[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

# Asymmetric Synthesis in an Aldol Type Condensation of Ketone with Ester[1]

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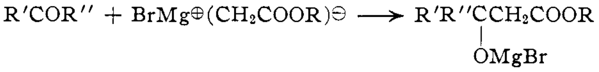
In aldol condensations with (−)-menthyl or (+)-bornyl acetate by means of diethylaminomagnesium bromide, *o*- and/or *p*-substituted benzophenones as well as α-naphthophenone gave, upon hydrolysis of the resulting esters, optically active β-hydroxy acids; however, the reaction of *p*-chlorobenzophenone with (−)-menthyl acetate afforded the optically inactive β-hydroxy acid. These results are interpreted in terms of a steric factor and a comparison is made with cases of ketone addition covered by Prelog's rule.

Prelog[2] has summarized the asymmetric synthesis of α-hydroxy acids by the action of the Grignard reagents on α-keto esters of optically active alcohols. In this condensation the reaction center, *i. e.*, the keto carbonyl group, and the asymmetric center, *i. e.*, the alkoxy group of the ester alcohol, are in the same molecule. Reid and Turner,[3] on the other hand, have reported asymmetric synthesis in a Reformatsky reaction where the reaction center and the asymmetric center are in different molecules. They obtained dextrorotatory 3-hydroxy-3-phenylbutyric acid from acetophenone and (−)-menthyl bromoacetate in about 33% optical yield.[4]

It has previously been reported from this Laboratory[5] that the condensation of the aldol type between various ketones and acetates can be effected by means of diethylaminomagnesium bromide. This reaction proceeds apparently through the enolate anion of the acetate which adds to the carbonyl group of the ketone; hence, it seems that this reaction takes essentially the same course as the Reformatsky reaction.

$$CH_3COOR + (C_2H_5)_2NMgBr \longrightarrow BrMg^{\oplus}(CH_2COOR)^{\ominus} + NH(C_2H_5)_2$$



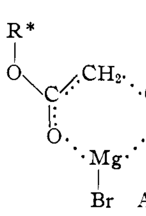
$$R'COR'' + BrMg^{\oplus}(CH_2COOR)^{\ominus} \longrightarrow \underset{\displaystyle OMgBr}{R'R''\overset{}{C}}CH_2COOR$$

In the present paper an asymmetric synthesis in this condensation has been studied using *p*-methoxy-, *p*-methyl-, *p*-chloro-, *o*-methyl- or *o,p*-dimethylbenzophenone as well as α-naphthophenone as the ketone and (−)-menthyl or (+)-bornyl acetate as the ester component.

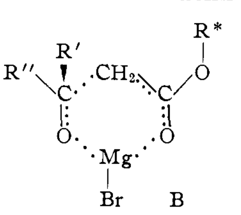
An equimolar solution of the respective ketone and ester was added at −5° to an excess (3 equivalents) of diethylaminomagnesium bromide in ether. The total β-hydroxy ester produced was saponified with an excess of alcoholic potash and the neutral substance was thoroughly extracted to remove the optically active alcohol introduced in the starting ester. In order to check the possibility of asymmetric hydrolysis,[6] saponification was repeated on the neutral substance, but no appreciable further acidic product was obtained. Acidification of the saponified product gave the slightly colored β-hydroxy acid which crystallized immediately in each case. The self-condensation of the acetate was apparently suppressed by the bulkiness of menthyl or bornyl group as it is by that of the *t*-butyl group,[5] since the over-all yield was fairly high (about 70–80%). The infrared spectrum of the optically active acid was compared with that of the pure *dl*-acid and both were essentially identical throughout the sodium chloride prism region. Reproducibility of the rotation could be achieved within 3% of the optical yield in duplicate experiments. Some methyl esters of the active acids were prepared with diazomethane and their optical rotations and infrared spectra were examined.

In order to estimate the optical yield, 3-(*p*-anisyl)-3-phenyl-, 3-phenyl-3-(*o*-tolyl)- and 3-(α-naphthyl)-3-phenylhydracrylic acid were resolved by means of cinchonine or brucine. Since side reactions, which should be considered in this system,[5] consume no hydroxy acid asymmetrically synthesized, the optical yields of the reaction could not be influenced by them. Representative results are summarized in Table I.

The cause of this asymmetric reaction, if irreversible,[7] can be visualized by assuming the quasi-six-membered cyclic states A and B.[8,9] Thus the diastereomeric transition state which is more stable will naturally lead to the predominant enantiomer, for there should be a definite difference in thermodynamic stabilities of A and B because of the steric interaction of the groups



A



B

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[1] Part of this paper was presented before the "Symposium on Mechanisms of Organic Reactions" promoted by the Chemical Society of Japan, Osaka, October, 1955. This program was supported in part by a research-grant from the Ministry of Education, Japanese Government.

[2] V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

[3] J. A. Reid and E. E. Turner, *J. Chem. Soc.*, 3365 (1949); 3694 (1950).

[4] Optical yield means the ratio of the optical purity of the product to the optical purity of the starting material in per cent.

[5] K. Sisido, H. Nozaki and O. Kurihara, THIS JOURNAL, **74**, 6254 (1952); see also C. R. Hauser and W. H. Puterbaugh, *ibid.*, **73**, 2972 (1951).

[6] A. McKenzie and H. Wren, *J. Chem. Soc.*, 680 (1920).

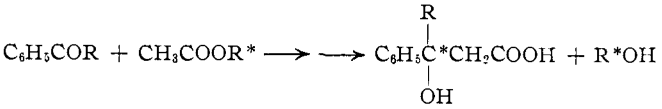
[7] C. R. Hauser and W. H. Puterbaugh, THIS JOURNAL, **75**, 4756 (1953). Though these authors have noticed dealdolization in this type of reaction, it would be safe to consider that the course of the reaction is kinetically controlled under the conditions adopted here (2 hours stirring at −5°).

[8] C. R. Hauser and H. G. Walker, Jr. (*ibid.*, **69**, 295 (1947)) have suggested similar cyclic transition state in the self-condensation of esters by means of diethylaminomagnesium bromide.

[9] In a paper by H. E. Zimmerman and M. D. Traxler (*ibid.*, **79**, 1920 (1957)) on the stereochemistry of the Ivanov reaction, the conformation of a transition state of this type having the lowest energy is discussed.

TABLE I

ASYMMETRIC SYNTHESIS OF β-HYDROXY ACIDS AT −5°



$$C_6H_5COR + CH_3COOR^* \longrightarrow \longrightarrow C_6H_5\overset{R}{\underset{OH}{C^*}}CH_2COOH + R^*OH$$

| Run | $C_6H_5COR$, R | $CH_3COOR^*$, R* | β-Hydroxy acid<br>Yield,[a] % | αD[b] | [α]D[b] | [α]D of pure isomer[b] | Optical yield, % |
|---|---|---|---|---|---|---|---|
| 1 | p-$CH_3OC_6H_4$ | (−)-Menthyl | 72 | +0.49° | + 2.3° | + 14.2° | 16 |
| 2 | p-$CH_3OC_6H_4$ | (+)-Bornyl | 72 | + .26 | + 1.0 | + 14.2 | 7 |
| 3 | p-$CH_3C_6H_4$ | (−)-Menthyl | 69 | + .04 | + 0.3 | | |
| 4 | p-$CH_3C_6H_4$ | (+)-Bornyl | 70 | + .13 | + 1.0 | | |
| 5 | p-$ClC_6H_4$ | (−)-Menthyl | 72 | Inactive | | | |
| 6 | p-$ClC_6H_4$ | (+)-Bornyl | 75 | +0.05° | + 0.2° | | |
| 7 | o-$CH_3C_6H_4$ | (−)-Menthyl | 72 | −5.56 | −80.5 | −168 | 48 |
| 8 | o-$CH_3C_6H_4$ | (+)-Bornyl | 73 | +1.24 | + 6.7 | −168 | 4 |
| 9 | o,p-$(CH_3)_2C_6H_3$ | (−)-Menthyl | 74 | −5.51 | −74.1 | | |
| 10 | o,p-$(CH_3)_2C_6H_3$ | (+)-Bornyl | 72 | +0.57 | + 7.7 | | |
| 11 | α-$C_{10}H_7$ | (−)-Menthyl | 79 | +3.13 | +43.7 | +207 | 21 |
| 12 | α-$C_{10}H_7$ | (+)-Bornyl | 82 | +4.63 | +63.5 | +207 | 30 |

[a] Over-all yield in steps of condensation, saponification and acidification. [b] For details, see Experimental.

attached to the keto carbonyl (R′ and R″) with the optically active group of esters (R*).[10]

When o-methyl- or o,p-dimethylbenzophenone was allowed to react with (−)-menthyl acetate, highly levorotatory 3-phenyl-3-(o-tolyl)- or 3-(o,p-dimethylphenyl)-3-phenylhydracrylic acid, respectively, was obtained (run 7 and 9). With (+)-bornyl acetate, on the other hand, both of these ketones gave slightly dextrorotatory products (run 8 and 10). The parallel sign and magnitude of rotation of the resulting β-hydroxy acids are reasonable, because the two benzophenone derivatives differ only in the additional p-methyl substituent and the effective bulkiness of the groups attached to the ketonic carbonyl seems essentially the same.

Comparison of the optical yields of the reaction of (−)-menthyl acetate with p-substituted benzophenones and o- or o,p-substituted ones as well as α-naphthophenone confirms the interpretation that p-substituents are less effective than o-substituents. It appears notable, however, that the reaction of (+)-bornyl acetate with o- or o,p-substituted benzophenones gives hydroxy acids in remarkably lower optical yields (run 8 and 10).

In accordance with expectation, the experimentally observed optical rotations of the products obtained from the p-substituted benzophenones were comparatively minute and in one case p-chlorobenzophenone gave the optically inactive hydroxy acid. The optical purity of these acids could be raised by a process of recrystallization: active acids with a respectable magnitude of rotation were obtained from the first mother liquors. The infrared spectra of these acids were completely identical with those of the authentic, optically inactive samples. In this way the dextrorotatory 3-(p-anisyl)-3-phenylhydracrylic acid was fractionated to about 50% optical purity. Optical rotations of the acids were also measured in sodium hydroxide solution.

Mosher and Parker[11] have obtained optically inactive benzhydrols from p-chloro- or p-methoxybenzophenone and an optically active one from o-chlorobenzophenone by the action of (+)-2-methylbutylmagnesium chloride in ether. They attributed the optical inactivity to the longer distance of the p-substituents of the benzophenones from the asymmetric carbon in the transition state. Though the same screening effect of the planar benzene ring toward substituents in the p-position should be at work in the present aldol type condensation, optically active β-hydroxy acids could actually be obtained from p-methoxy- and p-methylbenzophenone (run 1, 2, 3 and 4). The p-substituent of the phenyl group may be considered, therefore, to interact in the present cases with the asymmetric carbons of the alkoxy group of the acetate.

Prelog[2] has classified optically active alcohols on the basis of their configurations at the asymmetric carbinol carbon atom into two groups, type a and b, according to the sign of rotation of the α-hydroxy acids asymmetrically synthesized by the Grignard reaction with α-keto esters of such alcohols. Thus (−)-menthol is of type b and (+)-borneol of type a. This rule of Prelog's might be considered applicable to the cyclic transition state in the aldol type condensation, provided that the main chain of the reacting species could be assumed to be held planar and the difference in the reaction system could be neglected. It appears however, that this rule was not applicable as shown in Table I; namely, p-methoxy- and p-methylbenzophenone as well as α-naphthophenone gave β-hydroxy acids of the same sign of rotation irrespective of the alcohol type in the acetates. The discrepancy might be attributed to the following facts: (1) a methylene group is interposed between the carbonyl group and the ester group and (2), therefore the two asymmetric carbons in the optically active alcohol portion which are not attached directly to the oxygen may act as asym-

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[10] Attention was focused on the transition state of the asymmetric synthesis of this type by Reid and Turner (ref. 3); see also D. M. Bovey, J. A. Reid and E. E. Turner, *J. Chem. Soc.*, 3227 (1951).

[11] H. S. Mosher and E. D. Parker, THIS JOURNAL, **78**, 4081 (1956).

metry-inducing centers, this effect being neglected by Prelog in this $\alpha$-keto ester series. A further reasoning may be given by the fact that the optical yield are determined in the present aldol type condensation by the interaction between the asymmetric centers of the terpene alcohols and the *two* groups attached to the carbonyl group of ketones in the cyclic transition state, whereas the interaction with *one* entering group is important in the case of $\alpha$-keto esters.

## Experimental[12]

**(−)-Menthyl Acetate.**[13]—To a solution of 93 g. (0.6 mole) of (−)-menthol crystals in 92 g. (0.9 mole) of acetic anhydride several drops of saturated hydrogen bromide dissolved in acetic anhydride was added and the mixture was stirred for two hours at 65°. The reaction mixture was decomposed with water, extracted with ether and the combined ethereal extracts were washed with sodium bicarbonate solution and water. After drying over anhydrous sodium sulfate, ether was removed and the residue was distilled *in vacuo* through a column of approximately six theoretical plates to give (−)-menthyl acetate, b.p. 117.5–118° (24 mm.), $\alpha^{14}$D −73.92° (neat), yield 98 g. (83%).

**(+)-Bornyl Acetate.**[13]—The reduction product of *d*-camphor, a borneol–isoborneol mixture, was treated according to the method of Pickard and Littlebury.[14] (+)-Borneol[15] thus obtained, m.p. 204.5°, $[\alpha]^{21}$D +36.8° (*l* 2, *c* 9.99, toluene), was acetylated as above and distilled *in vacuo*, b.p. 92–93° (8 mm.), $\alpha^{14}$D +44.72° (neat).

**Interaction of *p*-Methoxybenzophenone with (−)-Menthyl Acetate in the Presence of Diethylaminomagnesium Bromide.**—A typical experiment in the aldol type condensation was (The final product crystallized immediately in each run.): To a Grignard reagent prepared from 16.4 g. (0.15 mole) of ethyl bromide, 3.7 g. (0.15 g. atom) of magnesium turnings and 60 ml. of ether was added a solution of 11 g. (0.15 mole) of diethylamine in 20 ml. of ether under stirring and cooling with ice. The mixture was stirred for 30 minutes at room temperature and then refluxed for 15 minutes. A solution of 10.6 g. (0.05 mole) of *p*-methoxybenzophenone[16] and 9.9 g. (0.05 mole) of (−)-menthyl acetate in 45 ml. of toluene was then added dropwise to the above prepared reagent during the course of 90 minutes under vigorous stirring at −5°. After stirring for an additional two hours at the same temperature, 15 ml. of saturated ammonium chloride solution was added to the reaction mixture. The supernatant organic layer was separated and the residual semi-solid was washed with ether repeatedly. The combined organic layers were washed successively with cold 10% sulfuric acid, water, sodium bicarbonate solution and again with water and the solvent was evaporated *in vacuo*. The washing with the aqueous sulfuric acid removed most of the coloration. All the materials obtained were dissolved in excess of 0.5 *N* alcoholic potash and the homogeneous solution was kept overnight at room temperature. The mixture was warmed for two hours at 50° and ethanol was removed *in vacuo*. The residue was shaken with benzene and water and the benzene layer was washed with water. The combined alkaline layers were repeatedly extracted with ether until the last extract showed no optical rotation. The alkaline layer was acidified with cold 2 *N* acetic acid under cooling with ice and extracted with ethyl acetate after addition of sodium chloride. The ethyl acetate solution was dried over sodium sulfate and concentrated to dryness *in vacuo*, when pale yellow solids were obtained. The product was kept over calcium chloride and sodium hydroxide *in vacuo* until the acetic acid odor disappeared. The yield of 3-(*p*-anisyl)-3-phenylhydracrylic acid (Ia) was 9.1 g. (67%); m. p. 155–156.5° (with foaming); $\alpha^{24}$D +0.23°, $[\alpha]^{24}$D +2.1° (*c* 10.89, dioxane).

A single crystallization from methanol resulted in the loss of most of the optical rotation. Repeated recrystallizations gave racemic 3-(*p*-anisyl)-3-phenylhydracrylic acid (*dl*-I), m. p. 160–160.5° (with foaming).

*Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.97. Found: C, 70.49; H, 5.96.

Duplicate experiment on a 0.05-mole scale: yield 9.8 g. (72%), m.p. 157–158.5° (with foaming), $\alpha^{15}$D +0.49°, $[\alpha]^{15}$D +2.3° (*l* 2, *c* 10.67, dioxane). After decolorization with active charcoal in ethyl acetate, the acid had $\alpha^{16}$D +0.47°, $[\alpha]^{16}$D +2.2° (*l* 2, *c* 10.80, dioxane). Recrystallization from methanol gave nearly inactive acid, m.p. 160–160.5° (with foaming), while the mother liquor gave acid Ib having higher optical activity: m.p. 153–154.5° (with foaming), $\alpha^{14}$D +0.83°, $[\alpha]^{14}$D +6.8° (*l* 2, *c* 6.08, dioxane), $\alpha^{18}$D +0.90° (*l* 2, *c* 6.12, 2 *N* NaOH).

When the neutral substances obtained by extracting the saponification mixture were subjected to resaponification, no appreciable amount of acidic material was obtained.

**Interaction of *p*-Methoxybenzophenone with (+)-Bornyl Acetate.**—A solution of 6.4 g. (0.03 mole) of *p*-methoxybenzophenone[16] and 5.9 g. (0.03 mole) of (+)-bornyl acetate in 20 ml. of toluene was added to 0.09 mole of diethylaminomagnesium bromide in 50 ml. of ether at −5° during the course of 30 minutes. Hydrolysis of the condensation product gave the acid Ic, the (+)-enantiomer predominating. The yield of 3-(*p*-anisyl)-3-phenylhydracrylic acid was 5.1 g. (63%), m.p. 159–160.5° (with foaming), $\alpha^{31}$D +0.16°, $[\alpha]^{31}$D +1.2° (*c* 13.21, dioxane).

Duplicate experiment on a 0.05-mole scale: yield 9.8 g. (72%), m.p. 152–153° (with foaming); (after decolorization) $\alpha^{23}$D +0.26°, $[\alpha]^{23}$D +1.0° (*l* 2, *c* 12.98, dioxane); the acid Id obtained from the first mother liquor of recrystallization: m.p. 151–153.5° (with foaming), $\alpha^{23}$D +0.46°, $[\alpha]^{23}$D +2.1° (*l* 2, *c* 10.98, dioxane).

**Examination of the Purity of 3-(*p*-Anisyl)-3-phenylhydracrylic Acid.**—In order to exclude the possibility of the presence of optically active impurities in the various preparations of this acid, the following experiments were carried out. The infrared spectra of *dl*-I, Ia, Ib, Ic and Id were taken as Nujol mulls because of the sparing solubility in usual solvents. These spectra showed appreciable differences in the fingerprint region, which might be due to the different crystalline forms between the racemic and the partially racemic acids. Approximately, these five spectra appear to be classified into two groups: *dl*-I and Ib; Ia, Ic and Id; common absorption bands to all: $\nu_{max}$ 2630, 2030, 1680, 1610, 1580, 1509, 1492, 1331, 1300, 1257, 1226, 1176, 1120, 1095, 1067, 1038, 1025, 1007, 985, 866, 805, 793, 736 and 702 cm.$^{-1}$; other specific bands ($\nu_{max}$, cm.$^{-1}$) for *dl*-I: 3564, 1398, 1194, 1168, 944, 931, 913, 893, 854, 832, 822 and 765; for Ib: 3564, 1398, 1194, 1168, 944, 931, 913, 893, 854, 842, 832, 822 and 765; for Ia: 3522, 1410, 1398, 952, 926, 897, 832, 822 and 775; for Ic: 3505, 1410, 952, 924, 897, 828, 818 and 775; for Id: 3510, 1410, 1398, 952, 928, 897, 830, 820, 775 and 765.

Racemic methyl 3-(*p*-anisyl)-3-phenylhydracrylate (*dl*-I′) was prepared from *dl*-I and diazomethane in ether and recrystallized from methanol, m.p. 110–110.5°.

*Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.49; H, 6.52.

The same procedure with no recrystallization gave the methyl ester of Ib (Ib′), m.p. 101–106°, $\alpha^{16}$D +0.64°, $[\alpha]^{16}$D +6.2° (*c* 10.30, dioxane); and that of Id (Id′), m.p. 106–108°, $\alpha^{15}$D +0.34°, $[\alpha]^{15}$D +2.0° (*c* 5.89, dioxane).

The ester was soluble in carbon tetrachloride and carbon disulfide. The infrared spectra of these three methyl esters (*dl*-I′, Ib′ and Id′) in solution were found completely identical throughout the sodium chloride prism region; $\nu_{max}$ ($CCl_4$): 3503, 3052, 3020, 2996, 2952, 2901, 2835, 1719, 1606, 1579, 1506, 1491, 1458, 1443, 1434, 1411, 1374, 1335, 1300, 1247, 1202, 1176, 1158, 1116, 1091, 1062, 1038, 1022, 1004, 995, 940, 923, 904, 896, 851; $\nu_{max}$ ($CS_2$): 830, 792, 762, 727 and 698 cm.$^{-1}$.

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[12] All melting points were uncorrected. The measurements of the optical rotations were made with a Schmidt and Haensch polarimeter, using a 1-dm. tube unless otherwise stated. The infrared spectra were taken with a Kôken DS301 double-beam spectrophotometer equipped with a sodium chloride prism. Microanalyses were performed by Miss K. Ogawa of this Laboratory.

[13] The acetylation is based on the unpublished work of this Laboratory; *cf.* K. Sisido and H. Nozaki, THIS JOURNAL, **70**, 3326 (1948).

[14] P. H. Pickard and W. O. Littlebury, *J. Chem. Soc.*, **91**, 1977 (1907).

[15] V. Prelog and H. L. Meier (*Helv. Chim. Acta*, **36**, 320 (1953)) obtained (+)-borneol having m.p. 206° and $[\alpha]^{18}$D +36.7° (*c* 9.941).

[16] Prepared by the method of L. Gattermann, R. Ehrhardt and H. Maisch (*Ber.*, **23**, 1199 (1890)) and recrystallized repeatedly from ether, m.p. 63–63.5°.

**Interaction of *p*-Methylbenzophenone with (−)-Menthyl Acetate.**—A solution of 9.8 g. (0.05 mole) of *p*-methylbenzophenone[17] and 9.9 g. (0.05 mole) of (−)-menthyl acetate in 40 ml. of toluene was used. Addition time was one hour. After hydrolysis the product formed the nearly colorless 3-phenyl-3-(*p*-tolyl)-hydracrylic acid (IIa), m.p. 182.5–184° (with foaming), $\alpha^{14}$D +0.03°, $[\alpha]^{14}$D +0.4° (*c* 6.92, dioxane), yield 9.7 g. (76%).

Repeated recrystallizations of the acid from methanol gave the racemic 3-phenyl-3-(*p*-tolyl)-hydracrylic acid (*dl*-II),[18] m.p. 187.5–188° (with foaming).

*Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.10; H, 6.41.

Duplicate experiment on a 0.05-mole scale: yield 8.8 g. (69%), m.p. 183–184° (with foaming); (after decolorization) $\alpha^{23}$D +0.04°, $[\alpha]^{23}$D +0.3° (*l* 2, *c* 6.43, dioxane); the acid IIb obtained from the first mother liquor of recrystallization: m.p. 179–181.5° (with foaming), $\alpha^{27}$D +0.11°, $[\alpha]^{27}$D +0.8° (*l* 2, *c* 6.74, dioxane).

**Interaction of *p*-Methylbenzophenone with (+)-Bornyl Acetate.**—A solution of 5.9 g. (0.03 mole) of *p*-methylbenzophenone[11] and 5.9 g. (0.03 mole) of (+)-bornyl acetate in 20 ml. of toluene was used. Addition time was 40 minutes. The slightly colored 3-phenyl-3-(*p*-tolyl)-hydracrylic acid (IIc) obtained upon hydrolysis weighed 5.0 g. (65%), m.p. 186.5–187° (with foaming), $\alpha^{14}$D +0.07°, $[\alpha]^{14}$D +1.2° (*c* 5.97, dioxane).

Duplicate experiment on a 0.05-mole scale: yield 9.0 g. (70%), m.p. 183–185° (with foaming); (after decolorization) $\alpha^{27}$D +0.13°, $[\alpha]^{27}$D +1.0° (*l* 2, *c* 6.53, dioxane). The acid IId obtained from the first mother liquor of recrystallization: m.p. 179–181° (with foaming), $\alpha^{27}$D +0.30°, $[\alpha]^{27}$D +2.3° (*l* 2, *c* 6.54, dioxane).

The infrared spectra of *dl*-II, IIa, IIb, IIc and IId in Nujol were identical: $\nu_{max}$ 3526, 2642, 1904, 1685, 1601, 1510, 1495, 1413, 1263, 1233, 1186, 1175, 1099, 1067, 1035, 1017, 1000, 985, 969, 956, 925, 899, 868, 849, 817, 803, 774, 734 and 701 cm.$^{-1}$.

**Interaction of *p*-Chlorobenzophenone with (−)-Menthyl Acetate.**—A solution of 6.5 g. (0.03 mole) of *p*-chlorobenzophenone[19] and 5.9 g. (0.03 mole) of (−)-menthyl acetate in 25 ml. of toluene was used. Addition time was 30 minutes. Hydrolysis of the condensation product gave the colorless 3-(*p*-chlorophenyl)-3-phenylhydracrylic acid (IIIa) which showed no optical activity; yield 3.4 g. (41%), m.p. 184–185° (with foaming), $\alpha^{28}$D <0.01° (*l* 2.2, *c* 12.13, dioxane).

Repeated recrystallizations from methanol gave the racemic 3-(*p*-chlorophenyl)-3-phenylhydracrylic acid (*dl*-III),[20] m.p. 188.5° (with foaming).

*Anal.* Calcd. for $C_{15}H_{13}O_3Cl$: C, 65.11; H, 4.74. Found: C, 65.41; H, 4.88.

Duplicate experiment on a 0.04-mole scale: yield 8.0 g. (72%), m.p. 182–183.5° (with foaming), $\alpha^{15}$D <0.01° (*l* 2, *c* 10.02, N,N-dimethylformamide); (after decolorization) $\alpha^{12}$D <0.01° (*l* 2, *c* 11.20, N,N-dimethylformamide).

**Interaction of *p*-Chlorobenzophenone with (+)-Bornyl Acetate.**—A solution of 6.5 g. (0.03 mole) of *p*-chlorobenzophenone[19] and 5.9 g. (0.03 mole) of (+)-bornyl acetate in 25 ml. of toluene was used. Addition time was 25 minutes. Hydrolysis of the condensation product gave 3-(*p*-chlorophenyl)-3-phenylhydracrylic acid (IIIb) which was slightly dextrorotatory; yield 4.6 g. (57%), m.p. 179–180.5° (with foaming), $\alpha^{25}$D +0.03°, $[\alpha]^{25}$D +0.1° (*l* 2.2, *c* 12.15, dioxane).

Duplicate experiment on a 0.04-mole scale: yield 8.3 g. (75%), m.p. 169–174° (with foaming), $\alpha^{15}$D +0.05°, $[\alpha]^{15}$D +0.2° (*l* 2, *c* 10.44, N,N-dimethylformamide). The acid IIIc obtained from the mother liquor of recrystallization: $\alpha^{14}$D +0.07° (*l* 2, *c* 12.66, N,N-dimethylformamide), $\alpha^{12}$D +0.08° (*l* 2, *c* 18.82, 2 *N* NaOH).

The infrared spectra of *dl*-III, IIIa, IIIb and IIIc in Nujol were identical: $\nu_{max}$ 3478, 2632, 1943, 1893, 1679, 1595, 1487, 1408, 1326, 1228, 1176, 1116, 1094, 1064, 1029, 1010, 998, 978, 962, 951, 917, 896, 865, 836, 823, 775, 750 and 695 cm.$^{-1}$.

**Interaction of *o*-Methylbenzophenone with (−)-Menthyl Acetate.**—A solution of 5.9 g. (0.03 mole) of *o*-methylbenzophenone[21] and 5.9 g. (0.03 mole) of (−)-menthyl acetate in 20 ml. of ether was used. Addition time was 30 minutes. The hydrolysis product was taken up with ether. The yield of 3-phenyl-3-(*o*-tolyl)-hydracrylic acid (IVa) was 5.5 g. (72%), m.p. 148–152° (with foaming), $\alpha^{29}$D −5.56°, $[\alpha]^{29}$D −80.5° (*c* 6.91, acetone).

Duplicate experiment on a 0.03-mole scale: yield 6.1 g. (79%), m.p. 149–151.5° (with foaming), $\alpha^{18}$D −5.45°, $[\alpha]^{18}$D −79.6° (*c* 6.85, acetone); (after decolorization) $\alpha^{18}$D −5.45, $[\alpha]^{18}$D −80.0° (*c* 6.81, acetone).

**Interaction of *o*-Methylbenzophenone with (+)-Bornyl Acetate.**—A solution of 5.9 g. (0.03 mole) of *o*-methylbenzophenone[21] and 5.9 g. (0.03 mole) of (+)-bornyl acetate in 20 ml. of ether was used. Addition time was 15 minutes. Hydrolysis of the condensation product gave dextrorotatory 3-phenyl-3-(*o*-tolyl)-hydracrylic acid (IVb), m.p. 148–150° (with foaming), yield 5.6 g. (73%), $\alpha^{29}$D +1.24°, $[\alpha]^{29}$D +6.7° (*c* 18.56, acetone); (after decolorization) $\alpha^{29}$D +1.24°, $[\alpha]^{29}$D +6.8° (*c* 18.36, acetone).

Upon a single recrystallization from methanol the optical activity was lost. Repeated recrystallizations gave the racemic 3-phenyl-3-(*o*-tolyl)-hydracrylic acid (*dl*-IV), m.p. 152.5–153° (with foaming).

*Anal.* Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.72; H, 6.28.

Duplicate experiment on a 0.03-mole scale: yield 4.9 g. (64%), m.p. 150–151° (with foaming), $\alpha^{23}$D +2.15°, $[\alpha]^{23}$D +11.5° (*c* 18.63, acetone); (after decolorization) $\alpha^{22}$D +2.15°, $[\alpha]^{22}$D +11.6° (*c* 18.48, acetone).

The infrared spectra of *dl*-IV, IVa and IVb in solution were identical; $\nu_{max}$ ($CCl_4$): 3521, 3058, 3012, 2604, 1953 1751, 1709, 1667, 1613, 1550, 1495, 1456, 1431, 1408, 1383, 1323, 1290, 1253, 1229, 1211, 1178, 1135, 1092, 1063, 1036, 1024, 953, 936, 925, 898; $\nu_{max}$ ($CS_2$): 754, 727 and 701 cm.$^{-1}$.

**Interaction of *o,p*-Dimethylbenzophenone with (−)-Menthyl Acetate.**—A solution of 6.3 g. (0.03 mole) of *o,p*-dimethylbenzophenone[22] and 5.9 g. (0.03 mole) of (−)-menthyl acetate in 20 ml. of ether was used. Addition time was 20 minutes. The hydrolysis product was taken up with ether. The yield of 3-(*o,p*-dimethylphenyl)-3-phenylhydracrylic acid (Va) was 4.9 g. (60%), m.p. 109–125° (with foaming), $\alpha^{16}$D −2.44°, $[\alpha]^{16}$D −73.8° (*c* 3.30, acetone).

Duplicate experiment on a 0.03-mole scale: yield 6.0 g. (74%), m.p. 106–125° (with foaming), $\alpha^{29}$D −5.51°, $[\alpha]^{29}$D −74.1° (*c* 7.44, acetone); (after decolorization) $\alpha^{29}$D −11.19°, $[\alpha]^{29}$D −75.4° (*l* 2, *c* 7.42, acetone).

**Interaction of *o,p*-Dimethylbenzophenone with (+)-Bornyl Acetate.**—A solution of 6.3 g. (0.03 mole) of *o,p*-dimethylbenzophenone[22] and 5.9 g. (0.03 mole) of (+)-bornyl acetate in 30 ml. of ether was used. Addition time was 35 minutes. Hydrolysis of the condensation product gave dextrorotatory 3-(*o,p*-dimethylphenyl)-3-phenylhydracrylic acid (Vb), m.p. 131–133° (with foaming), yield 5.8 g. (72%), $\alpha^{29}$D +0.57°, $[\alpha]^{29}$D +7.7° (*c* 7.43, acetone); (after decolorization) $\alpha^{29}$D +0.55°, $[\alpha]^{29}$D +7.6° (*c* 7.25, acetone).

The optical activity was lost on a single recrystallization from methanol. Repeated recrystallizations gave racemic 3-(*o,p*-dimethylphenyl)-3-phenylhydracrylic acid (*dl*-V), m.p. 137–137.5° (with foaming).

*Anal.* Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.46; H, 6.97.

Duplicate experiment on a 0.03-mole scale: yield 5.5 g. (68%), m.p. 132.5–133.5° (with foaming), $\alpha^{23}$D +0.82°, $[\alpha]^{23}$D +11.4° (*c* 7.13, acetone); (after decolorization) $\alpha^{22}$D +0.84°, $[\alpha]^{22}$D +11.7° (*c* 7.20, acetone).

The infrared spectra of *dl*-V, Va and Vb in solution were identical; $\nu_{max}$ ($CCl_4$): 3509, 2994, 2899, 2703, 2597, 1949, 1751, 1706, 1621, 1451, 1429, 1408, 1379, 1318, 1289, 1256, 1227, 1190, 1176, 1133, 1092, 1057, 1034, 1021, 922, 894, 881; $\nu_{max}$ ($CS_2$): 811 and 702 cm.$^{-1}$.

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(17) Prepared by the method of H. Meyer (*Monatsh.*, **28**, 1211 (1908)) and recrystallized repeatedly from petroleum ether (b.p. 30–70°), m.p. 53.5–54°.

(18) W. Kusjmin (*J. Russ. Phys.-chem. Ges.*, **41**, 1317 (1909); *Chem. Zentr.*, **I**, 739 (1910)) reported the melting point as 181° dec.

(19) Prepared by the method of P. Wegerhoff (*Ann.*, **252**, 1 (1889)) and recrystallized repeatedly from methanol, m.p. 76.5–77°.

(20) L. L. Alexander, A. L. Jacoby and R. C. Fuson (THIS JOURNAL, **57**, 2208 (1935)) reported the melting point as 188.5–189° dec.

(21) Prepared by the method of G. Reddelien (*Ber.*, **48**, 1462 (1915)) b.p. 134° (4 mm.), $n^{25}$D 1.5914.

(22) Prepared by the method of N. Meissel (*ibid.*, **32**, 2419 (1899)). b.p. 141° (3 mm.), $n^{25}$D 1.5873.

**Interaction of α-Naphthophenone with (−)-Menthyl Acetate.**—A solution of 11.6 g. (0.05 mole) of α-naphthophenone[23] and 9.9 g. (0.05 mole) of (−)-menthyl acetate in 35 ml. of toluene was used. Addition time was 10 minutes. The hydrolysis product was taken up with ether. The yield of 3-(α-naphthyl)-3-phenyl-hydracrylic acid (VIa) was 9.6 g. (66%), m.p. 129–131° (with foaming), $\alpha^{13}\text{D}$ +1.62°, $[\alpha]^{13}\text{D}$ +40.6° (*c* 4.00, acetone).

Duplicate experiment on a 0.03-mole scale: yield 6.9 g. (79%), m.p. 121–123° (with foaming), $\alpha^{17}\text{D}$ +3.13°, $[\alpha]^{17}\text{D}$ +43.7° (*c* 7.17, acetone); (after decolorization) $\alpha^{17}\text{D}$ +3.14°, $[\alpha]^{17}\text{D}$ +44.0° (*c* 7.12, acetone).

**Interaction of α-Naphthophenone with (+)-Bornyl Acetate.**—A solution of 11.6 g. (0.05 mole) of α-naphthophenone[23] and 9.8 g. (0.05 mole) of (+)-bornyl acetate in 35 ml. of toluene was used. Addition time was 15 minutes. Hydrolysis of the condensation product gave 3-(α-naphthyl)-3-phenylhydracrylic acid (VIb), m.p. 127–129° (with foaming), $\alpha^{10}\text{D}$ +4.42°, $[\alpha]^{10}\text{D}$ +60.0° (*c* 7.38, acetone), yield 11.0 g. (75%).

Duplicate experiment on a 0.03-mole scale: yield 7.2 g. (82%), m.p. 118–122° (with foaming), $\alpha^{17}\text{D}$ +4.63°, $[\alpha]^{17}\text{D}$ +63.5° (*c* 7.29, acetone).

The infrared spectra of the racemic *dl*-VI (see below), VIa, and VIb in solution showed some differences in the fingerprint region, presumably since the sample solution may have become heterogeneous during the determination because of the sparing solubility of the sample. Common absorption bands to all: $\nu_{\max}$ 3030, 2899, 2591, 1949, 1706, 1608, 1513, 1497, 1451, 1401, 1232, 1185, 1136, 1053, 1026, 981, 956, 947, 922, 896, 798, 778, 765, 733 and 701 cm.$^{-1}$. Other specific bands ($\nu_{\max}$ cm.$^{-1}$) for *dl*-VI: 3546, 1361, 1318, 1217, 1176 and 1096; for VIa: 3571, 1429, 1372, 1318, 1214, 1176 and 1099; for VIb: 3571, 1425, 1364, 1326, 1214, 1168 and 1099.

The pure racemic methyl 3-(α-naphthyl)-3-phenylhydracrylate was obtained by the methylation of *dl*-VI with diazomethane followed by recrystallization from methanol, m.p. 76.5–77.5°.

*Anal.* Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.27; H, 6.20.

The methyl ester of VIa, m.p. 72–74°, $\alpha^{16}\text{D}$ +3.59°, $[\alpha]^{16}\text{D}$ +38.6° (*c* 9.29, acetone) and that of VIb, m.p. 72–75°, $\alpha^{16}\text{D}$ +6.31°, $[\alpha]^{16}\text{D}$ +58.2° (*c* 10.84, acetone) were also prepared. The infrared spectra of these three methyl esters in solution were completely identical; $\nu_{\max}$ ($CCl_4$): 3438, 3024, 2932, 1938, 1714, 1592, 1502, 1487, 1443, 1432, 1410, 1373, 1330, 1267, 1245, 1220, 1194, 1171, 1157, 1090, 1072, 1048, 1028, 1020, 995, 971, 948, 933, 916, 896 and 864 cm.$^{-1}$.

**Resolution of 3-(*p*-Anisyl)-3-phenylhydracrylic Acid.**—When 9.1 g. (one equivalent) of *d*-cinchonine was added to a solution of 8.4 g. of the racemic acid dissolved in 200 ml. of hot ethanol, 10.6 g. of the salt separated out. Four recrystallizations from ethanol gave a material, $[\alpha]^{18}\text{D}$ +104° (*c* 2.01, chloroform), which was dissolved in chloroform and decomposed with dilute hydrochloric acid followed by extractions with sodium bicarbonate solution. The combined alkaline layers were extracted with chloroform and acidified. The resulting acid showed $[\alpha]^{14}\text{D}$ +12.3°: after recrystallizations from methanol (+)-acid having $[\alpha]^{14}\text{D}$ +14.2° (*c* 1.46, dioxane) and m.p. 153.5–154° (with foaming) was obtained. Further recrystallization led to no change in rotation.

*Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.97. Found: C, 70.59; H, 5.88.

The original mother liquor was concentrated and subjected to three cycles of fractional recrystallization from ethanol. The more soluble salt was decomposed as above and the resulted acid was recrystallized from methanol. The (−)-acid was obtained in less optical purity: $[\alpha]^{12}\text{D}$ −11.4° (*c* 5.04, dioxane), m.p. 153.5° (with foaming).

**Resolution of 3-Phenyl-3-(*o*-tolyl)-hydracrylic Acid.**—When 7.1 g. (one equivalent) of brucine tetrahydrate was added to a solution 3.9 g. of the racemic acid dissolved in 450 ml. of hot ethanol, 5.4 g. of the salt deposited. Since the partially racemic acid having $[\alpha]\text{D}$ −90°, which was regenerated from this salt, showed rotation similar to that of the product in run 7 (Table I), 3.6 g. of the product in run 7 and 6.6 g. of brucine tetrahydrate was added to the crop. After three recrystallizations from ethanol, a salt having $[\alpha]^{12}\text{D}$ −90° (*c* 1.49, chloroform) was obtained. Decomposition in the usual manner gave a specimen of acid having $[\alpha]^{10}\text{D}$ −159°: repeated recrystallizations from methanol afforded the (−)-acid, $[\alpha]^{13}\text{D}$ −168° (*c* 4.63, acetone), m.p. 153.5–154° (with foaming). Further recrystallization led to no change in optical rotation.

*Anal.* Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.22; H, 6.20.

The original mother liquor was concentrated and, after two cycles of fractional recrystallization, decomposed. The acid obtained from the more soluble salt had $[\alpha]^{8}\text{D}$ +129°: recrystallizations from methanol gave (+)-acid which was not quite optically pure, $[\alpha]^{13}\text{D}$ +151° (*c* 2.44, acetone), m.p. 154–154.5° (with foaming).

**Synthesis and Resolution of 3-(α-Naphthyl)-3-phenylhydracrylic Acid.**—Ethyl 3-(α-naphthyl)-3-phenylhydracrylate was prepared according to the procedure of Koelsch and Anthes.[24] Saponification with alcoholic potash and recrystallization from benzene gave 3-(α-naphthyl)-3-phenylhydracrylic acid (*dl*-VI), m.p. 136–136.5° (with foaming).

*Anal.* Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.25; H, 5.63.

When a mixture of 6.4 g. of the acid and 10.2 g. (1 equiv.) of brucine tetrahydrate was dissolved in 60 ml. of ethyl acetate, 14.8 g. of the salt separated out. Repeated digestions of this salt with ethanol followed by three recrystallizations gave the salt, $[\alpha]^{25}\text{D}$ −129° (*c* 3.30, chloroform), m.p. 234° dec. This was decomposed in the usual manner. The resulting acid had $[\alpha]^{19}\text{D}$ −159°: after recrystallizations from benzene it had $[\alpha]^{16}\text{D}$ −205° (*c* 1.56, acetone), m.p. 142.5–143.5° (with foaming).

*Anal.* Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.94; H, 5.69.

The first, second and third mother liquors of digestion on concentration to dryness yielded the residues: 4.1 g., $[\alpha]\text{D}$ +96°; 3.0 g., +80°; and 0.7 g., +73°, respectively. These crops were combined and recrystallized from methanol until further recrystallization led to no change in optical rotation and melting point: $[\alpha]^{15}\text{D}$ +115° (*c* 3.09, chloroform), m.p. 154–157°. Decomposition as above gave the acid having $[\alpha]^{17}\text{D}$ +194°; after recrystallizations it had $[\alpha]^{15}\text{D}$ +207° (*c* 1.69, acetone), m.p. 143.5–144° (with foaming).

Attempted resolution by means of *d*-cinchonine was not successful. The cinchonine salt of the (−)-acid was also less soluble than that of the (+)-acid.

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[23] Prepared by the method of E. Caille (*Compt. rend.*, **153**, 393 (1911); *C. A.*, **5**, 3413 (1911)) and recrystallized repeatedly from ether, m.p. 75.5–76°.

[24] C. K. Koelsch and J. A. Anthes, *J. Org. Chem.*, **6**, 558 (1941).