Notes

Photochemistry of 2(5*H*)-Furanone. Hydrogen Abstraction by the β-Carbon Atom

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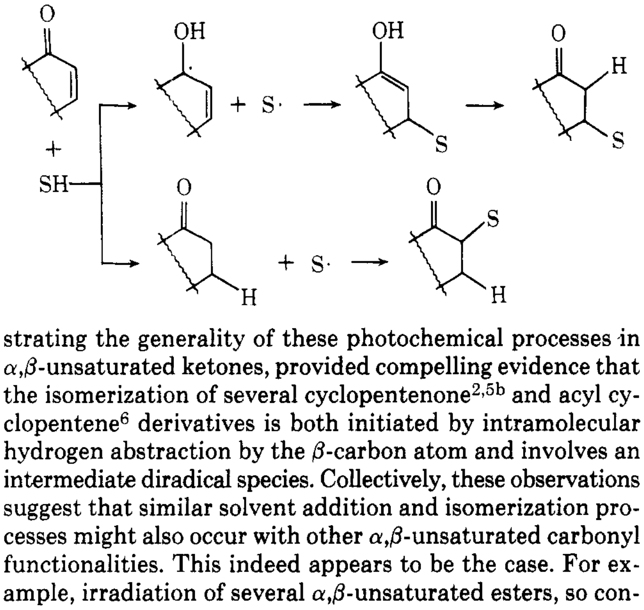
It is now well established that α,β-unsaturated ketones, including cyclopentenone,[1,2] cyclohexenone,[1] and their related derivatives,[1–3] undergo photochemical solvent addition to yield α and β solvent adducts. These photochemical reactions have been postulated in several cases[2,3] to involve hydrogen abstraction both by the carbonyl group to yield β-solvent adducts, and by the β-carbon atom to yield α adducts (see Chart I).[4,5] Furthermore, Agosta and colleagues, in demonstrating the generality of these photochemical processes in α,β-unsaturated ketones, provided compelling evidence that the isomerization of several cyclopentenone[2,5b] and acyl cyclopentene[6] derivatives is both initiated by intramolecular hydrogen abstraction by the β-carbon atom and involves an intermediate diradical species. Collectively, these observations suggest that similar solvent addition and isomerization processes might also occur with other α,β-unsaturated carbonyl functionalities. This indeed appears to be the case. For example, irradiation of several α,β-unsaturated esters, so constrained as to prevent photochemical cis–trans isomerization, led in methanol to formation of α-solvent adducts as well as to photoreduction of the olefinic bonds.[7] The parent α,β-unsaturated lactone, 2(5*H*)-furanone (**1**)[8] and 3-benzylidene-2(3*H*)-furanone (**6**),[9] on the other hand, led exclusively to β-solvent adducts when irradiated in isopropyl alcohol, while 1,3-dimethyluracil gave both α and β adducts in tetrahydrofuran.[10] More recently, the intramolecular cyclization of several α,β-unsaturated amides, leading to β-lactams, was postulated to proceed via hydrogen abstraction by the β carbon.[11] In general, however, these studies did not provide detailed information on the reaction pathway. With this consideration in mind, we record here our experience with the photochemistry of 2(5*H*)-furanone in hydrocarbon solvent.[12] The results indicate that both α and β solvent adducts are formed. In addition, evidence is presented which demonstrates conclusively that the α adduct arises via hydrogen abstraction by the β-carbon atom.

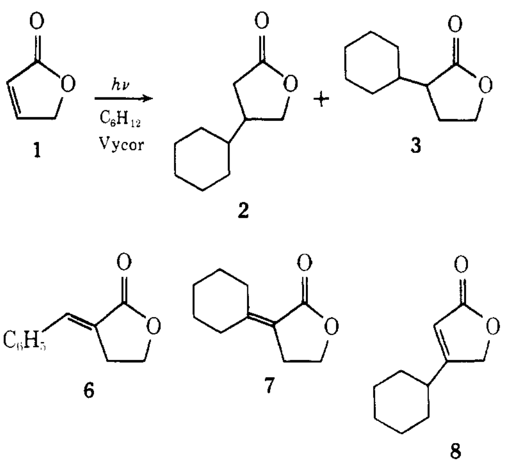
Chart I



Results and Discussion

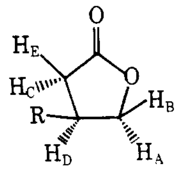
Irradiation of **1**[13] in cyclohexane (12 mM) through Corex (λ ≥2600 Å) or Vycor (λ ≥2100 Å) led to the formation of 4- and 3-cyclohexyldihydro-2(3*H*)-furanone (**2** and **3**) in 13–15 and 16–20% yield, respectively. Interestingly, even under these dilute conditions the previously described [2 + 2] cyclodimerization[14] of **1** also took place. Structures **2** and **3** were initially identified from their spectroscopic properties. In addition to a carbonyl frequency at 1780 cm^{-1}, typical of a five membered ring lactone, **2** and **3** yielded the 220-MHz NMR data shown in Table I. For comparison we have included the spectra of 4- and 3-methyldihydro-2(3*H*)-furanone (**4** and **5**). The five hydrogens associated with the lactone ring can in each case be assigned; a tentative structural assignment is therefore possible. Significant in this regard are the two methylene hydrogens on carbon bearing oxygen; in lactones **3** and **5** these hydrogens appear as a broad multiplet centered at δ 4.16, while in **2** and **4** the hydrogen cis to the vicinal alkyl substituent (e.g., H_b) experiences an expected[15] upfield shift (Δ ~0.40–0.60 ppm) relative to the trans hydrogen (H_a). Completion of the assignments derives from lanthanide shift reagent experiments as well as from further exploitation of the alkyl shielding. In particular the hydrogens α to the carbonyl group undergo a greater downfield shift relative to the β hydrogens when **2–5** are progressively doped with the shift reagent, Eu(fod)$_3$. Confirmation of structures **2** and **3** was obtained by spectral comparisons (IR, 220-MHz NMR, and VPC retention data) with authentic samples[16] prepared by hydrogenation of the known lactones **8**[17] and **7**.[18]

Chart II

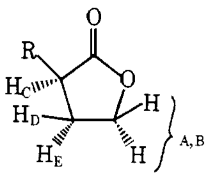


We next turned our attention toward defining the pathway for solvent addition. To this end **1** was irradiated through Corex in cyclohexane-d_{12} (99.5% D). In order to minimize the amount of cyclohexane-d_{12} required, experimental conditions involving repeated addition of **1** to the photolysis mixture and its subsequent destruction were devised.[19] In that event, **1** gave **2**-*d* and **3**-*d* in approximately the same ratio as observed previously; however, the overall yield was significantly reduced. Preparative VPC employing a Brownlee–Silverstein[20] thermal gradient collector provided a pure sample (ca. 400–600 μg) of each isomer for NMR analysis. As shown in Table I, **2**-*d* possessed deuterium only on the cyclohexane ring, while **3**-*d* contained in addition a total of one deuterium on the β carbon of the lactone ring. A combination of the previous NMR assignments and the results of NMR shift experiments with **3**-*d*, which allowed individual integration of the β hydrogens, indicated that this deuterium was equally apportioned cis and trans to the cyclohexyl ring thereby yielding lactones **3**-*d*-*cis* and **3**-*d*-*trans*. This labeling pattern provides, for the first time in a system other than an α,β-

Table I. NMR Spectra of 3- and 4-Alkyldihydro-2(3*H*)-furanones



2, R = C_6H_{11}
4, R = CH_3

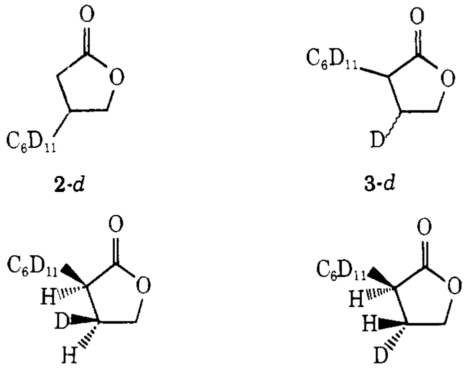


3, R = C_6H_{11}
5, R = CH_3

Registry no.		H_A	H_B	H_C	H_D	H_E	R
54996-29-1	2	4.29 dd, $J_{AB} = J_{AD}$ = 8 Hz, 1 H	3.84 dd, $J_{BA} = J_{BD}$ = 8 Hz, 1 H	2.41 dd, J_{CE} = 16 Hz J_{CD} = 8 Hz, 1 H	2.24 (m, 1 H)	2.06 dd, J_{EC} = 16 Hz J_{ED} = 9 Hz, 1 H	0.91–1.84 (br m, 11 H)
61129-25-7	2-*d*	4.29 dd, $J_{AB} = J_{AD}$ = 8 Hz, 1 H	3.84 dd, $J_{BA} = J_{BD}$ = 8 Hz, 1 H	2.41 dd, J_{CE} = 16 Hz J_{CD} = 8 Hz, 1 H	2.24 (m, 1 H)	2.06 dd, J_{EC} = 16 Hz J_{ED} = 9 Hz, 1 H	
40541-50-2	3	4.16 (m, 2 H)		2.30 (m, 1 H)	2.14 (m, 1 H)	2.03 (m, 1 H)	0.91–1.94 (br m, 11H)
61129-26-8 (cis) 61129-27-9 (trans)	3-*d*	4.16 (m, 2.00 H)[a]		2.30 (br d, 0.91 H)[a]	2.14 (m, 0.55 H)[a]	2.03 (m, 0.55 H)[a]	
1679-49-8	4	4.34 dd, $J_{AB} = J_{AD}$ = 8 Hz, 1 H	3.78 dd, J_{BA} = 8 Hz J_{BD} = 6 Hz, 1 H	2.57 (m, 2 H)		2.01 dd, J_{ED} = 7 Hz J_{EC} = 15 Hz, 1 H	1.17 (d, J = 6 Hz, 3 H)
1679-47-6	5	4.19 (m, 2 H)		2.42 (m, 1 H)	1.87 (m, 1 H)	2.42 (m, 1 H)	1.25 (d, J = 7 Hz, 3 H)

[a] Integrations accurate to ±5.0%.

Chart III



2-*d* **3**-*d*

3-*d*-*cis* **3**-*d*-*trans*

unsaturated ketone, direct evidence for hydrogen abstraction by the β-carbon atom.

The formation of the 1:1 mixture of **3**-*d*-*cis* and **3**-*d*-*trans* suggests, formally at least, that the abstraction process leading to α-solvent addition involves an intermediate radical pair, sufficiently long lived that its collapse occur in a totally nonstereoselective manner. This result would appear to rule out the theoretically interesting possibility that α-solvent addition proceed stereospecifically via a concerted $[_\sigma 2 + _\pi 2]$ cycloaddition of a cyclohexyl CH to the olefinic component of **1**.[21] This, however, may not be the case. That is, under our rather lengthy irradiation conditions, required to secure **3**-*d*, there is ample opportunity for the initially formed **3**-*d*-*cis* to undergo photochemical equilibration via an α-cleavage process. In this regard, Simonaitis and Pitts demonstrated several years ago that α-methyl-γ-butyrolactone yields *cis*-and *trans*-crotyl formate via an efficient (i.e., Φ = 0.39) α-cleavage process.[22]

Finally, our observation of β adduct **2**-*d*, labeled with deuterium only on the cyclohexyl ring, is completely consistent with the reaction pathway outlined in Chart I for β-solvent addition (i.e., hydrogen abstraction initiated by the carbonyl oxygen). However, it requires that the abstracted deuterium be completely lost to the environment during the course of the reaction. A similar, but incomplete, loss (ca. 90%) of deuterium in the photochemical cyclization of several α-methylene ketones was taken recently as strong support for the intermediacy of an enol.[23] All attempts on our part, however, to locate and/or retain a fraction of the initially abstracted deuterium on the α carbon of **2**-*d* met with failure. In addition, irradiation of **1** in cyclohexane saturated with D_2O did not lead to incorporation of deuterium in **2**. A detailed mechanism for formation of the β-solvent adduct therefore remains an open question.

Experimental Section

Materials and Equipment. VPC separations and yields were accomplished on either a Varian Aerograph Model 920 or a Perkin-Elmer Model 3920 gas chromatograph, the latter equipped with a thermal gradient collector. The following columns were employed: A,25% QF-1, 10 ft × 0.375 in.; B, 25% SE-30, 10 ft × 0.375 in.; C, 6% QF-1 10 ft × 0.25 in. The column oven was operated at 140–205 °C and the helium carrier gas flow rate was 100 ml/min. Compounds purified by VPC were obtained as colorless liquids. IR and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 337 spectrophotometer and the latter on a Varian A-60 (60 MHz) or HR-220 (220 MHz) spectrometer. Internal standard for the ^1H NMR spectroscopy was Me_4Si. Solutions were dried over $MgSO_4$. Spectroquality cyclohexane employed in the photochemical experiments was dried over 4A molecular sieves prior to use. Cyclohexane-d_{12} (99.5% D) was obtained from Stohler Isotope Chemicals. The photochemical experiments were carried out with a Hanovia Model L mercury lamp (no. 679A-36) in a quartz immersion well using Corex (no. 9700) or Vycor (no. 7910) as filter.

3-Cyclohexylidenedihydro-2(3*H*)-furanone (**7**).[17] Lactone **7** prepared by condensation of butyrolactone with cyclohexanone had the following spectral properties: IR 2935 (s), 1750 (s, br), 1655 (s), 1198 cm^{-1} (s); NMR (60 MHz) δ 1.4–3.18 (m, 12 H), 4.20 (t, J = 8 Hz, 2 H).

4-Cyclohexyl-2(5*H*)-furanone (**8**). Lactone **8**, prepared by the method of Linville and Elderfield,[18] had the following spectral properties: IR 2930 (s), 1755 (s, br), 1640 (m), 1035 cm^{-1} (s); NMR (60 MHz) δ 0.97–2.50 (m, 11 H), 4.62 (d, J = 1.8 Hz, 2 H), 5.63 (dd, $J_1 = J_2$ 1.8 Hz, 1 H).

3-Cyclohexyldihydro-2(3*H*)-furanone (**3**). A suspension containing 447 mg (2.70 mmol) of lactone **7**, 100 mg of palladium on carbon (10%), and 12 ml of MeOH was stirred under a H_2 atmosphere for 5 h at room temperature. The resulting suspension was filtered, poured into H_2O, and extracted with ether. The organic phase was washed with H_2O and brine and dried. Removal of the solvent in vacuo afforded 383 mg (85%) of lactone **3**. After VPC purification on column A, **3** had the following spectral data: IR 2940 (s), 2870 (s), 1780 (s), 1455 (m), 1375 (m), 1160 (m), 1090 (m), 1030 cm^{-1} (m); NMR (60 MHz) δ 0.80–2.58 (m, 14 H), 3.95–4.40 (m, 2 H); for 220-MHz NMR data see Table I.

4-Cyclohexyldihydro-2(3*H*)-furanone (2). A suspension containing 15 mg (0.90 mmol) of lactone **8**, 6 mg of palladium on carbon (10%), and 6 ml of MeOH was stirred under a H_2 atmosphere for 4 h at room temperature. The suspension was then filtered, poured into H_2O, and extracted with ether. The organic phase was washed with H_2O and brine and dried. Partial removal of solvent in vacuo afforded an oily residue from which lactone **2** was isolated by preparative VPC employing column B. Lactone **2** had the following spectral data: IR 2940 (s), 2860 (s), 1780 (s), 1455 (m), 1175 (s), 1050 (m), 1020 cm^{-1} (s); for 220-MHz NMR data see Table I.

Photolysis of 2(5*H*)-Furanone (1) in Cyclohexane. A solution of 220 mg (2.62 mmol) of lactone **1**[13] in 250 ml of cyclohexane was flushed with N_2 for 20 min and then irradiated through Corex for 7 h under nitrogen. The photolysate was then concentrated in vacuo to afford 261 mg of an oily liquid which contained **2** and **3** in 13 and 16% yield, respectively. After VPC separation on column A, **2** and **3** were identical in all respects (e.g., VPC retention time, IR, 220-MHz NMR) with the authentic samples prepared above.

Photolysis of 2(5*H*)-Furanone (1) in Cyclohexane-d_{12}. A solution containing 15 mg of lactone 1 and 5g of cyclohexane-d_{12} was placed in a quartz test tube (1×20 cm) fitted with a nitrogen inlet. The solution was flushed with nitrogen for 30 min and then irradiated through Corex for 20 h under nitrogen. After 20 h, the progress of the reaction was monitored by VPC on column C; approximately 80% of 1 was comsumed. To the photolysis mixture was added an additional 15 mg of **1**, and the mixture was irradiated for 20 h and then monitored. This process was continued until 480 mg of 1 had been destroyed. At this point the excess solvent was removed by distillation and the residue purified by VPC to yield (400–600 μg) **2**-*d* and **3**-*d*. The deuterium incorporation as determined by Fourier transform 220-MHz NMR is given in Table I. Model studies with α-deuterio-α-methyl-γ-butyrolactone indicate that deuterium was not lost during purification. Examination of the recovered solvent by NMR revealed negligible hydrogen incorporation.

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Registry No.—**1**, 497-23-4; **7**, 21681-63-0; **8**, 30088-97-2; butyrolactone, 96-48-0; cyclohexanone, 108-94-1; cyclohexane-d_{12}, 1735-17-7.

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Steroids and Related Natural Products. 94. Synthesis of Toad Venom Cardenolides[1]

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Some species of the milkweed butterfly family (Danaidae) have been found by Reichstein and colleagues to contain cardenolides.[3] The occurrence of such cardiac active plant constituents in these particular butterflies has been nicely correlated with their feeding habits which involve certain cardenolide containing plants (e.g., from the Asclepiadaceae family) and their need for an exogenous source of defensive substances. In 1970, Meyer and colleagues[4] reported the presence of seven cardenolides in the Chinese toad venom preparation Ch'an Su. The constituents included digitoxigenin (**1a**), sarmentogenin (**1b**), periplogenin (**2a**), and two previously unknown 14,15β-epoxycardenolides (**3a** and **3b**). Whether such cardenolides represent a normal biosynthetic pathway in venom production characteristic of certain amphibians of the Bufonidae family or instead are initially obtained by ingestion of Asclepiadaceae-type plant eating insects poses an interesting biochemical question. However, the discovery[4a] of two cardenolides bearing suberic acid ester groups (e.g., **1c**) in Ch'an Su and the more recent isolation[5] of sarmentogenin (**1b**), 3-suberoylarginine, and 3-pimeloylarginine esters from the skin of *Bufo vulgaris formosus*