Photoaddition Reaction of Biacetyl

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The photochemical reaction of biacetyl with various olefins has been investigated. Irradiations of biacetyl with indene, furan, and ethyl vinyl ether give oxetanes with higher orientational selectivity than that of monoketones. In the case of methyl-substituted olefins, it is found that novel products, 2-acetoethyl allyl ethers, accompany the oxetanes and are formed in good yield. The ratios of these products vary with the olefins used. The presence of biradical intermediates formed by addition of excited biacetyl to olefins is established by deuterium-labeling experiments. The quenching of biacetyl phosphorescence by an olefin indicates that the n-π^* triplet state of biacetyl is involved in these reactions. The absence of adduct in the case of electron-deficient olefins indicates that the excited biacetyl is electrophilic in its reaction with olefins. The mechanism of these reactions is best described as an electrophilic attack of the n-π^* triplet state of biacetyl to the olefins to give a biradical intermediate which undergoes competitive cyclization and disproportionation. The difference in the reactivity of biacetyl toward photoaddition relative to monoketones and *o*-quinones is discussed.

In recent years, the photochemical behavior of α-diketones has attracted a great deal of attention. The results reported in the literature[1-14] have produced considerable knowledge about the photochemical behavior of alkyl α-diketones.

It is well known that *o*-quinones undergo photoaddition to olefins to produce oxetanes and dioxenes.[15] Their formation is reasonably explained on the basis of a biradical intermediate. An interesting result, reported by Staab and Ipaktschi, was that irradiation of benzocyclobutanedione in the presence of olefins resulted in the formation of the spirolactonecyclopropane derivatives *via* carbene intermediates.[16] However, no report exists which describes photoaddition of acyclic alkyl α-diketones to olefins.

Biacetyl and other alkyl α-diketones exhibit phosphorescence in solution at room temperature, in spite of the general lack of phosphorescence from monoketones, and abstract hydrogen atoms with a rate constant which is very small relative to monoketones.[12d] Rubin and coworkers have demonstrated that photoreduction of *o*-quinones such as 9,10-phenanthrenequinone gives 1,2 and 1,4 adducts, whereas camphorquinone gives only 1,2 adducts.[17] Furthermore, Gream and coworkers have shown that the photoreactions of nonenolizable cyclic α-diketones with alcohols, amines, and olefins are not necessarily analogous to those of *o*-quinones.[8] These observations suggested to us that the photochemical behavior of acyclic alkyl α-diketones toward olefins might be different from that of monoketones and *o*-quinones. Hence, we investigated the photoaddition of biacetyl to various olefins and tried to compare our results with those of other compounds.[18]

Results

All photochemical reactions described herein were carried out with a 350-W high-pressure mercury lamp in Pyrex glass under nitrogen filtered through an *n*-hexane solution of naphthalene (λ >320 nm) at room temperature. Major products were 1:1 adducts in each case. The various adducts were isolated by distillation and preparative vapor phase chromatography, and their structures were determined by ir, nmr, and mass spectra and elemental analysis as detailed in the Experimental Section. The ratios of the products were determined by vpc.

The reactions of biacetyl with indene, furan, and ethyl vinyl ether gave oxetanes as main products. In the case of indene, two oxetanes, **1** and **2** (1:2), in which the C_2 position of indene was attached to the carbonyl oxygen of biacetyl, were obtained. The stereochemistry of **1** and **2** was assigned on the basis of the nmr spectra. Oxetane **3** and **4** were obtained from furan and ethyl vinyl ether, respectively.[19]

These results suggest that the addition of biacetyl proceeds with higher orientational selectivity than that of monoketones.[20] In no instance was there a detectable amount of dioxenes, and observation which contrasts with the results for 9,10-phenanthrenequinone.[15]

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[1] (a) W. H. Urry and D. J. Trecker, *J. Amer. Chem. Soc.*, **84**, 118 (1962); (b) W. H. Urry, D. J. Trecker, and D. A. Winey, *Tetrahedron Lett.*, 609 (1962).

[2] P. W. Jolly and P. de Mayo, *Can. J. Chem.*, **42**, 170 (1964).

[3] W. G. Bentrude and K. R. Darnall, *Chem. Commun.*, 810(1968).

[4] R. Bishop and N. K. Hamer, *J. Chem. Soc. C*, 1193 (1970); 1197 (1970).

[5] T. L. Burkoth and E. F. Ullman, *Tetrahedron Lett.*, 145 (1969).

[6] B. Äkermark and N.-G. Johasson, *ibid.*, 371 (1969).

[7] S. P. Pappas, J. E. Alexander, and R. D. Zehr, Jr., *J. Amer. Chem. Soc.*, **92**, 6927 (1970).

[8] (a) G. E. Gream, J. C. Paice, and C. C. R. Ramsay, *Aust. J. Chem.*, **20**, 1671 (1967); (b) G. E. Gream, J. C. Paice, and B. S. J. Uszynski, *Chem. Commun.*, 895 (1970); (c) G. E. Gream, M. Mular, and J. C. Paice, *Tetrahedron Lett.*, 3479 (1970).

[9] W. M. Horspool and G. D. Khandelwal, *Chem. Commun.*, 257 (1970).

[10] (a) J. Lemaire, *J. Phys. Chem.*, **71**, 2653 (1967); (b) J. Lemaire, M. Niclause, X. Deglise, J. C. Andre, and G. Penson, and M. Bouchy, *C. R. Acad. Sci., Ser. C*, **267**, 33 (1968).

[11] R. G. Zepp and P. J. Wagner, *J. Amer. Chem. Soc.*, **92**, 7466 (1970).

[12] (a) N. J. Turro and R. Engel, *Mol. Photochem.*, **1**, 143 (1969); (b) *ibid.*, **1**, 235 (1969); (c) *J. Amer. Chem. Soc.*, **91**, 7113 (1969); (d) N. J. Turro and T.-J. Lee, *ibid.*, **91**, 5651 (1969); (e) *ibid.*, **92**, 7467 (1970).

[13] (a) H. L. J. Backstrom and K. Sandros, *Acta Chem. Scand.*, **12**, 823 (1958); (b) K. Sandros and H. L. J. Backstrom, *ibid.*, **16**, 958 (1962); (c) K. Sandros, *ibid.*, **18**, 2355 (1964).

[14] E. J. Baum and R. O. C. Norman, *J. Chem. Soc. B*, 227 (1968).

[15] G. P. Fundt and G. O. Schenck in "1,4-Cycloadditions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, p 345.

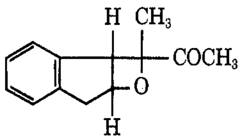
[16] H. A. Staab and J. Ipaktschi, *Chem. Ber.*, **101**, 1457 (1968).

[17] (a) M. B. Rubin and P. Zwitkowits, *Tetrahedron Lett.*, 2453 (1965); (b) M. B. Rubin and R. G. Labarge, *J. Org. Chem.*, **31**, 3283 (1966); (c) M. R. Rubin and R. A. Reith, *Chem. Commun.*, 431 (1966); (d) M. B. Rubin, *Fortschr. Chem. Forsch.*, **13**, 251 (1969); (e) M. B. Rubin and Z. Hershitik, *Chem. Commun.*, 1267 (1970).

[18] For preliminary accounts of a portion of this work, see (a) H.-S. Ryang, K. Shima, and H. Sakurai, *Tetrahedron Lett.*, 1091 (1970); (b) *J. Amer. Chem. Soc.*, **93**, 5270 (1971).

[19] Unfortunately, the configurations of **3** and **4** were not determined from present data.

[20] For example, The photoreaction of acetone with ethyl vinyl ether gave both 3-ethoxyoxetane (70%) and 2-ethoxyoxetane (30%), see (a) S. H. Schroeter and C. M. Orlando, Jr., *J. Org. Chem.*, **34**, 1181 (1969); (b) N. J. Turro and P. A. Wriede, *ibid.*, **34**, 3562 (1969).



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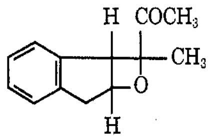

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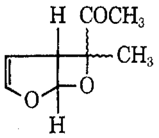

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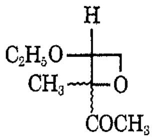

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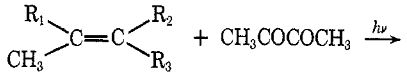
Photoaddition reactions of biacetyl were also carried out with methyl-substituted olefins, *i.e.*, 2-ethoxypropene (**5a**), α-methylstyrene (**5b**), isobutene (**5c**), 2-methyl-2-butene (**5d**), and 2,3-dimethyl-2-butene (**5e**). A new type of product, 1-acetoethyl allyl ethers **6**, accompanied the oxetane isomers **7** and **8** (Table I).



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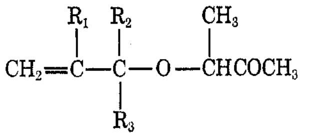
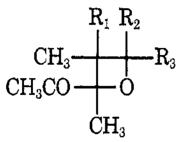


$$CH_2{=}\overset{R_1}{C}—\underset{R_3}{\overset{R_2}{C}}—O—\overset{CH_3}{C}HCOCH_3$$

6



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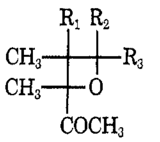

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a, $R_1 = OC_2H_5$; $R_2 = R_3 = H$
b, $R_1 = C_6H_5$; $R_2 = R_3 = H$
c, $R_1 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_2 = CH_3$; $R_3 = H$
e, $R_1 = R_2 = R_3 = CH_3$

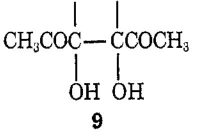
TABLE I

PRODUCT YIELD FOR DISPROPORTIONATION AND CYCLIZATION OF BIACETYL–METHYL-SUBSTITUTED OLEFIN PHOTOREACTION[a]

Olefin	Product yield, % 6	7	8	Ratio of (7 + 8)/6
5a	27	36	21	2.1
5b	27	41	7	1.8
5c	16	10		0.62
5d	54	21[b]		0.41
5e	70			0

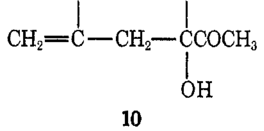
[a] Irradiated at room temperature. Product distribution determined by vpc. [b] An isomer of oxetanes alone has been observed.

The ratios of these products vary with the olefins used. Two oxetanes were produced from **5a** and **5b**, whereas only one of the four possible oxetane isomers was isolated from **5d**. Irradiation with **5c** gave, in addition to an allylic ether and an oxetane, the corresponding pinacol **9** and an unsaturated alcohol **10**



$$CH_3CO\underset{OH}{\overset{CH_3}{C}}—\underset{OH}{\overset{CH_3}{C}}COCH_3$$

9



$$CH_2{=}\overset{CH_3}{C}—CH_2—\underset{OH}{\overset{CH_3}{C}}COCH_3$$

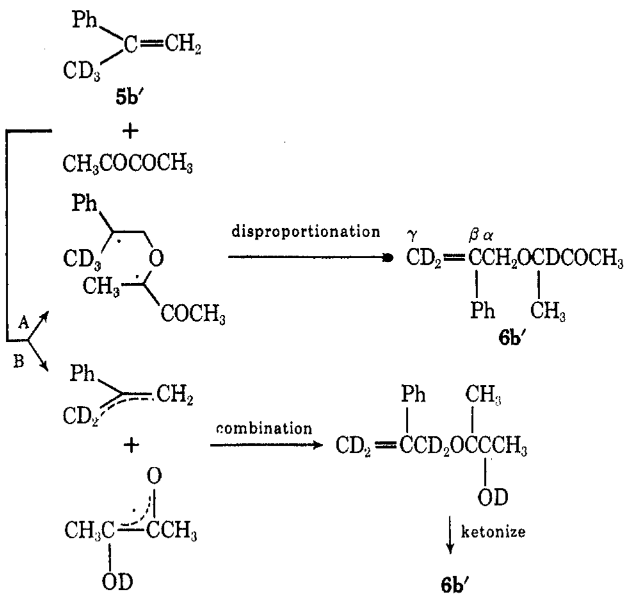
10

arising from initial hydrogen abstraction from **5c** by excited biacetyl and subsequent combination of the two radicals. No oxetane was isolated in the case of **5e**.[21]

The formation of **6** is of interest in comparison with the results from monoketones and *o*-quinones. Photostability studies[22] and constant product ratios during the irradiations[23] have shown that the adducts are the primary photochemical products.

It is generally recognized that α-diketones undergo primary photochemical addition to olefins in competition with hydrogen abstraction, α cleavage, and enol formation. This suggested to us that **6** is formed through either (A) an attack of the excited carbonyl oxygen of biacetyl on olefin to form a biradical intermediate followed by intramolecular hydrogen transfer or (B) initial hydrogen abstraction from olefin by the excited carbonyl of biacetyl followed by combination of the two radicals formed.[24]

In order to determine the mechanism for the formation of **6**, the photoreaction of biacetyl with *α-methyl-d₃*-styrene (**5b′**) was investigated. **5b′** was prepared by the Wittig reaction of trideuteriomethyl phenyl ketone with methyltriphenylphosphonium bromide.[25] Irradiation and isolation of the products were carried out as for **5b**. No deuterium was introduced into the position C_α of the allyl moiety in **6b′**.[26]



This result demonstrates that **6** is produced through path A, since path B would introduce deuterium equally into positions C_α and C_γ.

It is suggested that a two-step addition *via* the biradical intermediate is involved in this reaction, but

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(21) Several small peaks detected by vpc do not exclude the possibility of the presence of small amounts of oxetane.

(22) Adducts **6b**, **7b**, and **8b** were individually irradiated under the reaction conditions. Each adduct was recovered unchanged.

(23) The yields of **6b**, **7b**, and **8b** were proportional to the irradiation time with the same ratio as in Table I.

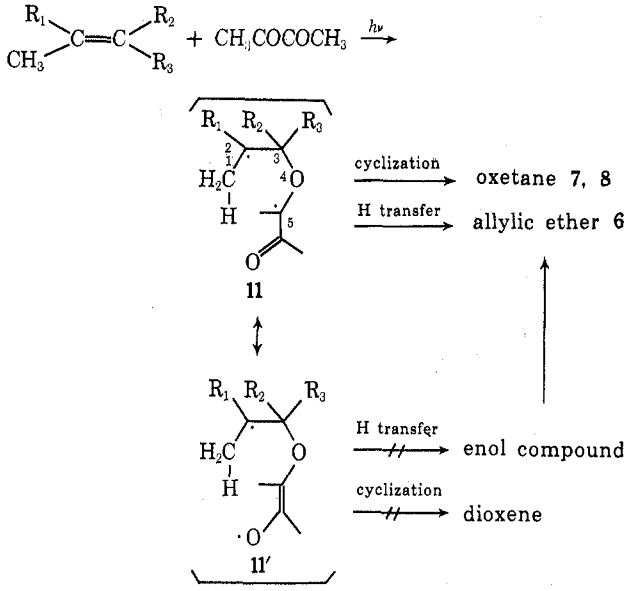
(24) A similar mechanism is discussed for the photoreaction of 2-cyclohexenone with isobutene and that of chromone with 2,3-dimethyl-2-butene, but exact mechanism for these reactions have not been determined, see (a) E. J. Corey, J. D. Bass, R. Lemahiew, and R. M. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (b) J. W. Hanifin and E. Cohen, *ibid.*, **91**, 4494 (1969).

(25) H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **86**, 677 (1967).

(26) Deuterium contents were determined by nmr. The oxetanes and the recovered olefin were deuterated the same per cent as the starting olefin (D = 87%), and no scrambling occurred in them.

there may be some question as to whether the hydrogen transfer proceeds *via* the carbon radical or the oxygen radical. It may be argued that the hydrogen transfer proceeds *via* a six-membered transition state involving the carbon radical, because hydrogen transfer to oxygen must involve an eight-membered transition state, where the probability of an encounter between the two active centers is lower than that in a six-membered transition state. Furthermore, the 1,4 cycloadduct is not obtained in this reaction. However, Padwa and coworkers have reported that irradiation of 2-phenylcyclobutyl phenyl ketone gave 1,5-diphenyl-4-penten-1-one, whose formation has been explained in terms of mechanism involving internal hydrogen abstraction followed by rearrangement of the enol to a carbonyl group.[27]

In order to clarify this point, a mixture of biacetyl and **5b** in deuteriomethanol was irradiated.[28] The nmr and mass spectra of the product showed no deuterium incorporation at any position. This observation can be reasonably interpreted in terms of hydrogen transfer *via* a six-membered transition state involving the carbon radical, since the deuterium atom should be introduced into the methine position if hydrogen transfer to oxygen occurred.



Irradiation of biacetyl in the presence of electron-deficient olefins such as acrylonitrile or *trans*-1,2-dichloroethylene were also carried out in a similar way, but adduct formation was not observed. These results suggest that excited biacetyl is electrophilic in its reaction with olefins.

In order to identify the excited state of biacetyl which is involved in these reactions, the emission of biacetyl (0.05 *M*) in the presence of **5e** (1.0 *M*) was examined in degassed benzene at room temperature and compared with the results in the absence of **5e**. The phosphorescence of biacetyl was completely quenched but the fluorescence was unaffected, which indicates that the reactions proceed by way of the n–π^* triplet of biacetyl.

Discussion

The most reasonable explanation for the above results is as follows. Electrophilic attack of the carbonyl oxygen of excited biacetyl (n–π^* triplet) on olefin leads to a biradical intermediate, which either cyclizes to form oxetane or disproportionates intramolecularly to give **6**. It is generally recognized that the free energy for cyclization is mainly governed by a strain factor and by the probability of the two active centers meeting each other.[29] It seems reasonable to think that the ratios of cyclization to disproportionation shown in Table I are governed by the difference in the activation energies between the two processes.

The results in Table I provide an interesting information on the behavior of the 1,4-biradical intermediates generated by biacetyl–olefin photoaddition (**11**). The decrease in amount of cyclization in going from **5c** to **5d** to **5e** suggests that R_2 and R_3 substituents affect this process considerably; *i.e.*, the decrease in cyclization for **5d** and **5e** is due to an increase of steric repulsion between the substituents at C_3 and C_5 positions in the transition state leading to oxetane formation. Lewis and Hilliard have shown that 1,3-diaxial interactions decrease cyclobutane formation which occurs *via* 1,4-biradical intermediate formed by γ-hydrogen abstraction in methyl-substituted butyrophenones.[30] The presence of a 1,3-diaxial interaction can be also considered as an important factor which governs ring closure *via* the biradical **11**. The more stereoselective oxetane formation for **5b** compared with **5a** may due to a 1,4 repulsive interaction which exists in **11** between the phenyl and acetyl groups. However, the ratios of cyclization to disproportionation for **5a** and **5b** markedly increase in comparison with that for **5c**. This result suggests that disproportionation rather than cyclization is influenced by R_1 substituents. The increase of these ratios for **5a** and **5b** may be due to the decrease in disproportionation for **5a** and **5b**. Probably, 1,4 steric repulsion by the large phenyl or ethoxy group decreases the probability of that conformation which leads to disproportionation in **11**.

In conclusion, the stereoselectivity of cyclization and the ratio of cyclization to disproportionation for biacetyl–olefin photoaddition are reasonably explained by considering steric interactions in 1,4-biradical intermediates. This indicates that the behavior of 1,4-biradical intermediates formed by biacetyl–olefin photoaddition is greatly influenced by substituents.

Our results unambiguously demonstrate that the photochemical behavior of biacetyl to olefins is different from that of monoketones and *o*-quinones such as 9,10-phenanthrenequinone, mainly in the following points: (1) the addition reactions give oxetanes with higher orientational and stereoselectivity than those of monoketones; (2) 1,4 cycloadduct is not formed in appreciable amount, which contrasts with the results for *o*-quinones; (3) in the case of monoketones or *o*-

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(27) A. Padwa, E. Alexander, and M. Niemcyzk, *J. Amer. Chem. Soc.*, **91**, 456 (1969).

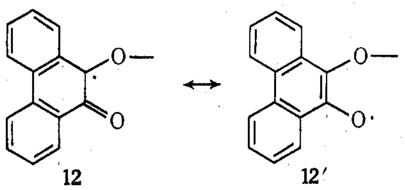
(28) A solution of biacetyl (0.03 *M*), **5b** (0.03 *M*), and MeOD (10 ml) in a Pyrex test tube was irradiated under the same conditions as in benzene. Deuterium incorporation of the isolated product was examined by nmr and mass.

(29) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 198.

(30) F. D. Lewis and T. A. Hilliard, *J. Amer. Chem. Soc.*, **94**, 3852 (1972).

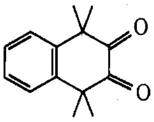
quinones, an adduct such as **6** has not been obtained in spite of the extensive studies of photoaddition of such carbonyl compounds to olefins.

More detailed experimental studies will be required to clarify the difference of the reactivity between these classes of compounds. However, previous mechanistic investigations and our own results prompt us to offer the following explanation on the mechanism of the photoaddition. The difference between biacetyl and *o*-quinones can be attributed to the difference in the contribution of the two resonance-stabilized radicals to the biradical intermediates. For *o*-quinones such as phenanthrenequinone, there exist two resonance semiquinone radicals **12** and **12′**; **12′** is more stabilized (4*n* + 2 electrons) than **12**. Hence, the contribution of **12′** is greater than that of **12**, whereas, in biacetyl which has no such resonance, the contribution of **11** is larger than that of **11′** because of the larger electronegativity of oxygen atom. Thus, the reactivity at the oxygen atom in the biradical derived from biacetyl is decreased in comparison with that of *o*-quinones.



12 **12′**

In addition, the steric difference between biacetyl and *o*-quinones may be an important factor. Gream and coworkers have shown that photoadditions of nonenolizable six-membered cyclic α-diketones (**13** and **14**) with cyclohexene, stilbene, or 2,3-dimethylbuta-1,3-diene gave dioxenes and keto oxetanes, while no dioxene was obtained for 3,3-dimethyl-1,2-dioxoindan (**15**).[8c] Dolling and coworkers have reported that irradiation of camphorquinone (**16**) in the presence of buta-1,3-diene gave the keto oxetanes as main products.[31] These facts suggest that 1,4 cycloadditions are strongly affected by the bond angle between the two carbonyl groups of *o*-quinones. In biacetyl, in contrast to *o*-quinones, the carbonyl groups are trans in the ground and probably the first excited triplet states. An attack of biacetyl in the trans conformation on olefin gives a biradical intermediate, where the bond between carbon atoms 5 and 6 must have double bond character because of conjugation with the adjacent carbonyl group. Hence, in any conformation of the biradical intermediate (**17**), the two carbon–oxygen bonds are most likely to be trans.[32] Such a situation is sterically unfavorable for reaction at the oxygen atom. The above interpretation would be in accord with the observed results and is supported by studies of the photoreduction of *o*-quinones[17,32b] and alkyl α-diketones.[1-3]



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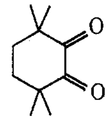

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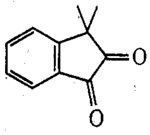

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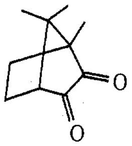

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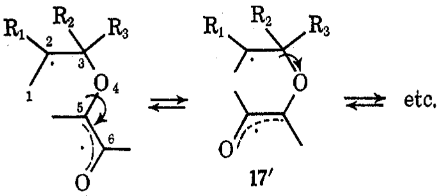

17 **17′**

Subsequently, we would like to consider the difference between biacetyl and monoketones. It is well known that free radicals undergoes competitive reactions.[33] In fact, several examples of competing reactions from a 1,4-biradical intermediates, whose nature is governed by the electronic and steric factors, have been reported, *i.e.*, 1,4-dithiane and thietane formation from photoaddition of thiobenzophenone to styrene,[34] and elimination, cyclization, and hydrogen reversal in type II photolysis of the ketones bearing γ hydrogen.[35] In addition, Liao and de Mayo in analogy with our results have reported that irradiation of adamantanethione and α-methylstyrene gave thietane and 2-adamantyl 2′-phenylallyl sulfide, and provided a reasonable explanation in terms of a mechanism involving competitive cyclization with hydrogen abstraction of an intermediate thiatetramethylene.[36]

While competitive cyclization and disproportionation in the reaction of biacetyl with olefins can be explained on the basis of steric repulsion in the biradical intermediate, monoketone–olefin photoaddition such as photoaddition of benzophenone to methyl-substituted olefins[37] gave no disproportionation products. Since all previous work shows that monoketones regardless of type predominantly form oxetanes, it is suggested that the difference in the behavior of biacetyl and monoketones toward photoaddition should be attributed to factors other than steric ones. More detailed mechanistic studies will clarify this point.

Further work on the nature of the 1,4-biradical intermediate during photoaddition as well as on the scope and application to other systems is currently underway and will be the subject of future reports.

Experimental Section

Nmr spectra were determined on a Hitachi Perkin-Elmer R-20 spectrometer or on a Jeol JNM JS-100 spectrometer in CCl_4 using tetramethylsilane as an internal standard. Infrared spectrometer were obtained on a Hitachi EPI-S2 infrared spectrophotometer. Mass spectra were performed on a Hitachi Perkin-Elmer RMU-60 mass spectrometer. Gas chromatographic analyses were run on a Shimadzu gas chromatograph (GC-3AF). Emission spectra were obtained with a Shimadzu MPF-2A spectrophotometer.

Organic Substrates.—The following substrates were prepared by the reported procedures: 2-ethoxypropene (**5a**),[38] 2-methyl-2-butene (**5d**),[39] and 2,3-dimethyl-2-butene (**5e**).[40] The remaining substrates were obtained from commercial sources.

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(31) W. L. Dilling, R. D. Kroening, and J. C. Little, *ibid.*, **92**, 928 (1970).

(32) Esr study has indicated that the monoprotonated semidione radical of biacetyl is trans; see (a) R. J. Pritchett, *Mol. Phys.*, **12**, 481 (1967); (b) B. M. Monroe and S. A. Weiner, *J. Amer. Chem. Soc.*, **91**, 450 (1969).

(33) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966.

(34) A. Ohno, Y. Ohnishi, and G. Tsuchihashi, *J. Amer. Chem. Soc.*, **91**, 5038 (1969).

(35) F. D. Lewis, *ibid.*, **92**, 5602 (1970), and references cited therein.

(36) C. C. Liao and P. de Mayo, *Chem. Commun.*, 1525 (1971).

(37) (a) D. R. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964); (b) N. C. Yang, M. Nussim, M. J. Jorgensen, and S. Murov, *ibid.*, 3657 (1964).

(38) M. A. Dolliver, T. L. Gersham, G. B. Kistiakowsky, E. A. Smith, and W. E. Vaugham, *J. Amer. Chem. Soc.*, **60**, 440 (1938).

(39) F. C. Whitmore, C. S. Rowland, S. N. Wrenn, and G. W. Kilmer, *ibid.*, **64**, 2970 (1942).

(40) I. Shurman and C. E. Boord, *ibid.*, **55**, 4930 (1933).

General Irradiation Procedure.—A mixture of 0.1 *M* of biacetyl and 0.1 *M* of an olefin in benzene (180 ml) was prepared in a Pyrex doughnut-type vessel. The solution was flushed with nitrogen for several minutes before being irradiated. Irradiation was run with a 350-W high-pressure mercury lamp in a quartz immersion well with water-cooled jacket at room temperature except for the case of isobutene (0°) using a filter solution with a path length of about 1 cm containing 12.8 g of naphthalene made up to 1 l. with distilled *n*-hexane which cut out wavelengths shorter than 320 nm and assured excitation of the first excited singlet state of biacetyl alone.

Biacetyl–Indene Photoadducts.—A solution of biacetyl and indene in benzene was irradiated for 48 hr. The volatile material was removed under reduced pressure and a fraction boiling at 100–120° (4 mm) (2.8 g) was collected; residues, 1.5 g. Vpc analysis using 3-m PEG 6000 column at 200° indicated two major peaks with the relative ratio of peak heights 1:2. A separation of these products was accomplished by preparative vpc on a 3-m PEG 6000 column (180°). The first component was identified as **1**: bp 120° (4 mm); *m/e* 202; ir 1720 (C=O) and 990 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.52 (3 H, s), 1.71 (3 H, s), 3.18 (2 H, d, *J* = 3.0 Hz), 3.90 (1 H, d, *J* = 5.5 Hz), 5.40 (1 H, q, *J* = 3.0 and 5.5 Hz), and 7.17 (4 H, m).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6,98. Found: C, 77.13; H, 6.87.

The second component was identified as **2**: bp 120° (4 mm); *m/e* 202; ir 1720 (C=O) and 990 cm^{-1} (oxetane ring); nmr (CCl_4) δ 0.86 (3 H, s), 2.31 (3 H, s), 3.13 (2 H, d, *J* = 3.0 Hz), 4.15 (1 H, d, *J* = 5.5 Hz), 5.25 (1 H, q, *J* = 3.0 and 5.5 Hz), and 7.20 (4 H, m).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.49; H, 7.11.

Biacetyl–Furan Photoadduct.—After irradiation of a mixture of biacetyl and furan for 48 hr, the volatile material was removed under reduced pressure and a fraction boiling at 94° (24 mm) (2.5 g) was collected; residues, 1.0 g. Vpc analysis (PEG 6000 or UCON LB 550x, 3-m, 140°) of the distillate showed one major peak. Redistillation gave pure **3**: *m/e* 154; ir 1730 (C=O), 1625 (C=C), and 970 cm^{-1} (oxetane ring); nmr δ (CCl_4) 1.33 (3 H, s), 2.28 (3 H, s), 3.85 (1 H, m, *J* = 4.0 and 3.0 Hz), 5.11 (1 H, t, *J* = 3.0 Hz), and 6.11 (1 H, d, *J* = 4.0 Hz).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.12; H, 6.78.

Biacetyl–Ethyl Vinyl Ether Photoadducts.—After 48-hr irradiation of a mixture of biacetyl and ethyl vinyl ether, the volatile material was removed under reduced pressure and two fractions boiling at 70° (20 mm) (3.7 g) and 100–110° (3 mm) (0.5 g) were collected; residues, 1.0 g. Vpc analysis (PEG 6000 or UCON LB 500×, 3-m, 130°) of the first distillate showed one major component. Redistillation of the first fraction gave pure **4**: *m/e* 158; ir 1725 (C=O) and 960 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.23 (3 H, t, *J* = 7.0 Hz), 1.38 (3 H, s), 2.28 (3 H, s), 3.43 (2 H, q, *J* = 7.0 Hz), and 4.10–4.90 (3 H, m, ring protons).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.54; H, 8.98.

Vpc analysis (UCON LB 550×, 1-m, 100°) of the second fraction showed many peaks which seemed to be decomposed materials. The mass spectrum and elemental analysis indicated that this fraction mainly consisted 2:1 adducts of biacetyl and ethyl vinyl ether, but the structure has not been determined yet because of its complex nmr spectrum.

Biacetyl–2-Ethoxypropene (5a) Photoadducts.—A mixture of biacetyl and **5a** was irradiated for 72 hr. After the removal of the unreacted materials, the fraction boiling at 80–98° (23 mm) (8.4 g) was collected; residues, 1.4 g. Vpc analysis using 3-m PEG-6000 column at 140° indicated three major peaks with the relative ratio of peak heights 1.7:1.0:1.3. The products were isolated by preparative vpc on 3-m PEG-6000 column at 150°. The first component was identified as **7a**: bp 87° (23 mm); *m/e* 172; ir 1730 (C=O) and 970 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.18 (3 H, t, *J* = 7.0 Hz), 1.31 (3 H, s), 1.40 (3, H, s), 2.15 (3 H, s), 3.38 (2 H, q, *J* = 7.0 Hz), 3.97 (1 H, d, *J* = 6.0 Hz), and 4.32 (1 H, d, *J* = 6.0 Hz).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.87; H, 9.38.

The second component was identified as **8a**: bp 87° (23 mm); *m/e* 172; ir 173 (C=O) and 970 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.07 (3 H, t, *J* = 7.0 Hz), 1.32 (3 H, s), 1.45 (3 H, s), 2.32 (3 H, s), 4.20 (1 H, d, *J* = 6.0 Hz), 3.30 (2 H, q, *J* = 7.0 Hz), and 4.48 (1 H, d, *J* = 6.0 Hz).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.54; H, 9.62.

The third component was identified as **6a**: bp 90° (23 mm); *m/e* 172; ir 1730 (C=O) and 1640 cm^{-1} (C=C); nmr (CCl_4) δ 1.24 (3 H, d, *J* = 7.0 Hz), 1.28 (3 H, t, *J* = 7.0 Hz), 2.12 (3 H, s), 3.74 (1 H, q, *J* = 7.0 Hz), 3.74 (2 H, q, *J* = 7.0 Hz), 3.83 (2 H, m), 3.94 (1 H, d, *J* = 1.5 Hz), and 4.09 (1 H, d, *J* = 1.5 Hz).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.49; H, 9.67.

Biacetyl–α-Methylstyrene (5b) Photoadducts.—A solution of biacetyl and **5b** was irradiated for 48 hr. After the removal of the unreacted material under reduced pressure, a fraction boiling at 110–120° (6 mm) (1.4 g) was collected; residues, 0.5 g. Vpc analysis using 3-m PEG-6000 column at 180° indicated three major peaks with the relative ratio of peak heights 5.8:1.0:3.8. These three photoproducts were isolated by preparative vpc on a 3-m PEG-6000 column at 180°. The first component was identified as **7b**: bp 85° (3 mm); *m/e* 204; ir 1725 (C=O) and 970 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.11 (3 H, s), 1.45 (3 H, s), 2.22 (3 H, s), 4.10 (1 H, d, *J* = 5.5 Hz), 4.96 (1 H, d, *J* = 5.5 Hz), and 7.12 (5 H, m).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.54; H, 7.96.

The second component was identified as **8b**: bp 85° (3 mm); *m/e* 204; ir 1725 (C=O) and 970 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.53 (3 H, s), 1.61 (3 H, s), 1.87 (3 H, s), 4.40 (1 H, d, *J* = 6.0 Hz), 5.10 (1 H, d, *J* = 6.0 Hz), and 7.12 (5 H, m).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.58; H, 8.13.

The third component was identified as **6b**: bp 90° (3 mm); *m/e* 204; ir 1730 (C=O), 1640 (C=C), and 1120 cm^{-1} (ether); nmr (CCl_4) δ 1.22 (3 H, d, *J* = 7.0 Hz), 2.00 (3 H, s), 3.74 (1 H, q, *J* = 7.0 Hz), 4.30 (2 H, m), 5.24 (1 H, d, *J* = 1.5 Hz), 5.42 (1 H, d, *J* = 1.5 Hz), and 7.22 (5 H, m).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.64; H, 7.86.

Biacetyl–Isobutene (5c) Photoadducts.—A solution of biacetyl and **5c** was irradiated 102 hr at 0° and distilled to obtain 2.4 g of photoproduct mixture, bp 60–90° (16 mm), and 0.7 g of residue. Dissolution of the distillate in hexane, cooling, and separation by suction filtration gave the pinacol **9** (0.4 g), recrystallized from hexane–ether: mp 95–96° (lit. mp 95–96°); nmr (CCl_4) δ 1.16 (3 H, s), 2.24 (3 H, s), and 4.46 (1 H, s). These were in accord with reported values.[2]

The filtrate was analysed by vpc (6-m PEG-6000 or UCON LB 550 ×, 110°). Three major peaks with the relative peak heights 1:1.6:4.1 were detected. The first and the second components [bp 55–60 (22 mm)] were separated as a mixture from the third component [bp 80° (22 mm)] by preparative vpc (3-m, UCON LB 550×, 110°), owing to the close retention time between the first and second components. Elemental analysis and mass spectra by a directly coupled gas chromatograph–mass spectrometer (Hitachi RMS-4) of a mixture of the first and the second component indicated that these components were 1:1 adduct of biacetyl and **5c** (*m/e* 142 for each component). Ir spectrum showed a carbonyl peak at 1720, vinyl peak at 1620, ether peak at 1110, and oxetane ring at 970 cm^{-1}. Nmr spectrum (100 MHz) of the mixture in CCl_4 showed that the first component was 3,3,4-trimethyl-4-acetyloxetane, having δ at 1.16 (3 H, s), 1.24 (3 H, s), 1.39 (3 H, s), 2.25 (3 H, s), and 4.13 (2 H, AB quartet, *J* = 5.5 Hz), and the second component was an allylic ether **6c**, having δ 1.31 (3 H, d, *J* = 7.0 Hz), 1.81 (3 H, m), 2.17 (3 H, s), 3.71 (1 H, q, *J* = 7.0 Hz), 4.87 (1 H, m), and 4.95 (1 H, m).

Anal (of the mixture). Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.89; H, 9.99.

The third component was identified as **10**: *m/e* 142; ir 3450 (OH), 1720 (C=O), and 1650 cm^{-1} (C=C); nmr (CCl_4) δ 1.30 (3 H, s), 1.72 (3 H, m), 2.17 (3 H, s), 2.38 (2 H, s), 3.40 (1 H, broad), 4.64 (1 H, m), and 4.78 (1 H, m).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.39; H, 9.72.

Biacetyl–2-Methyl-2-butene (5d) Photoadducts.—A mixture of biacetyl and **5d** was irradiated for 50 hr. After the removal of unreacted materials, the fraction boiling at 60–80° (25 mm) (5.3 g) was collected; residues, 1.5 g. The products were analyzed and separated by vpc using 3-m PEG 6000 at 130°. The relative ratio of peak heights of the two major peaks was 2.4:1.0. The first component was identified as **6d**: bp 65°

(20 mm); m/e 156; ir 1720 (C=O), 1650 (C=C), and 1110 cm^{-1} (ether); nmr (CCl_4) δ 1.22 (3 H, d, J = 7.0 Hz), 1.28 (3 H, d, J = 7.0 Hz), 1.72 (3 H, m), 2.11 (3 H, s), 3.70 (1 H, q, J = 7.0 Hz), 3.93 (1 H, q, J = 7.0 Hz), and 4.87 (2 H, m).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.29; H, 10.58.

The second component was identified as 2,3,3,4-tetramethyl-4-acetyloxetane: bp 70° (20 mm); m/e 156; ir 1720 (C=O) and 990^{-1} (oxetane ring); nmr (CCl_4) δ 0.95 (3 H, s), 1.10 (3 H, s), 1.18 (3 H, d, J = 7.0 Hz), 1.33 (3 H, s), 2.15 (3 H, s), and 4.40 (1 H, q, J = 7.0 Hz).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.47; H, 10.13.

Biacetyl-2,3-Dimethyl-2-butene (5e) Photoadducts.—A mixture of biacetyl and **5e** was irradiated for 48 hr. After the removal of unreacted materials, the fraction boiling at 73–84° (13 mm) (8.1 g) was collected; residues, 0.6 g. Vpc analysis (3-m PEG 6000 or UCON LB 550 X, 140°) indicated that the photoproduct mixture contained one major component **6e** and several minor components (**6e**:others = 5.0:1.0). The ir spectrum of the fraction mixture indicated that the minor components mainly consisted of alcohol compounds. Separation by preparative vpc (3-m PEG 6000, 140°) gave pure **6e**: bp 74° (13 mm); m/e 170; ir 1728 (C=O), 1650 (C=C), and 1110 cm^{-1} (ether); nmr (CCl_4) δ 1.16 (3 H, d, J = 7.0 Hz), 1.23 (3 H, s), 1.28 (3 H, s), 1.73 (3 H, m), 2.08 (3 H, s), 3.61 (1 H, q, J = 7.0 Hz), and 4.86 (2 H, m).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.39; H, 10.57.

Irradiation of Biacetyl to *α-methyl-d_3*-Styrene (5b′).—**5b′** (D = 87%) was prepared by the Wittig reaction of methyltriphenylphosphonium bromide and trideuteriomethyl phenyl ketone.[26] A mixture of 2.6 g (0.03 *M*) of biacetyl and 3.6 g (0.03 *M*) of **5b′** in 180 ml of benzene was irradiated for 60 hr. After the recovery of **5b′** (1.6 g), a boiling fraction at 110–120° (6 mm) (0.7 g) was collected; residues, 0.4 g. Vpc analysis and isolation of the products done by the same conditions as for **5b**. The ratio of **6b**:**7b**:**8b** = 2.0:5.8:1.0. The % D of starting and recovered **5b′** and the photoproducts were determined by nmr. No deuterium was introduced into position C_α of the allyl moiety of **6b′** (% D of C_γ and methine protons, 87%).

Biacetyl–Isobutene Photoaddition at Room Temperature.—A mixture of biacetyl (0.01 *M*) and isobutene (0.01 *M*) in benzene was irradiated at room temperature in a Pyrex test tube for 6 hr. The reaction mixture was analyzed as described above. It was shown that the ratio of **6c**:oxetane was 1.62:1.0.

Registry No.—**1**, 26995-37-9; **2**, 26995-38-0; **3**, 26959-33-1; **4**, 26959-34-2; **5a**, 926-66-9; **5b**, 98-83-9; **5b′**, 16914-16-2; **5c**, 115-11-7; **5d**, 513-35-9; **5e**, 563-79-1; **6a**, 40519-21-9; **6b**, 40519-22-0; **6c**, 40519-23-1; **6d**, 26959-35-3; **6e**, 40519-25-3; **7a**, 40519-26-4; **7b**, 40519-27-5; **8a**, 40580-22-1; **8b**, 40519-28-6; **10**, 40519-29-7; biacetyl, 431-03-8; indene, 95-13-6; furan, 110-00-9; ethyl vinyl ether, 109-92-2; 3,3,4-trimethyl-4-acetyloxetane, 40519-30-0; 2,3,3,4-tetramethyl-4-acetyloxetane, 26959-36-4; methylphenylphosphonium bromide, 1779-49-3; trideuteriomethyl phenyl ketone, 17537-31-4.

A Simple, High Yield Synthesis of Arginine Vasopressin

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Biologically fully active arginine vasopressin has been synthesized *via* the stepwise active ester and fragment condensation methods. The synthesis was begun with proline at the carboxyl terminus utilizing the trityl group for sulfhydryl protection of cysteine and the Boc group for amino nitrogen protection. Synthesis of Boc-Cys(Trt)-Tyr-Phe-Gln-Asn-Cys(Trt)-Pro was followed by cyclization of the cysteine moiety in 70% yield with I_2 in 80% acetic acid. The remaining dipeptide unit, Arg-Gly-NH_2, was attached to proline by means of the hydroxysuccinimide ester of the cyclized heptapeptide. The guanidyl group was protected as a picrate. The Boc group was then removed from protected vasopressin with 90% TFA to give, after final purification, vasopressin in an overall yield of 11%.

Many syntheses of the antidiuretic hormone arginine vasopressin, (**18**) have been published over the past 18 years. Most of these syntheses[1–5] have involved the fragment condensation method, the exception being the guanylation of a protected ornithine nonapeptide[6] and a solid phase synthesis.[7]

In all of these methods, however, the benzyl group has been utilized for the protection of the sulfhydryl group of cysteine. Treatment of a fully protected nonpeptide with sodium in liquid ammonia and subsequent oxidation to form the disulfide bridge has afforded the desired hormone in varying degrees of yield and purity. The main disadvantage of such an approach has been the rather low yield of pure material obtained in the final cyclization step.

In an effort to minimize side reactions during the cyclization to form the disulfide bridge and in order to obtain intermediates for biological testing, we have used a different approach in synthesizing this hormone. We achieved sulfhydryl protection by means of the easily removed trityl group, masking of the α-amino nitrogen with the *tert*-butoxycarbonyl (Boc)[8] group and blocking of the guanidyl group of arginine by protonation. The complete synthesis is outlined in Chart I and was achieved with an overall yield of 11% [based on Boc-Cys(Trt)-OCP] of biologically fully active hormone.

All coupling reactions were performed in DMF *via* active esters and all intermediates, other than **15**, have been characterized. Initially, 90% trifluoroacetic acid (TFA) was used to remove the Boc group. Although trityl groups apparently were removed from sulfur atoms to some extent during the procedure,[9] subsequent removal of the solvent *in vacuo* at 40° reversed the equilibrium and retritylated the peptide. Addition of ether to the resulting oily residue afforded a solid TFA

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[1] V. du Vigneaud, D. T. Gish, and P. G. Katsoyannis, *J. Amer. Chem. Soc.*, **76**, 4751 (1954).

[2] P. G. Katsoyannis, D. T. Gish, and V. du Vigneaud, *ibid.*, **79**, 4516 (1957).

[3] V. du Vigneaud, D. T. Gish, P. G. Katsoyannis, and G. P. Hess, *ibid.*, **80**, 3355 (1958).

[4] R. O. Studer and V. du Vigneaud, *ibid.*, **82**, 1499 (1960).

[5] R. O. Studer, *Helv. Chim. Acta*, **46**, 421 (1963).

[6] M. Bodanszky, M. A. Ondetti, C. A. Birkhimer, and P. L. Thomas, *J. Amer. Chem. Soc.*, **86**, 4452 (1964).

[7] J. Meienhofer, A. Trzeciak, R. T. Havran, and R. Walter, *ibid.*, **92**, 7199 (1970).

[8] Abbreviations according to IUPAC-IUB recommendations: *Biochem. J.*, **126**, 773 (1972). In addition, OCP = 2,4,5-trichlorophenoxy and OPP = pentachlorophenoxy. All amino acids have the L configuration.

[9] I. Photaki, J. Taylor-Papadimitriou, C. Sakarellos, P. Mazarakis, and L. Zervas, *J. Chem. Soc. C*, 2683 (1970).