electron donating ability of the methoxyl group (138). The difference in chemical shift of the same protons in powellane and crinane is 14.2 cps. If this difference of 1.5 cps is real, it would seem to indicate that there is some small degree of shielding of the aromatic protons by the protons introduced at the C_1 position. A comparison of the chemical shifts of the C_1 olefinic resonances reveals that the proton in powelline is more shielded than the corresponding one in crinine. The difference in chemical shift is 6.3 cps. A possible explanation which can account for this difference is that protons attached to an ethylenic double bond are usually deshielded according to the amount of ring current present in the system (139). Increased charge density at a proton can cause shielding to occur, resulting in resonance higher upfield than anticipated (140). The paramagnetic shift of the olefinic proton in powelline can be attributed to this latter cause. As described pre-

viously the C_{10} aromatic hydrogen is shifted 12.7 cps in powelline relative to that one in crinine because of the introduction of the C_7 methoxy group. The reason cited for this is the increased electron density at the ten position. The proton at C_1 can "see" this increased electron density, but since it is not attached directly to the electron rich cite cannot differentiate pi from sigma electrons. In effect all that the proton sees is a larger amount of negative charge than the corresponding hydrogen atom of crinine. It is this increased negative charge which accounts for the paramagnetic shift of the C_1 olefinic proton in crinine.

Since rotatory dispersion phenomenon are subject to much more subtle structural changes than NMR spectroscopy, it can be anticipated that these differences which cause the NMR spectra to be slightly different will be magnified when viewed with circularly polarized light. An example of the sensitivity of circular dichroism is that of biphenyl. In biphenyl itself there is no dichroism, but in substituted analogs where the two rings are only 10 to 20 degrees out of coplanarity there is a large dichroism (69). These same compounds exhibit no changes in their UV spectra for angles between the two aromatic rings of up to 40 degrees. It is understandable then that the changes in the sign of the Cotton effects of the powelline series of compounds can probably be accounted for by stereoelectronic interactions between the pi electrons of the aromatic ring and the pi system on powelline or the saturated

carbon at C_1 in powellane. Examination of Figures 44 and 45 and of Dreiding models shows that in the olefins the C_1 proton is very close (ca. 1.9A) to the C_{10} aromatic proton. Removal of this interaction can account for a number of the changes noted. The dihydro derivatives can be seen to introduce two new interactions. Both of these involve the pi cloud of benzene, as both protons cut diagonally across the lobes of the pi orbitals. These interactions should be greater in the methylenedioxymethoxy alkaloids than in those with the methylenedioxy group. Both of the hydrogens at C_1 are within the usual 1-3 hydrogen interaction distances usually used to account for steric effects in six membered rings*. The proton at C_{4a} is also within this same distance from the aromatic ring. If the increased electron density of the powelline type alkaloids increases the effective size of the p orbitals of the aromatic ring, the interaction of the C_{4a} proton with the ring should be increased. This may be another contributing factor to the change in sign of the Cotton effects of the aromatic ring.

A change in the hybridization at C_1 in the methylenedioxymethoxy alkaloids causes a change in sign of the Cotton effects of the benzene chromophore appears to be a general phenomenon. Buphanamine was shown to have a small positive dichroism at 290 mu corresponding to a benzene absorption at that same wave length. The corresponding unsaturated

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*These distances were measured using the scale provided in Framework Molecular Models, Prentice-Hall, Inc., Englewood Cliffs, New Jersey.

ketone, oxobuphanamine has a negative dichroism at 290 mu. As no change in the stereochemistry at C_{10a} had occurred, it must be concluded that this sign change was caused by stereoelectronic effects rather than steric ones. The $C_2 - C_3$ double bond in buphanamine and its oxo derivative is too far from the benzene ring to interact effectively with the benzene ring. However, the pi system of the carbonyl group at C_1 has been shown to be close enough to form a homoconjugated system with the benzene ring. Removal of the carbonyl group by reduction replaces a pi-pi interaction with a H-pi interaction and results in a change in sign of the Cotton effect of the 290 mu band. A comparable effect is found in powelline.

Undulatine has been shown to undergo a change in sign of its 285 mu benzoid dichroism upon reduction to dihydroundulatine. This compound is quite similar to those discussed above in terms of the change in hybridization from $sp^{2.n}$ to sp^3. Although the reduction of the epoxide ring is not the same as the reduction of a double bond, the final product in this case can be considered completely analogous with respect to the protons at C_1. The two C_1 protons in dihydroundulatine have the same relationship to the benzene ring as do those in dihydropowelline. This change in sign of the Cotton effect corroborates the statements made earlier that one of the prerequisites for a sign change is a saturated carbon atom at the 1 position in the Amaryllis. It supports the statement that a change in hybridization at C_1 is also responsible for this sign change.

All of the above conclusions were drawn from consideration of the Cotton effects of the powelline-dihydropowelline-powellane system. However, all of the alkaloids possessing the methylenedioxymethoxy benzene chromophore underwent these same changes.

Further evidence that the change in sign of the first benzene band was stereoelectronic in origin was provided by an examination of the CD spectrum of morphine in acid and base. In alkaline solution morphine shows a positive band at 295 mu and the second band at 255 mu was positive also. It was reasoned that the anion of the aromatic hydroxyl group must increase the electron density in the aromatic ring and that the same type of pi-pi orbital interaction must be occurring as in the powelline type alkaloids. If this were true, acidification of the solution should regenerate the phenolic proton thereby decreasing the amount of conjugation which occurs in the anion. This should result in a change in sign of the first benzene dichroism if only stereoelectronic effects were responsible for the changes in the first place. The experimentally found ellipticities were negative at 295 mu and positive at 255 mu respectively, demonstrating that electronic effects can be solely responsible for a change in sign of the long wave length dichroism band in this type compound. The CD spectra of the acidic solution of morphine was virtually superimposable upon that of codeine.

The preceding paragraphs have presented a qualitative interpretation of the observations made. They account for the change in sign of the Cotton effects of a number of compounds in terms of a readily under-

standable model, which is based on a number of simple assumptions. The interpretation advanced may not be correct in the absolute sense, but it can account for a large number of experimental observations which otherwise would have been found completely analogous. It is possible by using this approach not only to account for the observed spectra, but also to predict with a fair degree of certainty when to expect the sign of a particular Cotton effect to change. It is now possible to rationalize the mirror image spectra of powellane and crinane at 280-290 mu in terms of their electronic structures, and at the same time be certain that they have the same relative configurations at the bridge position.

There are a number of observations which cannot be explained on the basis of the above phenomenon. The most obvious question that arises pertains to the antipodal nature of the two benzene bands. There is no a priori reason why these two Cotton effects should be antipodal. The rotatory power of any optically active transition depends upon the product of two vector quantities, the electric and magnetic transition moments. The rotation of a given asymmetric center is directly proportional to their dot product, i.e.,

$$\text{Rotation} \propto \bar{R}_{ij} \cdot \bar{M}_{ji} = |R_{ij}| \cdot |M_{ji}| \cos \Theta$$

where:

R_{ij} = electric transition moment $\sim \sqrt{E}$ between the states i and j

M_{ji} = magnetic transition moment

E = extinction coefficient of chromophore under observation

Θ = angle between R and M.

The magnetic and electric transition moments can assume an infinite number of orientations in space, however, only two of these correspond to the maxima and minima of their vector products. In the former case R_{ij} may be completely aligned with M_{ji} to give a maximum value which can arbitrarily be set at (+) 1. This is given in Equation 11.

$$11. \qquad |R_{ij}| \cdot |M_{ji}| \cos 0 = |R_{ij}| \cdot |M_{ij}| = +1$$

The minimum value of the products of these two vectors is (-1) and occurs when they are equal and opposite each other. Equation 12 is applied in this case.

$$12. \qquad |R_{ij}| \cdot |M_{ji}| \cos 180 = |R_{ij}| \cdot |M_{ji}| = -1$$

The values of R_{ij} and M_{ji} can be obtained from the integrals

$$R_{ij} = \int \psi_i \bar{R} \psi_j \, d\tau \quad ; \quad M_{ji} = \int \psi_j L \psi_i \, d\tau$$

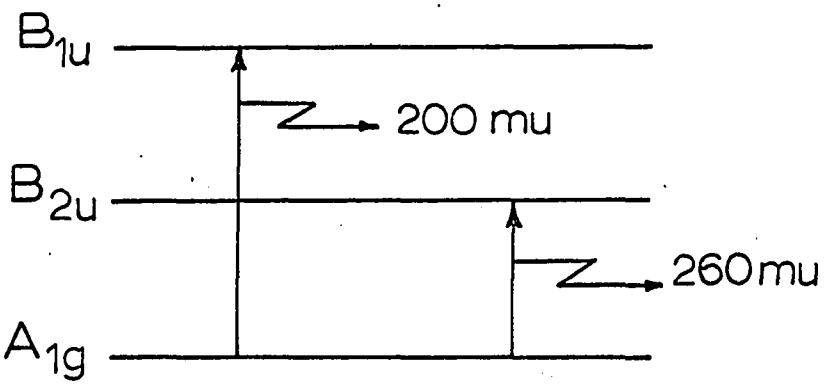
where:

$\bar{R}$ = distance operator

L = angular momentum operator.

The wave functions ψ_i and ψ_j are difficult to evaluate for simple benzene derivatives and are impossible to solve for something as complicated as an Amaryllis alkaloid with as many as five substituents on the aromatic

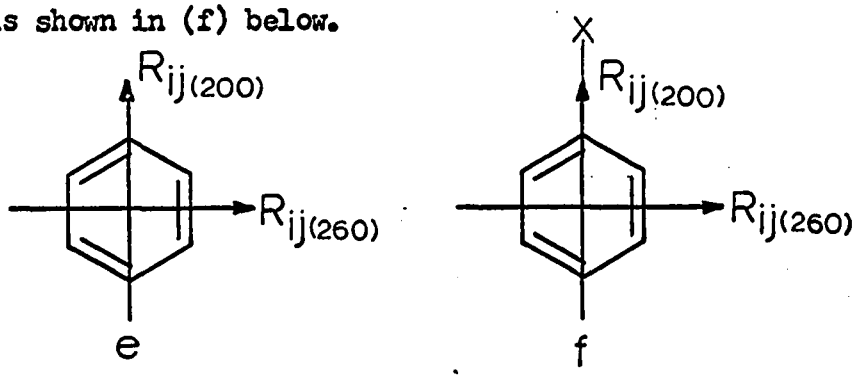
ring. It becomes necessary to discuss the electronic transitions of the benzene ring using simplified schemes such as the one shown below.



In a completely unsubstituted benzene these transitions represent electronic transitions from p-pi ground states to the p-pi* excited state. Two of these occur in the UV at 200 mu and 260 mu (141). These correspond to the 240 mu and 295 mu bands observed in the Amaryllis alkaloids. The electric transition moments of these two bands are perpendicular in benzene (e) and it can be shown in this case that the dot product of R_{ij} and M_{ji} is zero.

$$13. \qquad |R_{ij}| \cdot |M_{ji}| \cos 90 = 0$$

It has been shown by linear dichroism measurements that in a substituted benzene the highest energy transition lies along the substitution axis (141). This is shown in (f) below.

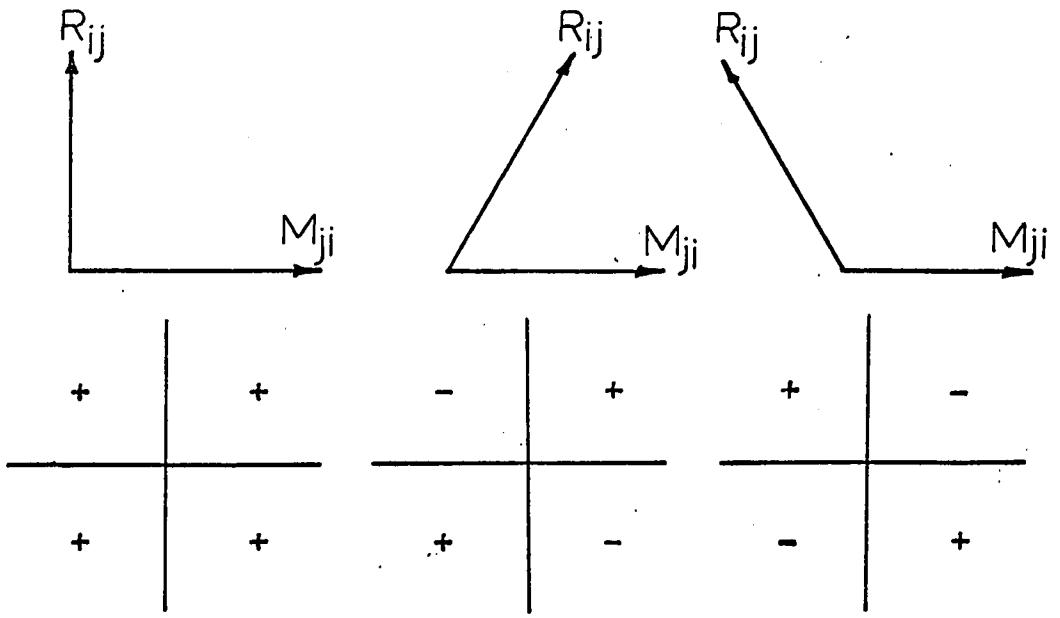


Supporting evidence that the electric transition moments are perpendicular has been obtained from magnetic circular dichroism measurements (142). In an unsubstituted benzene the transitions are unperturbed and no optical activity can exist since the entire molecule and its electronic structure are symmetrical. Introduction of a substituent into the ring removes this symmetry of the electronic structure. Excitations involving only the p electrons of the benzene ring cannot give rise to an optically active transition. It is necessary to introduce mixing of the d_{xy} orbitals of an atom adjacent to the benzene ring. Usually this is an asymmetric center on some atom or group of atoms capable of perturbing the aromatic pi electrons. It is possible to write an equation describing this new excited state.

14. $$\Pi^{*'} = \Pi^{*} + \sum_{i} A 3d_{xy}$$

where A is a constant involving the products of the original pi* orbital, the perturbing potential of the non-aromatic portion of the molecule responsible for producing the asymmetry in the benzene system and the $3d_{xy}$ orbitals of the aromatic ring. This discussion is strictly analogous to that used by Kauzmann and Moscowitz in discussing the induced optical activity of the carbonyl group in an asymmetric environment (143, 51). It must be concluded that in this case of the substituted benzene the dot product of the electric and magnetic transition moments is no longer zero. However, rotations of the benzene derivatives are small compared to those of ketones and enones and it can be assumed that

the components of the electric transition moment parallel to M_{ji} are also small. Since these components can be in the same or opposite direction as M_{ji} the resultant of the vector quantities R_{ij} and M_{ji} can give rise to rotations of different sign. This is shown schematically below with each situation projected onto a set of coordinates.



The first drawing depicts the situation in benzene where there is no optical activity. The second and third denote optically active transitions of different sign. Since the two observable bands in benzene are of opposite sign in the normal Amaryllis spectra, an interpretation such as this seems quite tenable. This explanation supports the fact that the dichroisms of the 240 mu and 295 mu bands have opposite signs, but it cannot account for why. There is no a priori reason why the same aromatic ring should be effected in two different ways by the same asymmetric center.

A more difficult question to answer is why the sign of the 295 mu band changes so readily. One possible rationalization is that since the 240 mu band is of higher energy it takes more energy than is available in any given perturbation to change its mode of transition. The 295 mu band is of lower energy and it takes less to change it. The important point, which cannot be stressed too heavily, is that the sign of the low energy band is not to be relied upon to provide meaningful information about the asymmetry at the aromatic chromophore. From the work reported here and from that of Velluz (98), the usual relationship between the first two benzene dichroism is an antipodal one. If this is not observed, it is more than likely that the sign of the highest wave length dichroism has changed and does not reflect the true stereochemistry of the asymmetric center. In the more than sixty aromatic alkaloids studied here the sign of the second benzene band at ca. 240 mu reliably reflects the absolute stereochemistry of the asymmetric carbon atom adjacent to the benzene ring.*

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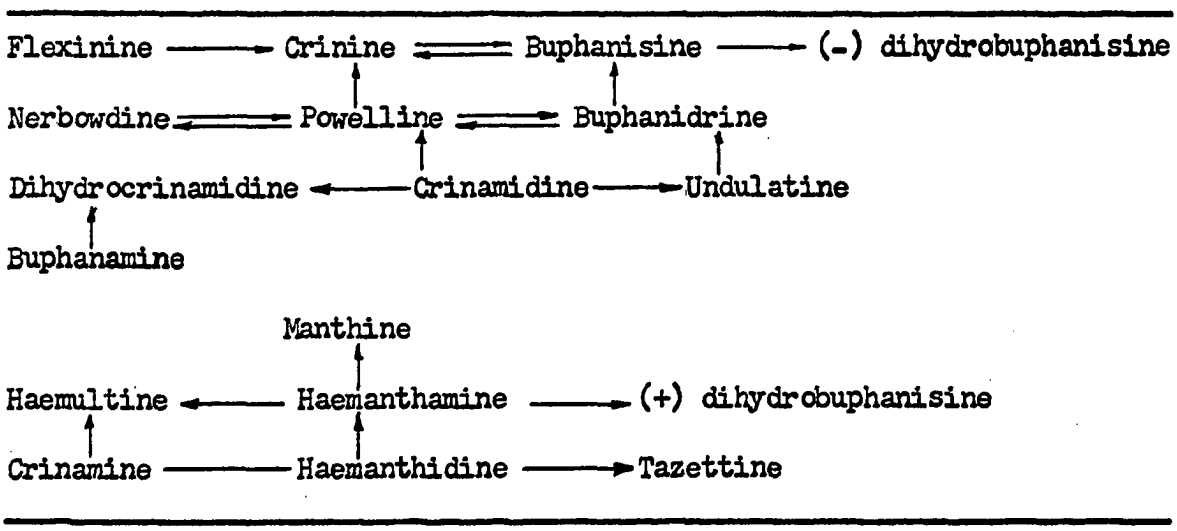
*The author is deeply indebted to Dr. John Foss for the long hours spent in discussing the above interpretation of the optical activity of the benzene ring. Most of the material presented here was taken from such discussions.

V. ABSOLUTE STEREOCHEMISTRY

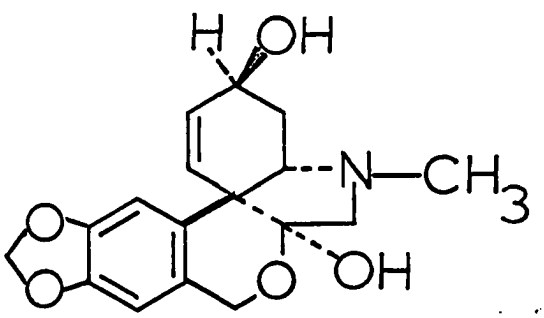
A. Amaryllis Alkaloids

The relative stereochemistry of the Amaryllis alkaloids has been reviewed (1), and for the most part rests on sound chemical transformations and spectral correlations. Alkaloids of the 5, 10b-ethanophenanthridine and [2]-benzopyrano[3,4c] indole series have been interconverted and the correlations which have been made are shown in Chart 1. Arrows do not imply that these transformations take place in one step but merely that they have been established (1). However it has not been possible to obtain a simple degradation product from any of these compounds which can be compared with a compound of known absolute configuration.

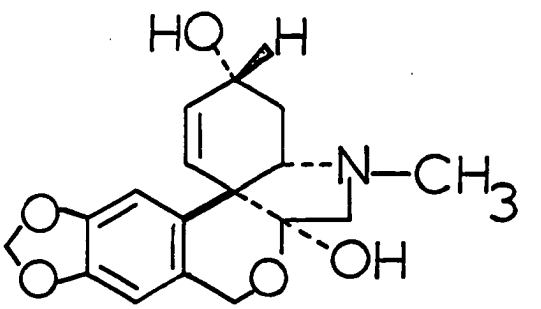
Chart 1. Interrelations among the Amaryllis alkaloids



The absolute and relative stereochemistry of Amaryllis alkaloids based on 5, 10b-ethanophenanthridine is derived from the studies of Uyeo (144) on the structure of tazettine (Fig. 50). Mild acid hydrolysis of tazettine produces two alcohols which were shown to be epimers, because each was oxidized to the same α,β-unsaturated ketone by manganese dioxide. One of these, tazettinol (XII), could be converted by methylation to tazettine methiodide. Methylation of isotazettinol (XIII) provided the isomeric methiodide. To remove the hemiketal function from the molecule, cyclic ethers, deoxytazettinol (XIVa) and deoxyisotazettinol (XIVb), were prepared by the lithium aluminum hydride reduction of tazettine.



XII



XIII

Acid cyclization and hydrolysis resulted in the above cyclic ethers. Deoxyisotazettinol was the major product of the sodium borohydride reduction of deoxytazettinone, and it was inferred that the iso series is the more thermodynamically stable of the two isomers. A comparison

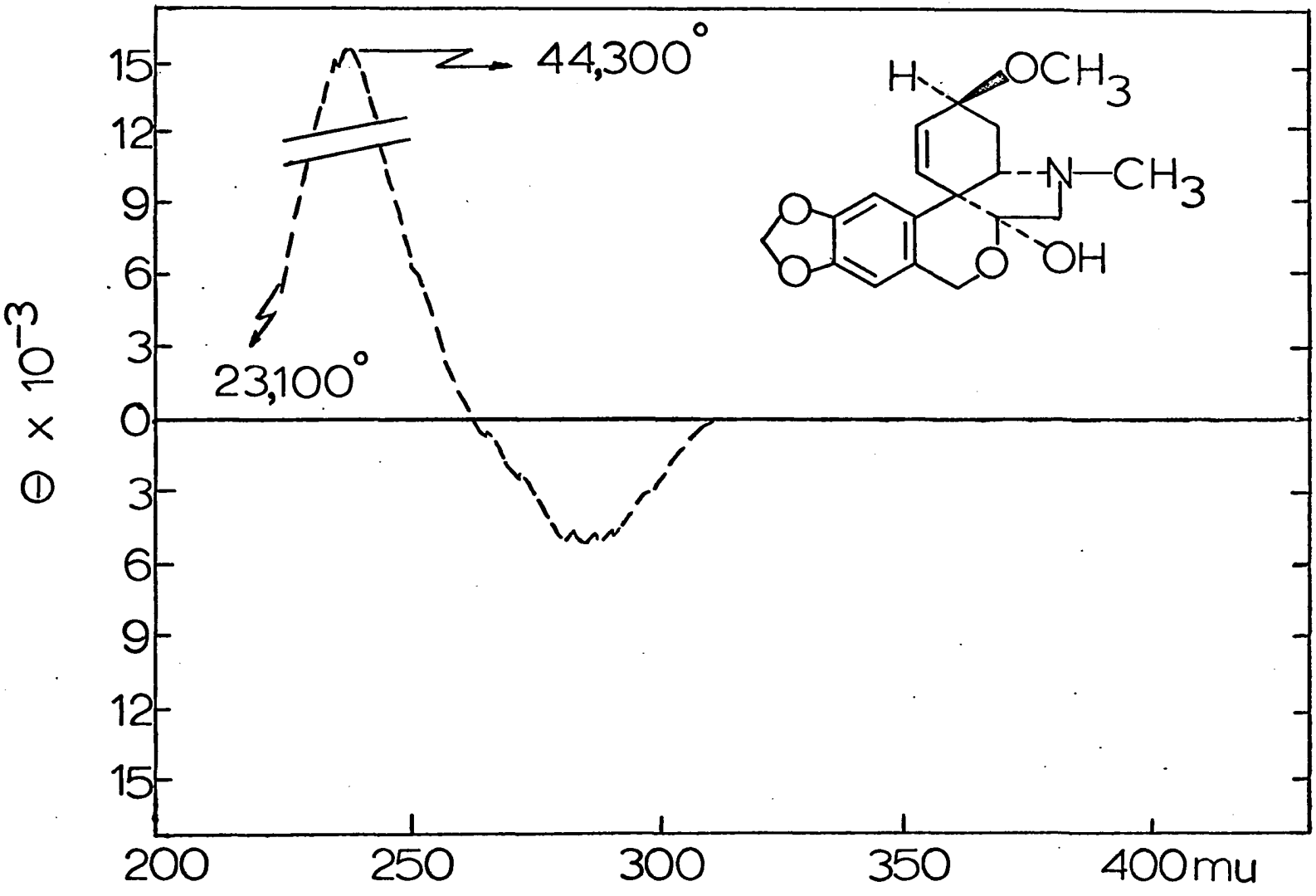


Fig.50

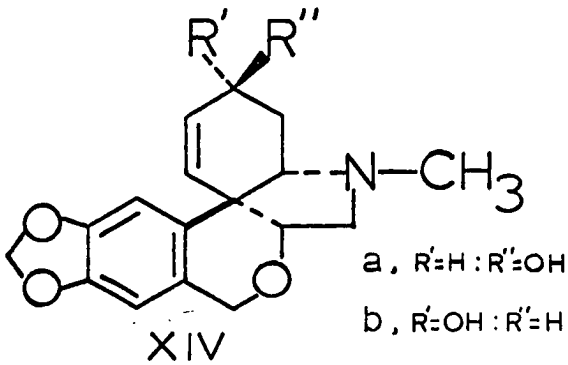
CD of TAZETTINE

of the basicities of deoxytazettinol and deoxyisotazettinol shows that the latter is the stronger base. This fact implied that the proton of the conjugate acid derived from deoxyisotazettinol (XIVb) is hydrogen bonded to the hydroxyl group, and thus the nitrogen and hydroxyl are cis in this compound. It could be argued, however, that the hydroxyl proton of (XIVa) can hydrogen bond to the aromatic ring leaving the lone pair of nitrogen electrons to bind a proton. The proton in the α configuration can hydrogen bond to the nitrogen therefore decreasing its basicity. It has also been postulated that a cis ring fusion exists between the five membered nitrogen ring and the cyclohexene ring, since the nitrogen must be able to assume a pseudo-axial configuration which facilitates the various elimination reactions of tazettine (145).

The relationship between the methoxyl and the phenyl groups of tazettine in ring C are of extreme importance. It has been shown that these groups are cis in tazettine (145). Degradation of dihydroisotazettinol (XV) by standard methods afforded a hydroxy ether (XVI), the structure of which was proven by synthesis. A key intermediate in this synthesis was the lactone (XVIIa). If hydrolysis of the lactone (XVII) occurs by attack of base at the carbonyl group, the stereostructure of the hydroxy acid must be represented by (XVIII) or its mirror image. Chloromethylation of (XVIIa) followed by reduction and cyclixation provides (XIX), or its mirror image, which had an infrared spectrum identical with optically active material derived from (XIII). Since

the immediate precursor of the lactone (XVIIa) was the hydroxy acid (XVIII), it was therefore concluded that the carboxyl and hydroxyl functions were cis in order for this lactone to form. Experimental verification that this was correct was the ready conversion of the lactone to the starting hydroxy acid and recyclization to the same lactone (145). Experimental proof that this lactone did not open via attack at saturated carbon was not presented. If such a mechanism were operative a trans opening of the ring would occur and a trans relative stereochemistry of the methoxyl and phenyl groups would be present. In order to remove any doubt as to the nature of the lactone ring opening a reinvestigation of this reaction is being carried out in the Wildman group laboratories. However since the hydroxy acid obtained from the lactone could be converted back to the same lactone, the assignment of a trans relationship between the methoxyl and phenyl groups of isotazettine and a cis relationship in tazettine is certainly most probable.

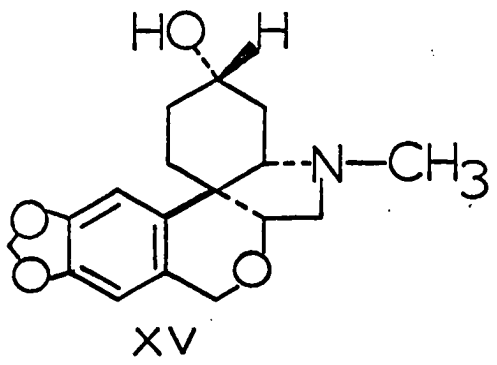
Additional support for a cis lactone ring opening is the reduction of (XVIIb) with lithium aluminum hydride to produce the triol (XX). Assuming that the hydroxyl and hydride anions react in a similar manner, attack at saturated carbon must be ruled out since this would have resulted in a methylene instead of a secondary hydroxyl group at position 3. The only reported case of attack at the carbon atom α to the lactone oxygen is that reported for β-propriolactone and its homolog β-butrolactone. This mode of attack is thought to predominate because



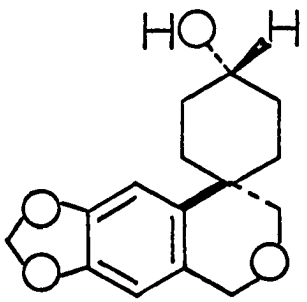
a, R'=H : R''=OH

b, R'=OH : R''=H

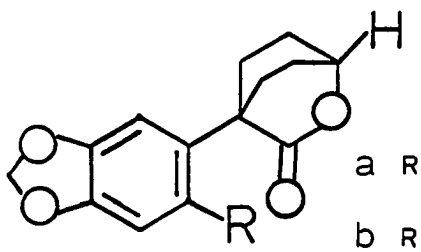
XIV



XV



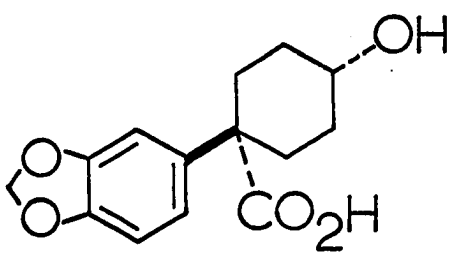
XVI



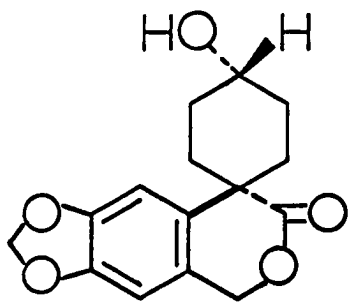
a R = H

b R = CH_2OH

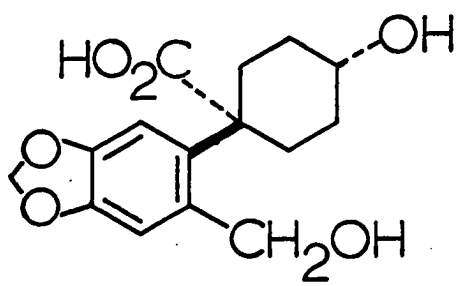
XVII



XVIII



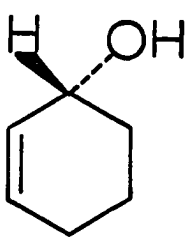
XIX



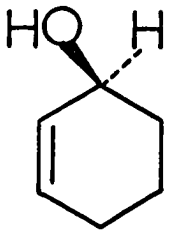
XX

of the strain involved in the four membered ring (146). The lactone (XVIIa) is nothing more than a substituted [2, 2, 2] oxabicyclooctane derivative and as such should be relatively strain free.

At this point Mill's rule was applied to tazettine and isotazettine in an attempt to assign the absolute stereochemistry at C_3 (144). Mill's rule is empirical and based on the rotations of many allylic steroids of known absolute configuration. These rotations are all taken at 589 mu. The rule states that of the two allylic alcohols (XXII) and (XXIII), (XXII) will have the more positive rotation.



XXII

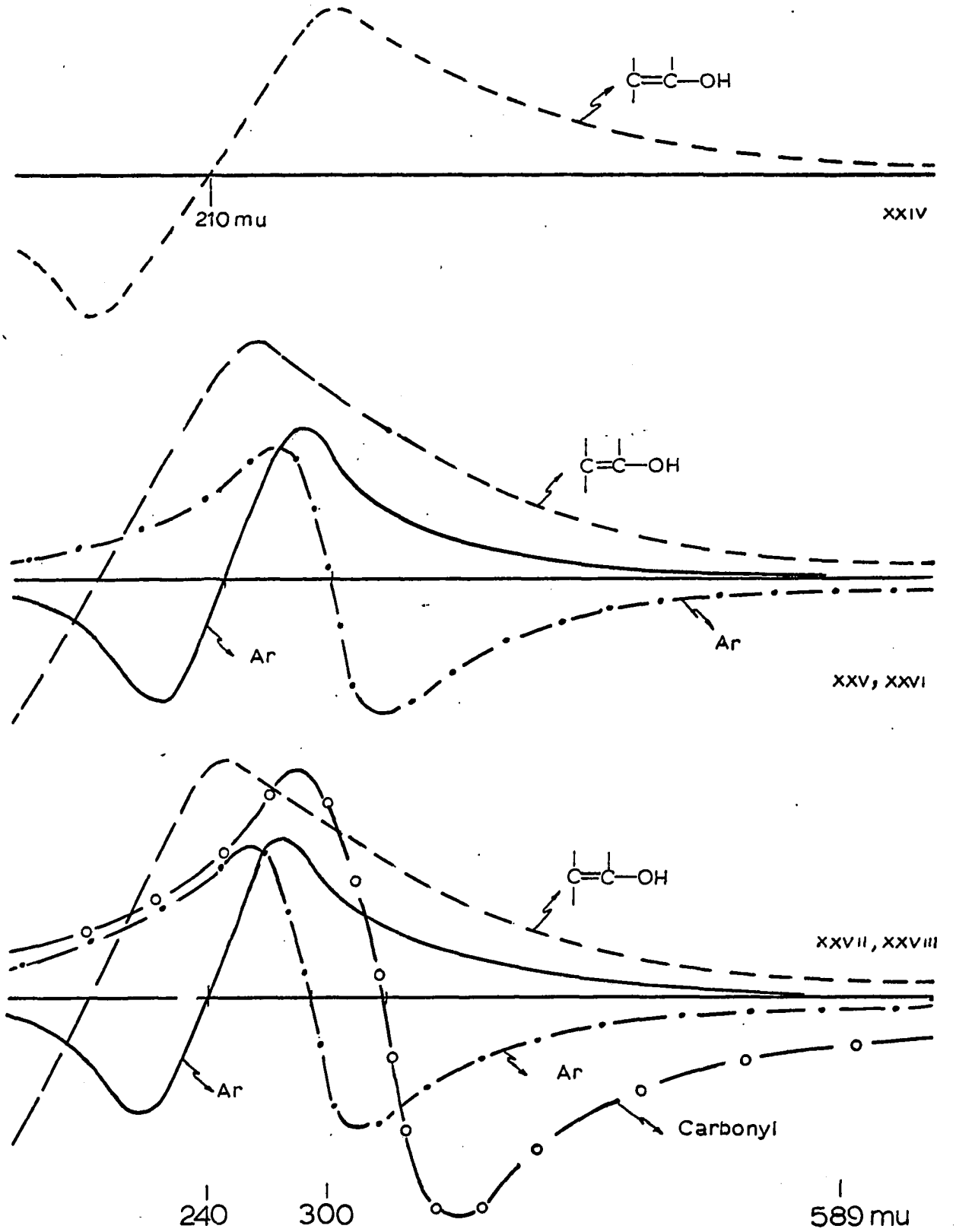


XXIII

Tazettine is less positive at 589 mu (+119°) than isotazettine (+260°) and the methoxyl group in tazettine was assigned the β configuration by this convention. This assignment was a very important one since tazettine, haemanthidine, haemanthamine and montanine have been interrelated chemically through reactions which did not alter the stereochemistry at either the bridgehead carbon atom or the allylic methoxyl group. This assignment in tazettine was also considered an assignment of absolute configuration in these other alkaloids. Mill's rule was derived from compounds lacking any chromophores absorbing above 215 mu. The rotation observed at 589 mu is nothing more than the tail of the

allylic hydroxyl dispersion occurring near 210 mu. Since there is no other dispersion between 589 mu and 215 mu in these compounds the interpretation of the sign of the rotation of the hydroxyl function is straightforward. For compounds which exhibit dispersions above 215 mu, i.e., optically active benzene and carbonyl derivatives, the application of Mill's rule for the assignment of absolute configuration of the hydroxyl group becomes highly questionable. This can best be shown schematically.

In a steroidal allylic alcohol there is no interference from other dispersions and the sign of the rotation at 589 mu is a true indication of the hydroxyl dispersion. The tails of the two benzene dispersions are probably as large as the hydroxyl dispersions, and it is impossible to differentiate between them at the sodium D line. This can be anticipated since the benzene absorption is 100 mu closer to 589 mu than the hydroxyl absorption and it is very likely that the benzene dispersion will be at least as large as that due to the tail of the hydroxyl. It should be noted however that if the hydroxyl dispersion were positive, a positive rotation would probably be observed. This is due to the addition of two positive rotations to one negative one. The third example points out what can happen when a carbonyl chromophore is introduced into the molecule. Any rotation observed at 589 mu will be dominated by the carbonyl group and would not reflect the hydroxyl dispersion. An example of the second case occurs with crinine and epicrinine. Both epimers give rise to negative Cotton effects. From


C=C—OH
210 mu
XXIV
C=C—OH
Ar
Ar
XXV, XXVI
C=C—OH
XXVII, XXVIII
Ar
Ar
Carbonyl
240
300
589 mu

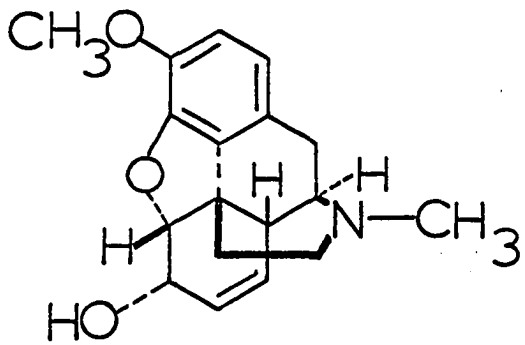
CD data and the calculations made it can be estimated that the benzene dispersion at 295 mu is (-) 6500°, and would still be quite large at 589 mu (ca. 250°). It is not possible to determine which dispersion one sees at the sodium D line as both the hydroxyl and the aromatic dispersions are negative. The ORD spectra of crinine and epicrinine show that the amplitude of the hydroxyl dispersion decreases rapidly with increasing wave length. This supports the hypothesis that one is, in reality, observing the benzene dispersion at 589 mu.

Jeffs (10) and Wildman (9) have assigned absolute configurations to a large number of 5, 10b-ethanophenanthridine Amaryllis alkaloids on the basis of Mill's rule. No other evidence, either degradative or X-ray data support these assignments.

It must therefore be concluded that although the relative stereochemistry of the 5, 10b-ethanophenanthridine, montanines and (2) benzopyrano (3, 4c) indole alkaloids has been established by sound chemical methods, the absolute stereochemistry of these compounds is open to question.

B. Morphine Alkaloids

The gross structures and stereochemistry of morphine and its derivatives has been the subject of a recent review (147). The stereostructure of morphine and codeine was elaborated both by chemical and X-ray analysis, and may be represented by (XIX).



XXIX

Optical rotatory dispersion spectra have been recorded for morphine, codeine and dihydrocodeine from 700 to 300 mu (96). Recently Kuriyama has carried out an ORD survey of a number of morphine derivatives, and Weiss (148) has examined the CD of similar compounds. All of the alkaloid derivatives studied were of known absolute configuration. The rotatory dispersion spectra are all straightforward, exhibiting clear cut peaks and troughs up to 250 mu. In all cases members of a given absolute configuration had the same sign for the first peak at ca. 275 mu. This indicated that removal of the oxide bridge in compound (XXX) did not change the sign of the first aromatic dispersion. The spectra of the three morphine derivatives (XXX, XXXI, XXXII) are reproduced in Figure 51.

Weiss has claimed that removing the oxide bridge in morphine alkaloids causes the sign of the 240 mu band Cotton effect to change. The CD and ORD spectra of 13 compounds show that in four of these compounds

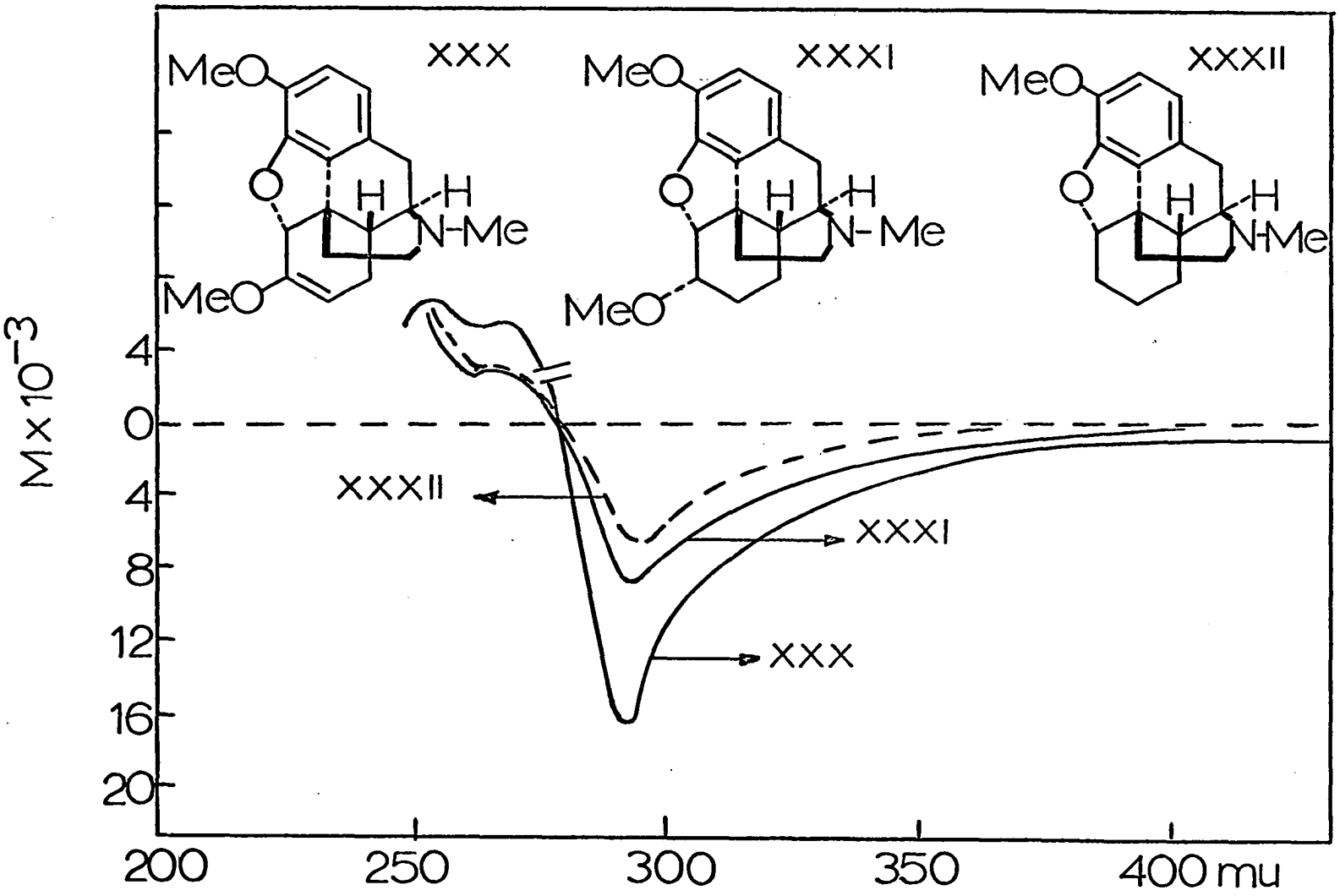


Fig. 51

ORD of MORPHINE DERIVATIVES

the 285 mu and 240 mu bands are of opposite sign and are identical to those found in morphine. These four compounds are dimethoxy derivatives in which the aromatic absorptions are at ca. 285 mu and 240 mu and can be observed with little difficulty on a commercially available instrument. The nine compounds in which the sign of the second band seems to have changed have their second absorption at ca. 225-230 mu and we have found that it is very difficult or impossible to observe this dichroisms, except under most favorable conditions. This is especially true when there is a chromophore in the molecule such as a hydroxyl or double bond having a large dichroism at ca. 200 mu. In none of Weiss' reported spectra were clearly defined maxima reported, only negative tails. An example of this difficulty is afforded by lycoramine. Catalytic hydrogenation of galanthamine (Fig. 83) forms lycoramine. This transformation shifts the low wave length aromatic absorption from 238 mu to 228 mu. Because there is a very large negative dichroism due to the hydroxyl function, it is impossible to observe this low wave length ellipticity. One can be easily misled into considering the negative tail as the benzene dichroism. Consecutive dilution of the sample results in the same negative tail shifted to shorter wave length. This is true beyond 228 mu. We feel that these factors have led to a misinterpretation of the circular dichroism spectra of the morphinanes described previously. The signs of the ellipticities of these compounds must be questioned until such a time when they can be proven conclusively.

The CD and ORD spectra of codeine were run and the results are given in Figure 52. The spectra of this compound are very similar to crinine, and it can be seen from the CD spectrum of codeine that the dichroism is normal. The large increase in the amplitude of the 240 mu band can probably be attributed to the oxide bridge, which introduced a strain in the molecule. The ORD spectrum of codeine and compound XXX are very similar which can be expected for molecules of such similar structures.

Dihydrocodeine (Fig. 53) showed a second (240 mu) dichroism band approximately half that of codeine.

Morphine (Fig. 54) is known to possess the same absolute stereochemistry as codeine and this is substantiated by a comparison of the CD spectra of the two compounds. The morphine available to us was in the form of the sulfate salt. Basification of a methanol solution results in the sodium salt of the phenol. The CD spectrum of this basic solution shows a positive 285 mu dichroism and a second band at 240 mu which is also positive. This change in sign upon going from the free phenol to the sodium salt of the phenol can be attributed either to stereoelectronic effects or a complete change in the aromatic chromophore. At this point it is impossible to distinguish between these two effects. Acidification of this solution caused the sign of the 285 mu band dichroism to become negative as in codeine. This return to a normal dichroism spectrum indicated that the dichroism of morphine arose from an electronic environment very similar to that in codeine. From

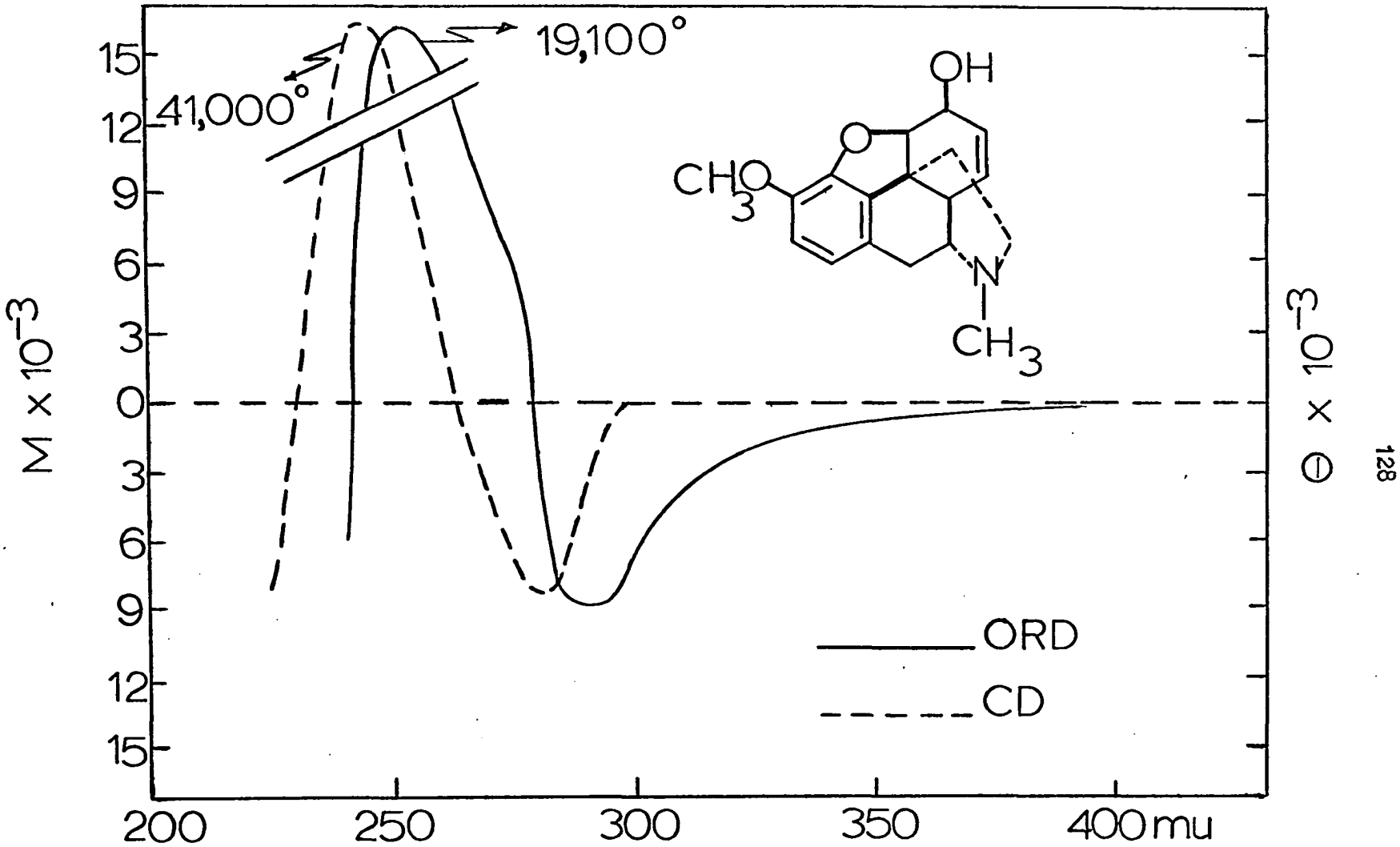


Fig. 52

ORD and CD of CODEINE

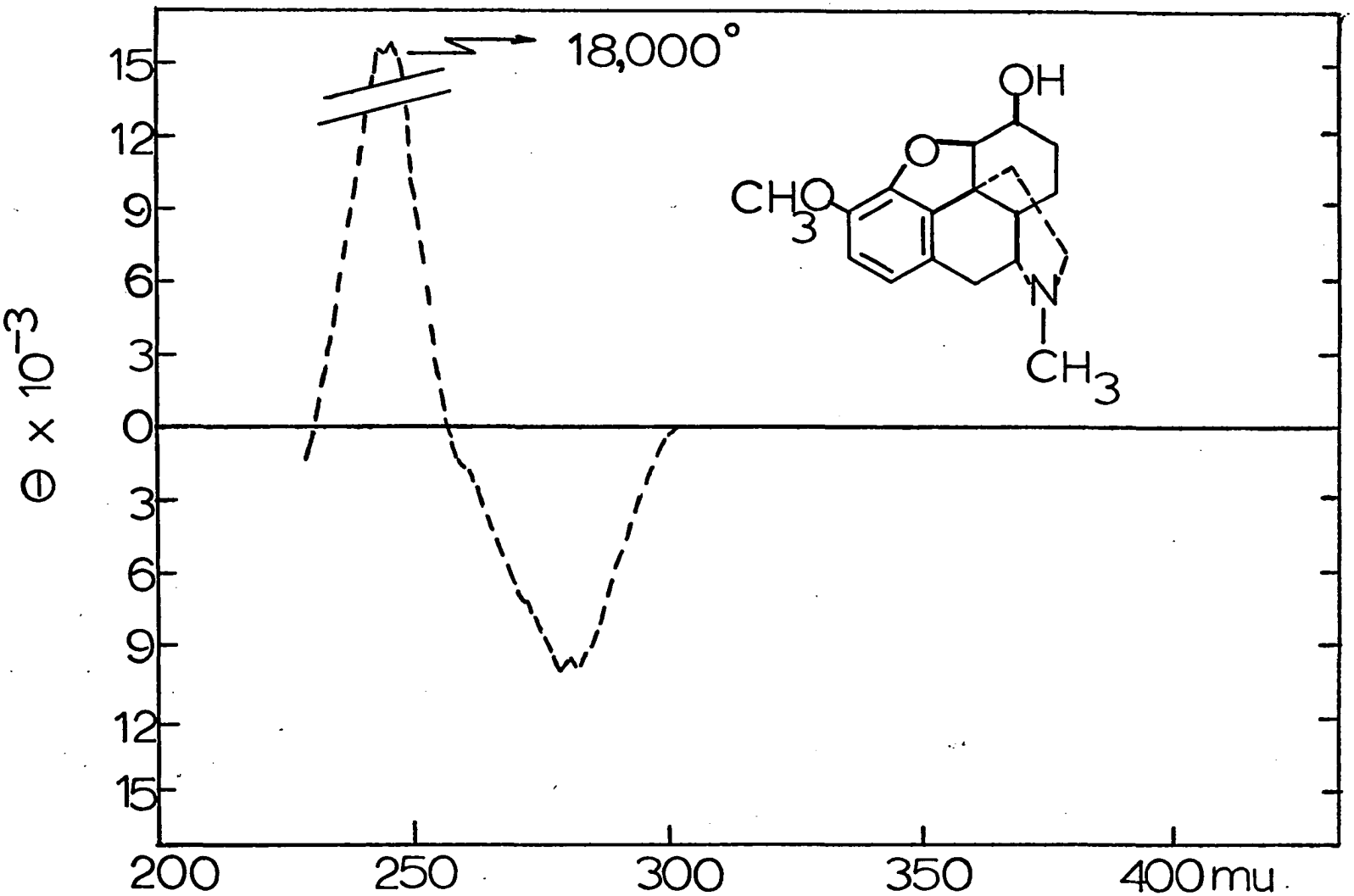


Fig. 53

CD of DIHYDROCODEINE

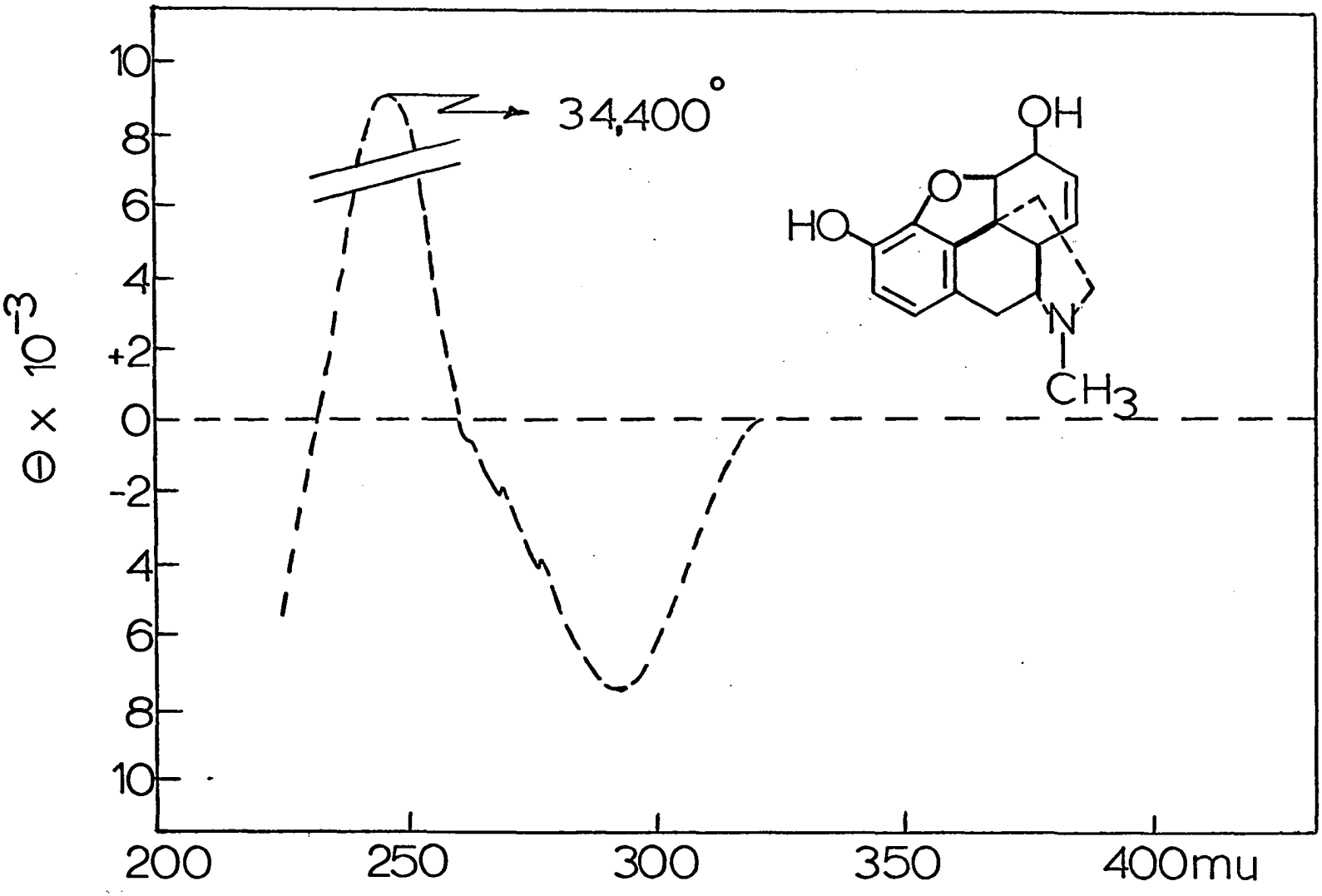


Fig.54

CD of MORPHINE

our work with the Amaryllis, it is known that the conversion of an alkaloid to its hydrochloride does not change the sign of the Cotton effects of the benzene ring, but results in decreased amplitudes.

Heroin (Fig. 55) gave the usual CD spectra for morphine type compounds, but the amplitudes of the dichroisms was reduced considerably relative to morphine and codeine. The acetyl group on the benzene ring is an electron withdrawing group and as such can account for this decrease. The secondary allylic acetyl group in ring C is optically active but does not absorb in the accessible UV. The maxima in the CD of heroin correspond to those found in the ultraviolet.

Thebaine (Fig. 56) can be thought of as a combination of chromophores. The aromatic chromophore has its absorptions at 226 mu and 285 mu, and the diene moity absorbs at ca. 274 mu when calculated from Woodward's rules. One clue that the diene band absorbs in this region is found in the CD spectrum. A very noticeable shoulder at 268 mu can be seen in both Weiss' and our spectrum of thebaine. The ultraviolet spectrum of thebaine has two absorptions, one of which (285 mu) is much broader than usual. The band width of the 285 mu band of codeine is 21 mu while that of thebaine is 31 mu. This difference can be attributed to a superposition of the aromatic band at 285 mu and the diene absorption at 274 mu. Weiss has attributed the entire ellipticity centered at 288 mu to the diene moity and does not assign any of the dichroism to the aromatic chromophore. This might be justified on the basis that the double bonds and the benzene ring can be considered to be homo-

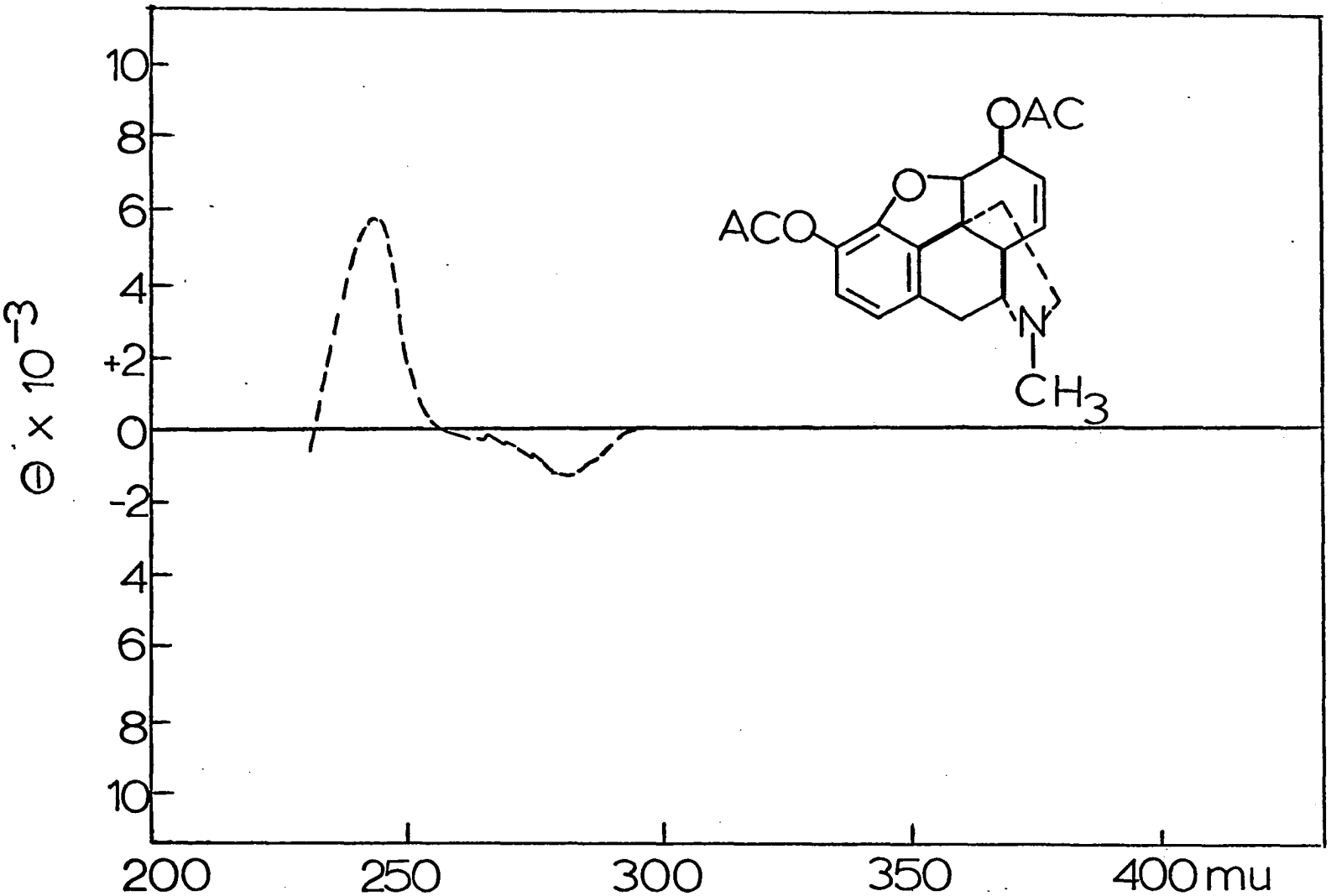


Fig.55

CD of HEROIN

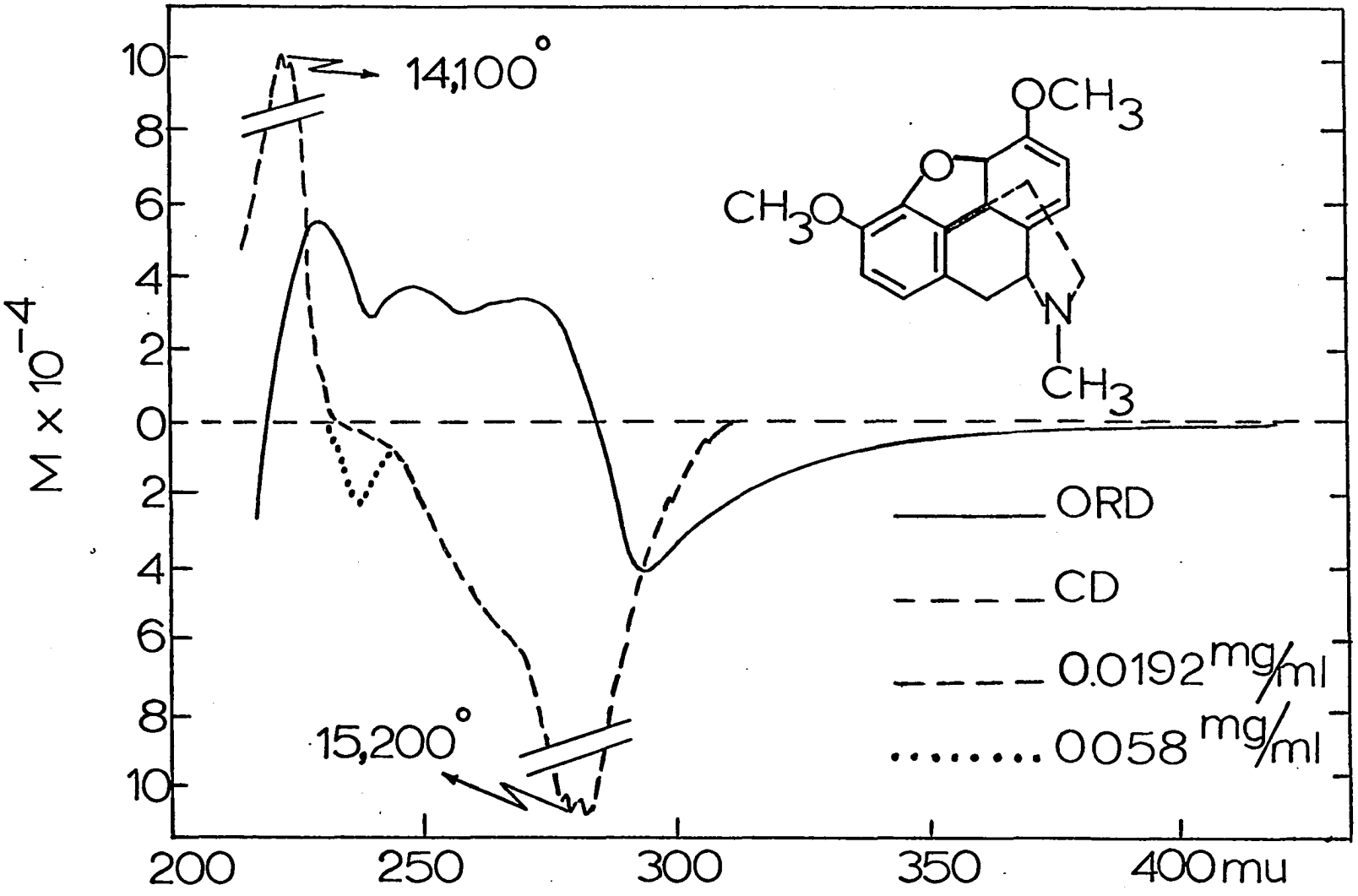
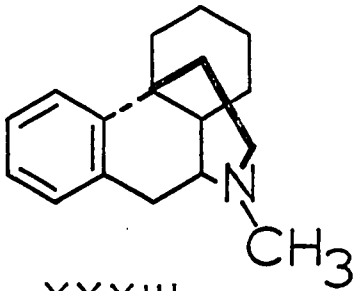


Fig. 56

ORD and CD of THEBAINE

conjugated to a certain extent. However, we feel that homoconjugation may account for the enhancement of the aromatic Cotton effect relative to codeine and in some cases may be responsible for a change in the sign of a given Cotton effect, but there is no reason to suggest that thebaine is sufficiently homoconjugated to result in a completely new chromophore. The fact that two dichroisms are evident at approximately the correct wave lengths for the individual absorptions also suggests that these are individual dichroisms. Removal of one double bond in thebaine results in dihydrothebaine. The ORD spectrum of this compound has been given previously (Fig. 51). It can be seen that the amplitude of the Cotton effect has decreased approximately 2.5 times. This change can arise from a number of causes. The amplitude of dihydrocrinine relative to crinine decreased by a factor of 4.8. This decrease can be due to removing the double bond from the vicinity of the benzene ring. This does not necessarily depend upon any special overlap of the orbitals. It can be postulated that the aromatic pi cloud does "feel" the effect of the C_1-C_2 double bond and in this sense is homoconjugated. This same reasoning can be used in the case of thebaine-dihydrothebaine. The shape of the ORD spectrum of these two compounds is the same while only the amplitudes of the dispersions have changed. At this time it can only be said that electron density at or near the chromophore under observation will effect that chromophore in one or more ways. It cannot even be said whether the effect of a β, γ double bond on a carbonyl chromophore will be the same as a β, γ double bond on the aromatic

chromophore. A superficial examination of dihydrocodeine and dihydrocrinine reveals a degree of similarity in these molecules which warrants a comparison of their ORD and CD spectra. Both molecules are T shaped and the bond angles are quite similar in all rings. The only major difference lies in the two carbon ethano bridge in the Amaryllis derivative versus a three atom bridge in the morphine analog. However, compound XXXIII, which has the absolute stereochemistry shown, affords a positive dispersion curve.



XXXIII

If crinane has the same absolute stereochemistry there is no logical reason why it should not exhibit a positive peak at its first dispersion maxima. Since the UV spectrum of these compounds are not as straightforward as those of other morphine alkaloids a comparison of the ORD and CD spectra of crinine and dihydrocrinine with those of codeine and dihydrocodeine were made. This resulted in the same dichotomy. Vittatine as drawn for the absolute configuration assigned to it has the same absolute stereochemistry as morphine and codeine at the asymmetric

center adjacent to the benzene ring. Morphine and codeine afford negative dichroisms at 296 mu and positive ones at 240 mu. These spectra are mirror images of those obtained from vittatine. Stated differently, codeine and morphine have CD spectra superimposable with those of crinine, but the absolute configuration assigned to crinine on the basis of Mill's rule is the opposite of that known for codeine and morphine. The oxide bridge in codeine gives rise to an asymmetric center, but this absorbs in a part of the spectrum not available to our instruments. A study of molecular models shows that there is very little if any change in the shape of the molecule upon removal of the oxide bridge. Because of this, the comparison between morphine and Amaryllis alkaloids is justifiable. A further comparison of properly substituted morphinanes in the ORD and CD have shown that the removal of the oxide bridge does not have a great effect on the dichroism of any given compound.

Supporting evidence that a reassignment of the absolute stereochemistry may be warranted comes from pharmacological data gathered at the National Cancer Institute, Bethesda, Maryland (149a). Test animals were injected with samples of (-) and (+) crinane and the various derivatives listed in Table 10. In most cases the (-) crinane derivatives were more potent analgesics than their (+) counterparts. Before an effective dose of a dl crinane mixture was reached it was necessary to feed almost twice as much as was used for (-) crinane. This indicates that only (-) crinane and derivatives had physiological activities comparable to the morphines. While evidence of this type cannot be

Table 10. Pharmacological data of some Amaryllis alkaloids

Compound	Stereochemistry	Results
Crinine	(-)	ED^{*}_{50} 29.4 mg
Epicrinine	(-)	ED_{50} 35.3 mg
Crinane	(-)	ED_{50} 8.4 mg
Crinane	(±)	ED_{50} 14.7 mg
Haemanthine	(-)	no significant effect
Crinamidine	(-)	no significant effect
Buphanidrine	(-)	ED_{50} 6.2 mg
Buphanisine	(-)	no significant effect
Powelline	(-)	inactive
(+) Dihydrobuphanisine	(+)	no significant effect
Crinamine	(+)	inactive
Haemanthamine	(+)	inactive
Vittatine	(+)	inactive

*ED = effective dose.

taken as conclusive, it warrants careful consideration.

C. Development of the Quadrant Rule

It has been shown that haemanthidine and 6-hydroxycrinamine can be converted to tazettine (Fig. 50) and criwelline (Fig. 57), respectively, by methylation with methyl iodide and treatment with dilute base. These conversions do not effect in any way the asymmetric center at C_{10b}. However, both transformations result in a complete inversion of the sign

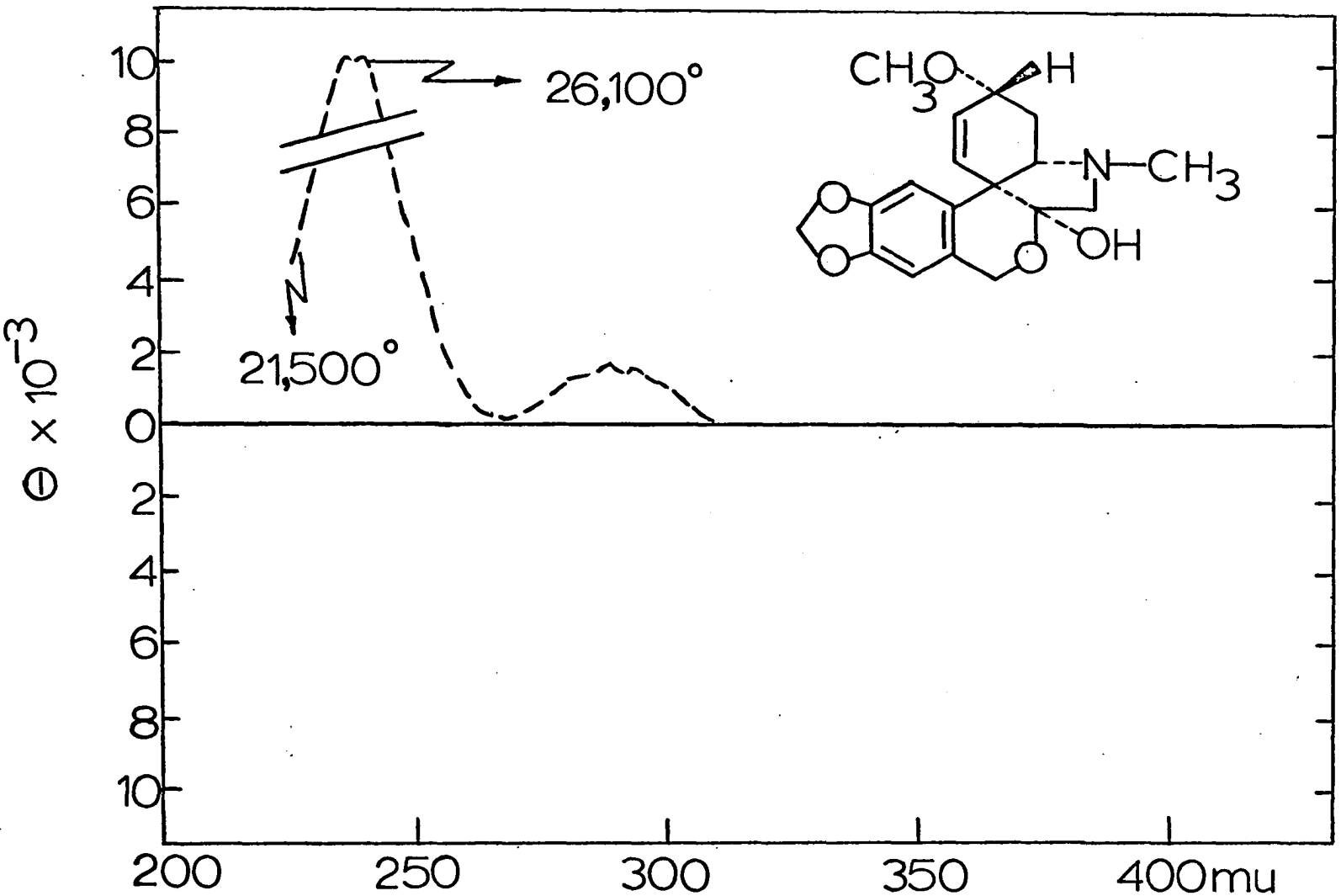


Fig.57

CD of CRIWELLINE

of the low wave length aromatic Cotton effect. It should be noted that the 295 mu band in criwelline is analogous and is of the same sign as the low wave length dichroism. Examination of Dreiding models shows that in tazettine, the C_3 methoxyl group is positioned directly over the benzene ring and can interact with it. This same methoxyl group in criwelline is well out of the way of the aromatic ring. This change in configuration at C_3 is equivalent to removing an electronic interaction and replacing it with a hydrogen-π bond interaction as in the powellane crinane case. The change in sign from tazettine to criwelline parallels that of crinane to powellane. The CD spectra of tazettine and criwelline are given in Figures 50 and 57.

A careful study of molecular models has shown that during the conversion of haemanthidine to tazettine the position of the non-aromatic portion of the molecules changes relative to the plane of the benzene ring. This prompted an investigation of the bond angle between the 10b-11 carbon-carbon bond and the plane of the benzene ring. In crinine this angle is $+110^{\circ}$ and in vittatine -110°. The positive sign designates above the plane of the ring and the negative sign below the plane. In all of the compounds having the crinine absolute stereochemistry (as assigned by Jeffs and others) this angle was positive; a negative angle was obtained for vittatine like structures. Codeine, measuring the same angle, has a negative value (-90°). Table 11 gives the results for a number of compounds and compares them with the observed dichroism of the 295 mu benzene band. It can be seen from the table that codeine

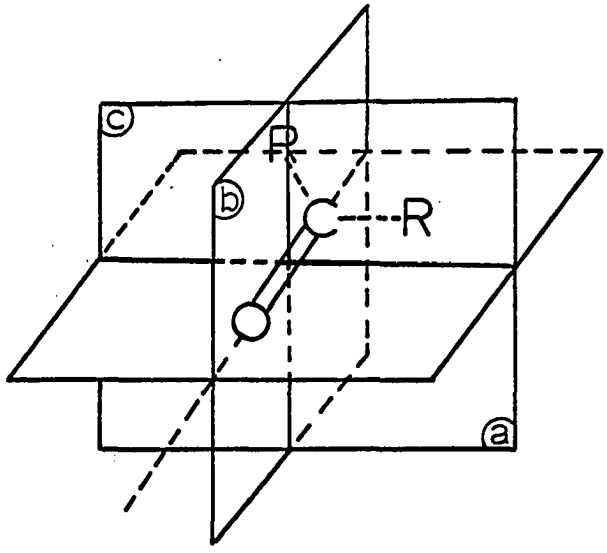
Table 11. Relationship between benzene plane and C_{10b}-C_{11} bond angle

Compound	Angle	Ellipticity (290 mu)
Codeine	(-) 90°	- 8600°
Crinine	(+) 110°	- 7300°
Tazettine	(+) 150°	- 4900°
Vittatine	(-) 110°	+ 7200°
Crinamine	(-) 110°	+ 8100°

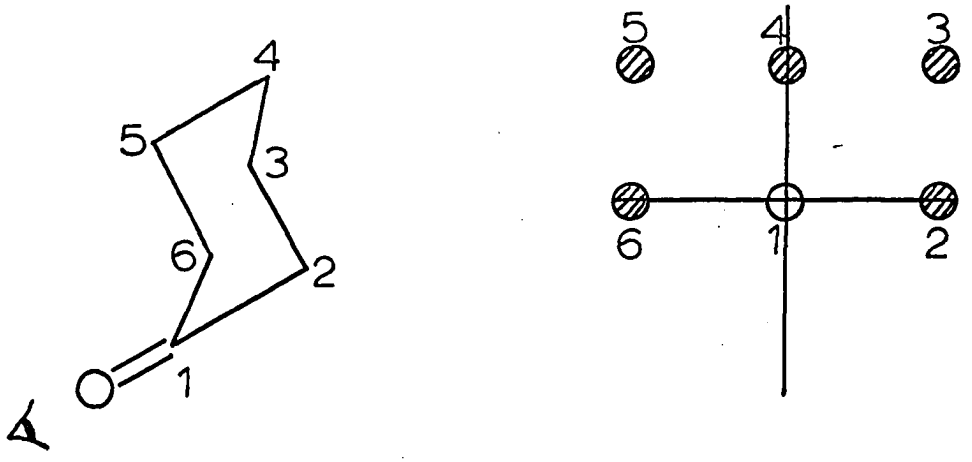
has both a negative angle and a negative dichroism. All of the Amaryllis, using Jeff's assignments have positive angles and negative dichroisms and visa versa. If the absolute configuration of crinine and tazettine type Amaryllidaceae alkaloids were reversed, the signs would then be the same as the morphines.

It is well known that the sign of rotation of any chromophore in an asymmetric environment is dependent upon the situation of the rest of the molecule around it. The octant rule for cyclohexanones is based upon this premise. Three orthagonal planes exist for the carbonyl group. One of these contains the carbonyl group and the two carbon atoms adjacent to it (plane a), the second plane is a perpendicular one which bisects the axis of the carbon oxygen bond of the chromophore (plane b). The third plane is perpendicular to the first two and cuts the carbonyl bond at a point between the carbon atom and the oxygen. These planes are the nodal planes, and are the planes of symmetry of the orbitals associated with the n--pi* transition of the carbonyl

group. The atoms of the molecular structure assume positions in these octants depending on the configuration and conformation of the particular compound. Their influence on the asymmetry of the carbonyl group is characterized by a sign according to which octant they occupy. There are actually front and rear octants for the carbonyl group, but since atoms are situated only very rarely in front of the carbonyl group, the front octants are not usually considered.

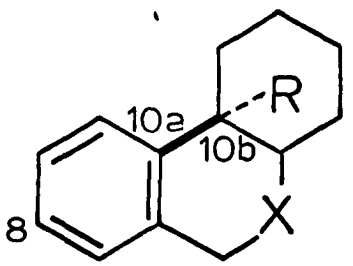


Since it is difficult to work with the three dimensional projection of the octants shown above, a two dimensional one is preferred.



Only those atoms actually situated in the octants effect the sign of the Cotton effects. Any atoms in the planes have no effect as they would either be in the node of an orbital or bisect one, and the effect would cancel.

The octant rule as discussed above was derived for the carbonyl group. There is no theoretical (149b) or chemical reason why similar octant rules cannot exist for other chromophores. Freely rotating chromophores such as the nitro and nitrile groups are not amenable to such a rule since it is not possible to know their position relative to the rest of the molecule. The aromatic ring should lend itself nicely to such considerations provided it is attached at more than one point to the rest of the molecule. The hypothetical compound (XXXIV) can serve as a model for the development of a quadrant rule for the aromatic ring in an asymmetric environment.

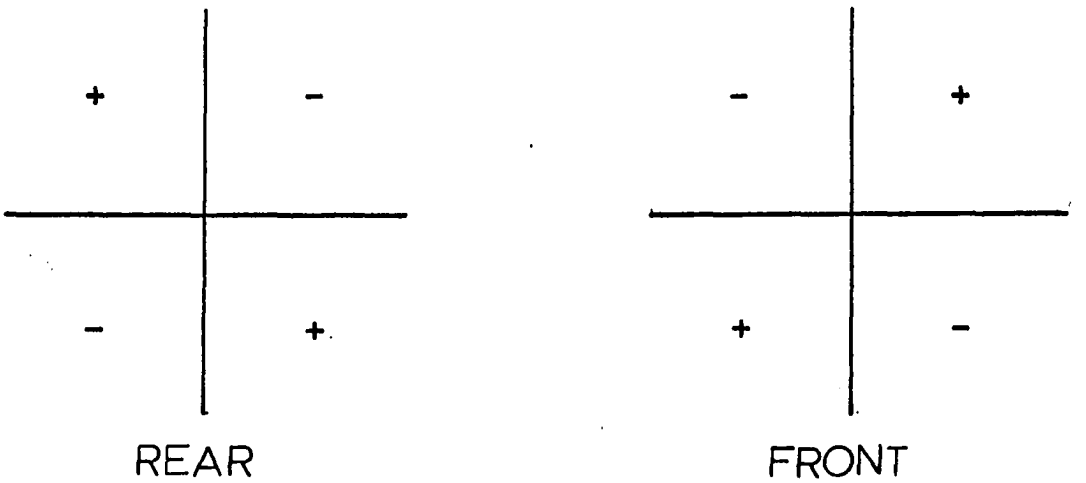


XXXIV

R = $\diagdown\!\!\diagup CH_2$

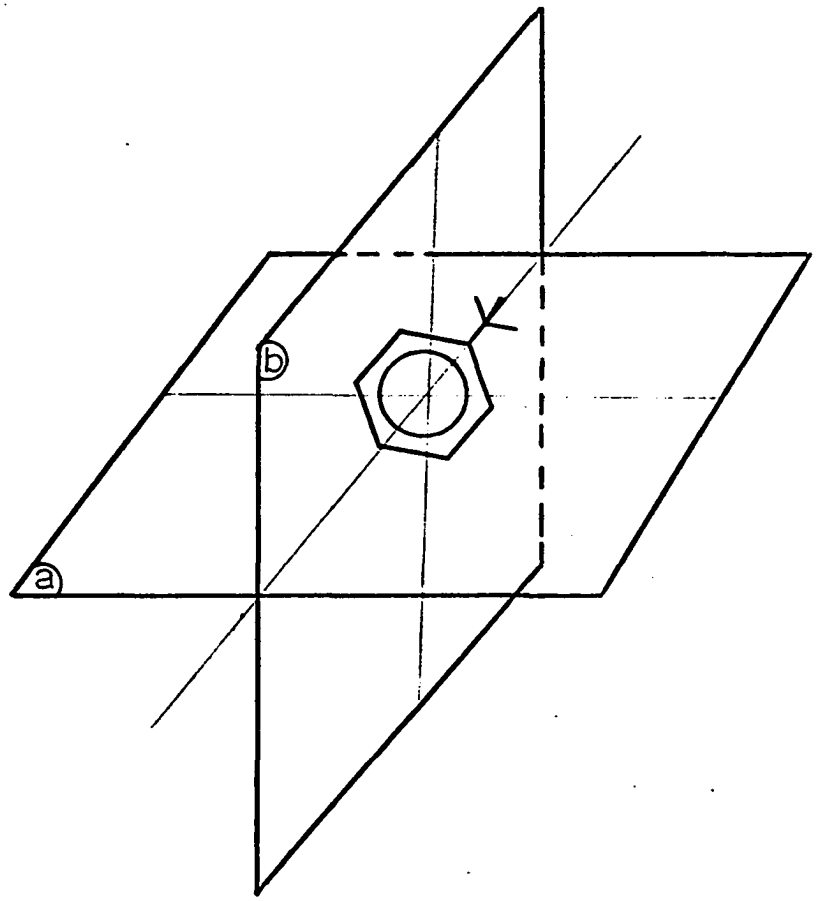
X = C, N, O

In the aromatic ring the electronic transitions which must be considered are the pi→pi* excitations. The transitions of the p electrons themselves cannot give rise to optical activity. The asymmetric center adjacent to the aromatic ring perturbs the pi system in such a manner that mixing of the d_{xy} benzene orbitals occurs. It is known that these perturbations effect the chromophore in a manner depending upon their orientation relative to it. The sign of the rotation is dependent upon which octant of the chromophore the rest of the molecule occupies. This is shown below for an octant system of front and rear octants.



Quadrants may be constructed in the same manner for an aromatic ring as for the carbonyl chromophore. The quadrant projection for the benzene ring is given in Figure 58. It can be seen that plane a is in the plane of the ring and will therefore be in the nodes of the pi system. Plane b bisects carbon atoms 8, 10a and 10b of XXXIV. Plane c is analogous to the plane in the octant rule which bisects the carbonyl group. In XXXIV this plane would bisect the ring into front and rear octants. Since a molecule with atoms in front of plane c would be rare, the front octants are not considered. This leads therefore to a quadrant rule instead of an octant rule. An atom or group of atoms in the planes mentioned above will have no effect on the sign of the rotation of the chromophore.

In order to use the quadrant rule for benzene derivatives, it is necessary to look parallel to the b plane at the asymmetric center in unsubstituted benzene derivatives. Theoretically one should look for



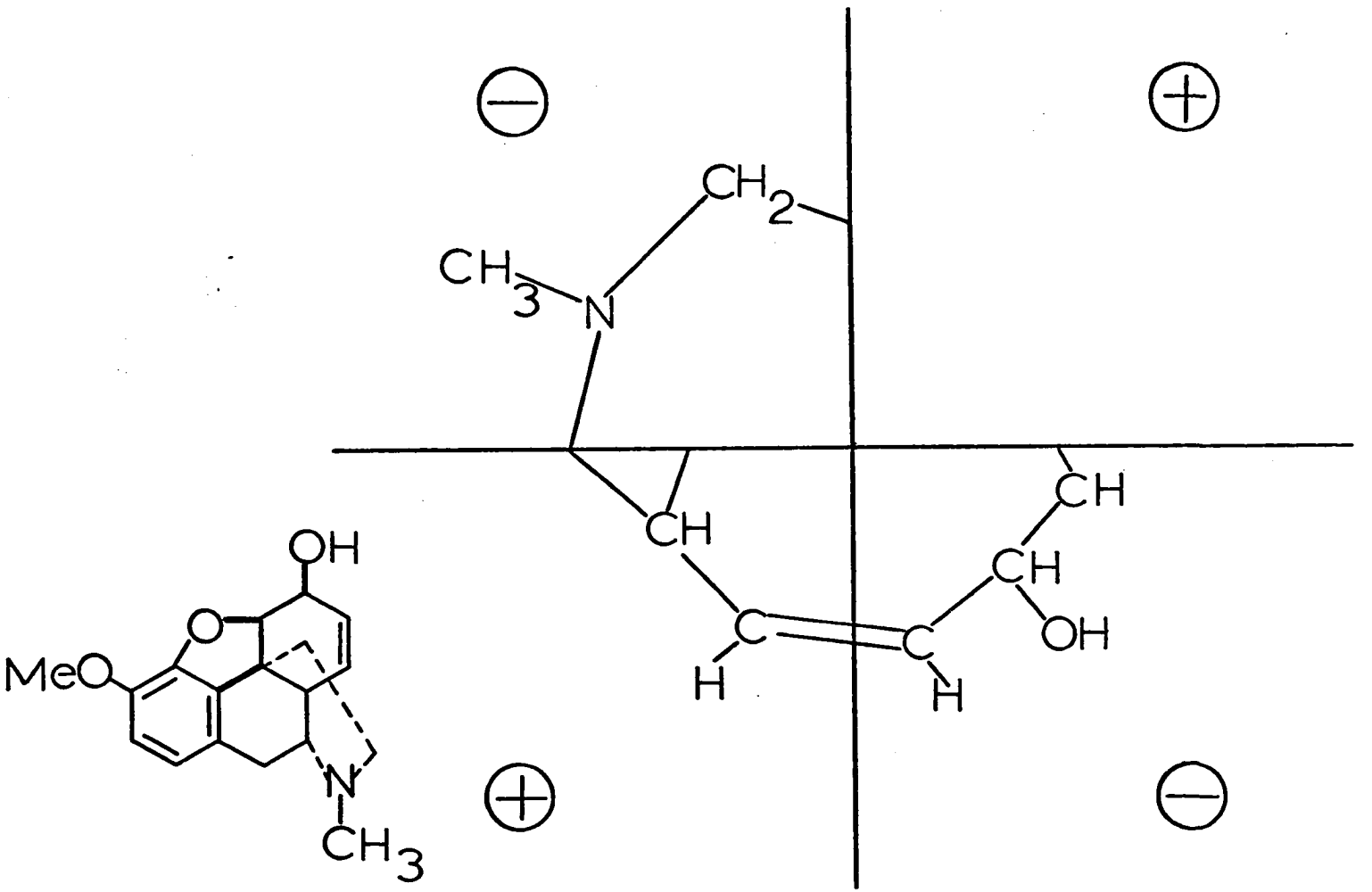
QUADRANT PROJECTION of the AROMATIC RING

Fig. 58

the best symmetry axis of the aromatic ring and look down it. In crinine this would be between the oxygens of the methylenedioxy group and in powelline it would be down the 8, 10a, 10b axis. This has been done specifically for crinine and crinamine. The quadrant rule applied as originally envisaged provides the same answer as when applied using the symmetry axis. However, in the former usage the hydroxyl at C_{11} and the methoxyl at C_3 are in plane b, and while one predicts the correct sign, no additional data concerning the amplitude of these Cotton effects is gained. When the symmetry axis is used, both the hydroxyl and the methoxyl shift positions in the quadrants. The hydroxyl group shifts to a negative quadrant and the methoxyl group shifts into the positive quadrant. This represents a gain in the positive quadrant of a CH_2 unit and can account for the increase in the Cotton effect of crinamine relative to vittatine. This is true for all of the crinine, tazettine and montanine type alkaloids. If there is a symmetry axis which can be found readily, this should be used in any of the other compounds which we have studied. In some cases there is no readily discernible symmetry axis and here we have simply used the plane analogous to 8, 10a, 10b axis in XXXIV. This has resulted in the correct predictions in all cases. We had completed almost all of the quadrant projections on the basis of sighting down the asymmetric center when Schellman (149b) predicted a quadrant rule on theoretical grounds based on the best symmetry axis in a given molecule. Therefore, all of the projections shown in this thesis are on the previously discussed basis.

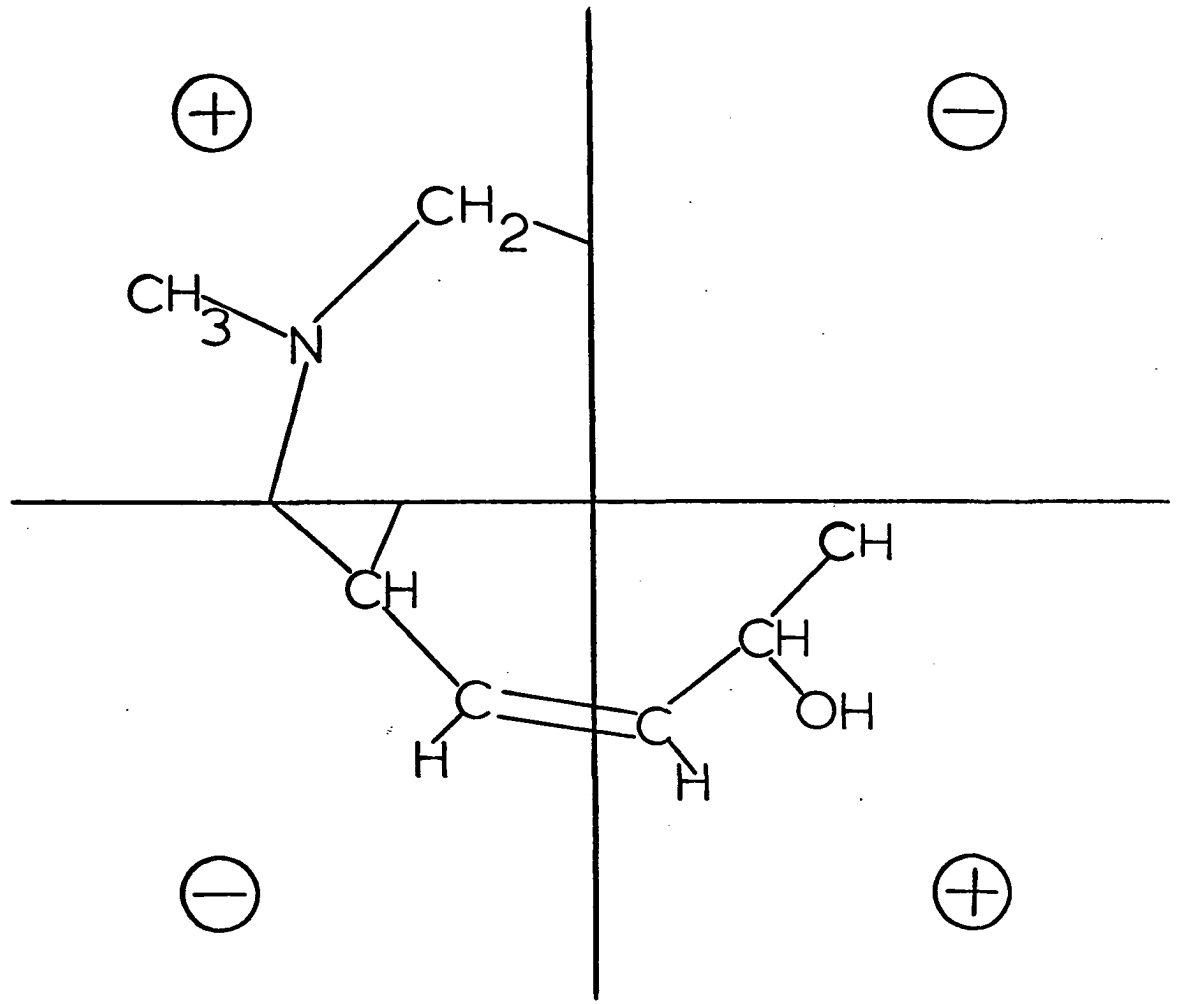
As has been pointed out this does not effect the results in any manner. It is possible, however, that as one applies the rule to a greater number of compounds, the symmetry axis of the molecule may provide the best answer. It is wise to look at any given molecule in both ways before coming to a conclusion about the sign of a dichroism.

The signs given to the four quadrants for both the 285 mu and 240 mu transitions of the benzene ring are given in Figures 59 and 60. The values in these figures are based on an examination of the quadrant rule as applied to the dichroisms of codeine and morphine, both of which are of known absolute configuration. Here, as in the octant rule, the situation of the atoms in the quadrants determines the signs of rotation in the ORD and CD spectra. For the carbonyl group there is only one dichroism and hence only one octant projection is needed, but each aromatic ring has two absorptions and gives rise to two dichroisms which in a normal situation are of opposite sign. This calls for two quadrant projections for each optically active benzene ring. We have previously defined a normal pair of aromatic dichroisms as being antipodal. In doing so it follows that in a molecule that has only a benzene ring absorbing between 215 mu and 260 mu has a "normal" dispersion spectra if it crosses the zero axis in the region of the maximum value of the benzene ultraviolet absorptions. An example of a normal benzene dispersion spectra is that of crinine, while an abnormal one is the spectrum of powelline. We have found that either normal or abnormal dichroism spectra gives rise to normal or abnormal dispersion



CODEINE PROJECTION $A_{1g} \longrightarrow B_{2u}$ (285mu)

Fig. 59



CODEINE PROJECTION $A_{1g} \longrightarrow B_{1u}$ (240mu)

Fig.60

spectra respectively. It is then possible to apply the quadrant rule to ORD data for which normal dispersion data have been recorded and for which the ultraviolet spectra is known.

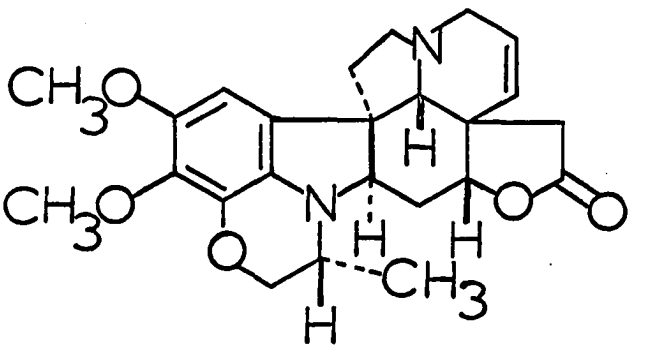
While the octant rule for the carbonyl group and the quadrant rule for the benzene ring are essentially the same, the latter is less subject to error. The carbonyl group is usually situated in a ring that has a certain amount of flexibility. This can result in conformational changes in the molecule which effect the sign and amplitude of the Cotton effect. In aromatic compounds the benzene ring is the chromophore and is conformationally rigid.

It now becomes necessary to test our postulated quadrant rule on a significant number of compounds of known absolute stereochemistry. The remainder of this thesis is devoted to this task.

All of the morphine derivatives studied by Kuriyama are of known absolute configuration. Unfortunately no circular dichroism spectra were run on these compounds. The CD spectra of morphine and codeine are normal and the ORD and CD curves of dihydrocodeine do not indicate that a change in sign of the low energy aromatic ellipticity has occurred upon hydrogenation. Because of the structural similarities between the morphines and codeines the ORD spectra of Kuriyama can be interpreted as reflecting the true stereochemistry of the asymmetric center. The spectra of XXX, XXXI and XXXII are very similar to that of crinine, which supports the above statement. Projection of XXX onto the quad-

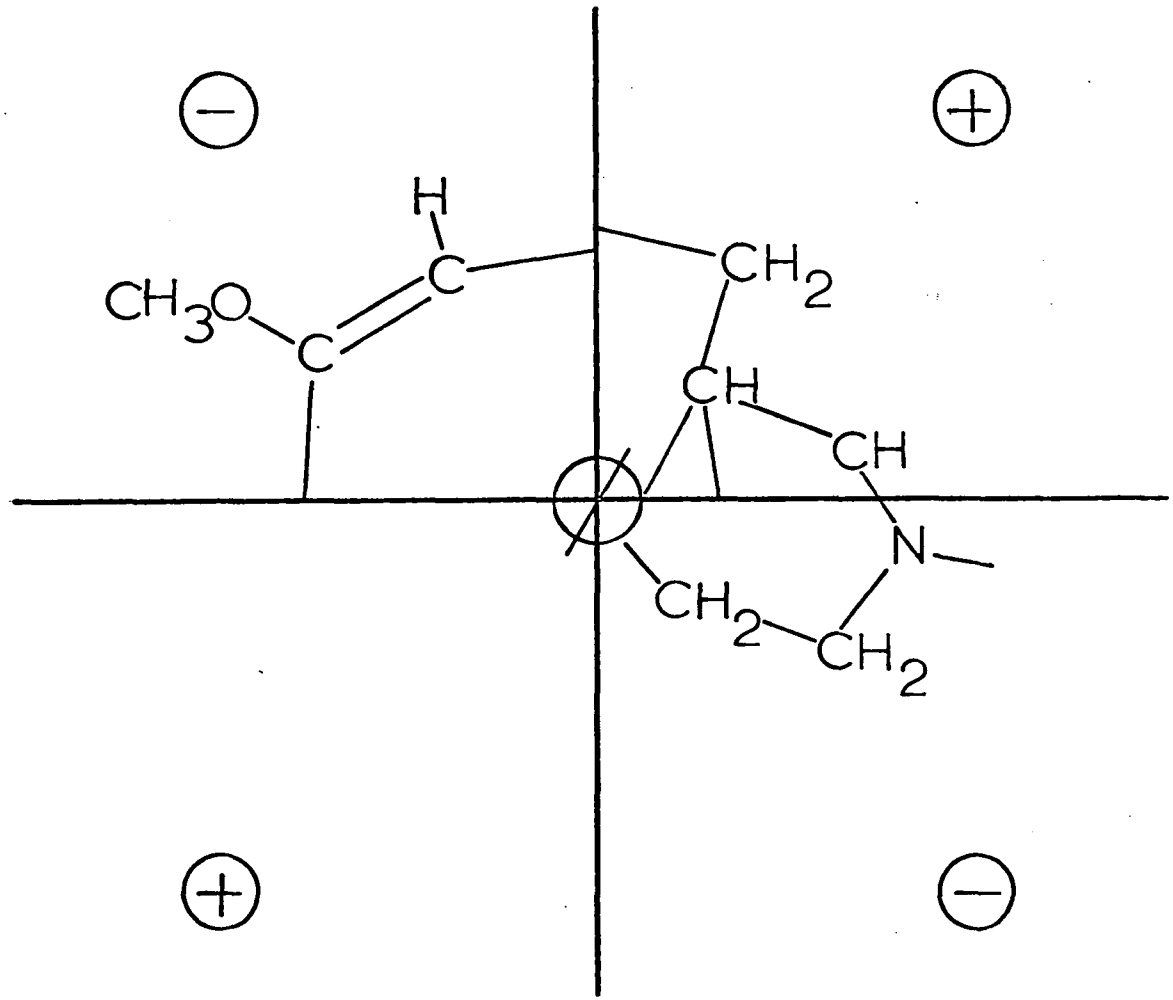
rants for the 275 mu benzene band predicts that the sign should be negative and this can be seen as correct (Fig. 61). Also shown is the projection of XXXV (Fig. 62). This predicts a positive sign for the 275 mu Cotton effect (Fig. 63), and this is observed.

The indole alkaloids have been the subject of extensive investigations, and the absolute configurations of many members of this group are known (150). The first member of this family of alkaloids to be tested was XXXVI. This is a new class of compounds for which the absolute stereochemistry is known. The first trough on the ORD spectrum is a large negative one and application of the quadrant rule to it resulted in agreement with the sign predicted for this stereochemistry (151).



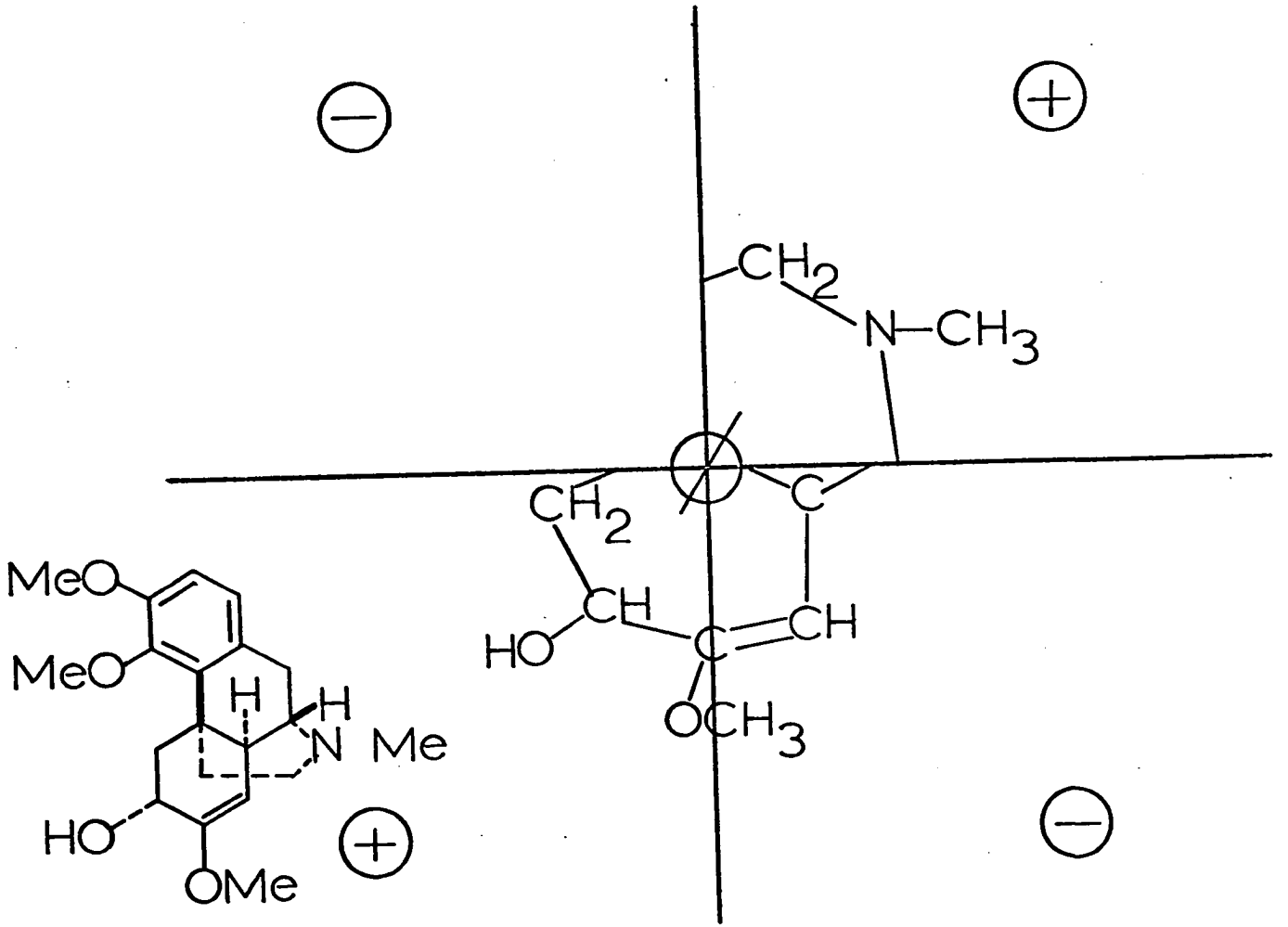
XXXVI

One prerequisite which is important for an interpretation of the CD spectrum of any compound is a knowledge of the UV spectrum. In most aromatic derivatives it is usually an easy matter to assign the benzene



XXX PROJECTION

Fig 61



xxxv PROJECTION

Fig.62

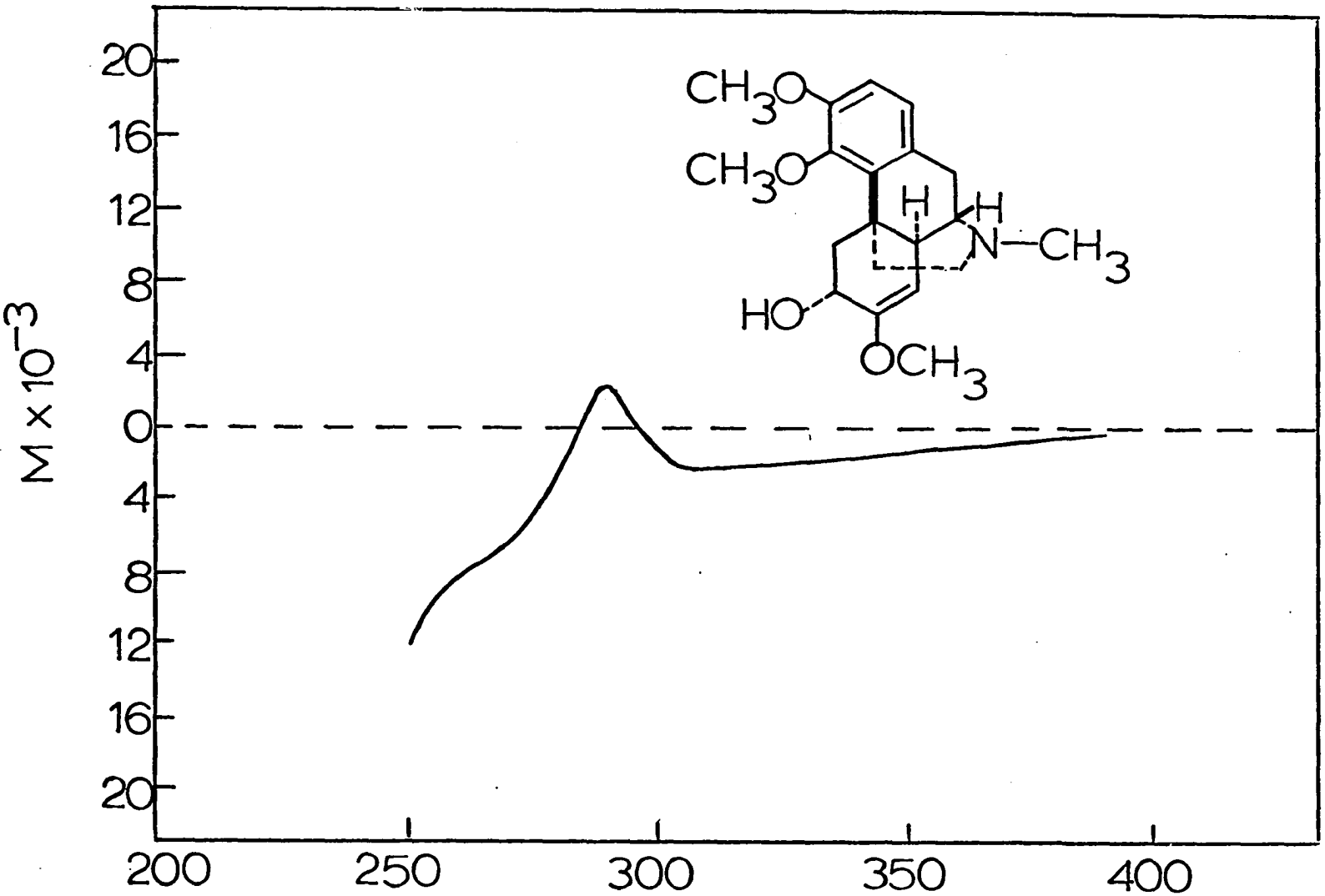
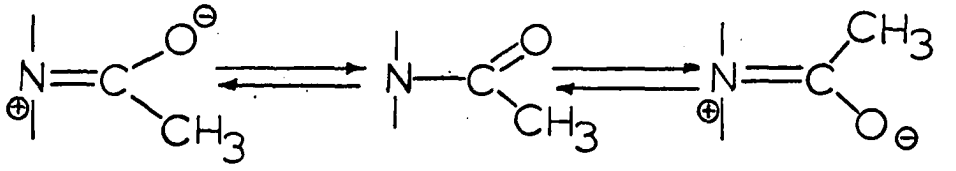


Fig.63

ORD of xxxv

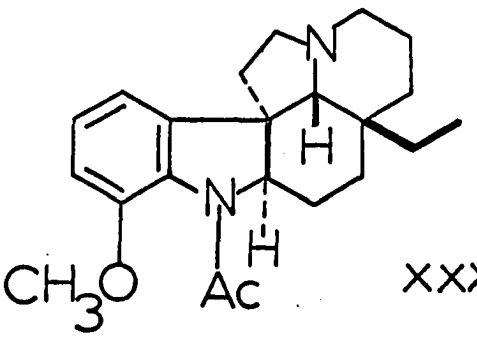
absorptions. Indole alkaloids are unusual in this respect as they are no longer simple benzene derivatives. The indole moity makes a contribution to the absorption spectra of certain compounds. That this is correct is evidenced by magnetic CD studies. A monosubstituted benzene derivative displays a single Cotton effect under the influence of a magnetic field, whereas indole has two Cotton effects of opposite sign (142). This second ellipticity is assigned to the heterocyclic portion of the molecule, probably arising from the α,β unsaturation. The indole alkaloids in which the double bond is removed display a simple benzene like absorption spectra, provided that there is hydrogen or saturated carbon attached to the nitrogen atom. (cf. ajmaline). N-acetyl derivatives of indole alkaloids have a shoulder at 286 mu which is usually never reported in the literature (152). Since it is of importance in the interpretation of the CD spectra of these compounds to know whether this band is benzoid in origin or due to a non-benzene portion of the molecule, the UV spectrum of aspidospermine was run in various solvents. Methanol provided the usual curve which lacks benzene fine structure. Pentane did provide evidence that the 286 mu shoulder was non-benzoid as it showed none of the fine structure associated with these bands. The major absorption displayed a great deal of fine structure, as expected for benzene bands. Supporting evidence that the absorption at 286 mu was due to some other part of the aspidospermine molecule was provided by the CD spectra. A large negative band centered

at 256 mu and a positive maximum at 225 mu corresponding to UV absorption bands at 256 mu and 219.5 mu were the only CD maxima found in aspidospermine. A possible rationalization of the unusual UV spectra might lie in the N-acetyl group. It is well known (153, 154) that the N-acetyl group can exist in two tautomeric forms.

15. 

Nuclear magnetic resonance data shows that these forms can be in as high as a 1:1 ratio in any given molecule. This means that in the N-acetyl indoles there would be introduced a degree of α, β unsaturation such as that found in indole itself. There is no experimental proof that this is the situation in the N-acetyl dihydroindoles, however, many of the N-acetyl derivatives and the lactam derivatives (cf. strychnine) have quite similar absorption spectra, all of which differ from the dihydroindole alkaloids.

The stereochemistry which has been proposed for aspidospermine on the basis of chemical correlations and X-ray data is given in XXXVII (155, 156).



XXXVII

This stereochemistry demands that the first Cotton effect be negative and the second positive. The spectrum in Figure 64 shows that this is obtained in accordance with predictions obtained from the quadrant rule (Fig. 65) for the 256 mu band dichroism.

The absolute configuration of ajmaline (Fig. 66) has been conclusively proven by chemical degradation and correlations with compounds of known absolute stereochemistry (157). The UV spectrum is straightforward. The only absorptions are at 290 mu and 245 mu, and each of these has a corresponding CD maxima. Application of the quadrant predicts a negative maxima at 290 mu and a positive one at 245 mu. This is observed. The octant projection for ajmaline (240 mu) is given in Figure 67.

Akuammicine is an interesting molecule as its rotation at the sodium D line is (-) 745°. The absorption spectra of akuammicine has maxima at 329 mu, 300 mu and 230 mu, whereas the CD spectrum (Fig. 68) has ellipticities at 325 mu, 285 mu and 245 mu. It was experimentally

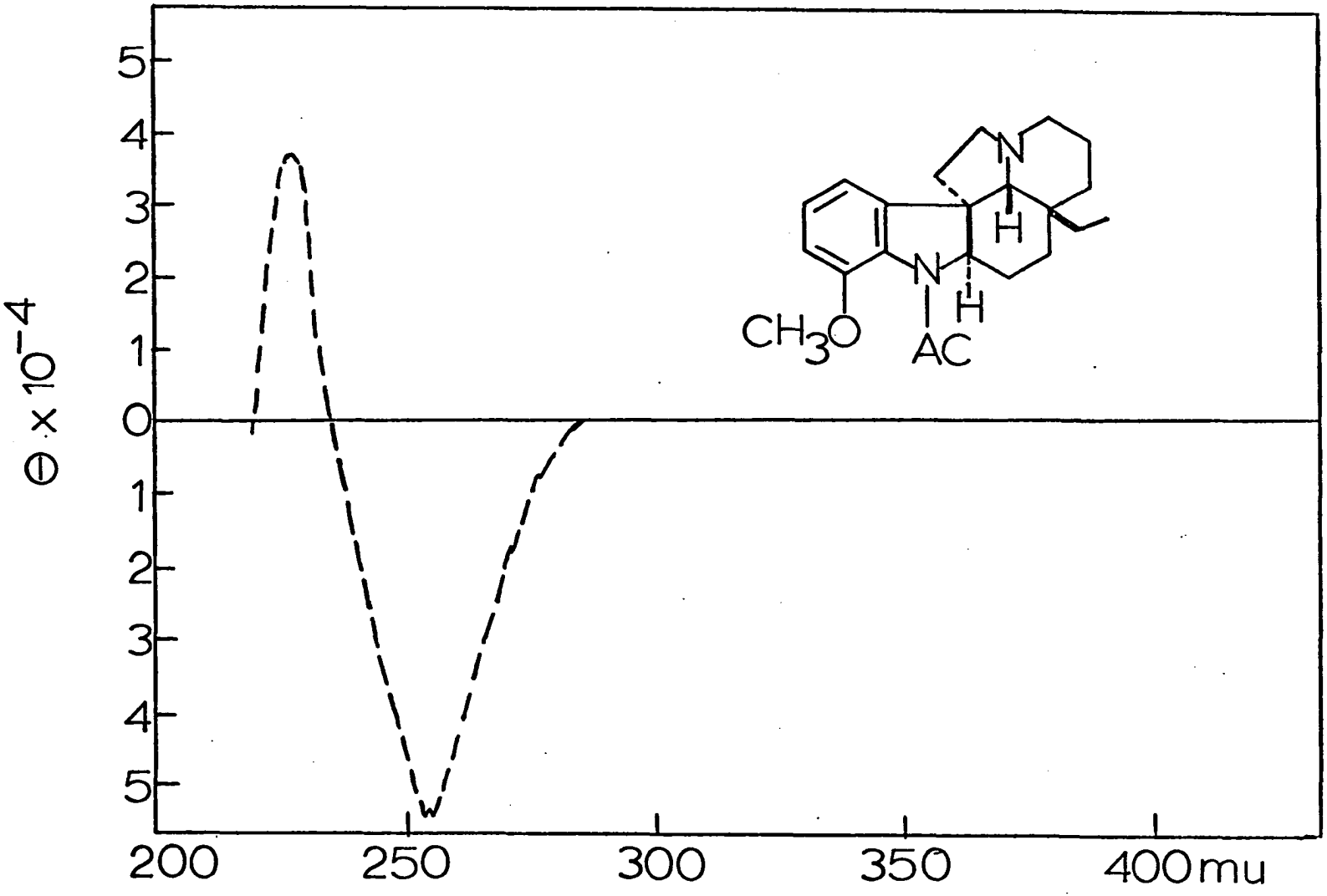
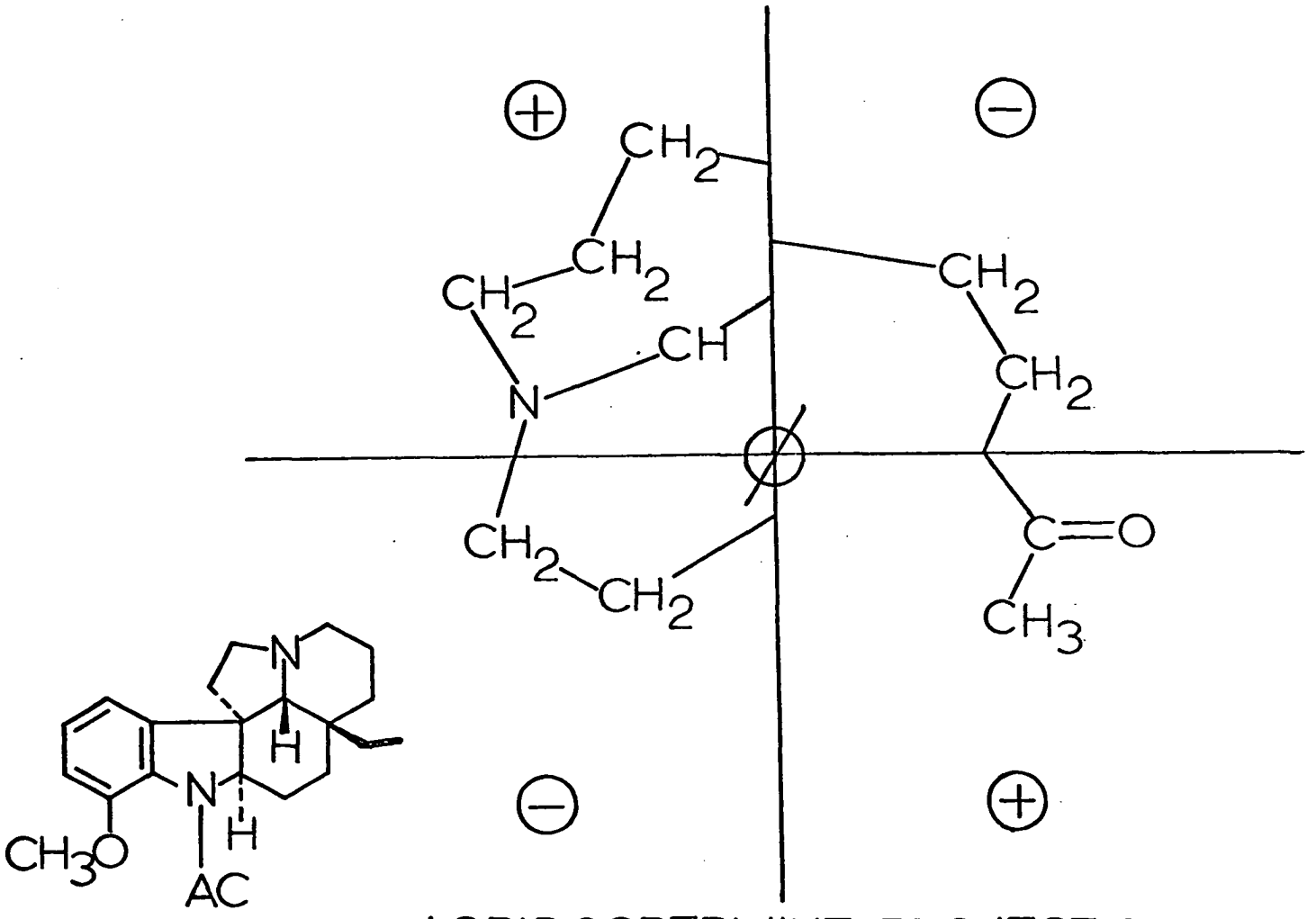


Fig.64

CD of ASPIDOSPERMINE



ASPIDOSPERMINE PROJECTION

Fig.65

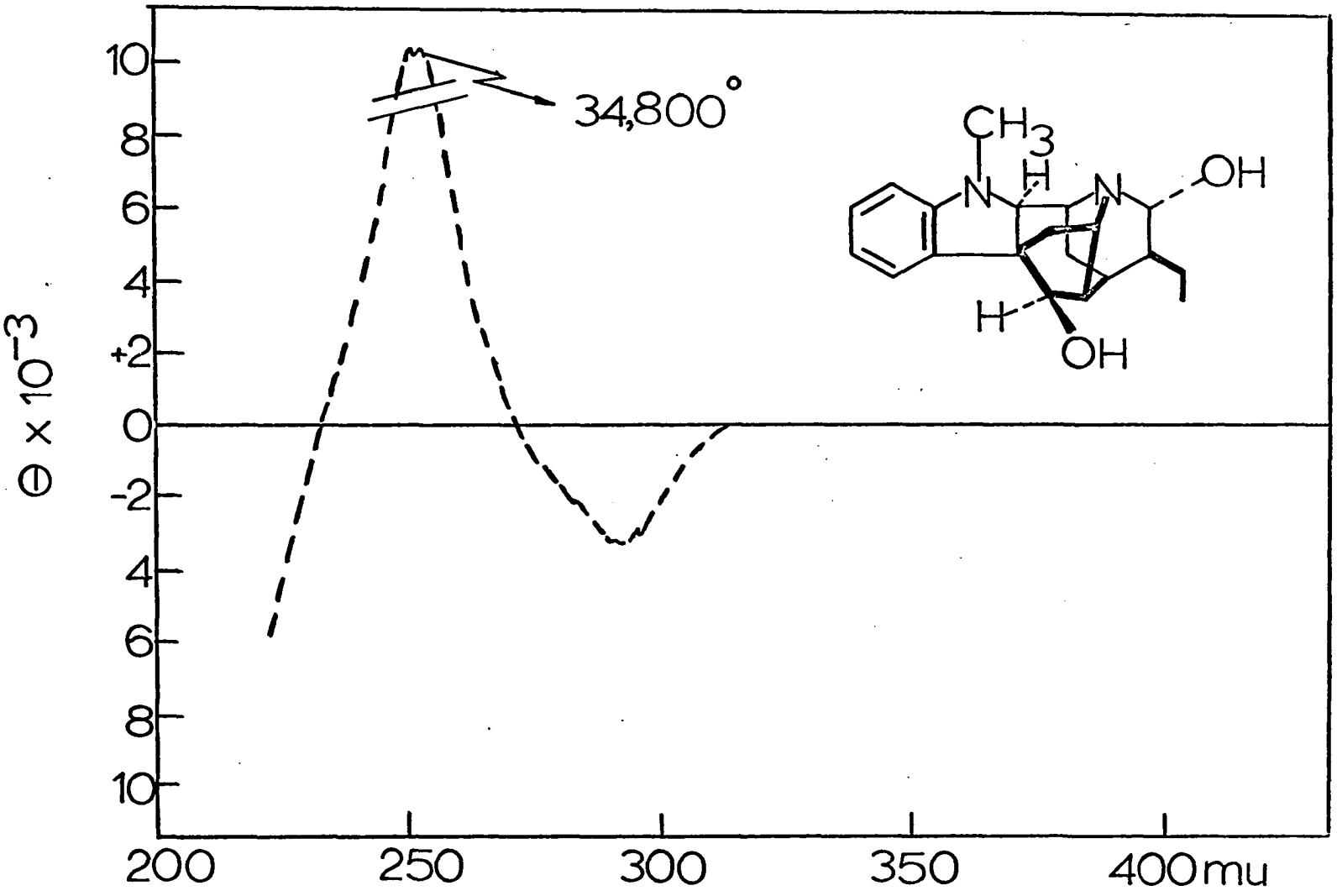
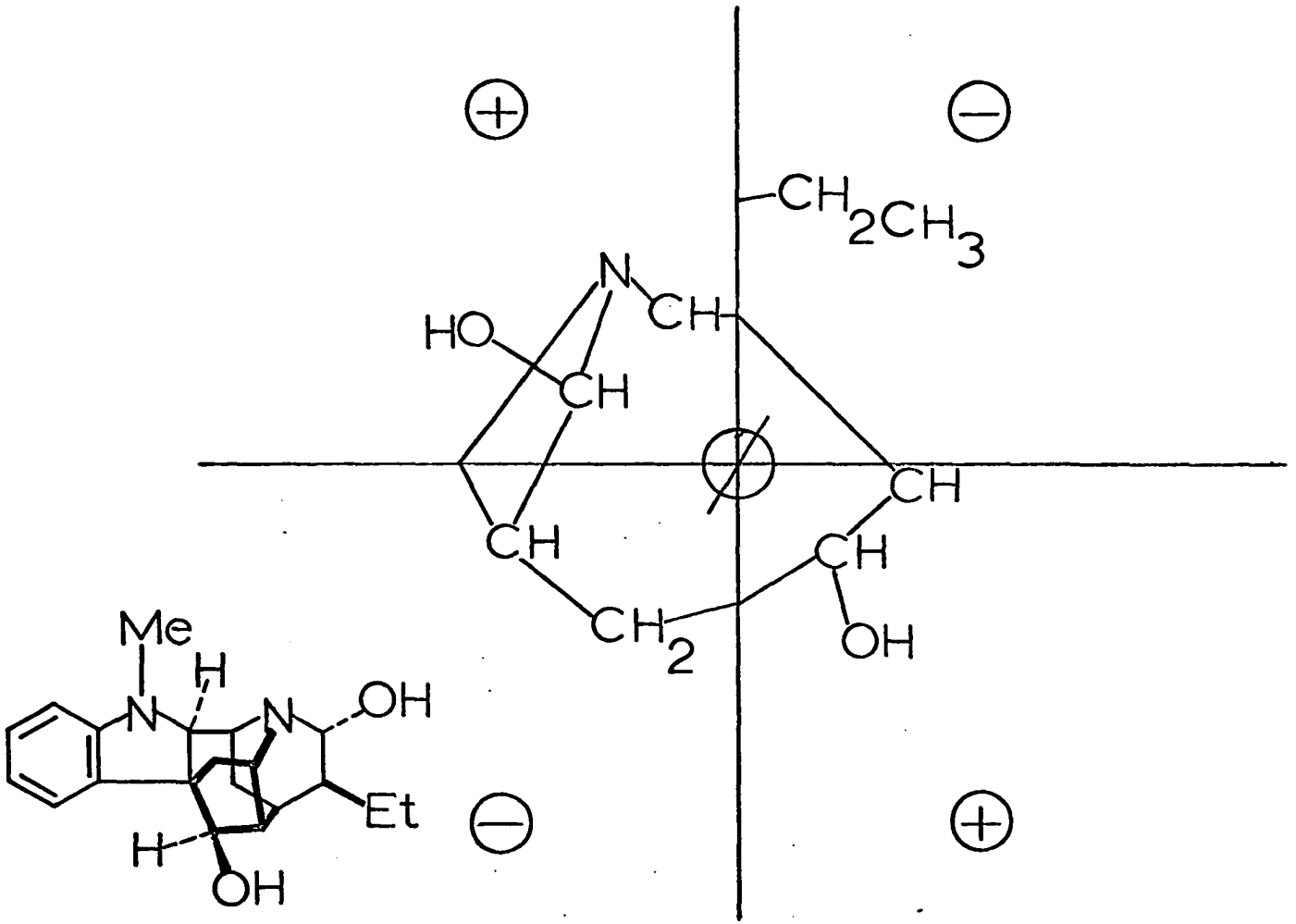


Fig.66

CD of AJMALINE



AJMALINE PROJECTION

Fig.67

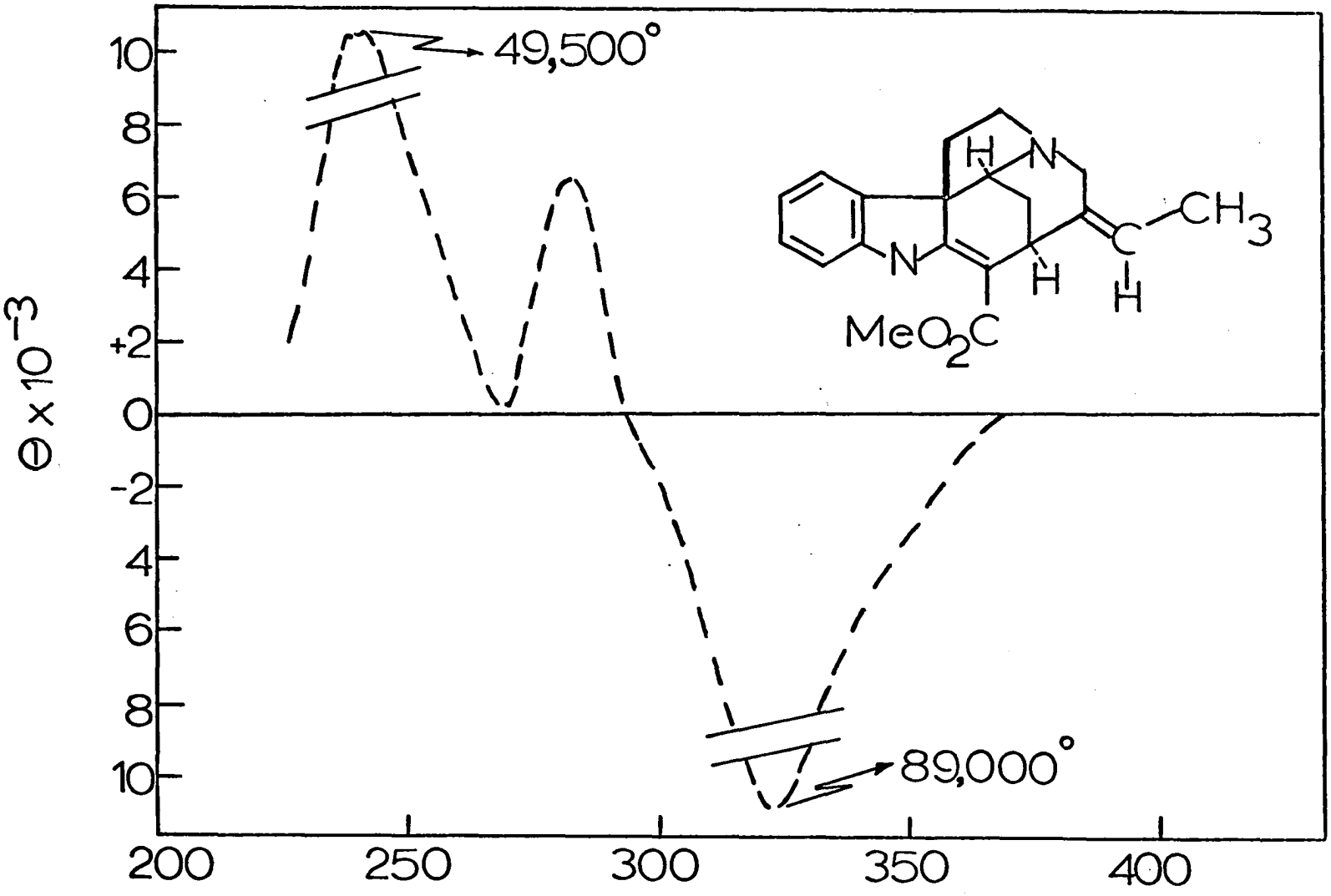
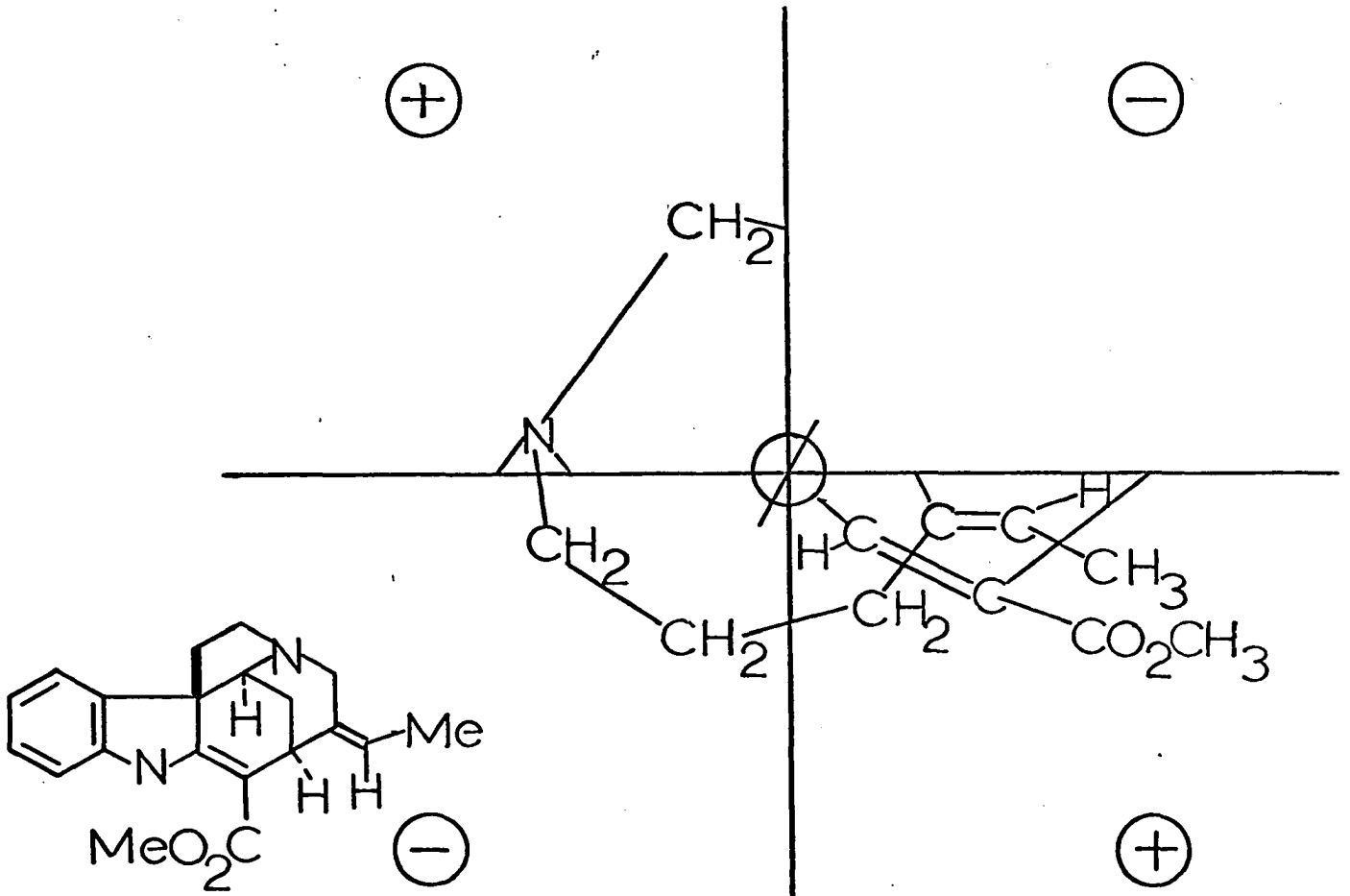


Fig. 68

CD of AKUAMMICINE

impossible to observe the 230 mu dichroism. The 245 mu CD maxima undoubtedly is the second benzene absorption, which is hidden in the UV by the large absorption band of the unsaturated ester at 230 mu (119). The difference of 55 mu between the two benzene bands is in agreement with that found for other aromatic alkaloids. The very large dichroism found at 325 mu can be assigned to the n→pi* transition of the carbonyl group, and the rotation at 589 mu can be attributed to this chromophore. The absolute stereochemistry of akuammicine is known from chemical correlations with strychnine (158). Projection of akuammicine on the octants for the 240 mu benzene band predicts that a positive dichroism should be observed, and examination of Figure 69 shows that this is what is found.

Strychnine and brucine (Fig. 70) have been the subject of extensive chemical and spectral investigations (150). The absolute stereochemistry has been determined by both degradative and X-ray methods (159, 160). Additional proof of the stereochemistry came from the superlatively elegant total synthesis of strychnine by R. B. Woodward (161). Strychnine and brucine may be considered N-acetyl indoles. This is evident from the UV spectrum of strychnine. It is very similar to that of aspidospermine, with the maximum absorption at 245 mu and two small shoulders at 281 mu and 289 mu. The absorption spectra of brucine is quite different. This difference may be attributed to the two methoxyl groups on the aromatic ring. The long wave length absorption band is shifted to 302 mu and the second benzene band to 265 mu. The CD bands



AKUAMMICINE PROJECTION

Fig.69

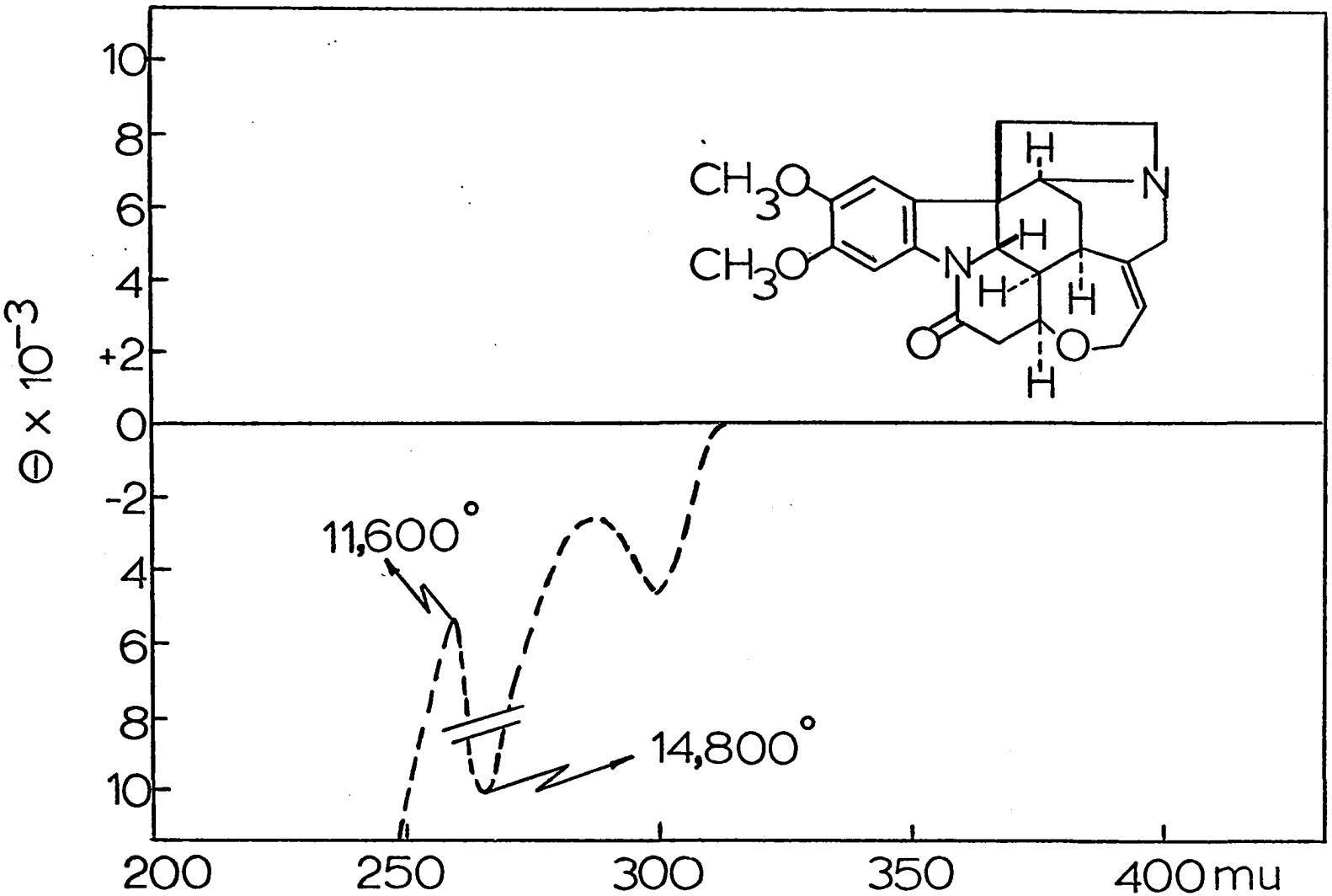
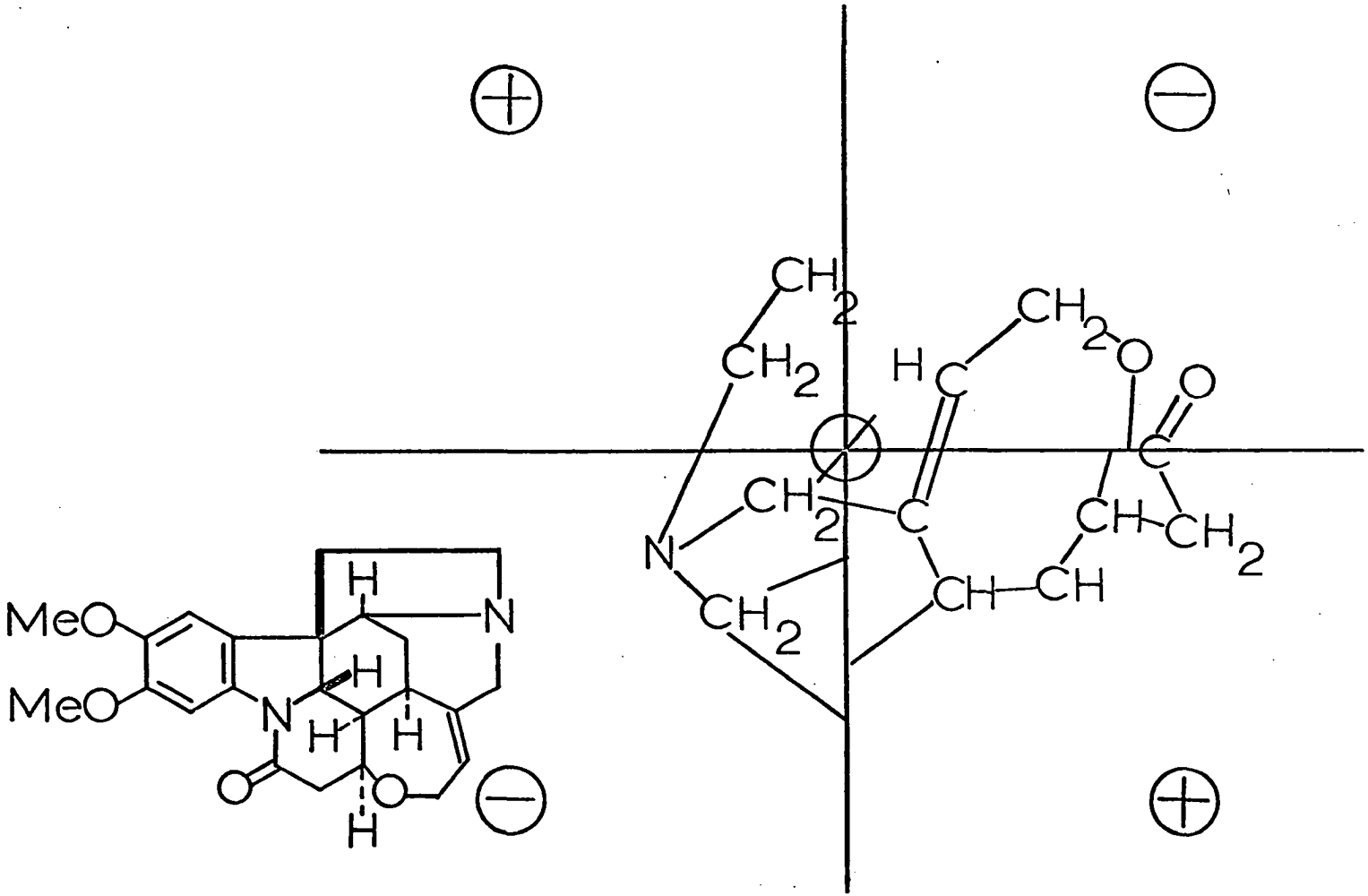


Fig. 70

CD of BRUCINE

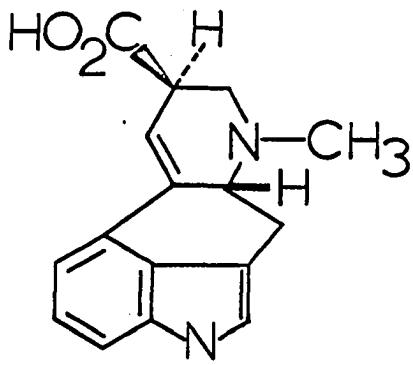
of brucine are at the same wave lengths as those in the UV, i.e., 302 mu and 255 mu. Both of the dichroisms are negative and hence not normal. However, application of the quadrant rule to brucine demands that the 255 mu band be negative, and as can be seen in Figure 71 this is correct. The second benzene band of strychnine is impossible to observe as it occurs at 210 mu. A CD spectra of strychnine run in water has shown that there is a large negative dichroism in this region. Since strychnine and brucine have been shown to be identical but for the substitution on the aromatic ring, the results obtained for brucine may safely be applied to strychnine even if the second band cannot be seen in its entirety. The octant projection of the 265 mu benzene dichroism of brucine is given in Figure 71.

Lysergic acid derivatives have received a great deal of attention lately, both by the chemist and by the public. This alkaloid is not amenable to the present study since it possess no asymmetric center adjacent to the aromatic ring. Dihydrolysergic acid does have the necessary center of asymmetry and has been studied by us. The absolute stereochemistry of lysergic acid (XXXVIII) and its dihydro derivatives have been elucidated by Hofmann and Stadler (162, 163).



BRUCINE. PROJECTION

Fig.71



XXXVIII

The CD spectra of dihydrolysergic acid (Fig. 72) displays a negative maximum at 280 mu and a positive one at 235 mu. This is in accord with the signs predicted for the first and second benzene bands using the quadrant rule. This is shown for the 235 mu band in Figure 73. Festuclavine (dihydrolysergic acid, CH_3 instead of CO_2H) was not at our disposal, but since it is known that small changes in parts of the molecule removed from the asymmetric center play a small role in the sign of the dichroisms (69), the absolute stereochemistry could be obtained from the spectrum of dihydrolysergic acid.

The ORD spectra of a number of isoquinoline alkaloids have been studied by Battersby (95), and the signs of the first Cotton effects correlated with their absolute stereochemistry. Since these correlations from the rotatory dispersion spectra proved to be correct, it follows that the ORD spectra reflect the correct configuration at the asymmetric

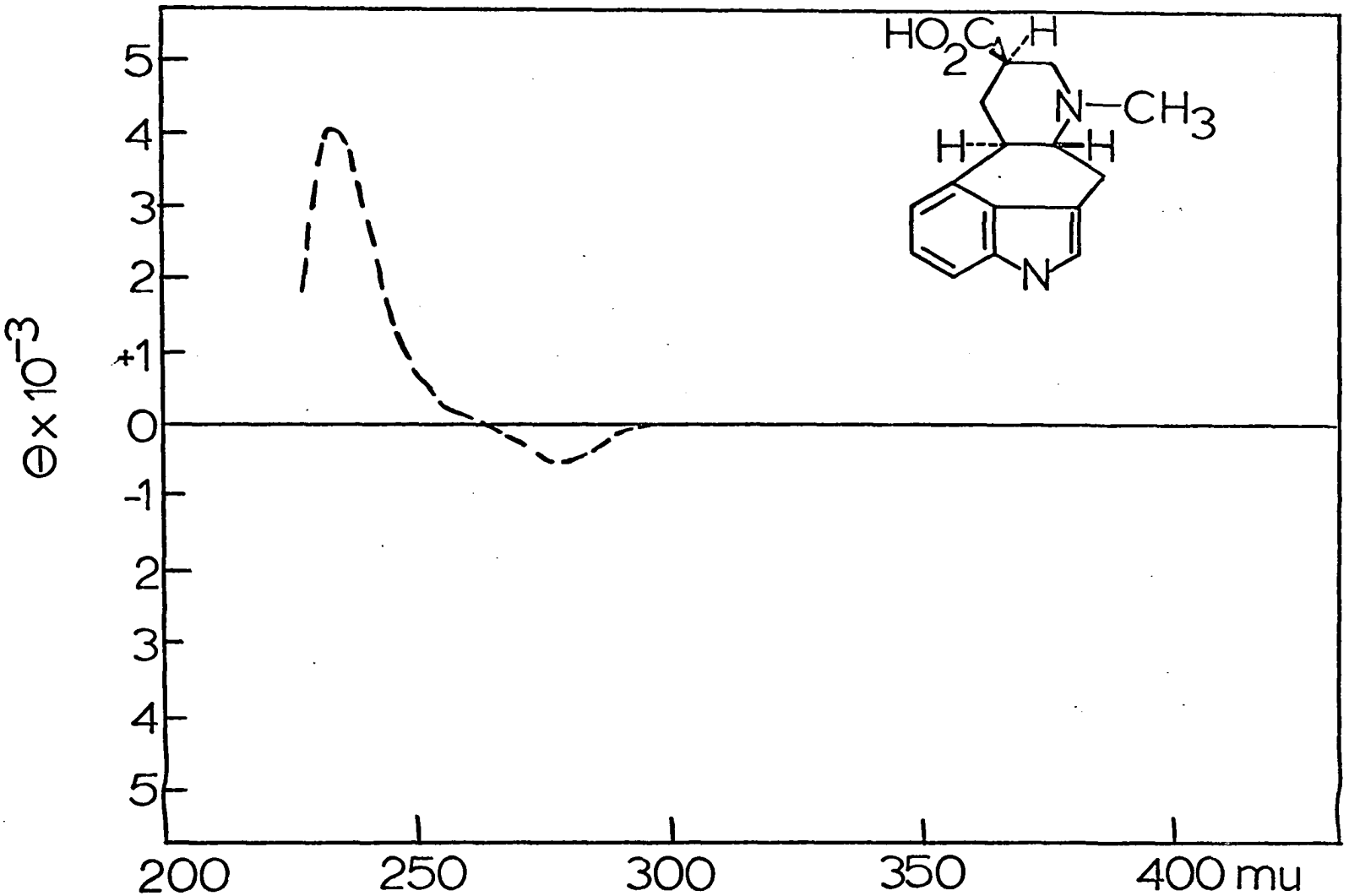
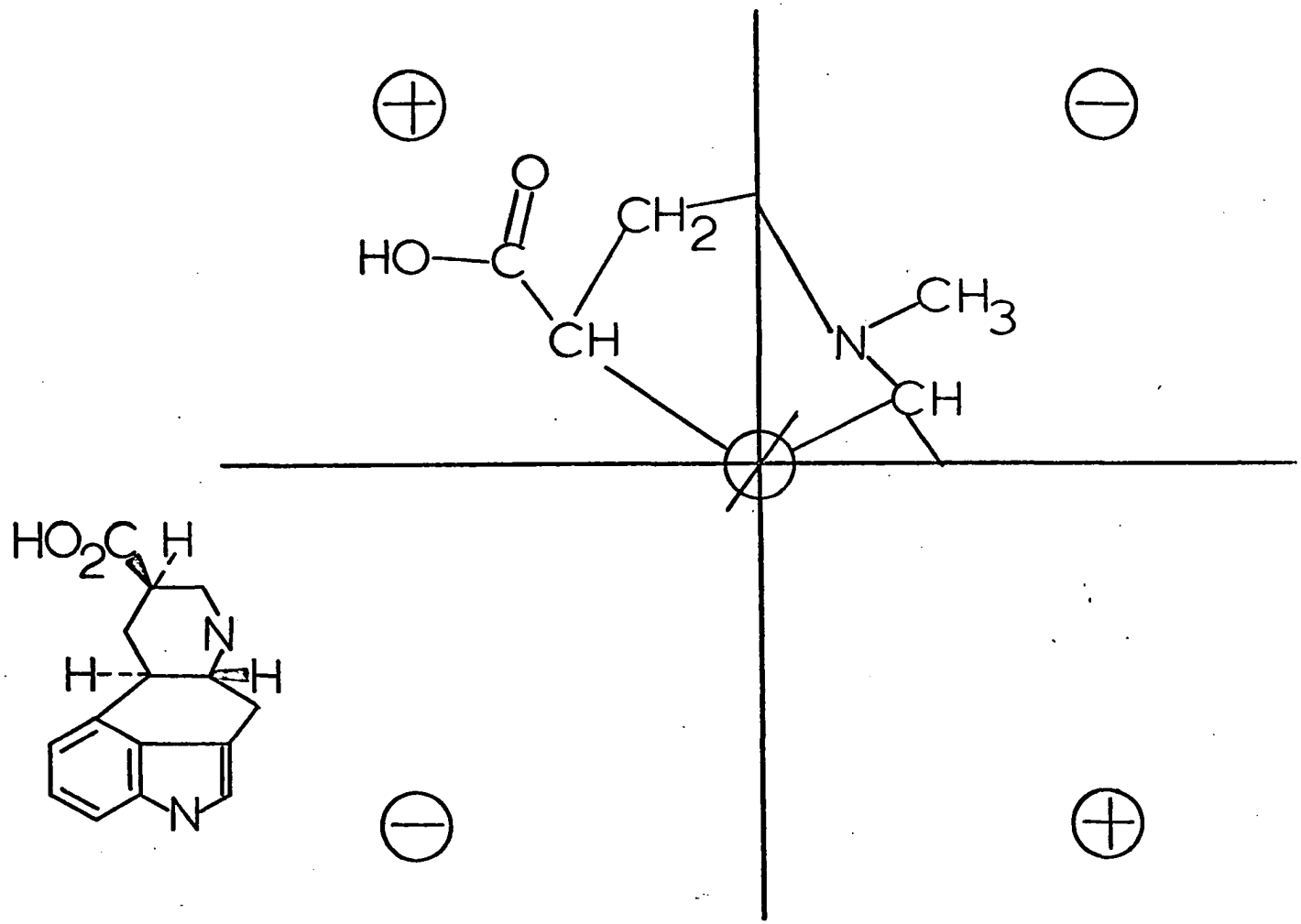


Fig 72

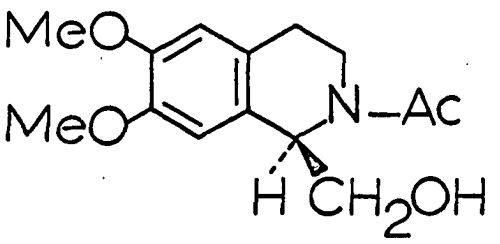
CD of DIHYDROLYSERGIC ACID



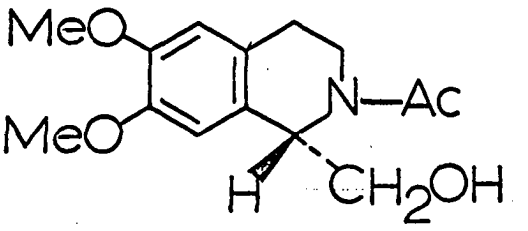
DIHYDROLYSERGIC ACID PROJECTION

Fig 73

center. Two of the compounds studied were directly applicable to the quadrant rule. These were XXXIX and XL, and the quadrant projection of each are given in Figure 74.

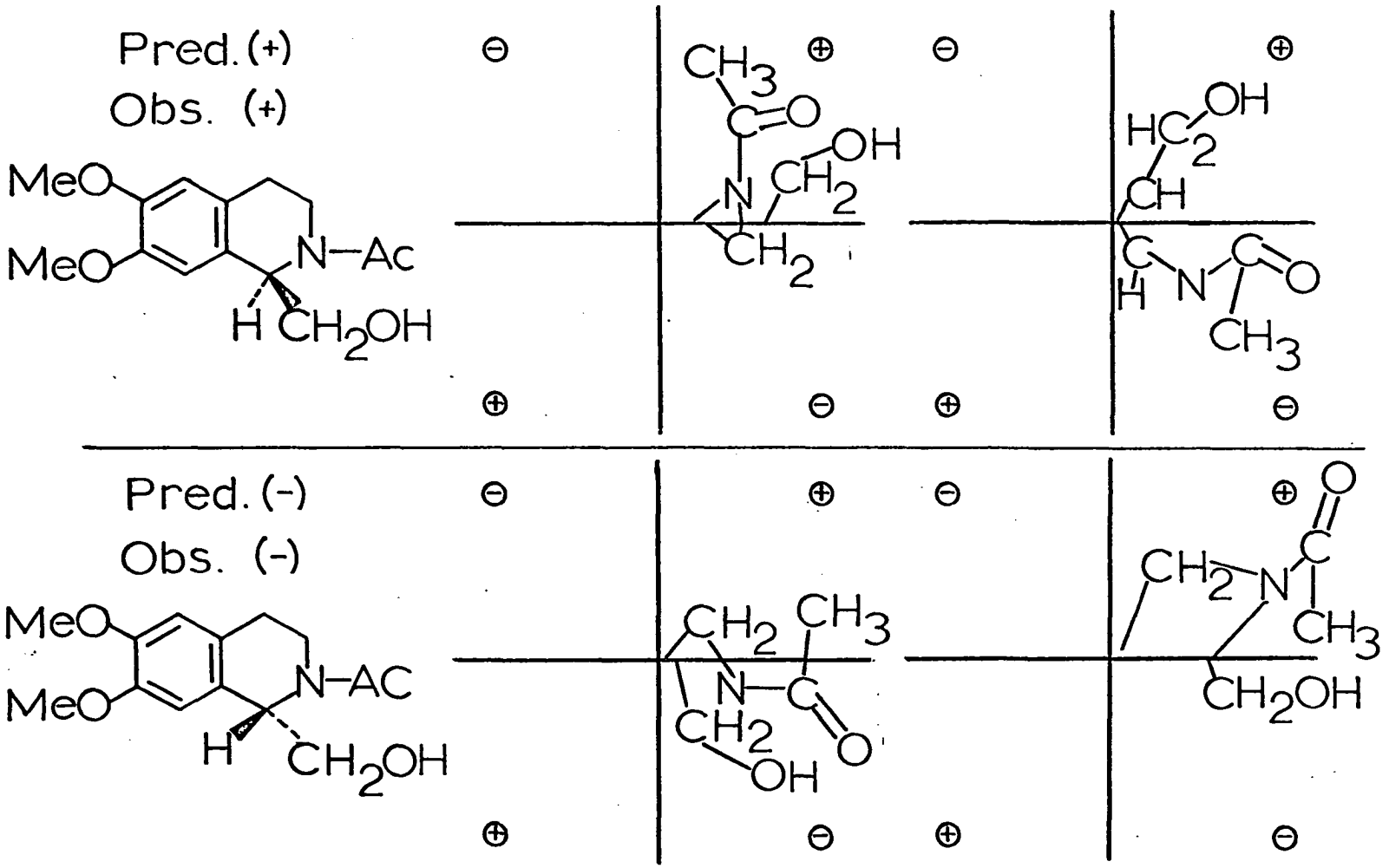


XXXIX



XL

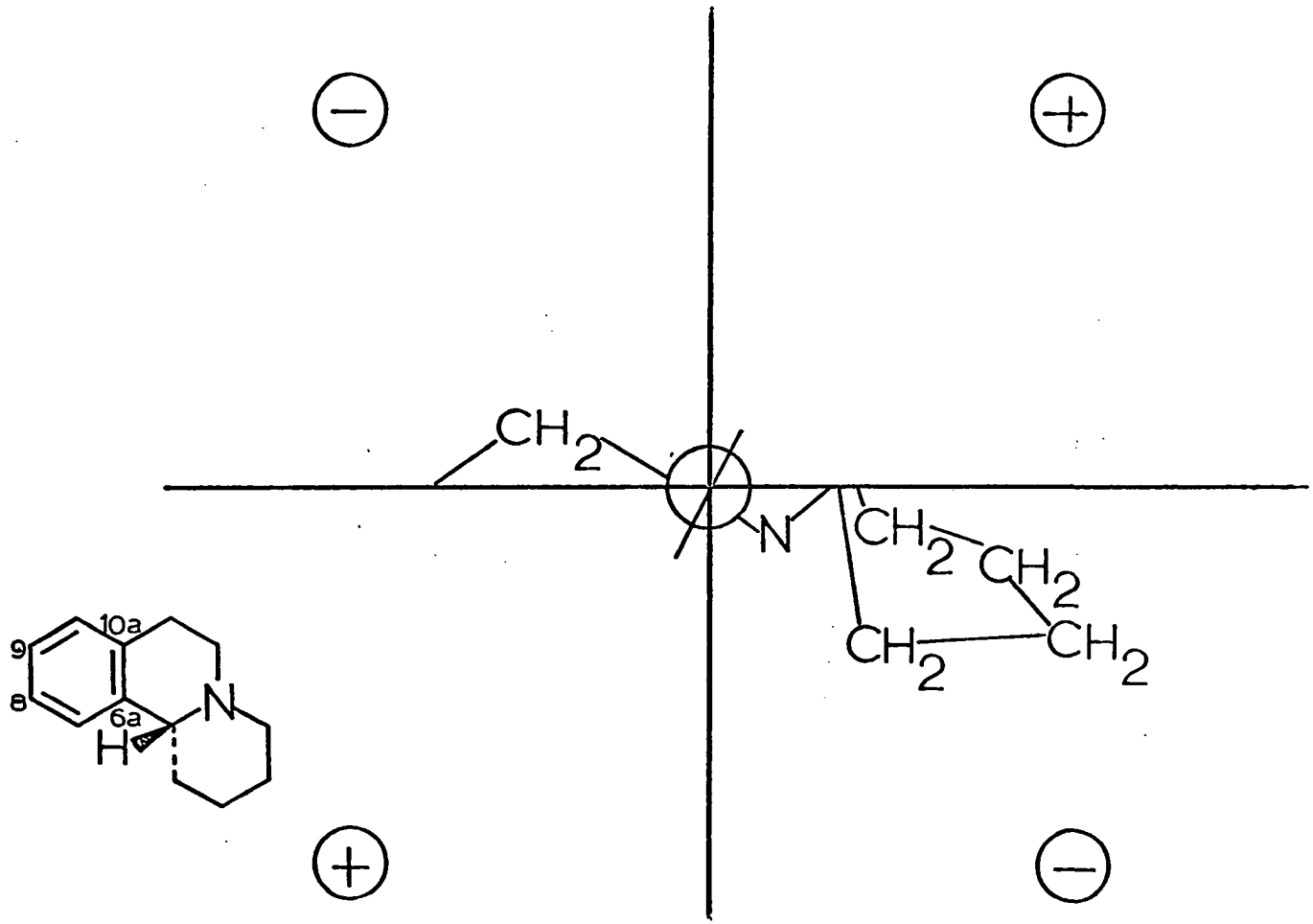
An examination of the Dreiding models of XXXIX and XL showed that each could exist in two conformations. Conformational analysis indicated that probably only one of these conformations would exist. The choice of conformers was governed by the following factors: a trans relationship between the lone pair on nitrogen and the benzylic hydrogen; an equatorial $-CH_2OH$ is more stable than an axial one; an equatorial $-COCH_3$ is more stable than an axial one; a quasi chair conformation of ring b is preferred to a quasi boat one; the conformation having all of the above is such that a strong hydrogen bond is formed between the hydroxyl proton and the oxygen of the carbonyl group. In both XXXIX and XL the choice was made on the basis of one conformer having all of the above prerequisites while the other conformer had none. The equatorial-axial consideration was especially important since, in the latter, both the $-CH_2OH$ and the $-COCH_3$ groups were axial at the same time and in this position were situated in the pi cloud of the benzene ring. On the



QUADRANT PROJECTIONS of XXXIX and XL

Fig. 74

basis of the most stable conformation contributing virtually all of the observed rotation, these two compounds were projected onto the octants for the first benzene band, and were found to exhibit the sign of rotation as called for by the rule. It seems that as the quadrant rule for aromatic compounds becomes more firmly established, its use can be extended to conformational analysis. The use of CD and ORD for conformational analysis has precedent in the work of Djerassi and coworkers (69). The isoquinoline derivative, benzoisoquinolizidine (Fig. 75), is a semirigid structure of known absolute stereochemistry (164). Its ORD spectrum has a trough at 304 mu followed by a positive peak which cannot be seen in its entirety. When this molecule is placed on its projection and viewed along the axis from the asymmetric center, there are three carbon atoms in the negative octants and a nitrogen and a carbon close to the plane of the benzene ring in a positive octant. It is difficult to decide whether the sign of the rotation should be positive or negative from this projection. However, when the molecule is viewed through its symmetry axis (C_8-C_9; C_{6a}-C_{10a}) this problem no longer exists as the nitrogen and four carbon atoms fall into a negative quadrant. The small size of the rotation at 304 mu may arise if the symmetry axis bisects the C_8-C_9 axis and the nitrogen atom. This would then leave four carbon atoms in the negative quadrant to contribute to the rotatory strength of the benzene ring. The quadrant projection of this compound is given in Figure 75.

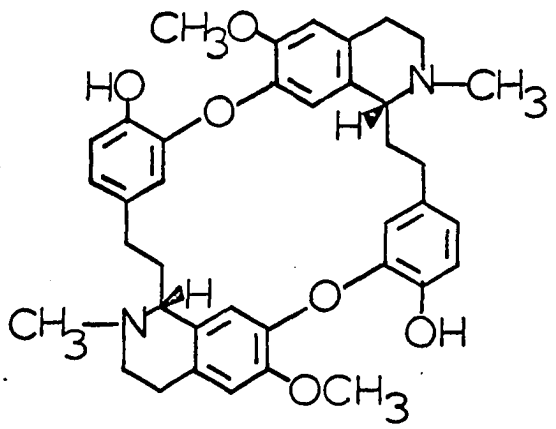


BENZOISOQUINOLIZIDINE PROJECTION

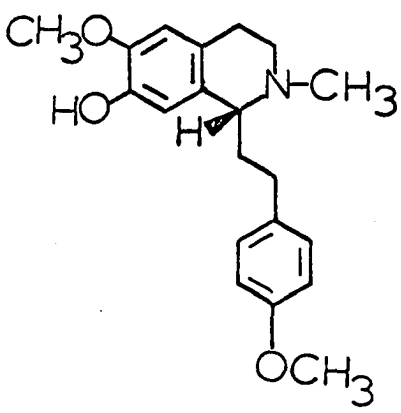
Fig. 75

A re-examination of the ORD spectra of the morphine derivatives discussed previously shows that as the substitution in ring C changes from a vinyl ether to a saturated ring the rotation decreases accordingly. This can be predicted by the quadrant rule because as each functional group is removed the total number of contributing groups in the negative quadrants decreases. With this in mind one predicts that the size of the dispersion decreases in going from XXX to XXXII. This is found to be the case.

Melanthiodine (XLI) is the second member of 1-phenylisoquinolines to be reported (165). Klyne has assigned the absolute stereochemistry to this compound on the basis of the ORD spectra, and its correlation with compounds of known stereochemistry (165). Dreiding models show that there can be a great deal of freedom of rotation around the carbon-carbon bonds but in all cases the atoms remain in the same octants when projected onto them. The one case where the atoms change octants is in the unlikely conformer where all four benzene rings are directly above one another. The quadrant rule predicts that the first Cotton effect be negative and this is what was found. This conclusion is in agreement with the fact that XLII has as its first Cotton effect a negative trough (166), which is predicted by the quadrant rule.

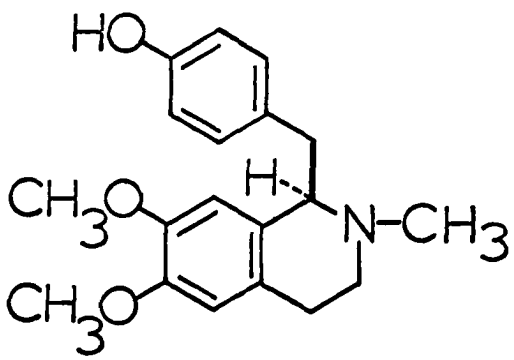


XLI

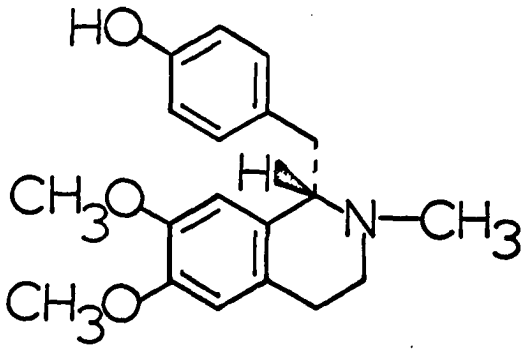


XLII

A number of benzylisoquinoline alkaloids have been correlated with their absolute stereochemistry by optical rotatory dispersion techniques (167). The ORD spectra if D-armepavine and L-norarmepavine are negative and positive at 290 mu respectively (XLIII and XLIV).



XLIII



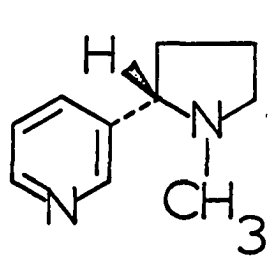
XLIV

Since the asymmetric center is α to one of the aromatic ring and β to the other, it is usual to assume that the greatest portion of the

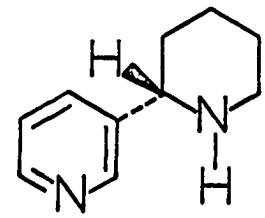
rotation is due to the former. In any case it is clear that the two spectra are mirror images, and that the compounds are true antipodes. As in the Amaryllis and morphine alkaloids, there are bands at 285 mu and 245 mu which can be assigned to the two benzene bands of ring A. This can be only a tentative assignment as no CD spectra of these compounds are available. The dimethoxybenzene chromophore in alkaloid 16 has absorption maxima at 286 mu and 235 mu, whereas the phenolic ring absorbs at 286 mu and 279 mu. The difference between the extinction coefficients of the phenolic absorptions (279 mu, E = 1950; 286 mu, E = 1780) and the absorption of ring A (286 mu, E = 4130) is not large enough to differentiate between them in the UV spectra, but they can be approximated from the ORD spectra. Since the benzene ring β to the asymmetric center contributes little to the total dispersion, the crossover points at 235 mu and 286 mu can be taken as the center of the absorption bands corresponding to ring A. The only trough which can be assigned with certainty is that one at 290 mu. This corresponds to the 286 mu dispersion of ring A. As no CD data are available it is not possible to tell how far each dispersion extends, and it is difficult to assign the rest of the peaks and troughs. Application of the quadrant rule results in the prediction that the first band in armepavine should be negative and that in norarmepavine positive. This is found to be true experimentally. These conclusions take into account the recent work of Dalton and Cava on benzylisoquinolines which states that

substituents on the nitrogen cause the phenolic ring to take position directly over ring A (168).

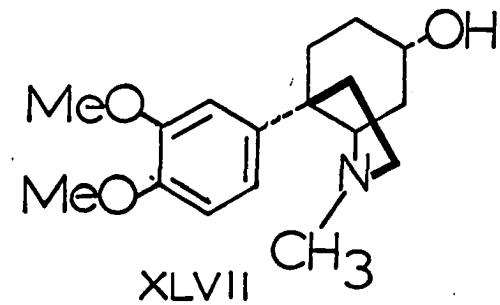
Nicotine (XLV), anabasine (XLVI) and mesembrinol (XLVII) present special problems when an attempt is made to apply the quadrant rule. In these compounds the optically active center adjacent to the aromatic ring is free to rotate. This is the first time that this situation is encountered. An examination of the Dreiding models of nicotine and anabasine did not point to any one rotamer as being inherently more stable than another. Even when the rule is used in reverse, i.e., knowing the sign of the rotation and the absolute stereochemistry (169), it is not possible to find a sound reason why one rotamer should predominate over any of the others. Since mesembrinol is a bulkier molecule than either nicotine or anabasine the same reasoning was used on this molecule, but with no more success than previously.



XLV



XLVI



XLVII

It is necessary to conclude at the present time that the quadrant rule should not be applied to compounds possessing a freely rotating asymmetric center adjacent to the aromatic ring. This does not imply

the rule breaks down for these compounds, but that it is not possible to determine which rotamers contribute most to the rotatory power of the chromophore.

The quadrant rule for the aromatic chromophore has been applied to a relatively large number of compounds of known absolute stereochemistry. The absolute configuration of these compounds has been proven unequivocably by either X-ray analysis, chemical interrelations or both. Table 12 gives all of the compounds to which the quadrant rule has been applied and the results obtained.

Table 12 is only a partial representation of the total number of compounds to which the rule applies if one considers the total number of alkaloids in each group. As an example, morphine and codeine represent but two of a large number of compounds of essentially the same structure. If the aromatic quadrant rule were available when the stereostructures of other derivatives in this large family were being studied, the correlations eventually derived by chemical degradations could have been obtained much more readily.

The quadrant rule has been developed from compounds of known absolute stereochemistry, and has been tested on a relatively large number of representative alkaloids from various families. The rule has always predicted the same absolute stereochemistry that X-ray analysis has proven to be correct. When the quadrant rule is applied to the Amaryllis alkaloids possessing either the crinine or the tazettine ring

Table 12. Compounds to which the quadrant rule has been applied and results obtained

Compound	Pred. CD		Obs. CD		Pred. ORD	Obs. ORD
	285 mu	245 mu	285 mu	245 mu	300 mu	300 mu
Morphine[a]	(-)	(+)	(-)	(+)	(-)	(-)
Codeine[a]	(-)	(+)	(-)	(+)	(-)	(-)
Dihydrocodeine	(-)	(+)	(-)	(+)	(-)	(-)
Thebaine	(-)	(+)	(-)	(+)	(-)	(-)
Heroin	(-)	(+)	(-)	(+)	---	---
XXX	---	---	---	---	(-)	(-)
XXXI	---	---	---	---	(-)	(-)
XXXII	---	---	---	---	(-)	(-)
XXXIII	---	---	---	---	(+)	(+)
XXXV	---	---	---	---	(+)	(+)
XXXVI	---	---	---	---	(-)	(-)
Aspidospermine	(-)	(+)	(-)	(+)	---	---
Akuammicine	(-)	(+)	(+)	(+)	---	---
Ajmaline	(-)	(+)	(-)	(+)	---	---
Brucine	(+)	(-)	(-)	(-)	---	---
Strychnine		(-)		(-)	---	---
Dihydrolysergic acid	(-)	(+)	(-)	(+)	---	---
XXXIX	---	---	---	---	(+)	(+)
XL	---	---	---	---	(-)	(-)
XLI	---	---	---	---	(-)	(-)
XLII	---	---	---	---	(-)	(-)
Benzoisoquinolizidine	---	---	---	---	(-)	(-)
Norarmepavine	---	---	---	---	(+)	(+)
Armepavine	---	---	---	---	(-)	(-)
Galanthamine	(-)	(+)	(+)	(+)	(+)	(-)
Lycorine	(-)	(+)	(-)	(+)	(-)	(-)
Dihydrolycorine	(-)	(+)	(-)	(+)	---	---

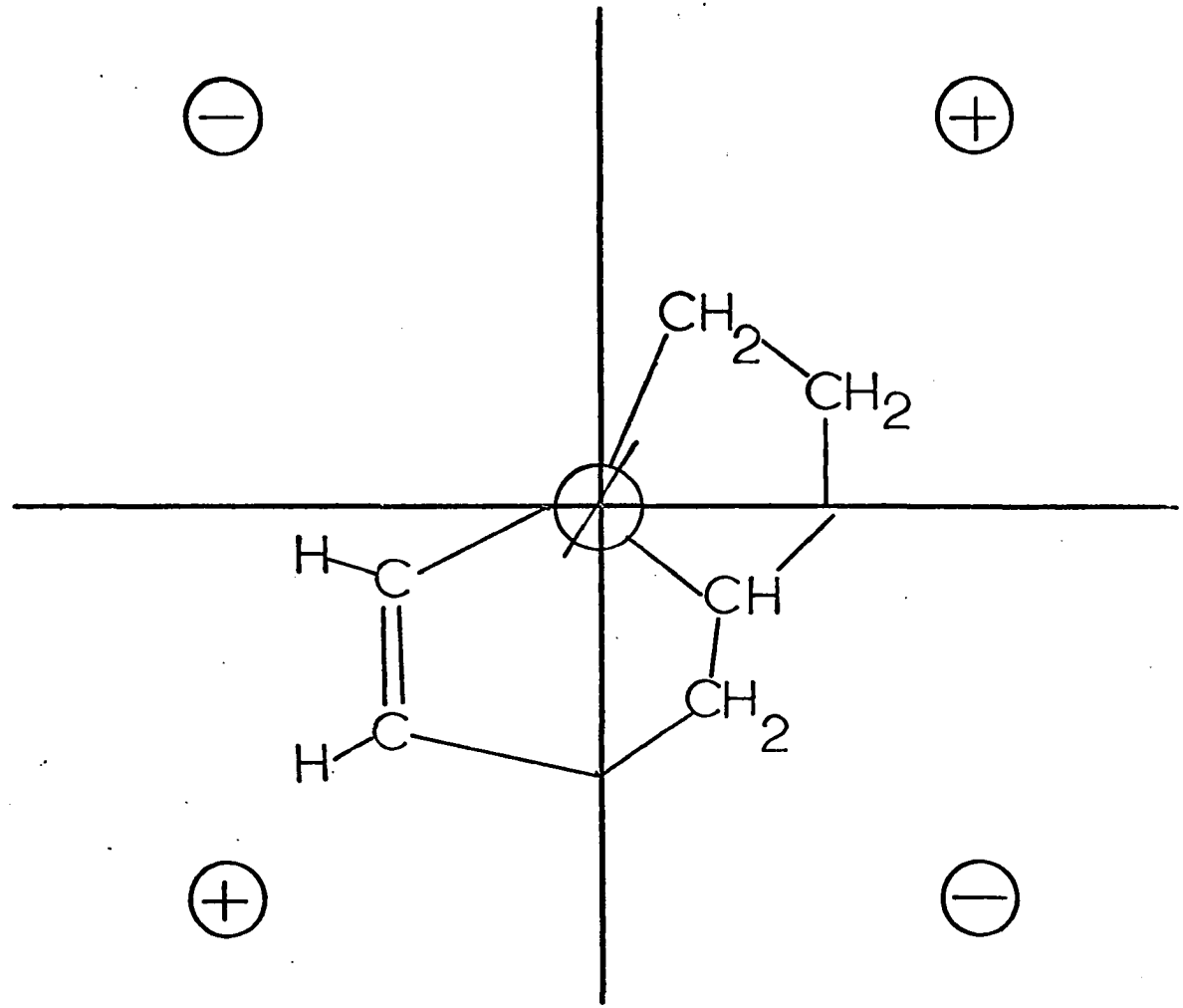
[a]Basis of quadrant rule.

systems, the predictions are in all cases the opposite of that expected for the presently accepted absolute stereochemistry. Therefore, the

quadrant rule demands that the absolute configurations of the crinine, tazettine and montanine types be reinterpreted. The arguments presented below are based on the quadrant rule as applied to these members of the Amaryllis alkaloids in the absolute configurations now accepted. All of the octant projections shown in the following sections are projections of this stereochemistry. In each case we shall demonstrate that this approach invariably leads to erronious conclusions concerning the absolute stereochemistry of these compounds.

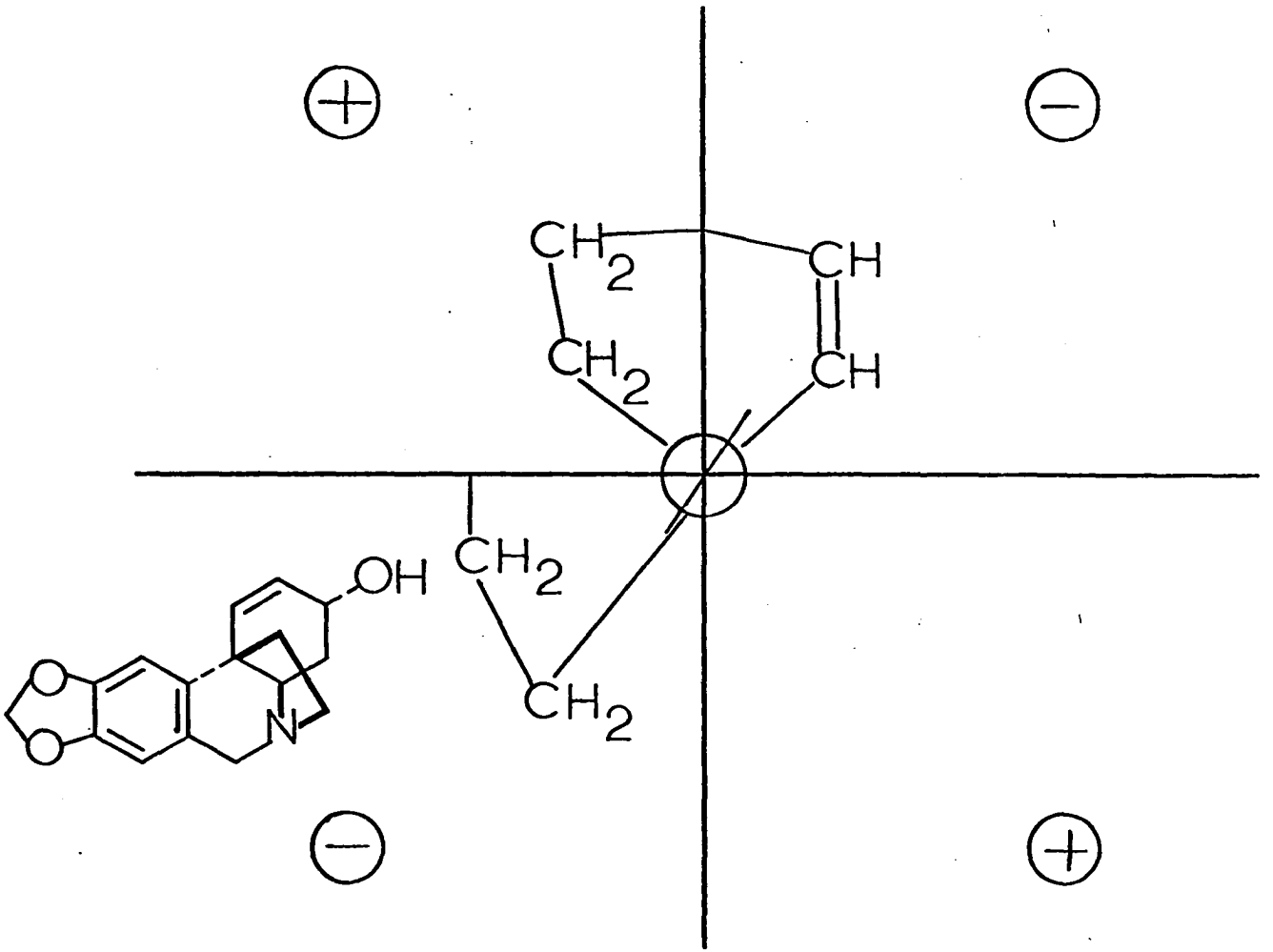
The octant projections for the 296 mu and 245 mu of crinine are given in Figures 76 and 77. From the positions of the atoms in the quadrants, it is clear that the first Cotton effect of crinine should be positive and the second negative. The reverse would be true for vittatine. Experimentally this is found not to be the case. The first Cotton effect in crinine is negative and the second is positive. Consistent results were obtained for powelline, buphanidrine, crinamine, haemanthamine, haemanthidine, 6-hydroxycrinamine and all other Amaryllis alkaloids for which the dichroisms are normal. In those compounds for which the sign of the first dichroism has changed, the sign of the second dichroism (which never changes), provides the same results.

In the series crinine, dihydrocrinine, crinane, the rotations and dichroisms decrease in a stepwise fashion as can be predicted from the quadrant rule. In undergoing these changes the aromatic ring is effected by fewer electrons and the dichroism decreases accordingly.



CRININE PROJECTION $A_{1g} \longrightarrow B_{2u}$ BAND

Fig. 76

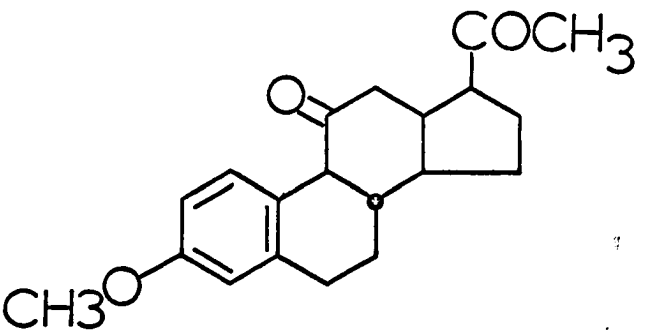


CRININE PROJECTION ($A_{1g} \rightarrow B_{1u}$)

Fig. 77

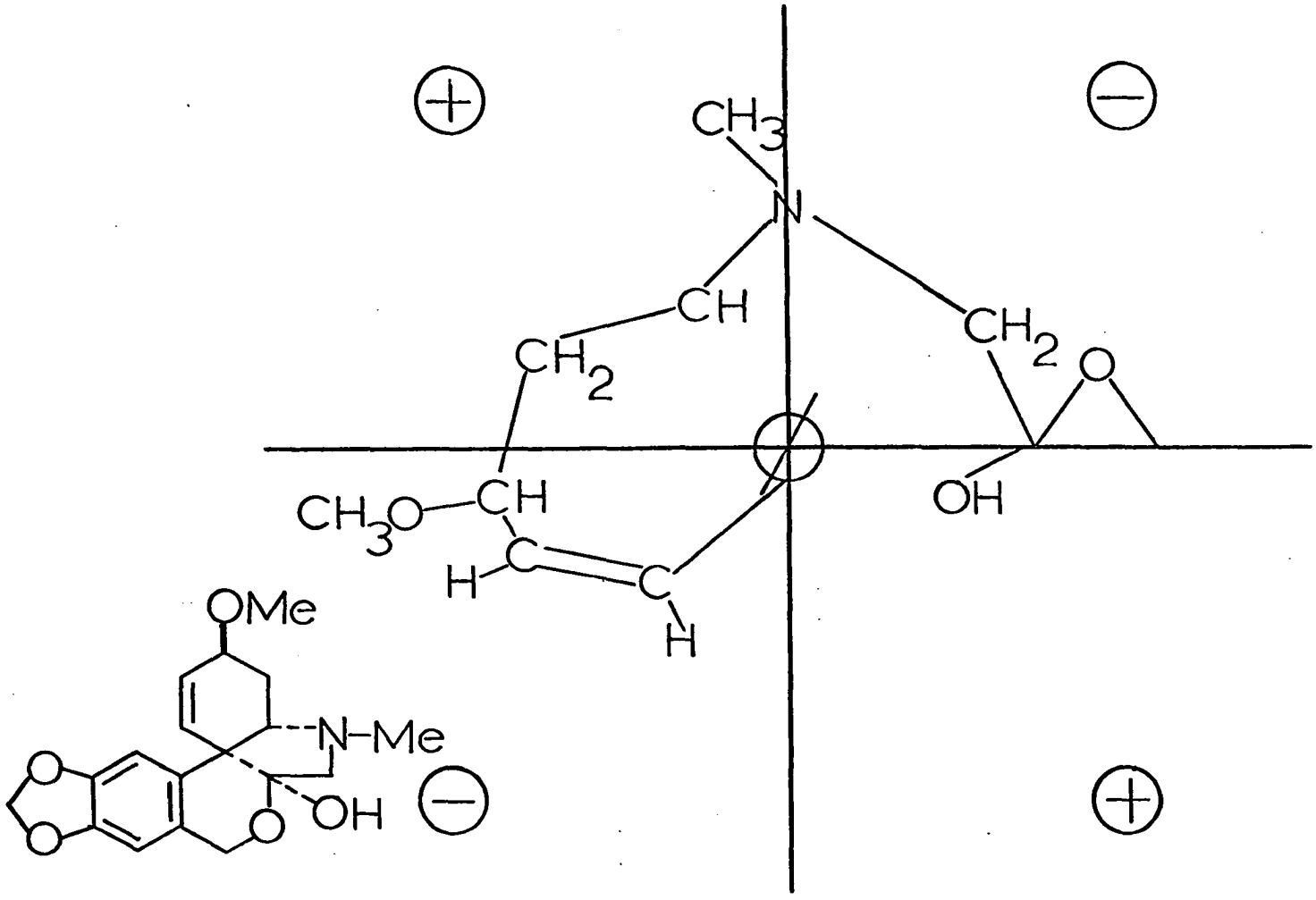
The change in sign of the CD spectra of haemanthidine and tazettine can be accommodated as the changing of the quadrant occupancy around the benzene ring while not changing the absolute configuration at position 10b. Figures 78 and 79 show the projections of tazettine and haemanthidine based on the presently accepted stereochemistry. It is apparent that the dichroisms are the opposite from those predicted by the quadrant rule on the basis of this stereochemistry. We submit that the absolute configurations now accepted for these molecules be reversed.

Excellent supporting evidence that a change in the absolute configuration of the 5, 10b-ethanophenanthridine alkaloids is necessary came from a study of the CD spectra of dihydrooxobuphanamine (Fig. 80). This compound is quite similar to the aromatic A-ring steroids (XLVIII) studied by Dreiding (131), since both compounds have conformations favoring homoconjugation of the pi orbitals of benzene with those on the carbonyl group.



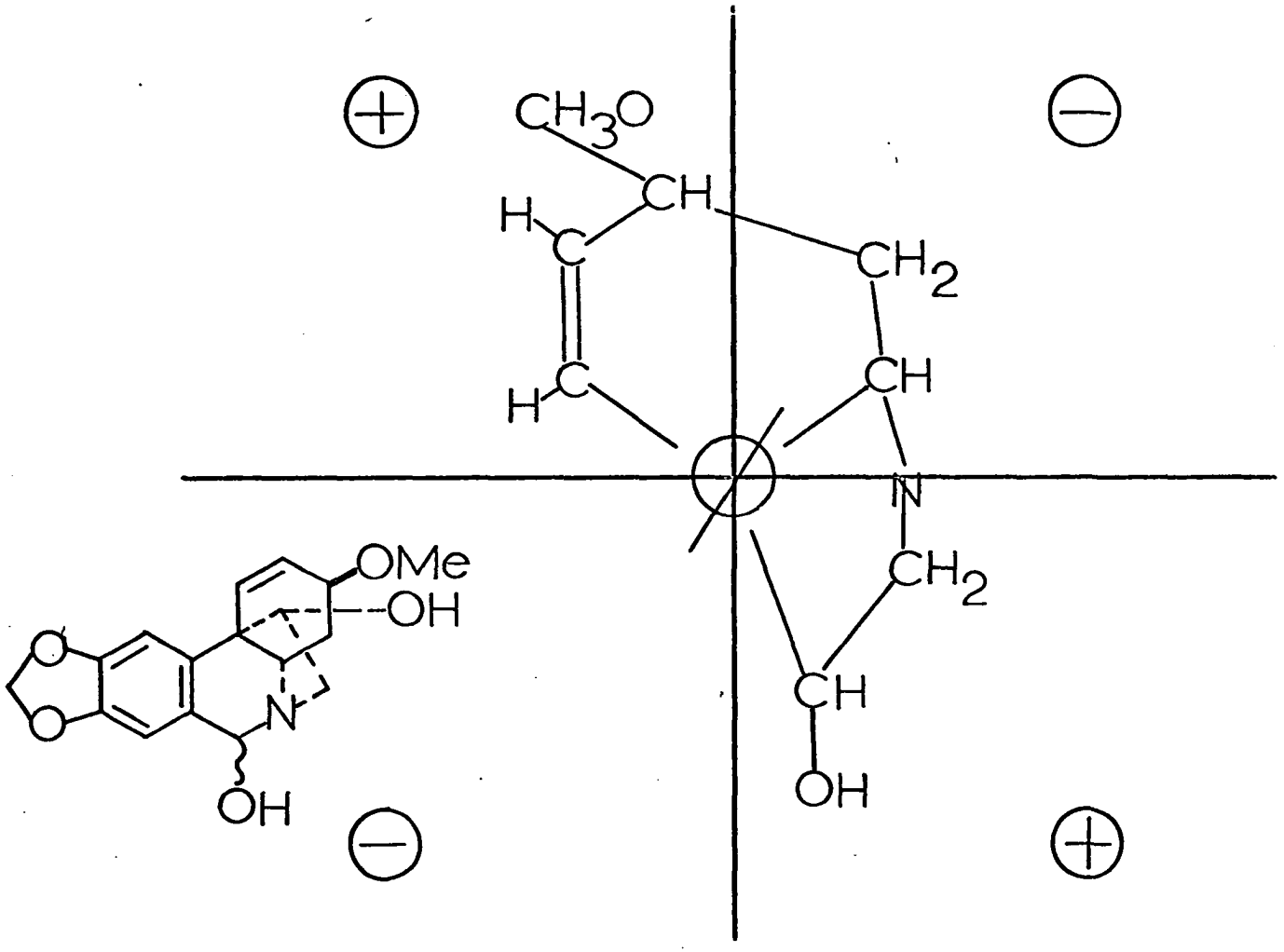
XLVIII

Dihydrooxobuphanamine gives rise to a positive Cotton effect at 295 mu which can be assigned to the carbonyl chromophore. There is no cor-



TAZETTINE PROJECTION

Fig. 78



HAEMANTHIDINE PROJECTION

Fig.79

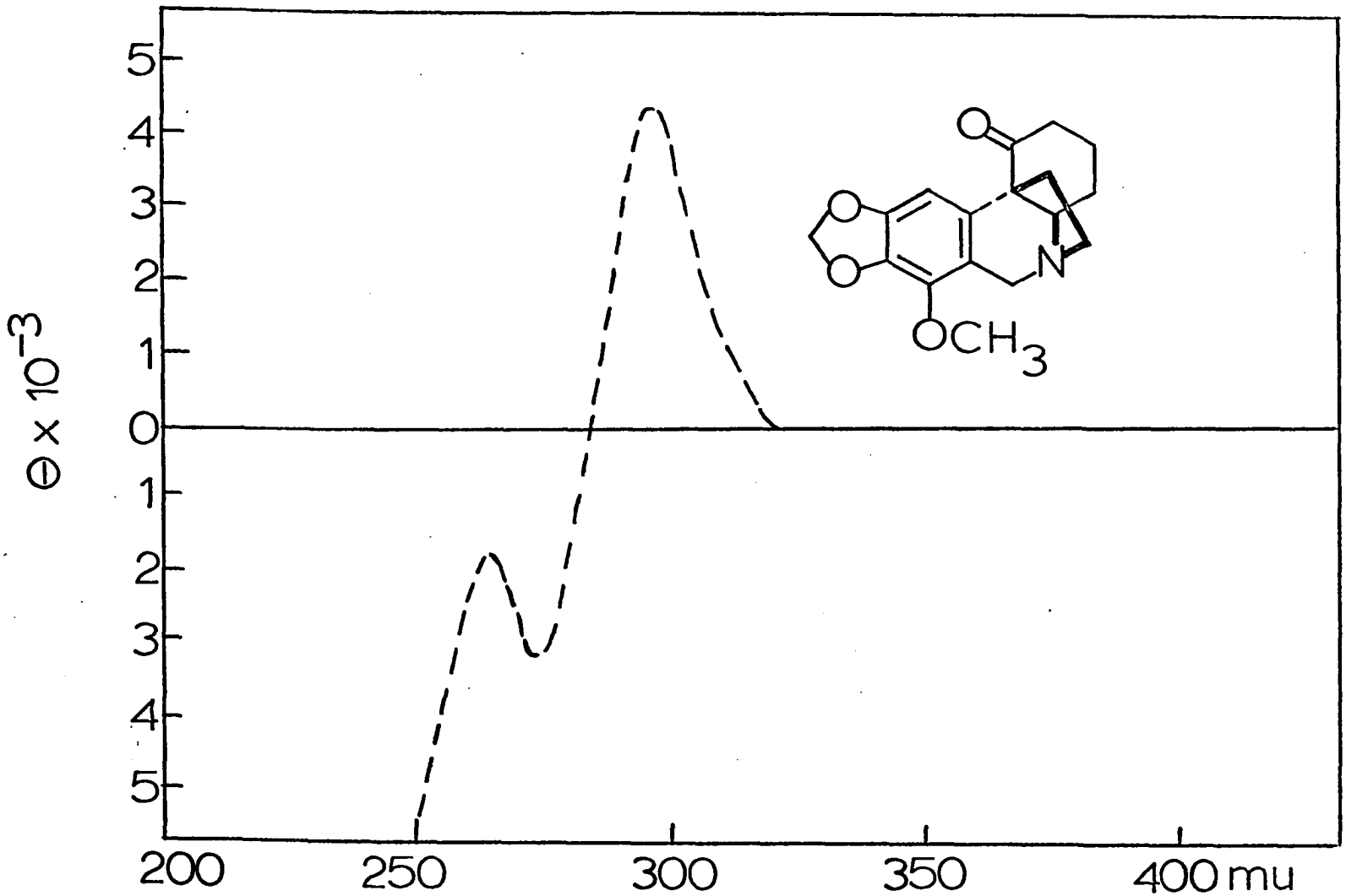


Fig.80

CD of DIHYDROOXOBUPANAMINE

responding absorption band at 295 mu in the UV indicating that this is an n→pi* transition of small extinction coefficient. The octant rule can now be applied in the usual manner, taking into account the fact that substituents lie in both the front and rear octants (60). The plane through the carbonyl bisects the aromatic ring in dihydrooxobuphanamine in such a manner as to leave the methylenedioxy group in a positive front octant and the methoxy group in a negative rear octant. A simple expedient would be to consider that the effects of the aromatic ring cancel and it is only necessary to consider the substituents. However, it is known from both NMR and CD studies that the methoxyl group in position 7 causes the electron density at C_{10} to be greater than in compounds where there is no C_7 electron releasing group. That this increased electron density is felt by the carbonyl group is evidenced in the CD spectrum of desmethoxyldihydrooxobuphanamine (Fig. 81). The molecular ellipticity of the carbonyl group in this derivative is (+) 1980° while that of dihydrooxobuphanamine is (+) 4360°. This is to be expected in view of the effects which an aromatic methylenedioxymethoxy ring has upon substituents at C_1 in these semirigid molecules. Because of these facts the aromatic carbon atoms should be included in the octant projections to determine what the sign of the dichroism will be. However, the same answer can be obtained if these are neglected. The projections for the front and rear octants and the resultant of these are given below. A starred carbon atom indicates an aromatic carbon

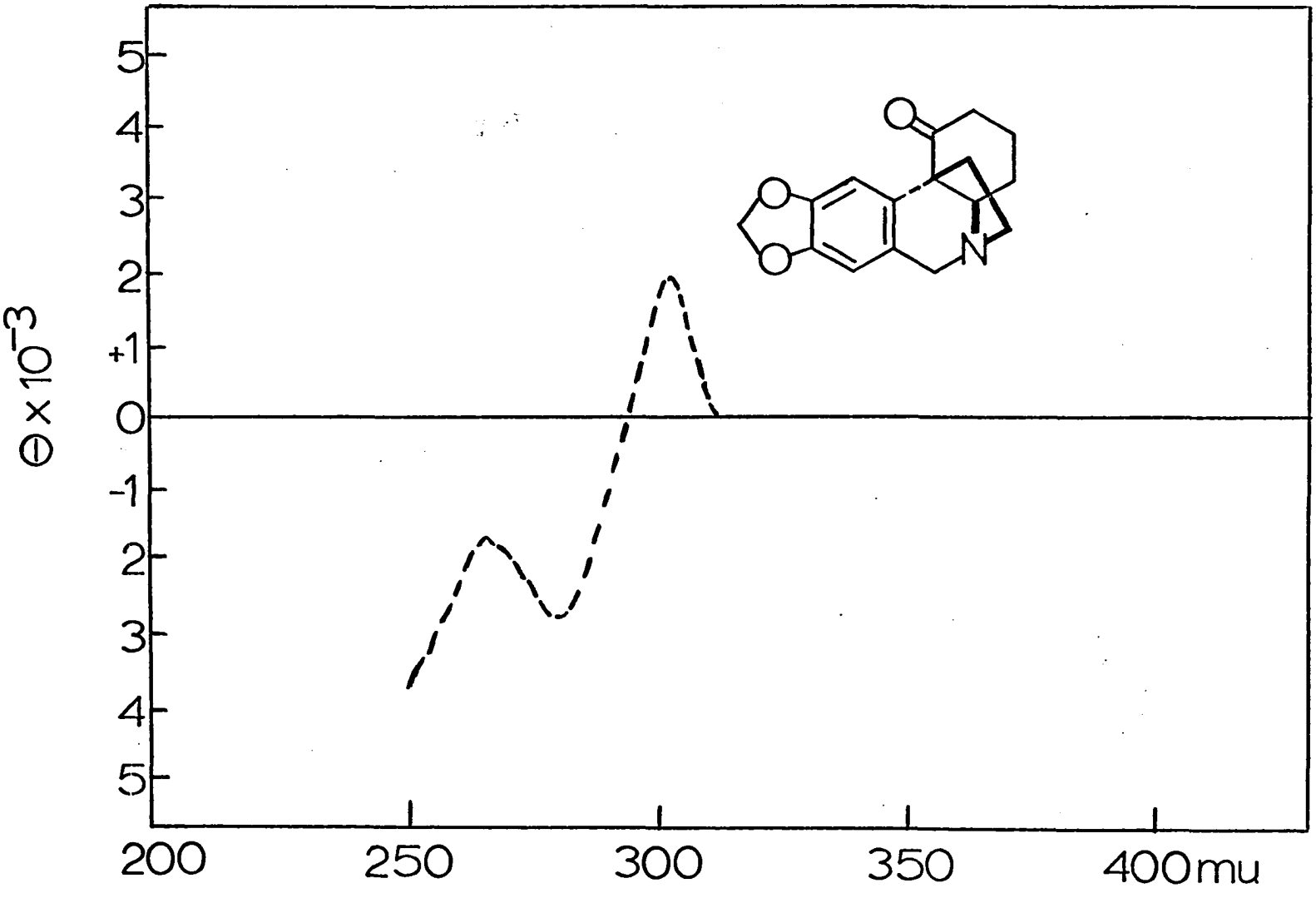
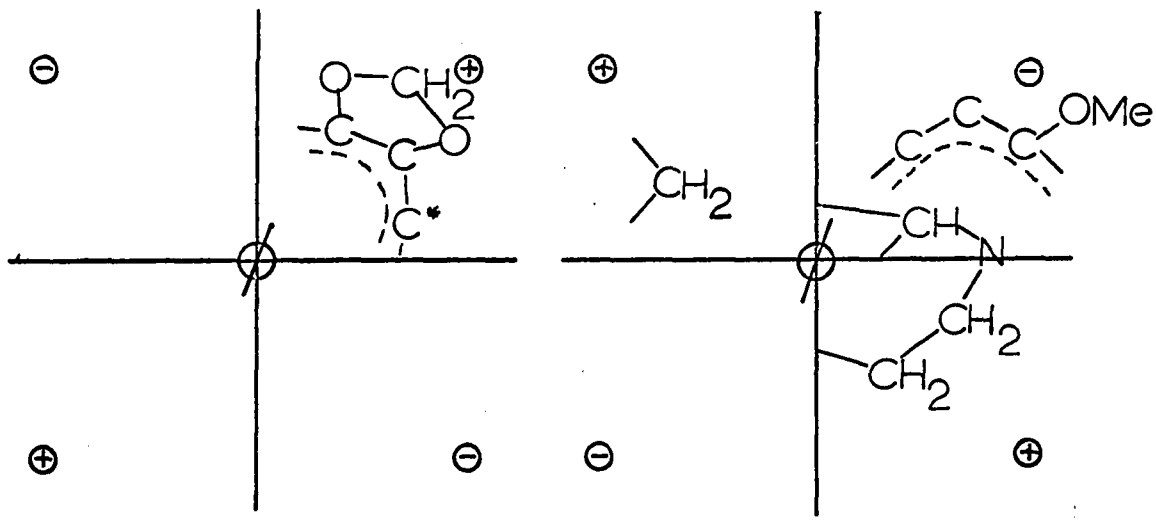


Fig.81

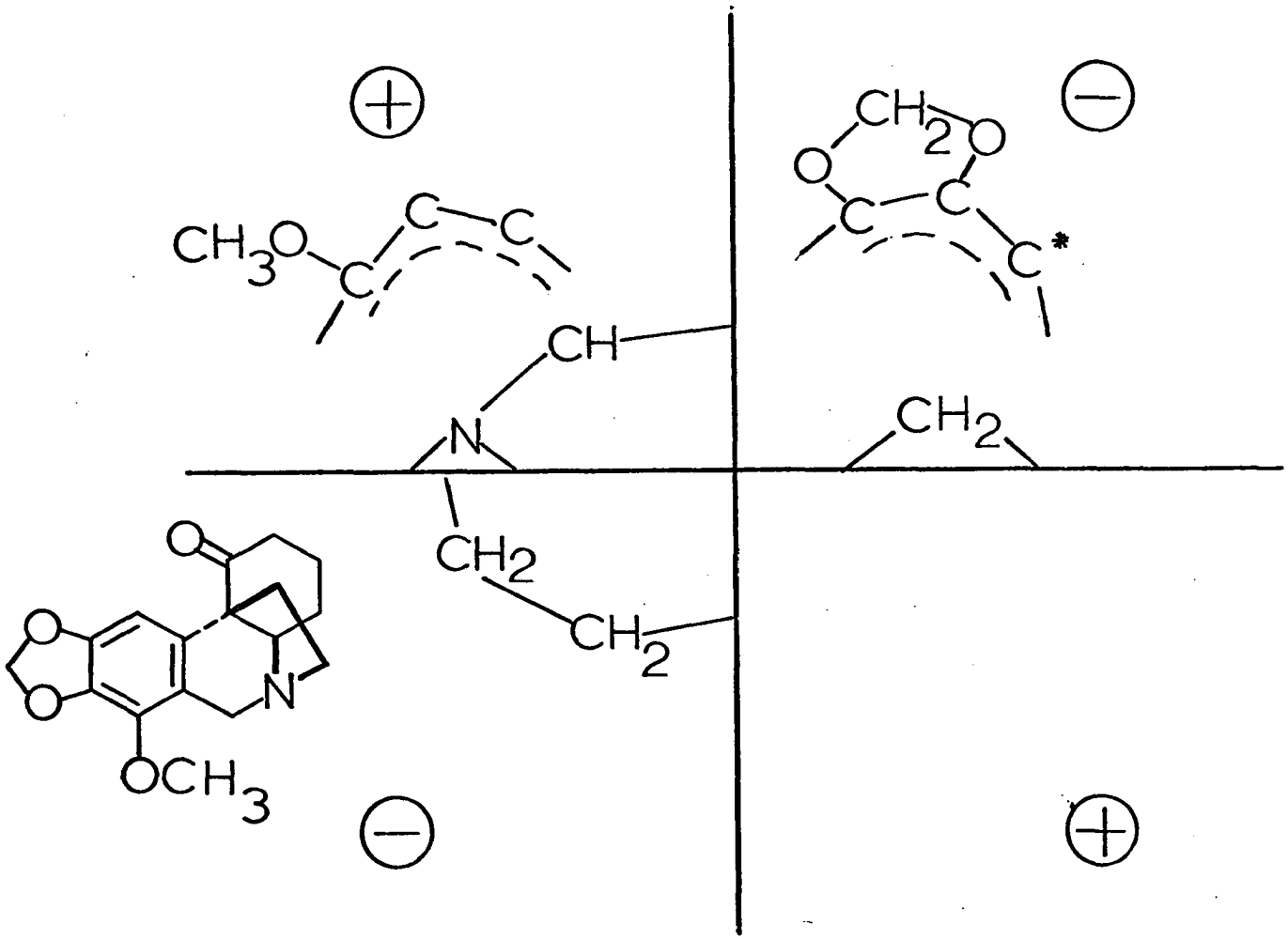
CD of DESMETHOXYDIHYDROOXOBUPHANAMINE

considered to be of high electron density in dihydrocoxobuphanamine. The resultant projection of the front and rear octants is given in Figure 82.



Application of the octant rule predicts a negative dichroism for the carbonyl group for the absolute configuration now accepted for dihydrocoxobuphanamine. Experimentally, a positive one is found. Figure 82 projects the atoms into octants which give a positive dichroism and calls for the opposite absolute configuration from that now assumed.

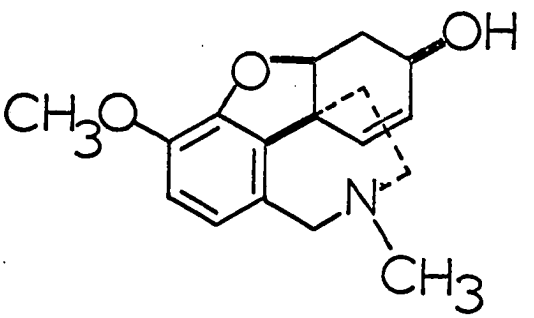
Recently, Rogers has determined the absolute stereochemistry of galanthamine methiodide (15) by X-ray methods, and has found that the ethano bridge has the same configuration as in the morphine alkaloids.



DIHYDROOXOBUPHANAMINE PROJECTION

Fig. 82

The complete structure of galanthamine is given below.



The CD spectra of galanthamine and epigalanthamine are given in Figures 83 and 84. The maxima at 288 mu and 240 mu correspond to those found in the UV spectra of these compounds, while the maximum at 250 mu has no accompanying absorption band which can be observed in either the free bases or in the hydrochlorides. The maxima at 288 mu and 240 mu are the same distance apart as in other disubstituted aromatic Amaryllis alkaloids, and if there were no other evidence available, they would be assigned the usual benzene bands as in other cases. Epigalanthamine affords a CD spectrum almost identical with galanthamine. It was originally suggested that the band at 250 mu was due to the oxide bridge in these compounds. This cannot be true since the morphine alkaloids have this same bridge and no 250 mu dichroism. There is no chromophore in this type of molecule which is known to absorb at this wave length, and the only alternative is to suggest that this band is an artifact arising from some peculiarity of the molecular structure. Dreiding models show that it is possible for the lone pair of electrons

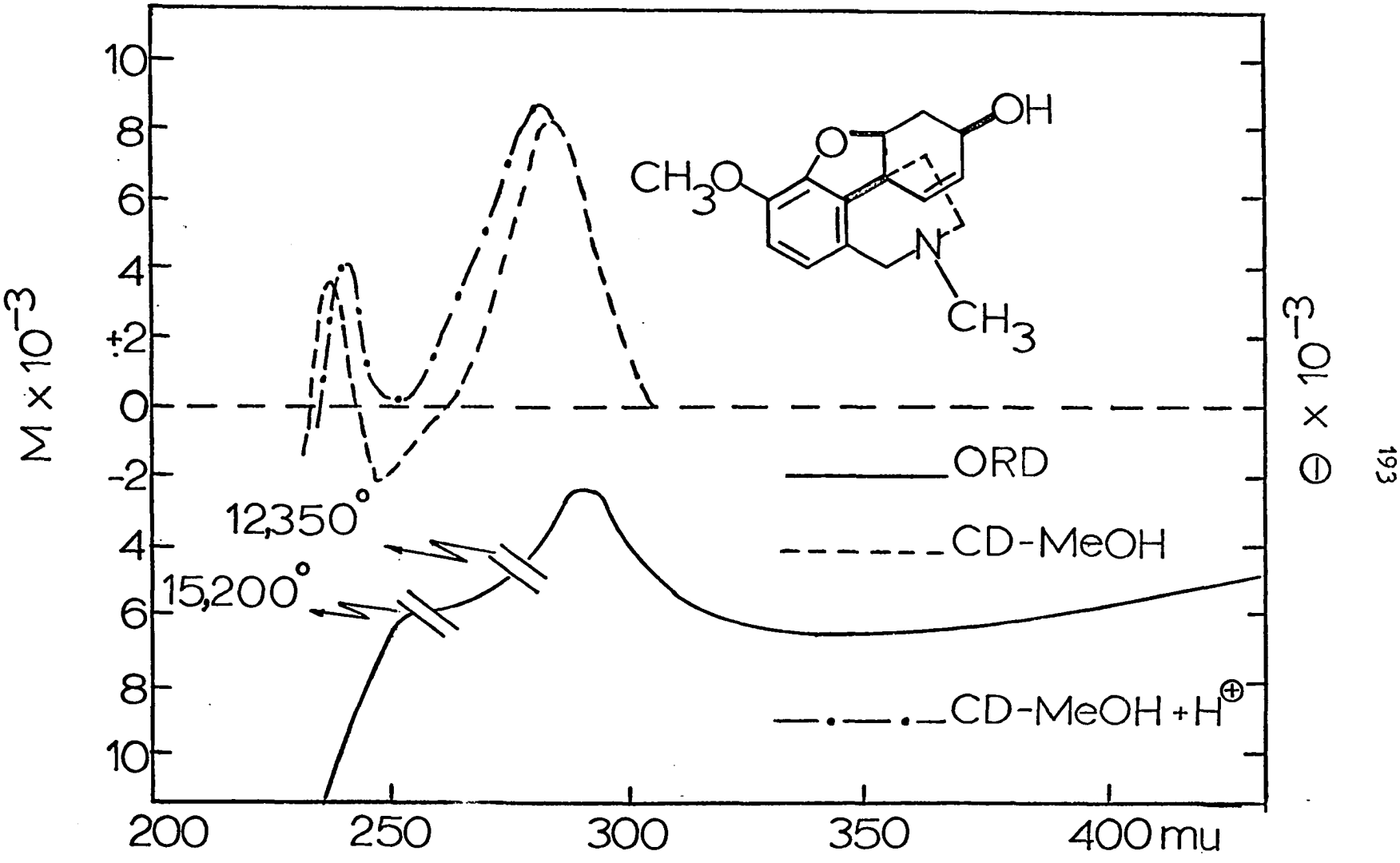


Fig.83

ORD and CD of GALANTHAMINE

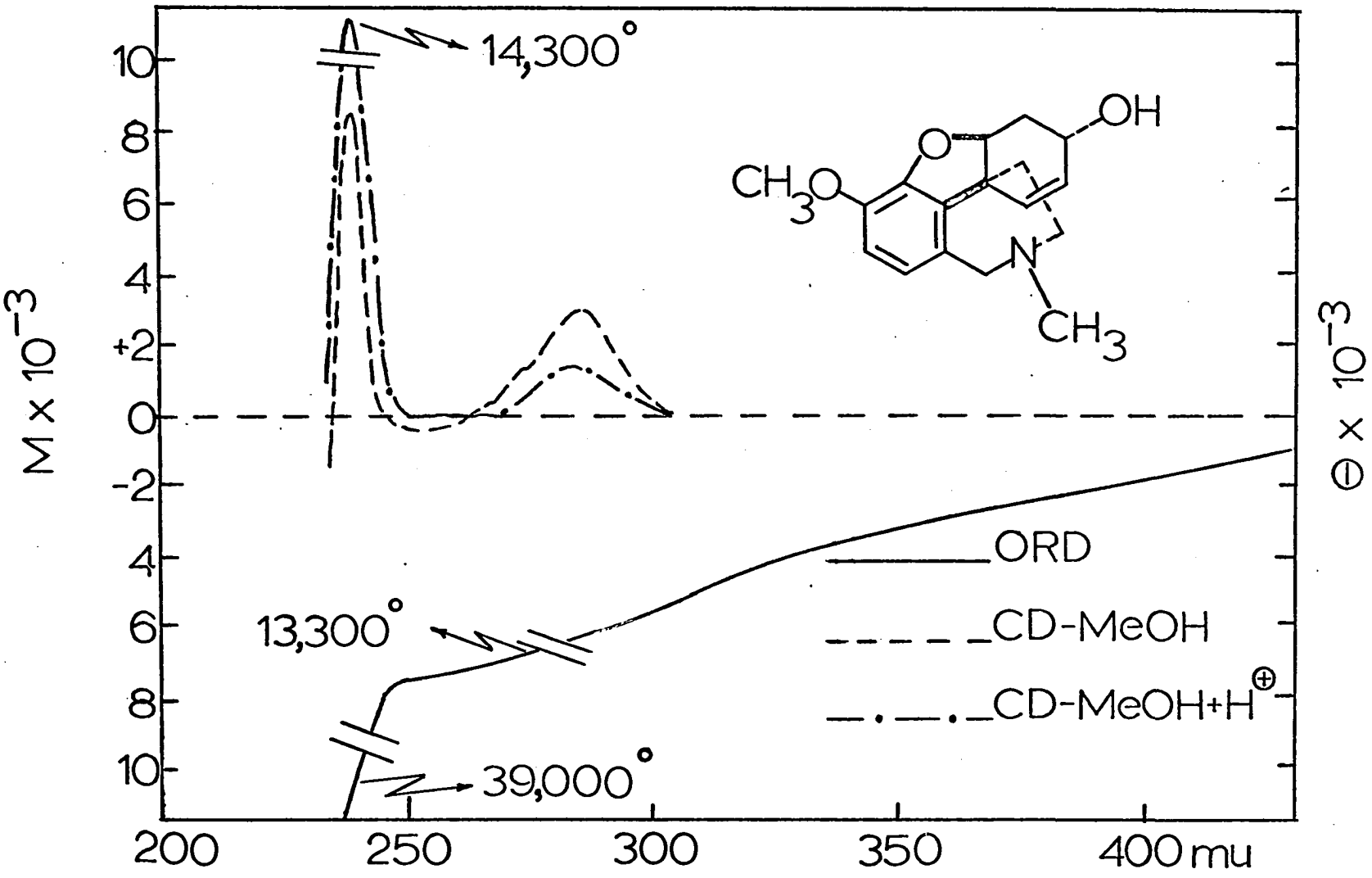
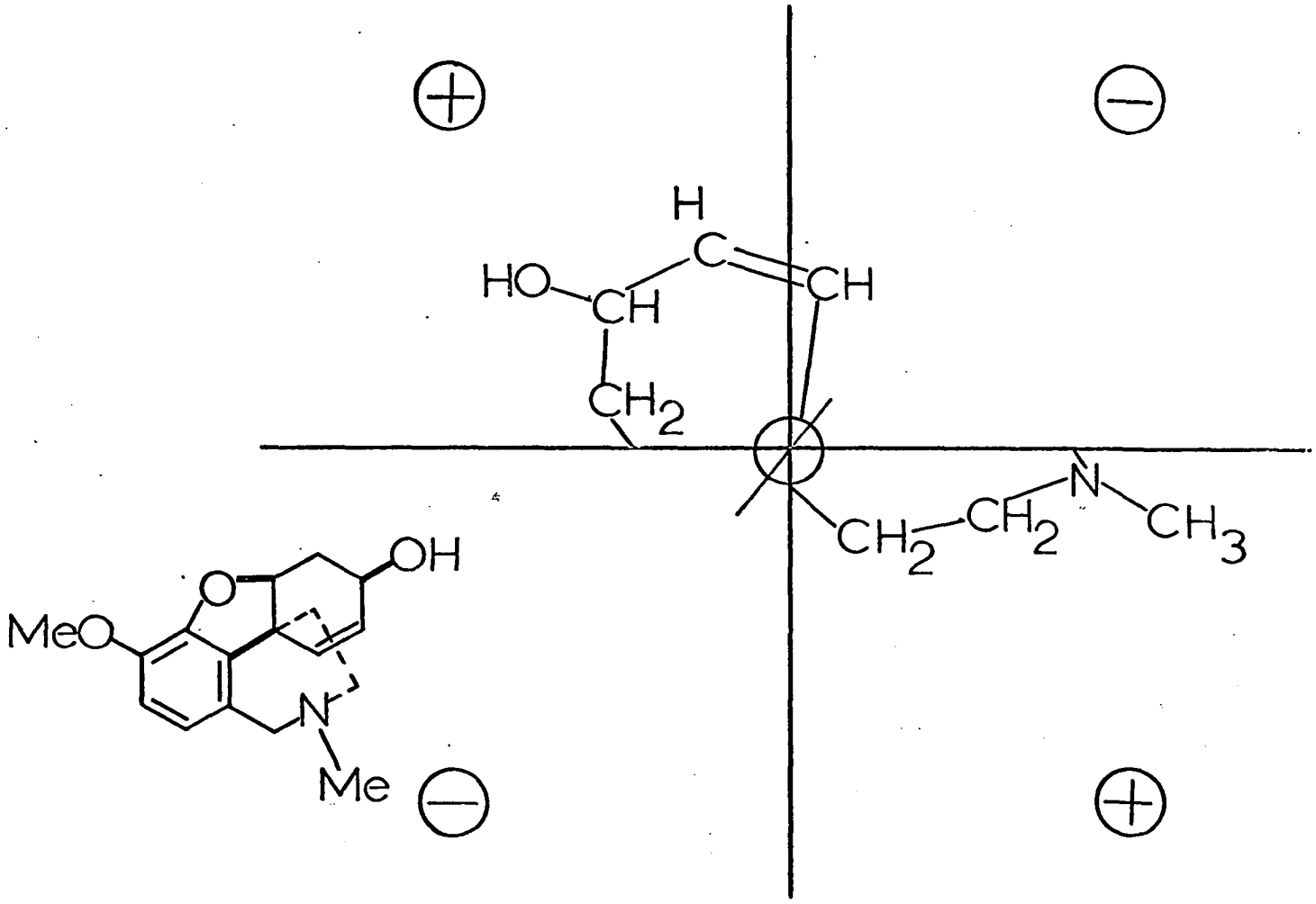


Fig.84

ORD and CD of EPIGALANTHAMINE

on the nitrogen atom to approach the pi orbitals of the C_4-C_5 double bond. If this were so, a situation would exist similar to a $\overset{|}{C}{=}\overset{|}{N}^{+}$ bond, which absorbs at ca. 255 mu. Acidification of the sample should protonate the nitrogen and remove the proposed pi-lone pair interaction. When this is done, the band at 250 mu in both galanthamine and epigalanthamine disappears. This interaction can exist only if the double bond and nitrogen exist in the molecule at the same time. These data suggest that the proposed interaction is probably real and does effect the CD spectra of these alkaloids. The most important point is not whether this particular interaction is real or not but that the circular dichroism spectra of complex molecules is quite often effected by seemingly insignificant forces. It is imperative that the scientist using these techniques to unravel a molecular structure be aware of them.

Application of the quadrant rule to the known absolute configuration of galanthamine results in the octant projection shown in Figure 85. This demands that the second benzene band at 240 mu be positive and this is found to be the case for the free base and the hydrochlorides of galanthamine and epigalanthamine. These results are what is called for by Roger's X-ray data. It was fortuitious that, of all the Amaryllis alkaloids which have been studied, only the galanthamine type posed a problem of band assignment and this question was answered by the X-ray analysis. Since the quadrant rule has been correct in all cases, it would have been possible to assign the correct CD bands by



GALANTHAMINE PROJECTION

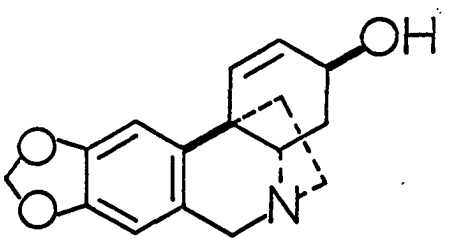
Fig. 85

choosing the one which agreed with that called for by application of the rule. As is obvious, this is the band at 240 mu.

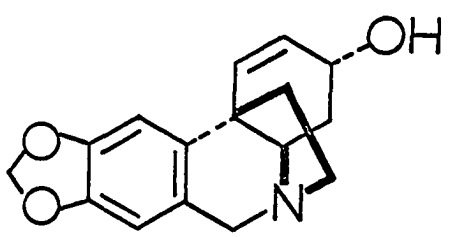
The ORD spectra of galanthamine and epigalanthamine were determined and are also given in Figures 83 and 84. The CD spectra of these compounds show that both of the benzene bands are positive and, except for the small dichroism at 250 mu, the only negative dichroism in the entire spectrum is the very large band beginning at 236 mu. This can be attributed to the hydroxyl group at C_3. In galanthamine the unusually large dichroism can be attributed to the strong hydrogen bond from the hydroxyl to the oxygen in the oxide bridge (15), and in epigalanthamine to a hydroxyl hydrogen bonded to the nitrogen. It has been shown that all of the Amaryllis participating in strong hydrogen bonding give rise to ORD spectra in which none of the dispersions due to the benzene bands can be seen (cf. buphanamine and ambelline). It is possible that, as more correlations of this type are made, ORD may be a useful tool for the identification of hydrogen bonded hydroxyl groups.

Barton applied Mill's rule to galanthamine and arrived at the correct absolute stereochemistry (170). This was fortuitous since the sign of the hydroxyl group was not only negative but was large enough to cancel any contribution from the positive benzene dispersion. These data and the supporting pharmacological data cited previously, as well as the very significant fact that the quadrant rule has not been incorrect to this point, leads us to propose that the absolute stereo-

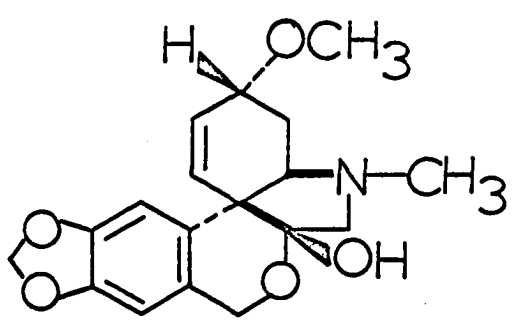
chemistry of the 5, 10b-ethanophenanthridine and the [2]-benzopyrano [3, 4c] indole Amaryllis alkaloids should be reversed. The new stereostructures which are proposed can be formulated as:



CRININE



VITTATINE



TAZETTINE

The lactonic Amaryllis alkaloids homolycorine and hippeastrine are isomeric with the lycorine type alkaloids. Structural and stereochemical correlations between these compounds have been made (171, 172). The structure of albomaculine has recently been established and related to the above alkaloids.

Homolycorine (Fig. 86) and related compounds of this series have been assigned the absolute stereochemistry on the basis of Hudson's lactone rule (173) and Klyne's (174) modification of it. This rule is similar in principle to Mill's rule in that it correlates absolute stereochemistry on the basis of molecular rotations at 589 mu. However, the rotation observed at 589 mu for these compounds is probably that of the lactone chromophore and is either the large n→pi* dispersion of the carbonyl or as in the case of the aromatic lactones the dispersion due to the electron transfer bands of the extended aromatic system. Application of Hudson's rule affords the absolute stereochemistry of position 5a, not the asymmetric center adjacent to the aromatic ring. Chemical evidence then completed the assignment of the relative stereochemistry of the remainder of the molecule. The absolute configuration of lycorine (Fig. 87) and 2-epilycorine have been postulated on the basis of Mill's rule. These results were then applied to other lycorine type alkaloids. Homolycorine has been converted to dihydropluvine (172) by a series of reactions which did not involve any of the asymmetric centers. Hippeastrine has been converted to lycorine methiodide, and conceivably could have been converted to lycorine since pluvine methiodide was converted into pluvine by these same workers. Lycorine and pluvine have been interrelated chemically and are known to have the same basic ring system and the same stereochemistry. Since the conversions of the lactonic alkaloids to the lycorines was carried

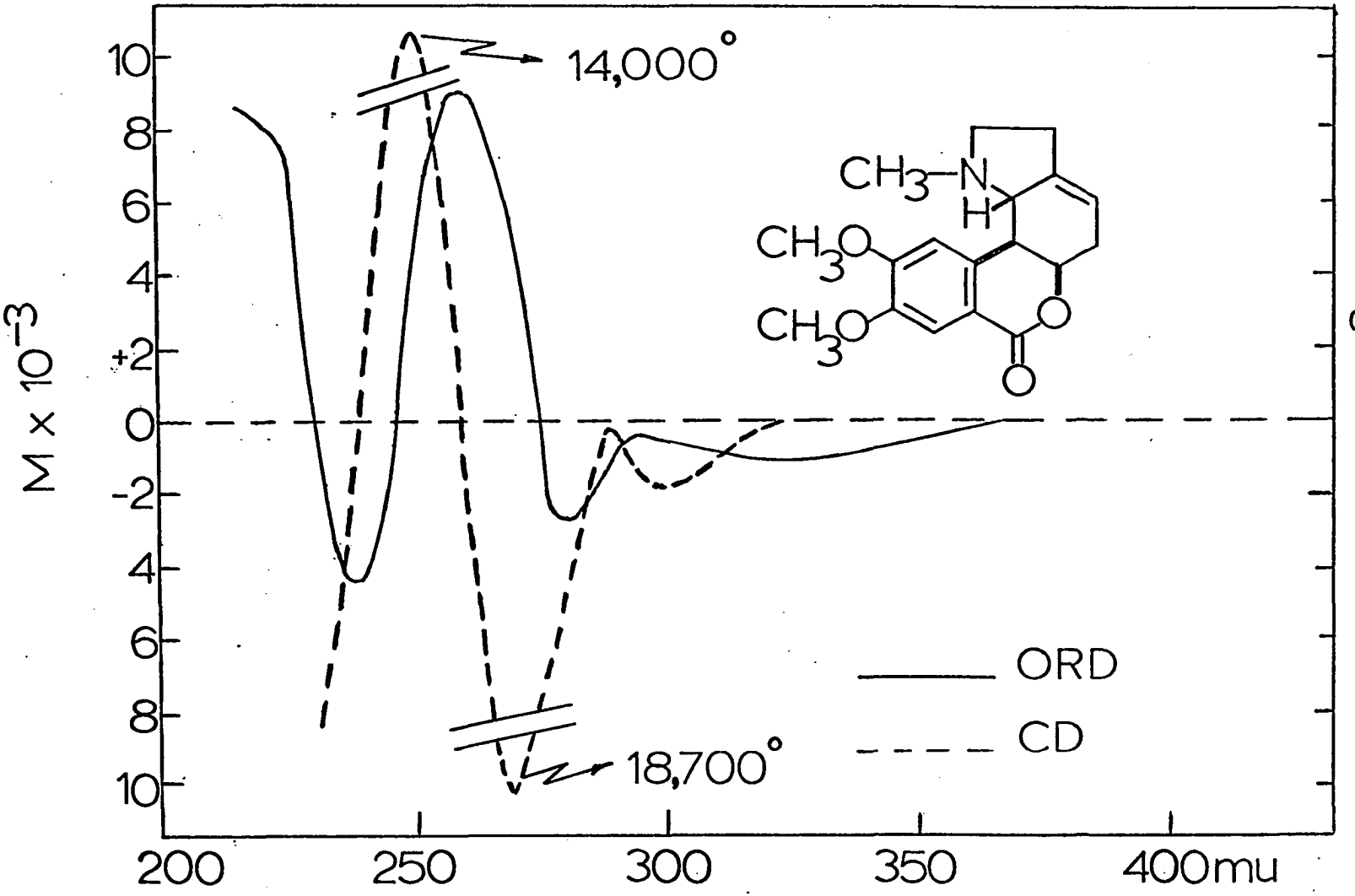


Fig. 86

ORD and CD of HOMOLYCORINE

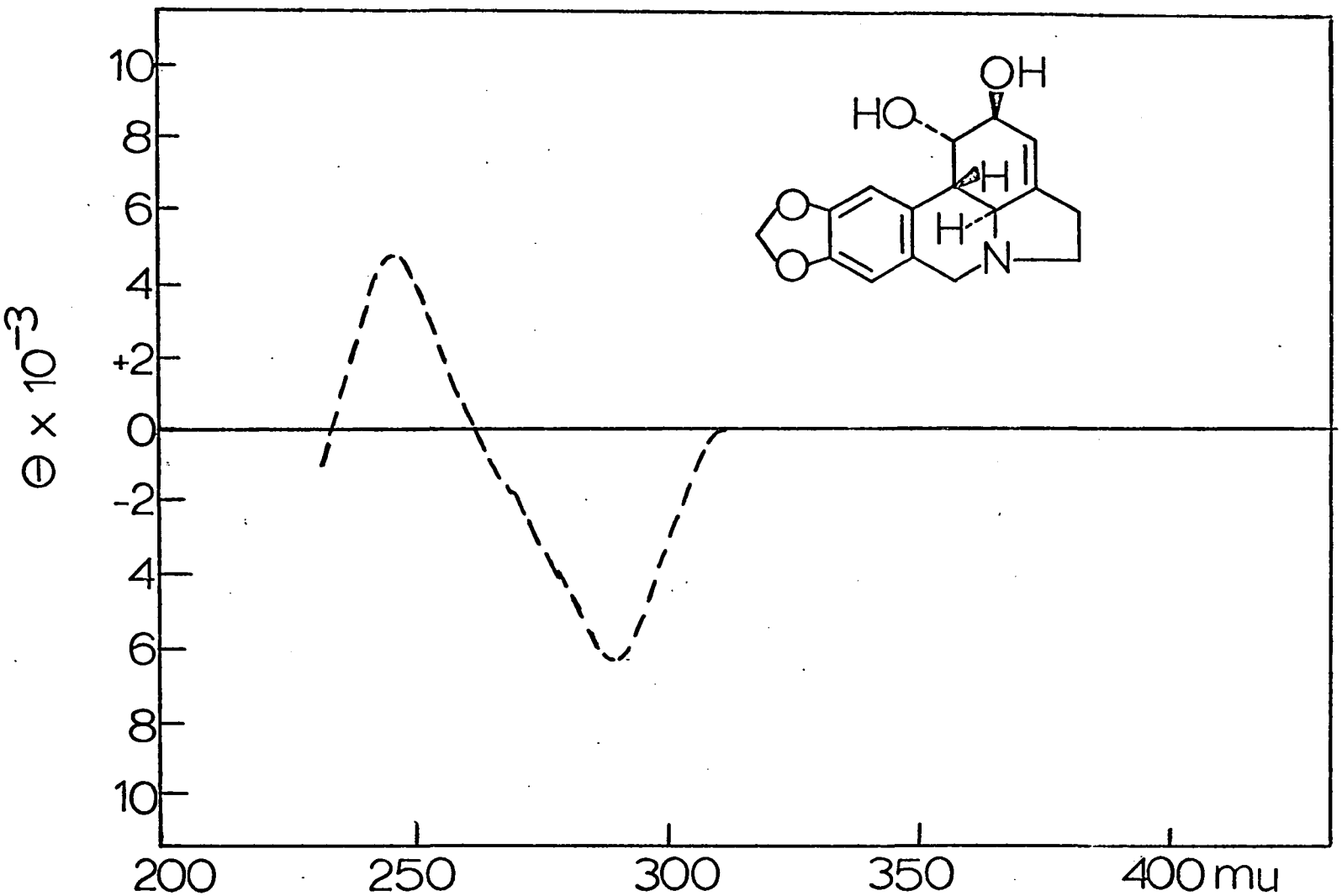


Fig.87

CD of LYCORINE

out with no change in the stereochemistry at C_{11}, the absolute configurations of lycorine and pluvine as assigned by Mill's rule were considered correct.

Since circular dichroism spectra of these aromatic compounds would afford data concerning the absolute stereochemistry of the asymmetric center adjacent to the aromatic ring a study of the available lactonic alkaloids was carried out. Homolycorine was the first compound studied and the spectra is shown in Figure 86. The UV maxima are at 303 mu, 268 mu and 228 mu, and the corresponding CD maxima are at 300 mu, 270 mu and the beginning of a large negative dichroism at 235 mu may be the large absorption band observed at 228 mu. The CD spectra also has a very well defined band at 250 mu, which is the only positive maxima in the spectra. This band is undoubtedly the one responsible for the positive rotation at 589 mu in the ORD curve. As assigned previously for the aromatic lactam, 6-hydroxycrinamine lactam, the CD ellipticities at 300 mu, 270 mu and 250 mu can be assigned to electron transfer bands. The large absorption band at 228 mu is probably the K band of the carbonyl (130). The three bands observed in the CD can be attributed to transitions of the chromophore formed between the benzene ring and the carbonyl group, and as such they reflect the stereochemical environment of the chromophore. From the sign of the Cotton effects associated with this chromophore it should be possible to assign the stereochemistry of position 11b independently. In 6-hydroxycrinamine lactam,

albomaculine (Fig. 88) and homolycorine there are three bands in the CD at ca. 300 mu, 275 mu and 250 mu, and in all cases the first two of these are of the same sign and the third one of opposite sign. There should be no reason why this relationship should not be a general one for compounds of this type. The quadrant rule predicts that the first dichroism should be negative followed by a positive one if the stereochemistry assigned to the lactonic alkaloids is correct. Since it makes no difference if one chooses the first and third maxima or the second and third maxima as the dichroisms which reflect the absolute stereochemistry at 11b, the first two bands may be taken as one large negative maxima and the band at 250 mu the positive one predicted (Fig. 89). Since the separation in benzene bands is usually about 55 mu, those at 300 mu and 250 mu could reasonably be chosen as the major contributors to the signals. This assignment is also consistent with the results.

If the absolute stereochemistry of the lactonic alkaloids is correct as written, the quadrant rule must predict a negative maxima at 295 mu and a positive one at 245 mu for lycorine in order to be consistent. Examination of Dreiding models of lycorine results in this prediction. The choice of signs of the CD maxima is not as easy as in the crinine and tazettine alkaloids, since lycorine is virtually a flat molecule. Examination of dihydrolycorine (Fig. 90) provides some additional support for this prediction as saturation of ring C makes the

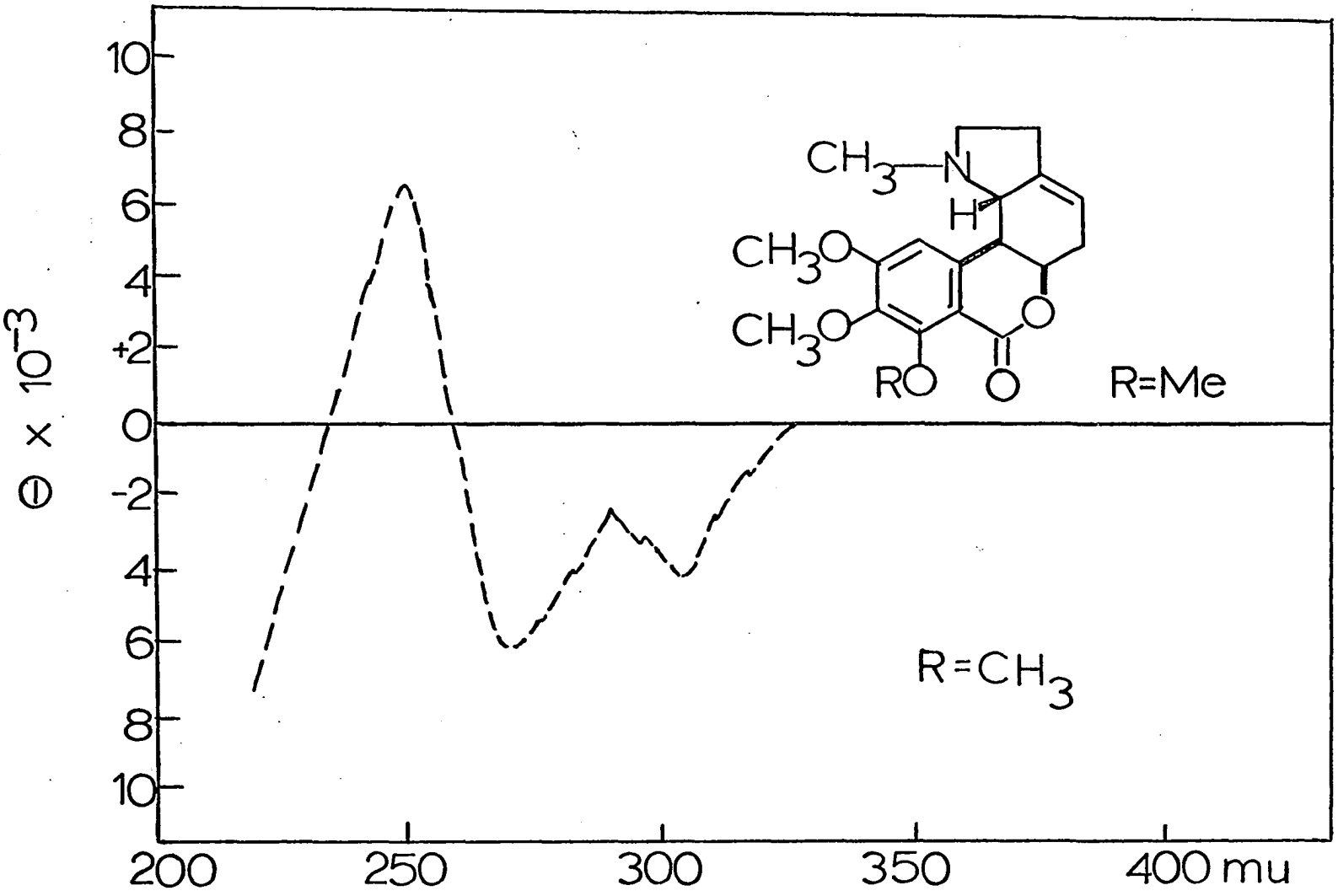
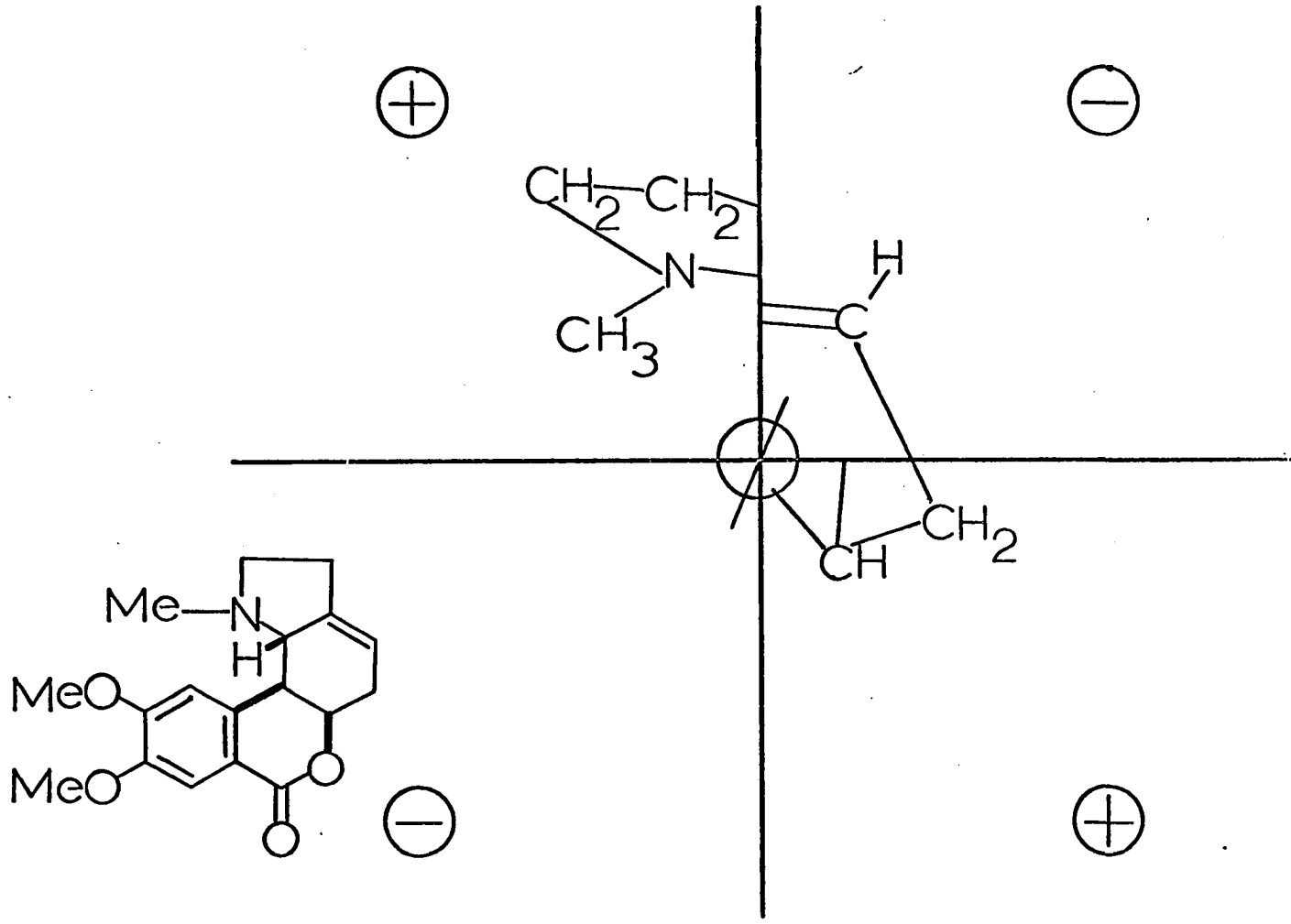


Fig.88

CD of ALBOMACULINE



HOMOLYCORINE PROJECTION

Fig.89

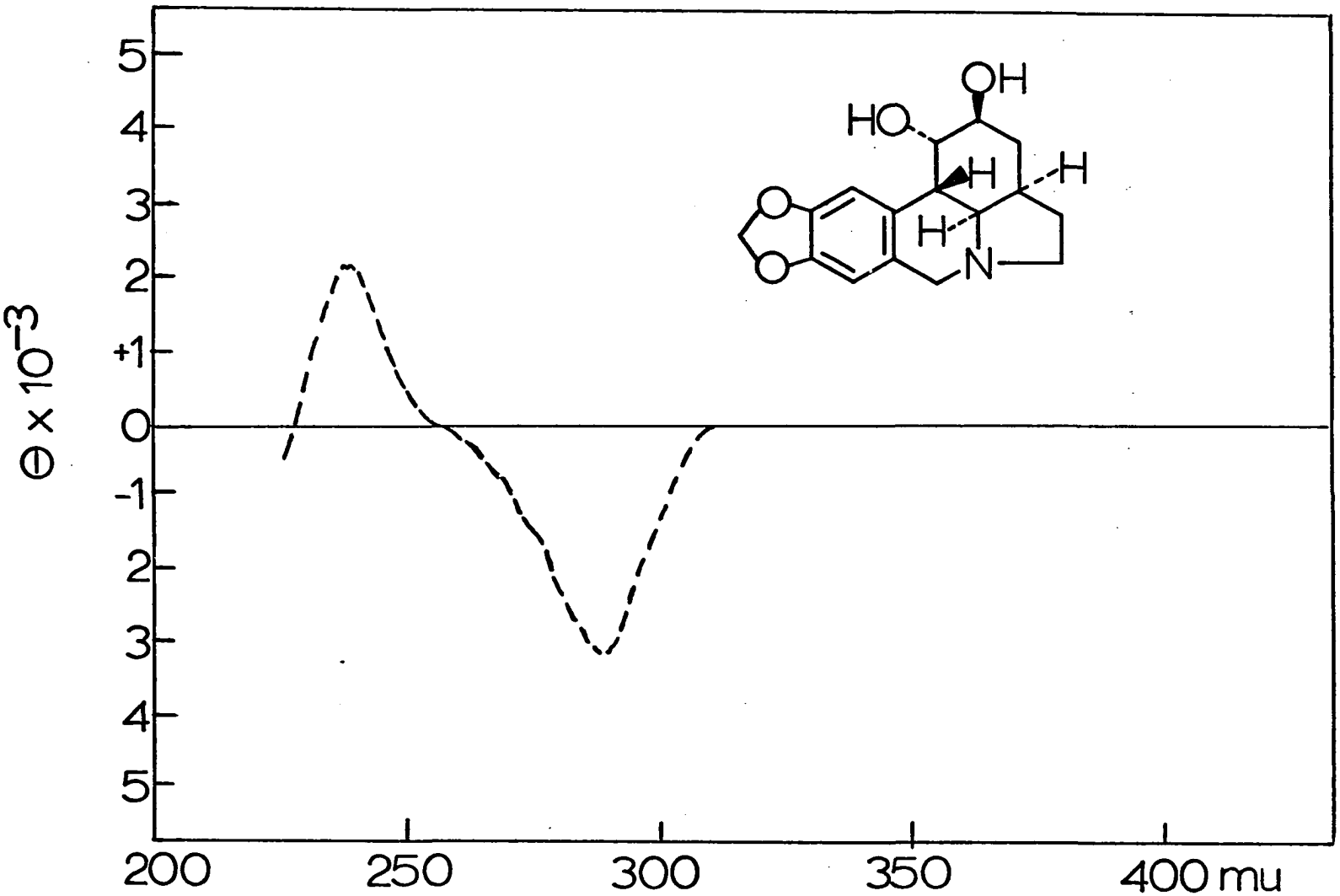
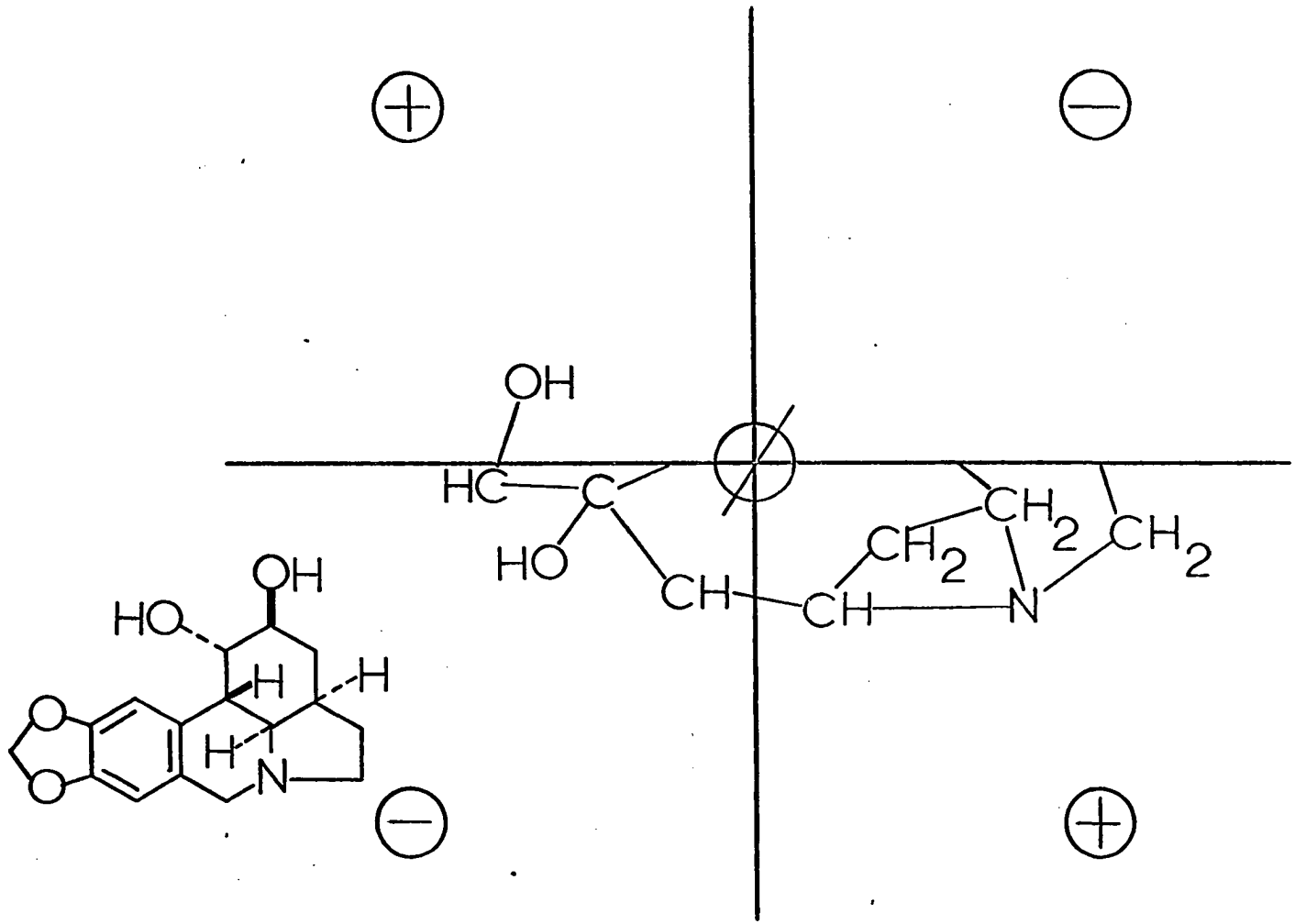


Fig.90

CD of DIHYDROLYCORINE

molecule less planar. The octant projections for homolycorine and dihydrolycorine are given in Figures 89 and 91 (245 mu). From the above it is concluded that the absolute configuration of the lycorine type and the homolycorine type alkaloids is correct as assigned. The conclusions drawn for these compounds were made on the basis of Hudson's lactone rule, the quadrant rule and Mill's rule, as well as chemical degradations. Recently an X-ray analysis at Shionogi Laboratories in Japan has confirmed these results (private communication; Dr. Koyama, Shionogi Laboratories, Japan, 1966).

The CD spectra of coccinine and montanine (Figs. 92 and 93) are virtually superimposable in all regions of the spectra. This is as expected since the dichroism we are examining is associated with the benzylic position and not the functional groups. As can be seen from the figure, both maxima are negative which signifies that this is not a normal pair of benzene bands. Application of the quadrant rule to these compounds results in predicting the second dichroism at 240 mu to be positive (Fig. 94) for the configuration as assigned originally. It has been shown that both haemanthamine and crinamine undergo rearrangement to (XLIX) and (L) respectively.



DIHYDROLYCORINE PROJECTION

Fig.91

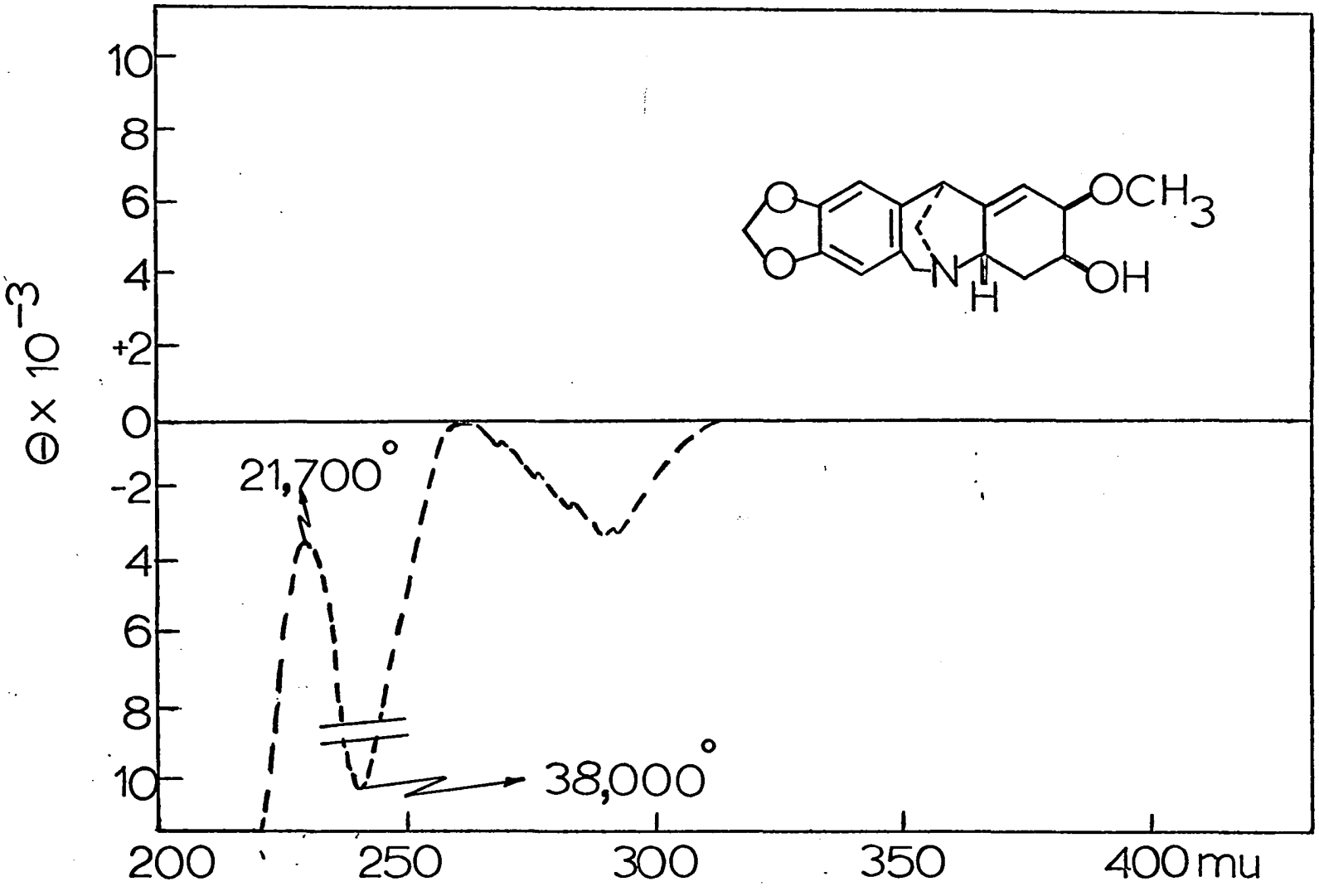


Fig.92

CD of COCCININE

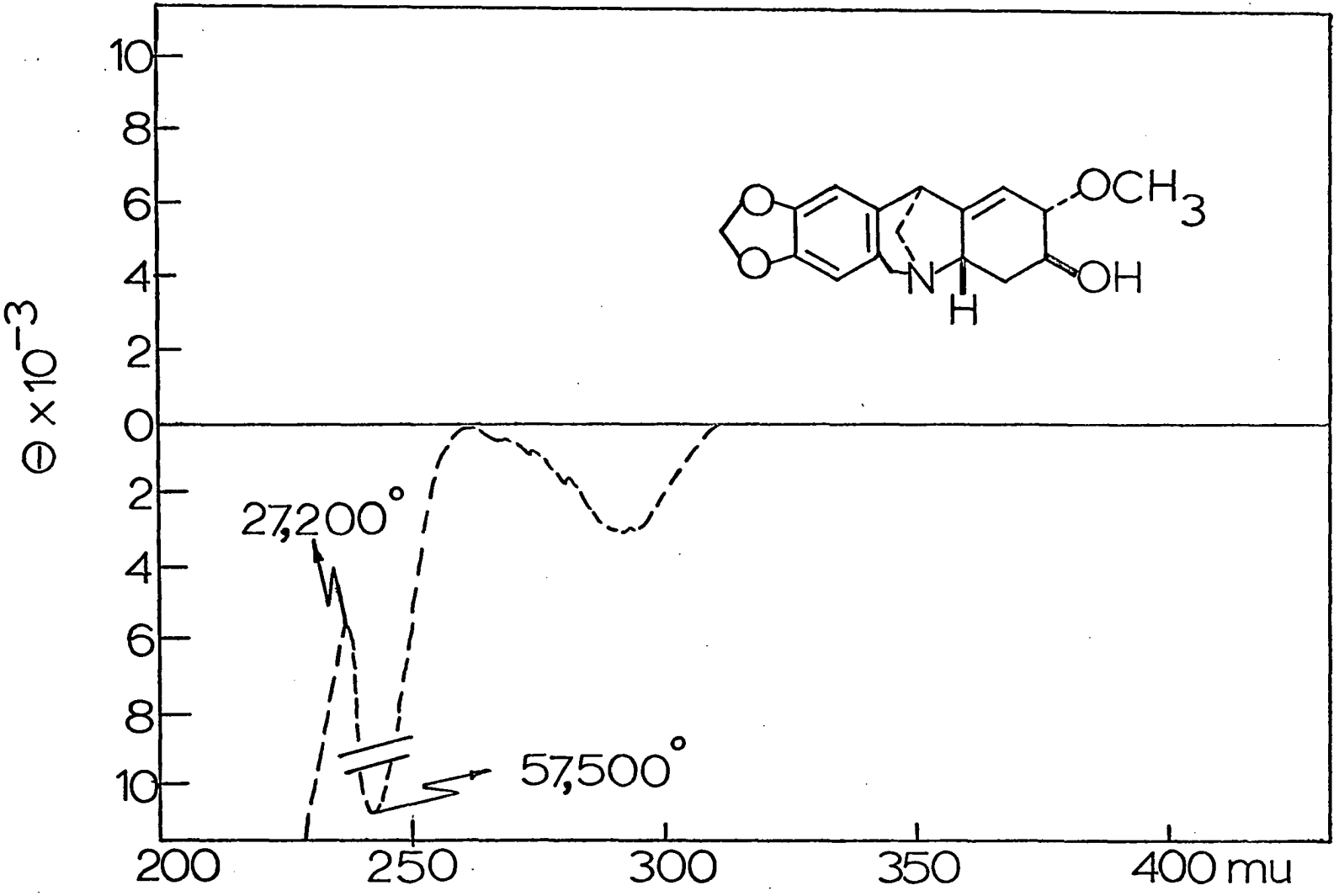
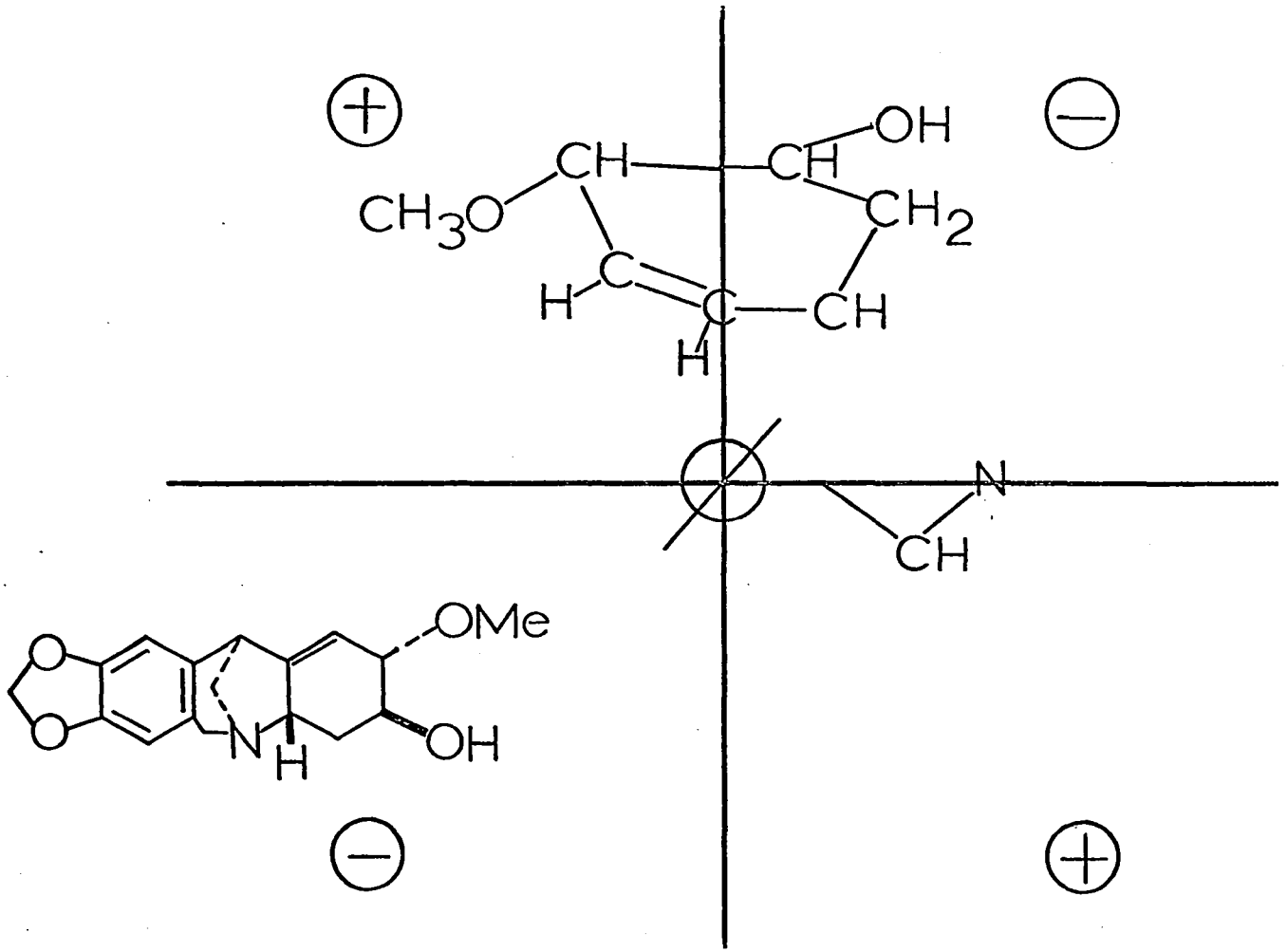


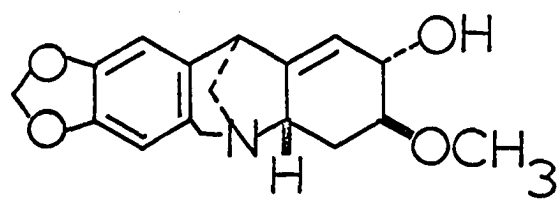
Fig.93

CD of MONTANINE

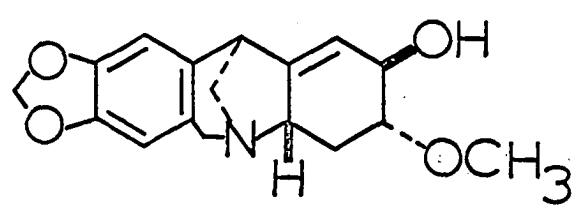


MONTANINE PROJECTION

Fig.94

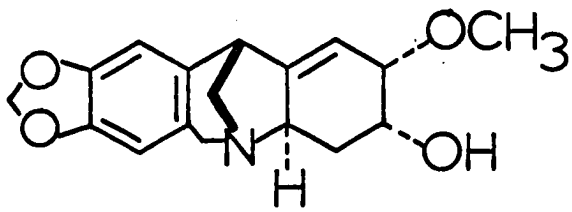


XLIX

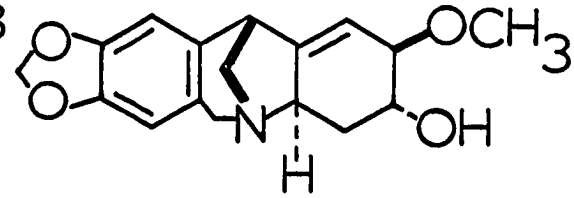


L

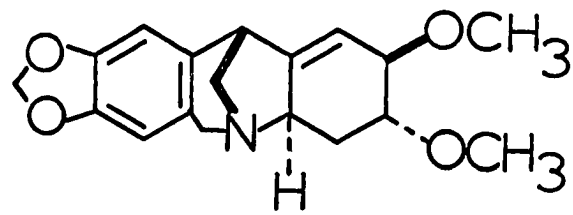
These compounds are simple isomers of coccinine, montanine and manthine (LI). The stereochemistry at the bridge (C_{11}) has been shown to be the same as in crinamine and haemanthamine (175). Since it has been suggested that the absolute stereochemistry of crinamine and haemanthamine should be reversed it follows that the stereostructure assigned to the coccinine type alkaloids should also be reversed. When this is done the predicted sign of the Cotton effect and the experimentally determined spectra are in agreement. The new absolute configurations assigned to coccinine, montinine and manthine are given below.



COCCININE



MONTANINE



MANTHINE(LI)

Chronologically, the development of the octant rule came after the original work on the powellane-crinane anomaly. The structures drawn on the spectra have all been drawn according to the old assignments in order to avoid changing from one convention to another midway through the thesis. In order to agree with the new assignments of absolute configuration it is necessary to reverse the absolute configuration of all Amaryllidaceae alkaloid containing the crinine, tazettine and montanine ring systems.

VI. SUMMARY

This thesis presents an exhaustive compilation of circular dichroism and rotatory dispersion spectra for compounds containing an asymmetric benzylic carbon atom. These spectra have provided information about the manner in which configurational changes of the functional groups effect the overall shapes of the ORD and CD spectra. The CD measurements have permitted an examination of the one asymmetric center adjacent to the aromatic ring. It has been demonstrated that the sign of the Cotton effect changes upon variation of the atoms at the benzylic center. This has led to the development of the quadrant rule, which appears to work exceptionally well for the optically active aromatic chromophore. The existence of a quadrant rule for the aromatic ring has been predicted from symmetry considerations (149b).

The original goal of this endeavor was to find the possible cause of the sign change in the Cotton effect of the $A_{1g} \longrightarrow B_{2u}$ aromatic absorption band dichroism in the methylenedioxymethoxy benzene Amaryllis alkaloids. It is very probable that stereoelectronic interactions between the benzene pi orbitals and the nearby atoms at C_1 and C_5 are responsible for this phenomenon. In addition, we have proven that the absolute stereochemistry of (+) powellane is the same as (-) crinane although a mirror image relationship between their ORD spectra from 600 mu to 300 mu has been recorded.

It has also been shown that the first benzene dichroism cannot be relied upon to reflect the stereochemistry at a benzylic asymmetric center. From this research we have proposed that the absolute stereochemistry of the 5, 10b-ethanophenanthridine and the [2]-benzopyrano [3, 4c] indole alkaloids of the Amaryllidaceae alkaloids be changed from that presently accepted to the corresponding mirror images.

VII. ACKNOWLEDGEMENTS

The author would like to express his deep appreciation to Dr. William C. Wildman, his major professor, for the opportunity to carry out research which was both stimulating and interesting, and the helpful criticism which often resulted in clearer thinking.

To Dr. John Foss of the Biophysics Department the author owes many hours of instructive conversation. He not only explained the mysteries of optical rotatory power to me, but left the instruments to measure this phenomenon at my disposal.

Mr. Michael E. McCarville and Mr. Norman E. Heimer provided the necessary heckling which always makes one think a little more carefully, thereby correcting mistakes before they are made. I am indebted to all of the members of the Wildman group who provided minute quantities of their precious alkaloids for my investigations.

Sincere and heartfelt thanks to my wife, Pat, who has never complained through all these years, and without whom this thesis could never have come to pass.

Finally I would like to thank my children, Daria, Lisa and Tracie, who have made sacrifices which they are not even aware of in order that this work could be completed.

The National Institute of Health provided a two year pre-doctoral fellowship (No. 5-FL-GM-25,271-02) for which I am grateful.

VIII. EXPERIMENTAL

All of the optical rotatory dispersion spectra have been recorded on a Jasco Model 5 ORD spectrophotometer and the circular dichroism spectra on a modified (176) Jouan dichrograph. The solvent used in all cases was methanol unless stated otherwise. The units of rotation used are degrees per decimeter; those of ellipticity are degrees per decimeter per mole per liter. In both cases these are simply recorded as degrees.

In order to test the accuracy of the Jasco ORD instrument a number of rotations at 589 mu were recorded and these were compared with values in the literature for the same compounds. These are shown in Table 13.

Table 13. Comparison of rotations at 589 mu for some Amaryllis alkaloids (deg/dec)

Compound	Observed	Reported
	589 mu	589 mu
Undulatine	(-) 30.3	(-) 31.8
Dihydroundulatine	(-) 33.7	(-) 37.0
Crinamine	(+) 141.0	(+) 156.6
6-Hydroxycrinamine	(+) 47.6	(+) 46.0
Tazettine	(+) 155.0	(+) 159.3
Criwelline	(+) 272.8	(+) 220.0
Crinine	(-) 21.5	(-) 19.0
(-) Crinane	(-) 6.98	(-) 6.3
Powelline	0.0	0.0
Dihydropowelline	(-) 8.6	(-) 11.9
Powellane	(+) 13.0 (436 mu)	(+) 10.0 (436 mu)
Buphanamine	(-) 182.5	(-) 195.0

Table 13. (Continued)

Compound	Observed	Reported
	589 mu	589 mu
Buphanisine	(-) 35.0	(-) 26.0
Ambelline	(+) 62.5	(+) 32.3
Dihydroambelline	(-) 17.8	(-) 16.0
Haemanthamine	(+) 55.0	(+) 33.0
Homolycorine	(+) 93.0	(+) 86.0
Caranine	(-) 197.0	(-) 196.6
Crinamindine	(-) 5.80	(-) 24.0
Vittatine	(+) 22.3	(+) 22.0

Crinine (Fig. 1): RD(C, 0.010; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -2640°; $(M)_{304}$ -6600°; $(M)_{290}$ 0.0°; $(M)_{280}$ +7800°; $(M)_{250}$ +8800°; $(M)_{240}$ 0.0°; $(M)_{230}$ -15,900°.

CD(C, 0.039; CH_3OH), 25°; $(\theta)_{308}$ 0.0°; $(\theta)_{290}$ -7300°; $(\theta)_{265}$ 0.0°; $(\theta)_{255}$ 0.0; $(\theta)_{240}$ +8200; $(\theta)_{235}$ 0.0°.

Dihydrocrinine (Fig. 3): RD(C, 0.038; CH_3OH), 25°; $(M)_{450}$ 0.0; $(M)_{320}$ -435°; $(M)_{304}$ -1360°; $(M)_{294}$ 0.0°; $(M)_{280}$ +1965°; $(M)_{250}$ +3600°; $(M)_{240}$ 0.0°; $(M)_{230}$ -1300; $(M)_{228}$ 0.0°.

CD(C, 0.120; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{295}$ -2680°; $(\theta)_{260}$ 0.0°; $(\theta)_{250}$ +2500°.

Crinane (Fig. 4): RD(C, 0.142; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -435°; $(M)_{300}$ -925°; $(M)_{293}$ 0.0°; $(M)_{275}$ +2140°; $(M)_{250}$ +3560; $(M)_{239}$ -0.0°; $(M)_{234}$ -1280°; $(M)_{225}$ 0.0°.

CD(C, 0.145; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{290}$ -1500°; $(\theta)_{270}$ 0.0; $(\theta)_{260}$ 0.0°; $(\theta)_{245}$ +2010°; $(\theta)_{235}$ 0.0°.

(-)Epicrinine (Fig. 11): RD(C, 0.064; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -3200°; $(M)_{304}$ -6800°; $(M)_{290}$ 0.0°; $(M)_{280}$ +1700°; $(M)_{260}$ +850°; $(M)_{250}$ 0.0; $(M)_{240}$ -11,800°; $(M)_{230}$ -18,000°.

CD(C, 0.096; CH_3OH), 25°; $(\theta)_{315}$ 0.0°; $(\theta)_{295}$ -5400°; $(\theta)_{245}$ 0.0; $(\theta)_{250}$ +2700.

(-)Dihydroepicrinine (Fig. 12): RD(C, 0.066; CH_3OH), 25°; $(M)_{450}$ 0.0; $(M)_{320}$ -815°; $(M)_{300}$ -1900°; $(M)_{280}$ 0.0°; $(M)_{280}$ +1400°; $(M)_{260}$ +1900°; $(M)_{245}$ +3100°; $(M)_{240}$ 0.0°; $(M)_{232}$ -2400°; $(M)_{222}$ 0.0°.

CD(C, 0.064; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{292}$ -2140°; $(\theta)_{265}$ 0.0; $(\theta)_{250}$ +2670°.

Vittatine (Fig. 13): RD(C, 0.010; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +2420°; $(M)_{304}$ +7200°; $(M)_{290}$ 0.0°; $(M)_{275}$ -4800°; $(M)_{250}$ -7200°; $(M)_{240}$ 0.0°; $(M)_{225}$ +13,300°.

CD(C, 0.065; CH_3OH), 25°; $(\theta)_{320}$ 0.0°; $(\theta)_{295}$ +7900°; $(\theta)_{255}$ 0.0°; $(\theta)_{240}$ 9400°; $(\theta)_{220}$ 0.0°.

Dihydrovittatine (Fig. 14): RD(C, 0.054; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +1350°; $(M)_{300}$ +3000°; $(M)_{295}$ 0.0°; $(M)_{275}$ -1500°; $(M)_{250}$ 2500°; $(M)_{243}$ 0.0°; $(M)_{233}$ +4700°; $(M)_{215}$ 0.0°.
CD(0.054; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{293}$ +3800°; $(\theta)_{260}$ 0.0°; $(\theta)_{245}$ -4800; $(\theta)_{250}$ 6160.

Alkaloid 16 (Fig. 15): RD(C, 0.096; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +740°; $(M)_{297}$ +4950°; $(M)_{284}$ 0.0°; $(M)_{275}$ -3800°; $(M)_{250}$ -2470°; $(M)_{243}$ 0.0°; $(M)_{235}$ +3100°.
CD(C, 0.12; CH_3OH), 25°; $(\theta)_{300}$ 0.0°; $(\theta)_{285}$ +5500°; $(\theta)_{267}$ 0.0°; $(\theta)_{240}$ -4750°; $(\theta)_{235}$ 0.0°.

(+)Eoicrinine (Fig. 17): RD(C, 0.04; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +1350°; $(M)_{295}$ +6100°; $(M)_{278}$ 0.0°; $(M)_{270}$ -2250°; $(M)_{250}$ -2400°; $(M)_{240}$ 0.0°; $(M)_{220}$ +20,300°.
CD(C, 0.080; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{290}$ +5200°; $(\theta)_{270}$ 0.0°; $(\theta)_{265}$ 0.0°; $(\theta)_{240}$ -7630°; $(\theta)_{228}$ 0.0°.

Buphanisine (Fig. 18): RD(C, 0.105; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -1620°; $(M)_{305}$ -4900°; $(M)_{295}$ 0.0°; $(M)_{285}$ +6400°; $(M)_{255}$ 8800°; $(M)_{245}$ 0.0°; $(M)_{225}$ -9800°.
CD(0.08; CH_3OH), 25°; $(\theta)_{315}$ 0.0°; $(\theta)_{295}$ -9300°; $(\theta)_{255}$ 0.0°; $(\theta)_{245}$ +10,700°.

Haemanthamine (Fig. 19): RD(C, 058; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +1700°; $(M)_{304}$ +5900°; $(M)_{293}$ 0.0°; $(M)_{275}$ -8500°; $(M)_{265}$ 8100°; $(M)_{250}$ -9300°; $(M)_{240}$ 0.0°; $(M)_{226}$ 14,400°.
CD(0.058; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{292}$ +11,900°; $(\theta)_{255}$ 0.0°; $(\theta)_{240}$ -13,800°; $(\theta)_{228}$ 0.0°.

Crinamine (Fig. 20): RD(C, 0.010; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{340}$ +2880°; $(M)_{320}$ +5750; $(M)_{304}$ 9600°; $(M)_{290}$ 0.0°; $(M)_{280}$ -3360°; $(M)_{250}$ -2150°; $(M)_{247}$ 0.0°; $(M)_{230}$ +24,000.
CD(0.053; CH_3OH), 25°; $(\theta)_{315}$ 0.0°; $(\theta)_{297}$ +6520; $(\theta)_{257}$ 0.0°; $(\theta)_{245}$ -5730°; $(\theta)_{238}$ 0.0°.

Dihydrocrinamine (Fig. 21): RD(C, 0.056; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +1710°; $(M)_{300}$ +2160°; $(M)_{290}$ 0.0°; $(M)_{270}$ -3240°; $(M)_{260}$ -2700°; $(M)_{250}$ -4320°; $(M)_{240}$ 0.0°; $(M)_{235}$ +1830°; $(M)_{230}$ 0.0°; $(M)_{220}$ -4330°; $(M)_{215}$ 0.0°.
CD(C, 0.112; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{290}$ +4900°; $(\theta)_{255}$ 0.0°; $(\theta)_{245}$ -3900°.

Alkaloid 13 (Fig. 22): RD(C, 0.048; CH_3OH), 25°; $(M)_{450}$ +2000°; $(M)_{304}$ +8550°; $(M)_{293}$ 0.0°; $(M)_{282}$ -8000°; $(M)_{250}$ -13,000°; $(M)_{240}$ 0.0°; $(M)_{230}$ +12,500°; $(M)_{220}$ +14,700°.
CD(C, 0.055; CH_3OH), 25°; $(\theta)_{315}$ 0.0; $(\theta)_{295}$ +8900°; $(\theta)_{260}$ 0.0°; $(\theta)_{240}$ -10,400°; $(\theta)_{230}$ 0.0°.

6-Hydroxycrinamine (Fig. 23): RD(C, 0.048; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +3550°; $(M)_{304}$ +6700°; $(M)_{290}$ 0.0°; $(M)_{280}$ -3160°; $(M)_{250}$ -2360°; $(M)_{240}$ 0.0°; $(M)_{225}$ +21,100°.

CD(C, 0.053; CH_3OH), 25°; $(\theta)_{315}$ 0.0°; $(\theta)_{290}$ 7400°; $(\theta)_{260}$ 0.0°; $(\theta)_{245}$ -6400°; $(\theta)_{230}$ 0.0°.

Dihydro-6-hydroxycrinamine (Fig. 24): RD(C, 0.066; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +1980°; $(M)_{300}$ +3960°; $(M)_{290}$ 0.0°; $(M)_{250}$ -4200°; $(M)_{230}$ 0.0°.

CD(C, 0.030; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{285}$ +5700°; $(\theta)_{265}$ 0.0°; $(\theta)_{240}$ -4270°; $(\theta)_{230}$ 0.0°.

11-Acetyl-6-hydroxycrinamine (Fig. 25): RD(C, 0.144; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +2400°; $(M)_{304}$ +5250; $(M)_{275}$ -2400°; $(M)_{265}$ -1450°; $(M)_{250}$ 0.0°; $(M)_{240}$ +9600°.

CD(C, 0.144; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{285}$ +8600°; $(\theta)_{250}$ 0.0°; $(\theta)_{240}$ -3700°; $(\theta)_{232}$ 0.0°; $(\theta)_{220}$ +3700°.

6, 11-diacetyl-6-hydroxycrinamine (Fig. 26): RD(C, 0.137; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ +1780°; $(M)_{304}$ +4560°; $(M)_{285}$ 0.0°; $(M)_{282}$ -2490°; $(M)_{260}$ 0.0°; $(M)_{225}$ +14,500°.

CD(C, 0.090; CH_3OH), 25°; $(\theta)_{315}$ 0.0°; $(\theta)_{290}$ +5100°; $(\theta)_{260}$ 0.0°; $(\theta)_{250}$ +880°.

Dihydro-6, 11-diacetyl-6-hydroxycrinamine (Fig. 27): RD(C, 0.169; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{325}$ +700°; $(M)_{300}$ +2100°; $(M)_{285}$ 0.0°; $(M)_{260}$ +2800; $(M)_{250}$ +4800°; $(M)_{235}$ 0.0°; $(M)_{220}$ +4600°.
CD(C, 0.137; CH_3OH), 25°; $(\theta)_{300}$ 0.0°; $(\theta)_{281}$ +1750°; $(\theta)_{255}$ 0.0°; $(\theta)_{250}$ +2520°.

Haemanthidine (Fig. 28): RD(C, 0.008; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{310}$ +2600°; $(M)_{304}$ +4500°; $(M)_{294}$ 0.0°; $(M)_{280}$ -6500°; $(M)_{252}$ -9100°; $(M)_{240}$ 0.0°; $(M)_{230}$ +6500°.
CD(0.078; CH_3OH), 25°; $(\theta)_{315}$ 0.0°; $(\theta)_{290}$ +8320°; $(\theta)_{265}$ 0.0°; $(\theta)_{242}$ -8700°; $(\theta)_{225}$ 0.0°.

6-Hydroxycrinamine lactam (Fig. 29): RD(C, 0.05; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{350}$ +3800°; $(M)_{340}$ +4400°; $(M)_{330}$ 0.0°; $(M)_{320}$ -7550°; $(M)_{305}$ -15,000°; $(M)_{293}$ 0.0°; $(M)_{285}$ +7600°; $(M)_{278}$ +6300° (min); $(M)_{270}$ 14,000°; $(M)_{258}$ +18,900°; $(M)_{250}$ +17,700° (min); $(M)_{242}$ +63,000°; $(M)_{230}$ 0.0°; $(M)_{215}$ -126,000°.
CD(0.045; CH_3OH), 25°; $(\theta)_{350}$ 0.0°; $(\theta)_{330}$ +9400°; $(\theta)_{305}$ 0.0°; $(\theta)_{295}$ -15,000°; $(\theta)_{280}$ -2830°; $(\theta)_{275}$ -7100°; $(\theta)_{250}$ 0.0°; $(\theta)_{230}$ +57,000°; $(\theta)_{225}$ 0.0°.

Powellane (Fig. 30): RD(C, 0.20; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ 0.0°; $(M)_{310}$ +145°; $(M)_{284}$ +790°; $(M)_{268}$ +315°; $(M)_{248}$ +1130°; $(M)_{239}$ 0.0°.
CD(C, 0.206; CH_3OH), 25°; $(\theta)_{290}$ 0.0°; $(\theta)_{280}$ +800°; $(\theta)_{255}$ 0.0°; $(\theta)_{247}$ +1800°; (More sample provided to complete spectrum) $(\theta)_{240}$ 0.0.

Powelline (Fig. 31): RD(C, 0.188; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -400°; $(M)_{290}$ -980°; $(M)_{276}$ 0.0°; (M) +680°; $(M)_{250}$ +995°; $(M)_{246}$ 0.0°; (M) -2780°.
CD(C, 0.129; CH_3OH), 25°; $(\theta)_{300}$ 0.0°; $(\theta)_{288}$ -1620°; $(\theta)_{260}$ 0.0°; $(\theta)_{250}$ +4200°; $(\theta)_{240}$ 0.0°.

Dihydropowelline (Fig. 32): RD(C, 0.404; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ 0.0°; $(M)_{290}$ +728; $(M)_{282}$ 0.0°; $(M)_{250}$ +2000°; $(M)_{247}$ 0.0°.
CD(C, 0.32; CH_3OH); 25°; $(\theta)_{320}$ 0.0°; $(\theta)_{295}$ -360°; $(\theta)_{288}$ 0.0°; $(\theta)_{282}$ +380°; $(\theta)_{270}$ 0.0°; $(\theta)_{245}$ +2840°; $(\theta)_{240}$ 0.0°.

Buphanidrine (Fig. 33): RD(C, 0.50; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -270°; $(M)_{288}$ -845°; $(M)_{278}$ 0.0°; $(M)_{250}$ +1180°; $(M)_{245}$ 0.0°.
CD(C, 0.26; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{285}$ -1270°; $(\theta)_{260}$ 0.0°; $(\theta)_{247}$ +3730°.

Epipowelline (Fig. 34): RD(C, 0.116; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{330}$ -2100°; $(M)_{320}$ -2500°; $(M)_{290}$ -3850°; $(M)_{280}$ -3000°; $(M)_{280}$ -4900°; $(M)_{250}$ -7600°; $(M)_{240}$.
CD(C, 0.116; CH_3OH), 25°; $(\theta)_{300}$ 0.0°; $(\theta)_{285}$ -1320°; $(\theta)_{260}$ 0.0°; $(\theta)_{250}$ +4400°; $(\theta)_{245}$ 0.0°.

Dihydroepipowelline (Fig. 35): RD(C, Ca. 0.18 -0.20; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{300}$ 740°; $(M)_{285}$ +1500°; $(M)_{272}$ +820°; $(M)_{260}$ +1640°; $(M)_{250}$ +2650°; $(M)_{245}$ 0.0°.
CD(C, 0.1; CH_3OH), 25°; $(\theta)_{288}$ 0.0°; $(\theta)_{276}$ +870°; $(\theta)_{260}$ +260°; $(\theta)_{255}$ +1425°.

Ambelline (Fig. 36): RD(C, 0.367; CH_3OH), 25°; $(M)_{450}$ +487°; $(M)_{360}$ +600°; $(M)_{320}$ +610°; $(M)_{295}$ 0.0°; $(M)_{272}$ +1050°; $(M)_{255}$ 0.0°; $(M)_{250}$ -1625°.
CD(C, 0.135; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{279}$ -1350°; $(\theta)_{260}$ 0.0°; $(\theta)_{245}$ +1300°.

Dihydroambelline (Fig. 37): RD(C, 0.340; CH_3OH), 25°; $(M)_{450}$ -1300°; $(M)_{390}$ -1900°; $(M)_{300}$ -3800°; $(M)_{260}$ -6200°.
CD(C, 0.285; CH_3OH), 25°; $(\theta)_{295}$ 0.0°; $(\theta)_{285}$ +440°; $(\theta)_{265}$ 0.0°; $(\theta)_{250}$ +585°.

Buphanamine (Fig. 38): RD(C, 0.103; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{350}$ -700°; $(M)_{300}$ -1750°; $(M)_{270}$ -3800°; $(M)_{250}$ -5200°; $(M)_{230}$ -8750°.
CD(C, 0.158; CH_3OH), 25°; $(\theta)_{294}$ 0.0°; $(\theta)_{288}$ +520°; $(\theta)_{275}$ 0.0°; $(\theta)_{260}$ 0.0°; $(\theta)_{248}$ +11,300°; $(\theta)_{245}$ 0.0°.

Oxobuphanamine (Fig. 39): RD(C, 0.175; CH_3OH), 25°; $(M)_{450}$ -343°; $(M)_{362}$ -2640°; $(M)_{245}$ 0.0°; $(M)_{320}$ +2400°; $(M)_{300}$ +1720°; $(M)_{280}$ +3100°; $(M)_{260}$ -3100°; $(M)_{250}$ 0.0°.

CD(C, 0.36; CH_3OH), 25°; $(\theta)_{385}$ 0.0°; $(\theta)_{345}$ -5800°; $(\theta)_{300}$ -2125°; $(\theta)_{280}$ -2900°; $(\theta)_{240}$ 0.0°; $(\theta)_{230}$ +840°.

Epoxypowelline (Fig. 40): RD(C, 0.30; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{330}$ -320°; $(M)_{300}$ -670°; $(M)_{290}$ -1260°; $(M)_{270}$ 0.0°; $(M)_{260}$ +420°; $(M)_{250}$ +940°; $(M)_{244}$ 0.0°.

CD(C, 0.30; CH_3OH), 25°; $(\theta)_{300}$ 0.0°; $(\theta)_{280}$ -910°; $(\theta)_{260}$ 0.0°; $(\theta)_{250}$ +900.

Crinamidine (Fig. 41): RD(C, 0.255; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{300}$ -135°; $(M)_{285}$ 0.0°; $(M)_{280}$ +150°; $(M)_{275}$ +270°; $(M)_{270}$ +130°; $(M)_{260}$ +550°; $(M)_{250}$ 1500°; $(M)_{245}$ 0.0°.

CD(C,0.067; CH_3OH), 25°; $(\theta)_{300}$ 0.0°; $(\theta)_{282}$ -1600°; $(\theta)_{265}$ 0.0°; $(\theta)_{260}$ +1600°.

Undulatine (Fig. 42): RD(C, 0.445; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -440°; $(M)_{285}$ -1110°; $(M)_{283}$ 0.0°; $(M)_{278}$ +1100°; $(M)_{264}$ +2200°; $(M)_{250}$ +5300°; $(M)_{240}$ 0.0°.

CD(C, 0.187; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{280}$ -450°; $(\theta)_{255}$ 0.0°; $(\theta)_{245}$ +500°.

Dihydroundulatine (Fig. 43): RD(C,0.421; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -360°; $(M)_{300}$ -470°; $(M)_{286}$ 0.0°; $(M)_{280}$ +710°; $(M)_{275}$ 0.0°; $(M)_{270}$ -310°; $(M)_{265}$ 0.0°; $(M)_{250}$ 2300°; $(M)_{242}$ 0.0°.
CD(C,0.285; CH_3OH), 25°; $(\theta)_{290}$ 0.0°; $(\theta)_{280}$ +300°; $(\theta)_{265}$ +100°; $(\theta)_{248}$ +1550°; $(\theta)_{240}$ 0.0°.

Codeine (Fig. 52): RD(C, 0.028; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -2220°; $(M)_{293}$ -9059°; $(M)_{282}$ 0.0°; $(M)_{275}$ +8430° (infl.); $(M)_{253}$ +19,100°; $(M)_{246}$ 0.0°; $(M)_{240}$ -37,400°.
CD(C, 0.028; CH_3OH), 25°; $(\theta)_{297}$ 0.0°; $(\theta)_{282}$ -8600°; $(\theta)_{265}$ 0.0°; $(\theta)_{243}$ 41,000°; $(\theta)_{232}$ 0.0°; $(\theta)_{231}$ -8000°.

Dihydrocodeine (Fig. 53): CD(C, 0.096; CH_3OH), 25°; $(\theta)_{300}$ 0.0°; $(\theta)_{280}$ -10,550°; $(\theta)_{255}$ 0.0°; $(\theta)_{245}$ +18,100°; $(\theta)_{230}$ 0.0°.

Morphine (Fig. 54): CD(C, 0.020; CH_3OH, NaOH), 25°; $(\theta)_{320}$ 0.0°; $(\theta)_{293}$ +7700°; $(\theta)_{260}$ +760°; $(\theta)_{255}$ +40,000°; $(\theta)_{240}$ 0.0°; $(\theta)_{237}$ -40,000°. CD; (C, 0.020; CH_3OH, HCl), 25°; $(\theta)_{320}$ 0.0°; $(\theta)_{293}$ -7500°; $(\theta)_{260}$ 0.0°; $(\theta)_{245}$ +34,400°; $(\theta)_{233}$ 0.0°.

Heroin (Fig. 55): CD(C, 0.132; CH_3OH), 25°; $(\theta)_{295}$ 0.0°; $(\theta)_{285}$ -1310°; $(\theta)_{255}$ 0.0°; $(\theta)_{244}$ +5740°; $(\theta)_{237}$ 0.0°.

Thebaine (Fig. 56): RD(C, 0.022; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{320}$ -10,700°; $(M)_{294}$ -40,300°; $(M)_{284}$ 0.0°; (M) +32,800°; $(M)_{262}$ +28,900°; $(M)_{250}$ +35,200°; $(M)_{242}$ +27,800°; $(M)_{232}$ +55,300°; $(M)_{220}$ 0.0°.

CD(C, 0.057; CH_3OH), 25°; $(\theta)_{315}$ 0.0°; $(\theta)_{285}$ -15,200°; $(\theta)_{270}$ -6200°; $(\theta)_{245}$ -1610°; $(\theta)_{238}$ -2320°; $(\theta)_{230}$ 0.0°; $(\theta)_{223}$ +14,100°; $(\theta)_{215}$ +7000°.

CD(C, 0.016; CH_3OH:HCl); $(\theta)_{315}$ 0.0°; $(\theta)_{285}$ -15,200°; $(\theta)_{270}$ -6200°; $(\theta)_{258}$ 0.0°; $(\theta)_{247}$ +6350°; $(\theta)_{240}$ 0.0°; $(\theta)_{225}$ +14,000°.

Tazettine (Fig. 50): CD(C, 0.069; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{286}$ -4950°; $(\theta)_{262}$ 0.0°; $(\theta)_{238}$ +44,300°; $(\theta)_{225}$ +23,100°.

Criwelline (Fig. 57): CD(C, 0.148; $CHCl_3$), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{290}$ +1560°; (C, 0.049; CH_3OH), 25°; $(\theta)_{255}$ 0.0°; $(\theta)_{239}$ +26,100°; $(\theta)_{225}$ +21,500°.

Aspidospermine (Fig. 63): CD(C, 0.068; CH_3OH), 25°; $(\theta)_{285}$ 0.0°; $(\theta)_{255}$ -57,500°; $(\theta)_{230}$ 0.0°; $(\theta)_{225}$ +37,000°; $(\theta)_{220}$ 0.0°.

Ajmaline (Fig. 65): CD(C, 0.023; CH_3OH), 25°; $(\theta)_{312}$ 0.0°; $(\theta)_{292}$ -3520°; $(\theta)_{270}$ 0.0°; $(\theta)_{250}$ +34,800°; $(\theta)_{230}$ 0.0°; $(\theta)_{225}$ -3500°.

Akuammicine (Fig. 67): CD(C, 0.031; CH_3OH), 25°; $(\theta)_{370}$ 0.0°; $(\theta)_{325}$ -89,000°; $(\theta)_{292}$ 0.0°; $(\theta)_{283}$ +6250°; $(\theta)_{270}$ 0.0°; $(\theta)_{240}$ +49,500°; $(\theta)_{220}$ 0.0°.

Brucine (Fig. 69): CD(C, 0.048; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{300}$ -4530°; $(\theta)_{290}$ -2250°; $(\theta)_{265}$ -14,800°; $(\theta)_{260}$ -11,600°; $(\theta)_{255}$ -24,400°. (Slit width at 255 mu, 1.4 mm).

Dihydrolysergic Acid (Fig. 71): CD(C, 0.133; CH_3OH), 25°; $(\theta)_{292}$ 0.0°; $(\theta)_{280}$ -645°; $(\theta)_{265}$ 0.0°; $(\theta)_{235}$ +4050°; $(\theta)_{230}$ 0.0°.

Dihydrooxobuphanamine (Fig. 79): CD(C, 0.148; CH_3OH), 25°; $(\theta)_{320}$ 0.0°; $(\theta)_{295}$ +4360°; $(\theta)_{285}$ 0.0°; $(\theta)_{275}$ -3270°; $(\theta)_{265}$ -1860°; $(\theta)_{250}$ -4300°.

Desmethoxydihydrooxobuphanamine (Fig. 80): CD(C, 0.064; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{305}$ +1980°; $(\theta)_{298}$ 0.0°; $(\theta)_{280}$ -2800°; $(\theta)_{265}$ -1950°; $(\theta)_{250}$ -2800°.

Galanthamine (Fig. 83): RD(C, 0.060; CH_3OH), 25°; $(M)_{350}$ -6650°; $(M)_{320}$ -6150°; $(M)_{295}$ -2380°; $(M)_{280}$ -12,350°; $(M)_{250}$ -15,200°; $(M)_{230}$ -32,200°.
CD(C, 0.112; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{285}$ +8200°; $(\theta)_{265}$ 0.0°; $(\theta)_{245}$ -2350°; $(\theta)_{243}$ 0.0°; $(\theta)_{238}$ +2700°; $(\theta)_{236}$ 0.0°.

Galanthamine Hydrochloride (Fig. 83): CD(C, 0.067; CH_3OH), 25°; $(\theta)_{275}$ +7700°; $(\theta)_{265}$ +2980°; $(\theta)_{255}$ +700°; $(\theta)_{245}$ +1050°; $(\theta)_{241}$ +4030°; $(\theta)_{238}$ 0.0°.

Epigalanthamine (Base IX) (Fig. 84): RD(C, 0.070; CH_3OH), 25°; $(M)_{450}$ -1660°; $(M)_{350}$ -3330°; $(M)_{300}$ -5850°; $(M)_{280}$ -13,300°; $(M)_{250}$ -20,800°; $(M)_{240}$ -39,000; $(M)_{230}$ -44,200.
CD(C, 0.070; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{288}$ +2750°; $(\theta)_{265}$ 0.0°; $(\theta)_{250}$ -485°; $(\theta)_{245}$ 0.0°; $(\theta)_{240}$ +8250°; $(\theta)_{238}$ 0.0°.
CD(C, 0.070; CH_3OH, HCl), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{286}$ +1360°; $(\theta)_{269}$ 0.0°; $(\theta)_{250}$ 0.0°; $(\theta)_{242}$ +14,300°; $(\theta)_{238}$ 1570° (slit width at 239.5 was 1.8 mm, at 240, 1.4 mm).

Homolycorine (Fig. 86): RD(C, 0.112; CH_3OH), 25°; $(M)_{450}$ 0.0°; $(M)_{325}$ -1128; $(M)_{295}$ -565°; $(M)_{280}$ -2820°; $(M)_{275}$ 0.0°; $(M)_{260}$ +9050°; $(M)_{242}$ 0.0°; $(M)_{240}$ -4220°; $(M)_{230}$ 0.0°; $(M)_{225}$ +7000°; $(M)_{215}$ +8000.
CD(C, 0.055; CH_3OH), 25°; $(\theta)_{325}$ 0.0°; $(\theta)_{300}$ -2000°; $(\theta)_{290}$ 0.0°; $(\theta)_{270}$ -18,700°; $(\theta)_{260}$ 0.0°; $(\theta)_{250}$ +14,000°; $(\theta)_{240}$ 0.0°.

Lycorine (Fig. 87): CD(C, 0.167; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{290}$ -6600°; $(\theta)_{250}$ 0.0°; $(\theta)_{245}$ +4600°; $(\theta)_{235}$ 0.0°.

Albomaculine (Fig. 88): CD(C, Ca. 0.1; CH_3OH), 25°; $(\theta)_{325}$ 0.0°; $(\theta)_{305}$ -4100°; $(\theta)_{290}$ -2700°; $(\theta)_{270}$ -6200°; $(\theta)_{260}$ 0.0°; $(\theta)_{250}$ +6300°; $(\theta)_{235}$ 0.0°.

Dihydrolycorine (Fig. 90): CD(C, 0.114; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{290}$ -3100°; $(\theta)_{260}$ 0.0°; $(\theta)_{255}$ 0.0°; $(\theta)_{240}$ +2160°; $(\theta)_{230}$ 0.0°.

Coccinine (Fig. 92): CD(C, 0.103; CH_3OH), 25°; $(\theta)_{305}$ 0.0°; $(\theta)_{295}$ -3300°; $(\theta)_{270}$ 0.0°; $(\theta)_{240}$ -38,000°; $(\theta)_{230}$ -21,700°; $(\theta)_{225}$ -45,000°.

Montanine (Fig. 93): CD(C, 0.089; CH_3OH), 25°; $(\theta)_{310}$ 0.0°; $(\theta)_{293}$ -3000°; $(\theta)_{260}$ 0.0°; $(\theta)_{243}$ -57,500°; $(\theta)_{239}$ -27,200°; $(\theta)_{235}$ -48,000°.

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