usual way to give the crude alcohol (2.15 g, 75%). This was purified by glpc to benzyl-α-*d* alcohol: $\alpha^{25}D$ +0.900° (*l* 1, neat); $n^{25}D$ 1.5285. The deuterium content was found to be 85% of the theoretical, and $[\alpha]^{25}D$ and asymmetric induction were +1.007° and 64.1%, respectively.

Reduction of Benzaldehyde-1-*d* with (−)-Bornyloxymagnesium Bromide.—The reagent was prepared in the same way as described before by using 8.7 g of (−)-borneol, 6.2 g of *n*-propyl bromide, and 1.3 g of magnesium. To the homogeneous solution of the reagent in ether–benzene, 2.5 g of benzaldehyde-1-*d* was added. The solution was stirred at room temperature for 1 hr, then at 60° for 1 hr, and finally decomposed with 10% aqueous sulfuric acid. The product was worked up in the usual way to give benzyl-α-*d* alcohol (2.0 g, 80%). The alcohol obtained after purification through glpc and acid phthalate had $\alpha^{25}D$ −1.008°, $n^{25}D$ 1.5293, and a deuterium content of 94% of the theoretical. The $[\alpha]^{25}D$ and asymmetric induction were −1.019° and 64.5%, respectively.

Registry No.—**1**, 22927-82-8; **3**, 4181-90-2; benzaldehyde-1-*d*, 3592-47-0; (−)-α-*d*-isobornyloxyaluminum dichloride, 22927-83-9; (−)-bornyloxyaluminum dichloride, 22927-84-0; (−)-isobornyloxymagnesium bromide, 22927-85-1; (−)-α-*d*-isobornyloxymagnesiumbromide, 22927-86-2; (−)-bornyloxymagnesium bromide, 22927-87-3.

Acknowledgment.—The authors wish to thank the Council of Scientific and Industrial Research, New Delhi, and the United States Educational Foundation in India, New Delhi, for their generous support of this work. We are also indebted to Professor E. L. Eliel of the University of Notre Dame for his kind encouragement and valuable suggestions. One of the authors (D. N.) is grateful to the University of New South Wales, Australia, for the award of a Leverhulme Visiting Fellowship.

Heterogeneous Reactions with Zinc. II.[1] A General Synthesis of Ketones from 1,2-Trisubstituted Glycol Monoesters and the Mechanism of the Serini Reaction

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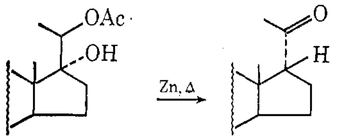
Secondary monoesters of open-chain, trisubstituted 1,2-glycols have been converted into ketones on heating with zinc dust. The reaction was found valid for benzoate and *p*-nitrobenzoate esters, as well as for acetates, better synthetic results being obtained with the former. In the presence of aromatic substituents at the secondary carbon atom, 1,2-aryl shifts, affording aldehydes, can also take place. Reactions of trisubstituted 1,2-glycol monoesters catalyzed by anhydrous zinc acetate led to results similar to those obtained using metallic zinc. These findings, in addition to other observations disproving the previously accepted assumptions concerning the mechanism of the Serini reaction in steroid systems, support the role of the zinc catalyst as a complexing Lewis acid. The values of the isotope effects k_H/k_D observed during the rearrangements suggest the participation of the migrating hydrogen in the ionization at the tertiary carbon atom. Diastereomeric systems have been used for the investigation of steric effects.

The zinc-promoted rearrangement of 17-hydroxy-20-acetoxy-sterol derivatives into C-20 ketones (eq 1) is



(1)

know as the Serini reaction,[2] and occurs with complete inversion at the C-17 center, even when less stable derivatives of "unnatural" configuration are formed. By labeling[3,4] it was found that the oxygen atom of the ester group attached to C-20 is not removed during the reaction, and that the conversion takes place by migration of the C-20 hydrogen to the C-17 center. After being considered of limited applicability even in the steroid field,[4] the Serini reaction was recently found to be of synthetic value in cyclic *cis* systems[5] where the application of other methods failed to lead to the desired results.

The objective of the present work was to extend the study of zinc-promoted rearrangements to open-chain, trisubstituted glycol monoacetates and to investigate the behavior of esters other than acetates, in order to define the scope of the reaction. The aim was also to gain more understanding of the reaction mechanism and of the influence of steric and electronic properties of the reactants on the reaction results.

Starting Materials and Synthetic Results.—The trisubstituted 1,2-glycols were prepared by appropriate methods, *e.g.*, hydroxylation of trisubstituted double bonds or adaptation of the Elphimoff-Felkin procedure[6] for the preparation of α-hydroxy ketones. The diastereomers **9–12** were prepared *via* reduction of 3-phenyl-3-hydroxy-2-butanone by lithium aluminum hydride followed by esterification. The *threo* isomer was predominant (66%), in agreement with Cram's rule for addition to α-hydroxy ketones (cyclic model).[7] The degree of stereospecificity was established by the nonequivalence of shifts in the nmr spectrum, the diastereomers being separated, after esterification, by column chromatography. The chemical shift of the secondary methyl group appears in the nmr spectrum at a higher file in the *threo* esters **11** and **12** than in the *erythro* esters **9** and **10**, indicating more shielding by the

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[1] For part I, see E. Ghera, *Chem. Commun.*, 1639 (1968).

[2] For reviews, see (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 628; (b) N. L. Wendler in "Molecular Rearrangements," Vol. II, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1039.

[3] F. Goto and L. F. Fieser, *J. Amer. Chem. Soc.*, **83**, 251 (1961).

[4] N. L. Wendler, *Proc. Chem. Soc.*, 422 (1960).

[5] E. Ghera, M. Gibson, and F. Sondheimer, *J. Amer. Chem. Soc.*, **84**, 2953 (1962); E. Ghera and F. Sondheimer, *Tetrahedron Lett.*, 3887 (1964); E. Ghera, *J. Org. Chem.*, **33**, 1042 (1968).

[6] I. Elphimoff-Felkin, *Bull. Soc. Chim. Fr.*, 784 (1955).

[7] D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2478 (1959).

TABLE I

ZINC-CATALYZED REARRANGEMENTS OF SECONDARY ESTERS OF TRISUBSTITUTED 1,2-GLYCOLS

(R_3 = alkyl group)

Starting materials $R_1R_2C(OH)CHR_3(OCOR_4)$					Temp, °C	Time, hr	Yield of products, %	
Compd	R_1	R_2	R_3	R_4			$R_1R_2CHCOR_3$	$R_1R_2C{=}R_3CH$
1	CH_3	CH_3	CH_3	CH_3	150	2.5–3.5	No reaction	
2	CH_3	CH_3	CH_3	C_6H_5	150	2.5–3.5	No reaction	
3	CH_3	CH_3	CH_3	p-$C_6H_4NO_2$	130	2.5	95[a]	...
4	CH_3	CH_3	C_2H_5	p-$C_6H_4NO_2$	130	2.5	89[a]	...
5	CH_3	CH_3	C_4H_9	CH_3	154	3.0	68[a]	11
6	CH_3	CH_3	C_4H_9	p-$C_6H_4NO_2$	130	2.5	91[a]	...
7	C_6H_5	C_6H_5	C_4H_9	CH_3	160	3.0	76[b]	12
8	C_6H_5	C_6H_5	C_4H_9	C_6H_5	160	3.0	75[b]	3
9 (*erythro*)	CH_3	C_6H_5	CH_3	CH_3	170	3.0	53[c]	32
10 (*erythro*)	CH_3	C_6H_5	CH_3	C_6H_5	160	3.0	70[c]	15
11 (*threo*)	CH_3	C_6H_5	CH_3	CH_3	170	3.0	67[c]	14
12 (*threo*)	CH_3	C_6H_5	CH_3	C_6H_5	160	3.0	78[c]	8

[a] Yields based on weight (after correction for purity, by vpc and nmr analysis, using integration). [b] Bp 124–126° (0.2 mm), $n^{25}D$ 1.561. *Anal.* Calcd for $C_{18}H_{20}O$: C, 91.47; H, 8.53. Found: C, 91.18; H, 8.68. Yield based on chromatographic separation. [c] The relative yields of ketones and aldehydes are based on vpc analysis; absolute yields were determined by chromatographic separation. Nmr analysis was used for the identification of the products and for the control of their purity.

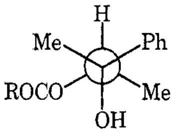
TABLE II

ZINC-CATALYZED REARRANGEMENTS OF SECONDARY ESTERS OF TRISUBSTITUTED 1,2-GLYCOLS WITH AN AROMATIC SUBSTITUENT AT THE SECONDARY CARBON

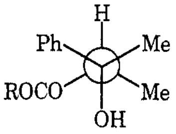
Starting materials $R_1R_2C(OH)CHAr(OCOR_4)$					Temp, °C	Time, hr	Yield of products, %		
Compd	R_1	R_2	Ar	R_4			$R_1R_2CHCOAr$	$R_1R_2ArCCHO$	$R_1R_2C{=}CHAr$
13	CH_3	CH_3	C_6H_5	CH_3	170	3	64[a]	9	14
14	CH_3	CH_3	C_6H_5	C_6H_5	160	2.5	78 ± 2[a]	14 ± 1	4
15	CH_3	CH_3	p-C_7H_7	C_6H_5	160	2.5	63 ± 2[a]	28 ± 1	4
16 (*threo*)	C_6H_5	CH_3	C_6H_5	CH_3	170	3	33[b]	35	12
17 (*threo*)	C_6H_5	CH_3	C_6H_5	C_6H_5	165	3	28[b]	44	6
18 (*erythro*)	C_6H_5	CH_3	C_6H_5	CH_3	170	3	52 ± 2[b]	3 ± 2	12
19 (*erythro*)	C_6H_5	CH_3	C_6H_5	C_6H_5	170	3	53 ± 2[b]	3 ± 2	9
20	C_6H_5	C_6H_5	C_6H_5	CH_3	175	3	74[b]	5	5

[a] The relative yields of olefins, aldehydes, and ketones are based on vpc analysis. Chromatographic separation gave the absolute yields. [b] Yields based on integration of nmr spectra and chromatographic separation.

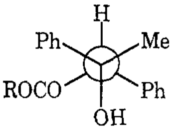
aromatic ring, as would be expected in the case of a *gauche* methyl–phenyl arrangement.[8] These results agree with conformation A for *threo*-2-phenyl-2,3-butanediol monoesters and conformation B for the *erythro* esters as the stablest conformations owing to steric reasons and hydrogen bonding. Accordingly, the methyl grouping of the acetate ester (R = CH_3) is less shielded in A (δ 2.08) than in B (δ 1.89), owing to the nonbonded methyl–phenyl interaction in the latter. The same conformational considerations are valid for the *threo* (C, **16**, **17**) and *erythro* (D, **18**, **19**) esters of 1,2-diphenyl-1,2-propanediol, the methyl grouping being found more shielded in the *threo* isomer. In view of analogous steric reasons locating the hydrogen between the two larger substituents at the tertiary carbon, secondary monoesters of all trisubstituted 1,2-glycols are considered to have a *gauche* arrangement of the two oxygen-containing functions; this should influence favorably the rate of the studied rearrangement, shown previously to occur only in *cis* cyclic diol monoacetates.[9,10]



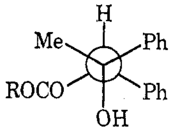
A



B



C



D

Zinc-catalyzed conversion of monoacetates of acyclic trisubstituted glycols afforded satisfactory results, except for some lower boiling esters (*e.g.*, ester **1**, Table I) which did not react at all; in other oily acetates (like ester **5**), the conversion into ketones was sometimes precluded by the presence of minor impurities. The rearrangement was shown not to be limited to acetate esters; use of p-nitrobenzoates of aliphatic diols ensured excellent yields, the reaction being performed at lower temperatures, as indicated in Table I. The method permits isolation of volatile ketones in a cooled trap, without need of work-up. For aryl-substituted reactants, benzoate esters were found to provide optimal rearrangement results. Reactions which occur with hydrogen shift exclusively are summarized in Table I. No alkyl shift was ever observed. The presence of an aromatic substituent at the secondary carbon atom also led to the formation of aldehydes by a 1,2-aryl shift (Table II). It was shown in separate experiments that no interconversion between aldehydes and ketones occurs during heating with zinc,

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[8] *Cf.* G. H. Schmidt, *Can. J. Chem.*, **46**, 3415 (1968).

[9] S. S. Wagle, Dissertation, Harvard University, 1949.

[10] E. Ghera, unpublished results.

as has been observed in some acid-catalyzed pinacol rearrangements of trisubstituted diols.[11] Thus neither 2-methyl-2-phenylpropanal nor 2,2-diphenylpropanal was converted into ketones on heating with zinc.

Finally, the rearrangement was shown to occur analogously on using anhydrous zinc acetate instead of zinc metal (Table III).

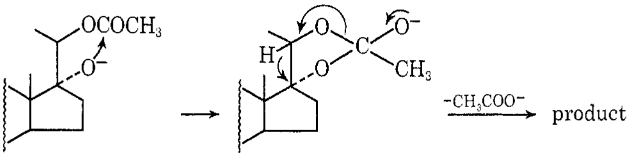
TABLE III
REARRANGEMENT OF TRISUBSTITUTED 1,2-GLYCOL MONOESTERS WITH ANHYDROUS ZINC ACETATE[a,b]

Ester	Ketone yield, %	Aldehyde yield, %
3	94	. . .
12	89	. . .
14	73	18
15	57	38
17	27	51
19	55	5

[a] For the structure of ketones and aldehydes, see the corresponding ester in Tables I and II. [b] Time and temperature conditions are identical with those used for the same esters in zinc-catalyzed rearrangements (Tables I and II).

Mechanism and Stereochemistry.—The presently obtained results, in addition to our previous findings in cyclic systems,[5] point to the general character of the reaction investigated. The clarification of the pathway by which the rearrangement takes place was considered of importance, since previous hypotheses seemed unsatisfactory. An initial assumption of an oxide intermediate[12] has been experimentally disproved.[3] Wagle[9] assumed a process starting by proton abstraction followed by the formation of an orthoacetate ion (Scheme I). The cleavage of the cyclic intermediate and a concerted 1,2 hydride shift followed by the elimination of the acetate ion should afford the ketone, with inversion at the migration terminus. This hypothesis was later supported on the grounds of labeling results.[3,4]

SCHEME I



The possibility of a radical intermediate[3] was based on the observation that the presence of oxygen was necessary during the reaction and that benzoyl peroxide can serve as a catalyst instead of zinc. The presently described reactions were, however, performed in the absence of oxygen, and no rearrangement to ketone was observed on refluxing ester **14** with benzoyl peroxide in toluene. Esr measurements performed during some of the reactions did not show the presence of radicals, but this observation may not be conclusive owing to the short lifetime of radicals and their resulting low concentration. Nonetheless, the radical mechanism does not seem viable, since the homolitic fission of the C–O bond involving a hydrogen 1,2 shift is questionable in ground-state chemistry,[13] although it is known to occur in photoexcited species. The formation of dimers, which is acceptable in the presence of radical intermediates, has not been observed. Wagle's assumption of an initial proton abstraction from the hydroxyl grouping was investigated by submitting reactants to basic, nonhydrolyzing conditions instead of zinc catalysis. Prolonged reflux of ester **14** with sodium hydride in toluene yielded only a small amount (5%) of isobutyrophenone, along with other products. The assumption of ortho ester ion formation and its cleavage, if correct, should allow the same zinc-catalyzed conversion into ketones to occur when starting from tertiary acetates of trisubstituted 1,2-diols. The preparation of these derivatives was attempted without success in several systems. Thus reduction of 3-methyl-3-acetoxy-2-butanone, using hydride reagents (under conditions not affecting esters), diborane, or hydrogenation under pressure always afforded secondary instead of tertiary acetates.[14] In view of this facile acyl migration, explained by steric compression, it seemed very doubtful that the reaction takes place by a pathway in which the cleavage of an orthoester ion with secondary → tertiary acyl migration provides the driving force for the hydride shift.

The rearrangement can be regarded as a heterogeneous catalytic process, and is believed to begin by adsorption of the reactant on the zinc surface. Little variation in the rates observed for different reacting esters, and inhibition of reactivity in the presence of minor impurities in reactants, suggest that the rate of diffusion of the reactant and adsorption on the zinc surface influences the overall rate of the reaction. A zero-order process has previously been suggested for some zinc-promoted eliminations.[15] The adsorption may be followed by formation of new bonds with the metal surface ("strong" chemisorption)[16] and may be of aid for proper orientation of the two oxygen-containing functions for the following nucleophilic attack.

Substitution of deuterium for the migrating hydrogen and determination of the corresponding isotope effect could provide information on the C–H bond-breaking process during the reaction. Accordingly, the isotope effect k_H/k_D was determined in two different systems.

The 3-*p*-nitrobenzoate of 2-methyl-2,3-butanediol (**3**) was chosen owing to its almost quantitative conversion, on heating with zinc, into 3-methyl-2-butanone (Table I). A mixture of equimolar amounts of **3** and the 3-d_1 analog were reacted with zinc, and the reaction was terminated after partial (10%) conversion of the reactants into the corresponding ketones. Analysis of the ketone mixture by mass spectroscopy gave, after corrections, a d_0/d_1 product ratio of 1.6 ± 0.05, which was considered as k_H/k_D.[17] Similar isotope-effect values have been obtained in the acid-catalyzed pinacol rearrangement of the related 2-methyl-2,3-butanediol (k_H/k_D = 1.5–1.8), independent of the acidity of the medium.[18] In this latter case the rate-determining

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(11) See, *e.g.*, J. W. Huffman and L. D. Browder, *J. Org. Chem.*, **27**, 3208 (1962).

(12) C. W. Shoppee, *J. Chem. Soc.*, 1671 (1949).

(13) C. Walling in "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 416 ff.

(14) Similar acyl migrations have recently been observed: (a) G. Berti, F. Bottari, and B. Macchia, *Tetrahedron*, 545 (1964); (b) H. Koch and F. Fischer, *Z. Chem.*, **7**, 18 (1967).

(15) J. Weinstock, S. N. Lewis, and F. G. Bordwell, *J. Amer. Chem. Soc.*, **78**, 6072 (1956).

(16) *Cf.* T. Wolkenstein, *Advan. Catal.*, **12**, 189 (1960).

(17) See, *e.g.*, a similar k_H/k_D determination by J. L. Coke and M. P. Cooke, Jr., *J. Amer. Chem. Soc.*, **89**, 6701 (1967).

(18) W. B. Smith, R. E. Bowman, and T. J. Kmet, *ibid.*, **81**, 997 (1959).

step has been considered to be the elimination of water and the formation of a carbonium ion, whereas the relatively high isotope effect has been explained by anchimeric assistance owing to hydrogen. The isotope effect was next observed in the rearrangment of benzoate **14**, the labeled and unlabeled ester being submitted separately to identical rearrangement conditions. The substitution of hydrogen for deuterium resulted in a different percentage composition of the products (eq 2). Assuming that the rate of phenyl migration,

$$\begin{array}{l} (CH_3)_2C(OH)CR(OCOC_6H_5)(C_6H_5) \longrightarrow \\ \qquad (CH_3)_2CRCOC_6H_5 + (CH_3)_2C_6H_5CRO \quad (2) \\ \qquad 78 \pm 2\% \qquad\qquad 14 \pm 1\% \\ \qquad 65 \pm 2\% \qquad\qquad 25 \pm 1\% \\ \qquad R = H \\ \qquad R = D \end{array}$$

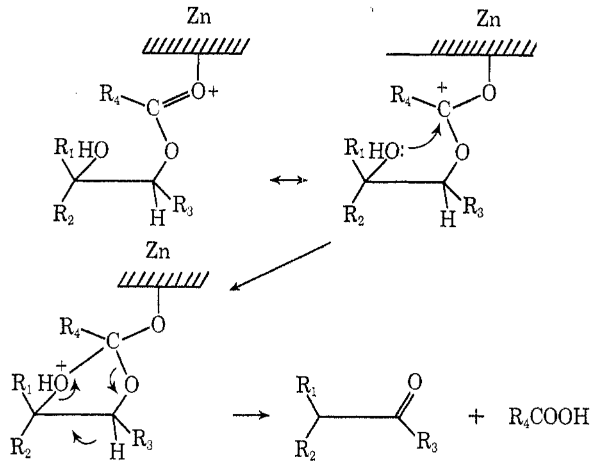
which results in 2-methyl-2-phenylpropanal formation, is not influenced by labeling, the approximate k_H/k_D was calculated from the effect on product composition[19] (eq 3) and again found within the range of values of

$$\frac{k_H}{k_D} = \frac{k_{Ph}}{k_D} \cdot \frac{k_H}{k_{Ph}} = 2.1 \pm 0.1 \qquad (3)$$

isotope effects of 1,2 shifts involving anchimerically assisted ionizations.[20] Comparison of rearrangement results of esters **14** and **15** (Table II) shows an increase of about double for the migratory aptitude of the tolyl group as compared with that of the phenyl group, as found in some acid-catalyzed rearrangements with participation of aryl groups.[21]

These observations, suggesting a Lewis acid role for the zinc catalyst, led us to attempt the duplication of the studied reactions, using zinc cations instead of metallic zinc. If the above assumption on the role of the metal catalyst is correct, a similar or even enhanced activity towards donor atoms would be expected with Zn(II) ions. In fact, the use of anhydrous zinc acetate under conditions analogous to those used previously for metallic zinc yielded results very similar to those obtained with the metal catalyst. The aryl/hydride shift ratio was slightly increased but the competition between the two shifts, as determined by electronic and steric factors, preserved the same pattern, providing a convincing argument that the same mechanism is responsible for the rearrangement by either reagent. The essential condition of *cis* arrangement of the functions involved, together with these results, support the role of the zinc as a complexing Lewis acid which coordinates with the carbonyl group. Adsorption on Zn_0 implies the existence of dual sites on the catalyst surface, the oxygen donor being bonded to the positive sites of the metallic lattice (Scheme II). The nucleophilic attack which follows leads to ionization at the tertiary carbon atom which, according to the isotope effects observed, probably takes place with the assistance of the migrating group. Desorption from the zinc surface after ketone formation yields the corresponding acid, which can eventually be isolated.

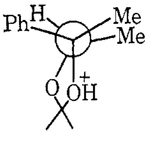
SCHEME II



Formation of olefins as by-products from reactions of acetate esters and, to a lesser extent, of benzoates can be regarded as a new zinc-promoted elimination, which follows the pattern of eliminations observed in other bifunctional compounds, in which at least one of the eliminated functions is a halogen atom.[22] In the diasteromeric systems investigated (esters **9–12** and **16–19**), the elimination was found to be nonstereospecific. The formation of *trans*-methylstilbene alone, from both *erythro-* and *threo*-1,2-diphenyl-1,2-propanediol esters, may be facilitated by the delocalization of the negative charge owing to the presence of an aromatic ring at the secondary carbon atom. The formation of an olefinic mixture of identical composition from both isomeric 2-phenyl-2,3-butanediol esters implies the formation of an intermediate carbanion (eq 4).

$$\begin{array}{l} R_1R_2C(OH)R_3CHOCOCH_3 + Zn \xrightarrow{-Zn(OAc)_2} \\ \qquad R_1R_2C(OH)R_3CH^- \longrightarrow R_1R_2C{=}R_3CH \quad (4) \end{array}$$

Examination of the stereochemical effects in the reactions studied shows that in both diastereomeric series higher rearrangement yields (leading to ketones and aldehydes) were obtained with *threo* isomers. These results are in agreement with the formation of cyclic intermediates with eclipsed substituents (E and F for esters **9–12** and G and H for esters **16–19**) and with the principle that steric interactions between groups of unequal size are less strong than the interactions between analogous groups of equal size.[23] The cleavage of the C–O bond and 1,2 migration that follow require a *trans* arrangement of the migrating and leaving groups, if the reaction proceeds through a bridged ion or a concerted mechanism. Stretching of the cyclic intermediate in the direction enabling a hydride shift is sterically preferred to the stretching suitable for phenyl migration, and therefore a hydride shift might be expected to predominate. While acid-catalyzed pinacol rearrangement of 1-phenyl-2-methyl-1,2-propandiol (using either diluted sulfuric acid[24] or formic acid[11]) is known to afford primarily 2-methyl-2-phenyl-



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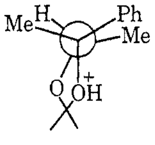

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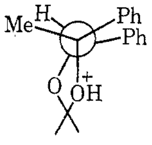

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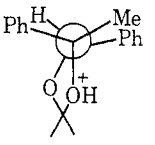

H

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[19] *Cf.* C. J. Collins, W. T. Rainey, W. B. Smith, and I. A. Kaye, *J. Amer. Chem. Soc.*, **81**, 460 (1959).

[20] See, *e.g.*, S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1968).

[21] J. C. Burr and L. S. Ciereszko, *J. Amer. Chem. Soc.*, **74**, 5426 (1952).

[22] See, *e.g.*, H. O. House and R. S. Ro, *ibid.*, **80**, 182 (1958).

[23] E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 138.

[24] M. Tiffeneau and A. Orekhoff, *Compt. Rend.*, **172**, 387 (1921).

propanal, under zinc catalysis the esters **13** and **14** of the above diol yielded isobutyrophenone as the major product. Thus the relative stability of the carbonium ion in the pinacol rearrangement permits more phenyl migration, while in the present reaction a stronger influence is exercised by steric control. Substantial amounts of aldehyde were, however, obtained in one system (from **16** and **17**), possibly owing to the nonbonded repulsion between the ester group and one of the substituents. This interaction may be stronger when the benzoate ester **17** is used instead of acetate **16**, the amount of aldehyde increasing accordingly.

Experimental Section

Melting points are uncorrected and were determined on a Kofler hot-stage microscope. Nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal standard and deuteriochloroform as solvent. Only the values of significant peaks are reported. Vapor phase chromatographic analyses were performed on an Aerograph (A90-p) using a 10% SE-30 Chromosorb W 20 ft × 0.375 in. column. Florisil 60–100 mesh was used for column chromatography and silica gel G plates were used for tlc analysis. The acetate esters were prepared by the usual method, with acetic anhydride in pyridine. All *p*-nitrobenzoates and benzoates were obtained by an analogous method; a single example is described in detail.

2-Methyl-2,3-butanediol[25] **and 2-methyl-2,3-butanediol-3-d_1**[18] were prepared by previously described methods. The **3-*p*-nitrobenzoate 3** was prepared by adding the diol (1.2 g) in dry pyridine (10 ml) to a stirred, ice-cooled solution of *p*-nitrobenzoyl chloride (2.6 g, 20% excess) in pyridine (50 ml). After 5 hr of stirring the cold mixture was brought to room temperature, poured into water, and extracted with ether, and the organic layer was washed several times with diluted hydrochloric acid, sodium bicarbonate solution, and water. The crude ester (2.8 g) was chromatographed (elution with pentane and 15–20% ether) and the pure product (2.2 g) was obtained: mp 68° (from pentane–ether); nmr δ 1.32 (s, 6), 1.38 (d, 3, $J = 12$ Hz), and 5.13 (q, 1).

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.72; H, 5.76; N, 5.26.

The corresponding 3-d_1 *p*-nitrobenzoate had a melting point of 68° (from penane–ether), nmr δ 1.32 (s, 6) and 1.39 (s, 3).

2-Methyl-2,3-pentanediol.—2-methyl-2-hydroxy-3-pentanone[6] (6 g) in dry ether (20 ml) was added to a suspension of lithium aluminum hydride (1 g) in ether (40 ml). After the mixture had been stirred for 3 hr at room temperature, the excess reagent was decomposed with saturated sodium sulfate solution and the mixture was dried using anhydrous sodium sulfate. Filtration afforded 5.5 g of diol,[26] homogeneous on tlc, which was used without further purification for the preparation of *p*-nitrobenzoate **4**, mp 72–73° (from pentane–ether).

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.72; H, 6.53; N, 5.10.

2-Methyl-2,3-heptanediol.—2-Methyl-2-heptene (17.5 g) was added to a mixture of 98% formic acid (84 ml) and 30% hydrogen peroxide (26 ml) and the solution was kept overnight at 40°, concentrated at reduced pressure, and made basic with a 10% KOH solution. After an additional 4 hr at 40° the product was extracted with ether using for washings saturated NaCl solution. Distillation yielded 10.8 g of diol, bp 120–122° (24 mm) [lit.[27] bp 109–113° (10.5 mm)]. The **acetate 5** had a boiling point of 124–126° (32 mm), n^{25}_{D} 1.439.

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.65; H, 10.86.

The **3-*p*-nitrobenzoate 6** had a melting point of 79–80° (from pentane–ether).

Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.84; H, 7.12; N, 4.78.

Esters of *erythro*- and *threo*-2-Phenylbutane-2,3-diol.—3-Phenyl-3-hydroxy-2-butanone[28] (11.8 g) was reduced with lithium aluminum hydride by the procedure described previously, affording a mixture of diastereomeric diols[29] (10.4 g) homogeneous on tlc: nmr of the crude mixture δ 0.95 (d, $J = 6.5$ Hz, *threo* CH_3), 1.14 (d, $J = 6.5$ Hz, *erythro* CH_3), 1.50 (s, *erythro* CH_3), 1.59 (s, *threo* CH_3), 66% *threo* and 34% *erythro* isomer by integration of peaks. Acetylation of the diol mixture (10 g) followed by chromatography on neutral alumina (activity II) yielded first, on elution with hexane and 10% ether, the **2-*threo*-acetate 11** (3.8 g): mp 68° (from pentane–ether); nmr δ 1.02 (d, 3, $J = 6.5$ Hz, CH_3), 1.52 (s, 3, CH_3), 2.08 (s, 3, CH_3CO), and 5.19 (q, 1, $J = 6.5$ Hz, CHOAc).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.45; H, 7.68.

Further elution provided (after fractions containing a mixture of both isomers) the **2-*erythro* acetate 9** (1.1 g): bp 144–145° (5 mm); n^{20}_{D} 1.515; nmr δ 1.18 (d, 3, $J = 6.5$ Hz, CH_3), 1.52 (s, 3, CH_3), 1.89 (s, 3, CH_3CO), and 5.21 (q, 1, $J = 6.5$ Hz, CHOAc).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.78.

The benzoates were prepared from the diol mixture and benzoyl chloride (like *p*-nitrobenzoates) and the diastereomers were separated by chromatography as shown for acetates. **2-*threo*-Benzoate 12** had a melting point of 105–106° (from ether–pentane), nmr δ 1.16 (d, 3, $J = 6.5$ Hz, CH_3), 1.62 (s, 3, CH_3), and 5.45 (q, 1, $J = 6.5$ Hz, CHOBz).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.36; H, 6.58.

2-*erythro*-Benzoate 10 had melting points of 62–63 and 68° (polymorphous, crystallized from ether–pentane), nmr δ 1.27 (d, 3, $J = 6.5$ Hz, CH_3), 1.62 (s, 3, CH_3), and 5.44 (q, 1, $J = 6.5$ Hz, CHOBz).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.42; H, 6.88.

1,1-Diphenyl-1,2-hexanediol.—1,1-Diphenyl-1-hexene[30] (1.8 g) in pyridine (20 ml) was added to a solution of osmium tetroxide (2 g) in ether (35 ml). After having been allowed to stand for 36 hr at room temperature, the mixture was diluted with ether (200 ml), the formed precipitate was filtered and dissolved in 30 ml of chloroform, and hydrogen sulfide was bubbled into the solution during 5 min. After 2 hr the black precipitate was removed by filtration and the solvent was distilled under reduced pressure. Chromatography [elution with pentane–chloroform (7:3)] yielded the diol (1.55 g), mp 110° (from hexane).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.12; H, 8.16.

2-Acetate 7 had a melting point of 128° (from hexane).

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.72; H, 7.81.

2-Benzoate 8 had a melting point of 139–141° (after two crystallizations from ethanol).

Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.32; H, 6.96.

1-Phenyl-2-methyl-1,2-propanediol was prepared by a known method,[31] mp 62°. The **1-acetate 13** had a boiling point of 146–148° (9 mm); n^{25}_{D} 1.510; nmr δ 1.16 (s, 6, 2 CH_3), 2.04 (s, 3, CH_3CO), and 5.65 (s, 1, CHOAc).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.96; H, 7.72.

1-Benzoate 14 had a melting point of 87–88° (from pentane–ether) [lit.[32] oil, bp 215° (2–3 mm)], nmr δ 1.26 (s, 6, 2 CH_3), 5.88 (s, 1, CHOBz), and 7.2–8.3 (m, 10, aromatic).

1-d_1-1-Phenyl-2-methyl-1,2-propanediol.—The crude tetrahydropyranyl ether of acetone cyanhydrine[6] (6 g) in dry ether (40 ml) was added under cooling to phenylmagnesiumbromide (from 2.4 g of Mg) and the mixture was stirred for 14 hr at room temperature, decomposed with saturated ammonium chloride solution, and extracted with ether. The dried and concentrated ether solution was saturated with hydrogen chloride and the formed precipitate was separated by filtration and dissolved in a mixture of 10% HCl (20 ml) and 10% AcOH (10 ml). Aftr being stirred for 2 hr at 50°, the mixture was diluted with water and extracted with ether, yielding 5 g of product. Purification by chromatog-

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raphy (elution with pentane and 20% ether) gave 3.2 g of 2-methyl-2-hydroxypropiophenone, homogeneous on tlc. Reduction with lithium aluminum deuteride (0.8 g) in dry ether (40 ml) afforded 2.9 g of 1-d_1-diol: mp 60°; nmr δ 1.02 (s, 3, CH_3), 1.14 (s, 3, CH_3), and 7.30 (s, 5, aromatic). The corresponding **1-d_1-benzoate** had a melting point of 88° (from pentane–ether).

1-*p*-Tolyl-2-methyl-1,2-propanediol.—2,4′-Dimethyl-2-hydroxypropiophenone, which served as starting material, was prepared by the adaptation of a known procedure,[6] as described previously for 2-methyl-2-hydroxypropiophenone, and in a yield similar to the latter. Reduction of the ketol by lithium aluminum hydride afforded the diol, mp 54–55° (from pentane, cold) (lit.[33] mp 56–57°. The **1-Benzoate 15** had a melting point of 84–85° (from pentane–ether), nmr δ 1.27 (s, 6, 2 CH_3), 2.30 (s, 3, $ArCH_3$), and 6.07 (s, 1, CHOBz).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.26; H, 6.93.

Esters of *threo*- and *erythro*-1,2-Diphenyl-1,2-propanediol.—The reported *threo*-[34] and *erythro*-diols[35] served for the preparation of corresponding esters.

1-*threo*-Acetate 16 had a melting point of 135–136° (from ethanol) (lit.[14a] mp 134–135°), nmr δ 1.46 (s, 3, CH_3), 1.94 (s, 3, CH_3CO), and 6.01 (s, 1, CHOAc).

1-*threo*-Benzoate 17 had a melting point of 168–169° (from ethanol), nmr δ 1.61 (s, 3, CH_3) and 6.22 (s, 1, CHOPh).

Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.62; H, 6.18.

1-*erythro*-Acetate 18 had a melting point of 116–117° (from pentane–ether) (lit.[14a] mp 115–116°), nmr δ 1.62 (s, 3, CH_3), 2.07 (s, 3, CH_3CO), and 5.97 (s, 1, CHOAc).

1-*erythro*-Benzoate 19 had a melting point of 143–144° (from pentane–ether), nmr δ 1.72 (s, 3, CH_3) and 6.23 (s, 1, CHOBz).

Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.38; H, 6.12.

General Procedure for Zinc-Catalyzed Rearrangements.—The reaction apparatus (Figure 1) consisted of a Pyrex reaction tube a (of size depending of amount of reactants) provided with a nitrogen inlet tube and connected at the top, by the aid of joints, with a bent tube b leading to a removable trap c. The trap was provided with a side arm for connection with a drying tube. A mixture of the powdered reactant and a 20-fold amount of freshly activated zinc dust[36] was introduced in the reaction tube with the help of a funnel. Grinding of reactants with zinc is not necessary and may lead to less satisfactory results. If they were oils, the reactants were first homogeneously mixed with zinc in a flask. The reaction tube was immersed into an oil bath at the desired temperature and a steady nitrogen flow (60 bubbles/min) carried the volatile products or by-products towards the trap cooled with Dry Ice–acetone. At the end of the reaction time the mixture was cooled and the product was separated from zinc by filtration using ether (or chloroform, for less soluble products). The solution was washed with 5% $NaHCO_3$ (in order to eliminate the acid formed) and water and thereafter dried (Na_2SO_4). The solvent was evaporated at reduced pressure or, in the case of volatile products, at normal pressure using a Vigreux column. Volatile products (such as the ketones formed from esters **3** and **4**) were collected at the end of the reaction directly in the trap, weighed, and checked for purity. The identification of products was secured by comparison with authentic samples or their semicarbazones, and the yields and purity were established by vpc analysis, integration of nmr spectra and chromatographic separation (for less volatile products). In the case of chromatography the olefins were separated by elution with pentane, whereas subsequent elution with 1–2% ether–pentane yielded first aldehydes (if present) and afterwards ketones. More polar byproducts, like unsaturated esters (from dehydration of starting materials) or diols, were obtained by elution with 5–20% ether–pentane.

Reactions with anhydrous zinc acetate were conducted in the same manner as reactions with zinc metal. The zinc acetate was dried before use at 160–170° for 3–4 hr and then powdered.

Reaction of Ester 14 with Benzoyl Peroxide.—Benzoyl peroxide (1 g) was added to a solution of benzoate **14** (100 mg) in toluene (5 ml). After a 5-hr reflux, tlc analysis showed that most of the starting material was converted into other products (several spots). The residue obtained from work-up with ether did not contain isobutyrophenone.

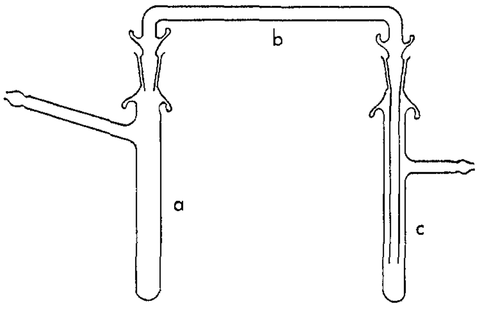

Figure 1.—Reaction apparatus.

Reaction of Ester 14 with Sodium Hydride.—Sodium hydride (60 mg) was added to a solution of benzoate **14** (200 mg) in dry toluene (10 ml) and the mixture was refluxed for 14 hr. The reagent was then decomposed by addition of ethanol, and the mixture was poured into water and extracted with ether. Isobutyrophenone (9 mg) was chromatographically separated from the mixture of products. Changes in reaction conditions did not improve the yield.

Reduction of 3-methyl-3-acetoxy-2-butanone was attempted by hydrogenation with palladium or platinum catalyst in ethanol solution, using pressure (up to 1000 psi). The product obtained was acetate **1**, nmr δ 4.85 (q, CHOAc). Analogous results were obtained using for reduction a diborane solution in tetrahydrofuran (at 10°, during 24 hr), sodium borohydride in tetrahydrofuran (8 hr stirring at room temperature), or lithium tri-*t*-butoxyaluminum hydride in ether (overnight).

Kinetic Isotope Effects in the Rearrangements of *p*-Nitrobenzoate 3 and Benzoate 14.—A mixture of equimolar amounts of ester **3** and the 3-d_1 3-*p*-nitrobenzoate of 2-methyl-2,3-butanediol (0.5 mmol) was treated with zinc during 15 min at 125°, care being taken for protecting from moisture the reaction mixture and the products (collected in the cooled trap). The obtained mixture of ketones (*ca.* 10% conversion) was analyzed directly in the mass spectrum at 15 eV. Separate experiments, using deuterated ester alone under identical reaction conditions, showed (mass spectrum) that not more than 5% loss of deuterium occurs in the resulting ketone. After introducing this correction and that for isotopic purity, the isotope effect was calculated from the ratio of 3-methyl-2-butanone-3-d_0/3-methyl-2-butanone-3-d_1 and was found to be $k_H/k_D = 1.6 \pm 0.05$ (average of eight determinations). The mass spectrum of the recovered unreacted material showed a stronger base peak for *m/e* 239 (M − 15 of d_1 ester) than for *m/e* 238 (M − 15 of undeuterated ester).

The isotope effect found in the rearrangement of the 1 benzoate of 1-phenyl-2-methyl-1,2-propanediol (**14**) and its 1-d_1 analog was calculated as shown in eq 2 and 3, submitting samples (200 mg) of normal and deuterated ester to identical reaction conditions (2.5 hr, 160°). The product composition was determined by vpc and the total yield of ketone and aldehyde was *ca.* 91%, the remaining material consisting of 2,2-dimethylstyrene and dehydration products. Nmr spectral examination of products obtained from deuterated ester showed that no replacement of deuterium for hydrogen occurred during the reaction (in conditions excluding moisture).

Formation of Phenylbutenes by Rearrangement of Esters 9–12.—The nonpolar olefinic mixture was separated from other products by chromatography and analyzed (vpc). The olefinic peaks appeared in order of retention times: *trans*-2-phenyl-2-butene, 2-phenyl-1-butene, and *cis*-2-phenyl-2-butene, the approximate ratio being 1:3:10, independent of the diastereomer used as starting material. The 2-phenyl-2-butenes were identified by their characteristic nmr spectrum,[37] whereas 2-phenyl-1-butene[38] showed nmr δ 1.08 (3, t, CH_3), 2.52 (q, 2, CH_2), and 5.08 (q, 1, J = 5 Hz, vinyl proton), and 5.30 (br s, 1, vinyl proton). In separate experiments, *cis*- and *trans*-2-phenyl-2-butene were heated with zinc during 3 hr at 160° under nitrogen; interconversion of isomers was not observed in these conditions.

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Registry No.—3, 22931-96-0; **3** (3-d_1 derivative), 22931-97-1; **4**, 23031-06-3; **5**, 22931-98-2; **6**, 22931-99-3; **7**, 22932-00-9; **8**, 22932-01-0; **9**, 22932-13-4; **10**, 22932-14-5; **11**, 22932-15-6; **12**, 22932-16-7; **13**, 22932-02-1; **14**, 4564-84-5; **15**, 22932-03-2; **16**, 13733-16-9; **17**, 22932-05-4; **18**, 22932-06-5; **19**, 22932-07-6; 1,1-diphenyl-1,2-hexanediol, 22932-08-7; 1-phenyl-2-methyl-1,2-propanediol, 20907-13-5; 1-d_1-1-phenyl-2-methyl-1,2-propanediol, 22932-11-2; 1-d_1-1-phenyl-2-methyl-1,2-propanediol (1-benzoate), 22932-12-3.

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The Reaction of Grignard Reagents with α-Bromocrotonic and α-Bromocinnamic Acids

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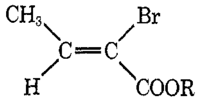
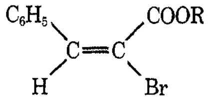
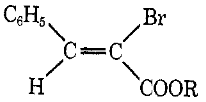
Phenylmagnesium bromide undergoes a 1,4 addition to α-bromocrotonic acid and its methyl ester. The α-bromoenolates formed are stable, and give on protonation two diastereoisomeric acids or esters. Methylmagnesium bromide reacts with *cis*- and *trans*-α-bromocinnamic acids and their esters in a 1,2 manner, but additional reactions were observed leading to other products such as 2-methylcinnamic acid.

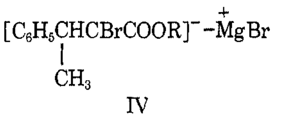
The ratio of 1,4 to 1,2 addition of Grignard reagents to carbonyl compounds having a conjugated double bond depends on the functional group.[2,3] Introduction of a second functional group on the same carbon as the first, as in unsaturated malonates or cyanoacetates, enhances the 1,4 addition owing to a larger polarization of the double bond and a larger stabilization of the formed carbanion than in the monofunctional compounds. A bromine atom situated on a double bond directs electrophiles powerfully away from the carbon to which it is attached, but in nucleophilic additions the position of attack is less known. α-Bromo carbanions were obtained recently by transmetalation.[4] It was of interest therefore, to study the effect of an α-bromo substituent on the mode of addition to unsaturated acids.

Three acids and their methyl esters were studied, *trans*-2-bromocrotonic acid (I) and *cis*- (II) and *trans*-2-bromocinnamic acid (III). The first acid was treated


I


II


III



$$[C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HCBrCOOR]^- \overset{+}{Mg}Br$$

IV

a, R = H
b, R = CH_3

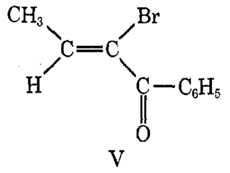
with phenylmagnesium bromide, and the other two with methylmagnesium bromide to test chemically whether the organomagnesium derivatives formed by 1,4 addition are the same in all cases or depend on the starting materials.

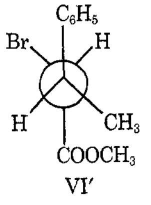
All reactions were performed by two methods. In the first one ("preparative"), the products were isolated and characterized by their spectra and analyses. In the second ("analytical") method, smaller amounts of reagents and higher dilutions (sevenfold) than in the first were used and the products were analyzed by glpc only.

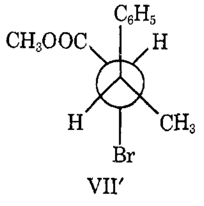
The reaction of Ia with phenylmagnesium bromide (3 or 5 equiv) gave similar results by both preparative and analytical methods. The addition was preferentially of the 1,4 type. *trans*-2-Bromocrotonophenone (V) was also formed by a 1,2 addition in about 10% yield. Two diastereoisomers, VI and VII, were obtained in a 2:1 ratio on protonation of the enolate. Their combined yield was approximately 70%. Addition of cuprous or cobaltous chloride to the Grignard reagent affected neither the amount of 1,4 addition nor the ratio of the diastereoisomers formed. Similarly, the 1,4 addition was the predominant mode of reaction of phenylmagnesium bromide with Ib. The ratio of diastereoisomers formed after treatment of the reaction mixture with water differed from that (1:1) from Ia. No influence of added cuprous or cobaltous chloride was found on the course of this reaction. No dilution effect was observed: the amount of 1,4 addition and the ratio of diastereoisomers were similar in the preparative and analytical reactions.

It is interesting that no carbene was formed from the enolate IV, even when its solution was left for several hours. Addition of cyclohexene did not yield a reaction product of a carbene, and the bromine atom was found in both products, that of the conjugate addition and that of the carbonyl addition.

The stereochemistry of *s*-*erythro*[5] VI and *s*-*threo* VII was tentatively assigned to the diastereoisomers on the


V


VI′


VII′

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