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THE BENZENE RING AS AN OPTICALLY ACTIVE CHROMOPHORE—II[1]

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Abstract—The optical rotatory dispersion (ORD) of several open chain compounds containing the benzene chromophore at the asymmetric center has been measured in the UV spectral region. The Cotton effects in the aromatic absorption regions of (−)-methyl 3-hydroxy-3-phenyl-butyrate, (+)-methyl 4-hydroxy-4-phenylvalerate, (−)-methyl 3-phenylvalerate, and (+)-methyl 3-hydroxy-3-phenylvalerate were too weak to be observed under the operating conditions. However, (−)-4-phenyl-pentane-1,4-diol and (−)-γ-phenyl-γ-valerolactone both exhibited relatively strong Cotton effects in the 260 mμ region. The results of this work, together with other examples in the literature, indicate that the aromatic Cotton effect in open chain systems is conformation dependent. Stabilization of a particular conformation in acyclic molecules by an effect such as intramolecular hydrogen bonding results in a marked increase in the intensity of the aromatic Cotton effect.

ORD is finding increasing use as a powerful and rapid method of structure determination.[4] Until relatively recently, the majority of studies have been carried out on optically active compounds containing the carbonyl chromophore.[5] Part of the interest in this class of compounds was dictated by the working range of spectropolarimeters which were available. The carbonyl group absorbs in an accessible spectral region (280–330 mμ) and has a low molar absorptivity ($\varepsilon \sim 30$). A small extinction is an important property of an optically active chromophore since it is only by measuring optical rotation in the region of an absorption band that the Cotton effect can be observed in ORD work. It is the unique shape of the Cotton effect curve for a given molecular configuration which imparts to ORD its powerful ability for structural analysis.

The recent availability of precision spectropolarimeters capable of rotational measurements to below 200 mμ has stimulated interest in other optically active chromophores. The wide occurrence of the benzene ring in many compounds of biological interest has prompted us to continue our investigations of this chromophore.[1]

The structural analysis of proteins by means of ORD is an extremely important application. Reports of aromatic Cotton effects in proteins are beginning to appear[6] but if ORD data are to be useful for the interpretation of molecular structure, more information on relatively simple systems is needed.

The literature contains conflicting reports concerning the rotatory behavior of a benzene ring attached to the asymmetric center of an open chain system. For example,

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[1] Part I, L. Verbit, *J. Amer. Chem. Soc.* **87**, 1617 (1965).

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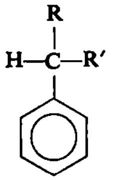
[4] P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco (1965).

[5] C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*. McGraw-Hill, New York (1960).

[6] For example, D. V. Myers and J. T. Edsall, *Proc. Natl. Acad. Sci. U.S.* **53**, 169 (1965); A. N. Glazer and N. S. Simmons, *J. Amer. Chem. Soc.* **87**, 2287 (1965).

Kuhn and Biller[7] measured the ORD of α-phenylethanol (I), into the aromatic absorption region and found no evidence of a Cotton effect. However, a reinvestigation of their work utilizing both ORD and CD measurements showed that the benzene chromophore in this molecule was indeed optically active.[1] Investigations of the ORD curves of mandelic acid, (II)[1,8] and of phenylalanine[9] indicated the absence of a Cotton effect in the aromatic absorption region. However, Moscowitz *et al.* subsequently proved the existence of an extremely weak aromatic Cotton effect in phenylalanine[10] and in mandelic acid.[11] The ORD spectra of these molecules will be considered in more detail in the Discussion section.



I R = OH R′ = CH_3

II R = OH R′ = CO_2H

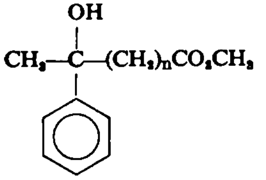
III R = C_2H_5 R′ = CH_3

The compounds discussed so far contain other chromophores in the molecule which absorb in a spectral region not far removed from that of the benzene substituent. In order to observe the behavior of a benzene chromophore unperturbed by other chromophoric groups, the ORD of 2-phenylbutane (III) was measured.[1] A Cotton effect of relatively small magnitude was found in the 260 mμ region.

In order to obtain more experimental evidence on the behavior of a benzene ring attached to the asymmetric center we have synthesized several open chain compounds and measured their ORD's in the UV spectral region.

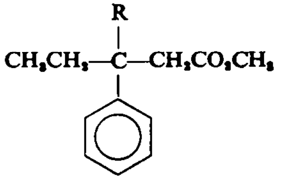
RESULTS

The ORD curves in methanol solution of (−)-methyl 3-hydroxy-3-phenylbutyrate (−)(IV), (+)-methyl 4-hydroxy-4-phenylvalerate (+)(V), (−)-methyl 3-phenylvalerate (−)(VI) and (+)-methyl 3-hydroxy-3-phenylvalerate (+)(VII) were plain over the spectral region from 360 to approximately 220 mμ



IV n = 1

V n = 2



VI R = H

VII R = OH

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[7] W. Kuhn and H. Biller, *Z. physik. Chem.* **B29**, 1 (1935).

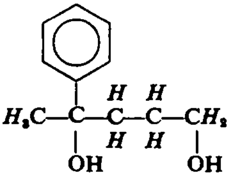
[8] I. P. Dirkx and F. L. J. Sixma, *Rec. Trav. Chim.* **83**, 522 (1964); J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 1847 (1965); T. R. Emerson, D. F. Ewing, W. Klyne, D. G. Neilson, D. A. V. Peters, L. H. Roach and R. J. Swan, *J. Chem. Soc.* 4007 (1965).

[9] T. M. Hooker, Jr. and C. Tanford, *J. Amer. Chem. Soc.* **86**, 4989 (1964); E. Iizuka and J. T. Yang, *Biochem.* **3**, 1519 (1964); J. P. Jennings, W. Klyne and P. M. Scopes, *J. Chem. Soc.* 294 (1965); J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 391 (1965).

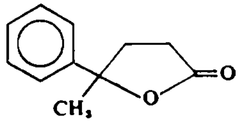
[10] A. Moscowitz, A. Rosenberg and A. E. Hansen, *J. Amer. Chem. Soc.* **87**, 1813 (1965).

[11] A. Moscowitz, University of Minnesota, private communication. The aromatic Cotton effect in II also has been observed by Prof. J. G. Foss, Iowa State University who has measured the CD in this region D-Mandelic acid exhibits a well-resolved positive dichroism centered at *ca.* 260 mμ (J. G. Foss and G. G. DeAngelis, private communication).

(Fig. 1). Changing the solvent from methanol to iso-octane had no effect on the shape of the dispersion curves although the absolute magnitude of the rotation decreased in agreement with the observed solvent dependence found in the related 1,2-diphenylethanol system.[12] Treatment of (+)V with LAH converted it to (−)-4-phenylpentane-1,4-diol, (−)(VIII). The ORD results for (−)VIII are shown in Fig. 2. A relatively strong Cotton effect is observed in the region of aromatic absorption. A cyclic analog of the ester system was prepared. The ORD results for γ-phenyl-γ-valerolactone, (−)(IX), are displayed in Fig. 3.



VIII



IX

DISCUSSION

The optically active benzene chromophore functions as an electronic probe with which to explore the molecular geometry in the vicinity of the chromophore. The usefulness of the benzene chromophore as a molecular probe in biological systems will depend upon an understanding of the optical behavior of this chromophore obtained from simple acyclic molecules. In contrast to rigid systems such as found in the steroids, an important problem existing in open chain systems is the lack of conformational homogeneity. The conformational dependence of the Cotton effect has been well established for cyclic systems. For example, the 17-acetyl group in pregnan-20-one derivatives has been shown to exist in two preferred conformations; one conformation exhibiting a strong positive Cotton effect, the other a negative one.[13] The absence of observable Cotton effects in the aromatic absorption regions of compounds IV, V, VI and VII is not unexpected in view of the results obtained with the related compounds, α-phenylethanol,[1] I, mandelic acid,[1,8,11] (II) and 2-phenylbutane[1], (III). Theoretically, a symmetric chromophore in a dissymmetric environment[14] is capable of exhibiting anomalous rotatory dispersion. However, the absorption band at *circa* 260 mμ in monosubstituted benzenes is of relatively low intensity ($\varepsilon \sim 250$) and corresponds to a low-energy π–π^* transition. Because the π^* state has the same electronic symmetry as the ground state, the transition is a forbidden one and is thus quite weak. Moscowitz *et al.*[10] have pointed out that for a monosubstituted benzene ring of effective local symmetry C_{2v}, optically active π–π^* transitions can be achieved only by mixing of the electric dipole transition moment of the aromatic ring with some perpendicular transition of the aromatic chromophore. In I and II, the oxygen atom of the α-hydroxyl group offers a source of non-bonding orbitals for n–π^* transitions. In III no such source is available and the weakly allowed electric dipole transition moment would have to mix with higher-energy σ–π^* transitions or those involving 3d or higher orbitals[10] and the observed Cotton effect in the 260 mμ region of III is thus a weak one. Some confusion may arise in distinguishing between the *strength* of these aromatic Cotton effects and their *observability* by means of ORD.

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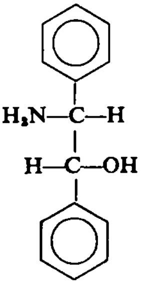
[12] V. M. Potapov and A. P. Terentev, *Zh. Obshch. Khim.* 34, 516 (1964).

[13] K. M. Wellman and C. Djerassi, *J. Amer. Chem. Soc.* 87, 60 (1965).

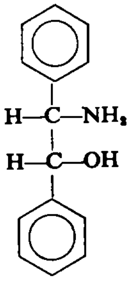
[14] A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *J. Amer. Chem. Soc.* 84, 1945 (1962).

The rotational strength can best be obtained by measurement of the CD, in which there is no background signal. However, in the ORD results discussed here, the molecules do not contain an isolated chromophore. There are contributions from other optically active transitions further into the UV to the observed rotatory dispersion curve in the 260 mμ region. This background curve, if it is steeply rising, will tend to obscure the weak Cotton effect and, *depending upon the slope of this curve, the aromatic Cotton effect may be unobservable under normal conditions.* In addition to the above reasons, the effect of lengthening the carbon chain on going from the above compounds to the four- and five- carbon esters of the present work introduces many more conformational possibilities for the molecule. The various sigma bonds of the esters allow free rotation so that the benzene chromophore is exposed to a variety of asymmetric environments, many of which have cancelling effects. Thus, any additional asymmetry in the vicinity of the benzene chromophore introduced by the longer carbon chains in these molecules is cancelled by the lack of conformational rigidity.

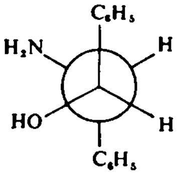
The effect of conformation on the intensity of electronic transitions is dramatically illustrated by the work of Lyle and Lacroix[15] who investigated the ORD of *threo* and *erythro*-2-amino-1,2-diphenylethanol (X). While the *threo*-isomer exhibited an intense Cotton effect in the 260 mμ region, the *erythro*-compound showed only a plain curve. The conformation of minimum torsional energy for *threo*-X is one in which the amino and hydroxyl functions are in a favorable position for hydrogen bond formation (see Newman projections). This conformation will thus be a more heavily populated one because of the stabilizing factor of hydrogen bond formation.



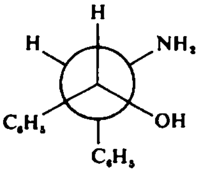
threo – X



erythro – X



threo – X



erythro – X

In contrast, hydrogen bond formation in *erythro*-X is unfavorable because the two benzene rings would then tend to become eclipsed. Consequently, the *erythro*-compound will not have a preferred conformation but several rotameric forms will exist in solution. The effect of the preferred conformation for the *threo*-compound

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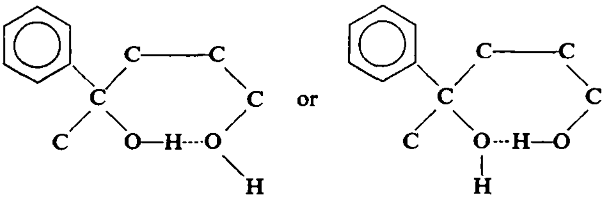
[15] G. G. Lyle and W. Lacroix, *J. Org. Chem.* **28**, 900 (1963).

and the lack of a preferred orientation for the *erythro*-isomer is manifested in the intense Cotton effect in the phenyl absorption region of the former and the absence of an observable Cotton effect in this region for the latter. The effect of conformation on the intensity of the aromatic Cotton effect in open chain systems is born out by the ORD results for VIII. Although the open chain ester (V) from which VIII was prepared showed no Cotton effect in the aromatic region (Fig. 1), VIII exhibits a relatively strong Cotton effect in this region (Fig. 2). An examination of molecular models indicates the possibility of a conformation which could be stabilized by intramolecular hydrogen bond formation. The IR spectrum of VIII in dilute carbon tetrachloride solution shows an OH absorption band at 3480 cm^{-1} which does not change its position with increasing dilution of the sample. The band is attributable to intramolecular hydrogen bond formation.[16] However, the ORD of VIII was measured in methanol solution. The existence of internal hydrogen bonds in this system was determined by the method described by Moscowitz *et al.*[17] in which intramolecular hydrogen bonds are broken by competition from an added species capable of forming strong hydrogen bonds. Upon successive additions of trifluoroacetic acid, the magnitude of the aromatic Cotton effect of VIII decreased indicating the destruction of the internal hydrogen bonds by the strong acid with resulting loss of the preferred conformation. (Under these conditions the diol was recovered in 77% yield.)



In order to demonstrate that, in the present series, conformational rigidity results in increased rotational strength, (−)-γ-phenyl-γ-valerolactone, (−)(IX), was synthesized as the cyclic analog of the open chain hydroxy-esters. A relatively intense multiple Cotton effect is found in the aromatic absorption region as well as the first extremum of the Cotton effect due to the lactone carbonyl chromophore at 245 mμ[18] (Fig. 3).

Our results for the ORD measurements of open chain systems containing the benzene chromophore at the asymmetric center indicate the aromatic Cotton effect to be conformation dependent. Appreciable population of many conformations results in extremely weak Cotton effects which are usually not observable under normal conditions of operation. Stabilization of a particular conformation by an effect such as intramolecular hydrogen bond formation results in a marked increase in the intensity of the aromatic Cotton effect.

[16] L. P. Kuhn, P. von R. Schleyer, W. F. Baitinger, Jr. and L. Eberson, *J. Amer. Chem. Soc.* **86**, 650 (1964).

[17] A. Moscowitz, W. C. Krueger, I. T. Kay, G. Skewes and S. Bruckenstein, *Proc. Natl. Acad. Sci. U.S.* **52**, 1190 (1964).

[18] T. Okuda, S. Harigaya and A. Kiyomoto, *Chem. Pharm. Bull. Japan* **12**, 504 (1964).

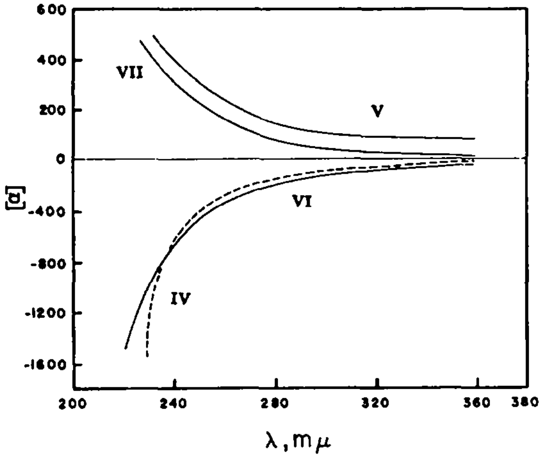


FIG. 1. ORD curves (MeOH) of (−)-methyl 3-hydroxy-3-phenylbutyrate (−)IV, (+)-methyl 4-hydroxy-4-phenylvalerate (+)V, (−)-methyl 3-phenylvalerate (−)IV and (+)-methyl 3-hydroxy-3-phenylvalerate (+)VII.

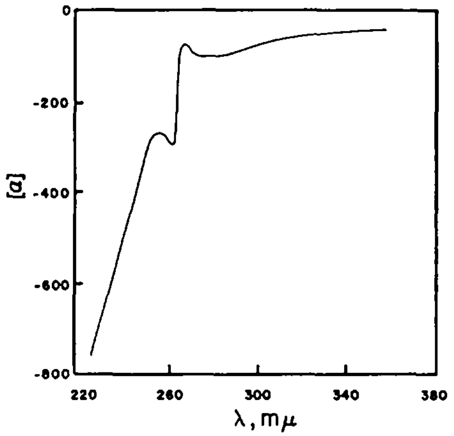


FIG. 2. ORD of (−)-4-phenylpentane-1,4-diol (−)VIII in MeOH.

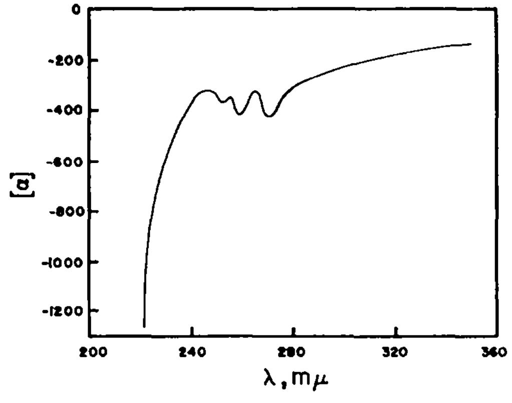


FIG. 3. ORD of (−)-γ-phenyl-γ-valerolactone (−)IX in MeOH.

EXPERIMENTAL

M.ps are corrected; b.ps are not. Microanalyses were carried out in the analytical section of the Dept. of Applied Science, Tohoku University. The ORD measurements were performed on a Cary Model 60 recording spectropolarimeter at a sample compartment temperature of 26°. The precautions discussed by Cary *et al.*[19] in the use of this instrument were followed. Fused silica cells (Pyrocell) of 1·0 and 10 mm fixed path length were employed. All measurements were carried out using spectral grade solvents at concentrations of approximately 5 × 10^{-2} M. The instrument was checked by comparing the ORD of (−)-1-butanol-1-*d* with that reported by Streitwieser *et al.*[20]

(−)-*Methyl 3-hydroxy-3-phenylbutyrate* (−)IV. The Grignard reagent prepared from 42·9 g (0·45 mole) EtBr and 11·1 g (0·46 g-at.) Mg turnings in 100 ml ether was cooled in an ice-bath and with vigorous stirring, 33 g (0·45 mole) diethylamine in 50 ml ether was slowly added. The mixture was stirred at room temp for 40 min, then refluxed for an additional 20 min. The reaction flask containing the diethylamide salt was cooled to −10° and a solution of 30 g (0·25 mole) acetophenone and 49·4 g (0·25 mole) (+)-menthyl acetate in 120 ml toluene was slowly added during the course of 1·5 hr. The mixture was stirred for 2 hr at −25° after addition was complete, then decomposed with 15 ml of sat. NH_4Cl aq. The organic layer was separated and the semi-solid residue in the reaction flask was extracted with several portions ether. The combined organic phases were washed with cold 10% H_2SO_4, water, sat. $NaHCO_3$ aq and again with water. The ether–toluene solution was dried (Na_2SO_4) and the solvent removed under red. press. The residue was dissolved in 0·5 N KOH and the solution refluxed for 4 hr. Upon cooling, the alkaline solution was extracted repeatedly with ether until the last ether extract exhibited no optical rotation. The alkaline solution was then acidified with cold 6 N H_2SO_4, saturated with NaCl, and extracted with ether. The ether was distilled off and the residue taken up in ligroin (60–75°). Upon standing, the solution deposited fine white crystals of (−)-3-hydroxy-3-phenylbutyric acid, 14·7 g (0·08 mole), 36% yield, m. p. 83·0–84·0° (lit.[21] m.p. 79–80°), $[\alpha]_D$ −8·02° (heptane). The (−)-acid was esterified by treatment with ethereal diazomethane to yield, after vacuum distillation, (−)IV, b.p. 119–120° (10 mm), $[\alpha]_D$ −10·54° (heptane) (Found: C, 68·13; H, 7·38. Calc. for $C_{11}H_{14}O_3$; C, 68·02; H, 7·27%.) ORD in MeOH, *c* = 1·704, *l* = 1·0 mm: $[\alpha]_{360}$ −54·0°; $[\alpha]_{300}$ −127°; $[\alpha]_{250}$ −429°; $[\alpha]_{230}$ −1410°.)

(−)-*γ-phenyl-valerolactone* (−)IX. The optically active lactone was prepared by the method of Reid and Turner[22] and had b.p. 134–135° (4 mm) [lit.[22] b.p. 134–139° (7 mm)], $[\alpha]_D$ −39·88° (EtOH). ORD in MeOH, *c* = 1·934, *l* = 1·0 mm: $[\alpha]_{360}$ −129°; $[\alpha]_{300}$ −235°; $[\alpha]_{270}$ −427°, trough; $[\alpha]_{265}$ −336°, peak; $[\alpha]_{258}$ −420°, trough; $[\alpha]_{255}$ −356°, peak; $[\alpha]_{250}$ −328°; $[\alpha]_{244}$ −320°, peak; $[\alpha]_{235}$ −868°.

(+)-*Methyl 4-hydroxy-4-phenylvalerate* (+)V (−)IX was dissolved in hot 2·5 N KOH and the solution cooled and gradually acidified with 5 N H_2SO_4. Fine white needles of (+)-4-hydroxy-4-phenylvaleric acid precipitated, m.p. 122·5–123·0° (lit.[22] m.p. 122–122·5°), $[\alpha]_D$ +3·12° (heptane). The (+)-acid was treated with an excess of ethereal diazomethane. The solvent was removed and the residue distilled under red. press. to yield (+)V, b.p. 124–125° (2 mm), $[\alpha]_D$ +34·49° (heptane). (Found: C, 67·97; H, 7·25. Calc. for $C_{11}H_{14}O_3$: C, 68·02; H, 7·29%.) ORD in MeOH, *c* = 1·995, *l* = 10 mm: $[\alpha]_{360}$ +59·6°; $[\alpha]_{300}$ +104°; $[\alpha]_{240}$ +410°.

(−)-*4-phenylpentane*-1,4-*diol* (−)VIII. The diol was prepared by the reduction of (+)V with LAH in ether. Recrystallization from ligroin–benzene afforded white granules of (−)VIII in 84% yield, m.p. 48·4–49·2°, $[\alpha]_D$–6.84° (EtOH). (Found: C, 73·48; H, 9·01. Calc. for $C_{11}H_{16}O_2$: C, 73.30; H, 8·95%.) ORD in MeOH, *c* = 1·069, *l* = 1·0 mm: $[\alpha]_{360}$ −32·8; $[\alpha]_{300}$ −84·2° $[\alpha]_{267}$ −75·7°, peak; $[\alpha]_{262}$ −286°, trough; $[\alpha]_{257}$ −263°, peak; $[\alpha]_{230}$ −769°.

(+)-*Methyl 3-hydroxy-3-phenylvalerate* (+)VII. (+)-3-hydroxy-3-phenylvaleric acid was prepared by the method of Mitsui and Kudo,[23] $[\alpha]_D$+ 21·55° (heptane). Treatment of the (+)-acid with ethereal diazomethane yielded (+)VII, m.p. 49·2–50·1° (from 60–75° ligroin),$[\alpha]_D$ +3·47°, (EtOH). (Found: C, 69·38; H, 7·59 Calc. for $C_{12}H_{16}O_3$: C, 69·21; H, 7·74%.) ORD in MeOH. *c* = 1·263, *l* = 10 mm: $[\alpha]_{360}$ +11·1°; $[\alpha]_{300}$ +35·2°; $[\alpha]_{230}$ +490°.

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[19] H. Cary, R. C. Hawes, P. B. Hooper, J. J. Duffield and K. P. George, *Appl. Optics* 3, 329 (1964).
[20] A. Streitwieser, Jr., L. Verbit and S. Andreades, *J. Org. Chem.* 30, 2078 (1965).
[21] J. A. Reid and E. E. Turner, *J. Chem. Soc.* 3694 (1950).
[22] J. A. Reid and E. E. Turner, *J. Chem. Soc.* 3219 (1951).
[23] S. Mitsui and Y. Kudo, *Chem. & Ind.* 381 (1965).

(−)-*Methyl 3-phenylvalerate*, (−)VI. A mixture of 2·0 g (0·0095 mole) (+)VII, 5 g Raney Ni, and 100 ml EtOH were placed in a flask equipped with a Teflon-covered magnetic stirring bar and the flask connected to a normal pressure hydrogenation apparatus. The hydroxyester was hydrogenolyzed at 28°. After the theoretical amount of H_2 had been absorbed, the catalyst was filtered and the filtrate distilled under red. press. to afford 1·8 g (0·0093 mole) 98% of (−)VI, b.p. 82–83° (0·2 mm), $[\alpha]_D = -25{\cdot}26°$ (MeOH). (Found: C, 74·74; H, 8·59; Calc. for $C_{12}H_{16}O_2$: C, 74·97; H, 8·39%.) ORD in MeOH $c = 0{\cdot}644$, $l = 1{\cdot}0$ mm; $[\alpha]_{360}$ −74·6°; $[\alpha]_{300}$ −160°; $[\alpha]_{250}$ −495°; $[\alpha]_{220}$ −1510°.

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