

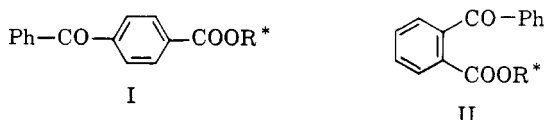
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF.]

Asymmetric Induction. II. Normal and Pseudo (-)-Menthyl Esters of *o*-Benzoylbenzoic AcidBY WILLIAM A. BONNER¹

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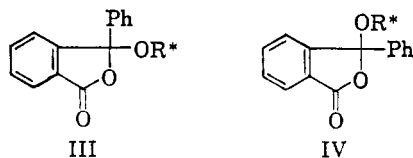
In order to test further the concept of "asymmetric induction" the preparation of (-)-menthyl *o*-benzoylbenzoate (II) has been undertaken. By several preparative methods, production of II was accompanied by formation of two diastereomeric ψ -esters, (+)-(III) and (-)-3-phenyl-3-(-)-menthoxyphthalide (IV). Methods for the separation of the three esters have been developed, and each isomer has been characterized using ultraviolet, infrared and thin layer chromatographic techniques. Optical rotatory dispersion measurements on the three esters have been undertaken and the applicability of simple Drude expressions to their visible rotatory dispersions has been investigated. The lithium aluminum hydride reduction of each isomer was found to produce optically inactive samples of *o*-hydroxymethylbenzhydrol, while reductions with sodium borohydride afforded optically inactive 3-phenylphthalide. These observations suggest again the failure of "asymmetric induction" to be transmitted through aromatic nuclei.

Two rationalizations of classical asymmetric syntheses are to be found in the literature, the earlier involving "asymmetric induction" and the later invoking purely steric interactions.² Recently we have attempted² to differentiate experimentally between these hypotheses by carbonyl reduction and Grignard addition reactions of (-)-menthyl *p*-benzoylbenzoate (I, R* = (-)-menthyl throughout). The absence of optical activity in the products of such reactions (after removal of the (-)-menthyl moiety) suggested strongly



that "asymmetric induction," whatever it comprised, was incapable of transmission across the *para* positions of aromatic nuclei in the manner of normal electronic interactions and lent weight to the current assignment of asymmetric bias to purely steric interactions. We have now undertaken to confirm these conclusions by application of similar reactions to (-)-menthyl *o*-benzoylbenzoate (II).

Esterification of *o*-benzoylbenzoic acid is complicated by the formation of ψ -esters accompanying the normal products.³ Thus in the preparation of the normal ester II one would expect concomitant production of the two diastereomeric ψ -esters, (+)-(III)⁴ and (-)-3-phenyl-3-(-)-menthoxyphthalide (IV),⁴ epimeric at C3. In 1945, Newman⁵ esterified *o*-benzoylbenzoic acid with (-)-menthol by several procedures, obtain-



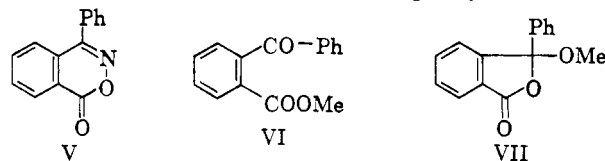
ing IV in pure crystalline form, m.p. 116–117°, [α]_D²⁵ -186° (MeOH), and II and III in impure states. We wish here first to present additional observations regarding the (-)-menthyl esters II, III and IV.

Fisher esterification ordinarily favors the formation of normal *o*-benzoylbenzoates,⁶ and the preparation of impure II by this method has been reported.⁵ Repetition of this latter procedure afforded (57%) a thick amber sirup, [α]_D²⁵ -87.0° (CHCl₃), investigation of which by silica thin layer chromatography (T.L.C.) and in-

frared spectroscopy revealed normal ester II contaminated with substantial quantities of ψ -esters. Alumina column chromatography separated the ψ -esters (25%) from the normal ester II (75%), which proved to be a thick sirup, [α]_D²⁵ -107.9° (CHCl₃).

The ψ -esters III and IV were prepared^{6,7} by action of (-)-menthol on *o*-benzoylbenzoyl chloride.⁸ There resulted a crude sirup (97%), [α]_D²⁵ -54.2° (CHCl₃), silica T.L.C. behavior of which again indicated a mixture of normal and ψ -esters. Extensive fractional crystallization from ligroin yielded sturdy prisms of IV, m.p. 115–116°, [α]_D²⁵ -200.3° (CHCl₃), in agreement with the findings of Newman. A large number of intermediate, lower-melting, levorotatory fractions was also collected, and the final mother liquors afforded a sirup, [α]_D²⁵ +39.9° (CHCl₃). Silica T.L.C. again revealed the presence of both ψ - and normal esters in the latter sirup. Alumina column chromatography effectively separated the mixture, and the ψ -ester fraction ultimately crystallized, affording pure III, m.p. 62–62.5°, [α]_D²⁵ +60.0° (CHCl₃).

An attempt to separate normal and ψ -ester mixtures in the above preparation by conversion of the normal component to its oxime resulted only in the formation (40%) of 4-phenyl-3,4-dehydro-1-oxo-2,3,1-benzoxazine (V). In addition, we have prepared methyl *o*-benzoylbenzoate^{6,9} (VI) and 3-phenyl-3-methoxy-



phthalide⁶ (VII) for the comparison purposes below.

Newman has employed both ultraviolet⁵ and infrared³ absorption spectra for analysis of normal and ψ -ester mixtures, and we have now used these techniques for characterization of these substances with general substantiation of his results. As regards ultraviolet absorption, Table I indicates that the normal esters II and VI have similar spectra and that the ψ -esters III, IV and VII have characteristic spectra reminiscent of those both of the parent phthalide and of 3-phenylphthalide (λ_{\max} 278, log ϵ 3.3).¹⁰ Other criteria below for differentiating the two ester types, however, are simpler and even more definitive than ultraviolet comparisons.

The infrared spectrum, for example, immediately and unambiguously distinguishes normal and ψ -esters

(1) We are indebted to the Abbott Laboratories for a research grant which supported a portion of this investigation.

(2) M. J. Kubitschek and W. A. Bonner, *J. Org. Chem.*, **26**, 2194 (1961); earlier references to these theories are given herein.

(3) M. S. Newman and C. W. Muth, *J. Am. Chem. Soc.*, **73**, 4627 (1951).

(4) Stereochemical designation is not implied in structures III and IV.

(5) J. R. Schaefgen, F. H. Verhoek and M. S. Newman, *J. Am. Chem. Soc.*, **67**, 253 (1945).

(6) H. Meyer, *Monatsh.*, **25**, 475 (1904); **34**, 69 (1913).

(7) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1537 (1941).

(8) H. C. Martin, *J. Chem. Soc.*, **117**, 1142 (1916).

(9) H. Plaskuda, *Ber.*, **7**, 987 (1874).

(10) H. Schmid, M. Hochweber and H. v. Halban, *Helv. Chim. Acta*, **31**, 354 (1948).

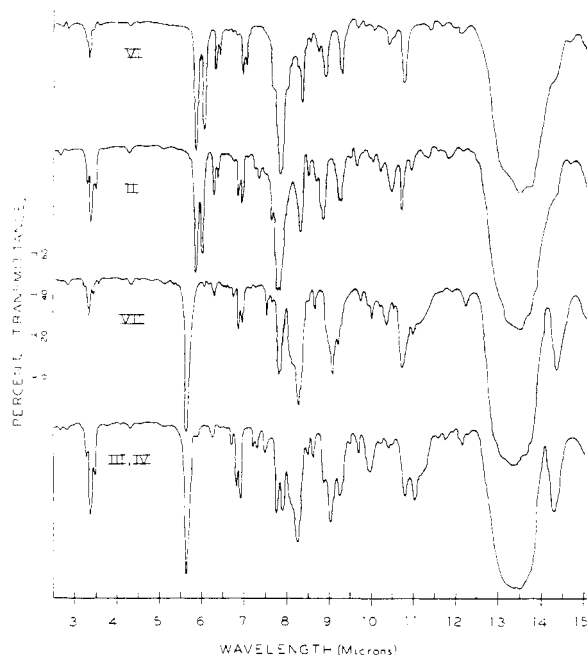


Fig. 1.—Infrared spectra of normal and pseudo esters.

and conveniently shows mixtures of the two. The normal esters II and VI in Fig. 1 show two carbonyl bands at 5.82 and 6.00 μ , a characteristic doublet at 6.25–6.30 μ and similarities in the 7.5–9.5 μ region. The normal *p*-isomer I also shows two carbonyl bands at 5.85 and 6.03 μ . The ψ -esters III, IV and VII (Fig. 1), on the other hand, show only the single carbonyl absorption at 5.65 μ which we find characteristic also of the parent phthalide.

TABLE I
ULTRAVIOLET ABSORPTION SPECTRA

Compound	λ_{\max} , m μ (log ϵ)	λ_{\min} , m μ (log ϵ)
I	255(4.47)	228(4.25)
VI	275(3.60), ^a 245(4.21)	228(4.11)
II	275(3.56), ^a 243(4.21)	228(4.15)
VII	276, 283(3.04) ^b	255(2.70)
III	277, 283(3.17) ^b	255(2.90)
IV	277, 283(3.09) ^b	260(2.95)
Phthalide ¹¹	280(3.28)	277(3.21)
	273(3.28)	248(2.54)
	227(4.06)	215(3.80)
VIII	264(2.58), 258(2.66), 252(2.55) ^b	

^a Shoulder. ^b "Doublet" or "triplet" (VIII).

Thin layer chromatography¹² with silica also provides a rapid means of distinguishing isomeric normal and ψ -esters and of detecting mixtures. Table II, showing typical R_f values for the esters in question, indicates that the ψ -esters run significantly faster than do the isomeric normal esters.

TABLE II
SILICA THIN LAYER CHROMATOGRAPHY OF *o*-BENZOYL BENZOATES

Ester	R_f in benzene ^a	
	Normal	Pseudo
Methyl	0.11	0.16
(-)-Menthyl	0.20	0.33(III), 0.33(IV)

^a Values determined on a single plate.

Optical rotatory dispersion (O.R.D.) is another physical property which is widely different for the normal ester II and the ψ -esters III and IV (Fig. 2). The

(11) These agree substantially with the data of W. A. Schroeder, P. E. Wilcox, K. N. Trueblood and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951).

(12) E. Demole, *Chromatographic Revs.*, **1**, 1 (1959).

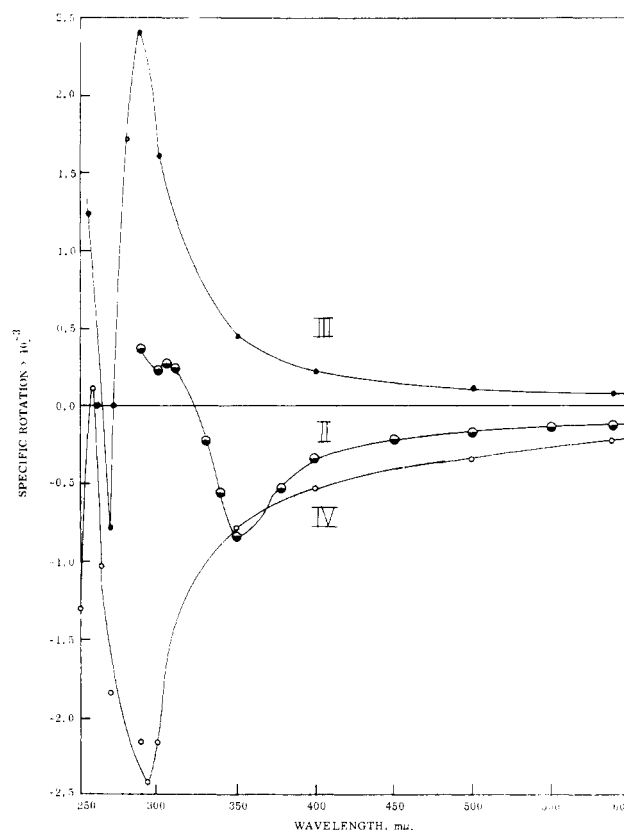


Fig. 2.—Optical rotatory dispersions.

dextrorotatory ψ -ester III shows a positive single Cotton effect curve with an amplitude¹³ of 3180° and a breadth¹³ of 20 m μ , while the levorotatory ψ -ester IV shows an almost mirror image negative single Cotton effect curve with amplitude -2537° and breadth 37 m μ . The normal ester II, on the other hand, shows a much weaker and less distinct negative Cotton effect curve with no striking features within the range of our measurements (it is not presently clear whether the slight inflection at 300 m μ is real or an artifact). The mean (*ca.* 276 m μ) of the peak and trough wave lengths of III and IV in Fig. 2 corresponds almost exactly to the observed λ_{\max} 277, 283 m μ (Table I) for these ψ -esters, and it is clear that one or both of these (presumably secondary¹⁴) benzene bands are the "optically active absorption bands" determining the rotatory dispersions of these compounds. The O.R.D. curve of the normal ester II, however, shows its broad, shallow trough far outside of the region of aromatic absorption of II, and it is apparent that its optically active absorption bands must lie in the inaccessible ultraviolet. The negative displacement of curve IV relative to the mirror image of curve III in Fig. 2 is presumably explainable in terms of the background rotatory contribution (not equivalent to curve II) of the (-)-menthyl moiety of these compounds.

We have also measured the O.R.D. of esters II, III and IV at a number of points over a portion (491–693 m μ) of the visible region of the spectrum and find that these dispersions are quite accurately described by simple Drude equations such as (1). The values of the

$$[\alpha]_{\lambda} = K/(\lambda^2 - \lambda_0^2) \quad (1)$$

rotation constant (K) and the dispersion constant (λ_0^2) in 1 for each ester are shown in Table III, as well as the limits of error with which each empirical equation de-

(13) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 13 ff.

(14) L. Doub and J. M. Vandenberg, *J. Am. Chem. Soc.*, **69**, 2714 (1947); **71**, 2414 (1949).

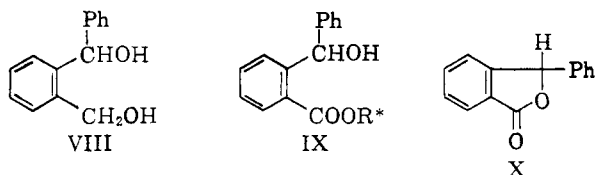
TABLE III
 SIMPLE DRUDE EQUATION DATA

Ester	K	λ_0^2, μ^2	$\lambda_0, m\mu$	Error, $\pm\%$
I	-19.43	-0.008 ± 0.002	..	0.4-0.9
II	-28.60	$+ .077 \pm .002$	278	.4-0.8
III	+12.22	$.093 \pm .001$	305	.5-1.3
IV	-55.80	$.045 \pm .002$	212	.6-1.1
V ^a	-55.80	$.063 \pm .001$	251	.3-0.6

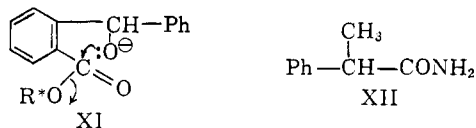
^a In CHCl_3 ; all others in EtOH.

scribes the O.R.D. of the sample in the spectral region in question. Column 4 of Table III indicates that eq. 1 does not accurately predict the ultraviolet spectral characteristics of these esters, and suggests that their visible O.R.D. actually should be described by multi-term Drude equations.^{15,16}

In connection with our original intention of using II to investigate "asymmetric induction" as a rationalization of asymmetric synthesis, the following experiments are pertinent. Lithium aluminum hydride reduction of both the normal ester II and the ψ -esters III and IV led to samples of *o*-hydroxymethylbenzhydrol (VIII) which were completely void of optical activity. Attempts utilizing sodium borohydride to achieve selective partial reduction of II to IX, wherein the original asymmetric centers of II remain intact, resulted in the formation of 3-phenylphthalide (X), which again was totally optically inactive. Similar results were noted when the (-)- ψ -ester IV was reduced with sodium



borohydride. In view of Newman's report⁵ that 3-phenyl-3-methoxyphthalide (VII) is rapidly converted to normal methyl *o*-benzoylbenzoate (VI) in a mildly alkaline environment, it appears likely that the conversion of the ψ -ester IV into X with sodium borohydride proceeds *via* the normal ester II. The well known reductive preference of sodium borohydride for carbonyl groups over ester functions¹⁷ argues, we believe, that the new asymmetric center at C3 in X must have been formed *prior* to elimination of the (-)-menthoxy moiety of II or IV. Once reduction of the keto-function of II is achieved, a facile intramolecular transesterification leading to X would be expected under alkaline conditions, as depicted in XI.



That the optical inactivity of X obtained from II or IV was inherent in its formation and not due to subsequent racemization was suggested by the following experiment. When optically active 2-phenylpropionamide (XII) was treated with sodium borohydride under conditions slightly more drastic than those prevailing during the above reductions, it was racemized to the extent of only 28%. One would anticipate that the asymmetric center in XII, activated by both phenyl and carboxamide groups, should be *more* subject to racemization in an alkaline environment than would be the asymmetric center in X. Ac-

cordingly, we feel that any optical activity present in the intermediate XI should appear in part at least in the final product X, and that the observed optical inactivity of X is a valid indication that no asymmetric synthesis has occurred during the sodium borohydride conversions of II \rightarrow (XI) \rightarrow X and IV \rightarrow (II) \rightarrow (XI) \rightarrow X. These results appear to substantiate our original disclosure² of the failure of "asymmetric induction" to be transmitted through the unsaturation electrons of aromatic nuclei.

It might be anticipated, that because of the *ortho* proximity of the benzoyl and carbo-(-)-menthoxy groups in II, there should be asymmetric bias in the conversion of II to X on purely steric grounds. Examination of Hirschfelder models of II, however, fails to reveal a clearly preferable steric path for the attack of borohydride on the keto function of II. In this connection, contrary to an earlier report,¹⁸ a recent study¹⁹ of the somewhat related lithium aluminum hydride-*d*-camphor reduction of ketones to alcohols has also failed to reveal asymmetric induction.

Experimental

Methyl *o*-benzoylbenzoate (VI) was prepared by action of diazomethane²⁰ in ether (100 ml.) on *o*-benzoylbenzoic acid (12 g.). The crude, sirupy product (10.8 g.; 85%) was crystallized from methanol (10 ml.) to produce 8.84 g., m.p. 51-52.5°, in agreement with the literature.^{6,9} The crude product ran as a single component with R_f 0.11 in silica T.L.C. using benzene as eluent.

3-Phenyl-3-methoxyphthalide (VII).—*o*-Benzoylbenzoic acid (25 g.) and thionyl chloride (50 ml.) were heated under reflux for 20 minutes, then the latter was removed. The residue was treated with a mixture of methanol (50 ml.) and pyridine (25 ml.), then allowed to stand for 2 days, after the procedure of Newman.⁵ The mixture was poured into water and processed in the usual way, yielding 25.5 g. of thin sirup which, on silica T.L.C. with benzene eluent, ran as two components, one with R_f corresponding to *o*-benzoylbenzoic anhydride and the other with R_f 0.16. No spot corresponding to normal methyl *o*-benzoylbenzoate was noted. The crude sirup, dissolved in methanol (18 ml.), seeded and chilled, yielded 22.6 g. (86%) of crystalline product, m.p. 81-82° in agreement with the literature.^{6,9} In an earlier experiment before seed crystals were available²¹ the first crystalline product obtained (3% of the total) had m.p. 139.5° and showed no mixed m.p. depression with *o*-benzoylbenzoic anhydride.

(-)-Menthyl *o*-Benzoylbenzoate (II).—A mixture of *o*-benzoylbenzoic acid (6.0 g.), (-)-menthol (18 g.), *p*-toluenesulfonic acid hydrate (1 g.) and benzene (25 ml.) was heated on the steam-bath for 20 hours, then was cooled and washed with 10% sodium hydroxide.⁵ Acidification of the alkaline extract produced a substantial quantity of unesterified acid. The benzene layer was steam distilled to remove menthol and the residue was extracted with ether. The extract was washed with 10% sodium hydroxide, dried over sodium sulfate, decolorized and freed of solvent to yield 3.05 g. (35%) of thick, amber sirup, $[\alpha]_D^{25} -92.1^\circ$ (c 3.1, CHCl_3). Silica T.L.C. and the infrared spectrum of this material indicated it to be normal ester (80%) containing smaller quantities (20%) of ψ -esters. Column chromatographic separation (hexane-benzene eluent) on Activity II alumina (600 g.) afforded a number of fractions all but the first two of which were T.L.C.-homogeneous samples of normal ester. These were combined; 1.36 g., $[\alpha]_D^{25} -107.9^\circ$ (c 1.0, CHCl_3), -110° (c 0.13, dioxane).

Anal. Calcd. for $\text{C}_{24}\text{H}_{26}\text{O}_3$: C, 79.09; H, 7.74. Found: C, 78.79; H, 7.88.

When the above preparation was repeated on a 2-fold scale using a Dean-Stark tube containing calcium chloride to remove the water produced during esterification, the yield of crude product, $[\alpha]_D^{25} -87.0^\circ$ (c 3.3, CHCl_3), was increased to 57%. This crude product, containing about 75% normal ester, was used in the sodium borohydride reductions below.

The following general observation appears noteworthy. In all reactions herein, work-up of which involved removal of menthol by steam distillation, it was found that the rate of menthol removal was markedly increased by the frequent addition of xylene to the steam distillation flask. This presumably resulted from the fact that the xylene kept the insoluble residue

(18) A. A. Bothner-By, *J. Am. Chem. Soc.*, **73**, 846 (1951).

(19) P. S. Portoghesi, *J. Org. Chem.*, **27**, 3359 (1962).

(20) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(21) Seed crystals were generously furnished by Prof. M. S. Newman.

(15) W. A. Bonner, *J. Am. Chem. Soc.*, **71**, 3384 (1949).

(16) H. Hunter, *J. Chem. Soc.*, **125**, 1198, 1389 (1924).

(17) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962 p. 243.

in suspension and prevented its "gumming up" on the still-pot walls.

(-)-Menthyl *p*-Benzoylbenzoate (I).—*p*-Benzoylbenzoic acid was prepared by oxidation of methyl *p*-tolyl ketone according to Wertheim.²² The acid (6.0 g.) was esterified with (-)-menthol using *p*-toluenesulfonic acid as described above to yield 8.00 g. (83%) of thick sirup, $[\alpha]_D^{25} -54.4^\circ$ (*c* 7.6, EtOH), in agreement with our previous observation.² Silica T.L.C. revealed the product to be homogeneous.

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 79.09; H, 7.74. Found: C, 79.15; H, 7.94.

The Diastereomers (III and IV) of 3-Phenyl-3-(-)-menthoxyphthalide.—*o*-Benzoylbenzoic acid (50 g.) in thionyl chloride (65 ml.) was heated at 60° for 2 hours, then was freed of excess thionyl chloride *in vacuo*. The crude acid chloride was treated with (-)-menthol (36.2 g., 1.05 moles) and pyridine (65 ml.) and the mixture was heated on the steam-bath for 3 hours, cooled, poured into water and extracted with ether. The extract was washed with water, dilute hydrochloric acid, water and sodium carbonate solution, then dried, decolorized and freed of solvent, affording 74.7 g. (92.7%) of amber sirup, $[\alpha]_D^{25} -54.2^\circ$ (*c* 9.9, EtOH). This was dissolved in ligroin (55° , 140 ml.) and allowed to stand overnight, yielding crystalline material. Further crops were recovered from the mother liquors by chilling and concentrating. The crystalline material was subjected to extensive fractional recrystallization from ligroin, ultimately affording two pure crystalline products and a sirupy residue. The first crystalline product was (-)-3-phenyl-3-(-)-menthoxyphthalide (IV), 13.7 g., m.p. $115-116^\circ$; $[\alpha]_D^{25} -200.3^\circ$ (*c* 1.0, $CHCl_3$), -183.5° (*c* 2.1, EtOH), -185.6° (*c* 2.0, MeOH), -216° (*c* 0.12, dioxane). Newman reports⁵ m.p. $116-117^\circ$ and $[\alpha]_D^{25} -186^\circ$ (*c* 2.1, MeOH) for this ψ -ester.

The second pure crystalline compound, 3.0 g., m.p. $142-143^\circ$, was shown by elemental analysis, mixed m.p. and the identity of its infrared absorption spectrum with that of an authentic sample to be *o*-benzoylbenzoic anhydride.²³

The above residual sirup, 3.83 g., $[\alpha]_D^{25} +39.9^\circ$ (*c* 5.1, $CHCl_3$), was investigated by silica T.L.C. using benzene eluent. It showed two spots, a heavy one having R_f identical with that of the above IV and a light one with R_f corresponding to that of the normal ester II. Chromatographic separation was accomplished as before with Activity II alumina (690 g.) using hexane-benzene (55:45) as eluent. The combined earlier fractions, 2.58 g. of sirup, were free (T.L.C.) of normal ester and showed $[\alpha]_D^{25} +46.5^\circ$ (*c* 1.4, $CHCl_3$), $+48.5^\circ$ (*c* 4.5, EtOH). On standing for several months this material partially crystallized; 0.32 g. The solid was recrystallized twice from ethanol to yield 0.08 g. of pure (+)-3-phenyl-3-(-)-menthoxyphthalide (III), m.p. $62-62.5^\circ$ (microscope hot-stage between crossed polaroid filters²⁴), $[\alpha]_D^{25} +60.0^\circ$ (*c* 0.47, $CHCl_3$), $+88^\circ$ (*c* 0.32, dioxane).

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 79.09; H, 7.74. Found: C, 78.90; H, 7.67.

During the above fractional crystallization a number of intermediate crystalline fractions totalling 13.5 g. was obtained. These had specific rotations ($CHCl_3$) varying between -1° and -76° and m.p.'s in the range $80-90^\circ$. They showed silica T.L.C. R_f values and infrared spectra identical in all respects with those of the pure ψ -esters described above, and were chromatographically free of normal ester. They appeared to be mixtures of the two diastereomeric ψ -esters of such compositions that separation by fractional crystallization was not feasible.

4-Phenyl-3,4-dehydro-1-oxo-2,3,1-benzoxazine (V).—An attempt was made to prepare a crystalline oxime from crude (-)-menthyl *o*-benzoylbenzoate prepared as above *via* the acid chloride. A mixture of crude ester (0.6 g.), hydroxylamine hydrochloride (0.6 g.), absolute ethanol (3 ml.) and pyridine (3 ml.) was heated on the steam-bath for 20 hours, freed of solvents and triturated with water, filtering the solid, 0.15 g. (40%), m.p. $162-162.5^\circ$. Recrystallization from methanol (5 ml.) gave 0.12 g., m.p. $162.5-163.5^\circ$. The same product resulted when the above procedure was applied to *o*-benzoylbenzoic acid. Combustion analysis indicated the product to be 4-phenyl-3,4-

dehydro-1-oxo-2,3,1-benzoxazine, the m.p. of which is reported²⁵ as 162° .

Spectra.—The ultraviolet absorption spectra listed in Table I were measured in absolute ethanol using a Cary Model 14M recording ultraviolet spectrophotometer. The infrared spectra shown in Fig. 1 were measured using 0.1 *M* solutions in chloroform in 0.1-mm. cells in a Perkin-Elmer Infracord, compensating for the chloroform solvent.

Optical Rotatory Dispersions.—The O.R.D. curves presented in Fig. 2 were obtained with a modified Rudolph automatic recording spectropolarimeter, samples being prepared in dioxane solution. These measurements were obtained through the courtesy of Prof. C. Djerassi. The visible O.R.D. data summarized in Table III were obtained in the manner fully described previously.¹⁶

Lithium Aluminum Hydride Reduction of (-)-Menthyl Esters of *o*-Benzoylbenzoic Acid.—The above crystalline ψ -ester IV (0.50 g.) in ether (10 ml.) was added with stirring to a solution containing excess lithium aluminum hydride in ether (20 ml.). The excess hydride was then destroyed with water and the alumina was dissolved with dilute sulfuric acid. The ether layer was evaporated and the residue was steam distilled to remove menthol. Salting, then extracting the aqueous residue with ether (Norit decolorization) yielded 0.25 g. (86%) of clear glass which crystallized on standing. This was recrystallized from ether (1.5 ml.) and hexane (1.0 ml.) to give 0.22 g. of white solid, m.p. $72-72.5^\circ$, unchanged on further recrystallization. The *o*-hydroxymethylbenzhydrol product (VIII) proved optically inactive in chloroform (*c* 2.4). In an earlier experiment the product was distilled prior to crystallization, b.p. $155-158^\circ$ (0.05 mm.).

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.37, 78.42; H, 6.59, 6.71.

Precisely similar results were obtained on lithium aluminum hydride reduction of both the above ψ -ester III and sirupy normal ester II, optically inactive VIII resulting in each case.

Sodium Borohydride Reduction of (-)-Menthyl *o*-Benzoylbenzoate.—The above crude normal ester II (containing approximately 25% ψ -ester, 4.5 g.) was dissolved in 2-propanol (50 ml.) and treated with sodium borohydride (0.5 g.). The mixture was heated under reflux for 0.5 hour, cooled, added to 10% hydrochloric acid (150 ml.) and extracted twice with ether. The extracts were washed with sodium bicarbonate solution, dried and freed of solvent to yield 3.91 g. of amber oil smelling of menthol. This was treated with hexane (5 ml.), causing immediate crystallization; 1.73 g., m.p. $114-115^\circ$. The product was recrystallized from a mixture of 2-propanol and hexane to give a pure sample, m.p. $116.5-117^\circ$, optically inactive (*c* 2.3, $CHCl_3$). The product was shown by its combustion analysis, infrared spectrum and m.p. (reported²⁶ m.p. 117°) to be 3-phenylphthalide. Silica T.L.C. examination of the mother liquors from the above crystallization showed the presence of small quantities of the diol VIII.

Sodium Borohydride Reduction of (-)-3-Phenyl-3-(-)-menthoxyphthalide.—The above ψ -ester IV (1.00 g.), sodium borohydride (0.1 g.) and 2-propanol (15 ml.) were heated under reflux for 0.5 hour. The mixture was processed as described above, affording 0.10 g. of solid, m.p. $112-115^\circ$. One recrystallization gave pure 3-phenylphthalide, m.p. $116-117^\circ$, optically inactive (*c* 1.1, $CHCl_3$). Silica T.L.C. investigation of the mother liquors again revealed the presence of the diol VIII.

Action of Sodium Borohydride on (+)-2-Phenylpropionamide.—To test whether the racemization of 3-phenylphthalide in the above experiments occurred during or after its formation, the following experiment was conducted. (+)-2-Phenylpropionamide (m.p. $96.5-97.5^\circ$, $[\alpha]_D^{25} +48.8^\circ$ (*c* 0.84, $CHCl_3$), 0.30 g.), sodium borohydride (0.06 g.) and 2-propanol (4 ml.) were heated under reflux for 0.5 hour, whereupon the product was isolated as described above. The crude material, 0.26 g. (87%), was recrystallized from a mixture of benzene (1 ml.) and hexane (2.5 ml.) to yield 0.13 g. of white platelets, m.p. $92.5-93.5^\circ$, mixed m.p. with starting material $94-96^\circ$, $[\alpha]_D^{25} +35.1^\circ$ (*c* 1.22, $CHCl_3$). The optical rotation of the recovered product indicates that racemization to the extent of 28% had occurred under the above reaction conditions.

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