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OPTICALLY ACTIVE AROMATIC CHROMOPHORES—IX[1]

OPTICAL ROTATORY DISPERSION AND CIRCULAR DICHROISM STUDIES IN THE α-ARYLETHYL SERIES

L. VERBIT

Department of Chemistry, State University of New York at Binghamton, Binghamton, New York

A. S. RAO

National Chemical Laboratory, Poona, India

and

J. W. CLARK-LEWIS

School of Physical Sciences, The Flinders University of South Australia, Bedford Park, South Australia

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Abstract—ORD and CD measurements in the UV spectral region are reported for a series of compounds possessing the α-arylethyl structure. The compounds examined are *S*-(+)-2-(*p*-tolyl)butane, *S*-(+)-2-methyl-6-(*p*-tolyl)heptane, *R*-(−)-2-(*p*-anisyl)propionic acid, *S*-(+)-3-(*p*-anisyl)butanoic acid, *S*-(+)-3-(*p*-tolyl)butanoic acid, *S*-(+)-3-(*p*-carboxyphenyl)butanoic acid, *S*-(+)-4-(*p*-tolyl)pentanoic acid, *S*-(+)-4-(*p*-tolyl)pentanol-1, and *S*-(+)-2-methyl-6-(*p*-tolyl)heptanone-4. Two positive Cotton effects, due to the ^1L_a and ^1L_b transitions of the aromatic ring are observed. Carboxyl and hydroxyl functions separated from the chiral center by at least one methylene group do not affect the sign of either aromatic Cotton band. In contrast, a carboxyl group attached directly to the chiral center results in aromatic Cotton effects of negative sign.

WITHIN the past few years considerable progress has been made in establishing the origin of Cotton effects found in the ORD and CD spectra of relatively simple molecules containing the phenyl ring. In 1965 the ^1L_b transition[2] in the 260 nm spectral region was shown unequivocally to be optically active.[3,4] More recently, the Cotton effect found in the 210–225 nm region of monosubstituted benzenes has been demonstrated to have its origin in the ^1L_a transition[2] of the aromatic ring.[5,6]

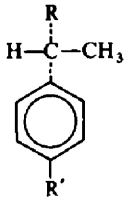
In this paper we report the results of an ORD and CD investigation of systematic structural variations in the α-arylethyl series. For most members of the series it was possible to carry out measurements through the region of UV absorption to about 210 nm.

The compounds investigated are *S*-(+)-2-(*p*-tolyl)butane, (+)-**1**; *S*-(+)-2-methyl-6-(*p*-tolyl)heptane, (+)-**2**; *R*-(−)-2-(*p*-anisyl)propionic acid, (−)-**3**; *S*-(+)-3-(*p*-anisyl)-butanoic acid, (+)-**4**; *S*-(+)-3-(*p*-tolyl)butanoic acid, (+)-**5**; *S*-(+)-3-(*p*-carboxyphenyl)butanoic acid, (+)-**6**; *S*-(+)-4-(*p*-tolyl)pentanoic acid, (+)-**7**; *S*-(+)-4-(*p*-tolyl)pentanol-1, (+)-**8**; and *S*-(+)-2-methyl-6-(*p*-tolyl)heptanone-4, (+)-**9**.

The propionic acid (−)-**3** was obtained by oxidation of (−)-angolensin with alkaline hydrogen peroxide and its configuration established[7,8] by comparison with *R*-(−)-2-phenylpropionic acid.[9] The butanoic acid homolog (+)-**4** was obtained by direct oxidation of *S*-(+)-1-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)propane.[8]

Configurational assignments were confirmed by Arndt-Eistert homologation[8] of (−)-**3** to give (+)-**4**, identical to that obtained by oxidation of the propane. Since the Arndt–Eistert synthesis has been shown to result in retention of configuration,[10] (−)-**3** and (+)-**4** are of the same absolute configuration, as indicated in the stereoformulas.

Compounds **1**, **2** and **5**–**9**, all of the *S*-(+)-designation, are derived from (+)-*ar*-turmerone[11] or (−)-curcumene[11] of established absolute configuration.



	R	R'
(+)-**1**	CH_2CH_3	CH_3
(+)-**2**	$(CH_2)_3CH(CH_3)_2$	CH_3
(−)-**3**	COOH	OCH_3
(+)-**4**	CH_2COOH	OCH_3
(+)-**5**	CH_2COOH	CH_3
(+)-**6**	CH_2COOH	COOH
(+)-**7**	CH_2CH_2COOH	CH_3
(+)-**8**	$(CH_2)_3OH$	CH_3
(+)-**9**	$CH_2COCH_2CH(CH_3)_2$	CH_3

RESULTS AND DISCUSSION

The simplest member of the present series with respect to electronic absorption bands is the hydrocarbon *S*-(+)-2-(*p*-tolyl)butane, (+)-**1**. Only the *p*-tolyl ring possesses transitions in the spectral region above ca. 200 nm. The ORD curve of (+)-**1** in methanol solution is shown in Fig. 1. A weak multiple Cotton effect associated with the ^1L_b transition is observed in the 270 nm region. Measurements at shorter wavelength reveal the first extremum of a relatively intense positive Cotton effect due to the ^1L_a transition near 210 nm.

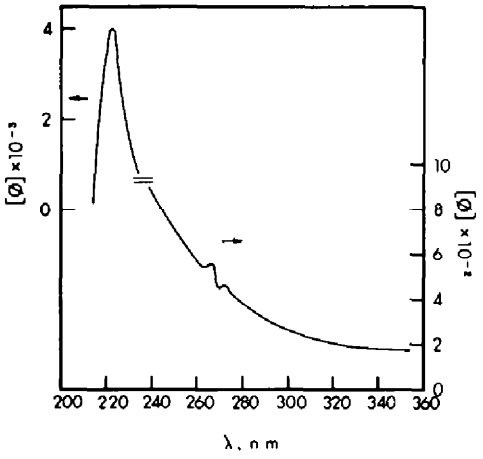


FIG. 1 ORD in methanol solution of *S*-(+)-2-(*p*-tolyl)butane, (+)-**1**.

The only other reported observation of a Cotton effect in simple alkyl-substituted benzenes is that of a very weak one in the 260 nm region of the related compound *S*-(+)-2-phenylbutane.[4] However, Verbit[4] was not able to carry out ORD measurements below 230 nm and did not observe the ^1L_a Cotton effect. Even with our improved instrumentation it was not possible to extend measurements much below 210 nm due to the high molecular absorptivity and low rotational strength of the alkyl-substituted benzenes. Indeed, the unfavorable anisotropy ratio, $\Delta\varepsilon/\varepsilon$, precluded CD measurements even though such measurements were possible for other members of the series.

ORD data for the related branched hydrocarbon (+)-**2** are similar to that for (+)-**1** and are given in the Experimental section.

The homologous *para*-methoxyphenyl carboxylic acids (−)-**3** and (+)-**4** are of interest because of the difference in their signs of rotation even though both acids are of the same configuration. A similar situation occurs in the corresponding 2-phenylpropionic acid and 3-phenylbutanoic acid of the same configuration.[10] For configurationally identical homologues such a difference in sign of the D-line rotation is expected to indicate that the ORD curve of one compound is shifted to higher (or lower) rotational values so that the curve in the visible spectral region lies on the opposite side of the zero rotation axis. However, in the region of electronic absorption the corresponding Cotton effect of homologous molecules having the same configuration should be of similar sign. It is well established for rigid systems such as steroids that structurally related compounds of *enantiomeric* configuration will exhibit Cotton effects of *opposite* sign, i.e. the ORD curves will be mirror images of each other.[12]

The ORD curves in the UV region of (−)-**3** and (+)-**4** are quasi-enantiomeric (see Experimental). The opposite signs of the Cotton effects are clearly seen in the corresponding CD spectra, Fig. 2.† The Cotton effects near 270 and 230 nm are due to

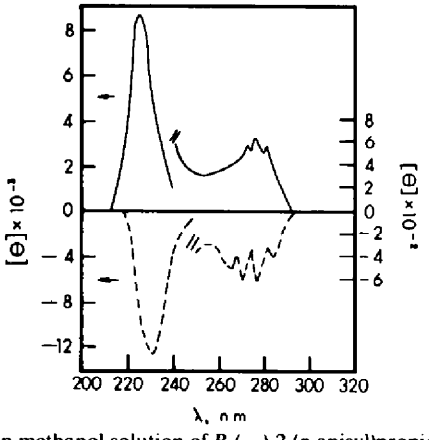


FIG. 2 CD spectra in methanol solution of *R*-(−)-2-(*p*-anisyl)propionic acid, (−)-**3**, (dashed curves), and *S*-(+)-3-(*p*-anisyl)butanoic acid, (+)-**4**, (solid curves). See footnote † on this page for explanation of the ordinate scales.

† Because of the relative weakness of the Cotton effect in the 270 nm region, the CD curves (*which are continuous*) were divided into two parts: the right-hand ordinate refers to the longer wavelength Cotton effects and the left-hand ordinate refers to the bands below ca. 240 nm.

at least two different electronic transitions.[3–6] Since (−)-**3** and (+)-**4** are known to be of the same configuration† it is particularly significant that under identical conditions of solvent, temperature, and concentration the two compounds possesses CD spectra which are virtual mirror images (Fig. 2). The effect of the carboxyl group at the chiral center is a profound one since, for (+)-**4** and, as we shall show, for other compounds of the same series having a carboxyl, hydroxyl, or carbonyl function one or more carbons removed, the aromatic Cotton effects are positive as far as can be ascertained.

The ORD and CD spectra, Fig. 3, of *S*-(+)-3-(*p*-tolyl)butanoic acid, (+)-**5**, are similar to those of the *para*-methoxy analog (+)-**4**, thus indicating no important contribution by the *n*-electrons of the *para*-methoxy group to the sign of either aromatic Cotton effect. However, the absorption bands of (+)-**5** are shifted hypsochromically compared to (+)-**4**.

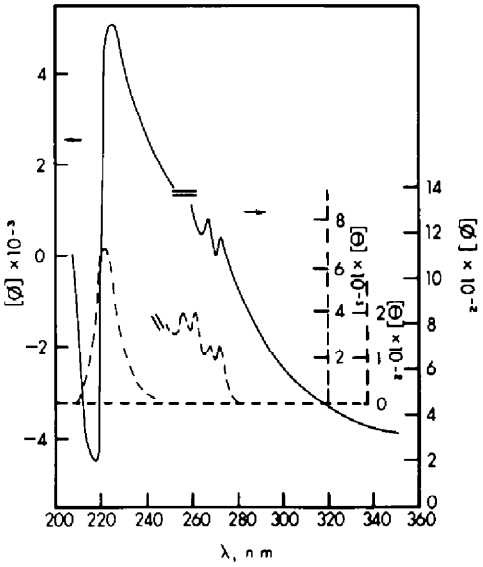


FIG. 3 ORD (solid curves) and CD (dashed curves) spectra in methanol solution of *S*-(+)-3-(*p*-tolyl)butanoic acid, (+)-**5**.

Since the availability of *n*-electrons in the *para*-position of the phenyl ring seems to have no pronounced effect on the observed optical activity in the present system,[13] it was of interest to examine a *para*-substituent possessing π^*-orbitals. The *para*-carboxyphenyl analog of (+)-**4** and (+)-**5** was investigated and the ORD results for (+)-**6** (see Experimental) were found to be similar to that of its *para*-methoxy and *para*-methyl analogs. As in the case of the *para*-methoxy group relative to a *para*-methyl, a bathochromic shift is observed for the *para*-carboxy substituent.

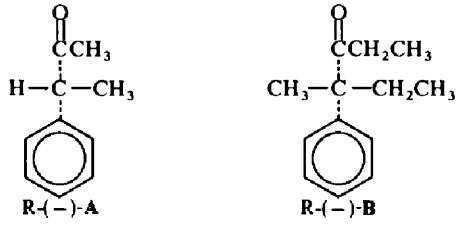
The observed inversion of the Cotton effect when the carboxyl group is directly attached to the chiral center compared to when it is one carbon removed required the investigation of the case when the carboxyl function is separated from the chiral center by two carbon atoms. *S*-(+)-4-(*p*-tolyl)pentanoic acid, (+)-**7**, was investigated and the ORD results (see Experimental) found to be similar to that of the next

† Although application of the Sequence Rule leads to the *R* and *S*-designations for (−)-**3** and (+)-**4**, respectively, both compounds are of the same absolute configuration.[7,8,10]

lower homologue, (+)-**5**. In addition, the ORD data do not differ markedly from that of the hydrocarbon (+)-**1**.

Replacement of the carboxyl function of (+)-**7** by a CH_2OH group gives the pentanol (+)-**8**. Since the absorption region of primary alcohols occurs below 200 nm,[14] the ORD curve of (+)-**8** should resemble that of the saturated hydrocarbons (+)-**1** and (+)-**2**. The data for (+)-**8** (see Experimental) agree with this, indicating that a carboxyl or hydroxyl group separated from the chiral center by two or three saturated carbons causes a negligible perturbation of the rotatory dispersion in the region above ca. 210 nm.

The aryl ketone (+)-**9** was of particular interest because of its structural similarity to the hydrocarbon (+)-**2** and also because of its homologous relationship to the α-phenyl ketones (−)-**A**[15] and (−)-**B**,[16] whose ORD curves have been reported.



Although the instrumentation available to these earlier workers[16,17] did not permit measurements into the aromatic absorption region, the first extremum of the carbonyl Cotton effect near 300 nm was reached and found to be negative for both (−)-**A** and (−)-**B**.

The ORD and CD spectra in the ultraviolet absorption region of (+)-**9** are shown in Fig. 4. A relatively intense positive Cotton effect near 286 nm due to the n–π*

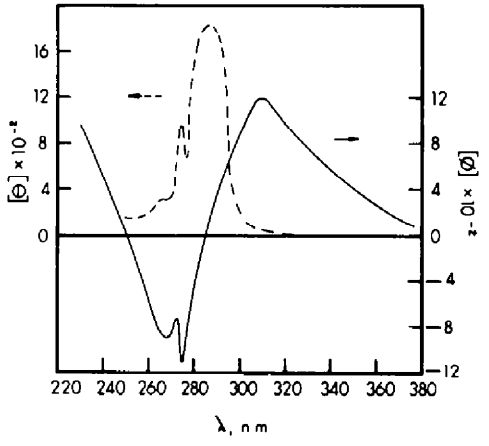
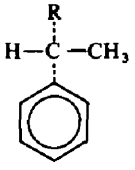


FIG. 4 ORD (solid curve) and CD (dashed curve) spectra in methanol solution of *S*-(+)-2-methyl-6-(*p*-tolyl)heptanone-4, (+)-**9**.

transition of the carbonyl group overlaps the ^1L_b transition and obscures the sign of the latter band. Examination of the CD spectrum (dashed curve) clearly indicates that both transitions are positive. Hence, with respect to the α-phenyl ketones (−)-**A** and (−)-**B**, the data for (+)-**9** show that inversion of the carbonyl Cotton effect occurs

in the α-arylethyl system when the chromophore is moved one carbon away from the chiral center.

In summary, the optically active α-phenylethyl system in which the aromatic ring may be *para*-substituted by a CH_3, OCH_3, or COOH group, exhibits two Cotton



effects associated with the ^1L_a and ^1L_b transitions of the aromatic ring in the accessible spectral region above ca. 210 nm. For the *S*-configuration both of these aromatic Cotton effects are positive when R = alkyl, carboxyalkyl, or hydroxyalkyl. When R = COOH, both Cotton effects are negative.

EXPERIMENTAL

ORD and CD measurements were carried out using a JASCO Model ORD/UV/CD-5 instrument. The conditions for measurements were those described earlier.[17] The sensitivity in the CD mode has been increased to 1×10^{-5} ΔA per mm of chart paper. The entire optical system and cell compartment were under a constant N_2 purge obtained from the boil-off of liquid N_2. All measurements were made at a sample temperature of 27°.

S-(+)-2-(p-*Tolyl*)*butane*, (+)-**1** (Fig. 1). $[\alpha]_D^{27°}$ +30·3° (*c* 0·032, MeOH); ORD in MeOH (*c* 0·032). $[\phi]_{600}$ +45·3°, $[\phi]_{500}$ +67·7°, $[\phi]_{400}$ +116°, $[\phi]_{300}$ +260°, $[\phi]_{273}$ +460° (pk), $[\phi]_{270}$ +450° (tr), $[\phi]_{267}$ +560° (pk), $[\phi]_{264}$ +550° (tr), $[\phi]_{250}$ +730°, $[\phi]_{223}$ +4000° (pk), $[\phi]_{214}$ 0°.

S-(+)-2-*Methyl*-6-(p-*tolyl*)*heptane*, (+)-**2**. $[\alpha]_D^{27°}$ +30·9° (*c* 0·95, MeOH); ORD in MeOH (*c* 0·266). $[\phi]_{600}$ +61·4°, $[\phi]_{500}$ +98·2°, $[\phi]_{400}$ +195°, $[\phi]_{300}$ +480°, $[\phi]_{273}$ +860° (pk), $[\phi]_{270}$ +830° (tr), $[\phi]_{263}$ +1000° (pk), $[\phi]_{261}$ +970° (tr), $[\phi]_{250}$ +1200°, $[\phi]_{224}$ +3900° (pk), $[\phi]_{215}$ 0°.

R-(−)-2-(p-*Anisyl*)*propionic acid*, (−)-**3**, (Fig. 2). $[\alpha]_D^{27°}$ −67·0° (*c* 1·10, MeOH); ORD in MeOH (*c* 0·332). $[\phi]_{600}$ −115, $[\phi]_{500}$ −190, $[\phi]_{400}$ −330, $[\phi]_{300}$ −1000, $[\phi]_{285}$ −1800 (tr), $[\phi]_{282}$ −1370° (pk), $[\phi]_{280}$ −1650° (tr), $[\phi]_{250}$ −3550°, $[\phi]_{239}$ −7200° (tr), $[\phi]_{231}$ 0°, $[\phi]_{222}$ +10,000° (pk), $[\phi]_{213}$ +5300°.

CD in MeOH, $3·66 \times 10^{-4}$M; $[\theta]_{284}$ −430 (max), $[\theta]_{277}$ −610 (max), $[\theta]_{271}$ −610 (max), $[\theta]_{266}$ −510 (max), $[\theta]_{231}$ −12,600 (max), $[\theta]_{218}$ 0.

CD in heptane, $3·11 \times 10^{-4}$M; $[\theta]_{284}$ −890 (max), $[\theta]_{277}$ −940 (max), $[\theta]_{274}$ −770 (max), $[\theta]_{271}$ −850 (max), $[\theta]_{231}$ −19,500 (max), $[\theta]_{220}$ 0.

S-(+)-3-(p-*Anisyl*)*butanoic acid*, (+)-**4**, (Fig. 2). $[\alpha]_D^{27°}$ +36·5° (*c* 1·02, MeOH); ORD in methanol (*c* 0·348).

$[\phi]_{600}$ +70·1°, $[\phi]_{500}$ +110°, $[\phi]_{400}$ +210°, $[\phi]_{300}$ +650°, $[\phi]_{284}$ +1200° (pk), $[\phi]_{280}$ +950° (tr), $[\phi]_{276}$ +1100° (pk), $[\phi]_{272}$ +850° (tr), $[\phi]_{240}$ +3500°, $[\phi]_{231}$ +5300° [pk], $[\phi]_{225}$ 0°, $[\phi]_{210}$ −2300°.

CD in MeOH, $3·60 \times 10^{-4}$M; $[\theta]_{280}$ +550 (max), $[\theta]_{276}$ +650 (max), $[\theta]_{270}$ +550 (max), $[\theta]_{240}$ +710, $[\theta]_{225}$ +7000 (max), $[\theta]_{211}$ 0.

CD in heptane, $2·81 \times 10^{-4}$M; $[\theta]_{283}$ +400 (max), $[\theta]_{276}$ +570 (max), $[\theta]_{250}$ +190, $[\theta]_{226}$ +10,600 (max), $[\theta]_{213}$ 0.

S-(+)-3-(p-*Tolyl*)*butanoic acid*, (+)-**5**, (Fig. 3). $[\alpha]_D^{27°}$ +43·1° (*c* 1·30, MeOH); ORD in MeOH, (*c* 0·13). $[\phi]_{600}$ +70·0°, $[\phi]_{500}$ +115°, $[\phi]_{300}$ +600°, $[\phi]_{273}$ +1200° (pk), $[\phi]_{271}$ +1100° (tr), $[\phi]_{268}$ +1260° (pk), $[\phi]_{265}$ +1190° (tr), $[\phi]_{240}$ +2800°, $[\phi]_{226}$ +5100° (pk), $[\phi]_{221}$ 0°, $[\phi]_{218}$ −4500° (tr), $[\phi]_{208}$ 0°.

CD in MeOH, $7·31 \times 10^{-3}$M; $[\theta]_{272}$ +130 (max), $[\theta]_{268}$ +130 (max), $[\theta]_{262}$ +200 (max), $[\theta]_{257}$ +200 (max), $[\theta]_{240}$ +540, $[\theta]_{222}$ +6800 (max), $[\theta]_{212}$ 0.

S-(+)-3-(p-*Carboxylphenyl*)*butanoic acid*, (+)-**6**. $[\alpha]_D^{27°}$ +37·6° (*c* 1·5, MeOH); ORD in MeOH, (*c* 0·05). $[\phi]_{600}$ +71·9°, $[\phi]_{500}$ +125°, $[\phi]_{400}$ +217°, $[\phi]_{300}$ +670°, $[\phi]_{277}$ +1220° (pk), $[\phi]_{275}$ +1190° (tr), $[\phi]_{270}$ +1230° (pk), $[\phi]_{267}$ +1220° (tr), $[\phi]_{243}$ +5700° (pk), $[\phi]_{232}$ 0°, $[\phi]_{220}$ −1400°, $[\phi]_{210}$ 0°.

S-(+)-4-(p-*Tolyl*)*pentanoic acid*, (+)-**7**). $[\alpha]_D^{27°}$ +29·1° (*c* 0·99, MeOH); ORD in methanol, (*c* 0·10). $[\phi]_{600}$ +53·9°, $[\phi]_{500}$ +79·6°, $[\phi]_{400}$ +140°, $[\phi]_{300}$ +340°, $[\phi]_{272}$ +570° (pk), $[\phi]_{270}$ +540° (tr), $[\phi]_{267}$ +640° (pk), $[\phi]_{266}$ +610° (tr), $[\phi]_{264}$ +650° (pk), $[\phi]_{222}$ +2400° (pk), $[\phi]_{220}$ +2100°.

S-(+)-4-(p-*Tolyl*)*pentanol*-1, (+)-**8**. $[\alpha]_D^{27°}$ +24·4° (*c* 1·27, MeOH); ORD in MeOH, (*c* 0·14). $[\phi]_{600}$ +40·7°, $[\phi]_{500}$ +63·5°, $[\phi]_{400}$ +117°, $[\phi]_{300}$ +290°, $[\phi]_{273}$ +470° (pk), $[\phi]_{270}$ +460° (tr), $[\phi]_{266}$ +520° (pk), $[\phi]_{264}$ +490° (tr), $[\phi]_{240}$ +970°, $[\phi]_{222}$ +3500° (pk), $[\phi]_{210}$ +1000°.

S-(+)-2-*Methyl*-6-(p-*tolyl*) *heptanone*-4, (+)-**9**, (Fig. 4). $[\alpha]_D^{27°}$ +36·2° (*c* 1·24, MeOH); ORD in methanol, (*c* 0·138).

$[\phi]_{600}$ +77·5°, $[\phi]_{500}$ +122°, $[\phi]_{400}$ +250°, $[\phi]_{310}$ +1200° (pk), $[\phi]_{286}$ 0°, $[\phi]_{275}$ −1150° (tr), $[\phi]_{273}$ −700° (pk), $[\phi]_{269}$ −900° (tr), $[\phi]_{251}$ 0°, $[\phi]_{230}$ +1000°.

CD in MeOH, $8·88 \times 10^{-4}$M; $[\theta]_{300}$ +130, $[\theta]_{287}$ +1850 (max), $[\theta]_{272}$ +1000 (max), $[\theta]_{250}$ +160.

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