ethanol with 1 g. of platinum oxide was shaken with hydrogen until the theoretical amount was taken up (about 16 hours). The catalyst was removed by filtration and the filtrate was evaporated to dryness under vacuum on the steam-bath. The residue was taken up in 10 ml. of water and to this was added a solution of potassium carbonate (50 g.) in 75 ml. of water; the resulting mixture was extracted with four 75-ml. portions of benzene. The benzene extracts were dried over anhydrous potassium carbonate, the benzene was evaporated under vacuum, and the residue was distilled giving 10 g. (55% yield) of material boiling at 145–150° (0.02 mm.).

Anal. Calcd. for $C_{12}H_{23}N_3O_2$: C, 59.72; H, 9.61; N, 17.41. Found: C, 59.85; H, 9.41; N, 17.30.

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[Contribution from the Department of Chemistry and Chemical Engineering, Stanford University]

Asymmetric Reductions. III. The Action of (+)-2-Methylbutylmagnesium Chloride on Substituted Benzophenones

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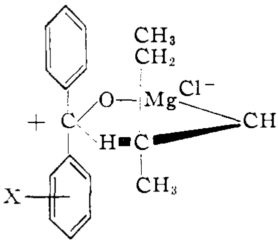
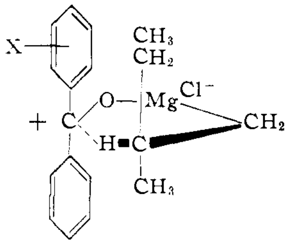
The action of the Grignard reagent prepared from (+)-2-methylbutyl chloride on *p*-chlorobenzophenone, *p*-methoxybenzophenone and *o*-chlorobenzophenone gave the corresponding benzhydrol in each case. In the cases of *p*-chlorobenzophenone and *p*-methoxybenzophenone optically inactive benzhydrols were obtained, whereas the *o*-chlorobenzhydrol was optically active. These findings are in complete agreement with the predictions made on the basis of the mechanism for Grignard reductions involving a hydrogen transfer within a six-membered ring transition state.

It has been proposed by Whitmore[1] that the reduction of carbonyl compounds by Grignard reagents proceeds *via* a six-membered ring transition state. Evidence has been obtained in support of this mechanism in the asymmetric reduction of methyl *t*-butyl ketone with (+)-2-methylbutylmagnesium chloride[2] and in the non-asymmetric reduction of this same ketone with (+)-3-methylpentylmagnesium chloride.[3] Additional evidence is now presented based on the reduction of three substituted benzophenones by (+)-2-methylbutylmagnesium chloride.

The transition state for the reduction of a substituted benzophenone by such an optically active Grignard reagent may be represented as in either A or B. If the shift of hydrogen with its accompanying electron pair takes place through the transition state represented by A, then one isomer will be formed; B leads to its enantiomorph. This mechanism would require that the presence of a substituent in the *para* position should not appreciably favor one transition state over the other, since the substituent in the *para* position of the planar benzene ring is too distant from the methyl and ethyl groups of the reducing reagent to exert any selective steric effect. In other words, the *para* substituted phenyl group should have essentially no more steric interference in this reaction than an unsubstituted phenyl, and a racemic product should be formed. But if the substituent is in the *ortho* position, then one would predict that the energy of activation of the transition state represented by A would be less than that for B since in A the substituent interferes with the methyl group, while in B it interferes with the more bulky ethyl group.[4] These predictions are made on the assumption that the factors governing this asymmetric reduction are steric and independent of the electronic nature of the substituent group.[4]



A



B

The predictions have been tested and confirmed in the reactions of *p*-chloro-, *p*-methoxy- and *o*-chlorobenzophenone with the Grignard reagent from (+)-2-methylbutyl chloride. The results and essential data are presented in Table I.

In the case of the two *p*-substituted examples there was isolated only one product in near quantitative yield which was at once crystalline and optically inactive. The reduction product of *o*-chlorobenzophenone, on the other hand, was a dextrorotatory oil. It retained its activity after two successive distillations at 2 mm. and was converted in 91% yield to a crystalline levorotatory half-phthalate. That the activity was a property of the half-phthalate of *o*-chlorobenzhydrol and not of an impurity was demonstrated conclusively by repeated recrystallization, infrared spectra and analysis. The more active material concentrated in the mother liquors, in accord with reported solubilities of the racemic and active forms.

Experimental[5]

The Action of (+)-2-Methylbutylmagnesium Chloride on *p*-Chlorobenzophenone.—The Grignard reagent was pre-

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(1) F. C. Whitmore, paper presented before the Atlantic City Meeting of the American Chemical Society, April, 1943.

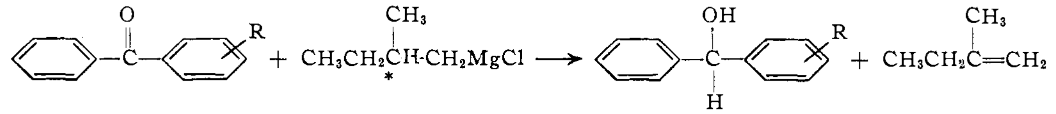
(2) H. S. Mosher and E. La Combe, This Journal, **72**, 3994 (1950).

(3) H. S. Mosher and E. La Combe, *ibid.*, **72**, 4991 (1950).

(4) It would, of course, be better to test this prediction with a 2,6-disubstituted benzophenone since this would prevent the substituted benzene ring from assuming an orientation in which the substituent could be directed away from the interfering groups. To our knowledge no 2,6-disubstituted benzhydrol has been resolved. Until such a compound has been resolved, no information beyond that already obtained from the reduction of the simple *o*-substituted benzophenone can be obtained by such an experiment. In addition a preliminary experiment with 2,6-dichlorobenzophenone has shown that this is a more complex reaction giving very little if any simple reduction product.

(5) All melting points taken on Kofler hot-stage, uncorrected.

TABLE I



R	Yield reduction product, %	Observed rotation	Specific rotation	Specific rotation of pure isomer
p-Cl	101.0[a]	0.00 ± 0.02°[b]	0.0 ± 0.3°	−32.1° + 13.7°[e]
p-OCH$_3$	99.5	.00 ± .02°[c]	0.0 ± 0.3°	+47.8°[f]
o-Cl	98.5	+ .10 ± .01°[d]	+0.48 ± 0.06°	−4.5° + 4.7°[g]

[a] Crude product not completely dry before recrystallization. [b] α^{26}D, *l* 1, *c* 6.70, chloroform. [c] α^{26}D, *l* 1, *c* 6.63, carbon disulfide. [d] α^{25}D, *l* 0.5, *c* 42, absolute alcohol. [e] C. Green and J. Kenyon, *J. Chem. Soc.*, 751 (1950); resolution reported as complete. [f] J. Kenyon, *et al.*, *J. Chem. Soc.*, 605 (1942); resolution probably complete. [g] M. P. Balfe, *et al.*, *J. Chem. Soc.*, 801 (1946); resolution not reported as complete.

pared in 85% yield from 18 g. (0.17 mole) of (+)-2-methylbutyl chloride, α^{26}D +1.42° (*l* 1, neat), and 5.6 g. (0.23 mole) of magnesium turnings in 200 ml. of ether under dry nitrogen atmosphere, with the temperature during formation kept below 25°.[2] The filtered Grignard solution was added over a period of 45 minutes to a solution of 15.1 g. (0.070 mole) of *p*-chlorobenzophenone[6] in 100 ml. of ether. The mixture, after being stirred at room temperature overnight, was refluxed on a steam-bath for 75 minutes, and then hydrolyzed by pouring onto a solution of 15 g. of ammonium chloride and 150 g. of ice-water. Evaporation of the washed and dried ether solution yielded 15.4 g. of white solid, m.p. 59–62°. A solution of this material in chloroform had no observable rotation (*c* 6.70, *l* 1). This product, after two recrystallizations from petroleum ether, had a melting point of 61.0–62.0°, and a mixture melting point with an authentic sample of *dl*-*p*-chlorobenzhydrol[7] showed no depression; infrared spectra of the two samples (in Nujol mull) were superimposable. The reference sample of *dl*-*p*-chlorobenzhydrol was prepared in 80% yield by a Raney nickel catalyzed reduction of the ketone at 2 atmospheres pressure and room temperature.

The Action of (+)-2-Methylbutylmagnesium Chloride on *p*-Methoxybenzophenone.—The Grignard reagent, 520 ml., was prepared in 96% yield as described above from 56.5 g. (0.53 mole) of (+)-2-methylbutyl chloride, α^{26}D +1.42 (*l* 1, neat), and 17.8 g. (0.73 mole) of magnesium turnings. A portion of this solution, 175 ml., was added to 21.2 g. (0.10 mole) of *p*-methoxybenzophenone[8] in 100 ml. of ether and worked up in the same way as was the *p*-chlorobenzophenone mixture. The 21.3 g. of white solid obtained, m.p. 62–65°, had no observable rotation in carbon disulfide (*c* 6.63, *l* 1). Its infrared spectrum (Nujol mull) was identical with that of an authentic sample of *dl*-*p*-methoxybenzhydrol. A mixture melting point of the two samples, recrystallized to 66.9–67.5° and 66.3–67.1°, respectively, was undepressed.[9] The reference sample was prepared in a crude yield of 97% by Raney nickel catalyzed hydrogenation of *p*-methoxybenzophenone at room temperature and 2 atmospheres pressure.

The Action of (+)-2-Methylbutylmagnesium Chloride on *o*-Chlorobenzophenone.—The remaining Grignard solution from the above preparation, 345 ml., was added to a solution of 41.0 g. (0.19 mole) of *o*-chlorobenzophenone[10] in about 160 ml. of dry ether at room temperature. The reaction mixture was treated as in the two preceding cases and gave 40.8 g. of a viscous dextrorotatory yellow oil, α^{24}D +0.11 ± 0.01° (*l* 0.5, *c* 10.2 in chloroform). Small portions of the oil were subjected to evaporative distillation at 2 mm. The residue was negligible, and the distillate, a colorless oil, had α^{24}D +0.15 ± 0.01°, $[\alpha]^{24}$D +2.9° (*l* 0.5, *c* 10.2 in chloroform). A small amount of the levorotatory primary active amyl alcohol was found in the cold trap, accounting for the slight increase in rotation after distillation. The infrared spectrum of the oil after distillation was identical, but for sharpening of the bands, with that taken before. Accordingly there is no question concerning the partially asymmetric reduction which has occurred in the case of *o*-chlorobenzophenone as compared to the *para*-substituted benzophenones. Seeding of this product with an authentic sample of *dl*-*o*-chlorobenzhydrol[11] forced out crystalline inactive material, about 25% of the initial weight, but the active residue, α^{24}D +0.19° (*l* 0.5, *c* 10.3 in chloroform), was of such a composition that it could not be obtained crystalline. A 2.20-g. portion of twice distilled dextrorotatory Grignard reduction product, α^{24}D +0.19°, $[\alpha]^{24}$D +2.61° (*l* 0.5, *c* 14.5 in absolute ethanol) was used for preparation of the acid phthalate ester by the pyridine method. The total resulting crude acid phthalate, 3.38 g. (91% of theory), m.p. 135–180°, was very slightly *levorotatory:* α^{23}D −0.05 ± 0.02° (*l* 1, *c* 2.6 in absolute ethanol), $[\alpha]^{23}$D −1.9 ±, 0.7°, α^{23}D −0.07 ± 0.02° (*l* 1, *c* 4.0, absolute ethanol), $[\alpha]^{23}$D −1.7 + 0.5°. Balfe, *et al.*,[12] also found that the dextrorotatory carbinol gave the levorotatory acid phthalate. Successive recrystallizations of this acid phthalate concentrated the optical activity in the more soluble fractions, α^{23}D 0.09 ± 0.02° (*l* 1, *c* 2.6, absolute ethanol), m.p. 162–163°.

Anal. Calcd. for $C_{20}H_{14}O_4Cl$: C, 67.89; H, 3.99. Found: C, 67.76, 67.80; H, 4.26, 4.24.

The original acid phthalate was dissolved in 5% sodium carbonate and the solution extracted with ether. The carbonate soluble material was saponified with sodium hydroxide to give the regenerated *o*-chlorobenzhydrol, α^{25}D +0.10 ± 0.01° (*l* 0.5, *c* 42 in abs. ethanol), $[\alpha]^{25}$D +0.48 ± 0.06°.[13] This corresponds to a percentage asymmetric reduction, using Kenyon's value of $[\alpha]^{22}$D +4.7° for the pure isomer, of approximately 10% based on this regenerated material.[13]

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(6) Eastman "Practical" grade, purified by three recrystallizations to m.p. 76.8–77.1°.

(7) C. Green and J. Kenyon, *J. Chem. Soc.*, 751 (1950).

(8) Prepared from benzoyl chloride, anisole, and anhydrous aluminum chloride in carbon disulfide [P. Peterson, *Am. Chem. Jour.*, **46**, 335 (1911)] in 55.2% yield; m.p. 61.7–62.3°.

(9) J. Kenyon, *et al*., *J. Chem. Soc.*, 605 (1942).

(10) Prepared from benzene and *o*-chlorobenzoyl chloride by the method of V. Auwers, *et al.*, [*Ber.*, **58**, 50 (1925)] in 65% yield, m.p. 44.2–46.5°, boiling point 129–133° (4 mm.). We wish to thank Charles Haber for the preparation of this material.

(11) The reference sample of *dl*-*o*-chlorobenzhydrol was prepared in quantitative yield by reduction of the ketone using sodium borohydride in methanolic solution. Raney nickel reduction, eminently satisfactory for preparing *p*-chloro- and *p*-methoxybenzhydrols, resulted in this case solely in loss of halogen with none of the desired *o*-chlorobenzhydrol being isolated.

(12) M. P. Balfe, E. A. Downer, A. A. Evans, J. Kenyon, R. Poplett, E. C. Searle and A. L. Tarnoky, *J. Chem. Soc.*, 801 (1946).

(13) There was a loss in optical activity from $[\alpha]^{24}$D +2.61° to $[\alpha]^{25}$D +0.48° in the conversion of the *o*-chlorobenzhydrol fraction to the acid phthalate and subsequent regeneration. The exact reason for this is not known but very probably it is the presence of a small amount of (+)-*o*-(2-methylbutyl)-benzophenone in the original *o*-chlorobenzhydrol fraction. In support of this the infrared spectrum of the original fraction showed the presence of a small amount of carbonyl impurity. In addition, the action of the Grignard reagent from (+)-2-methylbutyl chloride on 2,6-dichlorobenzophenone was found to be quite complicated, the major product being a strongly dextrorotatory, chlorine free, ketone which in analysis corresponded to (+)-2,6-di-(2-methylbutyl)-benzophenone. We hope to study this latter reaction in greater detail in the future. It can be inferred that a similar reaction taking place to a lesser extent with *o*-chlorobenzophenone would account for the presence of a small amount of optically active ketone in the above *o*-chlorobenzhydrol fraction.