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# Grignard Synthesis of 2-Phenyl-2-butanol in Optically Active Solvents

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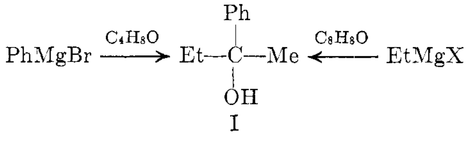
1. The preparation of 2-phenyl-2-butanol in benzene and (+)2,3-dimethoxybutane from ethyl halides and acetophenone gives a degree of enantiomeric preponderance varying as Cl < I < Br. 2. The optical activity of 2-phenyl-2-butanol prepared in benzene and (+)2,3-dimethoxybutane from bromobenzene and 2-butanone is about 5 times that of the product from ethyl bromide and acetophenone. 3. The 2-phenyl-2-butanol prepared in benzene and hexamethyl mannitol or pentamethyl arabitol is obtained in yield lower than is the case with comparable reaction in dimethoxybutane. Also the optical rotation is opposite in sign. 4. The asymmetric resolution of 2,3-diphenylpropanoic acid from 1,2-diphenylchloroethane and phenylisocyanate is cited as an instance where bulkiness of the entering organic group tends to increase the optical activity of the product over that of smaller groups.

Although Cohen and Wright[1] performed a partial asymmetric synthesis by addition of ethyl chloride and bromide Grignard reagents to ethyl benzoylformate in a benzene and (+)2,3-dimethoxybutane medium, the example was unfavorable from the aspect of interpretation. Because of the presence of the carboethoxy group it was considered advisable to use "inverse" addition (of Grignard reagent into the ketoester), but even this limitation could not eliminate the possibility that the ester group partook of coordination in the system. In consequence, we have chosen another reaction which is simpler and more amenable to variations.

By choice of 2-phenyl-2-butanol as a product, the extent of asymmetric synthesis can be calculated easily because this tertiary alcohol has been resolved,[2] $[\alpha]_D^{22}$ +17.45°. Moreover the carbinol can be obtained by the alternative paths: ethyl halide Grignard reagents with acetophenone or bromobenzene Grignard reagent with 2-butanone. Finally, these Grignard reagents are preparable in the optically active ether-benzene media which we have chosen to use.



$$\mathrm{PhMgBr} \xrightarrow{C_4H_8O} \mathrm{Et{-}}\overset{\mathrm{Ph}}{\underset{\mathrm{OH}}{C}}\mathrm{{-}Me} \xleftarrow{C_8H_8O} \mathrm{EtMgX}$$

I

In addition to the (+)2,3-dimethoxybutane ($C_6H_{14}O_2$) described previously,[1] we have prepared and used three other optically active ethers. D(+)mannitol hexamethyl ether ($C_{12}H_{26}O_6$) has been prepared by a modification of the previous preparation[3] while D(−)arabitol pentamethyl ether, ($C_{10}H_{22}O_5$) has been prepared anew. Only the third (+)1-methoxy-2-methylbutane ($C_6H_{14}O$),[4,5] prepared from sodium 2-methylbutoxide and methyl *p*-toluenesulfonate, is ineffective for induction of optical activity into the product. This behavior conforms with the previous observation[1,6] that monoethers will not function in the asymmetric synthesis, and extends the observation to an ether in which both alkyl groups attached to oxygen in the ether are primary. The reactions which we have carried out in the various ethers are recorded in Table I.

*Effect of variation in halogen.* Table I shows that the specific activity of 2-phenyl-2-butanol prepared from ethyl Grignard reagents and acetophenone

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[1] H. L. Cohen and G. F Wright, *J. Org. Chem.*, **18**, 432 (1953).

[2] H. H. Zeiss, *J. Am. Chem. Soc.*, **73**, 2391 (1952).

[3] W. Freudenberg and J. T. Sheehan, *J. Am. Chem. Soc.*, **62**, 558 (1940).

[4] Guye and Chavanne, *Bull. soc. chim.* [3] **15**, 301 (1896).

[5] H. G. Rule, E. B. Smith, and J. Harrower, *J. Chem. Soc.*, 376 (1933).

[6] D. S. Tarbell and M. C. Paulson, *J. Am. Chem. Soc.*, **64**, 2842 (1942).

TABLE I

REACTIONS PRODUCING 2-PHENYL-2-BUTANOL

| Expt. No. | Halide | Ether | Grignard Yield, % | Ketone | 2-Phenyl-2-butanol | | |
|---|---|---|---|---|---|---|---|
| | | | | | Yield, % | $[\alpha]_D$ at $T$ | °C. |
| 1 | $C_2H_5Br$ | $C_4H_{10}O$ | 91 | $C_8H_8O$ | 85 | | |
| 2 | Same | $C_6H_{14}O_2$ | 76 | Same | 45 | $+0.62 \pm 0.04$ | 21 |
| 3 | Same | Same | 80 | Same | 50 | $+0.55 \pm 0.02$ | 25 |
| 4 | Same | Same | [a] | Same | 40 | $+0.61 \pm 0.04$ | 24 |
| 5 | Same | Same | 79[b] | Same | 54 | $+0.51 \pm 0.02$ | 21 |
| 6 | $C_2H_5I$ | Same | — | Same | 42 | $+0.44 \pm 0.06$ | 21 |
| 7 | Same | Same | — | Same | 38 | $+0.50 \pm 0.05$ | 26 |
| 8 | $C_2H_5Cl$ | Same | 82 | Same | 58 | $+0.08 \pm 0.05$ | 21 |
| 9 | Same | Same | 80 | Same | 61 | $+0.09 \pm 0.01$ | 24 |
| 10 | $C_6H_5Br$ | Same | 56 | $C_4H_8O$ | 54[c] | $+3.04 \pm 0.06$ | 20 |
| 11 | $C_2H_5Br$ | $C_{12}H_{26}O_6$ | 50 | $C_8H_8O$ | 17 | $-2.00 \pm 0.14$[d] | 21 |
| 12 | $C_2H_5Cl$ | Same | 66 | Same | 17 | $-0.42 \pm 0.15$[d] | 21 |
| 13 | $C_6H_5Br$ | Same | 47 | $C_4H_8O$ | 11 | $-0.75 \pm 0.10$[d] | 20 |
| 14 | $C_2H_5Br$ | $C_{10}H_{22}O_5$ | 33 | $C_8H_8O$ | 14 | $-1.15 \pm 0.07$[d] | 20 |
| 15 | $C_6H_5Br$ | Same | 24 | $C_4H_8O$ | 7[e] | $+0.4 \pm 0.4$[b] | 20 |
| 16 | Same | $C_6H_{14}O$ | 42 | Same | 55[f] | $-0.02 \pm 0.08$ | 22 |

[a] Excess magnesium filtered off. [b] Molar equivalent of magnesium bromide added. [c] Yield calculated from rotations of crude and final products. [d] Minimum value of rotation calculated after dilution with inactive carbinol. [e] Yield calculated on the Grignard reagent basis. [f] Crude material.

($C_8H_8O$) varies from a low of (+)0.08 ± 0.05° when ethyl chloride is used to a high value of (+)0.62 ± 0.04° from the ethyl bromide Grignard reagent, the medium being benzene plus one molar equivalent of (+)2,3-dimethoxybutane. However, this order is not directly related to the ordinary reactivity of alkyl halides since the phenylbutanol from ethyl iodide Grignard reagent shows $[\alpha]_D$ (+)0.44 ± 0.06 which is intermediate between the optical activity of the product from the other two halides. However, it should be noted that the same order is found with respect to enolate formation, since about 10% of acetophenone is recovered from the systems involving ethyl bromide and iodide, but none is recovered from the system containing chloride. The duplicate experiments, 2 and 3, 6 and 7, 8 and 9, show that the results are reproducible. Moreover the same order of effectiveness is shown (experiments 11 and 12) when the medium is benzene containing one molar equivalent of mannitol hexamethyl ether. These results are contrary to those observed by Cohen and Wright[1] but the two studies may not be comparable. The present Grignard reagents (except those from methyl iodide) are homogeneous whereas the earlier ones consisted of two phases. Furthermore, inverse addition of reagent to the ketoester was employed by Cohen and Wright.

An explanation of these results cannot be expected on the basis of the limited data of these two studies. However, we suggest tentative consideration of the $R_2Mg$ and $RMgX$–$MgX_2$ content of these systems. The amount of diethylmagnesium in a diethyl ether solution of ethyl chloride Grignard reagent has been reported as 42% in comparison with 29% of $Et_2Mg$ in ethyl bromide Grignard reagent.[7,8] But diethylmagnesium seems not to coordinate appreciably, at least with diethyl ether.[9] In so far as diethylmagnesium would not coordinate with the optically active ether, but would coordinate with acetophenone, the 2-phenyl-2-butanol thus formed would be optically inactive.

The argument is weak in several aspects. The diethylmagnesium content of ethyl iodide Grignard reagent is about the same (29%) as that of the analogous bromide yet the optical rotation of the product from the iodide is about 70% of the phenylbutanol from the bromide. But this discrepancy is not serious in view of the quantitative unreliability of the precipitation analysis of the "Schlenk Equilibrium."[7] Likewise the significance of the diethylmagnesium content of these systems might seem to be vitiated by experiment 5, Table I, in which an equivalent of added magnesium bromide did not appreciably alter the optical rotation of the product. But, again, it has been shown that such attempts to shift the Schlenk equilibrium[10] are not quantitatively successful[11] and, indeed, very little of the magnesium bromide seemed to dissolve in the reagent of experiment 5, Table I. This is of interest although it is not necessarily surprising in view of the fact that the alkoxy group content of the system was only adequate on the 2ROR.1RMgX basis for the magnesium salts in solution before the introduc-

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(7) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York (1954), p. 105.

(8) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).

(9) W. Schlenk, Jr., *Ber.*, **64**, 736 (1931).

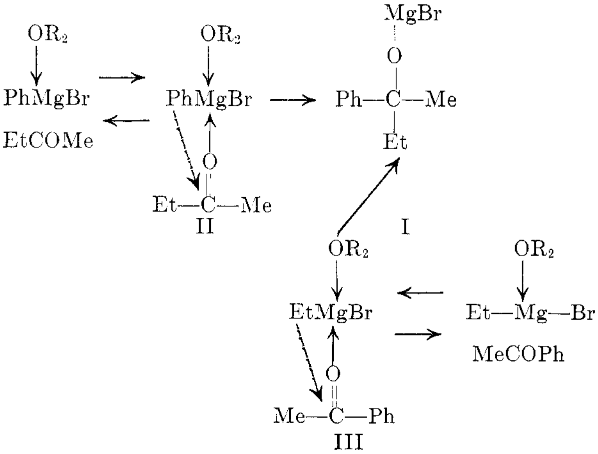
(10) W. Schlenk and W. Schlenk, Jr., *Ber.*, **62**, 920 (1929).

(11) C. R. Noller and D. C. Raney, *J. Am. Chem. Soc.*, **62**, 1749 (1940).

tion of additional magnesium bromide. In short, the argument concerning the significance of diethylmagnesium in these systems is not weak *per se* but only because of our ignorance of the constitutional nature of Grignard reagents. It is increasingly necessary that this situation, persisting for more than 50 years, be improved.

*Effect of variation in organo group of the reagent.* At any rate the $R_2Mg$ content of the Grignard systems cannot account for the marked difference in asymmetric induction shown by experiments 3 and 10. Both experiments have been carried out identically in benzene-dimethoxybutane. Yet acetophenone added to ethyl bromide Grignard reagent yields 2-phenyl-2-butanol which is enantiomeric to the extent of 3.6% while the same carbinol (although in lower yield) from 2-butanone into bromobenzene Grignard reagent is 17.4% preponderant in one enantiomer. This is the most asymmetry yet induced by the influence of an optically active ether, and is of the same magnitude as was obtained by Mosher and LaCombe[12] by use of an optically active Grignard reagent. When one equivalent of the ether can induce as much activity as the Grignard reagent itself, it is obvious that the ether is of primary importance in the reaction.

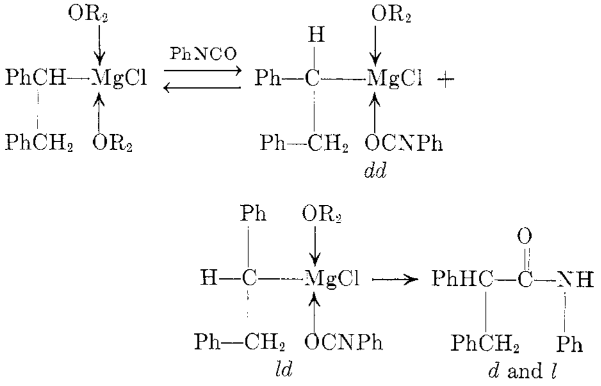
Therefore it is important to consider the possible ether-Grignard reagent-ketone complexes which would be involved in the reactions of experiments 2 and 10, which lead irreversibly to the same bromomagnesium *tert*-alkoxide, I. For simplicity the concepts of 6-atom quasicyclic transitory states (reference 7, p. 142) or of hexacovalent anions[13] are disregarded in favor of a 1:1:1 ether-magnesium-ketone complex. The complexes comprised of 2,3 or 4 monoether to 2 magnesium to 1 ketone which are described in references 7 and 13 probably do not contribute to the present problem and, at any rate, undoubtedly are only approximations to Grignard reagent structure, especially when colloidal agglomeration is possible.[13]



According to the formulation the difference in behavior of the 1:1:1 complexes, II and III, involves the steric preference depending on whether a phenyl or an ethyl group is undergoing transfer, but equally important are the mobile equilibria[1] among II, III, and their component parts. While either of the transitory diastereomers comprising II or III would react eventually to form the alkoxide I if they were formed irreversibly, the obvious reversibility of this transitory diastereomer formation will accentuate the tendency of either *dd* or *dl* II or III toward conversion to *d* or *l* I because of the difference in activation energy of the system *dd* II (or III) → *d* I *versus* *dl* II (or III) → *l* I.

One is tempted to attribute these steric preferences to bulkiness of the transferring group, admittedly upon the questionable assumption that migration is occurring in an otherwise rigid constellation of atoms. One cannot expect that this simple concept will be rigorously applicable. Nevertheless, we find that in a related instance of asymmetric resolution (in which the transition state must resemble that postulated for asymmetric synthesis), there is a trend toward higher optical activity as the bulk of the organic group becomes greater.

Previously it has been shown[1] that 2-methylbutanoic acid was 1.6% enantiomeric when it was prepared *via* 2-chlorobutane Grignard reagent and phenyl isocyanate in benzene-(+)2,3-dimethoxybutane. Under the same circumstances 1-chloro-1-phenylethane yielded 2-phenylpropanoic acid which was 2.6% enantiomeric. Now we have treated the Grignard reagent from 1,2-diphenylchloroethane [in benzene and (+)dimethoxybutane] with phenyl isocyanate.



The pure 2,3-diphenylpropanoic acid derived from the anilide has specific rotation $[\alpha]^{25}_{D}$ (+)3.16 ± 0.10°. Since the rotation of the pure enantiomer[14] is $[\alpha]^{20}_{D}$ (+)94° our reaction product is about 3.4% enantiomeric. In this series the extent of enantiomeric preponderance in the product seems to be related to the bulkiness of the group involved in the irreversible rearrangement.

*Effect of variation in ethers.* Polyethers such as

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(12) H. S. Mosher and E. LaCombe, *J. Am. Chem. Soc.*, **72**, 3994 (1950).

(13) M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., New York, 1956.

(14) H. Rupe and W. Kerkovins, *Ber.*, **45**, 1398 (1912).

hexamethylmannitol and pentamethylarabitol are of little value for the study of coordination with a Grignard reagent because of their complexity. They were used mainly as easily obtainable enantiomers with which the study could be extended beyond the use of (+)dimethoxybutane. However, two characteristics of their use are worthy of mention. First, the rotations of 2-phenyl-2-butanol prepared in benzene and (+)hexamethylmannitol or (−)pentamethylarabitol tend to be opposite in sign from 2-phenyl-2-butanol prepared in (+)2,3-dimethoxybutane. Second, the low yields of carbinol which are recorded in experiments 11–15, inclusive, are quite consistent. These yields probably reflect the high electron-donating tendencies which have been observed before[15] in polyethers. Because of such high coordination energy the displacement of ether by carbonyl would be inhibited, with consequent low yield of carbinol.[16]

## EXPERIMENTAL[17]

*General reagents.* Sublimed magnesium (Dominion Magnesium Co., Haley, Ontario) was broken up and finely ground in a coffee mill giving fibrous particles up to 1 × 1 × 5 mm. This metal was activated by etching away 2% by means of bromobenzene in dry ether; the Grignard mixture was hydrolyzed briefly with dilute hydrochloric acid. The metal was thoroughly washed with water, acetone, and ethanol and was then vacuum dried. It contained 34 p.p.m. of iron,[18] 2.5 p.p.m. of copper (sodium diethyldithiocarbamate method) and traces of manganese, zinc, calcium, strontium (?), and silicon (?) that were barely detectable by arc spectrum.

Organic halides were washed with 75–95% (w./v.) sulfuric acid, water, 10% aqueous bicarbonate, saturated sodium chloride and were dried with calcium chloride prior to distillation under anhydrous conditions. Magnesium bromide was prepared by Noller's method.[11] Benzene was purified from sodium benzophenone ketyl but was distilled from sodium just prior to use. The (+)2,3-dimethoxybutane,[1] b.p. 111° uncor., $d_4^{20}$ 0.853, $n_D^{20}$ 1.3935, $[\alpha]_D^{23}$ +3.76° ± 0.03, was treated likewise.

*Arabitol pentamethyl ether.* To a 5-l. three-necked flask equipped with dropping funnel, strong stainless steel stirrer and condenser for downward distillation was added 50 g. (0.328 mole) ($[\alpha]_D^{20}$ 8.0 ± 0.4°, *c*, 9.27 in saturated aqueous borax solution, m.p. 100–102°) of D-arabitol (kindly supplied by Prairie Regional Research Laboratory, National Research Council, Saskatoon, Saskatchewan) and 40 ml. of water. With a surrounding water bath at 55°, a solution of 240 ml. (2.5 moles) of dimethyl sulfate in 350 ml. of carbon tetrachloride was introduced with rapid stirring (throughout the reaction). Then 1 l. of 60% aqueous sodium hydroxide was added at 2–3 drops per second so as to maintain the temperature at 55°. After 20 min., when the distillation of carbon tetrachloride ceased, the remaining alkali was added quickly. The bath temperature was raised to 70° and maintained at 70–75° while 390 ml. (4.1 moles) of dimethyl sulfate was added at 5 drops per second. When addition was complete the heating bath was raised to 100° for 30 min., then cooled at 25°, when 1.5 l. of water was added to dissolve sodium sulfate. Fourfold extraction with chloroform gave a liter of nonaqueous solution which was dried with sodium sulfate and distilled, finally at 0.05 mm., b.p. 77–87°, 61.9 g. (85%), $n_D^{20}$ 1.4310, $d_4^{20}$ 1.021, $[\alpha]_D^{20}$ −5.57 ± 0.06° (neat).

This initial methylation[19] was supplemented by treatment of the 61.9 g. under nitrogen in a 2-l. three-necked flask equipped with strong sealed stirrer, ammonia inlet with acetone–Dry-Ice cooled condenser and introduction tube for 17.5 g. (0.45 g. atom) of metallic potassium[20] with 200 ml. of dry (condensed) liquid ammonia. Gaseous ammonia was then introduced slowly while the potassium was added during 14 hr. Then, when the color of dissolved potassium persisted, the reflux condenser and metal-addition tube were replaced by a dropping funnel and condenser for downward distillation. The ammonia was evaporated off in a nitrogen stream, then 200 ml. of benzene was added and evaporated *in vacuo* with the flask at 40°.

The condenser of the flask was replaced for cold water and Dry-Ice cooling so as to retain the 130 g. (0.9 mole) of methyl iodide which was now added in 300 ml. of benzene. After 3 hr. of stirring and reflux the volatile components were removed *in vacuo* at 45°. This entire methylation was then repeated with additional 7 g. (0.18 g.-atom) of potassium and 57 g. (0.4 mole) of methyl iodide. The final residue was dissolved in water under nitrogen and then extracted four times with chloroform. The 500 ml. of extract was distilled, finally at 0.04 mm., b.p. 71–73°, 44.4 g. (over-all, 61%), $d_4^{20}$ 1.013, $n_D^{20}$ 1.4294, $[\alpha]_D^{20}$ −5.22 ± 0.03° (neat).

For use in the Grignard reaction the ether was dissolved in 40 ml. of benzene, refluxed over sodium for 4 hr. and distilled finally at 0.02 mm., b.p. 67–70°, $d_4^{20}$ 1.010, $n_D^{20}$ 1.4290 $[\alpha]_D^{20}$ −5.21 ± 0.02° (neat).

*Anal.* Calc'd for $C_{10}H_{22}O_5$: C, 54.0; H, 9.98. Found: C, 54.2; H, 9.82.

The ether is miscible with water. It cannot be made to crystallize at −60° but it is chromatographically homogeneous when it is eluted from silicic acid by chloroform + 2% ethanol.

*Mannitol hexamethyl ether.* This ether, prepared in 65% yield essentially as described above for pentamethylarabitol, was a solid, fusion point 18.2–20.7°, after crystallization from diethyl ether (5 ml. per g.) at −70°. For Grignard use a benzene solution was dried over sodium and distilled, finally at 87–88° (0.01 mm.), $d_4^{20}$ 1.033, $n_D^{20}$ 1.4378, $[\alpha]_D^{20}$ +12.69 ± 0.02°. The compound is chromatographically homogeneous.

*Anal.* Calc'd for $C_{12}H_{26}O_6$: $OCH_3$, 69.92. Found: 69.85.

*1-Methoxy-2-methylbutane* (prepared by G. A. Dauphinee). A suspension of 7.4 g. (0.3 mole) of sodium hydride in 600 ml. of dry xylene (b.p. 138–139°) and 26.4 g. (0.3 mole) of 2-methyl-1-butanol, $[\alpha]_D^{22}$ −5.60 ± 0.06, was stirred under nitrogen for twelve hours, then refluxed with 20 ml. of *tert*-butyl alcohol for four hours. The *tert*-butyl alcohol was distilled off under 20 mm. and the residual solution was stirred while 74.5 g. (0.4 mole) of methyl *p*-toluenesulfonate was added under nitrogen. After ten hours the system was drowned with 250 ml. of water. The nonaqueous phase was dried with calcium chloride and 175 ml. was distilled from it. The remainder was distilled *in toto* under reduced pressure, then refluxed under nitrogen with 4 g. of sodium hydride until a positive sodium benzophenone ketyl test was obtained. Distillation (90–93°, 750 mm.) gave 13.5 g. (45%), $d_4^{20}$ 0.753, $n_D^{20}$ 1.385, $[\alpha]_D^{21}$ +0.61 ± 0.04°.

*2,3-Diphenylpropanoylanilide.* The 1,2-diphenylchloroethane was washed at 4° with cold 75% aqueous sulfuric acid, then was separated, diluted with 2 vol. of benzene and treated with aqueous potassium carbonate. The solu-

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(15) G. F. Zellhoefer, M. J. Copley, and C. S. Marvel, *J. Am. Chem. Soc.*, **60**, 1337 (1938).

(16) R. N. Lewis and J. R. Wright, *J. Am. Chem. Soc.*, **74**, 1253 (1952).

(17) Melting points have been corrected against reliable standards.

(18) S. Abbey, *Anal. Chem.*, **20**, 630 (1948).

(19) E. S. West and R. F. Holden, *J. Am. Chem. Soc.*, **56**, 930 (1934).

(20) M. L. Wolfrom, W. W. Binkley, W. L. Shelley, and H. W. Hilton, *J. Am. Chem. Soc.*, **73**, 3553 (1951).

tion was then dried over potassium carbonate and distilled in the presence of dry potassium carbonate, finally at 0.001 mm., b.p. 92–95°, $d_4^{20}$ 1.096, $n_D^{20}$ 1.5823.

To 4.1 g. (0.17 g. atom) of magnesium in a flamed, nitrogen-swept, conical three-necked flask[21] equipped with a sharp-blade 1300 r.p.m. stirrer were added a few ml. of a solution of 3.68 g. (0.017 mole) of purified halide and 2.49 g. (0.02 mole) of (+)2,3-dimethoxybutane in 30 ml. of benzene. After 10 min. at 20°, heat was evolved and a positive Gilman test was obtained. After 2 hr. of subsequent addition and 30 min. more at 25°, titration indicated 94% of Grignard reagent.

To this reagent was added during 30 min. 1.82 g. (0.015 mole) of phenyl isocyanate in 10 ml. of benzene. Hydrolysis in 50 ml. of cold 10% hydrochloric acid gave 1.94 g., m.p. 163.5–165°, augmented by 0.47 g., m.p. 164–167°, by benzene crystallization (3 ml. per g.) of the residue from evaporation of the benzene layer. The first 1.94 g. of this 50% yield was crystallized from 33 ml. of 95% ethanol; 69% recovered, m.p. 167–168°, $[\alpha]_D^{27}$ +0.90 ± 0.11° (7% solution in 2,5-dioxahexane). After recrystallization from benzene (10 ml. per g., 80% recovery, m.p. unchanged) rotation was $[\alpha]_D^{26}$ +0.30 ± 0.11°.

*2,3-Diphenylpropanoic acid.* Both pure and impure portions of the anilide were recombined and refluxed for twelve hours with 30 ml. of 1:1 (by volume) of water–sulfuric acid, then diluted to 200 ml. with water and extracted wih 115 ml. of ether. One half of the solution was extracted with two 20-ml. portions of 5% aqueous sodium carbonate. The alkaline extract was washed with chloroform, acidified with dilute sulfuric acid, then extracted with 60 ml. of chloroform. This solution dried by sodium sulfate was evaporated *in vacuo* leaving 0.45 g. (26% on the phenyl isocyanate basis) of yellowish product, m.p. 78–79.5°, $[\alpha]_D^{23}$ +3.31 ± 0.10° (16% in acetic acid).

Of this product, 0.40 g. was dissolved in 0.8 ml. of ethyl acetate and 8 ml. of hexane. This was applied to a partition chromatographic column of 2.5 cm. i.d. and was developed with hexane equilibrated with water-methanol–sulfuric acid.[22] The first six 25-ml. fractions contained only traces of the acid but subsequent fractions gave: 7, 0.036 g., m.p. 81–84°; 8, 0.154 g., m.p. 95–96°; 9, 0.136 g., m.p. 81–84°; 10, 0.027 g., m.p. 81–84° or 89% of the original acid. The racemic acid may melt at 82°, 88–89° or 95–96°[23] and the enantiomers are reported to melt at 83–89°.[14] When fraction 8 was dissolved in diethyl ether and was seeded with a crystal from fraction 9 it melted at 81–84°. Rotation of an 11% solution of fractions 8 and 9 in acetic acid was $[\alpha]_D^{25}$ +3.16 ± 0.10°.

*2-Phenyl-2-butanol from ethyl halides in (+)dimethoxybutane.* The formation of Grignard reagent from 1.25 g. (0.051 g. atom) of magnesium, 5.45 g. (0.05 mole) of ethyl bromide and 6.0 g. (0.05 mole) of (+)2,3-dimethoxybutane and 40 ml. of benzene under circumstances outlined above commenced within 5 min. Addition was complete within an hour and titration showed 76% of basic magnesium. The chilled reagent was treated with 4.20 g. (0.035 mole) of acetophenone in 15 ml. of benzene during 1 hr. at 4°. After 3 hr. more stirring at 4–25° (Gilman test negative) the system was poured into 50 ml. of saturated aqueous ammonium chloride and ice. The aqueous phase was twice extracted with 50 ml. total of benzene which was combined with the benzene phase of the hydrolysate and washed with two 20-ml. portions of saturated aqueous sodium chloride. The solvents were then removed under reduced pressure, and recovered by a dry-ice trap in order that the dimethoxybutane could be purified for re-use.

After removal of the solvents, the remainder was distilled at 42–50° (0.15 mm., bath at 60–80°) leaving 1.50 g. of residue (36% of the weight of acetophenone). The 2.81 g. of distillate was refluxed one hour with a mixture of 20 g. of Girard's "P",[24] 2.5 g. of acetic acid and 22.5 ml. of absolute ethanol, then poured into a solution of 1.98 g. of sodium carbonate in 100 ml. of water plus ice. The cold mixture was extracted rapidly with four 25-ml. portions of chloroform; this extract was dried with sodium sulfate and distilled, 2.21 g. (79% of crude distillate, 45% of theoretical), b.p. 52° (0.11 mm., bath at 70°), inert toward dinitrophenylhydrazone reagent, $n_D^{20}$ 1.5192, $d_4^{20}$ 0.977, $[\alpha]_D^{26}$ +0.60 ± 0.01° (neat). This product was twice crystallized by solution in 10 volumes of hexane in a flat-bottomed tube through the side arm of which passed nitrogen. Upon cooling to −70° and scratching or seeding, the crystals formed after two hours were freed from solvent by a close-fitting "filter stick." After drying under 10 mm. with calcium chloride and paraffin wax, the product (recovery 77%) had a fusion point −13° to −8°, $[\alpha]_D^{21}$ +0.62 ± 0.04°, $n_D^{20}$ 1.5185. The ultraviolet spectrum (0.16 g./l. in absolute ethanol) showed the characteristics (λ, mμ, E)—Maxima: 266.5, 99; 263, 154; 257, 215; 251.5, 189; 247.5, 151. Shoulder: 241.5, 115. Minima: 262, 123; 255, 160; 228, 48. These physical constants are essentially unchanged by further purification except for fusion point, −11° to −8°.

The aqueous phase from Girard treatment was made 0.5*N* in sulfuric acid and thrice extracted with chloroform. The 60 ml. of extract was dried with sodium sulfate and evaporated at 50° under 300 mm. The residue was dissolved in 3 ml. of absolute ethanol and treated with 50 ml. of methanolic dinitrophenylhydrazine–hydrogen chloride reagent: 0.82 g. of acetophenone dinitrophenylhydrazone, m.p. 235°. A similar control mixture of acetophenone and 2-phenyl-2-butanol gave an 80% yield of the dinitrophenylhydrazone, m.p. 235°, so the derivative is equivalent to 0.41 g. (10%) of the acetophenone originally added to the Grignard reagent. This value is accounted in calculation of the 2-phenyl-2-butanol yield. Both dinitrophenylhydrazones on crystallization from benzene (100 ml. per g.) melted at 243–244°.

In a duplicate experiment the values were: 80% RMg*X*, 8% recovered acetophenone, 35% of high boiling material and 50% of 2-phenylbutanol, $[\alpha]_D^{25}$ +0.55 ± 0.02° (not crystallized). In a third experiment where the excess magnesium was removed from the reagent the acetophenone recovery was 15%, high boiling material 25%, 2-phenylbutanol 40%, $[\alpha]_D^{24}$ +0.61 ± 0.04°. In one experiment 9.2 g. (0.05 mole) of anhydrous magnesium bromide[25] was added to a filtered reagent but little of it dissolved.

Comparable experiments with ethyl iodide (light-protected) Grignard reagents were not amenable to reagent titration (10% yield in supernatant) because of precipitation in the system. Yields and properties shown in Table I were obtained by procedures identical with those described above. Recovery of acetophenone was 10%; high boiling material was 36% of the weight of original acetophenone.

The preparation of the ethyl chloride reagent differed only because a large excess (5 g., 0.2 g. atom) of magnesium was used. Initiation of Grignard reaction required 25 min. No acetophenone could be recovered and only 10% of the weight of original acetophenone was isolated as high-boiling by-product.

All samples of 2-phenyl-2-butanol could be converted by treatment for 16 days with phenyl isocyanate to a magma from which, by extraction with boiling hexane, 75–82% of the same crude urethane could be obtained. Crystallized from hot hexane (7 ml. per g.), the urethane of 2-phenyl-2-butanol melted[26] at 89–90° (45–62% recovery).

*2-Phenyl-2-butanol from ethyl halides in polyethers.* When mannitol hexamethyl ether was used with ethyl bromide

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under the standardized conditions outlined above, initiation of Grignard reagent formation required 15 min. Acetophenone equivalent to the 50% Grignard yield was added with standard processing except that the portion of mannitol hexamethyl ether which codistilled with the product had first to be removed by six 400-ml. water washings of the distillate dissolved in 25 ml. of benzene. Recovery of acetophenone (as its 2,4-dinitrophenylhydrazone) was 9%. A portion (0.220 g.) of the 17% yield of slightly impure 2-phenyl-2-butanol, $[\alpha]^{24}_{D}$ −1.70 ± 0.10°, $n^{20}_{D}$ 1.5174, was diluted with 0.280 g. of the inactive carbinol and twice crystallized from hexane at −70°. The 63% recovery had $n^{20}_{D}$ 1.5183, $[\alpha]^{21}_{D}$ −0.88 ± 0.06°, indicating the minimum rotation of the reaction product as $[\alpha]^{21}_{D}$ −2.00 ± 0.14°.

Titration showed 33% of Grignard reagent from ethyl bromide in benzene-arabitol pentamethyl ether. An equivalent amount of acetophenone gave a product yielding 4% of recovered acetophenone and 14% of 2-phenyl-2-butanol, $[\alpha]^{21}_{D}$ −0.98 ± 0.08, which was purified by the dilution method described above to give an estimated $[\alpha]^{20}_{D}$ −1.15 ± 0.07° for the pure reaction product.

The reaction of ethyl chloride with magnesium in benzene-mannitol hexamethyl ether required strong heating for initiation, though a 66% yield of reagent was obtained. In this instance the polyether was washed by water from the benzene solution after treatment with acetophenone. The usual technique yielded 2% of recovered acetophenone and 17% of 2-phenyl-2-butanol, $[\alpha]^{25}_{D}$ −0.63 ± 0.06°, $n^{20}_{D}$ 1.5179; purified by dilution technique final estimation was $[\alpha]^{21}_{D}$ −0.42 ± 0.15°.

*2-Phenyl-2-butanol from bromobenzene.* (*a*). *In benzene and (+)2,3-dimethoxybutane.* When the Grignard reagent from bromobenzene was prepared as described above a two-phase system was obtained—yellowish upper layer of 40 ml. (containing a 20% yield of Grignard reagent by titration) and a brown lower phase (8 ml.) containing brown gelatinous precipitate. Subsequent treatment with 2-butanone showed by negative Gilman test that less than 75% of reagent was present. The yield of 2-phenyl-2-butanol indicated about 30% of Grignard reagent yield but only 3% of the possible biphenyl was isolated.

The preparation was repeated in a Waring Blendor adapted like a gas-tight three-necked flask, the stirrer seal being packed with silicone grease. After adding 50 ml. of benzene and 15 ml. of a solution of 7.85 g. (0.05 mole) of bromobenzene and 6.1 g. (0.05 mole) of (+)2,3-dimethoxybutane in 50 ml. of benzene, stirring was begun at 8000–10,000 r.p.m. When reflux occurred after several minutes, the addition was continued for 30 min. with spontaneous reflux. The reagent, siphoned into a standard three-necked flask, was amber, slightly turbid, and almost homogeneous; titration showed 56% conversion to Grignard reagent.

An equivalent amount (2.0 g., 0.028 mole) of 2-butanone in 15 ml. of benzene was added and the system was processed as is described above, b.p. 53–56° (0.45 mm.), 3.35 g. (80%), $n^{20}_{D}$ 1.5182, $[\alpha]^{21}_{D}$ +2.05 ± 0.02°, inert toward dinitrophenylhydrazine reagent. This crude 2-phenyl-2-butanol was dissolved in 33 ml. of hexane, cooled to −70°, and filtered "by the stick" leaving 0.40 g. of biphenyl, m.p. 69–70° (10%). The filtrate, evaporated to 20 ml. gave crystals at −70° which were recrystallized in the same way (recovery 50%, $[\alpha]^{20}_{D}$ +2.90 ± 0.06°) and then crystallized a third time at −70°, recovery 86%, $[\alpha]^{20}_{D}$ +3.04 ± 0.06°. The change in rotation indicated that the material before crystallization contained 67% of 2-phenyl-2-butanol; the yield was thus 54% on the basis of the ketone used in the reaction.

(*b*). *In benzene and (+)-1-methoxy-2-methylbutane.* The Grignard reagent from 7.4 g. (0.047 mole) of bromobenzene and 1.20 g. (0.049 g.-atom) of magnesium in 4.8 g. (0.047 mole) of 1-methoxy-2-methylbutane and 40 ml. of benzene required 15 min. at 20° for initiation. After 2 hr. of addition, stirring was continued for 10 hr. The system then was comprised of 34 ml. deep red-brown upper phase (30% basic Mg) and 12 ml. of a light-red lower phase (14% basic Mg). Upon treatment with 1.36 g. (0.0188 mole) of 2-butanone and with standardized processing the system gave a 5.5% yield of biphenyl and a 55% yield (ketone basis) of 2-phenyl-2-butanol, $[\alpha]^{21}_{D}$ 0.00 ± 0.06°, as well as 1.69 g. of high-boiling material.

(*c*). *In benzene and mannitol hexamethyl ether.* To 3 g. (0.12 g.-atom) of magnesium was added during one hour a solution of 4.71 g. (0.03 mole) of bromobenzene in 7.99 g. (0.03 mole) of manno-hexamethoxyhexane; initiation was induced by first heating to 80°. Stirring was continued at 20° for 8 hr. after completion of addition (basic Mg, 16%) and then for 3 hr. more at 65° (basic Mg, 47%). After 3 more hr. at 65° the titer did not change. The system was homogeneous.

After treatment with 0.95 g. (0.0132 mole) of 2-butanone the system was processed as described above (a benzene solution of the initial distillate being washed with 300 ml. of water to remove the polyether) to give 0.283 g. of crude 2-phenyl-2-butanol. This product was developed from a 1.6 × 16 cm. column of 4:1 Baker and Adamson silicic acid-Celite (dried at 90° after washing with acetone and water) by means of 1.5:98.5 ethanol-chloroform (V:V). The intermediate fractions contained 0.21 g. which was diluted with 0.305 g. of inactive 2-butanol and crystallized from 10 volumes of hexane at −70°, 61% recovery, $n^{20}_{D}$ 1.5184, $[\alpha]^{20}_{D}$ −0.29 ± 0.04° (neat), expected spectrum, so that the 2-phenyl-2-butanol before dilution had at least $[\alpha]^{20}_{D}$ −0.75 ± 0.10°.

(*d*). *In benzene and arabitol pentamethyl ether.* Since preliminary experiments showed that this Grignard reagent was difficult to prepare, a "semimicro" Waring Blendor unit (Central Scientific Co. 4282F) was modified by brazing on a water jacket around the fluted portion and by replacing the monel lid by a tight-fitting Teflon lid which was machined for the interchangeable joints of condenser and dropping funnel. After oven drying and displacement of air by nitrogen, the reagent was prepared from 2.0 g. (0.08 g.-atom) of magnesium (which had been heated under nitrogen in a separate container), 4.71 g. (0.03 mole) of bromobenzene, and 6.66 g. (0.03 mole) of arabo-pentamethoxypentane by maintaining the system at reflux temperature (steam in jacket) during 30 min. at 10,000 r.p.m. Subsequently the heated system (basic magnesium 14%) was stirred for 11 hr. at 65° (basic magnesium 24%). Treatment with 1.16 g. (0.016 mole) of 2-butanone and with processing described in the preceding experiment gave a 7% yield of 2-phenyl-2-butanol the rotation of which was essentially zero.

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