[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NORTHWESTERN UNIVERSITY]

The Stereochemistry of Ketonization. VIII.[1,2] Acyclic Enols

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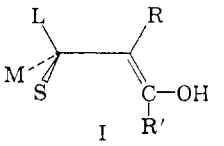
Hitherto, a solution to the problem of the stereochemistry of ketonization of acyclic enols has been frustrated by the unavailability of theory allowing selection of the lowest energy conformation of the enolic reactant. The necessary theory has now been derived and a general solution to the problem of acyclic ketonization is offered. The proposed stereochemical mechanism has been tested by an investigation of the stereochemistry of ketonization of the enol of 2,3-diphenylbutyrophenone and a reinvestigation of the stereochemistry of ketonization of the enol of 2,3-diphenylvalerophenone. A further test is provided by literature data.

Previously,[3-7] it has been demonstrated that the stereochemistry of a large number of organic reactions involving enolic intermediates may be interpreted on the basis of an essentially sp^2-hybridized ketonization transition state in which proton transfer occurs from the less hindered approach.[8] These studies were concerned with cyclic enolic systems, in which selection of the least hindered approach is straightforward and a test of the theory, unequivocal.[9]

In contrast, the stereochemistry of ketonization of acyclic enols has resisted elucidation. The difficulty lies in the fact that for an enol such as I there are an infinite number of conformations about the central carbon to carbon single bond, and as a

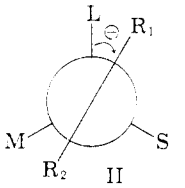


I

result it is not apparent which is the least hindered approach to the enolic double bond.[10]

The present research was initiated in the hope of solving this difficult problem. At the outset it was apparent that a fruitful attack on the problem first would necessitate theoretical consideration of the general question of the preferred conformation of a system such as I. Secondly, it would require investigation of the stereochemical course of ketonization of some appropriately selected acyclic enolic intermediates. Finally, prediction based on the theoretical model would have to be compared with the experimental results as well as with literature information.

Clearly, a solution to the problem of determining the preferred conformation of acyclic enols requires expressing the potential energy of the tetrahedral–trigonal system, formulated simply as II, as a function of the conformational angle θ and finding the value of θ at which the potential energy of the system is minimized.



II

Since S, M, L, R_1 and R_2 in systems of interest represent a variety of groups of varying sizes and shapes, it seemed most profitable to determine the preferred conformation of a general and idealized system in which these groups are of well defined dimensions, perhaps spherical. Elucidation of the properties of the model system promised an improved understanding of real molecular situations.[11]

(1) For paper VII in this series see H. E. Zimmerman and B. S. Thyagarajan, THIS JOURNAL, **80**, 3060 (1958).

(2) Abstracted from the Ph.D. Thesis of Wen-Hsuan Chang, Northwestern University, 1959.

(3) For the first paper in this series and an introduction to the problem see H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1956).

(4) H. E. Zimmerman, THIS JOURNAL, **78**, 1168 (1956).

(5) H. E. Zimmerman and H. J. Giallombardo, *ibid.*, **78**, 6259 (1956).

(6) H. E. Zimmerman, *ibid.*, **79**, 6554 (1957).

(7) (a) H. E. Zimmerman and T. E. Nevins, *ibid.*, **79**, 6559 (1957); (b) H. E. Zimmerman and T. W. Cutshall, *ibid.*, **80**, 2893 (1958).

(8) While in general it is the relative accessibility of the proton donor to the two lobes of the α-carbon p-orbital which controls the ketonization stereochemistry, in the special case of endocyclic cyclohexane enols there is superimposed on this driving force a second effect, this deriving from the need for continued overlap of the p-orbital of the α-carbon atom with that of the carbonyl carbon atom. As has been pointed out by E. J. Corey (ref. 10), in ketonization of endocyclic cyclohexane enols this overlap requirement is fulfilled by axial protonation.

Since the less hindered approach of the proton donor may be either that resulting in introduction of an axial hydrogen or instead that affording product with an equatorial hydrogen, depending on molecular circumstances, the two effects may coöperate or oppose one another; in the latter event the net stereochemical outcome depends on the magnitude of the steric effects characteristic of the given system.

Thus the results of Professor Corey and those published by ourselves do not conflict but rather are complementary.

(9) E. J. Corey and R. A. Sneen, THIS JOURNAL, **78**, 6272 (1956).

(10) It was originally suggested by N. H. Cromwell, R. P. Cahoy, W. E. Franklin and G. D. Mercer, *ibid.*, **79**, 922 (1957), that the transition state for ketonization of acyclic enols resembles product energetically and geometrically with formation of the stable diastereomer. This conclusion accommodated the finding that the same diastereomer is formed as an intermediate in certain ethyleneimino-ketone-forming reactions both where R = Br with ketonization by attack of H^+ and where R = H by attack of Br^+. More recently, N. H. Cromwell and R. P. Cahoy [*ibid.*, **80**, 5524 (1958)] have concluded that an sp^2-hybridized transition state resembling reactant is more likely.

(11) That a model with spherical groups affords results applicable to real systems is not fortuitous. Corresponding to each of most real groups there will exist a hypothetical spherical group exhibiting the same van der Waals interaction with the adjacent asymmetric center. For groups such as methyl, halogen or hydrogen this is immediately understandable. In the case of groups such as ethyl, benzyl or phenethyl the preferred conformation is such that the large portion of the group orients itself away from the asymmetric center so that the energy of interaction of these groups approximates that of methyl; since methyl may be represented as a spherical group, so may these. It seems likely that even flat groups such as phenyl may be approximated as spheres. This approach is least justified where the group assumes a non-symmetrical orientation with respect to the asymmetric carbon atom so that the center of the sphere required to give an equivalent van der Waals effect would not coincide exactly with the center of the real group.

This reasoning is implicit in the several literature generalizations involving effective sizes of groups. Although the model is imperfect, its use is justified by the orderly consideration of stereochemical effects

Now V, the portion of the potential energy which is dependent on the conformational angle θ, is composed of six contributing terms, each arising from van der Waals interaction[12] of one of the three groups (L, M or S) on the asymmetric carbon atom with one of the two groups (R_1 or R_2) on the trigonal carbon atom. Thus

$$V = \sum_{\substack{i = \text{L,M,S} \\ j = 1,2}} V_{ij} = V_{L1} + V_{L2} + V_{M1} + V_{M2} + V_{S1} + V_{S2} \quad (1)$$

Each of the six van der Waals interaction terms (V_{ij}) depends on the distance[12] d_{ij} between the two groups concerned, and in turn the distance between the two groups depends on the conformational angle θ_{ij}.

By use of analytic geometry it may be shown as indicated in Fig. 1 that the distance d_{ij} between two such groups (P_i and P_j in Fig. 1) is given by

$$d_{ij}^2 = (m_i - m_j \cos\theta)^2 + m_j^2\sin^2\theta + l_i^2 = m_i^2 + m_j^2 + l_{ij}^2 - 2m_im_j\cos\theta_{ij} \quad (2)$$

where m_i and m_j are the perpendicular distances of groups i and j to the axis of the single bond between C_α and C_β and where l_{ij} is the z component of the distance between the groups.

Similarly, each of the individual conformational angles may be expressed in terms of any one of these, say $\theta_{L1} = \theta$. Thus from inspection of II it is concluded that

$$\theta_{ij} = \theta + \phi_{ij} \quad \text{where} \quad \left.\begin{array}{ll} \phi_{L1} = 0 & \phi_{M2} = 5\pi/3 \\ \phi_{L2} = \pi & \phi_{S1} = 4\pi/3 \\ \phi_{M1} = 2\pi/3 & \phi_{S2} = \pi/3 \end{array}\right\} \quad (3)$$

With relations 1, 2 and 3 available describing the dependence of the potential energy of the component interaction energies and giving the distance between each pair of interacting groups as a function of the conformational angle θ, one piece of information is still needed in order to relate the potential energy V to the conformational angle θ; needed is the dependence of each of the individual van der Waals interaction terms (V_{ij}) on the distance (d_{ij}) separating the groups concerned.

Several suitable expressions have been used in the literature; for example, van der Waals attractive forces may be represented by an inverse sixth power function while van der Waals repulsive forces are expressed by either an inverse twelfth power or as a negative exponential of distance.[13] Thus

$$V_i = -2E_{ij}\left(\frac{r_{ij}}{d_{ij}}\right)^6 + E_{ij}\left(\frac{r_{ij}}{d_{ij}}\right)^{12} \quad (4)$$

where r_{ij} is the sum of the van der Waals radii of the interacting groups and E_{ij} is the energy at the minimum, and the potential energy of the system is thence written as a function of θ

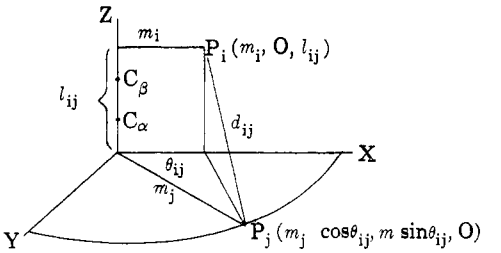


Fig. 1.

$$V = -2\sum_{\substack{i = \text{1,M,S} \\ j = 1,2}} \frac{r_{ij}^6E_{ij}}{[m_i^2 + m_j^2 + l_{ij}^2 - 2m_im_j\cos(\theta + \phi_{ij})]^3} + \sum_{\substack{i = \text{1,M,S} \\ j = 1,2}} \frac{r_{ij}^{12}E_{ij}}{[m_i^2 + m_j^2 + l_{ij}^2 - 2m_im_j\cos(\theta + \phi_{ij})]^6} \quad (5)$$

Inspection of the properties of this function should lead to the desired conformational information.[14] A plot of V *versus* θ is shown in Fig. 2.

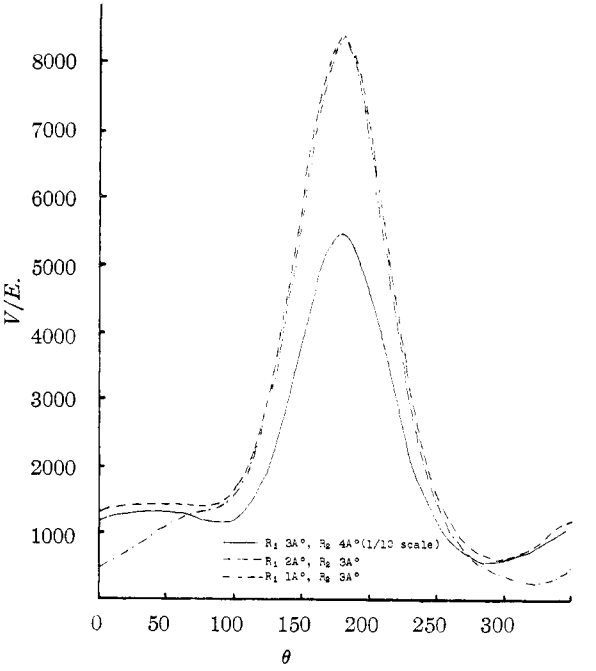


Fig. 2.—Potential energy *vs.* conformational angle θ (as given by eq. 5).

The results are listed in Table I and Fig. 3. Similar results are obtained by use of a simpler but less accurate function

$$V = \sum_{\substack{i = \text{1,M,S} \\ j = 1,2}} A_iA_je^{-2\sqrt{m^2 + m_j^2 + l_{ij}^2 - 2m_im_j\cos(\theta + \phi_{ij})}} \quad (6)$$

resulting from establishing the many cases fitting an idealized picture and noting the few exceptions.

No inclusion is made of polar effects as might arise where both one of S, M, L and one of R_1 and R_2 possess large dipoles.

(12) Where the groups involved are relatively large it is clear that the repulsive forces involved are of the classical van der Waals variety arising from the disinclination of two orbitals, each fully occupied, to overlap. The interaction energies are large compared to those arising from the phenomenon observed in cases such as ethane and recently discussed in the Proceedings of the National Academy of Sciences; E. B. Wilson, **43**, 816 (1957); H. Eyring, G. H. Stewart and R. P. Smith, **44**, 259 (1958); L. Pauling, **44**, 216 (1958).

(13) *Cf.* T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948), for a discussion of the problem.

(14) In order to evaluate V it is necessary to assume values of the E_{ij}'s. It seemed desirable to take these as equal to keep the treatment general and limited to steric effects. Since in practice the contribution of the sixth power attractive term to the total potential energy was small, the error incurred by assuming an average value of the E_{ij}'s may be seen to be equivalent to using slightly incorrect values of the r_{ij}'s; however, the error is minor since $r_{ij}(\text{err})/r_{ij} = (E_{ij}/E_{av})1/12$. In any event, the shape of the V versus θ curve is essentially unchanged by this assumption.

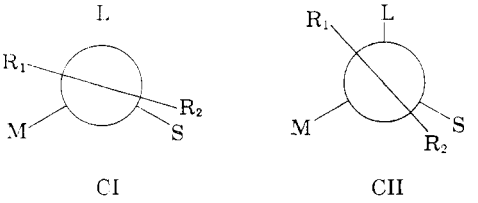


Fig. 3.

which disregards van der Waals attractive forces. The results are given in Table II.

The striking result of these calculations is the occurrence of one of two conformations depending on the relative size of R_1 and R_2. Where R_2 is much larger than R_1, conformation CII represents the energy minimum, while where R_2 is only slightly larger than R_1, CI predominates. In the case of an acyclic enol R_2 represents the entire enolic grouping =CR'OH.

TABLE I

CONFORMATION OF MINIMUM ENERGY AS OBTAINED FROM EQUATION 5

r_s, Å.	r_m, Å.	r_1, Å.	r_1, Å.	r_2, Å.	θ_{min}	Conformational designation
1	2	3	3	4	295°	CI
1	2	3	2	3	295°	CII
1	2	3	1	3	330°	CII

TABLE II

CONFORMATION OF MINIMUM ENERGY AS OBTAINED FROM EQUATION 6

A_s	A_m	A	A_1	A_2	θ_{min}	Conformation designation
1	2	3	1	4	330°	CII
1	2	3	1	3	330° + 280°	CII + CI
1	2	3	1	2	280°	CI

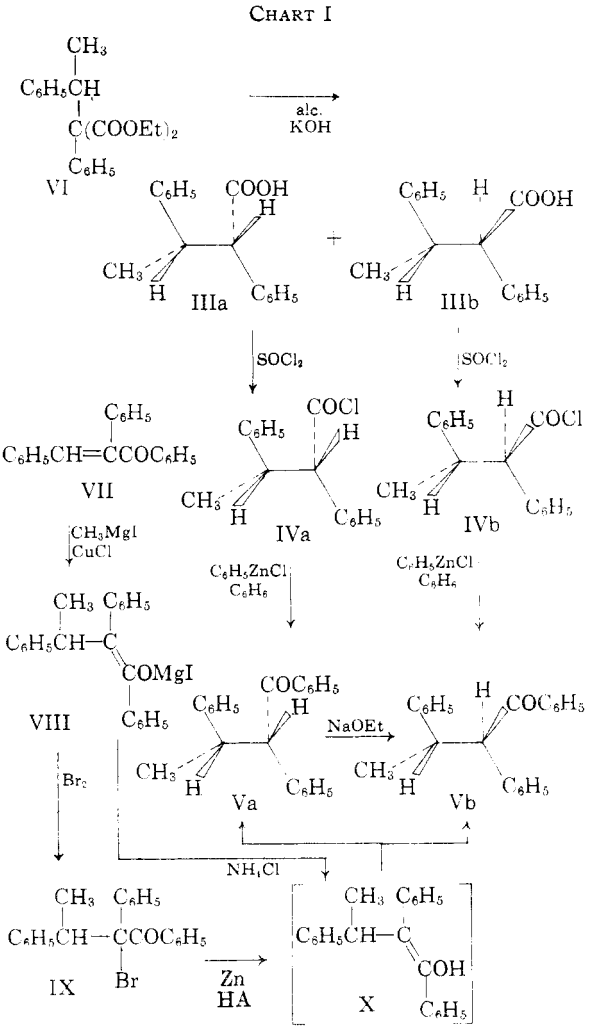
The theory necessary for determining the preferred conformation of an acyclic enol having been derived, a discussion of the experimental results obtained in the present study is in order.

Receiving attention first was ketonization of the enol of 2,3-diphenylbutyrophenone. This study required the synthesis of the diastereomeric 2,3-diphenylbutyrophenones, Va and Vb, and proof of their configurations. In addition, there were needed a means of generating the enol X and a method of analyzing mixtures of Va and Vb formed by ketonization of the enol X.

As indicated in Chart I both diastereomers of V were obtained from the conjugate addition of methylmagnesium iodide to benzaldesoxybenzoin (VII) followed by treatment of the magnesium enolate (VIII) with aqueous ammonium chloride; one stereoisomer (Va) melted at 104° while the other (Vb) had a melting point of 187°. Since the crude product mixture was badly contaminated with by-products and since isolation of the diastereomers was far from quantitative, no estimate of the relative yields of Va and Vb was possible.

In order to establish the configurations of the diastereomeric 2,3-diphenylbutyrophenones a stereospecific synthesis was devised, this utilizing as starting materials the *threo*- and *erythro*-2,3-diphenylbutanoic acids (IIIa and IIIb, resp.), whose configurations were known due to the work of Hauser.[15] *erythro*-2,3-Diphenylbutanoic acid was converted, as indicated in Chart I, by treatment with thionyl chloride under mild conditions to *erythro*-2,3-diphenylbutanoyl chloride, m.p. 145°, and thence with phenylzinc chloride to the 187° isomer Vb which must therefore have the *erythro* configuration.

CHART I



In a parallel sequence *threo*-2,3-diphenylbutanoic acid was converted into the 104° isomer Va of 2,3-diphenylbutyrophenone which as a consequence is assigned the *threo* configuration. These transformations are depicted in Chart I.

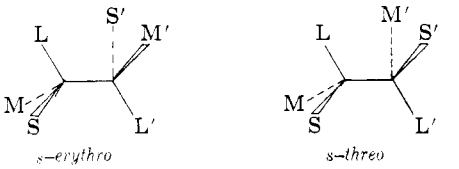
The next step in this investigation was the improvisation of an analytical technique for determining the relative amounts of the diastereomers Va and Vb in a mixture. Using the method described by us earlier[1,8] an accuracy of ±2% of *erythro* isomer was obtained (note Table XI in the Experimental Section for analysis of known mixtures of Va and Vb).

It was possible at this point to determine with accuracy the relative stabilities of *threo*- and *erythro*-2,3-diphenylbutyrophenone (Va and Vb, resp.). Starting with the *threo* isomer, treatment with 0.2 *M* sodium ethoxide in ethanol for 22 hours at room temperature (run 1, Table VII) afforded a mixture of the diastereomers analyzing for 42.8% *threo*-2,3-

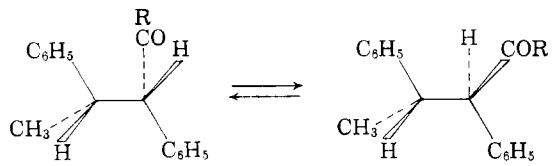
(15) W. R. Brasen and C. R. Hauser, THIS JOURNAL, **79**, 39 (1957).

diphenylbutyrophenone. Starting from the *erythro* diastereomer, the product contained 38.6% *threo*-2,3-diphenylbutyrophenone (run 2, Table VII). Thus the equilibrium composition consists of 40.9 ± 2.0% *threo*-2,3-diphenylbutyrophenone (Va) and 59.1 ± 2.0% *erythro* isomer Vb.

That *erythro*-2,3-diphenylbutyrophenone (Vb) is the thermodynamically favored isomer is of interest. It is true that its precursor, *erythro*-2,3-diphenylbutanoic acid (IIIb), is known[15] to be the stable isomer; however, this is expected, for this is the *s-erythro*[16] isomer which is in general the stable one.



Which diastereomer of 2,3-diphenylbutyrophenone is *s-erythro* is not as obvious, since the relative effective sizes of phenyl and benzoyl are close. The experimentally observed greater stability of



IIIa, R = OH
Vb, R = C_6H_5

IIIb, R = OH
Va, R = C_6H_5

erythro-2,3-diphenylbutyrophenone indicates that this is the *s-erythro* diastereomer, requiring that phenyl be the large group on carbon-2 and benzoyl be the medium one. Inspection of Fisher–Hirschfelder models suggests that the effectively smaller size of benzoyl results from the fact that the bulky portion of the benzoyl group (*i.e.*, phenyl) is more remote from the site of possible interaction on carbon-3.

Since the next objective was an investigation of the stereochemistry of ketonization of the enol X of 2,3-diphenylbutyrophenone, a means of generating the enol X was required. α-Haloketones have proved exceptionally useful for generating unstable enolic intermediates, these being converted to the enol either with dilute hydriodic acid or by treatment with zinc and a proton donor. The desired 2-bromo-2,3-diphenylbutyrophenone (IX) was prepared by reaction of bromine with the magnesium enolate VIII, obtained by conjugate addition of methylmagnesium iodide to 1,2,3-triphenylprop-2-ene-1-one (VII).

The debromination of this compound via the enol X to yield the diastereomeric 2,3-diphenylbutyrophenones was carried out with dilute hydriodic acid in acetone as well as with zinc and various proton donors. These results are given in Tables III, IV, V and VI. Two aspects of these results are striking. The first is the preferential formation under all conditions of *threo*-product; discussion of this point must await application of the derived conformational theory to the stereochemistry of

(16) It is convenient to designate diastereomers as *s-erythro* and *s-threo* (*i.e.*, sterically or size based *erythro* and *threo*) where the configurational assignment is based on similarity of relative size of groups rather than on the more commonly used similarity of functionality. In the cases of III and V the *s-threo* and *threo* designations apply to the same diastereomer; however, this is not invariably the case.

TABLE III

DEBROMINATION OF 2-BROMO-2,3-DIPHENYLBUTYROPHENONE WITH ZINC AND COLLIDINIUM CHLORIDE IN ALCOHOLS[a]

Run	Solvent	*threo* product, %	Average
1	Methanol	69.3	
2	Methanol	68.8	
3	Methanol	71.5	
4	Methanol	69.8	69.9 ± 1.6
5	Ethanol	78.5	
6	Ethanol	77.4	
7	Ethanol	76.5	77.5 ± 1.0
8	*t*-Butyl alc.	82.5	
9	*t*-Butyl alc.	83.2	
10	*t*-Butyl alc.	81.3	82.3 ± 1.0

[a] Each run was made at room temperature for 20 hr. under nitrogen.

TABLE IV

DEBROMINATION OF 2-BROMO-2,3-DIPHENYLBUTYROPHENONE WITH ZINC AND COLLIDINIUM CHLORIDE IN AMINE SOLVENTS[a]

Run	Solvent	*threo* product, %	Average
1	Pyridine–benzene	66.2	
2	Pyridine–benzene	65.4	
3	Pyridine–benzene	67.1	66.2 ± 0.9
4	Triethylamine–benzene	71.3	
5	Triethylamine–benzene	71.3	
6	Triethylamine	69.3	
7	Triethylamine	68.9	70.2 ± 1.3[b]
8	Tri-*n*-propylamine–benzene	67.5	
9	Tri-*n*-propylamine–benzene	67.2	
10	Tri-*n*-propylamine–benzene	69.0	
11	Tri-*n*-propylamine–benzene	69.2	68.2 ± 1.0
12	Tri-*n*-butylamine–benzene	72.7	
13	Tri-*n*-butylamine–benzene	70.7	
14	Tri-*n*-butylamine–benzene	70.1	
15	Tri-*n*-butylamine–benzene	71.7	
16	Tri-*n*-butylamine	69.3	70.9 ± 1.8[c]
17	Collidine–benzene	80.6	
18	Collidine–benzene	78.3	79.5 ± 1.2

[a] All runs were made at room temp. for 20 hr. under nitrogen. [b] Average of 4 runs with and without benzene present. [c] Average of 5 runs with and without benzene present.

TABLE V

ZINC DEBROMINATION OF 2-BROMO-2,3-DIPHENYLBUTYROPHENONE UNDER MISCELLANEOUS CONDITIONS[a]

Run	Solvent	*threo* product, %
1[b]	Acetone	75.3
2[b]	Acetonitrile	72.6
3[b]	Acetonitrile	69.8
4[b]	Acetonitrile	66.5
5[b]	Acetonitrile	68.5
6	Acetonitrile–acetic acid	64.0
7	Acetic acid	68.1
8	Acetic acid–ether	68.7
9	Propionic acid	68.8

[a] Run for 22 hr. at room temperature under nitrogen. [b] Collidinium chloride used.

TABLE VI

DEBROMINATION OF 2-BROMO-2,3-DIPHENYLBUTYROPHENONE WITH HYDRIODIC ACID IN ACETONE AND ACETONITRILE

Run	Solvent	*threo* Product, %
1[a]	Acetone	81.3
2[b]	Acetone	83.3
3[a]	Acetonitrile	75.3

[a] 3.0 min. reaction time at room temperature. [b] 1.5 min. reaction time at room temperature.

TABLE VII

ISOMERIZATION OF THE DIASTEREOMERIC 2,3-DIPHENYLBUTYROPHENONES

Run	Reactant, isomer	Conditions	*threo* product, %
1	*threo*-	0.2 *M* NaOEt, r.t., 22 hr.	42.8
2	*erythro*-	0.2 *M* NaOEt, r.t., 22 hr.	38.6
3	*threo*-	10% HCl in HOAc, 1 hr. refl.	55.0
4	*erythro*-	10% HCl in HOAc, 1 hr. refl	35.5

acyclic ketonization (*vide infra*). The second noteworthy result is the marked dependence of the stereoselectivity of ketonization on the nature of the ketonization medium and proton donor.

The effect of the ketonization medium on the stereoselectivity of ketonization seems mainly attributable to the varying steric demands of the proton donors. In the alcoholic solvents, where debromination was effected with zinc and collidinium chloride, the lowest selectivity (69.9 ± 1.6% *threo* product; note Table III) was observed in solvent methanol, while the greatest selectivity (82.3 ± 1.0% *threo* product) was obtained with *t*-butyl alcohol as solvent. It is clear that one must differentiate between the proton source, here collidinium ion common to all these runs, and the actual proton donor, an alkyloxonium ion in alcoholic solvent, whose steric characteristics govern stereoselectivity. The greater steric demands of the *t*-butyloxonium ion compared to methyloxonium ion account for the greater selectivity with *t*-butyl alcohol as solvent. Similarly, in amine solvents increasing stereoselectivity is observed with increasing steric demands of the proton donor. Here the sequence is solvent pyridine (66.2%) < *t*-amines (68.2 – 70.9%) < collidine (79.5%).

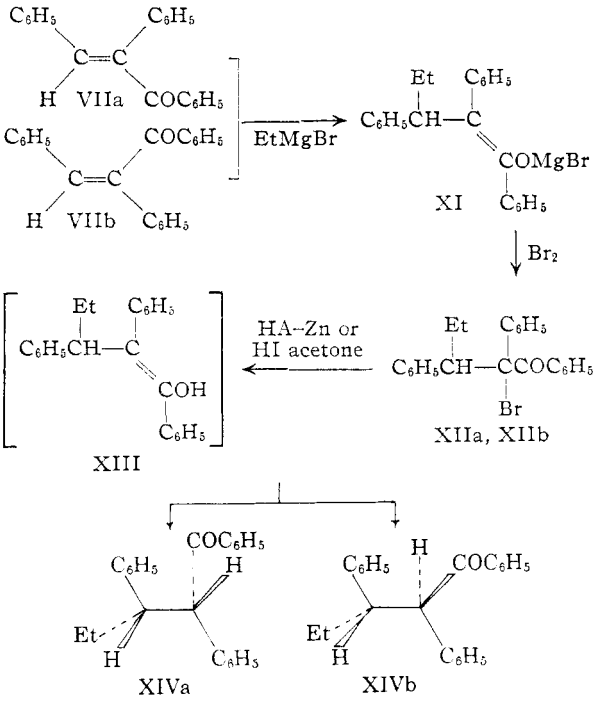
The stereochemistry of ketonization of a second acyclic enol was of interest. It had been reported by Kohler[17] that the magnesium enolate of 2,3-diphenylvalerophenone on acidification under mild conditions ketonized to afford exclusively the low melting isomer of this ketone, the configuration being unknown. In addition, Kohler reported the low melting isomer to be converted virtually completely to the higher melting diastereomer on equilibration with acid or base.

However, in view of the *ca.* 80% maximum stereoselectivity of ketonization of the closely related enol of 2,3-diphenylbutyrophenone and the far from complete formation of the *erythro* isomer at equilibrium, the report of Kohler seemed anomalous and a reinvestigation appeared desirable.

Repetition of the conjugate addition of ethylmagnesium bromide to the stereoisomers of benzaldesoxybenzoin (VIIa and VIIb) was found to afford a low melting material as reported by Kohler; however, infrared analysis showed this to be a complex mixture as was the case in the conjugate addition of methylmagnesium iodide (*vide supra*), and isolation of the pure diastereomers proved difficult.

By treatment of the magnesium enolate with bromine, there were obtained both diastereomers of 2-bromo-2,3-diphenylvalerophenone (XIIa and XIIb) [note Chart II]. The availability of

CHART II



both diastereomers of the bromoketone was fortunate, for a test of the reality of the proposed enolic intermediate in debromination would be provided. Since according to the proposed mechanism the same enolic intermediate is formed from each of the bromoketones, the debromination product distribution should not depend on the bromoketone stereoisomer employed. That this is the case may be seen from runs 1 and 2, and 5 and 6 of Table VIII.

TABLE VIII

DEBROMINATION OF 2-BROMO-2,3-DIPHENYLVALEROPHENONE UNDER VARIOUS CONDITIONS

Run	Bromoketone employed	Conditions	Lower melting diphenylvalerophenone, %
1	98° diastereomer	HI in acetone, 0°, 3 min.	75.3
2	129° diastereomer	HI in acetone, 0°, 3 min.	77.5
3	98° diastereomer	Zn and collid. chloride in methanol	51.6 ± 0.8[a]
4	129° diastereomer	Zn and collid. chloride in methanol	56.7 ± 0.8[b]
5	98° diastereomer	Zn and collid. chloride in *t*-butyl alc.	59.4 ± 1.0[b]
6	129° diastereomer	Zn and collid. chloride in *t*-butyl alc.	61.6 ± 0.2[b]

[a] Average of three runs. [b] Average of two runs.

The 5.1% difference in selectivity of debromination in methanol (runs 3 and 4) probably is not

(17) E. P. Kohler, *Am. Chem. J.*, **35**, 388 (1906).

significant. Thus the virtually complete selectivity reported by Kohler is not substantiated. Furthermore, Kohler had reported the lower melting diastereomer to be converted easily and completely to the higher melting isomer; in the present study the interconversion of stereoisomers was found not to be facile and an equilibrium constant favoring the higher melting isomer only slightly was found (note Table IX).

TABLE IX

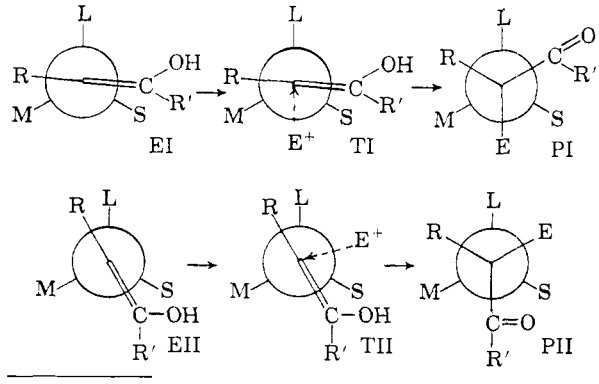
ISOMERIZATION EXPERIMENTS

Run	Conditions	Lower melting diphenylvalerophenone, %
1	0.665 *M* sodium ethoxide in ethanol, r.t., 20 hr.	50.0
2	0.665 *M* sodium ethoxide in ethanol, r.t., 20 hr.	43.8
3	10% hydrochloric acid in acetic acid, reflux, 4 hr.	52.4
4	10% hydrochloric acid in acetic acid, reflux, 4 hr.	45.0

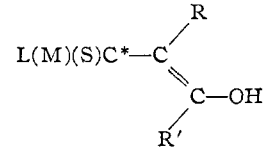
While the configurations of the 2,3-diphenylvalerophenones have not been rigorously determined, it is nevertheless reasonable to assume that the lower melting isomer, which is kinetically preferred in ketonization, is the *threo* diastereomer in analogy to the 2,3-diphenylbutyrophenone situation.[18]

It having been determined that the enols 2,3-diphenylbutyrophenone and 2,3-diphenylvalerophenone (X and XIII, respectively) ketonize with preferential formation of the *s-threo* products, it remains to utilize the conformation theory derived (*vide supra*) in mechanistically rationalizing these observations. In addition, since there are available in the literature considerable additional experimental data bearing on acyclic ketonization (*vide infra*), a further test of the concepts set forth is possible.

The conformational theory derived (*vide supra*) suggests that for each enolic reactant one of two conformers (EI or EII) will be preferred, depending on the relative size of the groups R– and R′C(OH)= on the trigonal carbon atom. Where R′C(OH)= is only slightly larger than R, conformation EI is preferred; while when R′C(OH)= is very much larger than R, conformation EII results. In the former situation the preferred transition state will be TI, the assumption being made that the ketonization transition state is reached before the α-carbon hydridization is appreciably changed and while the attacking electrophile E^+ is still sufficiently distant that the conformation is not appreciably perturbed.[19] The product configuration will then be PII. If, however, R′C(OH)= is much larger than R–, the preferred transition state becomes TII with formation of product PII.

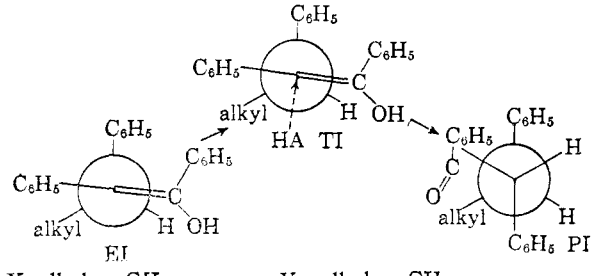


Now independent evidence has been presented in connection with some other studies[20a,b] that enolic intermediates have the geometric configuration about the enolic double bond allowing the greater accessibility of the oxygen atom to solvent. In the present case this is the isomer whose R′ group projects back toward the asymmetric carbon atom.



Thus, determining whether transition state TI or TII is utilized are the relative sizes of R– and R′–. In terms of actual groups the following assignments not only seem reasonable[21] but accommodate the experimental data: *R′C(OH) > R, and EI and TI are preferred for:* R′ = CH_3 and R = H or CH_3; R′ = aryl and R = Cl, Br or aryl. *R′C(OH) >> R, and EII and TII are preferred for:* R′ = aryl and R = H.

Applied to ketonization of the enols (X and XIII) of 2,3-diphenylbutyrophenone and 2,3-diphenylvalerophenone this mechanistic model correctly rationalizes the preferential formation of the *threo* product. Here both R and R′ are phenyl and conformation EI represents the energy minimum. The less hindered prototropic attack affords *threo*-2,3-diphenylbutyrophenone from enol X and *threo*-2,3-diphenylvalerophenone from XIII.



X, alkyl = CH_3 Va, alkyl = CH_3
XIII, alkyl = CH_3CH_2 XIVa, alkyl = CH_3CH_2

(18) In an interesting discussion this assignment has been suggested by H. Felkin, *Bull. soc. chim.*, [5] **23**, 1050 (1956). However, the assignment was based on the report of Kohler of a marked difference of stabilities of the diastereomer 2,3-diphenylvalerophenones together with the quite correct assumption that the *s-erythro* diastereomer (*erythro* based on size of groups; *cf.* footnote 15) is the stable one.

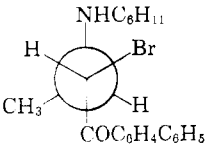
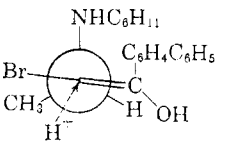
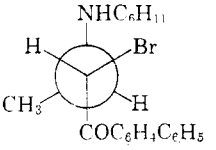
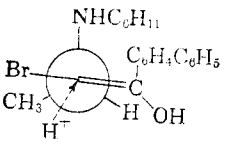
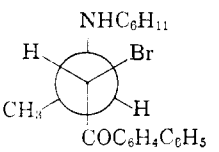
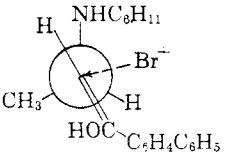
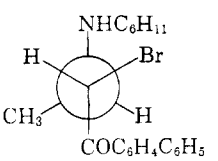
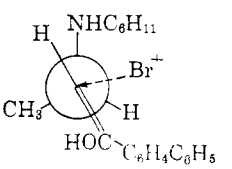
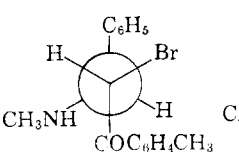
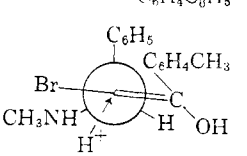
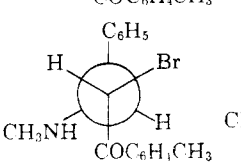
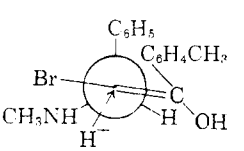
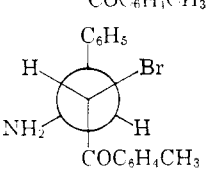
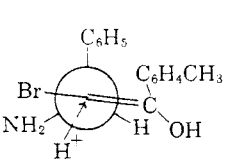
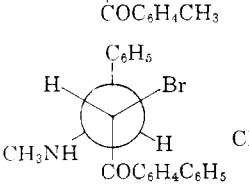
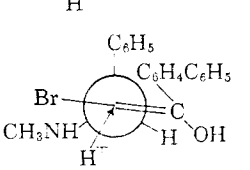
(19) This conclusion has been reached in studies of exocyclic enols as well. The only moderate change in stereoselectivity with huge changes in the bulk of the proton donor probably has its basis here. In the present case the result of a large steric interaction by E^+ would be to leave TI unchanged but to convert TII to TI.

(20) (a) H. E. Zimmerman, L. Singer and B. S. Thyagarajan, THIS JOURNAL, **81**, 108 (1959); (b) H. E. Zimmerman and L. Ahramjian, *ibid.*, **81**, 2036 (1959).

(21) That for R′ and R being the same group, R′C(OH) is effectively larger than R is not surprising, since the distance between R′ and the groups on the asymmetric center is smaller than that between R and the same groups.

TABLE X

SUMMARY OF ACYCLIC KETONIZATION STEREOCHEMISTRY

Reactants	Products	Low energy enol conformer	Major product acyclic precursor	Predicted preferred transition state
$CH_3CHBrCHBrCOC_6H_4$-*p*-C_6H_5 + cyclohexylamine	59% 1-cyclohexyl-*cis*-2-methyl-3-(*p*-phenylbenzoyl)-ethyleneimine 33% *trans*-isomer (ref. 24a)	EI		
$CH_3CH{=}CBrCOC_6H_4$-*p*-C_6H_5 + cyclohexylamine	62% 1-cyclohexyl-*cis*-2-methyl-3-(*p*-phenylbenzoyl)-ethyleneimine 34% *trans*-isomer (ref. 11)	EI		
$CH_3CH{=}CHCOC_6H_4$-*p*-C_6H_5 + cyclohexylamine + Br_2 or N-bromocyclohexylamine	1-Cyclohexyl-*cis*-2-methyl-3-(*p*-phenylbenzoyl)-ethyleneimine as major or only prod. (ref. 11)	EII		
$CH_3CHCH_2COC_6H_4$-*p*-C_6H_5 + N-$C_6H_{11}NH$ bromocyclohexylamine	85% 1-cyclohexyl-*cis*-2-methyl-3-(*p*-phenylbenzoyl)-ethyleneimine (ref. 11)	EII		
$C_6H_5CHBrCHBrCOC_6H_4$-*p*-CH_3 + CH_3NH_2	1-Methyl-*trans*-2-phenyl-3-(*p*-toluyl)-ethyleneimine 46% isolated, 54% indicated; no *cis* isomer (ref. 24b)	EI		
$C_6H_5CH{=}CBrCOC_6H_4$-*p*-C_6H_5 + CH_3NH_2	63% 1-methyl-*trans*-2-phenyl-3-(*p*-phenylbenzoyl)-ethyleneimine 29% *cis*-isomer (ref. 11)	EI		
$C_6H_5CHBrCHBrCOC_6H_4$-*p*-CH_3 + NH_3	61% *trans*-2-phenyl-3-*p*-toluyl-ethyleneimine (ref. 24b)	EI		
$C_6H_5CHBrCHBrCOC_6H_4$-*p*-C_6H_5 + CH_3NH_2	70% 1-methyl-*trans*-2-phenyl-3-(*p*-phenylbenzoyl)-ethyleneimine 20% *cis*-isomer (ref. 11, 25)	EI		

It may be noted that the formation of the less stable diastereomer is evidence against the earlier interpretation of Cromwell[11] that acyclic ketonization is controlled by a transition state resembling product with preferential formation of the more stable stereoisomer.

Furthermore, the mechanism presently proposed is capable of accommodating the results of the literature. These results derive from reactions in which Michael addition of amines to an α-bromo-α,β-unsaturated ketone followed by ketonization and internal SN2 displacement leads to an ethyleneimine ketone and reactions involving Michael addition of amines to an α,β-unsaturated ketone in the presence of bromine,[22] in which case ketonization by attack of bromine on the enol is followed by ethyleneimine formation. Where the product stereochemistry is known, it is possible to ascertain which diastereomer is formed in the

(22) Although with one exception the stereochemistry of the reaction of amines and iodine with unsaturated ketones is also in accord with the proposed mechanism, it may be that an enolic intermediate is not involved (*cf.* ref. 11). In these reactions the virtually complete stereospecificity, even where the bromine reaction is only slightly selective, suggests a different mechanism.

ketonization process. These results as well as the theoretical predictions are listed in Table X.[23] It may be seen that in each case the facts are in accord with prediction. The previously difficult fact to rationalize, the formation of the same diastereomer whether ketonization results from attack of bromine on an enol having R = H or instead from attack of a proton donor on an enol having R = Br, is now understandable, for in the former case conformation EII is involved while in the latter situation EI is of lower energy.

Experimental and Calculation[26]

Preparation of Ethyl 2,3-Diphenyl-2-carbethoxybutanoate.—To 3.85 g. (0.168 mole) of sodium shot suspended in 200 ml. of toluene was added 39.5 g. (0.168 mole) of ethyl phenylmalonate. After refluxing for one hour, at the end of which time all the sodium had reacted, the cooled mixture was treated with 31.1 g. (0.0168 mole) of α-phenylethyl bromide. The mixture was refluxed for 10 hr. Then the reaction mixture was concentrated *in vacuo* leaving 58 g. of crude product which was distilled affording: fraction 1, 13.0 g., b.p. 75° at 2 mm.; fraction 2, 1.5 g., b.p 75–156° at 0.04 mm., $n^{25.8}$ 1.5042; fraction 3, 17.55 g., b.p. 156–172° at 0.04 mm., 1.5343; fraction 4, 11.19 g., b.p. 166–172° at 0.04 mm., 1.5344; fraction 5, 8.35 g., b.p. 166–168° at 0.04 mm., 1.5356. Fractions 3 through 5 were product; fraction 4 was analyzed.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.07; H, 6.86.

Saponification and Decarboxylation of Ethyl 2,3-Diphenyl-2-carbethoxybutanoate.—To a solution of 40.30 g. (0.72 mole) of potassium hydroxide in 150 ml. of ethanol was added 28.4 g. (0.0845 mole) of ethyl 2,3-diphenyl-2-carbethoxybutanoate. The mixture was refluxed for 6 hr. During the reflux period the solution turned orange and a large amount of solid separated. The solid was filtered and the filtrate was concentrated under vacuum. The filter cake and the residue from the filtrate were combined and acidified with dilute hydrochloric acid affording a solid acid product which was filtered. This weighed 16 g. and melted at 120–165°. Recrystallization of the crude product from ether–pentane afforded 7.7 g. (39%) of *erythro*-2,3-diphenylbutanoic acid, m.p. 188°. This showed no depression on mixed melting with authentic[15] material (reported m.p. 184–185°).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.22; H, 6.57.

The mother liquor was concentrated and chromatographed on a 2.5 × 92 cm. silica gel column, slurry packed with 10% ether in hexane. The fraction eluted with 10% ether in hexane was subjected to slow crystallization from ether–hexane using seeds. There was obtained 5.2 g. (25%) of *threo*-2,3-diphenylbutanoic acid, m.p. 138–139° (reported[27] 133°).

***erythro*-2,3-Diphenylbutanoyl Chloride.**—To a 50-ml. flask fitted with a calcium chloride tube and a magnetic stirrer was added 8.0 ml. (0.111 mole) of thionyl chloride and 1.00 g. (0.00417 mole) of *erythro*-2,3-diphenylbutanoic acid. The mixture was stirred at room temp. for 18 hr. During this time the mixture had become homogeneous. The excess thionyl chloride was removed *in vacuo* at room temp. The residual product solidified and melted at 143.5–145.0°, wt. 1.1 g. It was crystallized twice from benzene–hexane affording pure *erythro*-2,3-diphenylbutanoyl chloride, m.p. 143–144°.

Anal. Calcd. for $C_{16}H_{15}OCl$: C, 74.24; H, 5.84. Found: C, 74.35; H, 5.65.

Conversion of 2,3-Diphenylbutanoyl Chloride to *erythro*-2,3-Diphenylbutyrophenone.—To an ethereal solution of phenylmagnesium bromide, prepared from 0.30 g. (12.3 mmoles) of magnesium and 2.0 g. (12.7 mmoles) of bromobenzene, was added 2.0 g. (14.7 mmoles) of freshly fused zinc chloride dissolved in a minimum of anhydrous ether. The phenylzinc chloride formed and dispersed in the solution as a gray powder. Then 100 ml. of anhydrous benzene was added and a downward condenser was connected to the flask. Ether was distilled until the boiling point reached 75°

Freshly prepared *erythro*-2,3-diphenylbutanoyl chloride from 1.00 g. (4.17 mmoles) of *erythro*-acid was dissolved in 25 ml. of anhydrous benzene and the solution was added slowly to the refluxing suspension of phenylzinc chloride. A pasty mass was formed. After refluxing for one hour, hydrolysis was effected by the addition of 50 ml. of ice-cold saturated ammonium chloride solution. The mixture was ether extracted and the extracts were washed successively with dilute hydrochloric acid, dilute sodium bicarbonate solution and water. The solid suspended in the ether phase was filtered, wt. 0.45 g. (36%); this melted at 186–188°, melting point undepressed on admixture with *erythro*-2,3-diphenylbutyrophenone. The filtrate was dried over calcium chloride and concentrated *in vacuo*, leaving 0.75 g. (60%) more of product, melting at 173–176°. Recrystallization from ether–hexane brought the melting point to 186–188°, again showing no melting point depression with the *erythro*-ketone. Quantitative infrared analysis of the 36% crop, m.p. 186–188°, and of the 60% fraction, m.p. 173–176°, showed these to be 95.2 and 94.7% stereochemically pure, respectively.

***threo*-2,3-Diphenylbutanoyl Chloride.**—Under the same conditions employed for preparation of the *erythro* isomer, *threo*-2,3-diphenylbutanoic acid afforded an oily acid chloride. This was employed directly in the succeeding preparation.

***threo*-2,3-Diphenylbutyrophenone.**—A benzene suspension of phenylzinc chloride (12.3 mmoles) was prepared in exactly the same manner as described above. To this was added a solution of *threo*-2,3-diphenylbutanoyl chloride, prepared from 1.00 g. of *threo*-2,3-diphenylbutanoic acid, dissolved in 25 ml. of anhydrous benzene. The suspension was refluxed for one hour and the product worked up as in the case of the *erythro* isomer. This weighed 1.80 g. and melted at 56–78°. This material was chromatographed on a 2.5 × 30 cm. silica gel column slurry packed with 20% ether in hexane. The material eluted with 2 liters of 20% ether in hexane melted at 98–99° and weighed 1.50 g. Two crystallizations from ether–hexane afforded 1.10 g. (88.2%) of pure *threo*-2,3-diphenylbutyrophenone, m.p. 102°. This exhibited no mixed melting point depression with the *threo*-ketone obtained by another route (*vide infra*). Quantitative infrared analysis of the 98–99° product showed it to be 92.1% stereochemically pure.

Conjugate Addition of Methylmagnesium Iodide to Benzaldesoxybenzoin.—A solution of methylmagnesium iodide in 40 ml. of ether was prepared from 1.71 g. (0.070 mole) of magnesium and 10.05 (0.070 mole) of methyl iodide. To this was added 0.05 g. of cuprous chloride in 20 ml. of anhydrous ether. Then 13.0 g. (0.047 mole) of benzaldesoxybenzoin, m.p. 101°, was added using a modified Soxhlet extractor allowing controlled siphoning. After the addition of the ketone was complete, the solution was refluxed for 15 min. and 2.0 g. of solid ammonium chloride was added. Then excess 5% hydrochloric acid was added. The mixture was ether extracted and the ether extract was washed with aqueous sodium bicarbonate and finally with water. Some solid which was suspended in the ether phase was filtered. This melted at 182°. The ether filtrate was dried over sodium sulfate and was concentrated *in vacuo* to a volume of 80 ml. The solid which had separated was filtered; this melted again at 182°. The combined 182° material weighed 5.2 g. (38.1%). After several crystallizations from ether pure *erythro*-2,3-diphenylbutyrophenone, m.p. 186.5–187.5°, was obtained.

Anal. Calcd. for $C_{22}H_{18}O$: C, 87.96; H, 6.71. Found: C, 87.55; H, 6.65.

The ether filtrate was concentrated *in vacuo* affording 6.3 g. of material melting at 80°. Three crystallizations from

(23) Omitted are a number of examples in which the stereoselectivity is essentially nil due to the similarity of bulk of two of the three groups on the asymmetric carbon atom.

(24) (a) N. H. Cromwell and R. J. Mohrbacher, THIS JOURNAL, **75**, 6252 (1953); (b) N. H. Cromwell, N. G. Barker, R. A. Wankel, P. J. Vanderhorst, F. W. Olson and J. H. Anglin, Jr., *ibid.*, **73**, 1044 (1951).

(25) N. H. Cromwell and M. A. Graff, *J. Org. Chem.*, **17**, 414 (1952).

(26) All melting points were taken with a Fisher–Johns block checked with compounds of known melting point.

(27) C. R. Hauser, D. Lednicer and W. R. Brasen, THIS JOURNAL, **80**, 4345 (1958).

ether–methanol yielded 4.6 g. (37.8%) of crystals of *threo*-2,3-diphenylbutyrophenone, m.p. 104°.

Anal. Calcd. for $C_{22}H_{18}O$: C, 87.96; H, 6.71. Found: C, 87.97; H, 6.63.

Equilibration of the 2,3-Diphenylbutyrophenone Stereoisomers.—To a sodium ethoxide solution prepared from 230 ml. of absolute ethanol and 1.15 g. of sodium was added 60 mg. of *erythro*-2,3-diphenylbutyrophenone. The clear solution was allowed to remain at room temp. for 20 hr. At the end of this time the mixture was neutralized with acetic acid and then concentrated under vacuum. The residue was taken up in ether and the ether solution was washed with aqueous sodium bicarbonate and then water. The dried extracts were concentrated leaving 57.8 mg. of mixed ketones. Quantitative infrared analysis indicated this to contain 38.6% of *threo*-2,3-diphenylbutyrophenone.

The same treatment of 60.8 mg. of *threo*-2,3-diphenylbutyrophenone afforded 63.6 mg. (solvent trace) analyzing for 42.8% *threo*-ketone.

Acid-catalyzed epimerization was carried out as follows: To 150 mg. of *erythro*-2,3-diphenylbutyrophenone was added 50 ml. of acetic acid and 5.0 ml. of concd. hydrochloric acid. The solution was refluxed for one hr. and was then treated with enough sodium acetate to neutralize the hydrochloric acid. The solution was concentrated *in vacuo* and the residue was extracted with water and ether. The ether extract was washed with 5% sodium carbonate solution and with water, and then was dried over calcium chloride. Concentration under vacuum left a residue of mixed stereoisomers which on quantitative infrared analysis was found to consist of 35.5% *threo*-2,3-diphenylbutyrophenone.

The same treatment of *threo*-2,3-diphenylbutyrophenone afforded a mixture analyzing for 55.0% *threo*-ketone.

2-Bromo-2,3-diphenylbutyrophenone.—A solution of methylmagnesium iodide in ether was prepared from 1.00 g. (0.0415 mole) of magnesium, 5.85 g. (0.0415 mole) of methyl iodide and 40 ml. of ether. To this solution was added 0.05 g. of cuprous chloride. To the mixture was then added 10.0 g. (0.0355 mole) of benzaldesoxybenzoin (101° isomer) using a modified Soxhlet extractor allowing controlled siphoning. At the end of the ketone addition the solution was refluxed under nitrogen for 15 min. and was then cooled to −40°. To the mixture was added dropwise 7.00 g. (0.045 mole) of bromine with vigorous stirring. The solution was allowed to warm to 0° during the addition, at which temperature the bromine was taken up. The reaction mixture then was poured into an aqueous sodium bicarbonate–sodium bisulfite solution cooled to 0°. The product was extracted with ether containing a trace of pyridine, this being found to inhibit decomposition of the crude bromoketone. The extract was filtered through a 2.5 × 30 cm. column packed in two sections with sodium sulfate and with alumina (Merck 71707). The filtrate was concentrated *in vacuo*, pentane was added and the solution was seeded. Crystals were obtained weighing 6.0 g., m.p. 90–92° (27%). After repeated recrystallization from ether (containing a trace of pyridine–pentane), pure 2-bromo-2,3-diphenylbutyrophenone, m.p. 102.5–103.0° dec., was obtained.

Anal. Calcd. for $C_{22}H_{19}OBr$: C, 69.67; H, 5.05. Found: C, 69.80; H, 5.17.

Hydriodic Acid Debromination of 2-Bromo-2,3-diphenylbutyrophenone.—To a solution of 0.20 g. of 2-bromo-2,3-diphenylbutyrophenone in 8.0 ml. of acetone was added a solution of 1.00 ml. of 47% hydriodic acid in 5.0 ml. of acetone; there was an instantaneous liberation of iodine. At the end of 1.5 min., 60 ml. of water and enough sodium bisulfite to decolorize the iodine were added. The solid suspension was filtered through a short column of Celite and the Celite was extracted with ether. The ethereal solution was washed with sodium bicarbonate solution and then water; it now was dried over calcium chloride and concentrated *in vacuo*, leaving 172 mg. of mixed ketone stereoisomers, whose infrared spectrum indicated it to consist of 81.3% *threo*-2,3-diphenylbutyrophenone.

Standard Procedure for Debromination in Alcohols, Acetonitrile or Acetic Acid.—To a ground glass 25-ml. erlenmeyer flask attached to a dry, oxygen-free nitrogen source were added 15 ml. of the given solvent, 0.25 g. of collidinium chloride, 0.30 g. of powdered zinc and 0.055 of the bromoketone. The air in the flask was swept out with nitrogen and then a positive pressure of nitrogen was maintained. The mixture was stirred magnetically for 22 hr. At the end of this time the mixture was poured into aqueous citric acid solution and then ether extracted. The ether extract was washed with water and dried over calcium chloride. Concentration *in vacuo* left a residue of mixed stereoisomers, which was placed under an oil-pump vacuum to remove the last traces of solvent and analyzed by quantitative infrared.

It was found that occasionally due to air leaks or incomplete flushing, the product showed hydroxyl absorption at 2.95 μ as well as foreign peaks at 5.65 and 5.85 (shoulder) μ; these runs were discarded. The results of these debromination experiments are listed in Tables III, V and VIII.

Standard Procedure for Debromination in Amine Solvents.—To a ground glass 25-ml. erlenmeyer flask attached to a dry and oxygen-free nitrogen source there were added 20 ml. of benzene, 0.25 g. of collidinium chloride, 0.30 g. of powdered zinc, 0.055 g. of the bromoketone and 0.50 ml. of the given amine. The mixture was stirred magnetically under positive pressure of nitrogen for 22 hr. The product was isolated and analyzed as described for runs in alcohol solvents. For runs without benzene, this was replaced by an equal volume of the amine. The results of these runs are given in Table IV.

The Stereoisomeric 2-Bromo-2,3-diphenylvalerophenones.—A solution of ethylmagnesium bromide was prepared from 0.855 g. (0.035 mole) of magnesium, 3.83 g. (0.035 mole) of ethyl bromide and 20 ml. of ether. To this was added 0.05 g. of cuprous chloride in 10 ml. of anhydrous ether. By use of a modified Soxhlet extractor allowing controlled siphoning there was added 6.26 g. of benzaldesoxybenzoin (0.022 mole; isomer m.p. 101°). Then the mixture was refluxed for an additional 15 min. The flask was cooled in an ice-bath while the contents were protected from air by nitrogen. To the cooled solution bromine was added dropwise until bromine was no longer consumed; this required 5.45 g. (0.03 mole). The mixture was poured onto ice and saturated ammonium chloride solution containing a small amount of sodium bisulfite. The product was ether extracted, and the extracts were washed with ice-water and dried over calcium chloride. The ether solution was concentrated *in vacuo* leaving 8.3 g. of oil which was treated with 3 ml. of acetone and 10 ml. of methanol, affording a solid which was recrystallized from chloroform–pentane to yield 2.76 g. (31%) of "α"-2-bromo-2,3-diphenylvalerophenone, m.p. 128.5° dec.

Anal. Calcd. for $C_{23}H_{21}OBr$: C, 70.23; H, 5.38. Found: C, 70.04; H, 5.25.

The filtrate was concentrated and treated again with 2 ml. of acetone and 10 ml. of methanol and was seeded. The solid obtained weighed 3.65 g. (42%) and melted at 78–85°. After repeated crystallization from acetone–methanol 2.0 g. of β-2-bromo-2,3-diphenylvalerophenone, m.p. 97.5–98.5°, was obtained.

Anal. Calcd. for $C_{23}H_{21}OBr$: C, 70.23; H, 5.38. Found: C, 70.15; H, 5.17.

The Stereoisomeric 2,3-Diphenylvalerophenones.—One gram of α-2-bromo-2,3-diphenylvalerophenone, m.p. 128.5°, was dissolved in 30 ml. of acetone. To this was added 5.0 ml. of 48% hydriodic acid and the mixture was stirred for 3 min. The solution then was cooled and poured into ice-cold sodium bicarbonate solution to which a small amount of sodium sulfite had been added. The product next was filtered and weighed 0.88 g.; it was triturated with 5.0 ml. of ether leaving a residue weighing 0.25 g. and melting at 145–146°. Recrystallization from benzene afforded 0.15 g. of *erythro*-2,3-diphenylvalerophenone, m.p. 169°. The ethereal extract above was treated with hexane and the ether was removed. On cooling, there was obtained solid of m.p. 145–158°; this on recrystallization from benzene gave 50 mg. of *erythro* product melting at 169°. The total yield was then 0.20 g. (25%) (reported[17] m.p. 170°).

Anal. Calcd. for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 87.55; H, 6.83.

The filtrates were concentrated and the residue chromatographed on a 2.5 × 30 cm. silica gel column slurry packed with 3% ether in hexane. The *threo* product was eluted with 4 liters of the same solvent and was recrystallized from methanol. Two types of crystals were discernible; the rhombic crystals, melting at 92°, formed more rapidly than the needle-like crystals, which melted at 100°. In contact

with methanol the rhombic crystals were transformed slowly into the needle modification; mixtures of the two melted at 89–93°. In chloroform solution the same infrared spectrum was given by the two crystalline modifications. Kohler[17] reported a m.p. of 92°.

Anal. Calcd. for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 87.83; H, 6.93.

Isomerization of the Diastereomeric 2,3-Diphenylvalerophenones.—To 0.10 g. (0.32 mmole) of each isomer of 2,3-diphenylvalerophenone was added a sodium ethoxide solution prepared from 100 ml. of absolute ethanol and 1.5 g. of sodium. The clear solution was allowed to stand at room temp. for 20 hr. The mixture then was neutralized by passing in carbon dioxide gas; the solution was filtered free of sodium carbonate and the filtrate was concentrated *in vacuo*. The residue was taken up in ether; the extract was washed with water, dried and concentrated again. The residue was analyzed by quantitative infrared. The results are listed in Table IX.

The acid-catalyzed equilibration experiments were carried out as follows: To 0.10 g. of each of the 2,3-diphenylvalerophenone stereoisomers was added 50 ml. of acetic acid and 5.0 ml. of concd. hydrochloric acid. The solution was refluxed for 4 hr. and then was treated with 4 g. of sodium acetate and concentrated *in vacuo*. The residue was ether and water extracted and the ether phase was washed with 5% sodium carbonate solution and then with water and was dried over calcium chloride. The dried ether solution was concentrated under vacuum and the residue analyzed by quantitative infrared.

Debromination Procedure Using Hydriodic Acid.—To a solution of 0.25 g. of each isomer of 2-bromo-2,3-diphenylvalerophenone in 8.0 ml. of acetone was added 1.0 ml. of 47% hydriodic acid in 5.0 ml. of acetone. At the end of the specified reaction time 60 ml. of water and enough sodium bisulfite to decolorize the iodine were added. The mixture was filtered through a short Celite column and the Celite ether extracted to dissolve the filtered product. The ether extract was washed with sodium bicarbonate solution and then with water. It was dried over calcium chloride and concentrated under vacuum. The residue was subjected to quantitative infrared analysis. The results are given in Table VIII.

Quantitative Infrared Analysis.—The method employed was that described previously,[1] utilizing the relation $R = Q \cdot F$ derivable from Beer's law. Here R is the ratio of *threo* to *erythro* isomer, Q is given by

$$Q = \frac{D_m' D_e'' - D_m'' D_e'}{D_m'' D_t' - D_m' D_t''} \text{ and } F = \frac{C_t}{C_e}$$

The D's are optical densities; the superscripts refer to the analytical wave lengths used and the subscripts m, t and e refer to a given mixture, the pure *threo* isomer and the pure *erythro* isomer, respectively.

The analytical wave lengths used in analyzing mixtures of the 2,3-diphenylbutyrophenones were 11.64 and 11.94 μ. These analyses were run using 2.0-mm. sodium chloride cells and total concentrations of 18 ± 1 mg./ml. of bromoform. The optical density was taken as zero at 4.8 μ. Table XI contains the calibration data and analyses of known mixtures. The average value of $F = 1.17$ was used to calculate the results in the last two columns.

TABLE XI

ANALYSIS OF KNOWN MIXTURES OF THE 2,3-DIPHENYLBUTYROPHENONES

Actual % *threo*	D'	D''	Q	Actual R	Calcd. F	Calcd. R	Calcd. % *threo*
0.0	0.0485	0.312	....	....	..	...	..
31.4	.108	.229	0.3890	0.4577	1.18	0.456	31.9
46.2	.134	.1974	0.6907	0.8587	1.24	0.810	44.8
67.6	.146	.1875	1.880	2.086	1.11	2.20	68.8
100.0	.292	.0815	....	....	..	...	..

Analysis of mixtures of the diastereomeric 2,3-diphenylvalerophenones was similar except in the following. Here 0.10-mm. cells were used. All spectra were run at a concentration of 275 ± 25 mg./ml. chloroform. The analytical wave lengths used were 10.15 and 10.26 μ. All optical densities were corrected by subtraction of the optical density at 4.80 μ. Calibration data are given in Table XII. Here an average value of $F = 1.59$ was used.

TABLE XII

ANALYSIS OF KNOWN MIXTURES OF THE 2,3-DIPHENYLBUTYROPHENONES

Actual % *threo*	D'	D''	Q	Actual R	Calcd. F	Calcd. R	Calcd. % *threo*
0.0	0.131	0.363	....	....	..	...	..
27.3	.169	.308	0.2420	0.3755	1.55	0.376	27.8
41.9	.193	.263	0.4486	0.7212	1.61	0.722	41.7
69.4	.230	.272	1.452	2.268	1.56	2.27	69.7
81.9	.264	.173	2.674	4.525	1.65	4.41	81.0
100.0	.372	.140	....	....	..	...	..

Calculations.—By the use of simple trigonometry and Fig. 4 it is found that $l_{ij} = 2.82$ Å., $m_i = 1.45$ Å. and $m_j = 1.33$ Å. Using these values and equations 3 and 5 it was

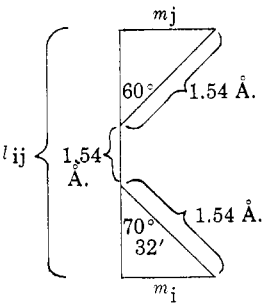


Fig. 4.

possible to evaluate V as a function of θ; the results are plotted in Fig. 2. The assumption is made that E_{ij} is independent of the groups involved, since a general solution is desired.

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