

scribed oxidations. The above carbinol (2 g.) was oxidized to yield 450 mg. (22%) of the desired aldehyde, m.p. 102–103°, $[\alpha]_D^{25} + 183.1 \pm 2.3^\circ$ (*c* 1.016, CHCl_3), infrared 1725 cm^{-1} ($\text{C}=\text{O}$), λ_{max} 297 $\text{m}\mu$ (ϵ 96.5, dioxane); R.D. in dioxane (*c* 1.115), 23°: $(\alpha)_{600} - 210^\circ$, $(\alpha)_{589} - 219^\circ$, $(\alpha)_{521} - 2614^\circ$, $(\alpha)_{277} + 3100^\circ$, $(\alpha)_{273} + 2820^\circ$.

Due to its instability an elemental analysis was not obtained. The aldehyde was reduced by lithium aluminum hydride to the corresponding alcohol, the m.p., mixed m.p. and infrared spectrum of which were identical with those of an authentic sample.

Addition of Diphenyldiazomethane to (–)-Menthyl Acrylate.—Diphenyldiazomethane (1.48 g., 0.0076 mole) dissolved in petroleum ether (30–60°) was added slowly to 1.61 g. (0.0076 mole) of (–)-menthyl acrylate at 110°. Immediate decoloration and nitrogen evolution occurred. The residual oil was dissolved in benzene, washed with hydrochloric acid, 5% sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was removed and in order to avoid any possibility of resolution of the diastereomers isolation at this point was avoided.

This viscous oil was saponified by refluxing with a solution of 0.85 g. of potassium hydroxide in 60 ml. of ethylene glycol for 52 hours. The reaction mixture was cooled, diluted with water, and extracted with ether. The neutral ether extract was dried and the ether evaporated. The residue was examined in the infrared and showed less than 0.1% of carbonyl absorption at 1720 cm^{-1} .

The aqueous layer was acidified to yield 1.1 g. (60%) of 2,2-diphenylcyclopropanecarboxylic acid, m.p. 163–164.5°, $[\alpha]_D^{25} - 4.7^\circ$ (CHCl_3), the infrared spectrum of which (CCl_4) was identical in all respects with that of an authentic sample.

Addition of Diphenyldiazomethane to (–)-Menthyl Methacrylate.—(–)-Menthyl methacrylate (2.1 g., 0.009 mole)

was treated with an excess of diphenyldiazomethane as described above. The viscous residual oil was refluxed with a solution of 10.0 g. of potassium hydroxide in 40 ml. of ethylene glycol for 60 hours. The reaction mixture was cooled to room temperature, diluted with water, extracted with ether and dried over anhydrous sodium sulfate. The residue from the ether extract showed no carbonyl absorption at 1720 cm^{-1} in the infrared.

The aqueous layer was acidified and the crude acid collected by filtration and dried to yield 1.82 g. (77.5%) of II. The crude acid was dissolved in ether and extracted with aqueous sodium bicarbonate. The aqueous solution was treated with charcoal, filtered and reacidified to yield 1.71 g. (74%) of the acid, m.p. 96–98°, $[\alpha]_D^{25} + 3.7^\circ$ (CHCl_3), the infrared spectrum of which (CCl_4) was identical in all respects with that of an authentic sample.

Saponification of (–)-Menthyl (±)-2,2-Diphenylcyclopropane-carboxylate.—To 0.5 g. (0.021 mole) of the acid (±)-I was added 6.0 g. (0.05 mole) of thionyl chloride and the reaction mixture was allowed to stand at room temperature for 8 hours. The excess thionyl chloride was removed *in vacuo* and the residue added to a solution of 4.0 g. (0.03 mole) of (–)-menthol in dry benzene. One equivalent of pyridine (6.0 ml.) was added; the reaction mixture was stirred for 1.5 hours, poured onto ice, and extracted with ether. The ether extract was washed with aqueous sodium hydroxide, water until neutral, and dried. Removal of the ether yielded 6.5 g. (82%) of product.

The ester (4.2 g.), without purification, was added to 6.2 g. of potassium hydroxide in 50 ml. of ethylene glycol and the solution heated to reflux for 48 hours. The reaction mixture was cooled, diluted with water and extracted with ether. The aqueous layer was acidified, yielding 2.1 g. (82%) of I, m.p. 170–171° and $[\alpha]_D^{25} 0^\circ$.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

Carbonyl Reactions. XII. The Kinetics and Mechanism of the *cis* to *trans* Isomerization of Substituted Chalcones^{1,2}

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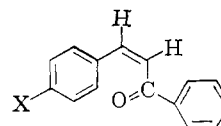
The rate and mechanism for the acid-catalyzed isomerization of substituted benzalacetophenones (chalcones) have been studied. The behavior of *cis*-4-methoxychalcone (II) differs from that of *cis*-chalcone (I), *cis*-4-chlorochalcone and *cis*-4-nitrochalcone. It is proposed that a new mechanism intervenes for the isomerization of II, involving direct rotation about the $\text{C}_\alpha\text{--C}_\beta$ bond in the salt of II. Arguments supporting this mechanism are presented, and deuterium isotope studies are reported which are consistent with this mechanism.

Introduction

In recent reports^{4,5} we have shown that the acid-catalyzed isomerization of *cis*-benzalacetophenone (I) proceeds *via* a rate-determining addition of water to the oxonium salt of I, leading to the formation of the enol of the β -hydroxyketone. It was also demonstrated that the rate of ketonization of the enol is slower than the loss of the elements of water to give *trans*-chalcone. The related studies⁶ of the mechanism of the dehydration of β -aryl- β -hydroxyketones provided evidence that the normal mechanism involved at the rate-determining process was the enolization step. However, in the

case of 4-(*p*-methoxyphenyl)-4-hydroxy-2-butanone, the normally operating mechanism is supplanted by a new mechanism. This new mechanism involves the benzylic carbonium ion in the rate-determining sequence, rather than the enol.

It thus seemed of value to study the acid-catalyzed isomerization of a group of substituted chalcones, in order to determine whether there was also a change in mechanism within this group of compounds and with this type of reaction as well. With this purpose in mind, we have examined the kinetics of the isomerization of *cis*-4-methoxychalcone (II), *cis*-4-chlorochalcone (III) and *cis*-4-nitrochalcone (IV). These compounds were chosen



I, X = -H; III, X = -Cl
II, X = -OCH₃; IV, X = -NO₂

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(2) Presented in part at the 8th Conference on Reaction Mechanisms, Princeton, N. J., September 6–10, 1960.

(3) National Institutes of Health Postdoctoral Fellow, 1959–1961.

(4) D. S. Noyce, W. A. Pryor and P. A. King, *J. Am. Chem. Soc.*, **81**, 5423 (1959).

(5) D. S. Noyce, G. L. Woo and M. J. Jorgensen, *ibid.*, **83**, 1160 (1961).

(6) D. S. Noyce and W. L. Reed, *ibid.*, **80**, 5539 (1958).

to give a wide range of electronic effects in the extended conjugated system.

Experimental

Purified dioxane⁷ was used in all experiments. Sulfuric acid-*d*₂ was prepared as described previously.⁵

Preparation of *cis*-4-Methoxychalcone (II).—A procedure similar to that used by Black and Lutz⁸ was employed for the preparation of *cis*-4-methoxybenzalacetophenone. The benzene solution of the *trans* isomer was irradiated with a 275-watt sunlamp for 1 week. After several crops of the *trans* isomer were obtained along with insoluble polymeric oils, further cooling of the isoöctane mother liquors in the deep-freeze afforded the *cis* isomer as deep yellow rosettes; a total of 350 mg. was obtained from 10 g. of the *trans* isomer. Recrystallization from hexane with protection from light afforded pure *cis*-*p*-methoxybenzalacetophenone, m.p. 32.5–33.0° (lit.⁸ 33–33.5°); $\lambda_{\text{max}}^{\text{EtOH}}$ 252 m μ (ϵ 19,000), 340 m μ (ϵ 8,800) [lit.⁸ $\lambda_{\text{max}}^{\text{EtOH}}$ 252 m μ (ϵ 17,760), 350 m μ (ϵ 10,810)].

Preparation of *cis*-4-Nitrochalcone (IV).—A procedure similar to that used by Black and Lutz⁹ was employed. The irradiation was carried out by means of a 275-watt sunlamp over a period of 20 hours. The *cis* isomer was formed in yields over 50%, as estimated spectrally, but isolation of the *cis* isomer in a pure state was made difficult by the similarity in solubility properties of both isomers. Crystallization from benzene–hexane afforded a mixture containing 10–20% of the *trans* isomer. After repeated crystallization, under protection from light, a small crop of the *cis* isomer, sufficient for the kinetic study, was obtained as flat, pale yellow needles, m.p. 97–98° (lit.⁹ 98–98.5°), ultraviolet spectrum as reported.⁸

Preparation of *cis*-4-Chlorochalcone (III).—The preceding procedure was used for this preparation. Irradiation, after 20 hours, afforded more than 50% of the *cis* isomer, but isolation of a pure sample of the *cis* isomer met with the same difficulty as in the case of *cis*-*p*-nitrobenzalacetophenone. Repeated crystallizations from benzene–hexane, under protection from light, afforded crops which were successively richer in the *cis* isomer. By recrystallizing late crops from the same solvent pair, a small amount of pure *cis*-4-chlorochalcone was obtained as deep yellow rosettes, m.p. 77–78°; $\lambda_{\text{max}}^{\text{EtOH}}$ 248 m μ (ϵ 15,200), 295 m μ (ϵ 9,250).

Anal. Calcd. for C₁₅H₁₁OCl: C, 74.23; H, 4.57. Found: C, 74.43; H, 4.84.

Preparation of *trans*-*p*-Methoxybenzalacetophenone- α -*d*.—A solution of 2.50 g. (0.021 mole) of acetophenone- α -*d*₃ in 7.0 ml. of anhydrous dioxane was added to a stirred cold solution of sodium deuterioxide, prepared by dissolving 0.62 g. (0.027 mole) of sodium in 10 ml. of deuterium oxide. Immediately afterward 2.80 g. (0.021 mole) of freshly distilled anisaldehyde was added. After stirring at room temperature for 20 hours, the layers were separated, the aqueous layer extracted with ether and the combined organic layers dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded 6.20 g. of pale yellow oil. Crystallization from aqueous ethanol afforded 1.10 g. of pale yellow plates, m.p. 74.5–75.3°, after two additional recrystallizations. The infrared spectrum (4% in CCl₄) showed bands at 1590, 1330, 1250, 1085, 1030, 930, 928 and 860 cm.⁻¹, absent in ordinary *p*-methoxybenzalacetophenone, and the lack of bands at 1630, 1340, 1020 and 985 cm.⁻¹ which are present in ordinary *p*-methoxybenzalacetophenone.

The Isomerization of *cis*-*p*-Methoxybenzalacetophenone in Sulfuric Acid-*d*₂-Dioxane.—To a solution of 11.32 g. of 5.68 *M* sulfuric acid-*d*₂ (*d*₂¹⁴ 1.402) in 12 ml. of anhydrous dioxane was added 0.20 g. of *cis*-*p*-methoxybenzalacetophenone. The solution was maintained at 50° for 30 minutes, cooled to room temperature and thoroughly extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and the solvent removed *in vacuo*, affording a yellow oil which was crystallized from ethanol to give 0.092 g. (46%) of *trans*-*p*-methoxybenzalacetophenone, m.p. 73.8–74.5°. The infrared spectrum of this material was completely superimposable upon the spectrum of undeuterated *trans*-*p*-methoxybenzalacetophenone.

(7) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

(8) W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, **77**, 5134 (1955).

(9) W. B. Black and R. E. Lutz, *ibid.*, **75**, 5990 (1953).

Under similar treatment, *trans*-*p*-methoxybenzalacetophenone- α -*d* did not lose its deuterium label but was recovered unchanged as shown by infrared spectral comparison with starting material.

Kinetic Measurements.—For the preparation of kinetic solutions, an exactly weighed quantity of the desired *cis* compound was dissolved in purified dioxane to give a solution 10⁻⁴ molar. A 5-ml. aliquot of this dioxane solution was diluted to volume in a 100-ml. volumetric flask with sulfuric acid of the desired strength. For kinetic runs in 10-cm. cells a dioxane solution containing 1/10 of the above concentration of the *cis* isomer was employed. Solutions for kinetic runs in sulfuric acid-*d*₂ were prepared gravimetrically in 10-ml. volumetric flasks to give compositions identical to those of ordinary runs. Blank solutions were prepared for each run in an identical manner to the kinetic solution and were used to compensate for solvent absorption. They were found to be stable for periods as long as the slowest kinetic run.

The acidity of the kinetic solutions was calculated by correcting the original acid concentration for the 5% volume replacement by dioxane. This correction gave acidity values in 1% agreement with those determined by direct titration of the kinetic solution over a range of acidities.

All kinetic measurements were made by reading the optical density of the kinetic solution with a Beckman DU spectrophotometer. Readings were made on one sample, placed in a thermostated cell compartment, and were continued for 80–90% reaction. Since strong medium effects on the position of the long wave length maximum were observed, the wave length chosen depended on the acidity of the medium. Infinity readings, taken after 10 half-lives, agreed with calculated values at the same acidity and were stable or showed only very slight decrease over an additional period of ten half-lives. In the slow runs with *cis*-*p*-nitrobenzalacetophenone, calculated end-points were used. The spectrum at total reaction as determined for a number of kinetic runs was identical with the ultraviolet spectrum of a solution of the pure *trans* isomer in the same acid medium.

Rate constants were calculated by analytical methods.

***H*₀ Measurements.**—The indicators 4-chloro-2-nitroaniline, 2,4-dichloro-6-nitroaniline, *N,N*-dimethyl-2,4,6-trinitroaniline and 4-nitrodiphenylamine were obtained from Aldrich Chemical Co.; they were checked by melting points and recrystallized when not adequately pure. The indicators *p*-nitroaniline, *o*-nitroaniline and 2,4-dinitroaniline were commercial samples purified by chromatography or repeated recrystallizations to constant melting point.

The *pK*_a values of indicators used are those of Paul and Long.¹⁰

The method used for the preparation of individual solutions for spectral measurement was similar to that used for the preparation of kinetic solutions. The necessary amount of the indicator, giving concentrations of the order of 10⁻⁴ to 10⁻⁵ *M* was accurately weighed out for each individual solution, dissolved in 5 cc. of dioxane and diluted to a volume of 100 ml. with water or the requisite strength of sulfuric acid. Measurements were taken with a Beckman DU spectrophotometer when the long wave length maximum was located below 400 m μ and with a Cary model 14 *M* spectrophotometer when this maximum appeared above 400 m μ . Agreement was demonstrated between both methods of measurement. Precise temperature control was not maintained; all measurements were made at 23 ± 2°.

The reference extinction coefficients for the indicators were obtained from measurements in aqueous 5% dioxane solutions for the more basic indicators. For the less basic indicators, the reference extinction coefficient for the basic form of the indicator was determined from measurement in 5% dioxane–sulfuric acid solutions of *H*₀ value two units below the *pK*_a of the indicator. This method minimizes difficulties caused by the medium shift upon position of the maximum.

Indicator ratios are average values of individual ratios calculated from extinction coefficients at four or five wave lengths across the long wave length maximum.¹¹ Indicators used at low acidities gave good results with only a small

(10) M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

(11) Cf. C. A. Bunton, J. B. Ley, A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 2327 (1957).

uncertainty by this method. For 4-nitrodiphenylamine¹² and indicators used at relatively high acidities¹³ substantial medium effects upon the position of the long wave length maximum were observed. For these compounds a modified procedure was used. By comparing the extinction coefficients of each maximum, constant indicator ratios were obtained, and the average of these was used. This method can be reduced to the procedure in which lateral displacements are made after determining the isobestic point; they give identical results.

Results

Choice of Solvent System.—The extremely limited solubility in water of the compounds which we desired to study dictated the use of a mixed solvent system. It is clear from several recent studies^{4,11,15} that any investigation of an acid-catalyzed reaction should be carried out in a mixed solvent as nearly aqueous as feasible. To avoid any possible complications with competition between water and the other component of a mixed solvent, e.g., ethanol or acetic acid, we have chosen to use dioxane as the cosolvent. The choice of 5% dioxane–95% water for our studies was made for solubility reasons. Even so, it was necessary to use 10-cm. absorption cells for some of the kinetic measurements.

The acidity function, H_0 , in 5% dioxane is slightly more positive than in water up to 6 molar sulfuric acid. Above this concentration H_0 is more negative in the mixed solvent. The results of measurements from 0.2 to 10 M sulfuric acid are recorded in Table I.

TABLE I

| H_0 VALUES FOR SULFURIC ACID IN 5% DIOXANE–95% H ₂ O | | | |
|---|---------------------------------------|-------|--------------------|
| H ₂ SO ₄ , M | log [BH ⁺ /B] ^a | H_0 | ΔH_0^b |
| 0.219 | 0.36 ^c | 0.63 | –0.13 |
| .500 | 0.78 ^c | .21 | –.08 |
| .954 | 1.59 ^c | –.17 | –.08 |
| .954 | –0.11 ^d | –.18 | –.09 |
| 1.65 | .30 ^d | –.59 | –.07 |
| 1.92 | .43 ^d | –.72 | –.09 |
| 2.56 | .01 ^e | –1.04 | –.11 |
| 3.36 | .39 ^e | –1.42 | –.14 |
| 4.93 | –.31 ^f | –2.19 | –.07 |
| 5.91 | .24 ^f | –2.74 | –.01 |
| 6.48 | –.15 ^g | –3.17 | + .16 ⁱ |
| 7.32 | .28 ^g | –3.60 | + .10 |
| 7.65 | .51 ^g | –3.83 | + .13 |
| 9.32 | .29 ^h | –4.82 | + .16 |
| 10.52 | .64 ⁱ | –5.42 | + .30 |

^a Ionization ratio, as given by Paul and Long.¹⁰ ^b H_0 in aqueous sulfuric acid¹⁰ – H_0 in 5% dioxane–95% H₂O. ^c Indicator *p*-nitroaniline, pK_a 0.99.¹⁰ ^d Indicator *o*-nitroaniline, pK_a –0.29.¹⁰ ^e Indicator 4-chloro-2-nitroaniline, pK_a –1.03.¹⁰ ^f Indicator *p*-nitrodiphenylamine, pK_a –2.50.¹⁰ ^g Indicator 2,4-dichloro-6-nitroaniline, pK_a –3.32¹⁰ [–3.61,¹² –3.16¹⁶]. ^h Indicator 2,4-dinitroaniline, pK_a –4.53¹⁰ (–4.42¹⁶). ⁱ N,N-dimethyl-2,4,6-trinitroaniline, pK_a = –4.81.¹⁰ ^j Protonation of dioxane (pK_a –2.92¹⁷) is significant above this acidity, possibly causing this change in sign of ΔH_0 .

(12) K. N. Bascombe and R. P. Bell, *J. Chem. Soc.*, 1096 (1959), have made a detailed study of the medium effects on this indicator and the consequence on pK_a and H_0 values.

(13) Strong medium shifts and a breakdown of parallelism with other indicators have been observed to be largest in the 60–80% sulfuric acid region.¹⁴

(14) L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, **54**, 2721 (1932).

(15) D. P. N. Satchell, *J. Chem. Soc.*, 2878 (1957).

(16) E. Högfeldt and J. Bigeleisen, *J. Am. Chem. Soc.*, **82**, 15 (1960).

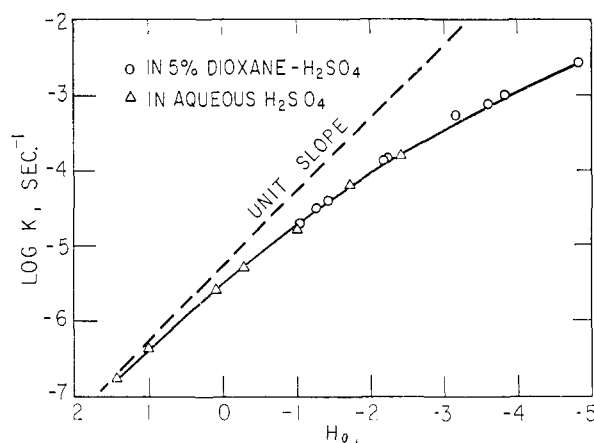


Fig. 1.—Rate of isomerization of *cis*-chalcone at 25.00°.

Isomerization of *cis*-Chalcone (I).—The rate of isomerization of *cis*-chalcone in 5% dioxane–95% H₂O has been measured for purposes of comparison. The results are presented in Table II, with portions

TABLE II

| RATE OF ISOMERIZATION OF <i>cis</i> -BENZYLACETOPHENONE IN 5% DIOXANE–95% H ₂ O | | | |
|--|--------------------------|--------------------|-----------------|
| H ₂ SO ₄ , M | k , sec. ⁻¹ | H_0 | log k + H_0 |
| $T = 25.00^\circ$ | | | |
| 0.0322 ^a | 1.58×10^{-7} | 1.44 | –5.36 |
| .0959 ^a | 4.16×10^{-7} | 1.00 | –5.38 |
| .525 ^a | 2.50×10^{-6} | 0.08 | –5.52 |
| 1.086 ^a | 5.15×10^{-6} | –0.31 | –5.60 |
| 2.32 ^a | 1.83×10^{-5} | –1.01 | –5.75 |
| 2.56 | 2.07×10^{-5} | –1.04 | –5.72 |
| 3.06 | 3.15×10^{-5} | –1.26 ^b | –5.76 |
| 3.36 | 4.00×10^{-5} | –1.42 | –5.82 |
| 3.72 ^a | 6.41×10^{-5} | –1.72 | –5.91 |
| 4.93 | 1.36×10^{-4} | –2.19 | –6.06 |
| 5.08 | 1.40×10^{-4} | –2.25 ^b | –6.10 |
| 5.30 ^a | 1.56×10^{-4} | –2.41 | –6.22 |
| 6.48 | 5.50×10^{-4} | –3.17 | –6.43 |
| 7.32 | 7.90×10^{-4} | –3.60 | –6.70 |
| 7.65 | 1.04×10^{-3} | –3.83 | –6.81 |
| 9.32 | 2.83×10^{-3} | –4.82 | –7.37 |

$T = 45.00^\circ$

| | | | |
|---------------------|-----------------------|-------------------|-------|
| 0.0959 ^a | 2.97×10^{-6} | 1.00 | –4.53 |
| 0.525 ^a | 1.96×10^{-5} | 0.08 | –4.63 |
| 1.00 ^c | 3.30×10^{-5} | –.20 ^b | –4.68 |
| 1.086 ^a | 4.18×10^{-5} | –.31 | –4.69 |
| 2.56 | 1.46×10^{-4} | –1.04 | –4.87 |
| 3.36 ^c | 2.77×10^{-4} | –1.42 | –4.98 |
| 4.93 ^c | 9.43×10^{-4} | –2.19 | –5.21 |
| 5.30 ^a | 9.77×10^{-4} | –2.41 | –5.42 |

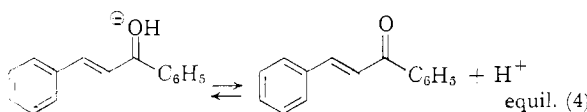
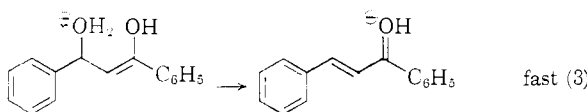
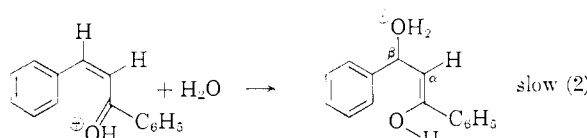
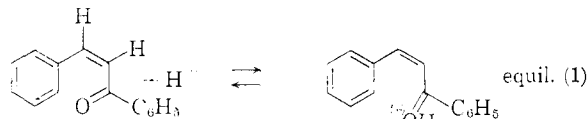
^a Calcd. from data in aqueous sulfuric acid, ref. 4. ^b H_0 values interpolated from a plot of values in Table I. ^c E_a = –18.3 kcal., ΔH^\ddagger = 17.7 kcal., ΔS^\ddagger = –23.7 e.u.

of the previously measured data⁴ which were measured in 99.8% H₂O–H₂O–0.2% ethanol. It is to be noted that in the region where measurements were made in both solvents, the data merge smoothly (Fig. 1). Hence we conclude that this solvent system is useful and easily compared with purely aqueous systems. It will also serve as a solvent in which the same criteria regarding con-

(17) E. M. Arnett and C. Y. Wu, *ibid.*, **82**, 4999 (1960).

clusions from acidity function dependence may be applied.

The mechanism of the isomerization of *cis*-chalcone involves the sequence shown in eq. 1-4, with the rate-determining step being the addition of water at the β -carbon of the salt of I (eq. 2), followed by rapid rotation about the C_α - C_β bond



(now single), and loss of water (step 3) to give the salt of *trans*-benzalacetophenone.

Isomerization of *cis*-4-Nitrochalcone (IV) and *cis*-4-Chlorochalcone (III).—The rate of isomerization of *cis*-4-nitrochalcone (IV) was measured at intervals from 1 to 10 *M* sulfuric acid; the results are given in Table III. Pertinent to the present discussion are the following facets of the data: the rate of isomerization of IV is uniformly slower (by nearly a factor of eight) than that of *cis*-chalcone (I) throughout the entire acidity range and the activation parameters are very similar for both I and IV.

TABLE III
RATE OF ISOMERIZATION OF *cis*-4-NITROCHALCONE IN 5%
DIOXANE-95% H₂O

| H ₂ SO ₄ , <i>M</i> | <i>k</i> , sec. ⁻¹ | <i>H</i> ₀ | log <i>k</i> + <i>H</i> ₀ |
|---|-------------------------------|-----------------------|--------------------------------------|
| <i>T</i> = 25.00° | | | |
| 4.93 | 1.90 × 10 ^{-5a,b} | -2.19 | -6.91 |
| 6.48 | 6.03 × 10 ⁻⁵ | -3.17 | -7.39 |
| | 5.95 × 10 ^{-5a} | | |
| 7.65 | 1.33 × 10 ⁻⁴ | -3.83 | -7.70 |
| | 1.33 × 10 ^{-4a} | | |
| 9.32 | 4.00 × 10 ⁻⁴ | -4.82 | -8.22 |
| 10.51 | 7.57 × 10 ⁻⁴ | -5.45 | -8.57 |
| <i>T</i> = 45.00° | | | |
| 1.00 ^c | 4.37 × 10 ^{-6a,b} | -0.20 | -5.56 |
| 4.93 | 1.34 × 10 ⁻⁴ | -2.19 | -7.06 |
| 6.48 ^c | 4.50 × 10 ⁻⁴ | -3.17 | -7.52 |

^a 10-cm. cells. ^b Calculated end-point used. ^c *E*_a = 19.0 kcal., ΔH^\ddagger = 18.4 kcal., ΔS^\ddagger = -25.5.

The rate of isomerization of *cis*-4-chlorochalcone (III) was also measured (Table IV), but over a more limited range of acidity. This region of acidity is more useful than a region of lower acidity, in showing distinctly the lack of direct proportion-

TABLE IV
RATE OF ISOMERIZATION OF *cis*-*p*-CHLOROBENZALACETO-
PHENONE IN 5% DIOXANE-95% H₂O

| H ₂ SO ₄ , <i>M</i> | <i>k</i> , sec. ⁻¹ | <i>H</i> ₀ | log <i>k</i> + <i>H</i> ₀ |
|---|-------------------------------|-----------------------|--------------------------------------|
| <i>T</i> = 25.00° | | | |
| 3.36 | 3.00 × 10 ^{-5a} | -1.42 | -5.94 |
| 4.95 | 9.17 × 10 ^{-5a} | -2.19 | -6.23 |
| 6.48 | 2.87 × 10 ^{-4a} | -3.17 | -6.71 |
| 7.65 | 7.22 × 10 ^{-4a} | -3.83 | -6.97 |
| 9.32 | 2.30 × 10 ⁻³ | -4.82 | -7.46 |

^a 10-cm. cells.

ality between the rate of isomerization and the acidity function.

Comparison of the data for *cis*-chalcone, *cis*-4-nitrochalcone and for *cis*-4-chlorochalcone shows very close similarities. All three compounds show a rate of isomerization which increases much more slowly with acidity than unit slope correlation with *H*₀ would predict. The plot of Fig. 1 shows the distinct downward curvature for the rate of isomerization of *cis*-chalcone. Such curvature has been associated^{4,6,18} with reactions requiring the intervention of water in the transition state. At the highest acidities where we have made measurements the slope is about 0.45 for I.¹⁹ For both III and IV similar slopes are obtained in the same acidity region, 0.55 for III and 0.50 for IV.

The similarities, both of rate-*H*₀ profile and of activation parameters, taken in conjunction with our previous studies^{4,5} on the mechanism of the isomerization of I, clearly indicate that I, III and IV are all undergoing isomerization by the same mechanism.

Isomerization of *cis*-4-Methoxychalcone (II).—The data for the rate of isomerization of *cis*-4-methoxychalcone (Table V) stands in striking

TABLE V
RATE OF ISOMERIZATION OF *cis*-*p*-METHOXYBENZALACETO-
PHENONE IN 5% DIOXANE-95% H₂O

| H ₂ SO ₄ , <i>M</i> | <i>k</i> , sec. ⁻¹ | <i>H</i> ₀ | log <i>k</i> + <i>H</i> ₀ |
|---|---------------------------------|-----------------------|--------------------------------------|
| <i>T</i> = 25.00° | | | |
| 0.219 | 9.60 × 10 ⁻⁶ | 0.63 | -4.39 |
| .500 | 2.53 × 10 ⁻⁵ | .21 | -4.39 |
| .602 | 3.06 × 10 ⁻⁵ | .12 ^a | -4.39 |
| .930 | 5.95 × 10 ⁻⁵ | -.16 ^a | -4.38 |
| 1.06 | 7.90 × 10 ⁻⁵ | -.24 ^a | -4.34 |
| 1.65 | 1.90 × 10 ⁻⁴ | -.59 | -4.31 |
| 1.92 | 2.90 × 10 ⁻⁴ | -.72 | -4.26 |
| 2.56 | 6.47 ± 0.25 × 10 ^{-4b} | -1.04 | -4.24 |
| 2.98 | 1.40 ± 0.03 × 10 ^{-3c} | -1.23 ^a | -4.08 |
| 3.46 | 2.63 ± 0.08 × 10 ^{-3d} | -1.46 ^a | -4.04 |
| <i>T</i> = 45.00° | | | |
| 0.219 | 8.00 × 10 ⁻⁵ | 0.63 | -3.47 |
| 0.602 ^e | 2.77 × 10 ⁻⁴ | .12 ^a | -3.44 |
| 1.00 ^e | 6.10 ± 0.03 × 10 ^{-4b} | -.20 ^a | -3.41 |
| 1.42 | 1.19 × 10 ⁻³ | -.44 ^a | -3.36 |
| <i>T</i> = 25.00° | | | |
| D ₂ SO ₄ | | | |
| 0.930 | 1.68 ± 0.01 × 10 ^{-4b} | | |

^a *H*₀ values extrapolated from a plot of values in Table I.

^b Average of two values. ^c Average of four values. ^d Average of three values. ^e *E* = 20.8 kcal., ΔH^\ddagger = 20.2 kcal., ΔS^\ddagger = -9.9 e.u.

(18) J. F. Bunnett, *J. Am. Chem. Soc.*, **82**, 499 (1960).

(19) At 9.32 *M* sulfuric acid (*H*₀ = -4.82) it is probable that *cis*-chalcone is protonated to an appreciable extent, since the *pK*_a of *trans*-chalcone is -5.6.

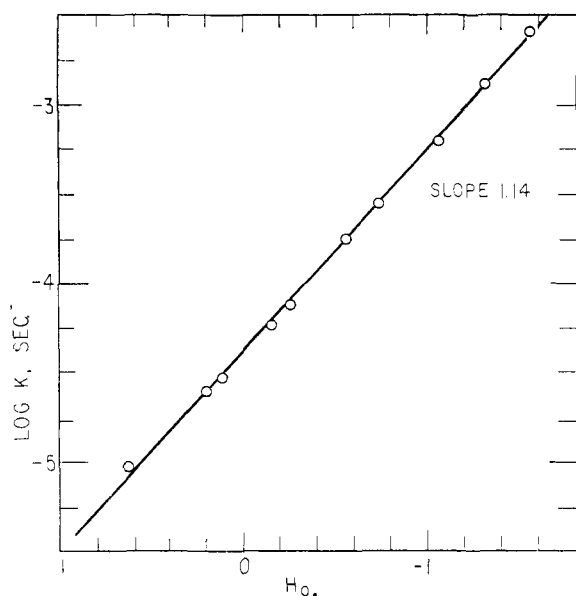


Fig. 2.—Rate of isomerization of *cis*-4-methoxychalcone at 25°.

contrast to that presented immediately above for the other compounds. The rate of isomerization of II parallels the acidity function with a slope of 1.14 (Fig. 2).

The rate of isomerization increases far more rapidly for II than for the other compounds. Compared with *cis*-chalcone, the rate of isomerization is 10 times faster in 0.1 *M* H₂SO₄, 17 times faster at 1 *M* H₂SO₄ and 65 times faster at 3.5 *M* H₂SO₄. At 6 *M* H₂SO₄, the extrapolated rate of isomerization of II is nearly 300 times that of I.

In contrast, the rate ratio I:IV is only 8, and remains very nearly the same from 1 *M* sulfuric acid to 10 *M* sulfuric acid.

A plot (Fig. 3) of the rate of isomerization at 6 *M* H₂SO₄ versus the σ -value for the groups also shows clearly that there is a discontinuity in the effect of the substituent upon the rate of isomerization. Even though one uses the σ^+ -values of Brown,²⁰ the discontinuity remains evident.

Likewise the entropy of activation of II shows a substantial change, and is much less negative than for I or IV.

These three lines of evidence indicate that we are dealing with a different mechanism for the isomerization of II; the change in H_0 correlation, the discontinuity in the rate ratios (non-linear ρ - σ correlation) and the abrupt change in the activation parameters.

We wish to propose that the new mechanism, applicable in the case of the isomerization of *cis*-4-methoxychalcone, involves the simple rotation about the C $_{\alpha}$ -C $_{\beta}$ bond in the salt of II, without the addition of water.

Deuterium Isotope Studies with II.—To obtain further evidence regarding the mechanism of the acid-catalyzed isomerization of *cis*-4-methoxychalcone, we have carried out studies in deuteriosulfuric acid. When the isomerization is conducted in

(20) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957).

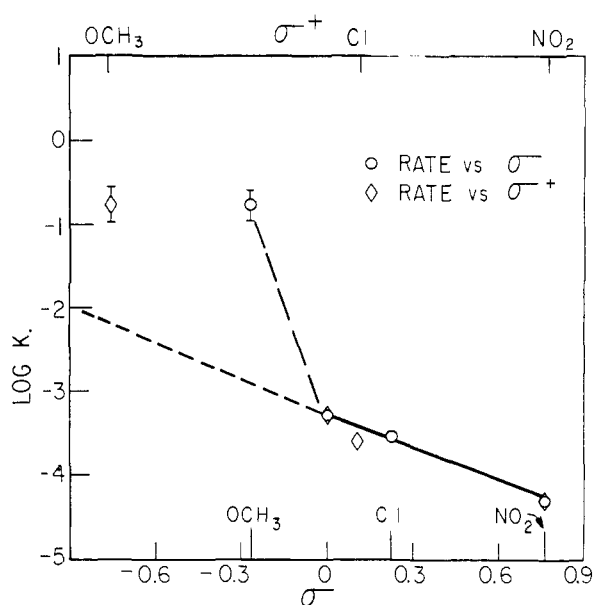


Fig. 3.—Rate of isomerization of substituted chalcones in 6.48 *M* sulfuric acid-dioxane.

deuteriosulfuric acid, the product is devoid of deuterium as shown by infrared spectrum. Furthermore, the rate of isomerization in D₂O-D₂SO₄ is faster than in aqueous sulfuric acid (*cf.* Table V). These results show that rate-determining proton transfer is not involved and that no carbon-bound deuterium is incorporated during the isomerization.

Discussion

Mechanism for the Isomerization of II.—A mechanism consistent with the facts is the following (Chart I, eq. 5-8): The salt of the ketone VI, which is resonance stabilized (two pertinent canonical structures shown), undergoes slow rotation about the C $_{\alpha}$ -C $_{\beta}$ bond without addition of water (step 6). The essential feature of this mechanism is that the transition state has the positive charge localized in the anisyl portion of the molecule. As represented in VII, the two portions of the ion are orthogonal one to the other.

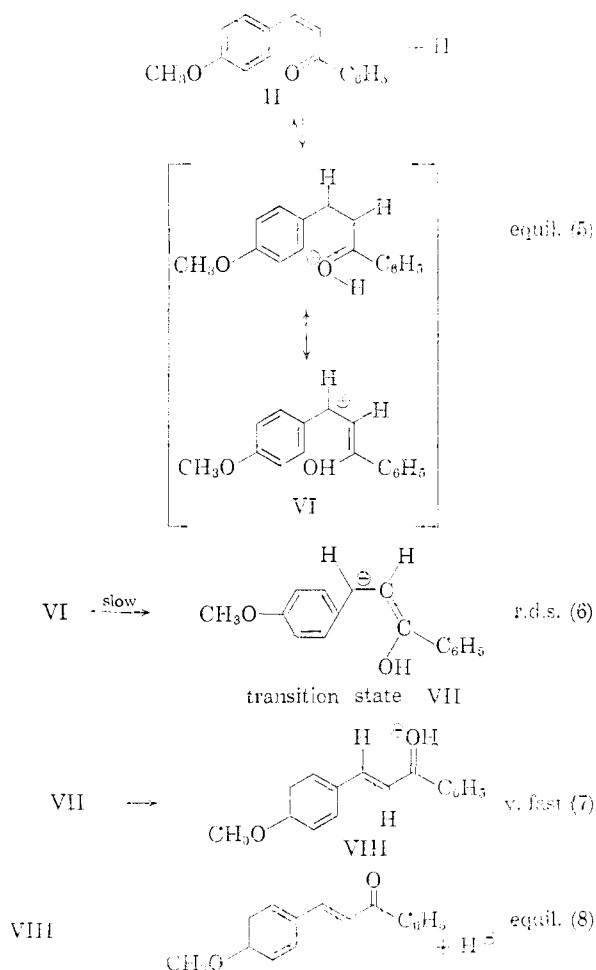
This mechanism requires, in effect, the conversion of the salt of *cis*-4-methoxychalcone to the *p*-methoxybenzyl carbonium ion. Such a transformation is energetically reasonable, as shown by the following argument.

It is first necessary to recall that the free energy difference between a β -hydroxyaldehyde and an α,β -unsaturated aldehyde is relatively small.²¹ Substituted chalcones will, of course, be somewhat more stable relative to the corresponding β -hydroxyketone, because of resonance interaction. However, in *cis*-chalcones this added stabilization will be less because of the hindrance preventing coplanarity.²²

(21) For example, acrolein is 90% hydrated to β -hydroxypropionaldehyde at equilibrium (D. Pressman and H. J. Lucas, *ibid.*, **64**, 1953 (1942)); β,β -dimethylacrolein is 28% hydrated to β -hydroxyisovaleraldehyde at equilibrium (H. J. Lucas, W. T. Stewart and D. Pressman, *ibid.*, **66**, 1818 (1944)); and mesityl oxide is 92-94% hydrated to diacetone alcohol at equilibrium (D. Pressman, L. Brewer and H. J. Lucas, *ibid.*, **64**, 1122 (1942)).

(22) Lack of coplanarity has been discussed in relation to the spectra of the chalcones (ref. 8 and 9).

CHART I
MECHANISM OF THE ACID-CATALYZED ISOMERIZATION OF
cis-4-METHOXYCHALCONE



We, therefore, take as a reasonable approximation that *cis*-4-methoxychalcone (II) and β -(*p*-methoxyphenyl)- β -hydroxypropiofenone (IX) are very similar in energy. Let us now construct mentally two alternative pathways to arrive at transition state VII. These are shown in Chart II. In the lower route protonation of IX with loss of water leads to a substituted benzyl carbonium ion (X).

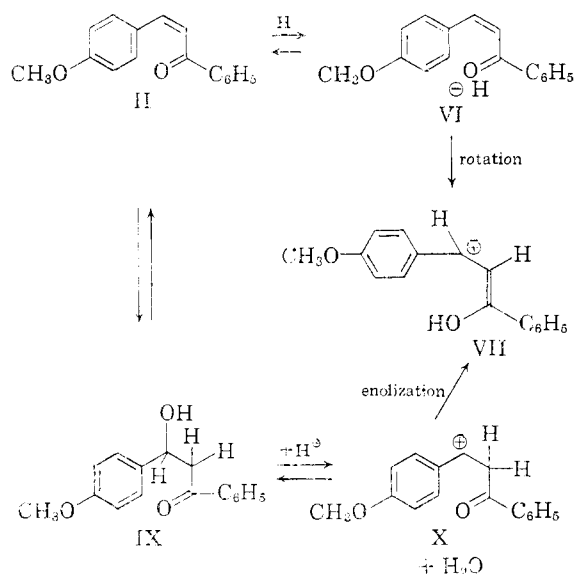
Deno²³ and his co-workers have shown that many substituted benzyl cations are formed from the corresponding benzyl alcohols in 90% sulfuric acid. From Deno's data it can be estimated that *p*-methoxy- α -methylbenzyl alcohol is half converted to the carbonium ion in 60-70% sulfuric acid. *trans*-4-Methoxychalcone is half converted to the salt VIII in 60% sulfuric acid.²⁴ *cis*-4-Methoxychalcone should show a similar, though somewhat reduced, basicity. Thus the two types of ions VI and X are of comparable stability.

To complete the mental transformation of IX to VII it now is necessary only to change the ketone to the corresponding enol. Such a transformation represents an easily accessible energy. The elec-

(23) N. C. Deno, P. T. Groves, J. J. Jaruzelski and M. N. Lugasch, *J. Am. Chem. Soc.*, **82**, 4719 (1960), and previous papers.

(24) Unpublished data of M. J. Jorgensen.

CHART II
SCHEME FOR EVALUATING THE ENERGETICS OF TRANSITION
STATE VII



trostatic influence of the orthogonal en-ol system in the benzylic cation VII is difficult to estimate; however, it is only a minor factor relative to the others just mentioned.

From an independent point of view, a further, though more qualitative, argument may be developed to suggest that the rotation step VI \rightarrow VII is energetically quite feasible.

In simple, substituted ethylenes thermal isomerization has an activation energy of 50-60 kcal. (dideuterioethylene 60,²⁵ *cis*-2-butene 52²⁶ kcal.).

Substitution of resonance stabilizing groups progressively and markedly reduces the activation energy (stilbene 43 kcal.,²⁷ cinnamionitrile 46 kcal.,²⁸ methyl cinnamate 42 kcal.,²⁹ *p*-methoxystilbene 35 kcal.,³⁰ 4-methoxy-4'-nitrostilbene, 29 kcal.,³⁰ dimethyl maleate, 26 kcal.³¹). With an anisyl system containing a positive charge the energy requirement would be expected to be substantially reduced still further. In other words, the bond order of the C _{α} -C _{β} bond is sufficiently reduced in the salt VI so that rotation no longer requires an undue expenditure of energy.

Correlation of the Two Mechanisms for the Isomerization of Substituted *cis*-Chalcones.—An excellent way to bring together the results which we have obtained is to consider the effect of changing the substituent in the aromatic ring upon the thermodynamic stability of each type of species involved, including possible intermediates and transition states. A correlation diagram for this purpose is given in idealized form in Fig. 4.

(25) J. E. Douglas, B. S. Rabinovitch and F. S. Looney, *J. Chem. Phys.*, **23**, 315 (1955).

(26) W. F. Anderson, J. A. Bell, J. M. Diamond and K. R. Wilson, *J. Am. Chem. Soc.*, **80**, 2384 (1958).

(27) G. B. Kistiakowsky and W. R. Smith, *ibid.*, **56**, 638 (1934).

(28) G. B. Kistiakowsky and W. R. Smith, *ibid.*, **58**, 2428 (1936).

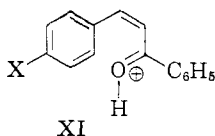
(29) G. B. Kistiakowsky and W. R. Smith, *ibid.*, **57**, 269 (1935).

(30) M. Calvin and H. W. Alter, *J. Chem. Phys.*, **19**, 768 (1951).

(31) M. Nelles and G. B. Kistiakowsky, *J. Am. Chem. Soc.*, **54**, 2208 (1934).

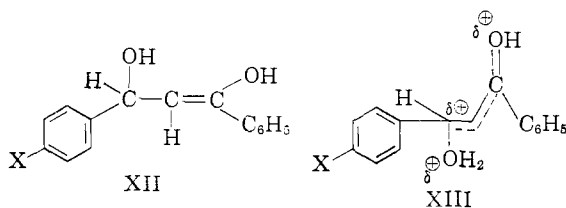
Curve A represents the energy level of the starting material, the substituted *cis*-chalcones (I-IV). It is apparent, of course, that in addition to the interaction of the substituent³² with the aromatic ring to which it is attached, there is a further interaction with the carbonyl group through the double bond. Because of steric interference with coplanarity in *cis*-chalcones, this interaction will be small; hence the slope of curve A is very low.

Curve B (in Fig. 4) represents the relative stability level of the salt of the *cis*-chalcones (XI). The interaction of the substituent with the charge



is much more pronounced; therefore curve B is steeper. Nevertheless, the same steric interference to fully effective resonance interaction is still present. The absolute position of this curve in the vertical sense is completely arbitrary; the slope is meant to give a good representation of the factors outlined above. A parallel may be drawn to the relative basicities of aromatic aldehydes³³ and ketones³⁴ which have been studied by Stewart and Yates.

Curve C represents the effect of structure on the stability of the β -hydroxyenol XII, which is the intermediate formed in the isomerization of I, III and IV. Since the substituent is on a benzene ring isolated from the rest of the unsaturated system by a tetrahedral carbon, there is *no* interaction beyond that of the substituent with the benzene ring. Hence, for the total compound, there is no change of stability as the substituent is changed, and curve C has zero slope.



Curve D represents the transition state XIII involving the attack of water upon the salt of the *cis*-chalcones. To the extent that the β -carbon is fully bonded to the oxygen of the incoming water molecule, the resonance will be "interrupted." Thus the slope of curve D is intermediate between curve B and curve C. Curve D will have a somewhat larger positive slope than curve A, in keeping with the observed small decrease in rate between *cis*-chalcone and *cis*-*p*-nitrochalcone.

Finally, curve E is given to show the influence of structure upon the energy of the transition state (e.g., VII) for the other proposed mechanism, involving the carbonium ion rotated 90° about

(32) We use as an arbitrary zero point on the energy scale, the monosubstituted benzene (*i.e.*, anisole, chlorobenzene, benzene, nitrobenzene) for each of the points on the abscissa. This makes it possible then to consider the effects of the substituents upon the relative free energy of each type of species to be considered.

(33) R. Stewart and K. Yates, *J. Am. Chem. Soc.*, **80**, 6355 (1958).

(34) K. Yates and R. Stewart, *Can. J. Chem.*, **37**, 664 (1959).

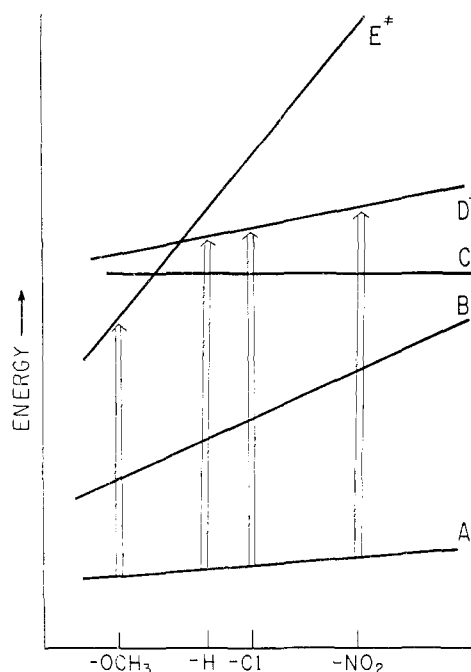


Fig. 4.—Energy correlation diagram showing effect of substituents upon possible intermediates and transition states in the acid-catalyzed isomerization of substituted *cis*-chalcones.

the α - β bond. The effect of the substituent upon the stability of such a transition state will be enormous. The positive charge is localized in the left ring and the benzylic carbon (by the fact that the p orbital at the α -carbon is orthogonal to that at the β carbon) and interacts *very* strongly with the substituent in that ring.

Changing substituents in VII should result in a change in stability like that observed in several related types of compounds. The solvolysis of cumyl chlorides,²⁰ the ionization of arylphenylcarbinols³⁵ and the rates of dehydration of β -aryl- β -hydroxypropionic acid³⁶ all show ρ -values near -5 , reflecting the extreme sensitivity of carbonium ion reactions to substituent, when these occur at the benzylic carbon atom.

Thus, the rate-determining process changes. The vertical arrows represent the transformation from ground state to transition state for the various compounds studied.

This picture provides a very easy and straightforward interpretation of the facts presented. The rate of isomerization of II follows the acidity function linearly; that is, it involves simply the salt of *cis*-4-methoxychalcone. The reaction is faster in deuteriosulfuric acid, k_D/k_H being 2.8. This shows that a rate-determining proton transfer is not involved. The entropy of activation is only slightly negative; an activated complex involving only *cis*-4-methoxychalcone and a proton is in accord. Finally the very much faster rate of isomerization of II suggests a carbonium ion mechanism; and the non-linear ρ - σ correlation points to a difference

(35) N. C. Deno and W. L. Evans, *J. Am. Chem. Soc.*, **79**, 5804 (1957).

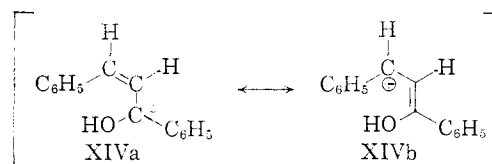
(36) D. S. Noyce, C. A. Lane, W. L. Reed and P. A. King, manuscript in preparation.

in mechanism for II, when compared with I, III and IV.

Finally, we wish to point out that these data also provide insight into the configurational stability of allylic cations.³⁷ Among the canonical set of resonance forms which may be written for the salt of *cis*-chalcone are an "allylic pair" (XIVa and XIVb). The conclusions regarding the mechanism of isomerization of I clearly demand configurational stability in this system, since the isomerization is effected only by the attachment of water (eq. 2).

(37) W. G. Young, S. H. Sharman and S. Winstein, *J. Am. Chem. Soc.*, **82**, 1376 (1960).

With sufficient stabilization for a positive charge provided at the ends of the "allylic" system, the



bond order of the C_{α} - C_{β} bond is reduced. The isomerization thus may become unimolecular, as observed in these studies for *cis*-4-methoxy-chalcone (II).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF TEXAS CHRISTIAN UNIVERSITY, FORT WORTH, TEX.]

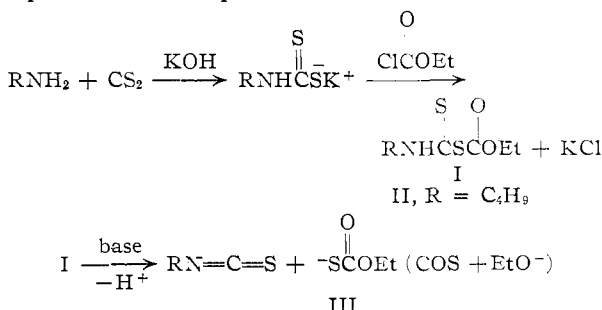
The Modified Kaluza Synthesis. II.¹ Kinetics and Mechanism

BY JOE E. HODGKINS, W. PRESTON REEVES AND YAO-TING GORDON LIU

RECEIVED DECEMBER 12, 1960

The decomposition of intermediate carboethoxy *n*-butyldithiocarbamates is shown to be subject to base catalysis and the evolution of carbon oxysulfide to proceed in three steps. The reaction is unusual in that the rate first increases with increasing concentration of buffer components, then levels and shows no further increase in rate. This behavior as well as the mechanism of the decomposition is discussed.

Introduction.—The modified Kaluza synthesis of isothiocyanates, recently introduced,¹ has been applied to the preparation of various aliphatic isothiocyanates from the corresponding amines with generally successful results. The method has been employed in the synthesis of alkyl,¹ alkenyl,² benzyl,³ *o*-, *m*- and *p*-methoxy benzyl,^{4,5} 3-hydroxypropyl,⁶ various substituted β -hydroxyethyl⁷ and ω -carbalkoxyalkyl⁸ isothiocyanates. The modification of the Kaluza method consists in utilizing base-catalyzed decomposition of intermediate carboethoxy dithiocarbamates, derived from amines by treatment with carbon disulfide and base followed by carboethoxylation with ethyl chlorocarbonate. The reaction can be carried out in aqueous¹ or non-aqueous^{1,7,8} solvents.



(1) J. E. Hodgkins and M. G. Ettlinger, *J. Org. Chem.*, **21**, 404 (1956), should be considered the first paper of this series.

(2) M. G. Ettlinger and J. E. Hodgkins, *J. Am. Chem. Soc.*, **77**, 1833 (1955).

(3) M. G. Ettlinger and J. E. Hodgkins, *J. Org. Chem.*, **21**, 204 (1956).

(4) M. G. Ettlinger and A. J. Lundeen, *J. Am. Chem. Soc.*, **78**, 1952 (1956).

(5) A. Kjaer and R. B. Jensen, *Acta Chem. Scand.*, **10**, 141 (1956).

(6) A. Kjaer and R. Gemlin, *ibid.*, **10**, 1193 (1956).

(7) A. Kjaer and R. Gemlin, *ibid.*, **11**, 906 (1957); A. Kjaer, R. Gemlin and R. B. Jensen, *ibid.*, **10**, 432 (1956).

(8) D. L. Garmaise, R. Schwartz and A. F. McKay, *J. Am. Chem. Soc.*, **80**, 3332 (1958).

In the first paper¹ of this series a path was proposed for the base-catalyzed decomposition reaction based on the general chemical behavior of the carboethoxy dithiocarbamate derivatives (I). No evidence was available, however, to ascertain the type of base catalysis or whether the evolution of carbon oxysulfide was concerted with proton removal or preceded by fission to thiocarbonate ion⁹ followed by rapid decomposition of this species. We wish now to present evidence that shows the decomposition to be subject to an unusual type of base catalysis and the evolution of carbon oxysulfide to proceed in two steps after proton removal.

Results.—The rate of decomposition of carboethoxy *n*-butyldithiocarbamate (II) was followed by measurement of the evolution of carbon oxysulfide and by ultraviolet light absorption measurement of undecomposed II. Gas evolution kinetics were employed only where qualitative comparisons were needed since the rate constants were invariably 20–30% lower than those measured spectrophotometrically, due, presumably, to the solubility of carbon oxysulfide in the solvent. By employing good gas-liquid equilibration techniques (see Experimental), reproducible kinetic results could be obtained from gas evolution measurements, but deviation from first-order kinetics occurred above the half-life and the results indicated only 50–70% completions. In solvents containing water and added salts, which reduces the solubility of carbon oxysulfide, the evolution kinetics closely approached the spectrophotometric measurements and the extent of completions increased to about 90%.

The uncatalyzed rate of decomposition of II at 41° in 83% (by volume) methanol or ethanol is barely detectable. The compound II is perfectly stable to 0.005 *N* HCl in the same solvents.

(9) O. E. Schultz and E. Barthold, *Arch. Pharm.*, **285**, 267 (1952), have isolated sodium O-ethyl thiocarbonate in the decomposition of these intermediates in the presence of strong sodium hydroxide.