difference between the two cases is too large to be ascribed to the difference in the potentials of zinc amalgam (the potentials of zinc amalgam in the presence and absence of polyvinyl alcohol are −1.04 v. and −1.01– −1.02 v. *vs.* S.C.E., respectively). It may be due to the surface activity of polyvinyl alcohol. The remarkable difference in the zinc amalgam potential–time relations between two cases supports this view, although a detailed discussion is impossible for the present.

The electrolytic reduction of carbonyl compound on cadmium or lead electrode may proceed by a mechanism similar to that of Clemmensen reduction, the low chemical activity of the metals being compensated by the voltage applied to the electrode.

Acknowledgment.—The author expresses his sincere thanks to Dr. Y. Takegami, Kyoto University for his useful suggestions.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF OAK RIDGE NATIONAL LABORATORY]

The Effect of Changing Reagent upon Stereoselectivity[1a]

BY JACK H. STOCKER,[1b] PADET SIDISUNTHORN,[1c] BEN M. BENJAMIN AND CLAIR J. COLLINS

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The stereoselectivities exhibited during several reactions in which a second, adjacent asymmetric carbon atom is formed have been observed. The effect of changing the organometallic reagent from phenyllithium to phenylmagnesium iodide to phenylmagnesium bromide to phenylmagnesium chloride also has been studied in the addition of these reagents to biacetyl or to phenylacetoin. It has been shown that the product *dl:meso* ratio is greater than one when either phenyllithium or phenylmagnesium iodide is employed, and less than one when phenylmagnesium bromide or chloride is employed. A similar series of reactions between benzil or methylbenzoin and the corresponding methyl reagents is also reported. All results are discussed in terms of the hypothetical intermediates.

Introduction

Our interest in the stereoselectivity of reactions in which a second, adjacent asymmetric carbon atom is introduced into a molecule stemmed from our need for stereospecifically phenyl-labeled 1,1-diphenyl-2-aminopropanol, successfully prepared[2] through the action of phenylmagnesium bromide upon the stannic chloride complex salt of 2-aminopropiophenone-*phenyl*-C^{14}. During the foregoing study it was demonstrated that the action of *p*-tolylmagnesium bromide upon 2-aminopropiophenone also was highly stereoselective, such that of the two possible diastereomeric products, one predominated over the other by a factor of about 99:1. Although other authors had hinted at such a possibility,[3] we believe the two examples[2] just mentioned provide the first clear-cut evidence that stereoselectivity of such a magnitude is possible.

We have now extended these studies to an investigation of the diastereomer ratios obtained when several α-hydroxy ketones, plus biacetyl and benzil, are treated with organometallic reagents or with lithium aluminum hydride.[4] The results with one monofunctional ketone and one monofunctional aldehyde are also included.

Results

In each of the reactions studied a carbonyl group was converted to an asymmetric center by (a) reduction with lithium aluminum hydride or (b) treatment with an organometallic reagent. In two of the reactions (runs 1 and 2) the carbonyl group was adjacent to an asymmetric center containing no functional groups, whereas in all of the other reactions considered, a carbonyl was either (a) adjacent to an asymmetric center containing a functional group or (b) adjacent to another carbonyl. Each reaction yielded two diastereomeric products. The ratios of diastereomers in all of the experiments were obtained through the carbon-14 dilution method,[5] in which labeled reactants and previously synthesized, unlabeled diluents, or unlabeled reactants and labeled product-diluents were employed.

In Table I are given the results of experiments 1–11, involving primarily the reactions of aryl or aralkyl α-hydroxy ketones with Grignard reagents, or with lithium aluminum hydride. In Tables II–V we have recorded the ratios of diastereomeric (*meso* and *dl*) 2,3-diphenyl-2,3-butanediols produced when several organometallic reagents are allowed to react with (a) biacetyl or phenylacetoin and (b) benzil or methylbenzoin. In Table II results are recorded in which the organometallic reagents employed were methyllithium and phenyllithium. In Table III the data concern methylmagnesium iodide and phenylmagnesium iodide, in Table IV methylmagnesium bromide and phenylmagnesium bromide, and in Table V methylmagnesium chloride and phenylmagnesium chloride.

Finally, we carried out one experiment not given in Tables I–V, namely, the addition of carbon-14-labeled phenylacetoin to diphenylmagnesium. The results (see Experimental section) show that *meso*-2,3-diphenyl-2,3-butanediol was formed in 13.0% yield, the *dl*-isomer in 28.4% yield, and that the *meso: dl* ratio is thus 1:2.18.

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[1] (a) This paper is based upon work performed at Oak Ridge National Laboratory, which is operated for the Atomic Energy Commission by Union Carbide Corporation. (b) ORINS research participant from Louisiana State University in New Orleans, June–September, 1959. (c) Participant of the United Nations International Atomic Energy Agency from Bangkok, Thailand, September, 1959, to January, 1960.

[2] B. M. Benjamin, H. J. Schaeffer and C. J. Collins, THIS JOURNAL, **79**, 6160 (1957).

[3] See, for example, A. McKenzie and H. Wren, *J. Chem. Soc.*, **97**, 473 (1910).

[4] A preliminary report of these results was given at the meeting of the American Chemical Society, San Francisco, Cal., April 13, 1958. See page 11-N of the Abstracts, Division of Organic Chemistry.

[5] See, for example, R. H. Mayor and C. J. Collins, THIS JOURNAL, **73**, 471 (1951); C. J. Collins, *ibid.*, **77**, 5517 (1955); H. J. Schaeffer and C. J. Collins, *ibid.*, **78**, 124 (1956); and B. M. Benjamin and C. J. Collins, *ibid.*, **78**, 4952 (1956).

TABLE I

DIASTEREOMER RATIOS OBSERVED UPON REACTION BETWEEN CARBONYL-CONTAINING COMPOUNDS AND GRIGNARD REAGENTS OR LITHIUM ALUMINUM HYDRIDE

Expt	Carbonyl reactant	Reagent	Yield of product *threo*	Yield of product *erythro*	Ratio *threo : erythro*
1[a,b]	$Ph(p\text{-}C_7H_7)CHCOPh$	$LiAlH_4$	49.4	52.2	0.946–1.055:1
2[a]	$Ph(p\text{-}C_7H_7)CHCHO$	PhMgBr	46.1	48.8	0.94–1.06:1
3[b,c]	$PhCHOHCO(p\text{-}C_7H_7)$	$LiAlH_4$	16.0	87.8	1:5.5
4[d]	$PhCOCHOH(p\text{-}C_7H_7)$	$LiAlH_4$	17.2	84.8	1:4.9
5[b]	$PhCHOHCO(p\text{-}C_7H_7)$	PhMgBr	70.6	1.1	64:1
6[b]	PhCHOHCOPh	$p\text{-}C_7H_7MgBr$	1.2	66.0	1:55
7[e,f]	$PhCHOHCOCH_3$	PhMgBr	67.4	2.5	27:1
8[e]	PhCHOHCOPh	CH_3MgI	2.9	80.8	1:28
9[g]	PhCHOHCOPh	$o\text{-}C_7H_7MgBr$	3.4	57.3	1:17
10[f,g]	$PhCHOHCO(o\text{-}C_7H_7)$	PhMgBr	18.0	0.94	19:1
11[b,h]	$PhCH(OCOCH_3)COPh$	$p\text{-}C_7H_7MgBr$	1.8	49.9	1:28

[a] Configurations of *threo* and *erythro* products for experiments 1 and 2 not known. [b] B. M. Benjamin and C. J. Collins, THIS JOURNAL, **78**, 4329 (1956). [c] M. Tiffeneau and S. Levy, *Bull. soc. chim.*, [4] **49**, 1738 (1931). [d] A. Weissberger, *J. Chem. Soc.*, 223 (1935). [e] M. Tiffeneau and J. Levy, *Bull. soc. chim.*, [4] **41**, 1351 (1927). [f] H. Wren, *J. Chem. Soc.*, **95**, 1592 (1909). [g] V. F. Raaen and C. J. Collins, THIS JOURNAL, **80**, 1409 (1958). [h] A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 69.

TABLE II

DIASTEREOMER RATIOS OBSERVED UPON REACTION, IN ETHER OR PENTANE, OF METHYLLITHIUM WITH BENZIL OR METHYLBENZOIN, AND OF PHENYLLITHIUM WITH BIACETYL OR PHENYLACETOIN

Expt.	Ketone or ketol	Organo-metallic reagent	Yield, *meso*	Yield, *dl*	Ratio, *meso : d*
12[a]	$\mathrm{Ph\overset{*}{C}O\overset{*}{C}OPh}$	CH_3Li[b]	84.6	10.8	7.8:1
13[a]	$\mathrm{Ph\overset{OH}{\underset{CH_3}{C}}{}^{*}-\overset{\overset{O}{\|}}{C}{}^{*}Ph}$	CH_3Li[b]	89.3	10.8	8.3:1
14[a]	$CH_3COCOCH_3$	PhLi[b,c]	7.65	67.0	1:8.8
15[a]	$\mathrm{CH_3{}^{*}\overset{OH}{\underset{Ph}{C}}\overset{*}{C}OCH_3}$	PhLi[b]	8.74	91.0	1:10.4
16[a]	$\mathrm{CH_3{}^{*}\overset{OH}{\underset{Ph}{C}}\overset{*}{C}OCH_3}$	PhLi[b]	8.33	80.0	1:9.6
17[a]	$\mathrm{CH_3{}^{*}\overset{OH}{\underset{Ph}{C}}-\overset{*}{C}OCH_3}$	PhLi[d]	9.39	81.0	1:8.6
18[e]	$\mathrm{Ph\overset{OH}{\underset{CH_3}{C}}{}^{*}-\overset{*}{C}OPh}$	CH_3Li	67.7	19.9	3.4:1
19[e]	$\mathrm{CH_3{}^{*}\overset{OH}{\underset{Ph}{C}}-\overset{*}{C}OCH_3}$	PhLi	12.6	63.2	1:5.2

[a] In ether. [b] Ketone or ketol added to methyllithium or phenyl lithium. [c] Biacetyl non-radioactive, diluents labeled with carbon-14. [d] Phenyllithium added to phenylacetoin. [e] In pentane.

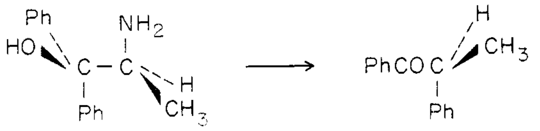
TABLE III

DIASTEREOMER RATIOS OBSERVED UPON REACTION, IN ETHER, OF METHYLMAGNESIUM IODIDE WITH BENZIL OR METHYLBENZOIN, AND OF PHENYLMAGNESIUM IODIDE WITH BIACETYL OR PHENYLACETOIN

Expt.	Ketone or ketol	Grignard reagent	Yield, *meso*	Yield, *dl*	Ratio, *meso:dl*
20	$\mathrm{Ph\overset{*}{C}O\overset{*}{C}OPh}$	CH_3MgI	27.6	14.3	1.93:1
21	$\mathrm{Ph\overset{OH}{\underset{CH_3}{C^{*}}}-\overset{*}{C}OPh}$	CH_3MgI	20.3	10.3	1.98:1
22	$\mathrm{Ph\overset{OH}{\underset{CH_3}{C^{*}}}-\overset{*}{C}OPh}$	CH_3MgI	40.5	20.5	1.98:1
23	$CH_3COCOCH_3$[a]	PhMgI	12.6	25.3	1:2.00
24	$\mathrm{CH_3{}^{*}\overset{OH}{\underset{Ph}{C}}\overset{*}{C}OCH_3}$	PhMgI	18.6	37.4	1:2.00
25	$\mathrm{CH_3{}^{*}\overset{OH}{\underset{Ph}{C}}\overset{*}{C}OCH_3}$	PhMgI[b]	19.3	32.6	1:1.69

[a] Diluents radioactive. [b] Excess MgI_2 added.

With the exception of *threo*- and *erythro*-1,2-diphenyl-2-*p*-tolyethanol (the products from both runs 1 and 2) all other compounds involved in this paper had previously been characterized. The question of whether the configurations of products are *threo* or *erythro* presumably was decided easily, except in the cases of the products (the 1,2-diphenyl-2-*p*-tolylethanols) from runs 1 and 2. Since, however, the diastereomer ratios for runs 1 and 2 were shown experimentally to be one, this problem is not, for the purpose of the present paper, an important one. The configurations of the other products of Table I were inferred as follows: Bernstein and Whitmore[6] showed that the optical activity exhibited by the product of deamination–rearrangement of (+)- or of (−)-1,1-diphenyl-2-aminopropanol represented a net *inversion* of configuration at the migration terminus



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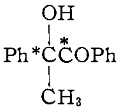
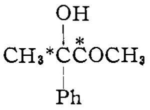
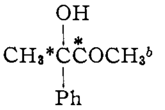
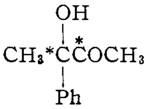
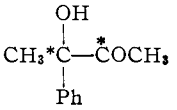
[6] H. I. Bernstein and F. C. Whitmore, THIS JOURNAL, **61**, 1324 (1939); see also A. McKenzie, R. Roger and G. D. Wills, *J. Chem. Soc.*, 779 (1926) and ref. 2

TABLE IV

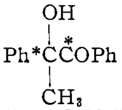
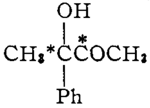
DIASTEREOMER RATIOS OBSERVED UPON REACTION, IN ETHER, OF METHYLMAGNESIUM BROMIDE WITH BENZIL OR METHYLBENZOIN, AND OF PHENYLMAGNESIUM BROMIDE WITH BIACETYL OR PHENYLACETOIN

Expt.	Ketone or ketol	Grignard reagent	Yield, *meso*	Yield, *dl*	Ratio, *meso*: *dl*
26	 $\mathrm{Ph^*}\overset{\mathrm{OH}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\overset{*}{\mathrm{C}}\mathrm{OPh}$	CH_3MgBr	76.0	25.8	2.95:1
27	$\mathrm{Ph}\overset{*}{\mathrm{C}}\mathrm{O}\overset{*}{\mathrm{C}}\mathrm{OPh}$	CH_3MgBr	40.7	17.2	2.36:1
28	$CH_3COCOCH_3$[a]	PhMgBr	53.9	22.8	2.36:1
29	 $\mathrm{CH_3^*}\overset{\mathrm{OH}}{\underset{\mathrm{Ph}}{\mathrm{C}}}\overset{*}{\mathrm{C}}\mathrm{OCH_3}$	PhMgBr	65.6	27.8	2.36:1
30	 $\mathrm{CH_3^*}\overset{\mathrm{OH}}{\underset{\mathrm{Ph}}{\mathrm{C}}}\overset{*}{\mathrm{C}}\mathrm{OCH_3}$[b]	PhMgBr	63.0	29.7	2.12:1
31	 $\mathrm{CH_3^*}\overset{\mathrm{OH}}{\underset{\mathrm{Ph}}{\mathrm{C}}}\overset{*}{\mathrm{C}}\mathrm{OCH_3}$	PhMgBr	49.2	23.1	2.13:1
32	 $\mathrm{CH_3^*}\overset{\mathrm{OH}}{\underset{\mathrm{Ph}}{\mathrm{C}}}\text{—}\overset{*}{\mathrm{C}}\mathrm{OCH_3}$	PhMgBr[c]	52.8	23.1	2.28:1

[a] Diluents radioactive. [b] Grignard reagent added to phenylacetoin. [c] Excess $MgBr_2$ added.

TABLE V

DIASTEREOMER RATIOS OBSERVED UPON REACTION, IN ETHER, OF METHYLMAGNESIUM CHLORIDE WITH BENZOIN OR METHYLBENZOIN, AND OF PHENYLMAGNESIUM CHLORIDE WITH BIACETYL AND PHENYLACETOIN

Expt.	Ketone or ketol	Grignard reagent	Yield, *meso*	Yield, *dl*	Ratio, *meso*: *dl*
33	$\mathrm{Ph}\overset{*}{\mathrm{C}}\mathrm{O}\overset{*}{\mathrm{C}}\mathrm{OPh}$	CH_3MgCl	36.6	14.5	2.53:1
34	 $\mathrm{Ph^*}\overset{\mathrm{OH}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\overset{*}{\mathrm{C}}\mathrm{OPh}$	CH_3MgCl	41.3	14.5	2.85:1
35	$CH_3COCOCH_3$[a]	PhMgCl	46.3	13.2	3.51:1
36	 $\mathrm{CH_3^*}\overset{\mathrm{OH}}{\underset{\mathrm{Ph}}{\mathrm{C}}}\overset{*}{\mathrm{C}}\mathrm{OCH_3}$	PhMgCl	62.5	18.8	3.33:1

[a] Diluents radioactive.

Curtin, *et al.*,[7] demonstrated that when the aminoalcohol formed by addition of a substituted-phenyl Grignard reagent to aminodesoxybenzoin was subjected to deamination, the predominant product was formed by migration of *phenyl,* rather than substituted phenyl. When the mode of addition was reversed, *i.e.*, when phenylmagnesium bromide was added to the appropriately substituted aminodesoxybenzoin and the product subjected to deamination, then the predominant product was formed with migration of *substituted phenyl* rather than phenyl. Since Curtin[1] has explained these phenomena through the *cis*-effect, he was able to establish the relative configurations of the two asymmetric centers of the aminoalcohols studied. If, in the present study, we presume that the substitution of hydroxyl for the amino group of aminodesoxybenzoin (or derivatives thereof) does not affect the steric course of Grignard addition, then we can establish the *threo* and *erythro* configurations of the reactants of runs 3–11 of Table I.[8]

The configurations of the *meso*- and *dl*-2,3-diphenyl-2,3-butanediols have been established.[8] We find, however, the melting point of the *meso* isomer to be 120–121.5°, rather than 117–118°,[9] and that of the *dl*-isomer to be 124°. We originally separated the *dl*-form by hand from a mixture of the reaction products of methylmagnesium iodide and benzil in ether. The *meso* form can be obtained from the same mixture by repeated crystallization of the mixture from hexane. When the results of Table II became known, however, it was obvious that the easiest method of preparing *meso*-2,3-diphenyl-2,3-butanediol is through the action of methyllithium upon benzil, and that the *dl*-form is most simply prepared through the interaction of phenyllithium and biacetyl.

Discussion

From Table I the following conclusions can be drawn: 1. Experiments 1 through 4 demonstrate that the steric effects, or "effective bulks" of phenyl and *p*-tolyl are, for these reactions, experimentally identical. This conclusion is not startling, since the methyl group of the *p*-tolyl is in a position remote from the reaction site, and thus would not be expected to exert a large steric effect upon the reactions.

2. Experiments 5 through 11 demonstrate once again the high stereoselectivity[2] exhibited during Grignard addition to ketones adjacent to functional groups which can thus presumably form five-membered magnesium-complex intermediates.[10] In general, the α-hydroxyl seems to impart somewhat less stereoselectivity to the reaction than does an α-amino group.[2]

3. A comparison of experiments 3 and 4 with experiments 5–11 shows a reduced stereoselectivity in the reductions with lithium aluminum hydride.

Tables II to V deal with the reactions 1, 2, 3 and 4 in which R in CH_3R and PhR is –Li, –MgI, –MgBr and –MgCl. Thus Table II is concerned with reactions of CH_3Li and PhLi: runs 12 through 17 being carried out in ether solution whereas runs 18 and 19 were performed in pentane. It is clear that when R = Li, and when the reactions are carried out in ether, the stereoselectivities of reactions 1 and 2 are experimentally the same as those of reac-

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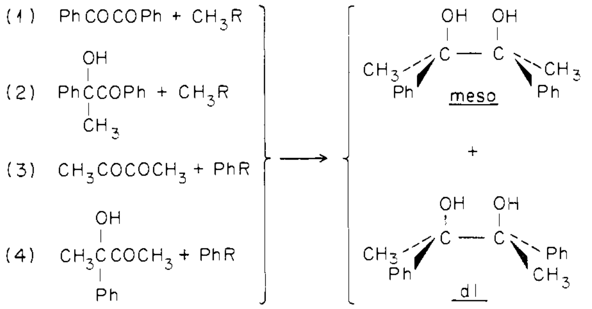
[7] P. I. Pollak and D. Y. Curtin, THIS JOURNAL, **72**, 961 (1950); D. Y. Curtin and P. I. Pollak, *ibid.*, **73**, 992 (1951); D. Y. Curtin, E. E. Harris and P. I. Pollak, *ibid.*, **73**, 3453 (1951); D. Y. Curtin and M. C. Crew, *ibid.*, **77**, 355 (1955).

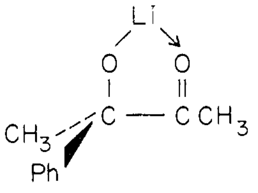
[8] Although not stated, we have tacitly employed this method four times previously to determine *threo* and *erythro* configurations of triaryl-substituted glycols: (a) B. M. Benjamin and C. J. Collins, *ibid.*, **78**, 4329 (1956); (b) L. W. Kendrick, Jr., B. M. Benjamin and C. J. Collins, *ibid.*, **80**, 4057 (1958); (c) V. F. Raaen and C. J. Collins, *ibid.*, **80**, 1409 (1958); (d) C. J. Collins and N. S. Bowman, *ibid.*, **81**, 3614 (1959). In references b and c above the radiochemical data obtained during rearrangement studies of the compounds involved supported these configurational assignments.

[9] D. J. Cram and K. R. Kopecky, THIS JOURNAL, **81**, 2748 (1959).

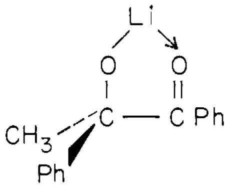
[10] D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952).



tions 3 and 4, although the ratio of product is reversed. When performed in pentane (runs 18 and 19), the stereoselectivity of the reaction is considerably lower. Since reaction 2 in Table II gives the same *meso:dl* ratio as reaction 1, and reaction 4 gives the same *meso:dl* ratio as reaction 3, we infer that each pair of reactions could have one intermediate in common, structure A for reactions 1 and 2, and structure B for reactions 3 and 4, having been proposed or implied previously.[1]

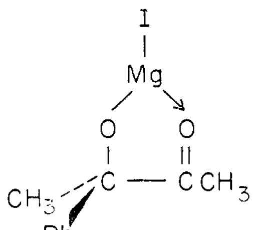


A

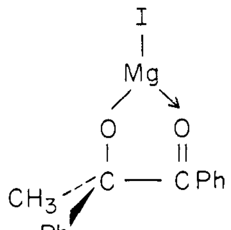


B

In Table III group –R in reactions 1–4 becomes –MgI. The results of runs 20–24 are qualitatively similar, save for degree, with those of runs 12–17 of Table II. When methylmagnesium iodide is the reactant, *meso*-2,3-diphenyl-2,3-butanediol predominates over the *dl*-isomer in the ratio 2:1, whereas when phenylmagnesium iodide is employed the *meso:dl*ratio becomes 1:2. The addition of excess, anhydrous magnesium iodide to phenylmagnesium iodide prior to reaction with phenylacetoin (run 25) has, at best, a small effect upon the stereoselectivity of the reaction. Although the foregoing reactions of methylmagnesium iodide and of phenylmagnesium iodide take place with considerably less stereoselectivity than do the reactions of the corresponding (Table II) organolithium compounds, the stereoselectivity dropping from about 8:1 to 2:1, it is tempting again to write the intermediates C and D (similar to A and B) and to postulate, as do Cram and Kopecky,[9] that methyl has an effective bulk smaller than phenyl, and that the preferred side for attack upon intermediates A, B, C and D is that for which the attacking group is opposed by a methyl rather than a phenyl group. That the situation is not this simple, however, is shown by the results given in Tables IV and V. Quite in contrast to the action of phenyllithium or phenylmagnesium iodide upon biacetyl and phenylacetoin, both phenylmagnesium bromide and phenylmagnesium chloride yield more *meso*-isomer than *dl*-isomer. The data of Tables IV and V, in fact, show that when R in reactions 1–4 is either –MgBr or –MgCl, the *meso*-isomer of 2,3-diphenyl-2,3-butanediol *always* predominates over the *dl*-isomer in the ratio of between 2:1 and 3.5:1. In all runs of Table IV, except 30, ketone or ketol was added to Grignard reagent, whereas in 30 phenylmagnesium bromide was added to phenylacetoin. In run 32 the Grignard reagent contained excess magnesium bromide. Thus neither the reversal of the order of addition of reagent nor the presence of excess magnesium bromide had any effect upon the *meso:dl* ratio. That this consistent preponderance of *meso*-isomer was not caused by product rearrangement was shown (see Experimental section) by subjecting the *dl*-isomer to treatment with phenylmagnesium bromide—under the conditions of the reactions of Table IV—followed by determination of reisolated *dl*-isomer (100%) and *meso*-isomer (0%) by the isotope-dilution method. The data of Tables IV and V thus leave us in the following positions: (1) if we accept the "rigid model" (A, B, C, D)[9,10] for the intermediates of Tables II–V, then we must conclude that in runs 12 through 27 the effective bulk of phenyl is greater than that of methyl, but that in runs 28–32, 35 and 36 the effective bulk of methyl is greater than phenyl; whereas (2) if we accept the "rigid model" (A, B, C, D) for the reactions of Table II and III, and the "open model"[9,10] for the reactions of Tables IV and V, then we are forced to disagree with the very reasonable assumption[9] that "the rigid model applies to the systems studied in which OH or OCH$_3$ occupies the asymmetric carbon of the starting material," and that "the same probably applies to any systems which carry groups on this carbon which are capable of reacting or complexing with organometallic reagents."[9,11]



C



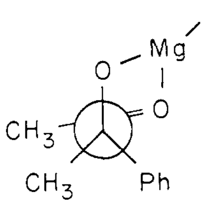
D

In our present state of knowledge it is not possible to decide why phenylmagnesium bromide and phenylmagnesium chloride react with biacetyl or with phenylacetoin to give more *meso*-2,3-diphenyl-2,3-butanediol than *dl*-isomer, particularly when all other reactions of Tables I–V appear to have been rationalized previously.[9,10] The situation is complicated by our lack of knowledge concerning the nature of the Grignard reagent.[12] If we are allowed to speculate, however, that the "rigid models" A, B, C and D (or their equivalents, depending upon the organometallic agents employed) apply for the reactions of Tables IV and V, then we must answer the question why do these intermediates sometimes act as though phenyl were larger in effective bulk than methyl (experiments 12–27, 33 and 34), whereas other times (experiments 28–32, 35

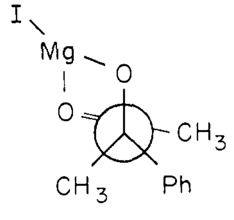
(11) The paper by Cram and Kopecky (ref. 9) appeared while our work was in progress. Professor Cram has recently sent us the results of further experiments in which he found also that the addition of phenylmagnesium bromide to phenylacetoin resulted in a larger yield of *meso*- than of *dl*-isomer. We are indebted to Professor Cram for furnishing us with his results prior to publication.

(12) See, for example, R. E. Dessy and G. S. Handler, THIS JOURNAL, **80**, 5824 (1958), and other references given therein.

and 36) the methyl appears to be larger in effective bulk than phenyl. One answer could be that the intermediates of the "rigid-model" type[9,10] have been written, as in A, B, C and D, with the two oxygens in eclipsed positions. If we deny the necessity for eclipsing these two oxygens however, then the intermediate C, for example, can exist in the two



C-1



C-2

conformations C-1 and C-2 which need not necessarily suffer attack by phenylmagnesium halide to yield the same ratio of *meso*-product to *dl*-product.

Several other speculative answers could also be devised to account for the results of Tables IV and V. In our opinion, however, the problem at present is too complicated to be explained in the same manner as have been less complicated[9,10] examples of stereoselective reactions.

Experimental

With the exception of the products of reactions 1 and 2, Table I, the compounds in this paper had already been prepared and characterized and their properties are recorded in the literature. The appropriate references are found in the footnotes of the tables. All the reactions were done in similar manner and yields of products were determined by isotope-dilution technique. A complete description of reactions 1 and 2, Table I, and several reactions from Table II, III, IV and V serve as typical examples for procedures. Melting points were determined on a Kofler-Heizbank, and radio-activity assays were performed by means of the Tolbert dry-combustion method using a sweep-gas consisting of 95% oxygen and 5% carbon dioxide.[13]

1,2-Diphenyl-2-*p*-tolylethanol.—A solution of 2.5 g. of *p*-tolydesoxy-benzoin in dry ether was added slowly to an ether solution of 0.3 g. of lithium aluminum hydride. The complex was decomposed by the careful addition of water until the precipitated alumina became grainy. The clear supernatant liquid was decanted and the alumina was washed twice with 25-ml. portions of ether. The combined ether solutions were concentrated on the steam-bath in a current of air until a solid remained. The solid material was dissolved in hot ligroin. Upon cooling, crystals, m.p. 80–84°, separated. After five crystallizations a material was obtained whose m.p. was 103–104°. This is referred to as the α-form because the absolute configuration was not determined and the term *erythro* or *threo* cannot be assigned.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.69; H, 7.03.

The acetyl ester was prepared by dissolving 1.7 g. of the pure α-carbinol in 10 ml. of pyridine and adding 5 ml. of acetic anhydride. After three days the mixture was poured into 200 ml. of water and the solid material was crystallized three times from ethanol. The ester had a m.p. of 107–108°.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.70; H, 6.87.

The filtrate from the first crystallization above was concentrated to about half its original volume and allowed to cool. The crystals which formed had a m.p. of 85–86°. After three crystallizations from ligroin the melting point remained at 85–86°. This is referred to as the β-form.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.68; H, 7.03.

The acetyl ester of the β-form, prepared exactly as described for the α-form, melted at 119–120° after two crystallizations from ethanol and one crystallization from ligroin.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 84.14; H, 6.89.

Determination of Yields of α- and β-Carbinols in the Reduction of *p*-Tolydesoxylbenzoin.—A sample of 0.2073 g. of carbon-14-labeled *p*-tolyldesoxybenzoin, 10.81 mc. carbon-14-labeled *p*-tolyldesoxybenzoin, 10.81 mc. carbon-14/mole, was reduced with lithium aluminum hydride. To the reaction mixture was added 1.009 g. of pure non-radioactive α-1,2-diphenyl-2-*p*-tolylethanol. The complex was decomposed and the α-carbinol was recovered and crystallized five times (Norit) from ligroin, m.p. 104°, 1.001 ± 0.011 mc. carbon-14/mole. This corresponds to a yield of 49.4% of the α-carbinol.

The yield of the β-carbinol was determined in exactly the same way, using 0.2082 g. of the carbon-14-labeled *p*-tolyldesoxybenzoin and 1.009 g. of non-radioactive β-carbinol. The recovered β-carbinol was crystallized four times from ligroin (Norit), m.p. 86°, 1.061 ± 0.001 mc. carbon-14/mole. This corresponds to a yield of 52.2% of the β-carbinol.

Determination of Yields of α- and β-Carbinols in the Reaction of Phenyl-*p*-tolylacetaldehyde with Phenyl Grignard Reagent.—Carbon-14-labeled phenyl-*p*-tolylacetaldehyde was prepared by the rearrangement of 6 g. of 1-phenyl-2-*p*-tolylethylene glycol according to the directions of Tiffeneau.[14] The aldehyde was distilled twice at 0.15 mm. and a fraction was collected at 113–114°. The radioactivity of the carbon-14-labeled aldehyde was measured by assaying its 2,4-dinitrophenylhydrazone, m.p. 179°, 5.687 ± 0.019 mc. carbon-14/mole. An ether solution of 1.056 g. of the aldehyde was added to the Grignard reagent prepared from 0.25 g. of magnesium and 1.5 g. of bromobenzene. After decomposing the complex with ammonium chloride solution the organic material was removed by several extractions with ether. The ether was removed by evaporation and the residue was diluted with hexane in a volumetric flask to 200 ml. After complete mixing of the solution, a 100-ml. aliquot was added to 1.521 g. of pure non-radioactive β-1,2-diphenyl-2-*p*-tolylethanol. The remaining 100-ml. aliquot was added to 1.005 g. of the pure non-radioactive α-carbinol. The α-carbinol was recovered and purified as described above m.p. 103–104°, 1.478 ± 0.002 mc. carbon-14/mole. The yield was 48.8%. Upon recovery and purification of the β-carbinol, m.p. 86°, 1.021 ± 0.003 mc. carbon-14/mole, the yield was found to be 46.1%.

Determination of Yields of *rac*- and *meso*-Glycols in the Reaction of Methylbenzoin with the Methylmagnesium Halides.—Carbon-14-labeled methylbenzoin, m.p. 65–66°, 8.794 ± 0.038 mc. carbon-14/mole, was prepared by the addition of one mole of methylmagnesium bromide to one mole of benzil-C^{14}. A solution of 1.0392 g. of the ketol in 100 ml. of dry ether was added rapidly and quantitatively to the Grignard reagent prepared from 1 g. of magnesium and 6 g. of methyl iodide in 100 ml. of ether. After being heated under reflux for 2 hours, the reaction mixture was decomposed with ammonium chloride solution. The organic material was separated quantitatively by several extractions with ether. All of the ether was evaporated and the residue was transferred to a 100-ml. volumetric flask with methanol and diluted to the mark. A 50-ml. aliquot of this solution was removed with a pipet and added to 0.9993 g. of pure non-radioactive *meso*-2,3-dimethyl-2,3-diphenylethylene glycol. The *meso*-glycol was reisolated and crystallized five times from hexane, m.p. 122°, 0.8939 ± 0.0028 mc. carbon-14/mole. This corresponds to a yield of 20.33% of *meso*-glycol. To the remaining 50 ml. of solution above was added 1.0044 g. of pure non-radioactive *rac*-glycol. The *rac*-glycol was reisolated and crystallized five times from hexane, m.p. 124°, 0.4730 ± 0.0064 mc. carbon-14/mole. This corresponds to a yield of 10.26% of *rac*-glycol. Therefore the ratio of *meso*- to *rac*-glycol is 1.98.

Benzil-C^{14} was allowed to react with the excess Grignard reagent prepared from methyl iodide and magnesium and

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[13] B. M. Tolbert, University of California Radiation Laboratory Report No. 3595, p. 12. We find this dry-combustion method superior to the wet-combustion procedure [see, for example, C. J. Collins, THIS JOURNAL, **77**, 5517 (1955)] which has been in use in this Laboratory for many years.

[14] M. Tiffeneau and J. Levy, *Bull. Soc. Chim.*, **49**, 1738 (1931).

the product ratio was determined in exactly the same way as described above. In an exactly analogous manner the product ratio was determined for the reaction of benzil-C^{14} or methylbenzoin-C^{14} with both methylmagnesium bromide and methylmagnesium chloride.

Determination of Yields of *rac*- and *meso*-Glycols in the Reaction of Phenylacetoin with the Phenyl Grignard Reagents.—Isonitrosopropiophenone-C^{14}[2] was treated with methylmagnesium iodide. The resulting oxime of phenylacetoin, m.p. 100°, 6.640 ± 0.019 mc. carbon-14/mole, was hydrolyzed to phenylacetoin-C^{14} by stirring it with 10% sulfuric acid at 45° for 3.5 hours. The oily product was distilled twice, b.p. 64–65° at 0.2 mm. A solution of 0.9490 g. of phenylacetoin-C^{14} was added to the Grignard reagent from 1 g. of magnesium and 6.9 g. of bromobenzene. After heating under reflux for 3.5 hours, the products were isolated as described before. Thus half of the product mixture was made homogeneous with 0.9575 g. of non-radioactive *meso*-glycol and the other half of the reaction product was mixed with 0.9208 g. of *rac*-glycol. The *meso*-glycol was reisolated and purified as before, m.p. 122°, 2.0284 ± 0.0026 mc. carbon-14/mole. This corresponds to a yield of 65.6% of *meso*-isomer. The *rac*-glycol was reisolated also as described above, m.p. 124°, 1.0774 ± 0.0033 mc. carbon-14/mole. Therefore the yield of *rac*-glycol was 27.8% and the ratio of *meso*-glycol to *racemate* was 2.03.

The reaction of biacetyl with the three Grignard reagents was done in exactly the same way as described for phenylacetoin, except that in these reactions the product from non-radioactive biacetyl was mixed with radioactive glycols for yield determination. Phenylmagnesium iodide was prepared from iodobenzene and magnesium in the usual way for making Grignard reagents. Phenylmagnesium chloride was prepared by heating equivalent amounts of chlorobenzene and magnesium under reflux overnight and taking up the viscous product in ether before addition of the carbonyl compound.[15]

Reactions in the Presence of Excess Magnesium Halides.—Magnesium bromide was prepared by passing dry hydrogen bromide into a flask containing 150 ml. of dry ether and 5 g. of magnesium. Before all the magnesium had reacted, the gas-delivery tube was removed and the mixture was heated under reflux for 2.5 hours. All the ether was removed by evaporation under vacuum. More ether was added and this was also distilled under vacuum to ensure complete removal of unreacted hydrogen bromide. To the remaining magnesium bromide was added the Grignard reagent from 2 g. of magnesium and 13.9 g. of bromobenzene, then phenylacetoin, 0.9085 g., 6.640 mc. carbon-14/mole, was added. From this point the reaction and work-up were carried out as already described. Half of the reaction product was mixed with 1.3360 g. of non-radioactive *meso*-glycol which was reisolated, 1.4290 ± 0.0184 mc. carbon-14/mole, 52.8% yield of the *meso*-isomer. The other half was mixed with 0.8700 g. of non-radioactive *rac*-glycol which was reisolated, 1.0335 ± 0.0005 mc. carbon-14/mole, 23.1% yield of the racemic isomer. The ratio of *meso*- to *rac*-glycol was 2.28.

Magnesium iodide was prepared by treating 3 g. of magnesium with 27.2 g. of mercuric iodide in 200 ml. of ether and 100 ml. of benzene. Mercury and excess magnesium were removed by filtration in an inert atmosphere. The solvents were removed in vacuum. To the dry magnesium iodide was added the Grignard reagent from 2 g. of magnesium and 17.9 g. of iodobenzene in 100 ml. of ether. The mixed magnesium iodide–phenylmagnesium iodide reagent was then treated with 1.1305 g. of phenylacetoin. After working up the reaction mixture and determining the product distribution in the usual way, it was found that the yield of *rac*-glycol was 31.6% and the yield of *meso*-glycol was 19.27 %. Therefore the *racemate* to *meso* ratio was 1.69.

Determination of Yields of *rac*- and *meso*-Glycols in the Reactions of Methylbenzoin with Diphenylmagnesium.—The Grignard reagent was prepared from 2 g. of magnesium and 13.8 g. of bromobenzene in 100 ml. of ether. To this was added 31 ml. of dioxane. A precipitate formed. The mixture was left standing overnight. The solids were then removed by filtration in an inert atmosphere. Phenylacetoin, 1.1990 g., 6.640 mc. carbon-14/mole, in 50 ml. of ether was added. The reaction mixture was worked up and the product distribution was determined in the usual way. *meso*-Glycol, 0.8110 g., was mixed with half of the reaction product and reisolated, 0.8273 ± 0.0003 mc. carbon-14/mole, 13.05% yield of *meso*-isomer. *rac*-Glycol, 0.6825 g., was mixed with half of the reaction product and reisolated, 1.788 ± 0.010 mc. carbon-14/mole, 28.4% yield of the racemate. Thus the ratio of *racemate* to *meso*-glycol was 2.18.

Determination of Yields of *rac*- and *meso*-Glycols in the Reaction of Methylbenzoin with Methyllithium.—Methyllithium was prepared by the gradual addition of methyl bromide to 0.75 g. of small pieces of lithium in 50 ml. of ether. To this reagent was added 0.9330 g. of methylbenzoin, 6.467 mc. carbon-14/mole. After 3 hours at reflux temperature, the reaction mixture was worked up in the same way as for the experiments in which Grignard reagents were employed. The product was diluted to 250 ml. in a volumetric flask. A 100-ml. aliquot was mixed with 0.5805 g. of non-radioactive *meso*-glycol. This was reisolated, 2.464 ± 0.017 mc. carbon-14/mole, 89.33% yield of *meso*-isomer. A 100-ml. aliquot was added to 0.9514 g. of *rac*-glycol and the racemate was reisolated, 0.2808 ± 0.003 mc. carbon-14/mole, 10.80% yield of racemate. A 50-ml. aliquot was added to 1.0190 g. of non-radioactive methylbenzoin. The material was reisolated and found not to be radioactive. Thus the ratio of *meso*-glycol to *racemate* is 8.27.

The reaction of phenylacetoin with phenyllithium and the subsequent product yield determination was done in a similar way with the use of appropriate compounds.

Attempted Isomerization of *racemic*-2,3-Dimethyl-2,3-diphenylethylene Glycol.—A sample of pure *rac*-glycol, 0.9660 g., 1.509 ± 0.003 mc. carbon-14/mole, in 40 ml. of ether was added to the Grignard reagent from 1 g. of magnesium and 6.9 g. of bromobenzene in 90 ml. of ether. The mixture was boiled for 3 hours and then hydrolyzed with ammonium chloride. The product was recovered and divided into two equal aliquots; to one aliquot was added 1.8365 g. of non-radioactive *meso*-glycol. This was reisolated and found to contain no radioactivity. To the second aliquot was added 0.8025 g. of non-radioactive *rac*-glycol. This was reisolated, 0.5680 ± 0.0003 mc. carbon-14/mole. Therefore there was recovered from the reaction mixture 0.9688 g. of *rac*-glycol (quantitative recovery).

OAK RIDGE, TENN.

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[15] R. H. F. Manske and A. E. Ledingham, *Can. J. Res.*, **27B**, 158 (1949).