with the Curtin–Hammett principle,[3] we also assume that the conformer having the greatest dissymmetry between the two faces will give the greatest relative ratio of diastereoisomers. Thus, for example, although **3** is more stable than **4** in the ground state, the latter might play a predominant role as far as asymmetric induction is concerned.

As can be seen from Table I, our method predicts

Table I

Compd	Rel energies in the ground state[a]	Charge density on carbon atom[b]	Direction of preferential attack[c]	
3	0	-1.0441×10^{-3}	F	
4	0.97	1.9537×10^{-3}	R	predominant term
5	0.89	-1.5025×10^{-3}	F	
6	0	1.8103×10^{-3}	R	predominant term
7	0.07	-1.1739×10^{-3}	F	
8	0	1.9805×10^{-3}	R	predominant term
9	0.39	-2.6641×10^{-4}	F	
10	0.75	-7.9986×10^{-5}	F	
11	2.09	2.5184×10^{-4}	R	
12	0	-1.4545×10^{-3}	F	predominant term
13		$+5.7762 \times 10^{-4}$	R	

[a] In kcal/mol. [b] A + sign means a negative charge above the carbonyl plane, *i.e.* front side, and a − sign a negative charge below the same plane, *i.e.* rear side. [c] F = front side, R = rear side.

the same stereochemical course as Cram's rules[4] for propanal, butan-2-one, and butanal, as Cornforth's rule[5] for 2-chloropropanal, and as Prelog's rule[6] for ethyl glyoxylate. We would like to emphasize *that steric factors have been completely neglected* in our reasoning. Also noteworthy is the fact that our "most reactive conformers" are those adopted in Cram's rules.

(3) It remains to be seen whether this hybridization effect is dominant. The energies of the "supermolecule" formed by a molecule of propanal and a hydride ion located on the vertical of the carbon atom at a distance of 1.5 Å have been determined by *ab initio* calculations. We found that in both conformers **3** and **4**, attack on the hydrogen side is preferred to attack on the methyl side by 4.6 and 4.3 kcal/mol, respectively. Thus, in effect, conformer **3** gives rise to one diastereoisomer whereas **4** gives rise to the other. Interestingly, the "right" isomer deriving from **4** is preferred to the "wrong" isomer deriving from **3** by 0.38 kcal/mol. This value is of the order of magnitude of the asymmetric induction caused by the difference between a hydrogen and a methyl group.[7]

Although those numbers are not to be taken at their face values, they show clearly that orbital factors cannot be neglected in comparison with steric factors. It seems reasonable to consider that asymmetric induction is controlled by both factors.[8]

When the distance between the reaction center and the inductive center is increased, both orbital and steric factors decrease. However, the rate of decrease of the former seems to be relatively small (*cf.* Table I) while it is usually considered that steric repulsion diminishes quite rapidly.[9] It seems then that at longer distances, orbital factors might be more effective than steric factors.

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(3) D. Y. Curtin, *Rec. Chem. Progr.*, **15**, 111 (1954).
(4) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, 74, 5828 (1952); T. J. Leitereg and D. J. Cram, *ibid.*, 90, 4011 (1968).
(5) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).
(6) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); *Bull. Soc. Chim. Fr.*, 987 (1956).
(7) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood-Cliffs, N. J., 1971, p 92.
(8) This hybridization effect may also intervene in the so-called "product development control."
(9) The repulsion energy is usually approximated by $\exp(-ar)$ or by r^{-12} (E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 449).

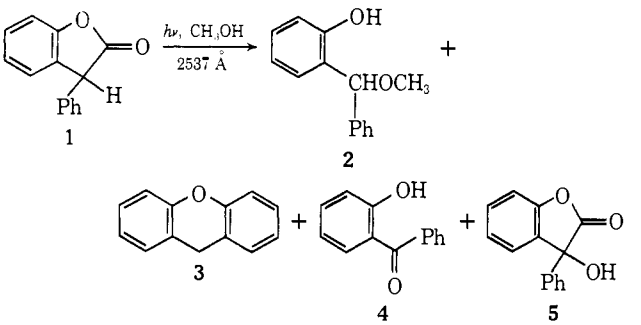
Nguyên Trong Anh,* O. Eisenstein
J-M. Lefour, M-E. Trân Huu Dâu
Laboratoire de Stéréochimie, Centre d'Orsay
Université de Paris-Sud
91405-Orsay, France
Received April 4, 1973

Tautomeric Control of the Photochemistry of 3-Phenylbenzofuran-2-one[1]

Sir:

The photochemical reactivity of β,γ-unsaturated lactams[2] and lactones[3,4] is a subject of current interest. These compounds undergo a facile photodecarbonylation producing unstable *o*-quinyl methide intermediates which can be trapped by protic solvents. Similar decarbonylation processes have been observed to occur with excited sultones,[3] carbonates,[3] and related substituted 2-indanones.[5] We now wish to report some fascinating variations to this behavior in the 3-phenylbenzofuran-2-one (**1**) system. Our observations indicate that this system displays a remarkable dependence on the tautomeric composition of **1** in solution.

Irradiation of **1**[6] in methanol with a low-pressure mercury arc (2537 Å) led to the formation of four major products (**2–5**) whose relative yields varied as a function



of the reaction conditions. Careful exclusion of oxygen from photolyzed solutions resulted in the formation of only *o*-hydroxybenzhydryl methyl ether (**2**) and xanthene (combined yield 40%). The ratio of **2**:**3** de-

(1) Photochemical Transformations of Small Ring Heterocyclic Compounds. L. For part XLIX see A. Padwa and J. Smolanoff, *J. Chem. Soc., Chem. Commun.*, 342 (1973).
(2) M. Fischer and F. Wagner, *Chem. Ber.*, 102, 3486, 3495 (1969).
(3) O. L. Chapman and C. L. McIntosh, *Chem. Commun.*, 383 (1971).
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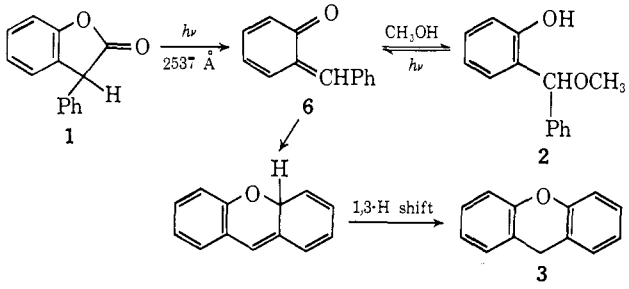
creased with irradiation time, and a control experiment revealed that photolysis of **2** led to the formation of **3**. Irradiation of **1** in acetonitrile (2537 Å) still resulted in the formation of xanthene. We conclude from these experiments that both **2** and **3** are initially formed, but that a competing side reaction further converts **2** to **3**.[7]

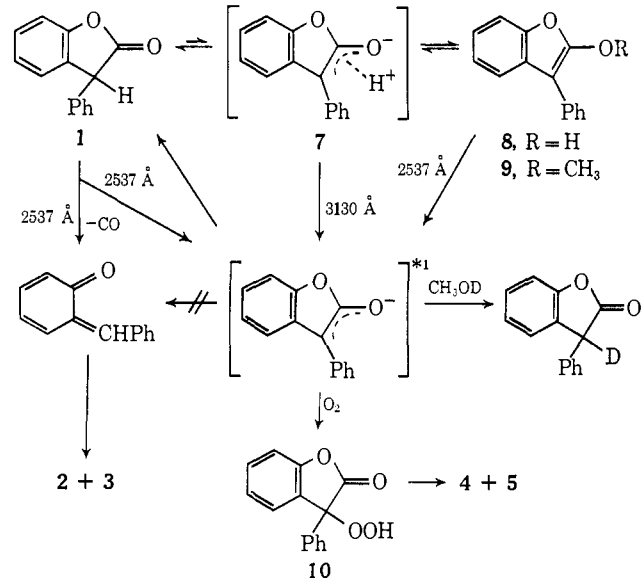
A reasonable intermediate which is capable of forming either **2** or **3** is the *o*-quinone methide **6**.[8] When



methanol is the solvent, **6** is predominantly trapped to give **2** (Φ = 0.058). This behavior is analogous to the characteristic high nucleophilic reactivity of related *o*- and *p*-quinone methides.[2,3,9-13] The formation of **3** (Φ = 0.004)[14] is readily explicable in terms of an electrocyclic closure of the *Z* isomer of **6** followed by a 1,3-H shift. In acetonitrile, the competitive trapping of **6** by methanol is absent and the quantum efficiency of formation of **3** is significantly enhanced (Φ = 0.006).

The nature of the photooxidation process which leads to *o*-hydroxybenzophenone (**4**) and hydroxylactone **5** is particularly interesting. We have found that trace amounts of oxygen are capable of effecting conversion of **1** to **4** and **5** with either 2537- or 3130-Å light in methanol or acetonitrile.[15] Most surprisingly, *compounds* **2** *and* **3** *are formed only upon irradiation of* **1** *with 2537-Å light.* With 3130-Å light **4** and **5** are the only detectable products. A clue to this seemingly anomolous behavior was obtained by examining the uv absorption spectrum of **1** in several solvents. In cyclohexane, lactone **1** shows two absorption maxima at 282 and 273 nm (ϵ 1700, 1720), whereas in acetonitrile solution a new long-wavelength absorption band at 346 nm (ϵ 40) is also present. Addition of a trace of base to the acetonitrile solution caused a dramatic increase in the 346-nm band. Similar behavior was also noted when methanol was used as the solvent.[16] It is worthy of mention that the corresponding methyl enol ether (**9**) shows maxima at 265 and 223 nm in acetonitrile with no trace of a long-wavelength absorption band. Based on the above spectral data, we propose that the photooxygenation sequence of lactone **1** is controlled by the tautomeric composition of **1** in solution (see Scheme I).

Scheme I



Excitation of the enolate ion **7** present in solution with 3130-Å light produces an excited state which is subsequently attacked by ground-state oxygen to give α-hydroperoxylactone **10**. This transient intermediate is subsequently converted to compounds **4** and **5**. Bordwell and others[17] have shown that related ketones undergo oxidative processes in the dark in the presence of base and oxygen *via* a similar intermediate (*i.e.*, **10**). Support for the above rationalization was obtained by finding that irradiation of **1** in degassed CH_3OD with 3130-Å light gave only recovered starting material containing >90% deuterium incorporation. Insignificant deuterium incorporation occurred when the solution was allowed to stand at ordinary laboratory conditions. The presence of excess piperylene (0.17 *M*) did not suppress either the deuterium exchange or the oxygenation reactions. From these experiments we conclude that it is the low-lying singlet state of **7** which is trapped by oxygen and which undergoes exchange with the protic solvent.[18] It is important to note that the irradiation of **1** in cyclohexane with a low-pressure mercury lamp[19] affords *o*-hydroxybenzophenone (**4**), even though the tautomeric concentration of **7** (and/or **9**) is negligible. In this case, it is tempting to speculate that photoenolization of **1** occurs on irradiation with 2537-Å light. Ample precedence for the enolization of excited carbonyl compounds can be found in the

(7) This transformation appears to involve *o*-quinone methide **6** by analogy to the recent results of Schmid and coworkers: R. Hug, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 1675 (1972).

(8) It should be pointed out that *o*-quinone methide **6** has two stereoisomers. Both the *Z* and *E* isomers can react with methyl ether 2, but only the *Z* isomer can give xanthene. The quantum yield data presented permit an estimate that 28 times as much 2 comes from the *E* as from the *Z* isomer. This assumes no solvent effect on the quantum yield of formation of xanthene.

(9) O. L. Chapman and C. L. McIntosh, *J. Amer. Chem. Soc.*, 92, 7001 (1970).

(10) M. P. Cava and R. J. Spangler, *ibid.*, 89, 4550 (1967).

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(13) H. A. Staab and J. Ipaktschi, *ibid.*, 583 (1966).

(14) When the irradiation of **1** was carried out at 2537 Å using deuteriomethanol, the xanthene isolated contained four atoms of deuterium. Details of this unusual transformation as well as attempts to detect the initial cyclized intermediate will be discussed in our full paper.

(15) Control experiments in the dark demonstrated that **1** is stable indefinitely in these oxygenated solvents. In the presence of excess base, **4** and **5** are slowly formed from **1**.

(16) See H. E. Zaugg and A. D. Schaefer, *J. Amer. Chem. Soc.*, 87, 1857 (1965), for similar results.

(17) F. G. Bordwell and A. C. Knipe, *ibid.*, 93, 3416 (1971), and references cited therein.

(18) An alternate path for the formation of **4** and **5** might derive from the reaction of the enol form of **1** (*i.e.*, **8**) with singlet oxygen. Although we have found that singlet oxygen can convert **1** to **4** and **5** under appropriate conditions, we have further demonstrated that during irradiation of **1** with either 2537- or 3130-Å light, the singlet oxygen reaction cannot be the primary source of **4** and **5**. Details of this interesting reaction will be discussed in our full paper.

(19) There is no spectroscopic evidence for the existence of **7** in a cyclohexane solution of **1**. In this solvent **1** can be recovered unchanged after prolonged irradiation (3130 Å) in the presence of oxygen. Xanthene was also formed when the irradiation was carried out at 2537 Å in the presence of oxygen.

literature[20-25] and provides reasonable analogy for the above suggestion.

It is interesting at this point to compare the photochemistry of **1** with that of the previously reported parent lactone, benzofuran-2(3*H*)-one (**11**). As noted by Chapman,[3] **11** give *o*-hydroxybenzyl methyl ether (**12**) upon irradiation in methanol. We have determined that the quantum yield for formation of **12** is 0.20 with 2537-Å light. Under optimal conditions **1** is converted to the analogous product (*i.e.* **2**) with a quantum efficiency of only 0.058. The difference in quantum yields in these two systems is apparently due to a number of competing photoprocesses which deactivate the excited state(s) of **1**. In addition to the visible modes of decay which produce **2** and **3**, an "invisible" process resulting in enolization of **1** decreases the efficiency of product formation. We could find no evidence for a similar process in the photochemistry of **11** and were unable to detect any significant amount of salicylaldehyde when the irradiation of **11** was carried out in the presence of oxygen. It would appear as though the phenyl substituent not only controls the tautomeric composition of the lactone but also markedly enhances the photoenolization route. The wavelength and solvent effects which we have noted for **1** suggest that tautomeric forms of carbonyl derivatives may yield diverse and interesting photochemistry. We are continuing to examine these effects and will report our complete findings at a later date.

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(27) National Institutes of Health Postdoctoral Fellow, 1971–1972.

Albert Padwa,*[26] George A. Lee[27]
Department of Chemistry, State University of New York at Buffalo Buffalo, New York 14214
Received February 17, 1973

Synthesis and Incorporation of (2*S*,3*S*)-[4-^{13}C]Valine into β-Lactam Antibiotics

Sir:

The entire carbon skeleton of L-valine has been shown to be incorporated into the thiazolidine ring of penicillin and the dihydrothiazine ring of cephalosporin.[1] We herein report the synthesis of (2*S*,3*S*)-[4-^{13}C]valine (**1**) and results which shed light on its asymmetric incorporation into penicillin N (**2**) and cephalosporin C (**3**) by *Cephalosporium acremonium*, mutant C91.[2]

(1) P. A. Lemke and D. R. Brannon in "Cephalosporins and Penicillins," E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972, pp 370–437.
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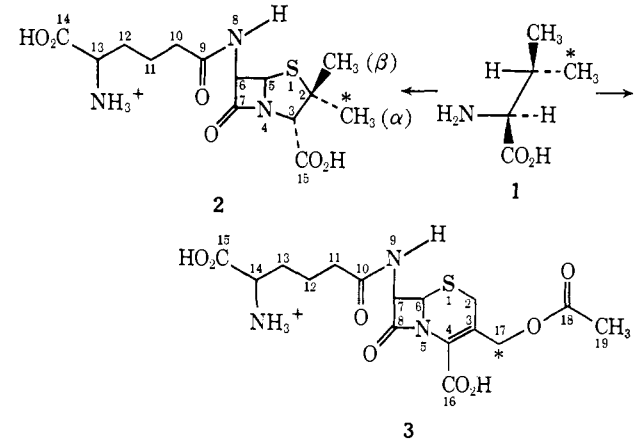
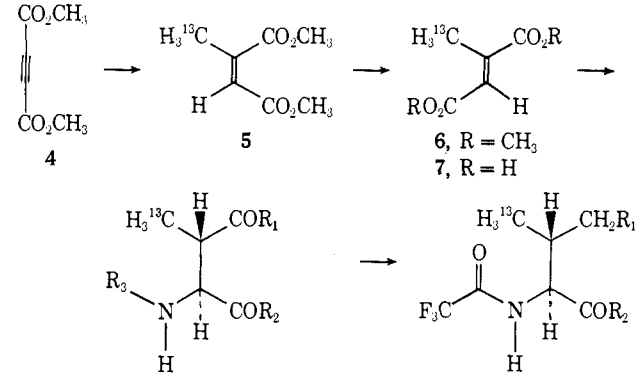


2 **1**

3

Scheme I outlines the reaction sequences used for

Scheme I



4 **5** **6**, R = CH$_3$; **7**, R = H

8, R$_3$ = H; R$_1$ = R$_2$ = OH
9, R$_3$ = CF$_3$CO; R$_1$ = R$_2$ = >O
10, R$_3$ = CF$_3$CO; R$_1$ = OH; R$_2$ = OCH$_3$
11, R$_3$ = CF$_3$CO; R$_1$ = OCH$_3$; R$_2$ = OH
12, R$_1$ = OH; R$_2$ = OCH$_3$
13, R$_1$ = OMs; R$_2$ = OCH$_3$
14, R$_1$ = I; R$_2$ = OCH$_3$
15, R$_1$ = H; R$_2$ = OCH$_3$

the synthesis of (2*S*,3*S*)-[4-^{13}C]valine. Reaction of **4** with [^{13}C]methyl copper[3] at −78° afforded dimethyl [*methyl*-^{13}C]citraconate (**5**) (70% yield), which was isomerized[4] by light and a trace of bromine to a mixture of **6** and **5** (95:5). Acid hydrolysis of **6** yielded **7** (81% from **5**). Exposure of [*methyl*-^{13}C]mesaconic acid (**7**) to β-methylaspartase[5] gave (2*S*,3*R*)-3-[^{13}C]methylaspartic acid (**8**) in 88% yield after recycling of recovered **7**. After quantitative conversion of **8** into its cyclic anhydride trifluoroacetamide derivative,[6] **9** was stirred in anhydrous methanol to give an isomeric mixture of **10** and **11** (8:2).[7] Treatment of **10** with diborane in THF at 0° afforded **12**, which was immediately converted to **13**. The mesylate **13** was refluxed with sodium iodide in acetone to afford **14** (66% from **8**). Hydrogenolysis of **14** in methanol–triethylamine (2:1) over 10% Pd/C at atomospheric pressure gave **15** in 92% yield. Acid hydrolysis of **15** gave (2*S*,3*S*)-[4-^{13}C]valine hydrochloride[8] in 84% yield: $[\alpha]^{25}$D +25.2°

(3) [^{13}C]Methyl iodide (90% isotopic purity, Merck & Co., Inc.) was allowed to react with lithium wire in ether at 0° under argon. The resulting methyllithium solution was diluted with THF and cooled to −78° before 1.1 equiv of a solution of cuprous iodide (29% w/w) in diisopropyl sulfide was added dropwise.
(4) V. C. F. Langworthy, *Ann.*, **304**, 145 (1899).
(5) H. A. Barker and R. D. Smyth, *Biochem. Prep.*, **8**, 89 (1962).
(6) F. Weygand and M. Reiher, *Chem. Ber.*, **88**, 26 (1955).
(7) F. Weygand and R. Geiger, *Chem. Ber.*, **90**, 634 (1957).
(8) The chromatographic behavior, proton magnetic resonance (pmr), and infrared spectra were all consistent with the assigned structure. Satisfactory carbon–hydrogen analyses were obtained for all the compounds reported herein.