130° for 47 hr under nitrogen. The mixture was poured onto ice water and extracted with benzene. From the benzene extract were obtained homoadamantanone (69% yield), adamantanecarboxyaldehyde (6%), and recovered dichloromethyladamantane (6%). Identification of homoadamantanone[6] was made by means of: ir (2910, 2850, 1695, 1450, 1360, 1280, 1180, 1080, 940, and 800 cm^{-1}); nmr (TMS, CCl_4, τ 7.2–7.57 (1 H), 7.45–7.6 (2 H), 7.7–8.5 (13 H)); and mass spectrum (*m/e* 163 (relative intensity 100), 136 (13), 135 (85), 121 (25)). The melting point of isolated homoadamantanone was 267–268° (uncorrected) without further purification (lit.[6] 270–271.5°). Its oxime melted at 145.5–147.5°. The amount of 1-adamantanecarboxyaldehyde formed was found to increase with temperature, being one of the major products over 170°. At higher temperatures, a small amount of adamantane was also obtained.

Although the actual mechanism of the hydrolytic rearrangement to homoadamantanone is not yet elucidated, one involving an intermediate carbonium ion (Chart I) seems to be plausible by analogy with the well-known adamantylmethyl type.[7]

(6) Homoadamantanone: (a) G. B. Gill and R. M. Black, *J. Chem. Soc. C*, 671 (1970); (b) P. von R. Schleyer, E. Funke, and S. H. Liggero, *J. Amer. Chem. Soc.*, 91, 3965 (1969). (c) Trimethylhomoadamantanone: K. Bott, *Tetrahedron Lett.*, 1747 (1969).

(7) H. Stetter and P. Goebel, *Chem. Ber.*, 96, 550 (1963).

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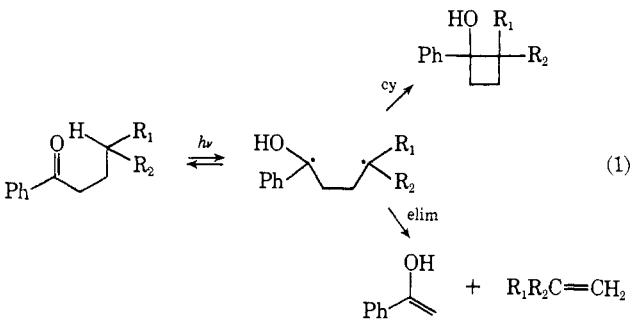
Photochemistry of Methyl-Substituted Butyrophenones. The Nature of the 1,4-Biradical Intermediates[1]

Sir:

The type II photoelimination and cyclization reactions of aryl alkyl ketones having a γ-hydrogen have been the subject of extensive investigations.[2-7] It is generally agreed that a 1,4-biradical intermediate formed upon γ-hydrogen abstraction by the carbonyl excited state gives rise to elimination and cyclization products as well as ground-state ketone formed by biradical disproportionation (eq 1). Whereas the effect of structure and solvent on the rate constant for γ-hydrogen abstraction and quantum yield for photoelimination have been extensively studied, little is known about the nature of the biradical and the factors which govern the relative rate constants for cyclization and elimination as well as the stereochemistry of

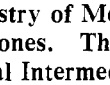
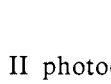
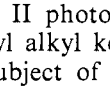
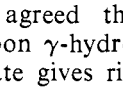
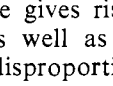
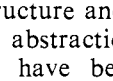
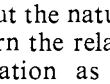
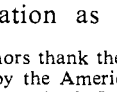
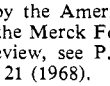


(1)

cyclization. As part of a study designed to provide information about the nature of 1,4-biradical intermediates,[8] the photochemistry of the methyl-substituted butyrophenones **1**–**10** has been investigated.

Ketones **2**, **5**, **7**, **8**, and **9** were synthesized by standard Grignard reactions, **3** and **6** by dialkylation of **1** and **4** with sodium hydride and methyl iodide, and **10** by the reaction of 3,3-dimethylacrylic acid with phenyllithium followed by conjugate addition of 2-propylmagnesium bromide in the presence of cuprous ion.[9] The ketones were purified by column chromatography or preparative vpc prior to photolysis. Quantum yields were determined on degassed 0.05 *M* benzene solutions irradiated to less than 5% conversion at 3130 Å using a merry-go-round apparatus and benzophenone–benzhydrol actinometers.[10] Quantum yields for type II elimination (Table I) are in reasonable

Table I. Quantum Yields and Kinetic Data for Photoelimination and Cyclization of Aryl Alkyl Ketones

	Ketone	Φ_{elim}	Φ_{cy}	Φ_{total}	% cy	$k_q\tau$, M^{-1}
1		0.36	0.042	0.40	10	670[a]
2		0.28	0.116 t	0.40	29	390
3		0.004	0.032	0.036	89	260
4		0.33	0.069 t 0.022 c	0.42	22	36[a]
5		0.17	0.094 t,t 0.030 t,c	0.29	43	37
6		0.012	0.044 t 0.018 c	0.074	84	44
7		0.26	0.045	0.30	15	245[a]
8		0.17	<0.005	0.17	<3	93
9		0.24	0.041	0.28	15	11[a]
10		0.014	~0.001	0.015	<10	5.6

[a] Values from ref 4a.

(1) The authors thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, The Research Corporation, and the Merck Foundation for support of this research.

(2) For a review, see P. J. Wagner and G. S. Hammond, *Advan. Photochem.*, 5, 21 (1968).

(3) P. J. Wagner, *J. Amer. Chem. Soc.*, 89, 5898 (1967).

(4) (a) P. J. Wagner and A. E. Kemppainen, *ibid.*, 90, 5896 (1968); (b) J. N. Pitts, D. R. Burley, J. C. Mani, and A. D. Broadbent, *ibid.*, 90, 5900 (1968); (c) P. J. Wagner and H. N. Schott, *ibid.*, 91, 5383 (1969).

(5) J. N. Barltrop and J. D. Coyle, *ibid.*, 90, 6584 (1968).

(6) F. D. Lewis and N. J. Turro, *ibid.*, 92, 311 (1970).

(7) F. D. Lewis, *ibid.*, 92, 5602 (1970).

(8) See ref 7 for the preceding paper in this series.

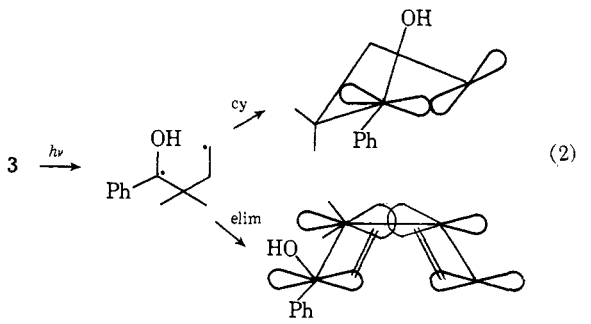
(9) J. A. Marshall and N. H. Andersen, *J. Org. Chem.*, 31, 667 (1966).

(10) W. M. Moore and M. Ketchum, *J. Amer. Chem. Soc.*, 84, 1368 (1962).

agreement with literature values[4] for ketones **1**, **4**, **7**, and **9**. The cyclobutanols were identified and their stereochemistry assigned by nmr analysis of samples obtained by preparative vpc. The percentage cyclization results for ketones **1**, **4**, and **9** are in good agreement with those of Barltrop and Coyle.[5] For ketones **3** and **6** benzaldehyde was formed in addition to the elimination and cyclization products, thus indicating competition of γ-hydrogen abstraction with α cleavage.[11] Using piperylene as a triplet quencher, linear Stern–Volmer plots with slopes equal to $k_q\tau$ (Table I) were obtained. Rate constants for γ-hydrogen abstraction can be estimated assuming that quenching occurs at a diffusion-controlled rate ($5 \times 10^9\ M^{-1}\ \text{sec}^{-1}$ [13]) and that γ-hydrogen abstraction is the major pathway for triplet deactivation.

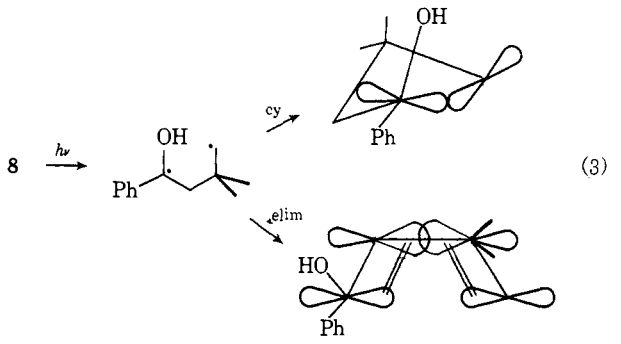
Several results in Table I are of considerable interest. The most striking is the increase in the percentage of cyclization upon α substitution. For example, α-methyl and α,α-dimethyl substitution of butyrophenone increases the percentage of cyclization from 10 to 29 and 89%, respectively. In contrast to the effect of α substituents, β substituents result in a small increase in the percentage of cyclization for β-methyl- and a decrease for β,β-dimethylbutyrophenone (compare **1**, **7**, **8**). The effect of γ substituents is similar to that for β substituents except for a less pronounced decrease in the percentage of cyclization for the γ,γ-dimethylbutyrophenone (**9**).

The observed substituent effects are best explained by examination of the transition states for cyclization and elimination of the 1,4-biradical intermediates formed upon γ-hydrogen abstraction. The transition state for cyclization of a 1,4-biradical intermediate requires overlap of the radical centers. However, the carbon skeleton probably is nonplanar so as to minimize 1,2-eclipsing interactions.[13] The most favorable transition state for elimination requires maximum overlap of both radical orbitals with the bond undergoing cleavage.[14] This requires the radical centers to be parallel to the β bond[17] and results in some eclipsing of α substituents with the hydroxyl and phenyl groups and of β substituents by γ substituents. The magnitude of these eclipsing interactions will depend upon the extent of rehybridization at the radical centers, being greatest for no rehybridization. Using these arguments, the biradical from **3** is probably subject to less severe 1,2-eclipsing interactions in the transition state for cyclization than in the one for elimination (eq 2).



(2)

For the biradical from **8** there are no serious eclipsing interactions for elimination, whereas the transition state leading to cyclization has a 1,3-diaxial methyl–hydroxyl interaction (eq 3). The strength of 1,3-diaxial interactions in cyclobutanes is shown by the fact that 1,3 cis disubstituted cyclobutanes, in which both substituents can be equatorial, are considerably



(3)

less planar than 1,3 trans disubstituted cyclobutanes, in which one of the substituents is axial in a nonplanar conformation.[18] The marked decrease in cyclization in going from **7** to **8** can thus be explained by the ability of the cyclobutanol ring to accommodate a single equatorial 3-methyl substituent as opposed to the more serious 1,3-diaxial interaction in the transition state leading to 3,3-dimethyl-1-phenylcyclobutanol. Ketone **10** was synthesized in order to investigate the effect of β,γ-eclipsing interactions on the elimination reaction.[19] However, since 1,3-diaxial interactions will be present in the transition state for cyclization, both cyclization and elimination should be impeded. The low total quantum yield for **10** could result from eclipsing of the β- and γ-methyls in the six-membered transition state for γ-hydrogen abstraction as well as inefficiency in product formation from the biradical. Since γ-substituents alone do not give rise to large nonbonded interactions in either the elimination or cyclization transition states it is not surprising that the percentage of cyclization does not change substantially in going from **1** to **4** to **9**.

Several of the aryl alkyl ketones in Table I can give more than one stereoisomeric cyclobutanol. Both **2** and **4** form 2-methyl-1-phenylcyclobutanol; however, whereas a 3.1:1 trans:cis ratio is observed for **4**, only the trans isomer (>95%) is observed for **2**. The specificity of **2** may be due to a repulsive interaction of

(11) α cleavage has been observed for *tert*-butyl phenyl ketone.[12] The photochemistry of *tert*-alkyl aryl ketones is under continued investigation.

(12) F. D. Lewis, *Tetrahedron Lett.*, 1373 (1970).

(13) J. B. Lambert and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 3384, 3891 (1965).

(14) Wagner[4a] has suggested such a conformational requirement for elimination. Similar arguments have been used by Turro and coworkers to explain the low efficiency of β cleavage from the 1,4-biradicals generated by γ-hydrogen abstraction from α-alkylcyclohexanones,[15] 1-adamantylacetone, and a number of keto steroids.[16] In these cases the conformations of cycloalkyl rings prevent maximum overlap of the radical orbitals with the β bond, whereas in our acyclic biradicals only 1,2-eclipsing interactions are involved. We thank Professor Turro for informing us of his results prior to publication.

(15) D. S. Weiss, N. J. Turro, and J. C. Dalton, *Mol. Photochem.*, **2**, 91 (1970).

(16) R. B. Gagosian, J. C. Dalton, and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 4752 (1970).

(17) The 1,4 biradical need not be cisoid as shown in eq 2 and 3 for elimination to occur.

(18) (a) F. Lautenschlaeger and G. F. Wright, *Can. J. Chem.*, **41**, 863 (1963); (b) E. Adman and T. N. Margulis, *Chem. Commun.*, 641 (1967); (c) E. Adman and T. N. Margulis, *J. Amer. Chem. Soc.*, **90**, 4517 (1968).

(19) Both primary and tertiary γ-hydrogen abstraction can occur for **10**; however, the large rate constant makes primary abstraction seem unlikely.

the phenyl and α-methyl groups in the 1,4 biradical. The interaction between the phenyl and γ-methyl groups in the biradical from **4** should be small until the 1,4 bond is almost completely formed. The 3.1:1 trans,trans to trans,cis ratio observed for **5** can be interpreted as a superposition of the α-methyl being all trans as in **2** and the γ-methyl being 3.1:1 trans:cis as in **4**. No cis,cis isomer was detected. The 2.4:1 trans:cis ratio for **6** again reflects the small trans preference of the γ-methyl.

Transition-state arguments do not directly take into account the effects of methyl substituents upon the stability of the olefins formed upon elimination. However, in view of the high energy content of the 1,4-biradical intermediate,[6,20] ground-state stabilities would not be expected to be controlling. The lack of correlation between olefin stability and the results in Table I support this conclusion. It should be emphasized that the results in Table I are consistent with a 1,4-biradical intermediate mechanism and are not easily explained by alternate mechanisms.

The kinetic data in Table I are of interest for two reasons. First, they further illustrate the lack of correlation between triplet-state reactivity and the quantum yield for product formation.[4,6] Second, they show that the reactivity toward γ-hydrogen abstraction depends primarily upon the extent of substitution at the γ carbon and is relatively insensitive to substitution at the α or β carbons. The small increase in rate constant in the series **1**, **7**, **8** seems to reflect the increase in the number of abstractable γ hydrogens.

In conclusion, the behavior of 1,4-biradical intermediates formed by γ-hydrogen abstraction in methyl-substituted butyrophenones is highly sensitive to the position and number of substituents. Particularly important from a synthetic viewpoint are the high percentage of cyclization products formed by α-methyl aryl alkyl ketones and the stereoselectivity of the cyclization reaction. Furthermore the transition state arguments used to explain the effects of α, β, and γ substituents upon the cyclization and elimination reactions should have general applicability in predicting the behavior of 1,4 biradicals. We are currently investigating such a possibility.

(20) E. D. Feit, *Tetrahedron Lett.*, 1475 (1970).

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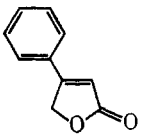
Received June 27, 1970

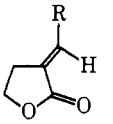
Chromophoric Lactones and the Mechanism of Chymotrypsin Action[1]

Sir:

The acylchymotrypsin intermediates formed in the chymotrypsin-catalyzed hydrolysis of esters and amides have been suggested to be in the cis (lactone-like) configuration rather than the normal ester trans configuration. This suggestion was initially made to account for the lability of the acylserine-195 bond[2] and subsequently to account for the red shifting of the λ_{max} value associated with the $\pi-\pi^*$ transition in native β-arylacryloylchymotrypsins[3] when compared to the denatured intermediate[4] and small *O*-(β-arylacryloyl)-*N*-acetylserine peptide derivatives.[5] To ascertain if the "cis hypothesis" could account for the spectral characteristics of acyl-enzyme intermediates we have compared the spectra of compounds I–IV to those for the corresponding β-arylacryloylchymotrypsins and *O*-(β-arylacryloyl)-*N*-acetylserinamides.[6]



I



II, R = C_6H_5
III, R = 2-furoyl
IV, R = 3-indolyl

The λ_{max} values for I and II (water) were found at 274 and 284.5 nm, respectively. When compared to λ_{max} for *trans*-cinnamoylchymotrypsin (Table I), the spectrum of II is seen to approach most closely that for the chymotrypsin derivative. The λ_{max} values for the exocyclic *trans*-lactones II, III, and IV are compared to those for β-arylacryloylchymotrypsins, *O*-(β-arylacryloyl)-*N*-acetylserinamides, and methyl β-arylacryloyl esters in Table I. From Table I the *O*-acylserinamides possess λ_{max} values identical with those of the corresponding denatured *O*-acylchymotrypsins, while the λ_{max} values for the lactones approach (in water) and are nearly identical (10 *M* LiCl) with those values for native *O*-acylchymotrypsins.

The reported values of ϵ_{max} for native and denatured acyl-α-chymotrypsins are however very similar (±5%).[11a] Since ϵ_{max} for a trans isomer (in a conjugated enone) is 10% > that of the corresponding s-cis isomer, it has been proposed by Oliver, *et al.*,[11b] that an s-cis → s-trans isomerization is not responsible for the difference in λ_{max} observed between the native and denatured acyl-α-chymotrypsins. The spectral shift could rather be explained as a result of the change in the polarity of the environment. However, the data of Table I show that a change in the polarity of the medium also leads to a change in ϵ_{max} for the chromophores, so that the observed spectral change for the acyl-α-

(1) This research was supported by a grant from the National Institutes of Health.

(2) (a) T. C. Bruice, *J. Polym. Sci.*, **49**, 101 (1961); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapter 2.

(3) E. Charney and S. A. Bernhard, *J. Amer. Chem. Soc.*, **89**, 2726 (1967).

(4) S. A. Bernhard, S. J. Law, and H. Noller, *Biochemistry*, **4**, 1108 (1965).

(5) M. L. Bender, G. R. Schonbaum, and B. Zerner, *J. Amer. Chem. Soc.*, **84**, 2540 (1962).

(6) Lactones I, II, and III were prepared by modification of published procedures (I, mp 90–92.5°, lit.[7] 94°; II, mp 116.5–118°, lit.[8] 115–116°; III, mp 91–93°, lit.[8] mp 95°). For lactone IV: α-(γ-butyrylactonylidene)triphenylphosphorane[9] (4.5 g; 0.013 mol) and indole-3-carboxyaldehyde[10] (1.88 g; 0.013 mol) were refluxed in 450 ml of tetrahydrofuran for 34 hr; after removal of solvent and recrystallization several times (charcoal) from methanol, mp 224–225.5°; ν_{max} (KBr) 1720 cm^{-1} (C=O). *Anal.* Calcd for $C_{13}H_{11}NO_2$: C, 73.2; H, 5.20; N, 6.57. Found: C, 73.09; H, 5.39; N, 6.65.

(7) M. Sutanbawa, P. Veeravagu, and T. Padmanathon, *J. Chem. Soc.*, 1262 (1960).

(8) W. Reppe, *Justus Liebigs Ann. Chem.*, **596**, 158 (1955).

(9) S. Fliszor, R. F. Hudson, and G. Salvadori, *Helv. Chim. Acta*, **46**, 1580 (1963).

(10) H. Zimmer and T. Pampalone, *J. Heterocycl. Chem.*, **2**, 95 (1965).

(11) (a) R. W. A. Oliver, T. Viswonatha, and W. J. D. Whish, *Biochem. Biophys. Res. Commun.*, **27**, 107 (1967); (b) J. T. Johnsen, R. W. A. Oliver, and I. B. Svendsen, *C. R. Trav. Lab. Carlsberg*, **37**, 87 (1969).