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THE ABSOLUTE CONFIGURATION OF A HYPOLIPIDEMIC 1-ARYL TETRALIN, NAFENOPIN

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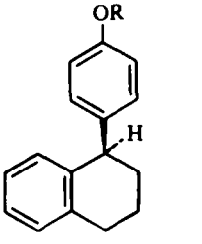
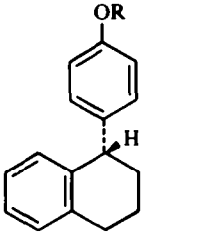
Abstract—A new hypolipidemic agent, 2-methyl-2-[*p*-(1,2,3,4-tetrahydro-1-napthyl)phenoxy] propionic acid, has been resolved. The absolute configurations of the enantiomers have been established by (a) ORD correlation with the lignans (b) application of the ORD skewed styrene rule to the derived dehydro compound and (c) the Bijvoet X-ray procedure on an iodo derivative.

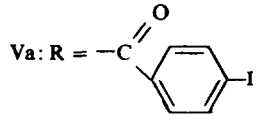
SEVERAL substituted tetrahydronapthalenes have been investigated[1, 2] and their stereochemistry elucidated.[3] We would now like to present evidence for the absolute configurations of the enantiomers, IVa and IVb, of 2-methyl-2[*p*-(1,2,3,4-tetrahydro-1-napthyl)phenoxy] propionic acid (IV). This substance has shown clinical efficacy as a hypolipidemic agent.[4]



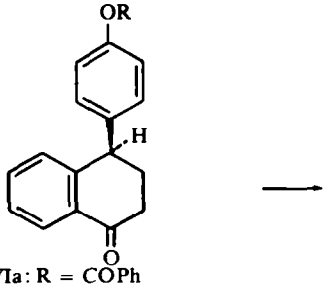
Ia: R = H [levorotatory]
IIa: R = *d*-camphorsulfonyl
IIIa: R = *l*-camphorsulfonyl
IVa: R = $-C[CH_3]_2CO_2H$



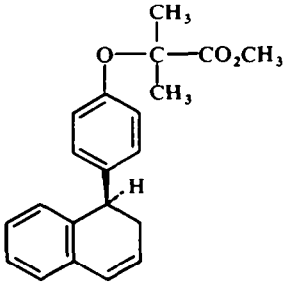
Ib: R = H [dextrorotatory]
IIb: R = *d*-camphorsulfonyl
IIIb: R = *l*-camphorsulfonyl
IVb: R = $-C[CH_3]_2CO_2H$



Va: R = $-C(=O)$-(4-I-phenyl)



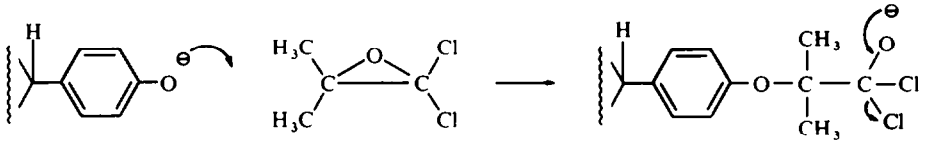
VIa: R = COPh
VIIa: R = $-C[CH_3]_2CO_2CH_3$



VIIIa

As IV is a carboxylic acid, one might consider resolving it by crystallization of the salt formed with an optically active base (e.g. brucine). However, resolution of the precursor phenol (I),[5,6] proved more satisfactory. The *d*-camphor-sulfonates (IIa and IIb) derived from I could be readily separated by fractional crystallization. Hydrolysis of the higher melting ester (IIa), yielded the levorotatory phenol (Ia). The lower melting isomer hydrolyzed to the dextrorotatory phenol (Ib). This latter compound could also be obtained by hydrolysis of the higher melting ester (IIIb) obtained from I and *l*-camphorsulfonyl chloride.

Conversion of the optically pure phenols (Ia and Ib) into the enantiomers of the drug (IVa and IVb) was effected using a mixture of chloroform and acetone in the presence of sodium hydroxide.[7] The first step in this reaction appears to be the condensation of acetone and chloroform to 1,1,1-trichloro-2-methyl-2-propanol (acetone-chloroform). Indeed use of this proposed intermediate with the phenol and base also affords the α-phenoxy-isobutyrate salt. The actual alkylating species is perhaps some especially reactive intermediate such as the epoxide.



There is no pathway under these reaction conditions which would lead to racemization of the resolved phenols, so the resolved acids (IVa and IVb) are obtained without loss of optical purity. The success of the resolution step is supported by the near mirror relationship of the ORD curves of IVa and IVb.

To establish the absolute configuration of these compounds the immediate solution seemed to be an ORD correlation with other substances of known absolute configuration.[8] The lignans are a group of natural compounds widely distributed in Nature. The characteristic skeleton of one group of the lignans is a 1-aryl-2,3-dialkyl-tetralin, and the stereochemistry of these substituents on the ring has been extensively investigated.[9,10] More particularly, Swan and Klyne have studied more than one hundred ORD curves of various lignans.[11,13] They have concluded that lignans exhibit two Cotton effects. The first in the range 280–290 mμ and the second between 230 mμ and 245 mμ. The regularities observed in the first Cotton effect led to the generalization that the 1-β-aryl-substituted tetralins give a positive Cotton effect and the 1-α-aryl-substituted tetralins show a negative one.[14] Thus, the stereochemistry of the alkyl groups at the 2 and 3 positions affected only the amplitude of the Cotton effect, and various oxygenation patterns in the aromatic rings affected both the amplitude and the position of the Cotton effect, within the above range. The absolute configuration of the 1-aryl substituent was the determining factor for the sign.

The first Cotton effect in the ORD curves of our 1-aryl tetralins (IVa and IVb) showed a slight shift towards shorter wavelengths and appeared in the range 275 mμ to 288 mμ. This is reasonable as there is less aromatic oxygenation in IVa and IVb than in the lignans. There is a certain degree of similarity between the ORD curves of the levorotatory acid IVa and that of the 1-β substituted lignan obtained from the review of Crabbé and Klyne.[14] However, the assignment of the absolute configuration of IVa based on the comparison of the ORD curves with those of the lignans is at best only suggestive.

The assignment of absolute configuration from the ORD curve derived from an inherently dissymmetric chromophore is a more reliable procedure.[15] An appropriate chromophore in our case would be the styrene of a compound such as VIIIa. VIIIa was prepared thus, chromic acid oxidation of the benzoate of Ia gave the 4-Keto compound VIa which was saponified. The keto phenol was converted to the isobutyric acid by procedure used for IV. The methyl ester VIIa was prepared by reaction with diazomethane. The keto ester VIIIa was reduced with sodium borohydride and the resulting carbinol dehydrated, to yield the dihydronaphthalene ester (VIIIa). The ORD curve of VIIIa is shown (Fig 1). The principal Cotton effect, centered at the UV maximum of this compound is negative. The chirality of the styrene (VIIIa) is then assigned from the skewed styrene rule.[16,17] The absolute configuration of VIIIa then follows with the assumption that the phenoxy group adopts a quasi equatorial conformation. Analysis of the NMR spectrum of this compound supports this assumption, as the proton on the carbon bearing the phenoxy substituent shows both a large and small coupling to the neighboring methylene protons. Use of the skewed styrene rule

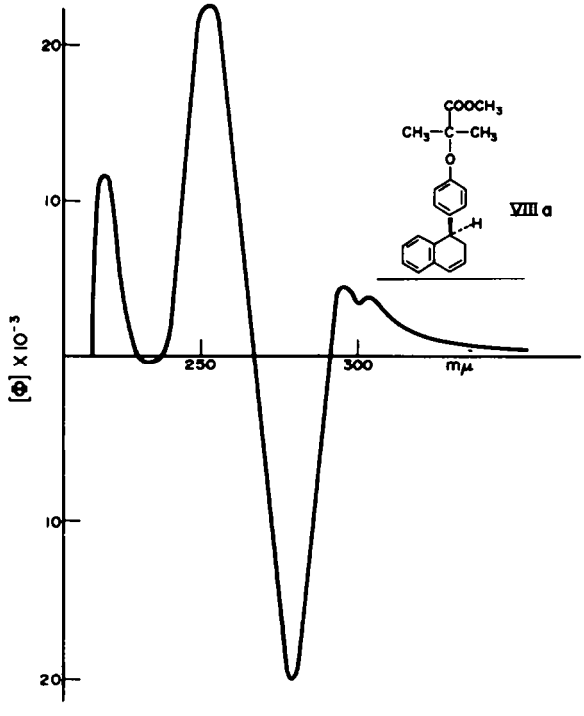


FIG 1. ORD Curve of VIIIa

was confused during the period that this work was carried out, by opposing statements appearing in print.[16] This has been clarified.[17]

Convincing proof that the assignments of absolute configuration derived by ORD are indeed correct was provided by application of the anomalous dispersion X-ray technique of Bijvoet.[18] Suitable crystals of the iodobenzoate (Va) of the levorotatory phenol (Ia) were obtained and subjected to a full single crystal structure analysis. This

derivative crystallizes in the monoclinic system with unit cell dimensions of a = 7·58, b = 8·88, c = 15·56 Å, β = 105° 5′, Z = 2. The space group was uniquely determined as P_{2_1} by the observed systematic extinctions of OkO absent for k odd and the presence of optical activity. The structure was solved in a straightforward manner by the heavy atom method[19] utilizing 1196 observed reflections from Weissenberg equi-inclination film data. All atoms in the molecule were clearly shown in the three dimensional electron density distribution phased on the I atom. The atomic coordinates were then refined by full matrix least squares calculations. When convergence was essentially complete (R = 15%), structure factor calculations including the anomalous dispersion

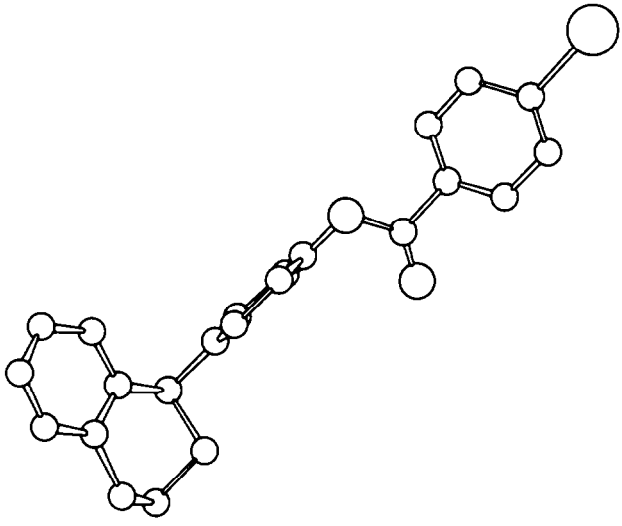


FIG 2. Absolute configuration of Va (levoratotory) by X-ray analysis

correction for the I atom were carried out for the two alternative configurations yielding values for R of 14·3% and 16·3% for the indicated stereochemistry of levorotatory phenol Ia and its enantiomer Ib respectively. Thus it is evident that the absolute configuration assigned via ORD is correct. In addition, examination of ten Bijvoet pairs of the type hkl and $h\bar{k}l$ indicated by the calculations as having anomalous dispersion effects of sufficient magnitude to be easily observable from the film data gave additional proof of the correctness of assignment. Three further cycles of least squares calculations utilizing the dispersion corrections and the correct absolute configuration yielded a final R of 12·4%. The iodobenzoate Va as it exists in the crystal is shown in Fig 2.

EXPERIMENTAL

M.ps are uncorrected and were determined in a Hoover m.p. apparatus. The IR spectra were taken as nujol mulls with a Perkin–Elmer IR spectrophotometer, Models 21 and 521. UV spectra were recorded on a Cary 14 spectrophotometer. NMR spectra were obtained on Varian A-60 NMR spectrometer. Optical rotations were determined in MeOH (c, g/100 ml) on a Rudolph and Sons Model 200 photoelectric polarimeter. Mass spectra were measured on a Associated Electrical Industries AEI MS 902 mass spectrometer. The ORD curves were obtained on a JASCO ORD/UV-S in MeOH in a 1 cm path length cell, with a scanning speed of 10 mμ/min.

p-(1,2,3,4-*Tetrahydro*-1-*naphthyl*)-*phenol*, (I). A suspension of anhyd $AlCl_3$ (14 g) in phenol (20 g) was stirred with cooling in ice water while a soln of 1-hydroxy- 1,2,3,4-tetrahydro-naphthalene (28·4 g) and phenol (20 g) in a 1:1 mixture of benzene and hexane (150 ml) was added dropwise. The addition lasted 4 hr and a steady stream of HCl evolution was observed. Thereafter the mixture was gradually heated to 50° and kept at this temp for 4 hr. It was allowed to stand at room temp for 18 hr. Reheating to 50° was necessary to pour it onto ice and conc HCl. EtOAc (40 ml) was stirred into the reaction mixture. The aqueous layer was separated and extracted with EtOAc and with benzene. The combined organic layers were washed with 6 N HCl, water, satd $NaHCO_3$ aq and dried. Evaporation to dryness afforded an oil which on treatment with hexane crystallized, 48 g, m.p. 75–95°, still containing phenol. It was recrystallized from ether and hexane (1:5) and from EtOH-water (1:1) to give 24·5 g of I, m.p. 124–125°. A sample was sublimed for analysis, m.p. 127–128° (Lit. 129–130°[5] and 129°[6]); γ_{max} 3200 (OH), 1600, 1608, 1365, 1235, 818, 736 cm^{-1}; NMR bands: δ 3·95 (1H, band-width 22 Hz) (benzylic H), 2·72 (2H, t) benzylic (H_2), 1·82 (4H, m). (Found: 85·86; H, 7·09. $C_{16}H_{16}O$ requires: C, 85·68; H, 7·19%).

The benzoate of I melted at 109–110°, Koenigs[5] reported 107–109°); γ_{max} 1732 (CO), 1270, 1200, 1062, 816, 760, 738, 710 cm^{-1}; NMR bands: δ 4·00 (1H, band-width 22 Hz) (benzylic H), 2·72 (2H, t), 1·78 (4H, m). (Found: C, 84·34; H, 6·14. $C_{23}H_{20}O_2$ requires: C, 84·12; H, 6·14%).

l(−), p-(1,2,3,4-*Tetrahydro*-1-*naphthyl*)-*phenol* d-*camphor-sulfonate* (IIa). Solns of NaOH (4·4 g, 0·11 mole) in water (30 ml) and *d*-camphor-sulfonylchloride[21] (25·0 g, 0·10 mole) in acetone (30 ml) were added in an alternating fashion in portions (2 ml) with stirring to a solution of I (20·0 g, 0·89 mole) in acetone (50 ml) at 30–40°. After completed addition the mixture was heated under reflux on the steam bath for 15 min. Most of the acetone was removed in vacuum and replaced with water. The oily product was extracted 3 times with ether, washed with water, sat NaCl aq and dried (Na_2SO_4). The ethereal extract yielded 31·0 g of an oily product which was taken up with MeOH (300 ml) and allowed to stand at 5° for 20 hr. The crystalline ppt was collected, 10·0 g, m.p. 96–106°. Recrystallization from boiling MeOH (250 ml) gave 6·3 g colorless prisms, m.p. 109–11°; once more from MeOH (200 ml) furnished 5·0 g flat plates, m.p. 113–116°, and finally from MeOH (100 ml) again yielded 4·2 g of IIa, m.p. 116–117°; $[\alpha]_D^{25} = +20·0°$ (*c*, 1·93, $CHCl_3$); γ_{max} 1748 (CO), 1356, 1148, 862, 842, 744 cm^{-1}; NMR bands: δ 7·16 (8H, m), 3·72 (1H, s), 3·30 (1H, s), 1·17 (3H, s) (CH_3), 0·91 (3H, s) (CH_3). (Found: 71·21; H, 6·99. $C_{26}H_{30}O_4S$ requires: C, 71·21; H, 6·90%).

d(+), p-(1,2,3,4-*Tetrahydro*-1-*naphthyl*)-*phenol* d-*camphorsulfonate* (IIb). In the above series of crystallizations the crude *d*-camphorsulfonate ester (31 g) was taken up with MeOH (300 ml) and gave 10 g crystalline ppt, m.p. 96–106°. The filtrate at this stage was concentrated to 100 ml on a hot plate in a stream of N_2. On standing at 5° for 24 hr this soln deposited 2·2 g colorless crystals, m.p. 80–86°. Two crystallizations from benzene and hexane furnished 1·05 g cubic crystals of IIb m.p. 91–92°; $[\alpha]_D^{25} = +38·8°$ (*c*, 2·10, $CHCl_3$); γ_{max} 1748 (CO), 1355, 1146, 878, 870, 841, 835, 738 cm^{-1}; NMR bands: δ 7·12 (8H, m), a broad signal centered at 4·10 (band-width approx 22 Hz) (1H, benzylic) 3·68 (1H, s), 3·28 (1H, s), 1·14 (3H, s) (CH_3), 0·88 (3H, s) (CH_3). (Found: C, 71·57; H, 7·05. $C_{26}H_{30}O_4S$ requires: C, 71·21; H, 6·90%).

l(−), p-(1,2,3,4-*Tetrahydro*-1-*naphthyl*)-*phenol* (Ia). A soln of IIa (4·0 g) and KOH (2·0 g) in MeOH (75 ml) was refluxed for 5 hr. The solvent was distilled off in vacuum. Water was added to the residue and the mixture was acidified with dil HCl. The liberated phenol was extracted 2 times with ether, washed with water, sat $NaHCO_3$ aq and dried. The crude yield of Ia was 2·0 g. It was twice recrystallized from EtOH and water, 1·4 g, m.p. 134–135°; $[\alpha]_D^{25} = -26·9°$ (*c*, 2·69); γ_{max} 3410 (OH), 1600, 1514, 1380, 1222, 825, 740, 732 cm^{-1}; NMR bands: δ 4·03 (1H, band-width 22 Hz) (benzylic H), 2·83 (2H, t), 1·84 (4H, m). (Found: C, 85·61; H, 7·26. $C_{16}H_{16}O$ requires: C, 85·68; H, 7·19%).

The benzoate of Ia was obtained by acylation of Ia (5·0 g) with benzoyl chloride (3·5 g) and NaOH (0·8 g) in acetone and water according to the Schotten–Baumann method. The yield was 6·7 g m.p. 128–131°; $[\alpha]_D^{25} = -26·8°$ (*c*, 1·16, in $CHCl_3$).

The *p*-iodobenzoate of Ia was prepared from Ia (2·0 g), *p*-iodobenzoyl chloride (2·7 g) and NaOH (0·4 g); Va m.p. 85–87° (from hexane); $[\alpha]_D^{25} = -33·9°$ (*c*, 0·25); ν_{max} 1728 (CO), 1583, 1268, 1190, 1068, 1002, 880, 842, 810, 745, 738, 734 cm^{-1}. (Found: C, 61·16; H, 4·17. $C_{23}H_{19}IO_2$ requires: C, 60·84; H, 4·21%).

d(+), p-(1,2,3,4-*Tetrahydro*-1-*naphthyl*)-*phenol* (Ib). The *d*-camphor-sulfonate ester of this phenol, IIb m.p. 91–92° (1·05 g) was hydrolyzed as above to give 0·35 g of Ib, m.p. 134–135°; $[\alpha]_D^{25} = +26·6°$ (*c*, 1·85). Hydrolysis of IIIb, m.p. 114–116°, yielded the same dextrorotatory Ib, m.p. 134–135°; $[\alpha]_D^{25} = +27·0°$ (*c*, 2·37). Spectral data as for Ia (Found: C, 85·68; H, 7·31. $C_{16}H_{16}O$ requires: C, 85·68; H, 7·19%).

d(+), p-(1,2,3,4-*Tetrahydro*-1-*naphthyl*)-*phenol* 1-*camphorsulfonate* (IIIb). Commercial *l*-camphor was sulfonated according to the procedure of Bartlett and Knox.[22] The resulting sulfonic acid was converted to *l*-10-camphorsulfonylchloride. Repetition of the Schotten–Baumann acylation using the same amounts of

I and reagents gave 7·8 g of IIIb; m.p. 115–116°; $[\alpha]_A^{25} = -18·5°$ (c, 1·00, $CHCl_3$); IR and NMR spectra same as for IIa. (Found: C, 71·13; H, 6·83. $C_{26}H_{30}O_4S$ requires: C, 71·21; H, 6·90%).

Hydrolysis of ester IIIb in methanolic KOH yielded the dextrorotatory Ib.

1(−), p-(1,2,3,4-*Tetrahydro*-1-*naphthyl*)-*phenol* 1-*camphorsulfonate* (IIIa). Solw evaporation of the mother liquors of IIIb furnished cubic crystals which upon recrystallization from MeOH gave 0·8 g of IIIa; m.p. 92–93°; $[\alpha]_D^{25} = -40·0°$; (c, 1·00, $CHCl_3$); IR and NMR spectra same as for IIb. (Found: C, 71·24; H, 6·98. $C_{26}H_{30}O_4S$ requires: C, 71·21; H, 6·90%).

2-*Methyl*-2(p-1,2,3,4-*tetrahydro*-1-*naphthyl*)-*phenoxy*)-*propionic acid* (IV). A soln of I (22·4 g, 0·1 mole) in acetone (300 ml) containing NaOH pellets (20·0 g, 0·5 mole) was heated to reflux temp with stirring. When reflux started a mixture of $CHCl_3$ (13·2 g, 0·11 mole) and acetone (100 ml) was added dropwise at such a rate that reflux was maintained without external heating. After completed addition the pasty suspension was stirred and refluxed for 1 hr. It was cooled and the Na salt of the product and the NaCl formed were collected and washed twice with acetone and then air dried (44 g). The salts were dissolved in water (300 ml) and the clear tea-colored basic soln was extracted with ether. The ethereal extract was discarded. The aqueous layer was acidified with conc HCl and extracted twice with ether, washed with NaCl aq and dried. The crude acid weighed 16·0 g. It was crystallized from ether and hexane. The ether was boiled off until the vapor phase reached 50°. On cooling the acid crystallized (12·0 g), m.p. 126–127°. A sample was recrystallized from aqueous EtOH, to give IV m.p. 127–128°; ν_{max} 1695 (COOH), 1608, 1240, 1150, 910, 818, 740 cm^{-1}; NMR bands: δ 4·06 (1H, band-width 22 Hz) (benzylic H), 2·84 (2H, t) benzylic H_2), 1·86 (4H, m), 1·58 (6H, s) ($2CH_3$). (Found: C, 77·56; H, 7·44. $C_{20}H_{22}O_3$ requires: C, 77·39; H, 7·14%).

l(−), 2-*Methyl*-2(p-(1,2,3,4-*tetrahydro*-1-*naphthyl*)-*phenoxy*)-*propionic* acid (IVa). This was prepared in the same way as the racemic isomer IV, from Ia (3·25 g), $CHCl_3$ (3·5 g) and NaOH (5·0 g) in acetone (85 ml). After two crystallizations from ether, hexane and aqueous EtOH, respectively, IVa was obtained, m.p. 117–118°, $[\alpha]_D^{25} = -27·0°$ (c, 1·42); ν_{max} 1710 (COOH), 1605, 1240, 1160, 910, 828, 750, 742 cm^{-1}; ORD (c, 0·027; MeOH), $(\phi)_{600} -230°$; $(\phi)_{350} -433°$; $(\phi)_{288} -1710°$; $(\phi)_{269} -6218°$; $(\phi)_{257} -3779°$; (c, 0·0055) $(\phi)_{234} -9835°$; $(\phi)_{230} -7706°$. (Found: C, 77·67; H, 7·20. $C_{20}H_{22}O_3$ requires: C, 77·39; H, 7·14%).

d(+), 2-*Methyl*-2-(p-(1,2,3,4-*tetrahydro*-1-*naphthyl*)-*phenoxy*)-*propionic acid* (IVb). This was prepared as the levorotatory antipode using Ib (3·3 g) and the same amount of reagents as above. The crude acid (4·0 g) was twice recrystallized from aqueous EtOH to afford IVb, 2·9 g, m.p. 117–118°, $[\alpha]_D^{25} = +25·0$ (c, 1·31). Fractionation by crystallization from aqueous EtOH gave a first crop exhibiting a smaller rotational value, and a second crop (600 mg), $[\alpha]_D^{25} = +26·0°$ (c, 1·64); ORD (c, 0·021 MeOH), $(\phi)_{600}$ 108°; $(\phi)_{589}$ 149°; $(\phi)_{288} -1980°$; $(\phi)_{268}$ 6253°; $(\phi)_{255}$ 3563°; (c, 0·007) $(\phi)_{232}$ 11642°. (Found: C, 77·54; H, 7·20. $C_{20}H_{22}O_3$ requires: C, 77·39; H, 7·14%).

1(−), p-(1,2,3,4-*Tetrahydro*-4-*oxo*-1-*naphthyl*)-*phenol benzoate* (VIa). A soln of Ia benzoate (6·5 g) in $CHCl_3$ (15 ml) was stirred in a cold bath (ice NaCl), while a soln of CrO_3 (6·5 g) in Ac_2O (30 ml) was added dropwise during the course of 30 min. The temp of the reaction mixture was kept between 0 and +10°. After addition was complete stirring was continued for 1 hr. The reaction mixture was poured onto ice and the excess of the oxidizing agent was decomposed with $NaHSO_3$. The product was extracted 4 times with ether. The combined extracts were washed with Na_2CO_3 and sat NaCl aq and dried (Na_2SO_4). The crude product was a viscous red oil weighing 5·0 g. A small amount of ether was added and the crystalline part was collected (1·1 g). Recrystallization from isopropyl alcohol gave VIa (0·9 g), m.p. 135–137°; $[\alpha]_D^{25} = -69·4°$ (c, 0·98 in $CHCl_3$); ν_{max} 1725 ($OCOC_6H_5$), 1678 (CO), 1598, 1210, 810, 755, 705 cm^{-1}. (Found: C, 80·52; H, 5·54. $C_{23}H_{18}O_3$ requires: C, 80·68; H, 5·30%).

1(−), *Methyl* 2-*methyl*-2-(p-1,2,3,4-*tetrahydro*-4-*oxo*-1-*naphthyl*)-*phenoxy*)-*propionate* (VIIa). The levorotatory VIa (1·0 g) was refluxed on the steam bath in MeOH (30 ml) containing KOH (1·0 g) for 10 min. The solvent was distilled off in vacuum and the residue was taken up in water, acidified with dil HCl and extracted 4 times with ether. The extracts furnished the intermediate phenol (0·7 g) which was recrystallized from ether and hexane, (0·6 g), m.p. 146–149°. Without further purification this intermediate was dissolved in acetone (6 ml) and powdered NaOH (800 mg) was added. The suspension was stirred and heated to reflux. At this point commercial 1,1,1-trichloro-2-methyl-2-propanol (700 mg) in acetone (6 ml) was added through the condenser in portions (3 × 2 ml). Stirring and reflux was continued for 90 min. The acetone was distilled off in vacuum and the reddish residue was dissolved in water (40 ml). The clear aqueous soln was acidified with dil HCl. The product precipitated and was extracted twice with ether. The crude acid weighed 570 mg. It did not crystallize and was further purified by dissolving it in $NaHCO_3$ aq (2 g $NaHCO_3$ in 50 ml water). This basic soln was extracted twice with ether. The extracts afforded an oil (30 mg) which was discarded. The aqueous layer was treated with charcoal, filtered, acidified and extracted twice with ether to

yield the acid again (370 mg). Attempts to crystallize the acid were without success. It was esterified with ethereal diazomethane. The crude oily VIIa weighed 300 mg. It was chromatographed on Al_2O_3 (10·0 g, Woelm, neutral, act. grade III). Benzene eluted 250 mg of a colorless oil which was distilled to give VIIa (200 mg), b.p. 170°/0·15 mm; $[\alpha]_D^{25} = -61·9$ (c, 2·33); mass spectrum: $M^+ = 338$; ν_{max} 1738 ($COOCH_3$), 1690 (CO), 1510, 1288, 1235, 1140, 832, 764 cm^{-1}; NMR bands: δ 4·22 (1H, band-width 22Hz) (benzylic H), 3·74 (3H, s) (OCH_3), 2·58 (4H, m), 1·58 (6H, s) ($2CH_3$). (Found: C, 74·42; H, 6·66. $C_{21}H_{22}O_4$ requires: C, 74·53; H, 6·55%).

α(+), *Methyl* 2-*methyl*-2-[p-(1,2-*dihydro*-1-*naphthyl*)-*phenoxy*]-*propionate* (VIIIIa). A soln of VIIa (100 mg) in MeOH (5 ml) was stirred in an ice bath with $NaBH_4$ (100 mg) for 5 hr. The excess of the reducing agent was destroyed with aqueous oxalic acid soln and most of the MeOH was removed in vacuum. The residue was neutralized with $NaHCO_3$ aq and extracted with ether. The intermediate secondary carbinol thus obtained weighed 90 mg. The IR spectrum was devoid of the band 1690 cm^{-1} (CO). This intermediate was dehydrated by refluxing it in 90% formic acid (2·5 ml) for 1 hr. Most of the formic acid was removed in vacuum. The residual oil was taken up in ether and washed with $NaHCO_3$ aq. The ethereal layer afforded the crude product as a straw-colored oil (70 mg). It was purified by chromatography on Al_2O_3 (3·0 g, Woelm, neutral, act grade III). A mixture of benzene and hexane (1:1) eluted 35 mg of a colorless oil which was distilled to give VIIIa (23 mg), b.p. 150–155°/0·1 mm; IR in CS_2: ν_{max} 1750 and 1738 ($COOCH_3$), 1610, 1385, 1240, 1135, 828, 780, 742 cm^{-1}; ORD (c, 0·0129; MeOH), $(\phi)_{600}$ 107°; $(\phi)_{589}$ 101°; $(\phi)_{299}$ 3483°; $(\phi)_{296}$ 2741°; (c, 0·00129; MeOH); $(\phi)_{290}$ 4432°; $(\phi)_{272}$ −21677°; $(\phi)_{247}$ 22237°; $(\phi)_{225}$ 0°; In gas chromatography substance VIIIa, as well as its racemic analog (VIII) exhibited a single symmetric peak with a retention time of 2·12 min. The gas chromatogram was recorded on a Microtec MT-220 instrument equipped with a 6′ 4 mm column. The support medium was 100–120 mesh Gaschrom Q with 3% high efficiency BP.8 as the stationary phase. The column temp was 240°, and N_2 was used as carrier gas at 65 ml/min.

The IR absorption curve of the racemic isomer VIII and that of the optically active specimen described here were found to be identical. UV spectrum: $\lambda_{max} = 263$ mμ (c, 9440). (Found: C, 77·97; H, 7·10. $C_{21}H_{22}O_3$ requires: C, 78·23; H, 6·88%).

Crystal structure analysis of 1-, p-(1,2,3,4-*tetrahydro*-1-*naphthyl*)-*phenol* p-*iodobenzoate* (Va), $C_{23}H_{19}O_2I$, $M = 454·31$; monoclinic, $a = 7·58$, $b = 8·88$, $c = 15·56$ Å,[6] $\beta = 105°$ 5′, $U = 1011$ Å,^{3} $Z = 2$. Space group $P_{21}(C_2^2)$ $F_{(000)} = 452$. Absorption coefficient for X-rays ($\lambda = 1·5418$ Å) $\mu = 126·9$ cm^{-1}.

The crystal selected for analysis was an elongated tablet of cross section 0·30 × 0·18 mm. All data were taken using Ni filtered Cu K radiation ($\lambda = 1·5418$ Å). The unit cell dimensions were evaluated from oscillation and precession photographs. The intensities were estimated visually from multiple-film equi-inclination Weissenberg photographs of the 0kl-6kl layers yielding 1196 observed reflections. The films were indexed systematically according to the method described by Bijvoet and Peerdeman.[20] Cylindrical absorption corrections were applied to the data using 0·24 mm as the effective diameter of the crystal.

The initial coordinates of the I atom were deduced from the three dimensional Patterson function. Structure factors were calculated and the resultant phases were used with the observed structure amplitudes to produce a 3-dimensional electron density distribution. Although all atoms were clearly shown, another round of structure factors was calculated using only the iodobenzoate portion of the molecule in order to break the pseudosymmetry of the map. The remaining atoms were then unambiguously assigned from the resulting electron density distribution. The parameters obtained were subjected to three cycles of full matrix least-squares calculations using isotropic temp factors giving a value for R of 25% at the end of the third cycle. The I atom was then assigned an anisotropic temp factor of the form. $T = \exp|-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)|$ and to more cycles were carried out yielding $R = 15·0$%. At this point structure factor calculations using the anomalous dispersion corrections for iodine were carried out for both alternative configurations. Values of $\Delta f'$ and $\Delta f''$ were taken from the "International Tables for X-Ray Crystallography, Vol. III". At all stages of the analysis, care was taken to preserve a right-handed set of axes in space group P_2. The resulting R values of 14·3 and 16·3% clearly indicated the former as that of the correct absolute stereochemistry (this is the configuration shown in Fig 3). Three more cycles of least squares using the correct configuration and taking the anomalous dispersion effect of the iodine into account resulted in a final R of 12·4%.

A copy of the final atomic parameters together with the observed and calculated structure factors can be obtained upon request from RTP. Calculations were carried out on a Univac 1108 using the X-Ray 67 System of programmes developed under Dr. James Stewart of the University of Maryland.

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