gave negative color tests with the Ehrlich reagent,[5] suggesting that the 2 position of the indole moiety was masked. The product was isolated by chromatographing the lyophilized residue on a column (1.0 × 42 cm) of the sulfonic resin Dowex-50, using 1% ammonia as eluent: 21.2 mg, 72.7%; the ir spectrum (KBr) gave a peak at 1690 cm^{-1}, clearly showing the presence of a carbonyl group conjugated with an aromatic system; the elemental analysis was in agreement with the expected one for 2-acetylskatole.

Anal. Calcd for $C_{11}H_{11}NO$: C, 74.68; H, 6.79; N, 8.64. Found: C, 74.19; H, 6.85; N, 8.65.

Irradiation of Methylene Blue in Acetic Acid Solution.—In one experiment, 100 mg of methylene blue in 250 ml of acetic acid were irradiated for 40 hr under N_2 by the apparatus previously described. Tlc analysis showed that methylene blue was slowly converted to three products. The major product (R_{f_2} 0.65) was isolated by chromatographing the lyophilized irradiated mixture on an alumina column (2 × 50 cm), using a 1:1 (v/v) $CH_3OH-CHCl_3$ mixture as eluent. The visible absorption maximum of the product in chloroform was located at 625 mμ; such a blue shift with respect to methylene blue (absorption maximum 637 mμ) was observed by Obata[12] for hydroxyphenthiazines. The ir spectrum (KBr) differed from that of methylene blue for the presence of a broadened band at 3340 cm^{-1} and of a doublet at 1200 cm^{-1}, as it is typical of phenolic OH. On the basis of these evidences, we tentatively identify the product as 3(or 6)-hydroxy-6(or 3)-dimethylaminophenothiazine.

Anal. Calcd for $C_{14}H_{14}N_2SO$: C, 61.84; H, 5.58; N, 12.02; S, 13.75. Found: C, 61.73; H, 5.55; N, 12.10; S, 13.69.

Registry No.—**2a**, 22329-38-0; **2b**, 486-84-0; **2c**, 33821-71-5; **2d**, 33821-72-6; **2e**, 23256-12-4; tryptophan, 6159-33-7; 1-ethyl-3-carboxy-β-carboline, 33821-74-8; 1-ethyl-β-carboline, 20127-61-1; 1-isopropyl-3-carboxy-β-carboline, 33821-76-0; 1-isopropyl-β-carboline, 22314-95-0; 1-*tert*-butyl-3-carboxy-β-carboline, 33821-78-2; 1-*tert*-butyl-β-carboline, 33821-79-3; 2-acetyl-*tert*-butoxycarbonyl-L-tryptophan ethyl ester, 33821-80-6; 2-acetylskatole, 16244-23-8; methylene blue, 61-73-4; 3-hydroxy-6-dimethylaminophenthiazine, 33821-82-8; 6-hydroxy-3-dimethylaminophenthiazine, 33821-83-9.

Acknowledgments.—This work received financial support from C. N. R. (Contract No. 71.01843.03). The authors are indebted to John D. Spikes for useful discussion.

Mechanism and Catalysis for Furfural Phenylhydrazone Formation[1]

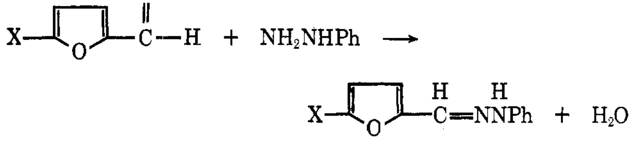
LUCIANO DO AMARAL

Departmento de Engenharia Química, Escola Politécnica, Universidade de São Paulo, São Paulo, Brasil

Received August 10, 1971

As is typical for the addition of amines to carbonyl compounds, the reaction of 5-substituted furfurals with phenylhydrazine exhibits rate-determining attack of the nucleophile under acidic conditions and rate-determining decomposition of the carbinolamine intermediate under neutral and basic conditions. The attack of phenylhydrazine on these substrates is subject to general acid catalysis by carboxylic acids, the Brønsted exponent $\alpha = 0.35$. Dehydration of the carbinolamine intermediates occurs *via* acid-catalyzed, pH-independent, and, in the case of the nitro derivative, base-catalyzed reaction pathways.

The principal features of the mechanisms for addition of weakly basic amines to carbonyl compounds[2,3] have been derived from a series of studies employing simple aliphatic and aromatic aldehydes and ketones.[4-12] Both to broaden the basis upon which our conclusions are founded and to explore substituent effects in heterocyclic aromatic systems, the kinetics of 5-substituted furfural phenylhydrazone formation have been investigated. While this study has, for the most part, reinforced previous conclusions, some interesting differences in detail do appear. The results are presented below.



Experimental Section

Materials.—5-Methylfurfural was prepared according to the method of Rinkes,[13] bp 84–86° (3 mm) [lit.[13] bp 83–85° (15 mm)]. The product is stable for several months at −10° in the absence of light and oxygen. Dilute solutions in 20% aqueous ethanol were found to be stable for several days at 0° in the dark. 5-Bromofurfural, mp 84° (lit.[14] mp 82°), and 5-nitrofurfural, mp 35–36° (lit.[15] mp 35–36°), were also prepared according to published procedures.[14-16] All other reagents employed were obtained commercially and, with the exception of reagent grade inorganic salts, were either redistilled or recrystallized prior to use. Solutions of phenylhydrazine were prepared just prior to use, as were those of carboxylic acids in 20% ethanol, to avoid formation of the ethyl esters.

Kinetic measurements[4,6,9] were carried out spectrophotometrically at 25° with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell holder through which water from a thermostated bath was continuously circulated. Reaction kinetics were monitored by observing the appearance of the furfural phenylhydrazones at appropriate wavelengths in solutions containing initial concentrations of the aldehydes of 5×10^{-5} *M*: 5-methyl, 343 nm; unsubstituted, 340 nm; 5-bromo, 348 nm; 5-nitro, 464 nm. In all cases a sufficient excess of phenylhydrazine was employed to ensure that pseudo-first-order kinetic behavior would be obtained. First-order rate constants were evaluated from plots of log ($OD_\infty - OD_t$) against time in the usual manner. Second-order rate constants were obtained by dividing first-order constants by the concentration of phenylhydrazine free base. In the pH region in which phenylhydrazine attack is principally rate-determining, rate constants have been

---

(1) Supported in part by the Conselho Nacional de Pesquisas and by the Fundacão de Amparo à Pesquisa do Estado de São Paulo.

(2) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

(3) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.

(4) W. P. Jencks, *J. Amer. Chem. Soc.*, **81**, 475 (1959).

(5) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 826, 832 (1962).

(6) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962).

(7) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *ibid.*, **88**, 2225 (1966).

(8) R. B. Martin, *J. Phys. Chem.*, **68**, 1369 (1964).

(9) M. P. Bastos and L. do Amaral, *J. Org. Chem.*, **36**, 3412 (1971).

(10) J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 6353 (1969).

(11) J. Hine, F. A. Via, J. K. Gotkis, and J. C. Craig, Jr., *ibid.*, **92**, 5186 (1970).

(12) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *ibid.*, **92**, 5194 (1970).

(13) I. J. Rinkes, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 393.

(14) Z. N. Nazarova, *Dokl. Akad. Nauk Uzbek SSR*, 40 (1953).

(15) H. Gilman and G. F. Wright, *J. Amer. Chem. Soc.*, **52**, 2550 (1930).

(16) H. Gilman and G. F. Wright, *Iowa State College J. Sci.*, **4**, 53 (1929).

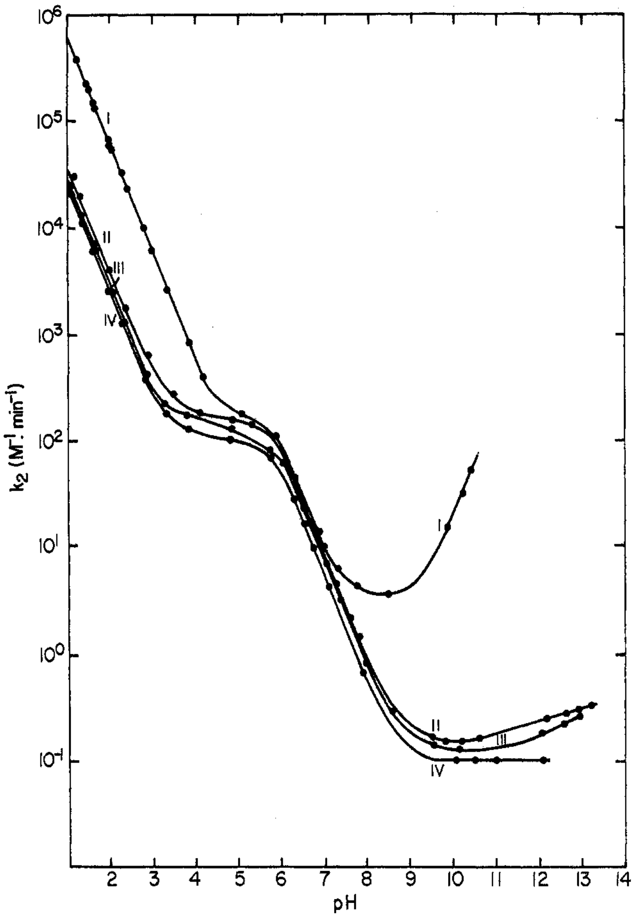


Figure 1.—Logarithms of second-order rate constants for phenylhydrazone formation from a series of 5-substituted furfurals in 20% ethanol at 25° and ionic strength 0.50 plotted as a function of pH. All points refer to zero buffer concentration. I, 5-nitrofurfural; II, 5-bromofurfural; III, furfural; IV, 5-methylfurfural.

corrected to account for the influence of the rate of carbinolamine dehydration as described by Sayer and Jencks.[10] Catalytic (third-order) rate constants were evaluated from the slopes of plots of second-order constants against the concentration of catalyst. All kinetic experiments were carried out in 20% ethanol at an ionic strength of 0.50, maintained with KCl, with 2×10^{-4} M EDTA. Values of apparent pH were recorded with a Radiometer Model PHM 4d pH meter equipped with a glass electrode. Calculations of the concentration of phenylhydrazine free base and undissociated carboxylic acids were made employing the Henderson-Hasselbalch equation and values of pK_a which refer to a solvent of water at zero ionic strength. Because of the opposing effects of high ionic strength and organic solvent on the values of pK_a, use of the indicated values is not unreasonable.[9] At any event, there is no conclusion drawn below that would be significantly modified by the choice of slightly different values of pK_a.

Product Analysis.—The products of condensation of phenylhydrazine with furfural, 5-methylfurfural, and 5-nitrofurfural were identified as the corresponding phenylhydrazones from their characteristic ultraviolet and infrared spectra. 5-Bromofurfural phenylhydrazone was prepared by mixing a solution of 1.0 g of phenylhydrazine hydrochloride in water with 50 ml of an ethanol solution containing 1.0 g of 5-bromofurfural. Yellow crystals of the phenylhydrazone, which became dark green upon drying, were obtained by the addition of small amounts of water after cooling the solution to 0°, mp 68–70°. *Anal.* Calcd: C, 49.83; H, 3.04. Found: C, 50.18; H, 3.17. The phenylhydrazone exhibited an absorption maximum at 358 nm.

Results and Discussion

Subsequent to the formulation of the Hammett equation,[17] a very large amount of experimental information concerning the effects of polar substituents on reaction rates and equilibria has been correlated with the appropriate substituent constants in the benzene series.[18–21] The only other aromatic nucleus treated in any detail is that of naphthalene.[22] Treatment of heterocyclic aromatic systems is quite limited, although some preliminary efforts have been made.[19,21,23] A set of $\sigma_F{}^{2,5}$ substituent constants (the designation of these constants follows the form employed by Dewar for the naphthalene system[22]) for 5-substituted 2-furyl derivatives has been calculated from the dissociation constants in water of the corresponding furoic acids.[24] These are linearly related to the usual σ constants, $\sigma_F{}^{2,5} = 1.40\sigma_p$. This result suggests that, for dissociation of the acids at least, the relative importance of inductive and resonance effects of polar substituents in the two cases is similar. Extension of this concept to nucleophilic reactions of the corresponding aldehydes is, as is developed below, not straightforward.

In Figure 1, second-order rate constants, extrapolated to zero buffer concentration where necessary, for phenylhydrazone formation from 5-substituted furfurals are plotted as a function of pH. The general shape of the curves is familiar and reflects (going from acidic to basic conditions) acid-catalyzed and water-catalyzed attack of the nucleophile, pK_a 5.2, as the rate-determining step and acid-catalyzed, water-catalyzed, and base-catalyzed dehydration of the carbinolamine intermediate as the rate-determining step.[2–4,9]

In the region of rate-determining attack of phenylhydrazine, the second-order rate constants are sensitive functions of the nature and concentration of buffers employed to maintain constant pH. Studies of the buffer catalysis demonstrated that, as usual, the catalysis is of the general acid type. As noted by Sayer and Jencks,[10] estimation of catalytic constants for the carboxylic acids for reactions of this type can be complicated by the varying importance of the rate of carbinolamine dehydration to the overall rate as a function of pH and buffer concentration. To avoid this difficulty, all second-order rate constants have been corrected to account for the influence of the rate of carbinolamine dehydration. Catalytic constants for various carboxylic acids were then evaluated in the usual way. These constants are collected in Table I. As may be judged from Figure 1, the rates for carbinolamine formation and dehydration are much more nearly equal for 5-nitrofurfural than for other substrates. One consequence of this fact is that, for this substrate, plots of uncorrected second-order rate constants against

---

[17] L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 96 (1937).

[18] H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

[19] P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

[20] S. Ehrenson, *Progr. Phys. Org. Chem.*, **2**, 196 (1964).

[21] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963.

[22] M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, **84**, 3548 (1962).

[23] R. C. Elderfield and M. Siegel, *ibid.*, **73**, 5622 (1951); T. Sasaki, *Chem. Pharm. Bull.*, **2**, 104 (1954); P. Zuman, *Chem. Zvesti*, **8**, 939 (1954); E. Imoto, R. Motoyama, and H. Kakiuchi, *Bull. Naniwa Univ.*, **A3**, 203 (1955); I. Stradius, S. Hillen, and Yu. K. Yur'ev, *Dokl. Akad. Nauk SSSR*, **129**, 816 (1959); R. Alan Jones, T. McL. Spotswood, and P. Cheuychit, *Tetrahedron*, **23**, 4469 (1967); H. C. Smitherman and L. N. Fergunson, *ibid.*, **24**, 923 (1968).

[24] F. Freeman, *J. Chem. Educ.*, **47**, 140 (1970).

Table I

Catalytic Constants of Several Acids, Expressed in M^{-2} min^{-1}, for the Attack of Phenylhydrazine on a Series of 5-Substituted Furfurals in 20% Ethanol, at 25° and Ionic Strength 0.50

Catalyst	pK_a	5-Methylfurfural	Furfural	5-Bromofurfural	5-Nitrofurfural
H_3O^+	−1.74	2.8×10^5	3.3×10^5	4.0×10^5	6.0×10^6
$NCCH_2CO_2H$	2.45		2.6×10^4		7.9×10^5
$ClCH_2CO_2H$	2.90	1.2×10^4	1.6×10^4	2.6×10^4	4.8×10^5
HCO_2H	3.75		8.3×10^3		3.5×10^5
$BrCH_2CH_2CO_2H$	4.00		9.2×10^3		2.4×10^5
CH_3CO_2H	4.76	4.6×10^3	4.8×10^3	5.0×10^3	4.1×10^4
PHH^+ [a]	5.20	1.3×10^4	2.1×10^4	3.1×10^4	3.2×10^4
H_2O	15.74	3.0	3.3	3.6	4.6

[a] Phenylhydrazinium ion.

catalyst concentration are nonlinear. Related cases identified include benzaldehyde semicarbazone and thiosemicarbazone formation.[6,10] Data of this type can also be the consequence of complexation of carboxylate ions with the aldehyde substrates to form unreactive species; *p*-nitrobenzaldehyde phenylhydrazone formation appears to provide one example of this type.[9]

Catalytic constants for the carboxylic acids are well correlated by the Brønsted catalysis law: least-squares treatment of the data yields a value of α of 0.35 for both furfural and 5-nitrofurfural. The same value of α has been obtained for general acid catalysis of benzaldehyde phenylhydrazone formation,[9] but smaller values appear to characterize a number of related reactions.[10]

Correlation of the rate constants for the attack of phenylhydrazine on the 5-substituted furfurals by the σ_F[2,5] substituent constants or by σ or σ^+ substituent constants fails. Examination of the data in Table I reveals the source of difficulty. With weakly acidic catalysts, including water, acetic acid, and phenylhydrazinium ion, the rate constants are quite insensitive to the nature of the polar substituent (and can, therefore, be correlated by essentially any set of substituent constants) while for more acidic catalysts, the 5-nitrofurfural is markedly more reactive than the other three substrates whose rate constants are, as above, rather insensitive to the nature of the polar substituent. While the reasons for the distinctive behavior of the 5-nitro derivative are not clear, it does suggest that, just as in the benzene series, a special set of substituent constants may be necessary to correlate rate constants for reactions involving electrophilic species in the furan series.

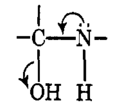
The rate constants for the water-catalyzed attack reaction are less sensitive to the nature of the polar substituent than are those for the acid-catalyzed reaction (Figure 1 and Table I). This situation is quite the opposite of that usually observed[6,9] for reactions of this class and is difficult to rationalize on the basis of the mechanism usually written for these reactions.[2,3,6] It is possible that this observation reflects the importance of the heterocyclic oxygen of the furan ring as a participant in the reaction through hydrogen bond formation with the catalyst *via* intervening water molecules. It is clear that a full explanation will await more detailed understanding of substituent effects in this system.

Rate constants characterizing the various reaction pathways for furfural phenylhydrazone formation under conditions of rate-limiting dehydration are collected in Table II. The acid-catalyzed pathway is quite insensitive to the nature of polar substituents; similar observations have been made for related reactions.[6,9,25] In contrast, the rate constants for the water-catalyzed (or uncatalyzed) reactions increase substantially with increasing electron withdrawal in the polar substituent (the rate constant for the 5-nitro derivative was evaluated by subtracting the rate constant for the acid-catalyzed and base-catalyzed reactions at the rate minimum). This reaction must occur in the following way (the corresponding reaction for Schiff base hydrolysis is known to occur with attack of hydroxide ion on the protonated substrate).[26,27]

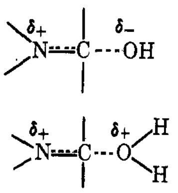
Table II

Rate Constants for the Acid-Catalyzed, pH-Independent, and Base-Catalyzed Reactions for 5-Substituted Furfural Phenylhydrazone Formation under Conditions of Rate-Determining Carbinolamine Dehydration

Substituent	$k_H \times 10^{-7}$, M^{-2} min^{-1}	k_{H_2O}, M^{-1} min^{-1}	k_{OH}, M^{-2} min^{-1}
Nitro	9.0	2.5	2.0×10^5
Bromo	8.0	0.31	
Unsubstituted	8.0	0.20	
Methyl	5.0	0.10	



The fact that the acid-catalyzed dehydration of the carbinolamine is less sensitive to the nature of polar substituents than is the uncatalyzed process suggests that the transition states for the two reactions may differ significantly in the extent of carbon–oxygen bond cleavage.



With the good leaving group, water, little C–O bond cleavage in the transition state is visualized, minimizing the effects of polar substituents. With the poorer leaving group, hydroxide ion, it is reasonable to assume

---

[25] B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.*, **82**, 1773 (1960).

[26] E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).

[27] K. Koehler, W. A. Sandstrom, and E. H. Cordes, *ibid.*, **86**, 2413 (1964).

a greater degree of progress toward sp^2 geometry at the transition state, increasing the extent of interaction, particularly by resonance, between the reaction center and polar substituents.

Dehydration of the carbinolamine derived from 5-nitrofurfural and phenylhydrazine is markedly susceptible to base catalysis, while those derived from other furfurals exhibit very small contributions from this pathway. Thus the polar effects on the base-catalyzed pathway are the largest for this particular dehydration pathway as they are for dehydration of benzaldehyde phenylhydrazine carbinolamine.[4] As above, this behavior must reflect the importance of electron withdrawal in the formation of the double bond in the product.

Registry No.—Phenylhydrazone, 100-63-0; 5-bromofurfural phenylhydrazone, 34220-06-9; 5-methylfurfural, 620-02-0; furfural, 98-01-1; 5-bromofurfural, 1899-24-7; 5-nitrofurfural, 698-63-5.

Acknowledgment.—The author is indebted to Dr. Eugene H. Cordes for helpful comments concerning this work.

The Influence of Configuration on Transmission of Electronic Effects in α,β-Unsaturated Ketones

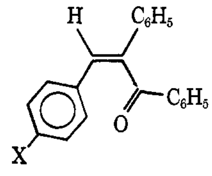
PEGGY J. DUKE[1] AND DAVID W. BOYKIN, JR.*

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303

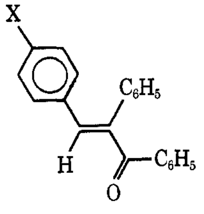
Received September 13, 1971

A series of zusamen (Z)- and entgegen (E)-α-phenylchalcones (1,2-diphenyl-3-arylpropenones) have been prepared and configurational assignments have been made to them. Their carbonyl stretching frequencies have been measured in carbon tetrachloride solutions. A good linear free-energy relationship was obtained between ν(C=O) and σ^+ for the E isomers (r = 0.980). On the other hand, the Z isomers gave only a poor correlation (r = 0.798). An unprecedentedly large ρ_E/ρ_Z ratio of ~6 was observed. The ρ value for the Z isomers suggests that this system is essentially insensitive to substituent effects. The data were also treated using the Swain–Lupton approach. Comparisons of the linear free-energy results obtained from the α-phenylchalcone system are made with other analogous systems.

The alteration of transmission of electronic effects through an intervening link by changing the geometric relationship between substituent and reaction site has been noted in several systems.[2] In aliphatic systems a change from E to Z isomers resulted in an increase in sensitivity to substituents as judged by the magnitudes of the Hammett ρ values and this observation has been attributed to field effects. In aryl systems a reduction in sensitivity to substituents with the same configurational change has been noted. In spite of growing interest and an increasing number of reports on linear free-energy relationships of α,β-unsaturated ketone systems,[3,4] the effect of geometric alterations on substituent effect transmission in such systems does not appear to have been reported. To attempt to assess this effect and as a continuation of a general investigation[4] of linear free-energy relationships of α,β-unsaturated ketones, we have measured the carbonyl stretching frequencies [ν(C=O)] of a series of (Z)- and (E)-α-phenylchalcones [1,2-diphenyl-3-(para-substituted phenyl)propenones] (I and II).



I



II

α-Phenylchalcones.—The α-phenylchalcones were prepared using the approach previously described by Stobbe[5] which usually resulted in a mixture of (Z)- and (E)-α-phenylchalcones. Frequently, the reaction sequence gave mainly the E isomer, and consequently to acquire adequate amounts of the Z isomer the E isomer was subjected to photoequilibration type conditions and the resulting mixtures were separated by column chromatography.

The configurations of the isomers were assigned on the basis of the extinction coefficient of their uv absorption maximum in analogy with the assignments made for **5**, **13**, **8**, and **16** by Lutz and Black.[6] The series of compounds assigned the E configuration consistently, with the exception of **16** as previously noted,[6] exhibited absorption maxima at wavelengths longer than the Z isomers. The series assigned the Z configuration exhibited ν(C=O) bands which were at higher frequencies, generally about 10 cm^{-1}, than the corresponding E isomers (see Table I). This is in accord with the idea that the steric interaction of the 3-aryl group with the benzoyl group in the Z isomer results in the deconjugation of the carbonyl and styryl groups and hence a shift of ν(C=O) to higher frequency. The configurational assignments[6] to the parent members of this series made by consideration of uv absorptions have now been independently confirmed by ir measurements.

---

[1] American Chemical Society Petroleum Research Fund Scholar.

[2] (a) K. Bowden and D. C. Parkin, *Can. J. Chem.*, **46**, 3909 (1968); (b) R. Fuchs and J. J. Bloomfield, *J. Org. Chem.*, **31**, 3423 (1966); (c) M. Charton, *ibid.*, **30**, 974 (1965); (d) A. B. Turner, R. E. Lutz, N. S. McFarlane, and D. W. Boykin, Jr., *ibid.*, **36**, 1107 (1971); (e) J. J. Bloomfield and R. Fuchs, *ibid.*, **26**, 2991 (1961); (f) R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, *ibid.*, **27**, 733 (1962).

[3] (a) J. R. Dimmock, P. L. Carter, and P. D. Ralph, *J. Chem. Soc. B*, 698 (1968); (b) S. Toma and A. Perjessy, *Chem. Zvesti*, **23**, 343 (1969); (c) A. Perjessy, *ibid.*, **23**, 905 (1969).

[4] (a) N. L. Silver and D. W. Boykin, Jr., *J. Org. Chem.*, **35**, 759 (1970); (b) M. L. Ash, F. L. O'Brien, and D. W. Boykin, Jr., *ibid.*, **37**, 106 (1972); (c) W. F. Winecoff, III, and D. W. Boykin, Jr., *ibid.*, **37**, 674 (1972); (d) R. W. Woodard and D. W. Boykin, Jr., *Chem. Commun.*, 628 (1970).

[5] H. Stobbe and F. J. Wilson, *Ann.*, **374**, 237 (1910).

[6] W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, **75**, 5990 (1953).