

## CHIROPTICAL PROPERTIES OF MORPHINAN DERIVATIVES\*

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*Cordially dedicated to Professor F. Šantavý on the occasion of his 60th birthday.*

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The CD of many derivatives of codeine has been measured in the range between 185 and 500 nm. The sign of the  $^1B_{2u}$  band CD can be predicted from ring chirality, the influence of different substituents in ring C onto the Cotton effects is discussed on the basis of the corresponding sector rule. A CD band found for two allyl iodides at 300–310 nm is tentatively assigned a forbidden transition of this chromophore.

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In the course of our investigations on the correlation between chiroptical data and structure we studied recently also the benzene chromophore<sup>1,2</sup>. It is important to have at hand series of compounds which contain the same basic skeleton but differ only in one substituent (type or/and configuration), and the morphinan alkaloids offer such a possibility. In connection with pharmacological screening and investigations of physical and chemical properties a large amount of derivatives of morphine have been prepared by the Debrecen authors<sup>3–16</sup>, and their CD spectra are described in this paper.

ORD and CD spectra of various compounds with the morphinan skeleton have already been published by several groups<sup>17–25</sup>, and only those are mentioned in the following which are directly related to the substances investigated by us.

The chromophore common to all these derivatives is a benzene ring incorporated into a tetralin system which is further bridged by a piperidine ring and connected to a dihydrofuran and one more cyclohexane ring. Another oxygen function is present in *o*-position to the O atom of the dihydrofuran ring. In the systematology used by us<sup>1</sup> this chromophore can thus be classified as an achiral aromatic ring incorporated into a chiral second sphere, twice further substituted by two achiral groups (Type *F*). In such a case the sign of the Cotton effects is determined by the chirality or helicity of the chiral second sphere *and* by the substitution pattern of the benzene ring.

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\*\* 1973/1974 guests in Bochum.

*P*-Helicity\* of the alicyclic ring leads to a positive  ${}^1\mathbf{B}_{2u}$  band CD for types *A–D*, a negative one for types *E–G*. The sign of the  ${}^1\mathbf{B}_{1u}$  band CD follows the same rule in very simple cases, it is, however, also dependent on the substitution at the benzylic C atoms. Similar to the rule proposed for the first  $\pi \rightarrow \pi^*$  Cotton effect of conjugated dienes<sup>27</sup> and enones<sup>27</sup> the  $\sigma$  bond to the pseudoaxial substituent which is best suited for orbital interaction with the  $\pi$  system of the aromatic ring has to be incorporated into the first sphere ("allylic axial chirality contribution"<sup>27</sup>). The  ${}^1\mathbf{E}_{1u}$  transition is degenerate in the benzene itself ( $D_{6h}$  symmetry) and gives rise to a strong CD couplet at around 200 nm<sup>1,28</sup> whose sign cannot be predicted at the moment because of lack

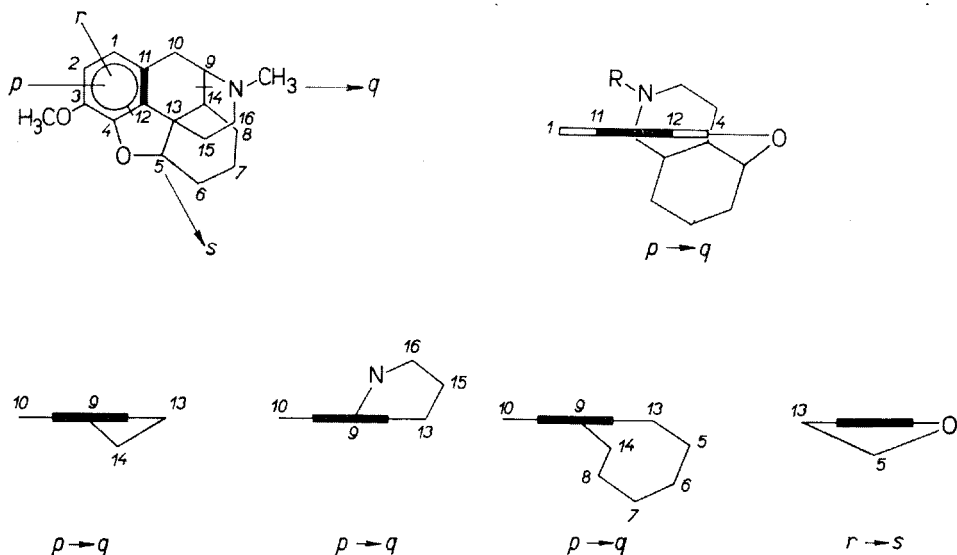


FIG. 1

Stereoformula of Dihydrodeoxy Codeine (*I*) and Projections in the Directions  $p \rightarrow q$  and  $r \rightarrow s$

\* According to Cahn, Ingold and Prelog<sup>26</sup> the conformation of a cyclohexene can be treated either as a primary or a secondary structure. In the first case the conformation can be specified by referring to the torsion angles, which are alternating positive and negative around the ring:



As, however, substitution may change the *P/M* descriptor for homochiral rings depending on the nature of the substituent according to the sequence rule we prefer to refer to the secondary structure as indicated:

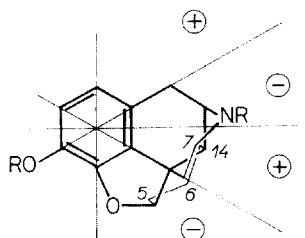


of enough data. In bridged compounds several chiral second spheres may be present. Experimentally it has been found that for ketones<sup>29</sup> and benzene derivatives<sup>1,29</sup> the smaller ring determines the sign of the CD, for lactones it is, however, the bigger one<sup>30</sup>.

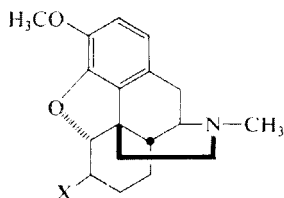
The stereoformula of a morphinan containing the dihydrofuran moiety is depicted together with the stereoprojection  $p \rightarrow q$  in Fig. 1. This drawing corresponds to a Dreiding model, and torsion angles read from this are very close to those measured *e.g.* in the crystalline state of codeine hydrobromide dihydrate<sup>31,32</sup> by X-ray diffraction.\* Altogether four second spheres are present, which are separately drawn on the same Fig. 1. Along the projection  $p \rightarrow q$  the atoms 11-10-9-14-13-12 form a cyclohexane sofa conformation with *P*-helicity, whereas a chiral eight-membered ring of *M*-helicity is formed by the atoms 11-10-9-N-16-15-13-12, a chiral ten-membered ring of *P*-helicity by the atoms 11-10-9-14-8-7-6-5-13-12. Atoms 12-13-5-O-4 build up a five-membered ring with  $C_s$  symmetry (looking along  $r \rightarrow s$ ). The influence of the last mentioned ring can be neglected, because it is geometrically achiral, of the others the smallest one has *P*-helicity, and a negative CD is thus expected for the  ${}^1B_{2u}$  band CD by taking into account the substitution pattern (type *F*). In accordance with this prediction all compounds of this type show a negative CD around 280 to 290 nm which can be ascribed to the  ${}^1B_{2u}$  transition. Its magnitude (in  $\Delta\epsilon$  units) is approximately 1.7–3 for compounds with a saturated ring C or a 7 : 8-unsaturation, in case of a 6 : 7-double bond the CD is approximately twice as strong. Only for *XXVIII* a very small  ${}^1B_{2u}$  band was found.

Contributions of substituents in ring C to the Cotton effect will be small because of the presence of a chiral second sphere, their sign can tentatively be predicted from the corresponding sector rule<sup>1</sup> (Fig. 2). Any group at  $C_{(7)}$ ,  $C_{(8)}$  or  $C_{(14)}$  is positioned in or very close to a nodal plane and has thus no direct influence upon the CD, a group attached to  $C_{(6)}$  should give a positive contribution. Weiss and Rüll<sup>17</sup> found  $\Delta\epsilon$  values (all in ethanol) of  $-2.93$  for dihydrodeoxy codeine *D* (*I*),  $-2.5$  for dihydro-

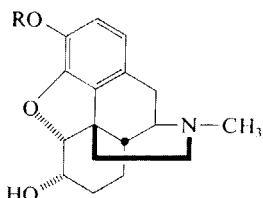
FIG. 2  
Sector Rule for the  ${}^1B_{2u}$  CD Band of the  
Compounds Investigated  
Signs refer to upper sectors.



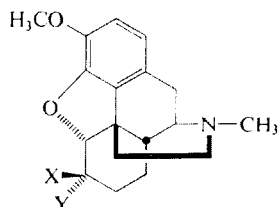
\* The figure corresponding to codeine hydrobromide dihydrate is in ref.<sup>32</sup> erroneously placed on p. 343. Furthermore, this figure and the signs of the torsion angles refer to the enantiomer of the natural alkaloid.



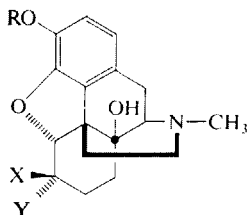
- I; X = H  
 II; X = OH  
 III; X = NH<sub>2</sub>



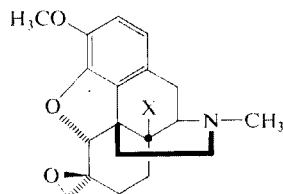
- IV; R = CH<sub>3</sub>  
 V; R =



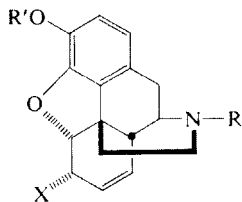
- VI; X = OH, Y = CH<sub>3</sub>  
 VII; X = CH<sub>3</sub>, Y = OH  
 VIII; X = C<sub>2</sub>H<sub>5</sub>, Y = OH  
 IX; X = CH=CH<sub>2</sub>, Y = OH  
 X; X = C≡CH, Y = OH  
 XI; X = C≡CH, Y = OCOCH<sub>3</sub>



- XII; X = Y = H, R = CH<sub>3</sub>  
 XIII; X = NH<sub>2</sub>, Y = H, R = CH<sub>3</sub>  
 XIV; X = OH, Y = R = CH<sub>3</sub>  
 XV; X = R = CH<sub>3</sub>, Y = OH  
 XVI; X = C<sub>2</sub>H<sub>5</sub>, Y = OH, R = CH<sub>3</sub>  
 XVII; X = C≡CH, Y = OH, R = CH<sub>3</sub>  
 XVIII; X = C≡CH, Y = OH, R = CH<sub>2</sub>OCH<sub>3</sub>



- XIX; X = H  
 XX; X = OH

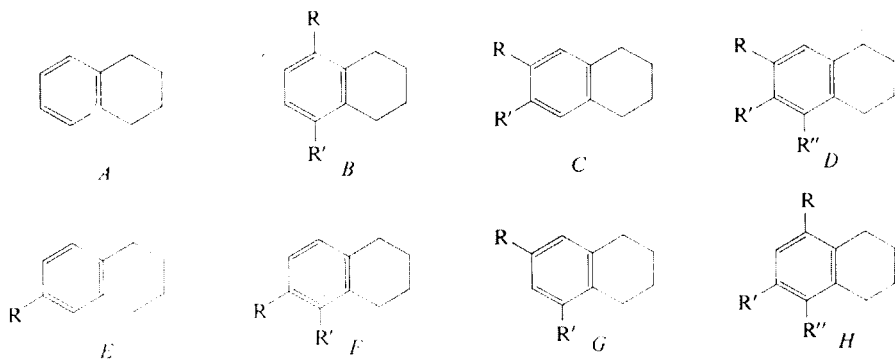


- XXI; X = H, R = R' = CH<sub>3</sub>  
 XXV; X = OH, R = R' = CH<sub>3</sub>  
 XXVI; X = OH, R = CH<sub>3</sub>, R' = H  
 XXVII; X = OH, R = CH<sub>2</sub>CH=CH<sub>2</sub>, R' = C<sub>2</sub>H<sub>5</sub>  
 XXVIII; X = OCOCH<sub>3</sub>, R = CH<sub>2</sub>CH=CH<sub>2</sub>, R' = C<sub>2</sub>H<sub>5</sub>  
 XXIX; X = OH, R = CH<sub>3</sub>, R' =

codeine (*IV*), and  $-2.0$  for dihydroisocodeine (*II*). The contribution of an OH-group in  $6\alpha$ - or  $6\beta$ -position is thus indeed positive, they are, however, not additive, as compounds gem-disubstituted at  $C_{(6)}$  (*VI*–*XI*) give the same CD as the monosubstituted ones. The nature of this substituent is also of minor importance (OH: *II*, *IV*, *VI*, *VII*, *VIII*, *X*;  $\text{NH}_2$ : *III*; alkyl: *VI*, *VII*, *VIII*), it may even contain a double (*IX*) or a triple bond (*X*, *XI*). Similar results are found in the 14-hydroxy series (*XII*–*XVIII*) with the exception of *XVIII* where the CD is stronger negative. In this compound the phenolic OH group is, however, not simply etherified like in all other compounds but transformed into an acetal grouping, so one perturber directly bond to the benzene chromophore has changed. A somewhat smaller CD is found for the epoxides *XIX* and *XX*.

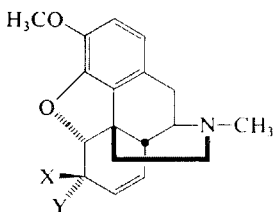
The three double-bond isomers *XXI*, *XXXV* and *XLVII* have already been investigated by Weiss and Rüll<sup>17</sup>, their CD curves cannot be directly compared, however, because they were not recorded all in the same solvent; the strongest Cotton effect was observed for the 6 : 7-isomer. We have measured the CD of many 7 : 8-unsaturated compounds with different substituents at  $C_{(6)}$ , without or with a hydroxy group at  $C_{(14)}$  (*XXXIII*–*XXXIV*) and found in all but one cases a similar CD curve as for the saturated analogues; only the acetoxy compound *XXVIII* gives an unusually weak (but also negative) Cotton effect. *XXVIII* is the single unsaturated compound available to us with a  $\text{CH}_3\text{COO}$  grouping at 6 position; as also the phenolic OH is acetylated in this case and not methylated, the change of the magnitude of the CD may result either from a direct interaction of the  $\pi$ -systems of the acetoxy group and the benzene ring, or from the other substitution at the aromatic ring.

All compounds investigated by us containing the 6 : 7-double bond (*XXXVI* to *XLVI*) show the increased  $^1\text{B}_{2u}$  CD band regardless of the type of substituent at  $C_{(8)}$ ; a 14-OH group is also without any influence upon this Cotton effect. Of some interest is the CD of the allyl iodides *XXXIX* and *XLIV*, where an additional positive

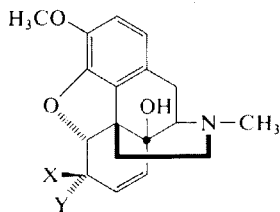


Cotton effect shows up at 300–310 nm. The UV-absorption spectra of tertiary iodides and of ethyl iodides differ only in their absorption coefficients but not in the position of the band maximum (approximately 267 nm)<sup>33</sup>. In chiral environments this absorption gives rise to a Cotton effect<sup>34,35</sup>, no examples of chiral allyl iodides have been recorded, however, to our knowledge. We tentatively correlate this long-wavelengths CD band with a forbidden transition of the C=C—C—I moiety.

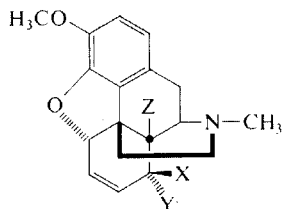
For all compounds a second CD band shows up around 240–245 nm which in agreement with the assignment proposed by Weiss and Rüll<sup>17</sup> is believed to be of  $^1B_{1u}$  origin with some admixture of  $n_O \rightarrow \pi_{ar}^*$  CT transition. It is medium positive besides in case of XVIII. There is no general relationship between the signs of the



- XXII; X = OH, Y = H  
 XXIII; X = F, Y = H  
 XXIV; X = Cl, Y = H  
 XXX; X = C≡CH, Y = OH



- XXXI; X = H, Y = OMs  
 XXXII; X = F, Y = H  
 XXXIII; X = Cl, Y = H  
 XXXIV; X = N<sub>3</sub>, Y = H



- XXXV; X = Y = Z = H  
 XXXVI; X = NH<sub>2</sub>, Y = Z = H  
 XXXVII; X = Cl, Y = Z = H  
 XXXVIII; X = Br, Y = Z = H  
 XXXIX; X = I, Y = Z = H  
 XL; X = -NCS, Y = Z = H  
 XLI; X = Z = H, Y = OH  
 XLII; X = Cl, Y = H, Z = OH  
 XLIII; X = Br, Y = H, Z = OH  
 XLIV; X = I, Y = H, Z = OH  
 XLV; X = N<sub>3</sub>, Y = H, Z = OH

TABLE I  
Circular Dichroism of Morphinan Derivatives

Substance	$\lambda_{\max} (\Delta\epsilon)^a$	Ref.
<i>III</i>	282 (-1.89), 245 (+5.08), 219 (-8.96), 202 (+2.95)	3
<i>V</i>	280 (-1.49), 229 (-8.57)	4
<i>VI</i>	285 (-2.02), 244 (+5.25), 217 (-8.36)	5
<i>VII</i>	282 (-2.24), 245 (+4.54), 221 (-8.50)	5
<i>VIII</i>	281 (-2.33), 244 (+4.92), 219 (-12.77)	6
<i>IX</i>	282 (-2.66), 244 (+4.67), 221 (-13.88)	6
<i>X</i>	281 (-2.53), 243 (+5.04), 223 (-8.96)	6
<i>XI</i>	283 (-2.63), 242 (+5.95), 223 (-6.14)	6
<i>XIII</i>	282 (-2.15), 245 (+3.49), 221 (-7.92), 205 (+7.25)	7
<i>XIV</i>	283 (-1.92), 244 (+4.32), 221 (-4.08)	5
<i>XV</i>	282 (-2.27), 245 (+3.60), 220 (-7.60)	5
<i>XVI</i>	280 (-2.25), 245 (+2.53), 218 (-11.26)	4
<i>XVII</i>	282 (-2.24), 243 (+2.66), 220 (-5.23)	4
<i>XVIII</i>	279 (-3.33), 231 (-5.20)	4
<i>XIX</i>	283 (-1.82), 242 (+5.65), 215 (-9.47)	5
<i>XX</i>	280 (-1.79), 241 (+4.65), 222 (-2.94)	5
<i>XXIII</i>	287 (-1.86), 242 (+7.48), 216 (-14.71), 202 (+5.52)	8
<i>XXIV</i>	287 (-1.71), 243 (+7.22), 216 (-62.02)	8
<i>XXVI</i>	287 (-1.76), 247 (+7.62), 218 (-10.31)	—
<i>XXVII</i>	288 (-2.56), 249 (+11.72), 219 (-22.72), 205 (+3.42)	9
<i>XXVIII</i>	283 (-0.63), 244 (+1.86), 227 (-3.44)	9
<i>XXIX</i>	288 (-0.29), 278 (+0.95), 272 (+1.07), 229 (-4.58)	4
<i>XXX</i>	286 (-2.05), 247 (+11.16), 217 (-32.70), 202 (-11.78)	6
<i>XXXI</i>	287 (-2.70), 252 (+7.29), 225 (-27.53), 206 (+10.25)	7
<i>XXXII</i>	285 (-1.67), 248 (+4.33), 220 (-5.47), 204 (+3.91)	10
<i>XXXIII</i>	285 (-1.98), 247 (+2.49), 215 (-18.65), 199 (-35.56)	10
<i>XXXIV</i>	283 (-2.72), 249 (+6.72), 222 (-21.71), 204 (+10.35)	7
<i>XXXVI</i>	285 (-5.03), 247 (+6.76), 224 (-15.49), 214 (-17.00), 191 (-20.77)	3
<i>XXXVII</i>	284 (-5.29), 245 (+6.52), 225sh (-8.42), 211 (-29.47)	8
<i>XXXVIII</i>	285 (-4.39), 244 (+7.58), 213 (-16.85), 195 (+33.70)	8
<i>XXXIX</i>	301 (+0.90), 287 (-1.87), 243 (+13.18), 217 (-4.33), 204 (-6.69), 192 (+10.62)	8
<i>XL</i>	286 (-5.44), 244 (+7.32), 224 (-3.09), positive at shorter wavelengths	11
<i>XLII</i>	286 (-5.08), 248 (+5.77), 224 (-15.58), 214 (-20.60), positive at shorter wavelengths	10

TABLE I (continued)

Substance	$\lambda_{\max} (\Delta\epsilon)^a$	Ref.
<i>XLIII</i>	286 (-4.56), 247 (+5.03), 214 (-19.21), 190 (+48.40)	10
<i>XLIV</i>	302 (+0.30), 286 (-4.23), 247 (+7.01), 213 (-26.54), 192 (+40.30)	10
<i>XLV</i>	284 (-5.98), 247 (+6.75), 222sh (-23.40), 216 (-28.21), 192 (+37.85)	7
<i>XLVI</i>	288 (-7.41), 249 (+55.34), 202 (-18.68)	12
<i>L</i>	297 (-3.52), 247 (+8.93), 212 (-24.23)	13
<i>LI</i>	290 (-1.78), 275sh (-0.92), 247 (+12.16), 215 (-21.78)	13
<i>LII</i>	309 (-3.14), 254 (+7.59), 217 (-20.34)	14
<i>LIII</i>	404 (-0.41), 382 (+0.15), 349 (+4.25), 289 (+0.32), 255 (-9.17), 222 (+11.47), 198 (-22.32)	14
<i>LIV</i>	402 (-0.33), 348 (+4.25), 302 (-1.21), 253 (-8.74), 221 (+6.99), 196 (-25.88)	15
<i>LV</i>	405 (+0.42), 324 (-4.03), 239 (+16.73), 213 (-31.63)	14
<i>LVI</i>	289 (-0.79), 248 (+4.60), 225 (-3.77)	6

<sup>a</sup> Taken with a Roussel-Jouan Dichrograph 185 at concentration of appr. 1 mg/ml at 20°C in cells of 0.01–1.00 cm thickness in acetonitrile solution.

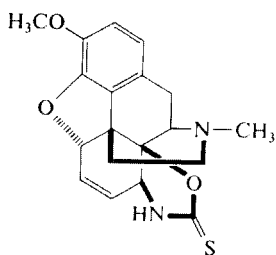
<sup>1</sup>**B**<sub>2u</sub> and <sup>1</sup>**B**<sub>1u</sub> CD bands. In simple cases they seem to follow the same rule and have the same sign<sup>1,29</sup>, for many natural products these two Cotton effects are, however, of opposite signs<sup>18,36</sup>. We expressed the opinion<sup>1</sup> that axial substituents at the benzylic C atom may be responsible for such sign inversions and believe that the <sup>1</sup>**B**<sub>1u</sub> transition is more prone to such a perturbation than the lower lying <sup>1</sup>**B**<sub>2u</sub> transition. The bond C<sub>(13)</sub>/C<sub>(15)</sub> is indeed axially disposed with respect to ring **B**, so that opposite signs for these two Cotton effects are expected. *XVIII* and *XXI* showed also anomalies for the <sup>1</sup>**B**<sub>2u</sub> CD band and the presence of negative <sup>1</sup>**B**<sub>1u</sub> band Cotton effects for them may perhaps be explained in a similar way as above for the first band.

Presence of a double bond either in 6 : 7- or in 7 : 8-position enhances the CD of the <sup>1</sup>**B**<sub>1u</sub> band by approximately 2Δε units in nearly all cases; this is in contrast with the influence upon the <sup>1</sup>**B**<sub>2u</sub> CD band, where the 7 : 8-enes showed no enhancement. Again the type of the substituent on ring **C** is of no great importance. Only the iodine derivative *XXXIX* gives a very intensive positive CD at 243 nm which, however, may be due to a great extent to the CD of the iodine chromophore.

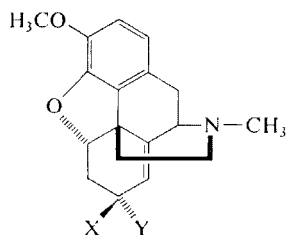
A third CD band whose onset was already seen in the spectra published earlier<sup>17,18</sup> could be measured fully in many cases (*III*, *VI*, *XVIII*, *XXIII*, *XXIV*, *XXVI*, *XXVII*, *XXX–XXXIV*, *XXXVI–XL*, *XLII–XLV*) around 220 nm, and sometimes even a fourth CD band at appr. 200 nm could be identified (*III*, *XIII*, *XXIII*, *XXVII*,



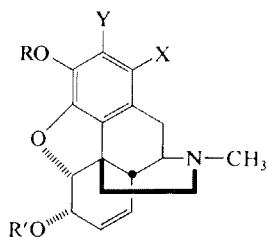
XXXI, XXXII, XXXIV, XXXVI, XXXVIII, XXXIX, XLIII–XLV). These two bands belong most probably mainly to the degenerate  ${}^1E_{1u}$  transition, as the very strong UV-absorption maximum appears in between these two CD bands. In accordance with such an assignment these two CD bands have the form of a couplet. At these short wavelengths other transitions will, however give also rise to the appearance of Cotton effects so that deviations from the symmetric form are not unexpected.  $\Delta\epsilon$  within the first of these two bands may be as big as  $-30$ , that within the 200 nm-CD band is in general somewhat smaller. Hitherto it is not yet known what determines the sign of this  ${}^1E_{1u}$  band couplet; the same sign for all the compounds investigated suggests that also for this Cotton effect second sphere chirality is more important than the influence of substituents in ring C.



XLVI

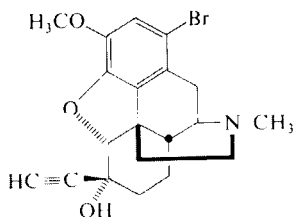


- XLVII; X = Y = H  
 XLVIII; X = OH, Y = H  
 XLIX; X = H, Y = OH



- L; X = OH, Y = R' = R, R = CH<sub>3</sub>  
 LI; X = OCOCH<sub>3</sub>, Y = H, R = CH<sub>3</sub>, R' = COCH<sub>3</sub>  
 LII; X = NH<sub>2</sub>, Y = R' = H, R = CH<sub>3</sub>  
 LIII; X = NO<sub>2</sub>, Y = R' = H, R = CH<sub>3</sub>  
 LIV; X = NO<sub>2</sub>, Y = H, R = CH<sub>3</sub>, R' = COCH<sub>3</sub>  
 LV; X = R = R' = H, Y = NO<sub>2</sub>  
 (HCl)

Inoue and coworkers<sup>21</sup> prepared *B/C-trans* morphinan derivatives and measured their chiroptical properties. ORD and CD curves are very similar to those of the natural *B/C-cis*-compounds which fact is in full agreement with our predictions, as ring B and even the second spheres including ring C do not change their chirality.



LVI

The two phenyltetrazol ethers *V* and *XXIX* both give the usual negative  ${}^1\mathbf{B}_{2u}$  CD band, but their magnitudes are reduced. An additional positive CD band appears at 272 nm for *XXIX*, the  ${}^1\mathbf{B}_{1u}$  CD band is negative for both compounds. This is reminiscent of the behaviour of the acetal *XVIII*. No CD has been detected which could be ascribed to the newly introduced chromophore, the high absorption prevented, however, measurements at shorter wavelengths. Isothiocyanates give Cotton effects at around 340, 260 and 205 nm<sup>37</sup>. For the compound *XL* we found a somewhat increased  ${}^1\mathbf{B}_{2u}$  CD band, whereas the  ${}^1\mathbf{B}_{1u}$  CD band was in the usual range. No CD could be detected at wavelengths longer than 300 nm, so obviously any Cotton effect which could have been caused by the  $-\text{N}=\text{C}=\text{S}$  chromophore must be very small. In the CD spectrum of the thiono oxazolidine derivative *XLVI* a very intense Cotton effect is observed at 249 nm ( $\Delta\epsilon = +55.34$ ) which must come from the newly introduced chromophore. The enhancement of the CD within the  ${}^1\mathbf{B}_{2u}$  band is the usual one found for 6 : 7-unsaturated compounds.

Compounds substituted at  $\text{C}_{(1)}$  have another substitution pattern in the chromophore, *viz.* type *H*. A similar treatment<sup>1</sup> as for the other types leads to the prediction that also in this case a *P*-helicity of the second sphere should lead to a negative CD within the  ${}^1\mathbf{B}_{2u}$  band. Such is indeed found for the hydroxy (*L*), acetoxy (*LI*), amino (*LII*) and bromo (*LVI*) derivatives, apart from small bathochromic shifts which are regular. Also the  ${}^1\mathbf{B}_{1u}$  CD band of these compounds is very similar to that of the other compounds investigated. The first band of the  ${}^1\mathbf{E}_{1u}$  couplet is quite strong for *L-LII*, but relatively small for *LVII*. As expected the nitro derivatives *LIII-LV* show several CD bands arising from the nitro group at longer wavelengths. It is interesting to note that the CD spectra of the 1- (*LIII-LIV*) and 2- (*LV*) nitro compounds are enantiomorphous in the wavelengths range from 210–450 nm.

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