CIRCULAR DICHROISM OF ALKALOIDS OF COLCHICINE TYPE AND THEIR DERIVATIVES*

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The CD spectra of 48 colchicine alkaloids and of some of their derivatives were given. The effects of the substituents and of the basic skeleton on the chiroptical properties of the measured compounds were discussed.

The ORD spectra of colchicine (*VIII*) and some of its derivatives show[1] two Cotton effects at 330 nm and 280 nm. In the "isoseries" (9-methoxy-10-ketones) the first effect is bigger than in the "normal series" (10-methoxy-9-ketones). This band has been found to come from a tropolone transition, whereas the second one was compared to the conjugation band of the full biaryl system. It had the same sign as for analogous biphenyls of identical absolute configuration. Colchinol (*XLIV*), which has such a biphenyl system, gave the strong Cotton effect around 260 nm identical in sign to that of simpler twisted biphenyls of same helicity[2-4]. The ORD of two lumicolchicines (*XXIX*, *XXXII*) also indicated the presence of two Cotton effects (no correlations with structure have been tried). In this paper, we report on the CD spectra of appr. 50 colchicine derivatives and the correlation of their Cotton effects with stereochemistry.

On the basis of the CD spectra, the studied alkaloids with tropolone ring (which form the main part of this paper) can be subdivided into the following groups (for the chemistry of these compounds see the reviews[5-9]: Colchicine type (*I–XXI*), isocolchicine type (*XXII–XXIV*), colchiceine type (*XXV–XXVII*), lumicolchicine types (*XXVIII* to *XXX* and *XXXI–XXXII*), colchicamide derivatives (*XXXIII–*

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** Guests at Bonn University in 1968–1970.

*** Guest at Bochum University in 1976–1977.

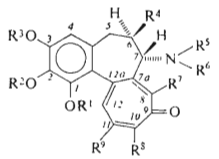
Colchiciline (*XVI*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = OH$, $R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = OCH_3$
2-Acetyl-2-demethylcolchicine (*XVII*)	$R^1 = R^3 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^2 = R^6 = COCH_3$, $R^8 = OCH_3$
3-Acetyl-3-demethylcolchicine (*XVIII*)	$R^1 = R^2 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^3 = R^6 = COCH_3$, $R^8 = OCH_3$
Speciosine (*XIX*)	$R^1 = R^2 = R^3 = R^5 = CH_3$, $R^4 = R^7 = R^9 = H$, R^6 = 2-hydroxybenzyl, $R^8 = OCH_3$
N-Benzoyl-N-deacetylcolchicine (*XX*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^6 = C_6H_5CO$, $R^8 = OCH_3$
O-Benzoyl-O-demethylcolchicine (*XXI*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = C_6H_5COO$
N-Methylcolchicamide (*XXXIII*)	$R^1 = R^2 = R^3 = R^5 = CH_3$, $R^4 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = NH_2$
N′-Butylcolchicamide (*XXXIV*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = NHC_4H_9$
N′-Acetylcolchicamide (*XXXV*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = NHCOCH_3$
Colchicide (*XXXVII*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = R^7 = R^8 = R^9 = H$, $R^6 = COCH_3$
8,11-Dibromocolchiceine (*XXXIXa*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = H$, $R^6 = COCH_3$, $R^7 = R^9 = Br$, $R^8 = OH$
8,11-Dibromocolchicine (*XXXIXb*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = H$, $R^6 = COCH_3$, $R^7 = R^9 = Br$, $R^8 = OCH_3$
Isocolchicine (*XXII*)	$R^1 = H$, $R^2 = OCH_3$
Ethylisocolchicine (*XXIII*)	$R^1 = H$, $R^2 = OC_2H_5$
N-Methylisocolchicine (*XXIV*)	$R^1 = CH_3$, $R^2 = OCH_3$
Isocolchicamide (*XXXVI*)	$R^1 = H$, $R^2 = NH_2$
N-Deacetylcolchicine (*I*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = R^6 = R^7 = R^9 = H$, $R^8 = OCH_3$
Demecolcine (*II*)	$R^1 = R^2 = R^3 = R^6 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^8 = OCH_3$
N,N-Dimethyldeacetylcolchicine (*III*)	$R^1 = R^2 = R^3 = R^5 = R^6 = CH_3$, $R^4 = R^7 = R^9 = H$, $R^8 = OCH_3$
2-Demethyldemecolcine (*IV*)	$R^1 = R^3 = R^6 = CH_3$, $R^2 = R^4 = R^5 = R^7 = R^9 = H$, $R^8 = OCH_3$
3-Demethyldemecolcine (*V*)	$R^1 = R^2 = R^6 = CH_3$, $R^3 = R^4 = R^5 = R^7 = R^9 = H$, $R^8 = OCH_3$
N-Deacetyl-N-formylcolchicine (*VI*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^6 = CHO$, $R^8 = OCH_3$
N-Formyldemecolcine (*VII*)	$R^1 = R^2 = R^3 = R^5 = CH_3$, $R^4 = R^7 = R^9 = H$, $R^6 = CHO$, $R^8 = OCH_3$
Colchicine (*VIII*)	$R^1 = R^2 = R^3 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = OCH_3$
N-Methylcolchicine (*IX*)	$R^1 = R^2 = R^3 = R^5 = CH_3$, $R^4 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = OCH_3$
N-Propionyldemecolcine (*X*)	$R^1 = R^2 = R^3 = R^5 = CH_3$, $R^4 = R^7 = R^9 = H$, $R^6 = COCH_2CH_3$, $R^8 = OCH_3$

Cornigerine[58] (*XI*)	$R^2 + R^3 = CH_2$, $R^1 = CH_3$, $R^4 = R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = OCH_3$
Colchicoside (*XII*)	$R^1 = R^2 = CH_3$, $R^3 = C_6H_{11}O_5$, $R^4 = R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = OCH_3$
3-Demethyl-N-formyl-N-deacetylcolchicine (*XIII*)	$R^1 = R^2 = CH_3$, $R^3 = R^4 = R^5 = R^7 = R^9 = H$, $R^6 = CHO$, $R^8 = OCH_3$
2-Demethylcolchicine (*XIV*)	$R^1 = R^3 = CH_3$, $R^2 = R^4 = R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = OCH_3$
3-Demethylcolchicine (*XV*)	$R^1 = R^2 = CH_3$, $R^3 = R^4 = R^5 = R^7 = R^9 = H$, $R^6 = COCH_3$, $R^8 = OCH_3$
Deacetylcolchiceine (*XXV*)	$R = H$
N-Formyl-N-deacetylcolchiceine (*XXVI*)	$R = CHO$
Colchiceine (*XXVII*)	$R = COCH_3$
β-Lumiformylcolchicine (*XXVIII*)	$R^1 = R^2 = CH_3$, $R^3 = CHO$
β-Lumicolchicine (*XXIX*)	$R^1 = R^2 = CH_3$, $R^3 = COCH_3$
β-Lumicornigerine (*XXX*)	$R^1 + R^2 = CH_2$, $R^3 = COCH_3$
γ-Lumiformylcolchicine (*XXXI*)	$R = CHO$
γ-Lumicolchicine (*XXXII*)	$R = COCH_3$
7-Oxo-7-deamidocolchicine (*XXXVIII*) (Colchicone)	
10,11-Oxy-10,12a-cyclo-10,11-secocolchicine (*XL*) (Secocolchicine)	
Oxycolchicine (*XLI*)	
Hexahydrocolchicine (*XLII*)	
1-Methoxy-3,4-dihydrofurane (*XLIII*)	
Colchinol.HCl (*XLIV*)	$R^1 = R^2 = R^4 = H$, $R^3 = OH$
Colchinolmethyl ether (*XLV*)	$R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$
N-Acetylcolchinolmethyl ether (*XLVI*)	$R^1 = COCH_3$, $R^2 = R^4 = H$, $R^3 = OCH_3$
N-Acetyldibromocolchinolmethyl ether (*XLVII*)	$R^1 = COCH_3$, $R^2 = R^4 = Br$, $R^3 = OCH_3$
Allocolchicine (colchicinic acid) (*XLVIII*)	$R^1 = COCH_3$, $R^2 = R^4 = H$, $R^3 = COOH$
Allocolchicine (colchicinic acid methyl esther) (*IL*)	$R^1 = COCH_3$, $R^2 = R^4 = H$, $R^3 = COOCH_3$

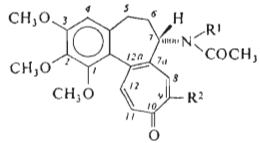
XXXV), isocolchicamide (*XXXVI*), colchicide (*XXXVII*), colchicone (*XXXVIII*), and dibromocolchicine derivatives (*XXXIXa*–*XXXIXb*). Other groups have a somewhat altered tropolone ring: secocolchicine (*XL*), oxycolchicine (*XLI*), hexahydrocolchicine (*XLII*), colchinole derivatives (*XLIV*–*XLVII*), and allocolchicine derivatives (*XLVIII*–*IL*).

Colchicine Type

The UV spectra of tropolone and its ethers[10-12] show a band system at 320 nm and at 240 nm. Both are composed of at least two $\pi \rightarrow \pi^*$ transitions, which may perhaps involve some charge transfer from oxygen to the ring. According to calculations[10,13-17] and absorption measurements of single crystals[14], the 206 nm band ($\varepsilon = 48\,500$) is polarized along the bisetrix of the bonds connecting the two oxygen bearing carbons, the 358 nm band ($\varepsilon = 28\,000$) is polarized perpendicular to it. The 314 nm band ($\varepsilon = 32\,000$) has its corresponding transition moment vector approximately along the C—O single bond and for the 223 nm band ($\varepsilon = 45\,000$) which is inclined by $\approx 60°$ to the latter. An $n \rightarrow \pi^*$ band has not been unequivocally identified, but the very weak band around 418 nm ($\varepsilon = 5$) for tropolone in HCl-containing ethanol may perhaps correspond to it[11]. Tropolone spectra resemble somewhat the spectra of analogous hydroxyacetophenones[12].



I - XXI, XXXIII - XXXV, XXXVII - XXXIXb



XXII - XXIV, XXXVI

XXV - XXVII

In colchicine and its derivatives, a pyrogallol moiety is conjugated with the tropolone system and the bands of the latter are both bathochromically and hyperchromically shifted. Many such UV spectra are published[18-20] and they may be compared with spectra of biphenyl compounds with similar substitution pattern. X-Ray diffraction analyses[21-23] of demecolcine (*II*), colchicine (*VIII*) and isocolchicine (*XXII*) showed that both the benzene and the tropolone ring are approximately planar, and the torsion angle between the two rings around their pivot bond is between 51° and 54°. The overall π system is thus inherently chiral and strong Cotton effects should be expected.

The CD spectra of alkaloids *I*–*XXI* containing the same chromophoric system as colchicine (*VIII*) shows up to 7 bands (Table I, Fig.1). The first one, *A*, is at 351 nm and has a $\Delta\varepsilon$ of approximately −9. We assign it to a $\pi \rightarrow \pi^*$ transition which is mainly localized in the tropolone ring, because of its low *g*-value. Band *B* at 293 nm in many cases is not resolved from the band *C* at 274 nm, but appears as a shoulder on the latter. Both are always negative and nearly as strong as band *A*. Band *D* at 245 nm

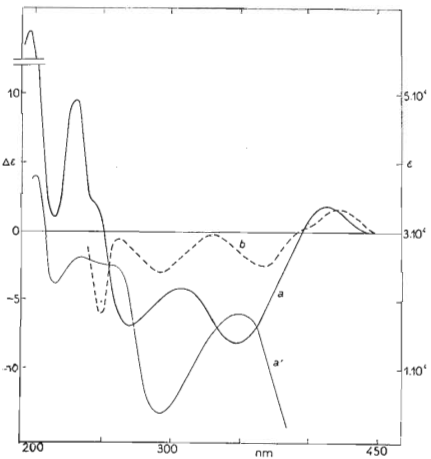


FIG. 1

CD Spectra of colchicine (*a*), colchicone (*b*) and the UV spectrum of colchicine (*a'*)

may either be positive or negative and can be seen in many cases only as a shoulder, either (positive) on the long wavelength side of band *E* or (negative) on the short wavelength side of band *C*. It may well be that the actual sign of the corresponding Cotton effect is always the same, but due to the experimental conditions this CD band may merge together with one of the two more prominent CD bands in its neighbourhood. The band *E* at 232 nm is positive, as is the band *G* at 196 nm. In between them there is not only a minimum, but a negative maximum, which is, however, not always distinctly detectable in the spectra. At least one of the two CD bands *E* and *G* is always very strong ($|\Delta\varepsilon| \leq 30$). Band *E* also follows the general trends found[25] for the position of benzene $\pi \rightarrow \pi^*$ bands of polyoxygenated phenyl derivatives. Although this band normally appears at 230–233 nm, for the methylenedioxy derivative cornigerine (*XI*) it is observed at 237 nm. Only in this molecule, the lone pair on the oxygen atom at $C_{(1)}$ can interact with benzene π-electrons, whereas in all 1-methoxy compounds, for steric reasons, this lone pair is forced approximately into the benzene plane and can, therefore, not anymore interact. The band *E* seems to come mainly from the B_{1u} transition of the benzenoid system of colchicine.

The alkaloid *I* with the chromophoric system containing a free NH_2 group in position $C_{(7)}$ gives an additional positive CD band at 410 nm. Since it is highly improbable that this free NH_2 has a direct or even indirect effect of that magnitude upon the circular dichroism of the tropolone system, we conclude that in these cases the free NH_2 group interacts in characteristic manner with the tropolone ring changing thus the chromophoric system (*cf.* also the CD spectra of deacetylcolchiceine (*XXV*)).

It is tempting to apply the exciton coupling to this system as has been done successfully for substituted twisted biphenyls[24,26]. Only those transitions which are not polarized along the direction of the pivot bond and have a large enough electric transition moment $\vec{\mu}$ can couple. The 358 nm band of the tropolone moiety fulfils these requirements and could give rise to the CD band *A*. The same holds for one component of the E_{1u} doublet of the benzene ring. The B_{1u} transition may also gain enough dipole strength by the substitution with three methoxy groups and the conjugation with the tropolone moiety, because only for two of these three oxygen atoms is is possible to adopt a conformation necessary to give $p-\pi$ overlap with the benzene π-system (*cf.* the X-ray data[21–23]). It is difficult without detailed calculations to make reasonable assumptions about the direction and "localization" of the corresponding transition dipole μ (B_{1u}). However, even if we allow for a great variation of these parameters, the application of the coupled oscillator theory[27,28] leads either to very small $\Delta\varepsilon$-values or to the wrong signs if the same conformation in solution is assumed as that which is present in the crystal[21,22]. The latter fact seems, however, sure because only with this geometry the acetamide grouping can adopt an equatorial conformation. For a few alkaloids the presence of this conformation in solution has been proved by ^{1}H NMR spectroscopy[29–31]. We conclude, therefore, that

TABLE I

Dichroic bands (λ_{max}, nm ($\Delta\varepsilon$)) of colchicine derivatives

Compound	*A*	*B*	*C*	*D*	*E*	*F*	*G*	Other
I	356 (− 9·60)	—	275 (− 5·74)	256 (−4·19)	232 (+28·5)	—	201 (+10·0)	413 (+ 2·19)
II	349 (− 7·75)	—	279 (− 4·66)	250 sh (+ 5·39)	233 (+20·4)	212 (−6·63)	198 (+10·0)	—
III	353 (− 8·16)	—	281 (− 3·34)	260 sh (− 1·49)	234 (+21·2)	213 (−11·5)	197 (+25·0)	—
IV	351 (− 8·56)	—	282 (− 4·51)	248 sh (+ 7·45)	231 (+19·4)	210 (−7·72)	195 (+13·0)	—
V	353 (− 5·95)	291 (−3·52)	—	250 sh (+ 5·81)	233 (+18·1)	210 (−7·55)	195 (+17·6)	—
VI	345 (− 9·37)	—	265 (− 8·21)	—	232 (+ 6·67)	217 (−1·03)	199 (+34·0)	—
VII	342 (− 8·39)	—	272 (− 9·05)	245 sh (+ 5·34)	232 (+14·3)	—	199 (+19·4)	351 sh (−8·04)
VIII	351 (− 9·26)	293 sh (−7·21)	274 (− 8·21)	245 sh (+ 2·20)	232 (+11·0)	213 (−0·96)	196 (+33·3)	—
IX	348 (− 9·72)	—	275 (−10·2)	246 sh (+ 6·53)	232 (+14·2)	—	199 (+24·0)	—
X	246 (− 9·13)	—	275 (− 9·20)	248 sh (+ 5·45)	232 (+12·6)	—	202 (+20·5)	—
XI	346 (− 9·49)	—	283 sh (− 7·14)	260 (− 9·71)	237 (+12·1)	226 sh (+7·14)	212 (−6·70)	—
XII	343 (− 7·77)	290 sh (−7·75)	268 (− 9·29)	246 sh (+ 2·00)	230 (+ 9·42)	214 (−3·50)	197 (+32·9)	—
XIII	347 (− 8·74)	306 sh (−6·25)	261 (− 6·68)	—	232 (+11·1)	214 (−6·68)	197 (+)	—
XIV	349 (− 7·12)	286 sh (−5·97)	263 (− 8·17)	—	233 (+ 9·72)	213 (−2·11)	197 (+)	—
XV	349 (− 9·70)	276 (−6·97)	263 (− 6·82)	—	231 (+ 8·34)	213 (−4·24)	197 (+)	—
XVI	367 (− 4·79) 335 (− 7·04)	289 sh (−6·72)	263 (−11·0)	—	232 (+12·9)	214 (−7·80)	—	—
XVII	347 (− 8·00)	290 sh (−4·45)	267 (− 9·40)	—	230 (+ 8·02)	—	197 (+35·0)	+

TABLE I
(*Continued*)

Compound	*A*	*B*	*C*	*D*	*E*	*F*	*G*	Other
XVIII	334 (− 6·33)	—	262 (−14·7)	240 sh (+ 4·15)	231 (+ 7·31)	213 (−7·81)	193 (+ 6·30)	377 (+ 0·87)
XIX	353 (− 6·18)	293 (−3·18)	—	250 sh (+ 5·62)	234 (+16·4)	214 (−9·51)	193 (+)	—
XX	347 (−10·5)	293 sh (−5·00)	272 (− 5·09)	253 sh (+ 1·73)	232 (+20·8)	—	199 (+22·8)	—
XXI	352 (− 7·18)	—	285 (− 4·26)	254 (+12·8)	233 (+20·7)	204 (−13·4)	191 (+11·4)	381 sh (− 5·00) 219 sh (+10·5)
				Isocolchicine type				
XXII	345 (−13·1)	—	275 sh (− 1·36)	257 (+ 2·31)	238 (+13·5)	217 (−1·78)	198 (+23·0)	—
XXIII	344 (−13·9)	—	276 sh (− 2·08)	257 (+ 1·80)	237 (+13·2)	216 (−2·32)	199 (+30·9)	349 sh (−13·8)
XXIV	347 (−13·9)	—	280 sh (− 1·91)	255 sh (+ 6·75)	238 (+16·9)	—	201 (+16·0)	—
				Colchiceine type				
XXV	342 (−11·4)	—	279 (− 3·72)	250 sh (+14·4)	236 (+18·5)	—	201 (+16·8)	407 (+ 0·71) 352 sh (−10·8)
XXVI	342 (− 9·90)	—	281 (− 3·44)	254 (+ 3·58)	236 (+ 7·57)	219 (−2·90)	199 (+21·5)	—
XXVII	341 (− 8·17)	—	288 (− 4·18)	254 (+ 3·82)	235 (+ 6·53)	218 (−3·73)	198 (+16·7)	—

exciton coupling plays only a minor role (if at all) as origin for the dichroic absorption within band *A*. The reason is most probably an unfavourable orientation of the $\vec{\mu}(B_{1u})$ in the benzene ring. This is in accord with the *g*-values calculated as $\Delta\varepsilon/\varepsilon$ for the individual CD bands of colchicine (*VIII*): They are $5 \cdot 10^{-4}$ (351); $2 \cdot 10^{-3}$ (293); $1{\cdot}3 \cdot 10^{-3}$ (274); $8 \cdot 10^{-5}$ (245 sh); $4 \cdot 10^{-4}$ (235); and appr. 10^{-3} (202 nm), resp.

For an exciton coupling g-values of appr. $8 \cdot 10^{-4}$ to $5 \cdot 10^{-3}$ have been observed,[27,32] so the most probable candidates would be the CD bands *B* and/or *C*. Band *B* coincides, however, with a minimum in the UV spectrum, so this also cannot be part of a couplet.

The CD band *C* may be one wing of such an exciton couplet caused by the coupling of the original 223 nm transition (tropolone chromophore), which should be bathochromically shifted by the further substitution, with one of the two E_{1u} transitions (benzene chromophore). If the direction of polarization of the first mentioned chromophore remains similar also in colchicine (along a line connecting $C_{(12)}$ with the midpoint of bond $C_{(8)}/C_{(9)}$), application of the exciton theory to the interaction of these transition moments gives a negative CD band ($\Delta\varepsilon = -5$) at 274 nm and a positive one ($\Delta\varepsilon = +7$) at 200 nm. To obtain this result that transition of the E_{1u}-doublet has to be used which is polarized along the line $C_{(1)}/C_{(4)}$. The positive wing of this couplet cannot be identified unequivocally as it is not any more resolved from other bands appearing at the same wavelength range.

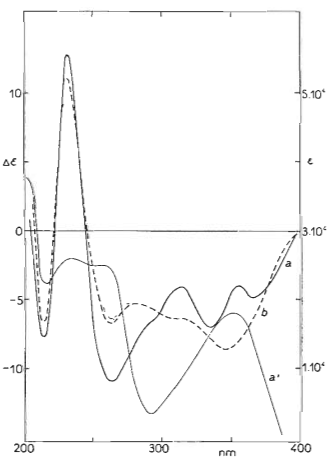


FIG. 2

CD Spectra of colchiciline (*a*), 3-demethyl-N-formyl-N-deacetylcolchicine (*b*) and the UV spectrum of colchiciline (*a'*)

The variation of the temperature of the probe (+20°C to −195°C) changes the CD spectrum of colchicine (*VIII*) only by less than 5% in the wavelength range from 420 to 220 nm proving that we are dealing with only one conformation.

The colchicine alkaloids with tropolone ring also include colchiciline (*XVI*) (Fig. 2) possessing a secondary hydroxyl group at $C_{(6)}$ which thus forms another chiral center[33]. The ^1H and also the ^{13}C NMR spectra show that this hydroxyl group is in the *threo*-position to the amido group at $C_{(7)}$. In the CD spectrum of *XVI*, the band *A* is split into two bands (Table I).

Isocolchicine Type

Comparison of the CD spectra of isocolchicine (*XXII*) (Table I, Fig. 3) and its derivatives *XXIII*, *XXIV* with those of the colchicine type shows that CD bands *A*, *E*, *F* and *G* are of the same signs and magnitudes in both series. The CD band *A* is slightly shifted hypsochromically by 5 nm which corresponds to a similar shift in the UV

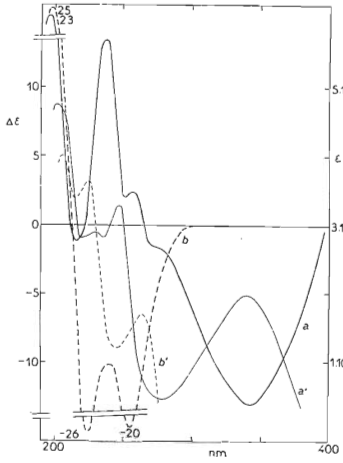


FIG. 3

CD Spectra of isocolchicine (*a*), hexahydrocolchicine (*b*) and the UV spectra of isocolchicine (*a'*) and hexahydrocolchicine (*b'*)

spectra. The CD spectra in the two series differ, however, greatly in the range of bands *B* to *D*. Those CD bands are very weak for *XXII*–*XXIV* which is in agreement with exciton theory. The approximate direction of polarization of the respective transition in the tropolone ring is now along a line connecting $C_{(7a)}$ with the midpoint of $C_{(10)}/C_{(11)}$, and the calculated CD values are +0·36 at 275 and −0·50 at 200 nm; the CD obtained by this mechanism is thus very small and will be overridden by other "local" terms for the rotational strength.

Colchiceine Type

Compounds *XXV*–*XXVII* are free tropolones and not tropolone ethers as all the other compounds, tautomerism is therefore possible (Table I). CD bands *A*, *E*, *F* and *G* have the usual appearance, in the range of bands *B* and *C* the $|\Delta\varepsilon|$ values are approximately 1/3 of those of colchicine type alkaloids. We can conclude that the tautomeric equilibrium is approximately 2 : 1 towards the side of the isocolchicine type.

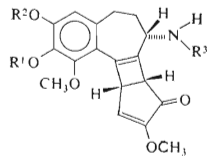
Lumicolchicines and Their Derivatives

β- (*XXIX*) and γ-Lumicolchicine (*XXXII*) and their derivatives (Table II, Fig. 4) contain a styrene and a cyclopentenone moiety which may interact with each other. The structure of *XXIX* and *XXXII* has been established[34,35] and appropriate models for the two partial chromophores are also available[36]. Whereas the conjugation band of the styrene in a system like *XLII* lies at 254 nm, ring closure to an ad-

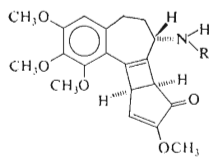
TABLE II
Dichroic bands (λ_{max}, nm ($\Delta\varepsilon$)) of lumicolchicine derivatives

Compound	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*
XXVIII	369 sh (+5·65)	349 (+11·6)	339 (+11·2)	293 (−43·9)	261 (+28·6)	234 sh (+ 5·54)	214 (−10·6)	194 (+16·2)
XXIX	371 sh (+6·20)	350 (+13·5)	341 (+13·3)	293 (−49·6)	263 (+29·2)	233 sh (+5·00)	212 (−15·9)	194 (+6·58)
XXX	369 sh (+6·31)	350 (+12·1)	340 sh (+11·8)	296 (−42·1)	265 (+25·0)	238 (+14·6)	213 (−19·1)	195 (+12·4)
XXXI	369 sh (−6·01)	348 (−12·3)	339 sh (−11·9)	293 (+34·7)	262 (−28·7)	241 sh (−21·4)	231 (−24·0)	200 (−1·59)
XXXII	369 sh (−8·20)	351 (−14·9)	340 sh (−14·0)	295 (+42·1)	264 (−34·0)	240 sh (−23·8)	230 (−28·4)	202 (−1·10)

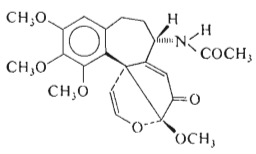
ditional four-membered ring shifts this absorption to 283 nm. The enone *XLIII* absorbs at 246 nm ($\varepsilon = 9\,200$) but its keto group is also homoconjugated to the double bond $C_{(7a)}/C_{(12a)}$. The negative exciton couplet found in the CD spectrum of β-lumicolchicine (*XXIX*) can be ascribed to the interaction of the electric dipol transition moments of the styrene and enone chromophores. From molecular models application of exciton theory leads indeed to such a negative couplet for *XXIX*. The *g*-value of the positive band at 315 nm ($\Delta\varepsilon = 13{\cdot}5$) is $7 \cdot 10^{-3}$ and this suggests an $n \rightarrow \pi^*$ transition of the enone moiety as the source of this band; its ε-value is



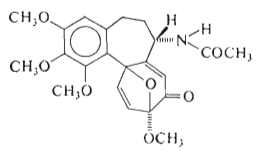
XXVIII – XXX



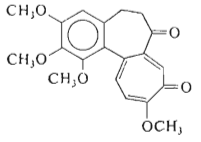
XXXI – XXXII



XL



XLI



XXXVIII

relatively great, in complete analogy to the behaviour of β,γ-unsaturated ketones. If the same mechanism is operating in both cases, a strong positive CD band is expected, which is in full accord with the experimental result. A possible through-space interaction between the *p*-type orbitals at $C_{(12a)}$ and $C_{(11)}$ should not change this result for a transition originating from an *n*-electron of the C=O moiety. The other CD bands (193 nm, 212 nm, and 233 sh) are smaller and will not be discussed in more detail. The CD spectra of the derivatives *XXVIII* and *XXX* are very similar to those of *XXIX*, a remarkable increase of $\Delta\varepsilon$ at 238 nm for *XXX* must be associated with better interaction of the lone pair of electrons of all three methoxy groups with the benzene ring π-electrons.

Ring B of γ-lumicolchicine (*XXXII*) and the corresponding formyl homologue *XXXI* should have similar conformation as in *XXIX*, the bicycloheptadienone moiety of the two isomers are, however, in enantiomeric relationship to each other. The CD spectra of *XXXI* and *XXXII* above 250 nm should, therefore, be of enantiomorphous appearance and this is found experimentally. There are quite distinct

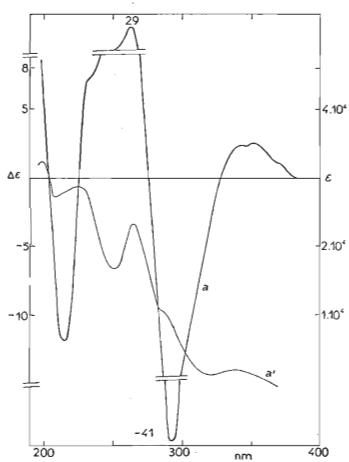


FIG. 4
CD Spectrum of β-lumicolchicine (*a*) and the UV spectrum of the same compound (*a'*)

deviations from real enantiomorphous relationship at shorter wavelength as can be expected for a pair of diastereoisomers. β-Lumicolchicine (*XXIX*) shows a smaller Cotton effect at 350 nm than γ-lumicolchicine (*XXXII*) because it has the possibility[37] to form a hydrogen bond between the carbonyl group of the ring D and the amidic hydrogen $NHCOCH_3$.

Colchicamide and Isocolchicamide Derivatives

Compounds *XXXIII*–*XXV* show CD spectra which are in their general appearance similar to those of the tropolone methyl ethers of colchicine type, the negative CD band *D* is, however, much bigger than in the spectra of the parent compounds (Table III). Additional CD bands are observable at 408 nm ($\Delta\varepsilon \simeq +2$) and around 375 nm (shoulder, $\Delta\varepsilon = -10$), and their appearance is here not confined to the secondary amine *XXXIII*. These bands must therefore correspond to "local" tropone $\pi \rightarrow \pi^*$ transitions which experience the known bathochromic shift due to amino substitution. N'-Acylation to *XXXV* shifts the 408 nm band below 400 nm and leads to sign inversion for it. The dichroic absorption between 370 and 260 nm is similar to that of *XXXIII* and *XXXIV*, band *D* is, however, positive and band *F* appears as a negative Cotton effect. The CD spectrum of the isocompound *XXXVI* shows similar differences to that of isocolchicine (*XXII*) ad *XXXIII* to that of N-methylcolchicine (*IX*).

Colchicide

Colchicide (*XXXVII*) (Table III) was the only tropone derivative available. In the UV, tropone itself shows[38] two bands between 350 and 260 nm and they are less bathochromically shifted by conjugation with the trimethoxy substituted benzene ring than those of tropolones. In the CD spectrum there appears one very broad negative band system, which fact can be explained only if one assumes the presence of 2 to 3 transitions in this area. A shoulder around 370 nm could come from the carbonyl $n \rightarrow \pi^*$ transition, which should be not distinctly observable in the tropolone spectra because the vicinal OR substituent exerts a hypsochromic shift. Between 260 and *c.* 210 nm only 2 Cotton effects are present.

Dibromocolchicine Derivatives

One of the important derivatives of colchicine degradation is dibromocolchicine (*XXXIXb*) which arises from substitution of two hydrogen atoms by two bromine atoms on the tropolone ring (Table III). The same substitution is also encountered in colchiceine[39,40]. This dibromination of colchicine leaves the CD spectrum nearly unchanged, one additional positive Cotton effect is, however, seen about 395 nm. The same holds for dibromocolchiceine (*XXXIXa*) which according to its CD spec-

TABLE III

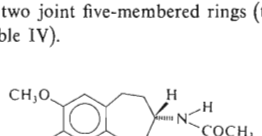
Dichroic bands (λ_{max}, nm ($\Delta\varepsilon$)) of the colchicamide, isocolchicamide, colchicide, colchicone, and dibromocolchicine derivatives

Compound	A_3	A_2	A_1	B	C	D	E	F	G
XXXIII	408 (+2·00)	373 sh (−9·00)	356 (−13·9)	286 (− 7·32)	276 (−6·58)	257 (−10·2)	233 (+8·48)	202 (+30·0)	196 —
XXXIV	413 (+4·44)	376 sh (−6·76)	353 (−13·5)	280 sh (− 6·18)	—	259 (−12·4)	232 (+5·60)	201 (+39·8)	—
XXXV	400 sh (−2·27)	380 sh (−4·00)	352 (− 6·78) 305 sh (− 4·24)	280 (−10·3)	—	254 (+ 3·63)	236 (+9·92)	221 (− 3·79)	201 (+20·5)
XXXVI	405 (+1·94)	367 sh (−8·79)	353 (−13·5)	289 (− 4·01)	275 (−2·53)	253 (− 7·71)	—	222 (+4·65)	201 (+32·1)
XXXVII	400 sh (−1·50)	370 sh (−4·60)	330 (− 7·76)	311 (− 7·76)	279 (−5·00)	250 (− 5·73)	—	215 (+22·7)	—
XXXVIII	428 (+1·94)	370 (−2·51)	—	295 (− 3·99)	—	250 (− 6·00)	—	—	—
XXXIXa	412 sh (+0·21)	387 (+1·20)	355 sh (− 2·80)	340 (− 5·56)	295 (−3·40)	275 (− 3·86)	256 (+2·47)	230 sh (+ 4·42)	207 (+ 9·10)
XXXIXb	—	382 (+0·55)	—	336 (− 7·53)	—	265 (− 7·73)	242 sh (+4·31)	230 (+ 7·35)	196 (+19·2)

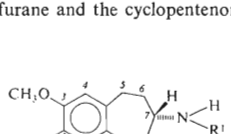
trum is also present in solution as an equilibrium of two tautomers (*cf.* the discussion of Colchiceine type).

Secocolchicine, Oxycolchicine and Hexahydrocolchicine

In secocolchicine[41] (*XL*), whose UV spectrum is similar to that of oxycolchicine[42,43] (*XLI*), the tropolone system is destroyed by the formation of two rings C and D with the difference that whilst in oxycolchicine the double bond is in the α,β-position (ring D) to the tertiary located methoxyl group, in secocolchicine this is not so, which evidently changes the direction of the Cotton band at 363, and 377 nm, respectively, in these two compounds. Furthermore, whereas in oxycolchicine the furane oxygen (ring D) belongs also to the six-membered ring C, in secocolchicine these are two joint five-membered rings (the dihydrofurane and the cyclopentenone ring) (Table IV).



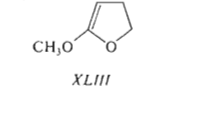
XLII



XLIV – IL

XLIII

L



LI

LII

In oxycolchicine (*XLI*), the molecular models show that the conjugated double bond is practically coplanar with the C=O bond, the isolated C=C bond is in such a relative position to the C=O that enhanced UV and CD bands may already be observed[4,10,44,45] although the conformation present is not ideal for such an interaction. The UV spectrum contains a band around 370 nm ($\varepsilon \approx 100$) assigned to the

$n \rightarrow \pi^*$ absorption which is red shifted because of the presence of the acetamido grouping. The conformation of this oxobicyclooctadiene system is rigid and independent of the conformation of the rest of the molecule. Its CD band ($\Delta\varepsilon = +2{\cdot}43$) is not extraordinarily high, indicating again that the geometry is not the best for this special type of interaction. From the positive sign of the band *A* we can conclude that the oxygen atom of the methoxyl group had attacked the system of the rings C and D from the rear side (Table IV).

Hexahydrocolchicine (*XLII*) contains only the styrene type chromophore which cannot be coplanar in this system as is clearly shown by its UV spectrum (*cf.* the discussion of lumicolchicine spectra) (Table IV, Fig. 3). The conjugation band will, of course, also be influenced by the substitution pattern of the aromatic ring, but

TABLE IV

Dichroic bands (λ_{max}, nm ($\Delta\varepsilon$)) of compounds with changed tropolone ring and colchinol derivatives

Compound	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*
XL	—	363 (−7·12)	—	—	272 (+10·4)	—	237 sh (−23·2)	218 (−88·3)
XLI	—	377 (+2·43)	—	284 (+ 7·97)	—	242 (−20·9)	223 sh (+5·60)	207 (+53·5)
XLII	—	—	—	292 sh (− 0·52)	—	256 (−20·4)	225 (−26·5)	202 (+25·9)
XLIV	299 (−0·13)	—	261 (−28·3)	237 (−10·3)	225 (−14·2)	—	215 (+31·0)	—
XLV	308 (−0·78)	291 (+1·04)	259 (− 8·17)	237 (−35·7)	—	—	214 (+29·4)	—
XLVI	320 (+0·20)	298 (−0·42) 285 sh (−4·20)	260 (−22·6)	236 sh (− 6·00)	224 sh (+ 8·20)	—	212 (+16·6)	197 (−11·2)
XLVII	—	—	270 (+11·9)	—	230 (−15·9)	—	209 (−24·4)	—
XLVIII	394 (+0·15) 365 sh (−0·69)	346 (−1·01)	294 (−19·5)	276 sh (−15·7)	228 (+ 9·02)	—	206 (−23·9)	—
XLIX	—	—	296 (−14·8)	272 sh (− 9·00)	231 (+ 6·71)	224 (+ 6·50)	206 (−22·7)	—

much less than the benzene Cotton effects. If again the equatorially arranged acetamide grouping determines the conformation of ring B, the torsion angle between the C=C bond and the *cisoid* bond of the benzene ring is positive. Such an absolute conformation should lead to a negative Cotton effect[46]. Indeed a very strong one is found for *XLII* at 256 nm ($\Delta\varepsilon = -18{\cdot}3$). At shorter wavelength a couplet-type circular dichroism is observed ($\Delta\varepsilon = -23{\cdot}4$ at 225 nm, $+24{\cdot}1$ at 202 nm) which can perhaps be ascribed to the two E_{1u} absorptions (degenerate in benzene). A similar situation was observed for 6,7-dihydroxy-1,2,3,4,4a,9,9a,10-octahydroanthracene[47]. The Cotton effects of the B_{2u} and B_{1u} transitions are relatively weak and could not distinctly be seen in the vicinity of the very intense CD bands mentioned.

Colchicone, Colchinole and Allocolchicine Derivatives (Biphenyl Analogues of Colchicine)

The UV and CD spectra of biphenyl derivatives have been explained by using mainly the theory of coupling of transition moments localized in the two individual

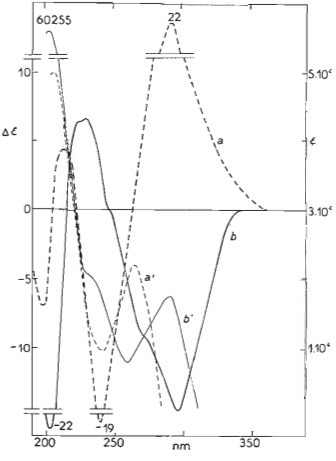


FIG. 5

CD Spectra of N-acetylcolchinol methyl ether (*a*), allocolchicine (*b*) and the UV spectra of N-acetylcolchinol methyl ether (*a'*) and allocolchicine (*b'*)

rings[26,48,49]. The "conjugation" band around 250–240 nm is believed to be characteristic for the absolute configuration of a twisted colchicone (*XXXVIII*), biphenyl (*XLIV–IL*), and those biphenyl compounds which are substituted at $C_{(2)}$, $C_{(6)}$, $C_{(2')}$ and $C_{(6')}$ by weak perturbers, as *e.g. L*, show a strong negative Cotton effect if their absolute configuration is as indicated in the formula[2–4]. For aporphines *LI* several Cotton effects have been reported[50–55] and the very intense one around 235 nm has been correlated with the absolute configuration by application of this same method[26]. The homologue (+)-multifloramine (*LII*) of same helicity of the biphenyl system gives in this wavelength range a (much smaller) negative CD band[56] and this has been cited[18] as a warning to use this "conjugation CD band" for the determination of absolute configuration. Only such compounds whose structures are very closely related are believed to give the same helicity sign relationship within this band (Table IV, Figs 1 and 5) and the reason may be that the biphenyl torsion angle is practically the same for all aporphine derivatives, whereas this differs for multifloramine (*LII*) because of the replacement of the bridging six-membered ring by a sevenmembered one.

The Cotton effect around 270 nm of aporphine is opposite to that about 235 nm, and it is smaller than the latter one. For multifloramine this Cotton effect is, however, rather intense and its sign for the (+)-enantiomer is negative[56], as it is for the aporphines of same sign of the biphenyl torsion angle.

N-Acetylcolchinolmethyl ether (*XLVI*), having the same skeleton as *LII*, gives nine Cotton effects between 320 and 190 nm, three of which (around 285–280 nm, 240–235 nm, and 225–220 nm) show up, however, only as shoulders in the CD spectra, and the sign of the Cotton effect at 260 nm is the same as that for (+)-multifloramine (*LII*), if that conformation of the cycloheptadiene ring is adopted in which the —NRR′ group is in a quasiequatorial position. Also the magnitudes of these Cotton effects are identical. The CD spectra of *XLIV* and *XLV* are completely analogous.

From the CD spectrum of colchicone[57] (*XXXVIII*) (having an eliminated chiral center at $C_{(7)}$ but, in spite of that, a very similar CD curve to that of colchicine (*VIII*)) (Table III, Fig. 1), it is to be seen that the chirality of colchicine compounds and their derivatives with maintained aromatic ring C is only due to the polysubstituted biphenyl system (atropoisomery).

For the 8,10-dibromo compound *XLVII* this same conformation becomes very improbable because of the steric interaction of the —NRR′ group with the Br atom at $C_{(8)}$, and the strong CD band at 270 nm which is positive may mirror this change of conformation. Such an interpretation of the sign inversion of the Cotton effect in question is reasonable, since the two bromo atoms are arranged symmetrically to the "long axis" of the biphenyl chromophore. For higher energetic transitions these bromo substituents will, however, be of greater influence.

In allocolchiceine (*XLVIII*) and its methyl ester *IL* similar symmetry arguments hold (Table IV, Fig. 5). By this substitution the 270 nm CD band is bathochromically shifted to 294 nm, its magnitude is of right order, and its sign is again consistent with a quasi equatorial arrangement of the $-NHCOCH_3$ group.

EXPERIMENTAL

The CD spectra were taken in ethanol solution at a concentration of appr. 1 mg/cm^3 and path length of 0·01 to 2·00 cm at room temperature with the dichrograph model 185 or the dichrograph Mark III from Jobin-Yvon (on-line connected to a PDP-8 computer).

The compounds *I*—*IL* were isolated or prepared at the Institute of Chemistry, Medical Faculty, Palacký University, Olomouc. For the verification of the purity of the measured compounds, the m.p. were re-examined and TLC was carried out.

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