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Circular Dichroism Studies of Aryl Diastereoisomers. 2. Dependence of ^1L_b Transition Sign upon the Nature of the Para Substituent in Various Chloramphenicol Derivatives

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The ^1L_b transition for (1*R*,2*R*)-chloramphenicol derivatives has a positive sign when the para substituent is H, NO_2, and C_6H_5, whereas it is negative when the substituent is CH_3CO, Br, I, cyclopropylformamido, ureido, phenylureido, NH_2CO, CH_3OCO, CN, and methylsulfonyl. The variation of sign with a remote substituent not able to influence the conformation of the molecule is unexpected. These effects are briefly discussed in connection with existing semiempirical predictive rules for aromatic transitions. The ^1L_a bands for the same compounds remain uniformly positive.

In the last two decades, the use of physical methods, such as X-ray, nuclear magnetic resonance, optical rotatory dispersion-circular dichroism, etc., has led to substantial progress in uncovering the relationship between molecular architecture and biological activity in many drug systems. Among the more rigid molecules, such as the morphine group and many of the steroids, the question of conformation, at least of the drugs themselves, has been settled reasonably well. This effort has led, in some instances, to the elaboration of fairly detailed relief maps of presumed receptor areas as a guide to further drug design,[1] although even here increased sophistication and refinement is still possible.[2] Far less satisfactory is the current situation with more flexible molecules and least of all with the extensive group of arylethanolamine drugs such as are typified by chloramphenicol, ephedrine, metaraminol, etc. Despite these uncertainties, receptor theories have been proposed for a number of these drugs by presuming that the receptor "freezes" the drug into the active conformation.[3] The resemblence between this active conformation and the shape of the molecule in dilute hydroxylic solvents is an important question under active study. Earlier work, in part from this laboratory, has demonstrated the power of combining X-ray data, nmr measurements, and CD data in working out the solution conformation of the tetracycline antibiotics[4-6] and the erythromycin macrolide antibiotics.[7,8] Attempts to carry out similar studies with the chloramphenicol-ephedrine, etc., group proved a great deal more difficult, primarily because of the unsettled state of our understanding of the CD spectra of flexible aromatic chromophores.[9]

It is a truism in ORD-CD work that knowledge of absolute configuration allows determination of conformation and vice versa. The two factors cannot ordinarly be solved simultaneously. Thus, a knowledge of the factors influencing the spectra of a series of drugs of common conformation and absolute configuration is necessary before one can turn confidently to the analysis of newer substances.

Many chiroptical (ORD-CD) studies have been reported in recent years in an attempt to find convenient, generally applicable means of assigning absolute stereochemistry of aryl compounds without resorting to laborious degradation schemes. (For recent reviews, *cf.* ref 10.) Because of the inherent complexity of the aromatic transitions, general rules and useful semiempirical relationships similar to the octant rule have been slow to emerge. Several recent proposals have been made, including three quadrant rules,[11-13] a sector rule,[14] and a mathematical treatment based upon coupled oscillator theory.[15]

One quadrant rule[11] emphasized the ^1L_a bands (equivalent to the benzene band at about 220 nm) and has been applied successfully to the *Amaryllis* bases, but the rule is not uniformly useful because exceptions occur when the ^1L_a and ^1L_b bands (the latter are equivalent to the benzene band at 262 nm) have the same absolute sign. The other two quadrant rules[12,13] utilize the weak ^1L_b bands. The ^1L_b bands are also not uniformly useful because numerous exceptional cases have now been reported[11,16] in which the sign of the ^1L_b bands is opposite for two closely related compounds of identical absolute configuration and whose conformation appears to be the same. The sector rule[14] presents useful warnings about the application of quadrant rules to rigid systems, which are by nature inherently twisted, and is designed to be used in rigid molecules. The coupled oscillator theory[15] is complex to apply.

Of the four diastereoisomeric chloramphenicols I-IV, only the 1*R*,2*R* derivative IV possesses useful antibiotic potency.[17] Further work has shown that the binding of chloramphenicol derivatives to susceptible ribosomes is stereospecific.[18-20] Alone among the major antibiotics, chloramphenicol is prepared by total synthesis and variations in the synthesis have led to the preparation of an extensive number of analogs. All of these materials require optical resolution and the investigator must be secure in the knowledge that he has selected the appropriate diastereoisomer before meaningful structure-activity analyses can be elaborated. The ephedrines were chosen as representatives of an analogous series where the same general considerations apply and where considerable exploration of stereochem-

istry and biological activity has been carried out.[21]

In the first paper in this series,[9] it was pointed out that ORD was much less useful than CD in this class of chromophore because extensive peak overlap in the ORD spectrum prevented secure assignment of sign to the various aromatic bands. It was further shown that the absolute configuration in both series could be assigned confidently from the CD spectrum in methanol solution provided both the sign and intensity of the ^1L_b band were considered. The solution conformation of chloramphenicol has been proposed from both X-ray[22] and nmr[23] data. Ephedrine has been studied similarly by nmr.[24] It has been concluded that the solution conformation differs in the two series. How, then, do we account for the CD correlation in the two series? The work reported in this paper was undertaken in an attempt to rationalize this apparent anomaly. In the earlier work[9] the examples contained para substituents limited to H and NO_2. If the side-chain conformations are indeed different, then the agreement in signs must be attributed to some effect not strictly dependent upon solution conformation. One of the possible explanations for the experimental results involves a consideration of the possible effect of a *p*-NO_2 group in reversing the expected sign because of some electronic effect. According to Moscowitz,[25] the rotatory strength of the aromatic transition is given by the expression

$$R = \mu_e \mu_m \cos\theta$$

where R is the rotatory strength, μ_e is the electric transition moment vector, μ_m is the magnetic transition moment vector, and θ is the angle between the two vectors. The sign of the rotation should, then, be sensitive to the direction of the electric transition vector, whether it be directed in the plane of the aromatic ring *toward* or *away* from the side chain. Because of the symmetry of the ring system in this series, the magnetic vector moment should not play a dominant role. These considerations are illustrated in Figure 1. It is immediately apparent that rotation of the aromatic ring about the R-S.C. axis will return the magnetic vector to the same orientation as that in the R-S.C. example and the effective sign will be the same. The electric vector, however, remains oriented in the same direction by this operation. As a first approximation, the direction of the electric transition vector should be the dominant influence in determining the sign of the Cotton effect if the two vectors are reasonably similar in absolute magnitude. If this analysis be correct, it should be possible to invert the sign of the ^1L_b Cotton effect for substances of constant absolute configuration and identical conformation by altering the electron-attracting and -releasing properties of the distant para substituent. The para substituent is well situated for electronic interaction with the benzylic carbon but is too distant to affect the rotamer population density. Measurement of appropriately substituted derivatives was undertaken. This paper presents spectra which, however, are not explicable readily by any of the presently available semi-

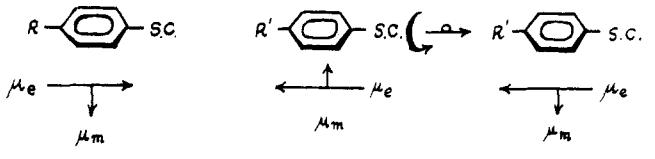


Figure 1. Electric and magnetic transition vectors for aryl chromophores of the chloramphenicol–ephedrine type. R is electron donating and R' is electron attracting.

Table I

Derivative	Para substituent	Sign of ^1L_b band	Sign of ^1L_a band
I (1*R*,2*S*)	NO_2	+	–
II (1*S*,2*R*)	NO_2	–	+
III (1*S*,2*S*)	NO_2	–	–
IV (1*R*,2*R*)	NO_2	+	+
V (1*R*,2*R*)	H	+	+
VI (1*S*,2*S*)	H	–	–
VII (1*R*,2*R*)	CH_3CO–	–	+
VIII (1*R*,2*R*)	NH_2CO–	*a*	+
IX (1*R*,2*R*)	NH_2–	*a*	+
X (1*R*,2*R*)	C_6H_5	+	+
XI (1*R*,2*R*)	c-PrCONH–	(–) at 286 nm	(+) at 242 nm
XII (1*R*,2*R*)	Br	–	+
XIII (1*R*,2*R*)	I	–	+
XIV (1*R*,2*R*)	–CN	–	+
XV (1*R*,2*R*)	CH_3SO_2–	–	+
XVI (1*R*,2*R*)	NH_2CONH–	–	+
XVII (1*R*,2*R*)	$C_6H_5NHCONH_2$–	–	+
XVIII (1*R*,2*R*)	CH_3O_2C–	Unsure	+
XIX (1*R*,2*R*)	CH_3OCONH–	–	+
XX (1*S*,2*S*)	C_6H_5	–	–

[a] Too weak for accurate measurement.

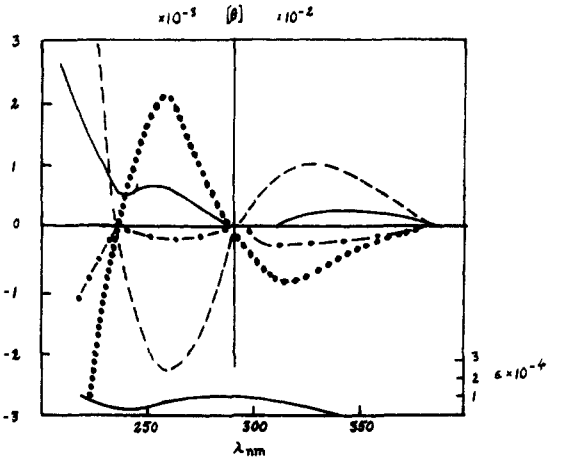


Figure 2. CD spectra of the four diastereoisomeric chloramphenicol isomers in methanol: I (1*R*,2*S*) (- - -), II (1*S*,2*R*) (· · ·), III (1*S*,2*S*) (· - · -), and IV (1*R*,2*R*) (—).

empirical rules but which do show that the sign of the ^1L_b band is dependent in some complex way upon the nature of the para substituent. The ^1L_a bands do not show this dependence. The results are summarized in Table I and are illustrated in Figures 2–6.

The CD *vs.* uv spectra of the four diastereoisomeric chloramphenicols I–IV are illustrated in Figure 2 for convenience and to include new, and more reliable, data for the ^1L_a transition (*vide infra*).[9] The ^1L_b band is expected at about 330 nm by use of the generalization that the ^1L_a and ^1L_b uv bands of benzene are shifted about equally by the introduction of auxochromic substituents.[26] The n–π^* transition of the NO_2 group probably lies in the same region and may help account for the broadness of the band. The intense band at 274 nm is the ^1L_a band. In the spectrum of natural chloramphenicol (IV, 1*R*,2*R*), both bands are positive, as previously reported.[9] In order to make a closer comparison with the ephedrines and to examine the special role, if any, of the NO_2 and C_3OH groups, the corresponding spectra of compounds V and VI, where the para substituent is H, were measured. From inspection of Figure 3 it is clear that the ^1L_b band at 260 nm and the ^1L_a band at 217 nm correlate exactly in sign with the corresponding

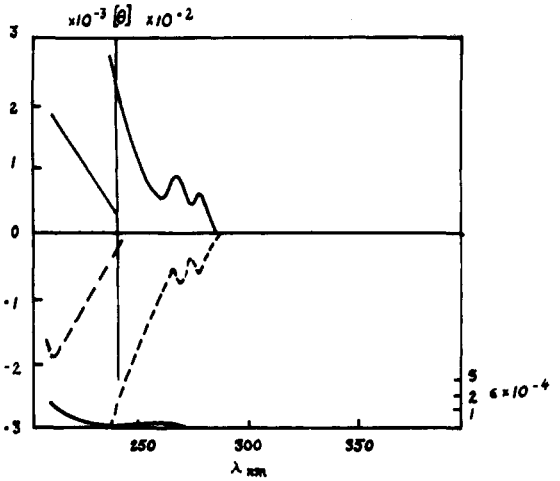


Figure 3. CD spectra of enantiomeric chloramphenicol derivatives V (1*R*,2*R*) (—) and VI (1*S*,2*S*) (- - -).

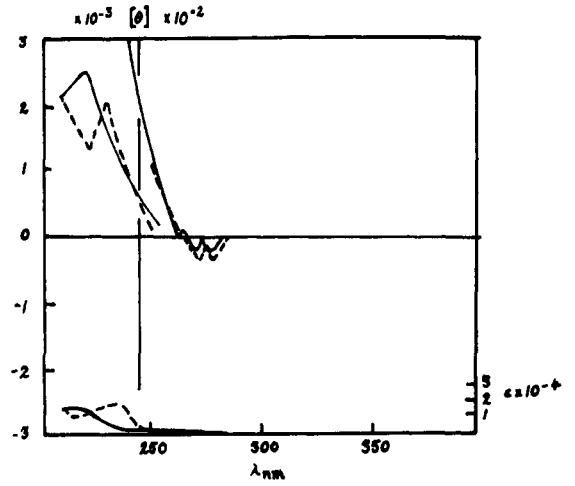


Figure 4. CD spectra of chloramphenicol derivatives XII (R = Br) (—) and XIII (R = I) (- - -).

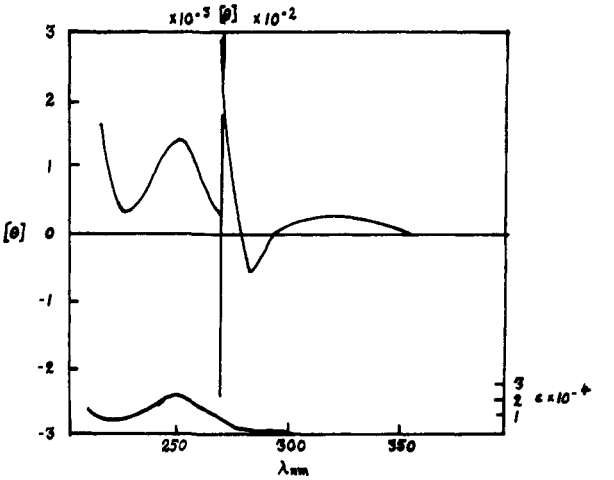


Figure 5. CD spectrum of chloramphenicol derivative VII (R = $COCH_3$) in methanol.

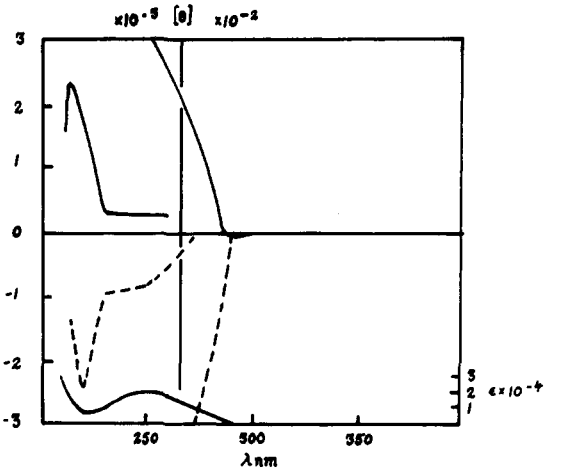


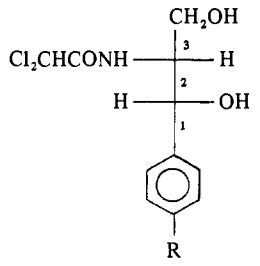
Figure 6. CD spectra of enantiomeric chloramphenicol derivatives X (1*R*,2*R*) (—) and XX (1*S*,2*S*) (- - -) in methanol.

chloramphenicols. This agrees with the earlier conclusion that the ^1L_b band reliably reflects stereochemistry when R = H or NO_2 but does not support the hypothesis that agreement between series is fortuitous because of a special electronic effect of the *p*-NO_2 group. This effect remains, at present, unexplained but inspection of the table clearly shows that the para substituent in many other cases does lead to sign inversion!

The *p*-amino derivative IX was next examined to evaluate the effect of electron-releasing substituents. Despite repeated measurements, we were unable to determine the ^1L_b band with satisfactory precision because of the unfavorable $\Delta\epsilon/\epsilon$ ratio for this substance. The ^1L_b band was expected at about 285 nm.[27] The electron-transfer band at 242 nm and the ^1L_a band at about 210 nm were both positive. Because of this failure, the spectra of the *p*-Br and *p*-I analogs (XII and XIII) were measured (Figure 4). The ^1L_b bands at about 270 nm are clearly negative for both! Thus, the implications in the Moscowitz equation are borne out by experiment. It is apparent that not only must stereochemistry be considered in the aromatic series but also the electronic character of the ring substituents, even when distant from the asymmetric centers. It is significant that the ^1L_a bands of these three substances remain positive.

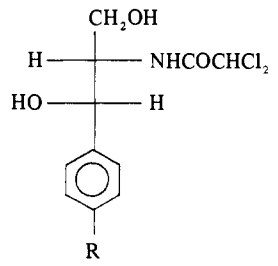
In acylated *p*-aminochloramphenicol derivatives, the nonbonded electrons conjugate with the acyl carbonyl group as well as with the ring. Reference to the CD spectra of analogs XI (*p*-cyclopropylformamido-), XVI (*p*-ureido-), XVII (*p*-3-phenylureido-), and XIX (*p*-CH_3OCONH-) as well as the electronically related analog VIII (*p*-NH_2CO-) shows that these substitutions lead uniformly to sign inversion with respect to the ^1L_b band while the ^1L_a band remains positive.

Somewhere between the extremes represented by *p*-NO_2 and the *p*-halo and acylamino derivatives, sign inversion occurs. Several additional spectra have been measured in an attempt to locate this on an electronegativity scale. The *p*-CH_3CO substituent of VII is strongly electron withdrawing. The spectrum is illustrated in Figure 5. The broad positive band at about 320 nm is the n-π^* transition. The ^1L_b band occurs at 286 nm and is negative in sign. The electron-transfer band at 250 nm and the ^1L_a band at about 210 nm are both positive. The *p*-CH_3OCO derivative XVIII also has a strongly electron-withdrawing group in the para position and the ^1L_b band at 284 nm is negative, while the ^1L_a band at 238 nm is positive. The *p*-CN (XIV) and *p*-methylsulfonyl (XV) derivatives also contain electron-withdrawing groups and, once again, negative signs are seen for the ^1L_b transitions. The *p*-C_6H_5 analog of chloramphenicol X is homoconjugatively similar to *p*-H, but the net electronic interaction should be withdrawal. This derivative has a positive ^1L_b band at about 254 nm. Its enantiomer XX gives an enantiomeric spectrum (Figure 6).



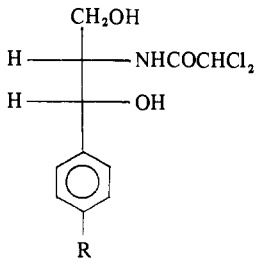
$D_g(-)$-*threo*-(1*R*,2*R*)

IV, R = NO_2
V, R = H
VII, R = CH_3CO–
VIII, R = –$CONH_2$
IX, R = NH_2
X, R = C_6H_5
XI, R = c-Pr-CONH–
XII, R = Br
XIII, R = I
XIV, R = –CN
XV, R = CH_3SO_2–
XVI, R = NH_2CONH–
XVII, R = $C_6H_5NHCONH$–
XVIII, R = CH_3O_2C–
XIX, R = CH_3OCONH–

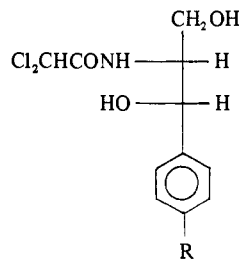


$L_g(+)$-*threo*-(1*S*,2*S*)

III, R = NO_2
VI, R = H
XX, R = C_6H_5



$L_g(+)$-*erythro*-(1*R*,2*S*)
I, R = NO_2



$D_g(-)$-*erythro*-(1*S*,2*R*)
II, R = NO_2

These spectra demonstrate that, for a relatively limited series, electron-donating groups (Br and I) invert the ^1L_b band as do acylamino groups, while strong electron-withdrawing groups give a mixed effect with some (NO_2 and C_6H_5) giving the same sign as H and others (CN, CH_3CO, CH_3SO_3) causing inversion. There is no simple, readily discernible relationship between the electron donating or resonance integral of the various substituents and the sign of the ^1L_b transition. The electronic or inductive effect is undoubtedly important but the underlying phenomenon requires more study.

The ^1L_b band is still useful in assigning stereochemistry, but only when the model substance chosen for comparison is selected with great care, and these results place very definite restraints upon the choice to be made. Until more spectra are in hand from which to delineate more precisely the basic factors underlying this phenomenon, proposal of additional empirical rules and diagrams for this transition is, indeed, "otiose."[16] Since the sign is not constant with constant stereochemistry, no quadrant or sector rule is applicable without considering this factor. The accompanying paper presents an alternate solution to the stereochemical problem by changing the chromophore to the Cupra A, transitions wherein these present ambiguities disappear.[28]

The ^1L_a bands in this series are more regular and seem to be insensitive to the nature of the para substituent. These more intense bands are uniformly positive when the side chain is 1*R*,2*R*. The wisdom of restricting semiempirical correlative rules to the ^1L_a band is emphasized by these findings.[11] Moffitt has predicted on theoretical grounds that the ^1L_a bands will be less sensitive to inductive effects than the ^1L_b.[29] This prediction was directed toward the uv spectrum but appears to hold for the CD as well.

In the spectrum of erythro analog I, the ^1L_a band is negative in sign while the ^1L_b band is positive (Figure 1). In this case the "normal" sign alternation most commonly[11] (but not invariably[11,16]) seen for the ^1L_a–^1L_b bands is observed. The apparent anomaly pointed out in our earlier work[9] in which the ^1L_a bands for I and III were inexplicably positive has been explained by further work. This was caused by an instrument artifact resulting from use of solutions that were too concentrated in an attempt to overcome the unfavorable $\Delta\epsilon/\epsilon$ ratios for these materials. When special care is taken to avoid dangerous concentrations, as was done throughout the present study, such problems are avoided and the new data for the ^1L_a transitions of I–IV are given in the Experimental Section.

The constancy of the ^1L_a bands in this study suggests the potential applicability of semiempirical relationships, such as that of DeAngelis[11] (which, incidentally, satisfactorily rationalizes the spectra of the chloramphenicols), but the relative paucity of data presently available in the literature for this transition in flexible monochromophoric series and the relatively dismal experience with the ^1L_b transition leads one to prefer, at present, not to overemphasize the significance of this present correlation but rather to produce more examples and, meanwhile, to use the convenient and, apparently, trustworthy Cupra A technique detailed in the accompanying communication.

Experimental Section

The derivatives used in this study were of spectroscopic purity and were gifts of The Parke Davis Co. The CD spectra were measured with a JASCO Model ORD/UV/CD-5 instrument at ambient temperature (29° in the sample chamber) in deg cm^2/dmole. Samples were measured in spectral grade methanol at the specified concentrations. Uv spectra were measured on a Cary Model 15 recording spectrophotometer in nm.

L-*erythro*-(1*R*,2*S*)-1-*p*-Nitrophenyl-2-dichloroacetamido-1,3-propanediol (I): CD (*c* 0.046, MeOH) $[\theta]_{290}$ 0, $[\theta]_{260}$ −2310, $[\theta]_{235}$ 0, $[\theta]_{218}$ +22,160*.

D-*erythro*-(1*S*,2*R*)-1-*p*-Nitrophenyl-2-dichloroacetamido-1,3-propanediol (II): CD (*c* 0.050, MeOH) $[\theta]_{285}$ 0, $[\theta]_{260}$ +1920, $[\theta]_{240\text{-}235}$ 0, θ_{220} −11,520, θ_{212} 0*.

L-*threo*-(1*S*,2*S*)-1-*p*-Nitrophenyl-2-dichloroacetamido-1,3-propanediol (III): CD (*c* 0.054, MeOH) $[\theta]_{275}$ −790, $[\theta]_{250}$ −1580, $[\theta]_{228}$ 0, $[\theta]_{215}$ −9480*.

D-*threo*-(1*R*,2*R*)-1-*p*-Nitrophenyl-2-dichloroacetamido-1,3-propanediol (IV): uv ϵ_{274} 9990, ϵ_{210} 12,840* (MeOH); CD (*c* 0.01948, MeOH) $[\theta]_{290}$ 0, $[\theta]_{250}$ +5200, $[\theta]_{230}$ +3285, $[\theta]_{212}$ +25,180*.

D-*threo*-(1*R*,2*R*)-1-Phenyl-2-dichloroacetamido-1,3-propanediol (V): uv ϵ_{255} 286 (br), ϵ_{210} 11,650* (MeOH); CD (*c* 0.974, MeOH) $[\theta]_{275}$ 0, $[\theta]_{268}$ +520, $[\theta]_{265}$ +245, $[\theta]_{260}$ +725, $[\theta]_{258}$ +440, $[\theta]_{253}$ +780, $[\theta]_{245}$ +12,440*; CD (*c* 0.195, MeOH) $[\theta]_{230}$ +7255*; CD (*c* 0.019, MeOH) $[\theta]_{230}$ +7068, $[\theta]_{212}$ +18,375*.

L-*threo*-(1*S*,2*S*)-1-Phenyl-2-dichloroacetamido-1,3-propanediol (VI): CD (*c* 0.159, MeOH) $[\theta]_{295}$ 0, $[\theta]_{268}$ −690, $[\theta]_{265}$ −400, $[\theta]_{264}$ −810, $[\theta]_{258}$ −605, $[\theta]_{225}$ −9800*; CD (*c* 0.016, MeOH) θ_{217} −19,600*.

D-*threo*-(1*R*,2*R*)-1-*p*-Acetophenyl-2-dichloroacetamido-1,3-propanediol (VII): uv ϵ_{290} 850 (br), ϵ_{252} 15,475, ϵ_{210} 16,675* (MeOH); CD (*c* 0.989, MeOH) $[\theta]_{360}$ 0, $[\theta]_{315}$ +283, $[\theta]_{295}$ 0; CD (*c* 0.198, MeOH) $[\theta]_{295}$ 0, $[\theta]_{286}$ −535, $[\theta]_{280}$ 0; CD (*c* 0.20, MeOH) $[\theta]_{280}$ 0, $[\theta]_{250}$ +13,350, $[\theta]_{225}$ +2670, $[\theta]_{214}$ +16,560*.

D-*threo*-(1*R*,2*R*)-1-*p*-Carboxamidophenyl-2-dichloroacetamido-

1,3-propanediol (VIII): uv ϵ_{300} 235, ϵ_{270} 1110 (sh), ϵ_{236} 14,445, ϵ_{210} 13,100* (MeOH); CD (*c* 0.191, MeOH) $[\theta]_{290}$ 0, $[\theta]_{250}$ +3658*; CD (*c* 0.019, MeOH) $[\theta]_{290}$ 0, $[\theta]_{235}$ +13,200, $[\theta]_{210}$ 26,050*.

D-*threo*-(1*R*,2*R*)-1-*p*-Aminophenyl-2-dichloroacetamido-1,3-propanediol (IX): uv ϵ_{285} 1170, ϵ_{242} 9960, ϵ_{210} 12,080* (MeOH); CD (*c* 0.951, MeOH) $[\theta]_{260}$ 0, $[\theta]_{245}$ +540*; CD (*c* 0.019, MeOH) $[\theta]_{260}$ 0, $[\theta]_{250}$ +3050, $[\theta]_{218}$ +10,170*.

D-*threo*-(1*R*,2*R*)-1-*p*-Phenylphenyl-2-dichloroacetamido-1,3-propanediol (X): uv ϵ_{300} 232 (infl), ϵ_{253} 20,400, ϵ_{210} 33,370* (MeOH); CD (*c* 0.195, MeOH) $[\theta]_{320}$ 0, $[\theta]_{292}$ −160, $[\theta]_{284}$ 0, $[\theta]_{280}$ +510*; CD (*c* 0.018, MeOH) $[\theta]_{260}$ +3190, $[\theta]_{230}$ +4790, $[\theta]_{217}$ +23,625, $[\theta]_{214}$ +13,400*.

D-*threo*-(1*R*,2*R*)-1-*p*-Cyclopropylformamidophenyl-2-dichloroacetamido-1,3-propanediol (XI): uv ϵ_{300} 380, ϵ_{250} 20,665, ϵ_{210} 19,990* (MeOH); CD (*c* 0.958, MeOH) $[\theta]_{295}$ 0, $[\theta]_{286}$ −260, $[\theta]_{280}$ 0; CD (*c* 0.038, MeOH) $[\theta]_{270}$ 0, $[\theta]_{242}$ +13,530, $[\theta]_{220}$ +7460, $[\theta]_{215}$ +11,510*.

D-*threo*-(1*R*,2*R*)-1-*p*-Bromophenyl-2-dichloroacetamido-1,3-propanediol (XII): uv ϵ_{260} 656 (br), ϵ_{220} 15,440 (MeOH); CD (*c* 0.925, MeOH) $[\theta]_{282}$ 0, $[\theta]_{276}$ −255, $[\theta]_{273}$ 0, $[\theta]_{270}$ −165, $[\theta]_{265}$ +90, $[\theta]_{262}$ 0, $[\theta]_{240}$ +3120*; CD (*c* 0.093, MeOH) $[\theta]_{255}$ 0, $[\theta]_{230}$ +12,230*; CD (*c* 0.019, MeOH) $[\theta]_{250}$ 0, $[\theta]_{220}$ +24,840, $[\theta]_{210}$ +21,650*.

D-*threo*-(1*R*,2*R*)-1-*p*-Iodophenyl-2-dichloroacetamido-1,3-propanediol (XIII): uv ϵ_{260} 1060 (br), ϵ_{232} 16,200, ϵ_{210} 13,530* (MeOH); CD (*c* 1.03, MeOH) $[\theta]_{285}$ 0, $[\theta]_{279}$ −325, $[\theta]_{275}$ −143, $[\theta]_{270}$ −370, $[\theta]_{263}$ 0, $[\theta]_{240}$ +5970*; CD (*c* 0.021, MeOH) $[\theta]_{240}$ +5840, $[\theta]_{230}$ +19,465, $[\theta]_{222}$ +13,300, $[\theta]_{210}$ +22,385*.

D-*threo*-(1*R*,2*R*)-1-*p*-Cyanophenyl-2-dichloroacetamido-1,3-propanediol (XIV): uv ϵ_{278} 666, ϵ_{275} 666, ϵ_{268} 880, ϵ_{260} 666, ϵ_{234} 18,730, ϵ_{210} 10,530* (MeOH); CD (*c* 0.501, MeOH) $[\theta]_{295}$ 0, $[\theta]_{280}$ −580, $[\theta]_{277}$ −220, $[\theta]_{273}$ −500, $[\theta]_{265}$ 0, $[\theta]_{250}$ +960*; CD (*c* 0.020, MeOH) $[\theta]_{233}$ +14,760, $[\theta]_{218}$ +1000, $[\theta]_{210}$ +10,000*.

D-*threo*-(1*R*,2*R*)-1-*p*-Methylsulfonylphenyl-2-dichloroacetamido-1,3-propanediol (XV): uv ϵ_{273} 1540, ϵ_{266} 1580, ϵ_{225} 15,430, ϵ_{205} 13,770* (MeOH); CD (*c* 0.919, MeOH) $[\theta]_{290}$ 0, $[\theta]_{274}$ −555, $[\theta]_{271}$ −250, $[\theta]_{268}$ −535, $[\theta]_{262}$ 0, $[\theta]_{240}$ +3875*; CD (*c* 0.018, MeOH) $[\theta]_{227}$ +15,035, $[\theta]_{216}$ +9500, $[\theta]_{210}$ +16,040*.

D-*threo*-(1*R*,2*R*)-1-*p*-Ureidophenyl-2-dichloroacetamido-1,3-propanediol (XVI): uv ϵ_{280} 630 (sh), ϵ_{242} 18,860, ϵ_{210} 14,240* (MeOH); CD (*c* 0.909, MeOH) $[\theta]_{310}$ 0, $[\theta]_{287}$ −320, $[\theta]_{270}$ +159*; CD (*c* 0.018, MeOH) $[\theta]_{236}$ +7325, $[\theta]_{220}$ +1830*.

D-*threo*-(1*R*,2*R*)-1-Phenylureidophenyl-2-dichloroacetamido-1,3-propanediol (XVII): uv ϵ_{295} 1300 (br), ϵ_{258} 40,510, ϵ_{210} 26,875* (MeOH); CD (*c* 0.163, MeOH) $[\theta]_{330}$ 0, $[\theta]_{290}$ −670; CD (*c* 0.016, MeOH) $[\theta]_{270}$ −2090, $[\theta]_{265}$ 0, $[\theta]_{250}$ +11,710, $[\theta]_{220}$ +7530*.

D-*threo*-(1*R*,2*R*)-1-*p*-Carbomethoxyphenyl-2-dichloroacetamido-1,3-propanediol (XVIII): uv ϵ_{282} 1310, ϵ_{275} 1510, ϵ_{238} 29,000, ϵ_{210} 17,480* (MeOH); CD (*c* 0.250, MeOH) $[\theta]_{300}$ 0, $[\theta]_{284}$ −445, $[\theta]_{274}$ 0, $[\theta]_{256}$ +2575*; CD (*c* 0.005, MeOH) $[\theta]_{236}$ +37,720, $[\theta]_{220}$ +11,100, $[\theta]_{210}$ +39,940*.

D-*threo*-(1*R*,2*R*)-1-*p*-Methoxycarbonylaminophenyl-2-dichloroacetamido-1,3-propanediol (XIX): uv ϵ_{275} 1010, ϵ_{240} 20,000, ϵ_{210} 12,850* (MeOH): CD (*c* 0.976, MeOH) $[\theta]_{320}$ 0, $[\theta]_{286}$ −330, $[\theta]_{280}$ −310; CD (*c* 0.488, MeOH) $[\theta]_{280}$ −330, $[\theta]_{270}$ 0, $[\theta]_{260}$ +350*; CD (*c* 0.020, MeOH) $[\theta]_{236}$ +9800, $[\theta]_{220}$ +2970, $[\theta]_{210}$ +17,220*.

L-*threo*-(1*S*,2*S*)-1-*p*-Phenylphenyl-2-dichloroacetamido-1,3-propanediol (XX): CD (*c* 0.039, MeOH) $[\theta]_{300}$ 0, $[\theta]_{275}$ −3280*; CD (*c* 0.020, MeOH) $[\theta]_{260}$ −5360, $[\theta]_{230}$ −11,920, $[\theta]_{221}$ −26,810, $[\theta]_{216}$ −13,700*.

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