[Contribution from the Chemistry Department of Northwestern University]

THE STEREOCHEMISTRY OF THE KETONIZATION REACTION OF ENOLS

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Although simple ketones enolize to only a very minor extent, the importance of the enolization process to an understanding of many ketone reactions is well recognized. The present paper will consider some stereochemical aspects of the reverse process, the ketonization of enols. It is clear that due to microscopic reversibility an improved understanding of either reaction will lead to a better comprehension of the other.

The present investigation owes its beginning to the occurrence of a 117°-ketone as a by-product in the synthesis of a compound required for another stereochemical study. The 117°-ketone, which was obtained by the writer and a co-worker as a minor product from the reaction of phenylmagnesium bromide with methyl *cis*-2-hydroxycyclohexanecarboxylate, seemed on the basis of analytical and infrared data to be most likely 1-phenyl-2-benzoylcyclohexane. Furthermore, it was suggested that this compound (Ia) arose by 1,4-addition of phenylmagnesium bromide to benzoylcyclohexene (II), which might reasonably have been formed under the reaction conditions[1] (1).

In order to test the validity of this structural assignment two new syntheses of Ia were attempted. The first of these involved the reaction of phenylmagnesium bromide with benzoylcyclohexene (II), the hypothesized precursor of the earlier work. Benzoylcyclohexene was prepared by the reaction of benzoyl chloride with cyclohexene in the presence of aluminum chloride as described by Fuson (2) followed by extensive fractionation of the product and also by a new route which employed the reaction of cyclohexenyllithium (3) with lithium benzoate. The infrared spectrum of II prepared by these two routes was invariant.

The reaction of II with phenylmagnesium bromide was run in the presence of a catalytic amount of cuprous chloride (4) to facilitate 1,4-addition. Indeed, the major product obtained from this reaction was a 117°-melting ketone whose identity with Ia was established by infrared comparison and mixture melting point determination. A minor product (Ib), shown to be formed in less than one-tenth the yield of Ia was a stereoisomer of Ia which melted at 124° and depressed the melting point of Ia. This formulation for Ib was supported by its carbon-hydrogen analysis and its infrared spectrum, which was identical with that of Ia below 7 microns but markedly different above this wavelength.

The second synthesis designed to confirm the structural assignment given to Ia began with the Diels-Alder reaction of benzalacetophenone with butadiene to yield 1-phenyl-2-benzoylcyclohex-4-ene (III) (5). This compound was then hydrogenated to 1-phenyl-2-benzoylcyclohexane. The sole isolable product was the

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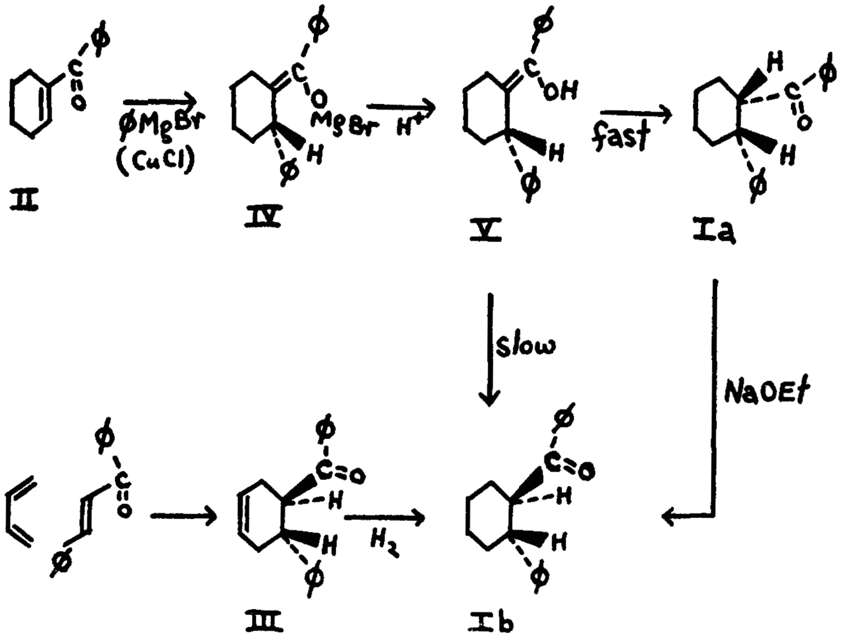
[1] This would be formed by *beta* elimination from the initially formed magnesium alkoxide of 2-benzoylcyclohexanol.

higher-melting isomer (Ib) which was the minor product of the Grignard reaction.

The *cis-trans* relationship of Ia to Ib was demonstrated by the conversion of Ia to Ib by sodium ethoxide in ethanol. The solid isomerization product was obtained in theoretical yield and was shown by melting point, mixture melting point, and infrared spectrum to be pure Ib. This evidence, which indicated that Ia was the *cis*-isomer of 1-phenyl-2-benzoylcyclohexane while Ib was the *trans*-isomer, was supported by the diene synthesis of Ib. The Alder rule (6) would predict that ordinary benzalacetophenone, m.p. 57°, which is known to be *trans* (7), must lead to the *trans*-isomer of III which on hydrogenation would yield *trans*-I.[2]



The formation in the Grignard synthesis of the less stable *cis*-1-phenyl-2-benzoylcyclohexane (Ia) in preference to the *trans*-isomer (Ib) is of great interest. It is clear that the magnesium enolate (IV) arising from 1,4-addition could conceivably lead to either stereoisomer, Ia or Ib. That Ia is in fact formed means that of the two possible ketonization processes[3] occurring on acidifying IV the process leading to the less stable ketonic product (Ia) has the greater rate. The preferred formation of Ia certainly is not equilibrium controlled, since it has been shown that Ib is the thermodynamically more stable isomer.

In order to test the hypothesis that the enol (V) reacts more rapidly to give

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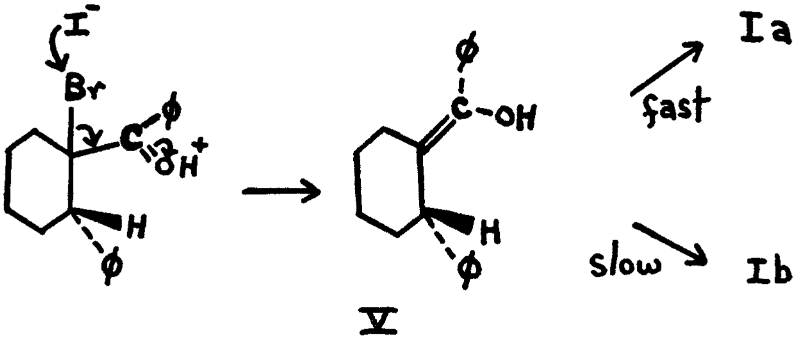
[2] In view of the reported lability of *cis*-benzalacetophenone (7) it is unlikely that under the reaction conditions any of this isomer could survive long enough to react to form *cis*-adduct.

[3] It seems likely that protopic attack on oxygen is faster than on carbon; thus the enol V is a likely intermediate. The argument, however, does not depend on this assumption.

the less stable ketonic product (Ia) further experiments were devised. Bromination of Ia in acetic acid led to 1-phenyl-2-bromo-2-benzoylcyclohexane (VI). Under similar conditions Ib was recovered unreacted. Repeated experiments indicated that whereas Ia was brominated readily under very mild conditions, Ib was extremely resistant to bromination. Since it is very likely that the ease of bromination depends on the rates of enolization of Ia and Ib (8), the marked difference in behavior can be ascribed to a much greater rate of enolization of Ia compared with Ib.[4]

With the object of again obtaining the enol (V) as an intermediate, 1-phenyl-2-bromo-2-benzoylcyclohexane (VI) was treated in acetone with hydriodic acid at room temperature. In an unusually facile reaction iodine was liberated with formation of the debrominated ketone. The sole product isolated, and this in virtually quantitative yield, was *cis*-1-phenyl-2-benzoylcyclohexane (Ia). This reaction may be formulated as follows:[5]



Hence, a second experiment supports the ketonization of the enol (V) to yield the less stable ketonic product (Ia).

Still to be considered are the explanation of the phenomenon and its generality. Table I lists reactions described in the literature which involve enol intermediates and lead to the less stable of two possible ketonized products.[6]

It would appear that the general phenomenon whereby exocyclic enols ketonize to yield the less stable of two isomers has escaped notice. *In addition to pointing out this generality the author wishes to postulate that this reaction course is determined by preferential prototopic attack on the less hindered side of the enol double bond.* Such an explanation has been advanced previously without elaboration by Jacobs and Florsheim (14) to account for case number five of Table I. These authors, however, were apparently unaware of the generality of the phenomenon in the cyclopentane series and its applicability to the cyclohexane cases.

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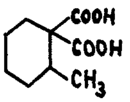
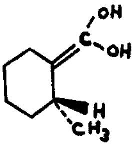
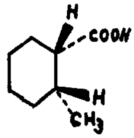
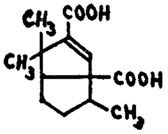
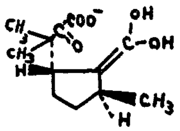
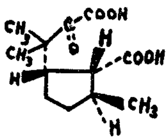
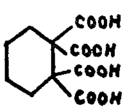
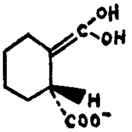
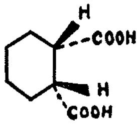
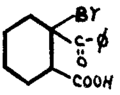
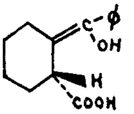
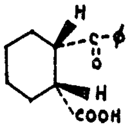
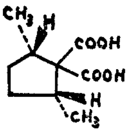
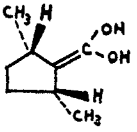
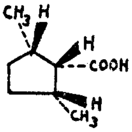
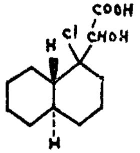
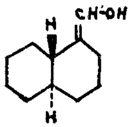
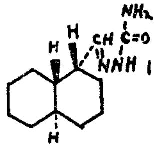
[4] A greater tendency of Ia to enolize is probably due both to its greater free energy content, observed in the equilibration experiment, and also to a better transition state between ketone and enol, supported by the ketonization experiments.

[5] This is the reverse reaction of halogenation and therefore follows the same reaction route. As an alternative possibility a six-membered ring may be written in the formation of V. The absence of any Ib is apparently due to a lack of equilibration under these conditions.

[6] There are many cases to be found in the literature where the more stable isomer is obtained under drastic conditions conducive to equilibration.

TABLE I

Reactant	Conditions	Enol Intermediate	Product	Ref.
	distillation			9, 10
	mildly alkaline $KMnO_4$			11
	30% alc. KOH			12
	HI in Acetone			13
	190–230°			14
	Pyridine $NH_2NH{-}\underset{\underset{O}{\|}}{C}{-}NH_2$			15

A priori, attack of a proton donor on a double bond exocyclic to a five-membered ring might occur from either side of the ring; the two transition states corresponding to these possibilities are pictured on p. 553 (VIIa leading to *cis*-product and VIIb leading to *trans*-product). Actually VIIa is the favored transition state, since here there is less interference by the ring substituent (R—) with the proton donor (HA).

For enols of the cyclohexane series the situation is slightly different. Study of molecular models indicates that of the two possible approaches to the enol carbon undergoing attack by the proton donor (transition states VIIIa and VIIIb), one (VIIIa) is much less hindered than the other (VIIIb) due to severe hindrance by axial hydrogens in the latter case.[7] Where a bulky ring substituent (R—) is

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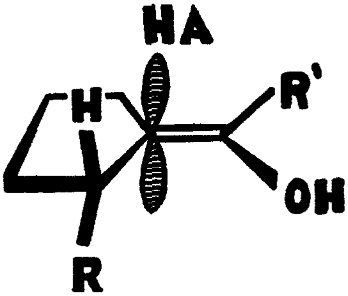
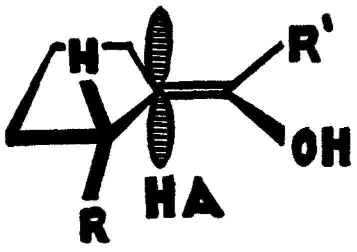
[7] Only the pertinent axial hydrogen atoms are indicated. No convenient terminology is available for the two types of attack (VIIIa and VIIIb); the writer would like to suggest the

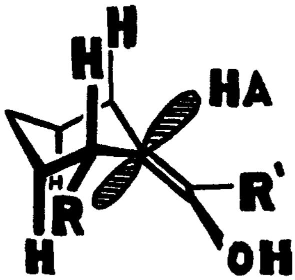


VIIa

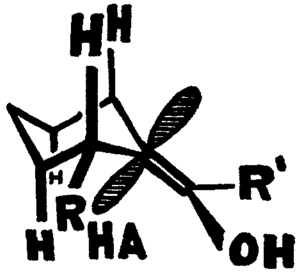


VIIb

present this occupies the more favorable equitorial position as shown for VIIIa and VIIIb.



VIIIa



VIIIb

It is interesting that the present evidence supports a transition state for ketonization (and hence enolization) whose geometry is a better approximation of the enol than of the corresponding ketone. Were the carbon atom undergoing protonation actually tetrahedral instead of sp^2 hybridized as suggested in the above models for the transition state, then this transition state would resemble the final product not only in geometry but also energetically.[8] This is seen experimentally not to be the case. Figure 1 summarizes the energy relationships which account for the kinetically determined formation of the less stable ketonic isomer under nonequilibrating conditions.

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term ("exo attack" for VIIIa and "endo attack" for VIIIb. The perferred "exo attack" has analogy in the acid-catalyzed hydrogenation of 2-substituted cyclohexanones to yield *cis*-2-substituted cyclohexanols.

[8] If the proton donor were extremely large, for example, due to very extensive solvation, this might not be true.

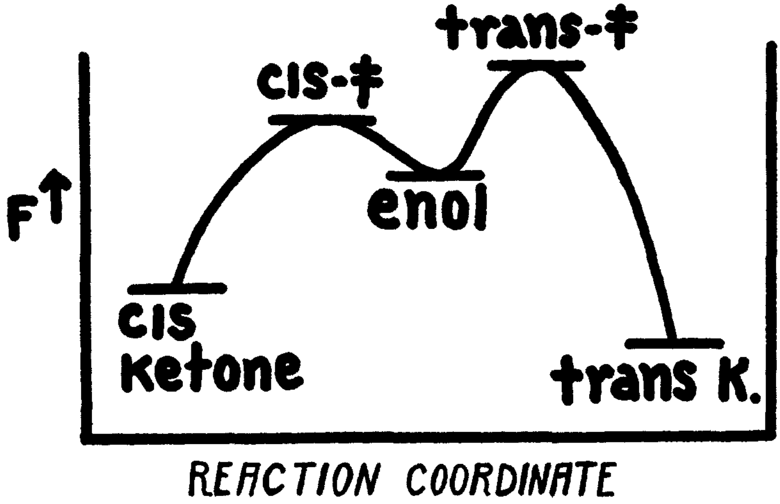

Fig. 1

Further work elaborating and extending the theme presented in this paper is being pursued in view of the many interesting consequences, synthetic and theoretical.[9]

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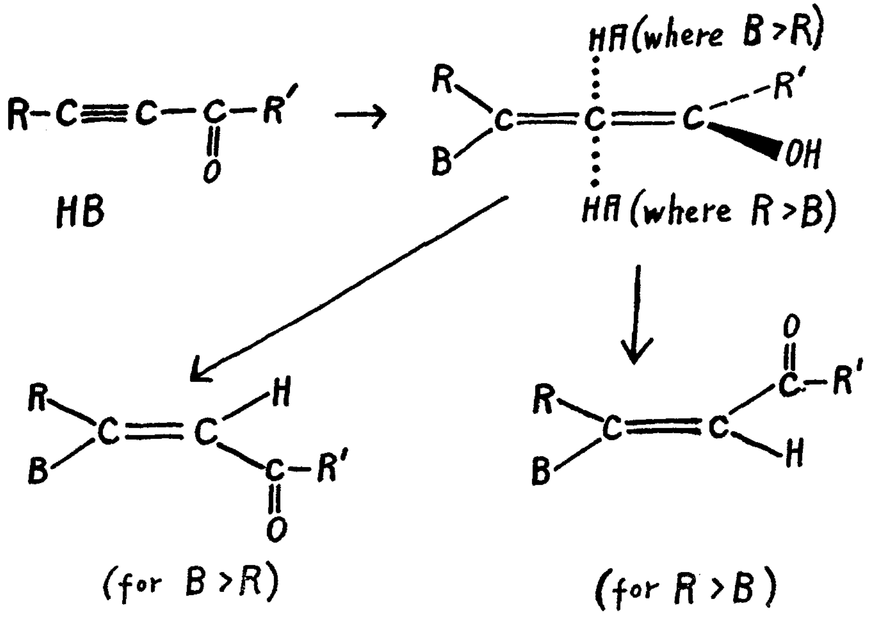
[9] Also of interest is a consideration of the stereochemistry of nucleophilic addition reactions of α,β-acetylenic carbonyl compounds, since the geometry of the addition product is most likely determined by the ketonization of an intermediate enol. It is apparent that an application of the principle set forth in this paper would suggest the kinetically favored formation of the less stable of two ethylenic ketones; in some cases this corresponds to *cis*-addition and in others to *trans*-addition. Sufficient evidence from the literature to test this point is not available mainly because of complication by equilibration.



EXPERIMENTAL[10]

Benzoylcyclohexene. This was prepared from 58 ml. of benzoyl chloride, 53 ml. of cyclohexene, and 66.5 g. of anhydrous aluminum chloride in 300 ml. of carbon disulfide essentially as described by Fuson (2) except that the reaction was run at −5° for 1½ hours. After treatment with alcoholic potassium hydroxide as described by Fuson the crude product weighed 56.0 g. Infrared analysis of this material showed the presence of two ketones, one absorbing at 5.98μ and the other at 6.09μ. This crude oil was subjected to fractionation in a four-foot Piros Glover spinning band column. The fractions b.p. 147–150° at 5.5 mm. n^{25} 1.5522 absorbed at 5.98μ in the infrared; the fractions b.p. 154–157° at 5.5 mm. n^{25} 1.5620 weighed 22.1 g. and absorbed at 6.09μ. This material yielded a semicarbazone melting at 209° [reported (16) 210°] and was benzoylcyclohexene. When runs were made at higher temperatures and with longer reaction times the yield of the conjugated ketonic product was reduced with an increase in the yield of nonconjugated product.

Benzoylcyclohexene was prepared by an independent route as follows: Cyclohexenyllithium was prepared from 14.5 g. of chlorocyclohexene and 1.78 g. of lithium in 250 ml. of ether essentially as described by Braude (3). To this solution in a 500-ml. three-necked flask equipped with a reflux condenser, dropping-funnel, and glass blade stirrer was added in small portions 16.6 g. of lithium benzoate which had been dried to constant weight. The mixture was stirred and refluxed for ten hours. Then 100 ml. of water was added dropwise and the ether phase was separated. The aqueous phase was ether-extracted and the combined ether solution was dried over sodium sulfate. Concentration *in vacuo* left 10.0 g. of yellow oil amost all of which distilled at 150–153° at 5.5 mm. (Claisen flask). The infrared spectrum of this material was identical with the product obtained above by the first synthesis.

cis-1-Phenyl-2-benzoylcyclohexane (Ia). To 0.2 mole of phenylmagnesium bromide in 75 ml. of ether in the usual apparatus (200 ml.) was added 0.2 g. of cuprous chloride. The mixture was stirred for 15 minutes. Then addition of 18.6 g. of benzoylcyclohexene in 30 ml. of anhydrous ether was begun with stirring. Gentle reflux was maintained by the heat of the reaction. The addition required 35 minutes after which time the mixture was refluxed for an additional half-hour. The reaction mixture was poured onto an ice-ammonium chloride mixture. The combined ether extracts were dried over sodium sulfate and concentrated *in vacuo* to leave an oil which crystallized. This was taken up in a hot benzene-ligroin (b.p. 86–100°). On cooling 7.4 g. of essentially pure Ia, m.p. 114–115°, separated. From the filtrate there was obtained a second crop of 5.0 g. of Ia, m.p. 111–113°. The oily filtrate would not crystallize and was subjected to chromatography on alumina eluting first with ligroin (b.p. 86–100°) and then with increasing amounts of benzene. Infrared analysis showed that only the first fraction, which weighed 1.2 g., contained product absorbing at 5.97μ and that this was a mixture of Ia and its stereoisomer Ib. As an alternative method of working up the oily residue after isolation of Ia by crystallization the oil was subjected to distillation. The fraction b.p. 151–156° at 0.01 mm. (bath temp. 189–200°) contained the product. On treatment with hexane 1.3 g. of slightly impure Ia, m.p. 110–112°, was obtained. The filtrate yielded a very minor amount of Ib. Recrystallization of Ia brought the melting point to 116–117°. The infrared spectrum contained a carbonyl absorption band at 5.97μ.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.32; H, 7.63.
Found: C, 86.71; H, 7.40.

trans-1-Phenyl-2-benzoylcyclohex-4-ene (III). To a 400-ml. steel hydrogenation bomb were added 20 g. of benzalacetophenone (Eastman, m.p. 55–57°) and 0.05 g. of hydroquinone. The bomb and contents were cooled to −5° and 16 ml. of butadiene was added. The bomb was closed and heated to 140° for ten hours. The crystalline material obtained was recrystallized from ethanol to yield 19 g., m.p. 103.0–103.5° [Reported (5) m.p. 101.5°].

trans-1-Phenyl-2-benzoylcyclohexane (Ib). Hydrogenation of 7.0 g. of *trans*-1-phenyl-2-

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[10] All melting points were taken with a Fischer-Johns block checked with pure compounds of known melting point.

benzoylcyclohex-4-ene in a mixture of 50 ml. of ethanol and 50 ml. of ethyl acetate with 50 mg. of platinum oxide catalyst yielded 6.5 g. of Ib, m.p. 119–120°. Recrystallization from ethanol brought the melting point to 124.0–124.5°. This product depressed the melting point of *cis*-1-phenyl-2-benzoylcyclohexane to 95°. The infrared spectrum of Ib was identical with that of Ia below 7μ but showed many differences above this wavelength.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.32; H, 7.63.
Found: C, 86.33; H, 7.24.

Conversion of cis-1-phenyl-2-benzoylcyclohexane (Ia) *to trans-1-phenyl-2-benzoylcyclohexane.* Compound Ia (500 mg.) was added to a sodium ethoxide solution prepared from 50 ml. of ethanol and 100 mg. of sodium. The clear solution was allowed to stand at room temperature for 20 hours. The mixture then was treated with 100 ml. of water and filtered. The precipitate was washed with water. After drying, the product weighed 498 mg., melted at 122–123°, and did not depress the melting point of pure *trans* ketone (Ib). The infrared spectrum of the product, without any purification, was identical with that of pure Ib.

1-Phenyl-2-bromo-2-benzoylcyclohexane (VI). To a 100-ml. round bottom flask fitted with a reflux condenser and thermometer were added 60 ml. of acetic acid, 1.0 g. of *cis*-1-phenyl-2-benzoylcyclohexane (Ia), and 0.80 g. of bromine. The reaction mixture was kept at 80° for ten minutes by which time the deep bromine color had changed to a light orange. The mixture was cooled and poured onto cracked ice and the solid was filtered and washed with water. This material weighed 1.3 g. and melted at 88–93°. Recrystallization from ligroin (b.p. 86–100°) gave 0.89 g. of prisms, m.p. 98–99°. The filtrate yielded 0.20 gram additional, m.p. 97–99°. The infrared spectrum of VI below seven microns was very similar to the spectra of Ia and Ib; above this wavelength there were distinct differences. For example, VI had two absorption bands near 8μ while Ia had only one. Also, VI gave an instantaneous reaction with HI in acetone with the liberation of iodine.

Anal. Calc'd for $C_{19}H_{19}BrO$: C, 66.48; H, 5.58.
Found: C, 66.84; H, 5.65.

Attempted bromination of trans-1-phenyl-2-benzoylcyclohexane. Under the same conditions found successful in the bromination of the *cis*-isomer (Ia) bromine was consumed extremely slowly. When the temperature was raised above 100° the bromine reacted but Ib was recovered unbrominated, acetic acid apparently competing successfully. When 1.00 g. of Ib and 0.64 g. of bromine were refluxed in only 10 ml. of acetic acid for two hours an oil which would not crystallize was obtained. The infrared spectrum of this oil suggested that it contained the same bromo compound obtained from Ia; however, additional absorption bands not found in any of the compounds of this series were also noted to be present.

Debromination of 1-phenyl-2-bromo-2-benzoylcyclohexane (VI) *with hydriodic acid.* To 30 mg. of VI in 1.0 ml. of acetone was added 0.1 ml. of Baker's 47% hydriodic acid; there was an immediate color of iodine. After three minutes 5 ml. of water was added to give a precipitate, the iodine being destroyed by the addition of a small quantity of sodium thiosulfate. The white solid was filtered and dried; this weighed 22.4 mg. and melted at 115–116°. There was no depression on melting a mixture of this material with pure *cis*-1-phenyl-2-benzoylcyclohexane (Ia), while a mixture with pure Ib had a depressed melting point.

Acknowledgment. The author wishes to thank Miss H. Beck for the carbon-hydrogen analyses.

SUMMARY

It is suggested that the stereochemistry of the ketonization reaction of enols is determined by a preferential attack of a proton donor on the less hindered side of the enol double bond. Examples from the literature are cited to support this hypothesis and new experimental evidence is described.

EVANSTON, ILLINOIS

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