88. Photochemistry of Chlorinated 2-Cycloalkenones

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Summary

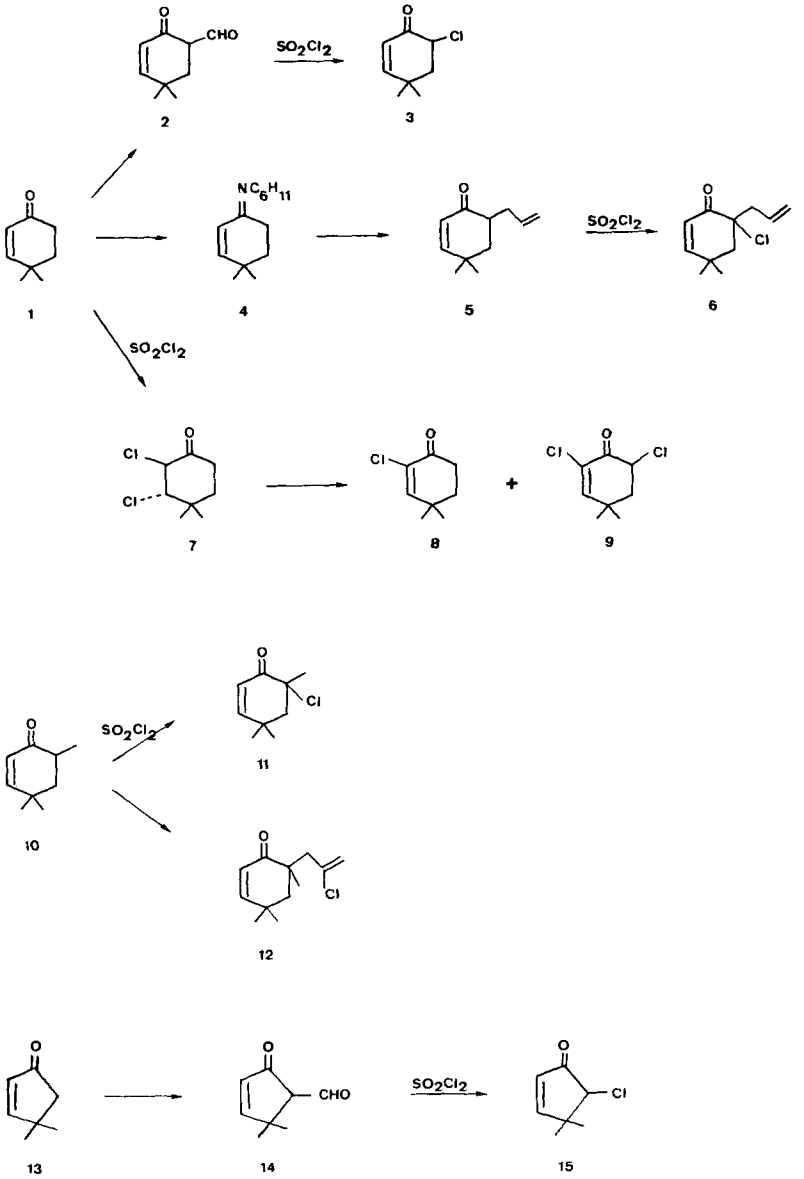
The 6-chloro-2-cyclohexenones **3**, **6** and **11**, and the 5-chloro-2-cyclopentenone **15** were newly synthesized. The results obtained with compounds **3** and **15** in photocycloadditions to olefins show that the oxetane *vs.* cyclobutane product ratio is reduced by the substitution of florine by chlorine in the α'-position of the enone. No oxetanes are formed in the intramolecular photocycloaddition of **6**. Compound **11** does not photoadd to olefins. The newly synthesized 2-chloro-3-cyclohexenones **8** and **9** are also photostable towards light of $\lambda = 366$ nm, but π-π^*-excitation ($\lambda = 254$ nm) in pentane leads to the formation of 4,4-dimethylcyclohexanone (**29**).

In preceding publications [1] [2] we have shown that the oxetane *vs.* cyclobutane product ratio in photocycloadditions of 2-cycloalkenones to olefins, as *e.g.* 2,3-dimethyl-2-butene, could be strongly enhanced by introducing fluorine in the α'-position of the enone. We have also shown that in comparable intramolecular photocycloadditions [3] cyclobutane formation occurred specifically.

In order to obtain additional information we investigated inter- and intramolecular photocycloadditions of 2-cycloalkenones bearing a chloro substituent on the α'-position. The simple synthetic approach to such compounds is described in *Scheme 1*. As can be seen from this scheme, chlorination with sulfuryl chloride only takes place on $C_{\alpha'}$ if this carbon atom is tertiary, as in **2**, **5**, **10** and **14**. Otherwise, as for **1**, the preferred reaction is addition of two chlorines to the C-C double bond. The so-formed dichloroketone **7** was unstable and decomposed to the 2-chloro-2-cyclohexenones **8** and **9**. As such systems had not been investigated before they were included in our study. Results on the photoadditions of 3-chloro-2-cyclohexenone to cyclopentene had been reported by *Cantrell* [4].

The results of the photoadditions of **3** and **15** to 2,3-dimethyl-2-butene are described in *Scheme 2* and the spectral data of the photoadducts summarized in *Table 1*. No addition at all took place under similar conditions with **8**, **9** and **11**. In fact these compounds were found to be photounreactive with light of $\lambda = 366$ nm. A comparison of the behavior of **3** and **15** with that of the corresponding fluoro compounds **22a** and **22b** shows that, with the exception of **15** in cyclohexane, the

Scheme 1



amount of oxetane formed is much smaller for the chloro compounds (*Table 2*). As the cyclic voltammetry curves for **3** and **22a** are very similar [5] it is not unreasonable to expect that the electronic distribution of these enones in their reactive triplet states is also similar. The difference in the oxetane *vs.* cyclobutane product ratio from **3** and **22a** is therefore most probably due to the steric effects, *i.e.* either greater hindrance in the approach of the olefin towards the carbonyl group or slower ring closure of the diradical giving oxetane due to the difference in size between the fluoro-

and chloro-substituents. Here again we do not know which rate constant(s) in the photocycloaddition reaction path [2] is (are) affected by this difference in size of the substituent on $C_{\alpha'}$. In return we cannot advance a plausible explanation for the different product ratio from **15** and **22b** in acetonitrile.

Scheme 2

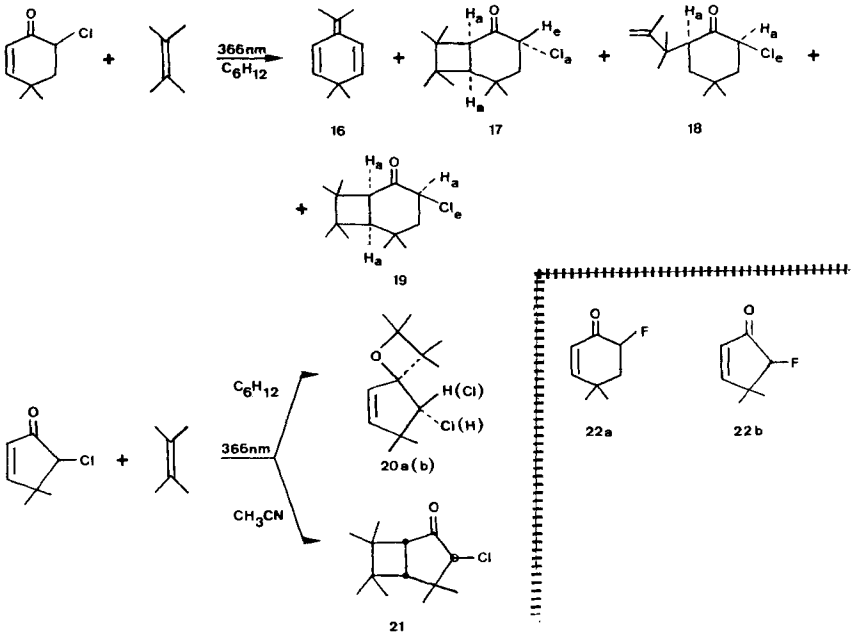


Table 1. *Yields and Spectral Data of the Photoadducts of* **3** *and* **15** *to 2,3-Dimethyl-2-butene*

Compound	Yield	MS.	IR. (CCl_4)	NMR. (CCl_4)
16	10[a])	[1]	[1]	[1]
17	12[a])	[b])	1734	3.95 (*t*, *J*=4 Hz, 1H); 3.20 (*d*, 1H); 1.90 (*d*, *J*= 14 Hz, 1H); 2.00 (*m*, 2H); CH_3: 0.89–1.40
18	18[a])	242 (M^+) *160, 83*	1738	4.70 (*s*, 2H); 4.40 (*d*×*d*, *J*=6.0; 12.0 Hz, 1H); 2.58 (*d*×*d*, *J*=7.0; 11.0 Hz); 2.00 (*m*, 2H); 1.66 (*s*, 3H); 1.50 (*m*, 2H); CH_3: 0.95–1.10
19	55[a])	242 (M^+) *137, 83*	1740	4.28 (*d*×*d*×*d*, *J*=1.4; 7.0; 14.0 Hz, 1H); 2.68 (*d*×*d*, *J*=1.4; 14.0 Hz, 1H); 2.00 (*m*, 2H); 2.00 (*d*, *J*=14.0 Hz, 1H); CH_3: 0.94–1.30
20a	65[a]) 0[c])	193 (M^+−Cl) *135, 109*	–	5.95 (*d*, 1H); 5.80 (*d*, *J*=6.0 Hz, 1H); 3.95 (*s*, 1H); CH_3: 1.00–1.40
20b	30[a]) 0[c])	[b])	–	5.90 (*d*, 1H); 5.75 (*d*, *J*=6.0 Hz, 1H); 3.65 (*s*, 1H); CH_3: 1.00–1.40
21	90[c]) 5[a])	228 (M^+) *97*	1758	4.60 (*s*, 1H); 2.40 (*d*, 1H); 2.30 (*d*, *J*=8.0 Hz, 1H); CH_3: 0.90–1.30

[a]) In C_6H_{12}. [b]) Not recorded. [c]) In CH_3CN.

Table 2. *Relative Ratios of Adducts (Oxetanes/Cyclobutanes) in the Photoaddition of* **3**, **15**, **22a** *and* **22b** *to 2,3-Dimethyl-2-butene*

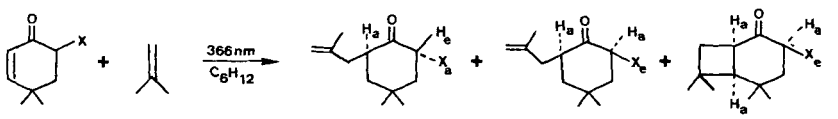
Enone	Solvent	Product ratio oxetane/ cyclobutane	Enone	Solvent	Product ratio oxetane/ cyclobutane
3	C_6H_{12}	10[a])/90[b])	**22a**	*i*-C_8H_{18}	90/10
	CH_3CN	0/100		CH_3CN	15/85
15	C_6H_{12}	94/6	**22b**	C_6H_{12}	100/0
	CH_3CN	0/100		CH_3CN	75/25

[a]) Oxetane decomposes to **16** (*cf.* [1]).
[b]) Corresponds to total amount of ketonic products **17**, **18** and **19**.

Similar, although less differentiated results are obtained in the photoadditions of **3** and **22a** to isobutene (*Scheme 3* and *Table 3*).

The effect of the α'-chloro-substituent in the intramolecular photocycloadditions of 6-allyl-2-cyclohexenones is considerable. Although the tricyclic ketone **26** is formed from **6** specifically – in analogy to **28** [3] – the efficiency of these two reactions differ

Scheme 3



3 X = Cl — 23a 24a 25a
22a X = F 16 + 23b 24b 25b

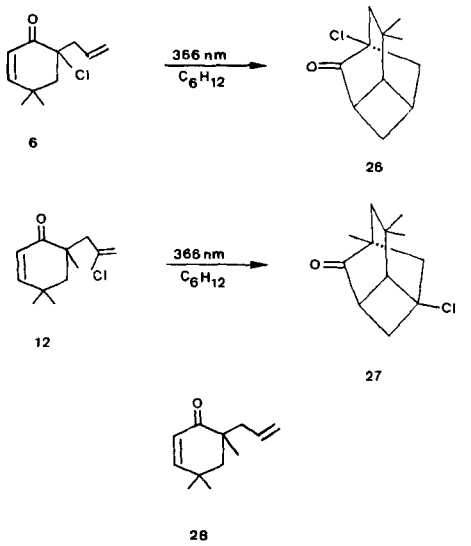
Table 3. *Yields and Spectral Data of the Photoadducts of* **3** *and* **22a** *to Isobutene*

Compound	Yield	IR. (CCl_4)	NMR. (CCl_4)
23a	7	1733	4.75 (*m*, 2H); 4.20 (*t*, *J* = 3.5 Hz, 1H); 3.18 (*m*, 1H); 2.80–1.60 (*m*, 6H); CH_3: 1.72, 1.40, 1.07
24a	49	1740	4.70 (*m*, 2H); 4.65 (*d* × *d*, *J* = 8.0, 12.0 Hz, 1H); 2.90–1.60 (*m*, 7H); CH_3: 1.68, 1.25, 1.05
25a	43	1748	4.50 (*d* × *d*, *J* = 6.0; 11.0 Hz, 1H); 3.05 (*d* × *d* × *d*, *J* = 6.0; 10.0; 13.0 Hz, 1H); 1.40–2.20 (*m*, 5H); CH_3: 1.26, 1.17, 1.10, 1.00
23b	38[a])	1731	4.70 (*m*, 2H); 4.55 (*d* × *t*, *J* = 3.5; 3.5; 50.0 Hz, 1H); 3.10 (*m*, 1H); 1.80–2.50 (*m*, 6H); CH_3: 1.70, 1.30, 1.05
24b	25[a])	1741	4.95 (*d* × *d* × *d*, *J* = 7.0; 12.0; 50.0 Hz, 1H); 4.75 (*m*, 2H); 2.85–1.40 (*m*, 7H); CH_3: 1.68, 1.30, 1.08
25b	25[a])	1749	4.88 (*d* × *d* × *d*, *J* = 7.0; 12.0; 48.0 Hz, 1H); 3.00 (*d* × *d* × *d*, *J* = 7.4; 9.2; 13.4 Hz, 1H); 1.40–2.20 (*m*, 5H); CH_3: 1.28, 1.20, 1.14, 1.07

[a]) Compound **16** isolated in 10% yield.

by a factor of 25 (Φ_{-28} = 0.19 [3], Φ_{-6} = 0.007). This finding strengthens the ar gument regarding the size of the chloro-substituent discussed above. The smalle quantum yield for the conversion **6** → **26** is probably due to energy dissipation causec by relatively high rates of reversion of either the exciplex or the diradical on the oxetane-forming reaction path [2]. The efficiency of the – again specific – conversior **12** → **27** (Φ_{-12} = 0.029) is also lower than the one for **28** (*Scheme 4* and *Table 4*).

Scheme 4



6 **26** **12** **27** **28**

Table 4. *Spectral Data of Tricyclo[3.3.1.0^{2,7}]nonan-6-ones* **26** *and* **27**

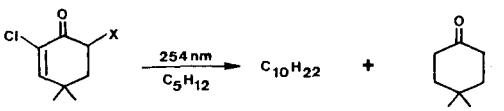
Compound	MS.	IR. (CCl_4)	NMR. ($CDCl_3$)[a])
26	198 (M^+) *141*	1747	3.10 ($d\times d\times d$, J=5.0; 5.0; 6.5 Hz, 1H); 2.78 (*m*, 1H); 2.70–2.20 (*m*, 4H); 2.05 (*AB*, 2H); 1.60 (*d*, J=10.0 Hz, 1H); 1.02 und 0.85 ($2CH_3$)
27	212 (M^+) *177* (M^+-Cl)	1730	3.02 ($d\times d$, J=6.2; 7.8 Hz, 1H); 2.68 ($d\times d\times d$, J=2.3; 7.8; 10.0 Hz, 1H); 2.65 (*d*, J=6.2 Hz, 1H); 2.30 (*AB*, J=12.5 Hz, 2H); 2.17 (*d*, J=10.0 Hz, 1H); 1.70 (*d*, J=14.0 Hz, 1H); 1.60 ($d\times d$, J=2.3; 14.0 Hz, 1H); 1.22, 1.04 und 0.90 ($3CH_3$)

[a]) For assignment of signals *cf.* [3].

Finally we report preliminary results on the photochemistry of the 2-chloro-2e-cyclohexenones **8** and **9**. As already stated above these compounds are unreactive towards light of λ = 366 nm. Due to the 2-chlorosubstituent, the energy of the S_2-stat- is lowered by 10 kcal/mol (E_{S_2} of **3** or **22a** ≃ 118 kcal/mol, E_{S_2} of **8** or **9** ≃ 108 kcal/mol). This facilitates π–π^*-excitation of **8** or **9** experimentally as it can be achieved with a low pressure mercury lamp. Indeed (*Scheme 5*) both compounds turned out to

be reactive in the presence of a hydrogen donor. Thus irradiation ($\lambda = 254$ nm) of **8** or **9** in pentane up to total reaction of the starting material gave as only products a unidentified C_{10}-hydrocarbon which originates from the solvent, and 4,4-dimethylcyclohexanone (**29**), which was identified on the basis of its NMR.-, IR.- and mass spectrum. We do not yet understand the mechanism of this photoreduction but the observed wavelength dependence indicates that the crucial step might be the C_α–Cl bond cleavage. If one assumes a value of $\simeq$ 83 kcal/mol [6] for the bond-energy, it appears reasonable that no reaction takes place with light of $\lambda = 366$ nm ($\triangleq$ 78 kcal/mol), but that the photoreduction occurs with light of $\lambda = 254$ nm ($\triangleq$ 112 kcal/mol).

Scheme 5



8 X = H
9 X = Cl

29

Experimental Part

General. Chemical shifts in the NMR. spectra are given in ppm relative to TMS (=0 ppm) as internal standard, absorptions in the IR. spectra in cm^{-1}, and in UV. spectra in nm.

1. New compounds. – 1.1. *6-Chloro-4,4-dimethyl-2-cyclohexenone* (**3**). A solution of 10 ml SO_2Cl_2 in 40 ml CCl_4 was added dropwise to 15.2 g (0.1 mol) **2** [1] in 200 ml CCl_4 at room temperature. Stirring was continued for 24 h. The solution was then washed with H_2O, 2N NaOH and NaCl aq., and dried. After evaporation of the solvent the residue was twice recrystallized from pentane yielding 6.0 g (38%) **3**, white crystals, m.p. 48–50°. – IR. (CCl_4): 1708, 1630. – UV. (C_6H_{12}): 332 (34), 221 (14200). – NMR. (CCl_4): 6.62 (*d*, 1H); 5.82 (*d*, $J = 10.0$, 1H); 4.53 (*d*×*d*, $J = 7.0$ and 12.0, 1H); 2.20 (*m*, 1H); 1.33 (*s*, 3H); 1.28 (*s*, 3H). – MS.: 158 (M^+), *96* ($M^+ - C_2H_3Cl$).

1.2. *6-Allyl-4,4-dimethyl-2-cyclohexenone* (**5**). Was obtained from **1** [7] *via* the *Schiff*-base **4** [8], which was metalated with $(CH_3)_2$CHMgBr and alkylated with allyl bromide in analogy to [9] in 45% yield, b.p. 43–46°/0.4 Torr. – NMR. (CCl_4): 6.60 (*d*, 1H); 5.85 (*d*, $J = 10.0$, 1H); 5.80 (*m*, 1H); 5.20 (*m*, 1H); 5.00 (*m*, 1H); 1.60–2.90 (*m*, 5H); 1.25 (*s*, 3H); 1.20 (*s*, 3H). – MS.: 164 (M^+), *96* ($M^+ - C_5H_8$).

1.3. *6-Chloro-6-allyl-4,4-dimethyl-2-cyclohexenone* (**6**). A solution of 5 ml SO_2Cl_2 in 20 ml CCl_4 was added dropwise to 8.2 g (0.05 mol) **5** in 100 ml CCl_4 at room temperature. Stirring was continued for another 2 h. The solution was washed with H_2O, $NaHCO_3$ aq. and NaCl aq., and dried. The residue was chromatographed on a silicagel column (benzene) and the product further purified by distillation to give 5.3 g (53%) **6**, b.p. 65°/0.1 Torr. – IR. (CCl_4): 1694. – NMR. (CCl_4): 6.60 (*d*, 1H); 5.80 (*d*, $J = 10.0$, 1H); 5.80 (*m*, 1H); 5.20 (*m*, 1H); 5.00 (*m*, 1H); 2.62 (*m*, 2H); 2.10 (*s*, 2H); 1.28 (*s*, 3H); 1.08 (*s*, 3H). – MS.: 198 (M^+), *96* ($M^+ - C_5H_7Cl$).

1.4. *Reaction of* **1** *with* SO_2Cl_2. A solution of 10 ml SO_2Cl_2 in 40 ml CCl_4 was added dropwise to 12.4 g (0.1 mol) **1** in 200 ml CCl_4 at room temperature. After 2 h the solution was treated as described under 1.3. Evaporation of the solvent at 10° gave crystalline **7** in nearly quantitative yield. – NMR. ($CDCl_3$): 4.55 (*d*, 1H); 3.85 (*d*, $J = 11.5$, 1H); 2.60 (*m*, 2H); 1.90 (*m*, 2H); 1.30 (*s*, 3H); 1.27 (*s*, 3H). – IR. (CCl_4): 1747.

Compound **7** was unstable and liberated HCl. To obtain **8** and **9** the residue was chromatographed on a silicagel column (benzene). The first product eluted was **9** which was recrystallized from pentane to yield 1.4 g (7%) white crystals, m.p. 76°. – UV. (C_6H_{12}): 321 (29), 243 (10300). – NMR. (CCl_4): 6.80 (*s*, 1H); 4.66 (*d*×*d*, 1H); 2.35 (*m*, 2H); 1.35 (*s*, 3H); 1.32 (*s*, 3H). – IR. (CCl_4): 1726, 1613. – MS.: 192 (M^+), *130* ($M^+ - C_2H_3Cl$).

The subsequently eluted **8** was distilled, affording 9.0 g (57%), b.p. 57–59°/0.3 Torr, m.p. ≃ 15°. – UV. (C_6H_{12}): 325 (28), 240 (12300). – IR. (CCl_4): 1708, 1613. – NMR. (CCl_4): 6.78 (*s*, 1H); 2.5 (*m*, 2H); 1.90 (*m*, 2H); 1.25 (*s*, 6H). – MS.: 158 (M^+), *116* ($M^+ - CH_2CO$).

1.5. *6-Chloro-4,4,6-trimethyl-2-cyclohexenone* (**11**). Similar procedure as 1.3. involving column chromatography (silicagel, benzene) and distillation. From 13.8 g (0.1 mol) **10** [10] were obtained 4.1 g (24%) **11**, b.p. 55°/0.5 Torr, m.p. ≃ 15°. – UV. (C_6H_{12}): 338 (70), 222 (12500). – IR. (CCl_4): 1695. – NMR. (CCl_4): 6.62 (*d*, 1H); 5.87 (*d*, J=10.0, 1H); 2.23 (*AB*, J=15.0, 2H); 1.60 (*s*, 3H); 1.45 (*s*, 3H); 1.12 (*s*, 3H). – MS.: 172 (M^+), *96* ($M^+ - C_3H_5Cl$).

1.6. *6-(2-Chloro-allyl)-4,4,6-trimethyl-2-cyclohexenone* (**12**). From **10** and 2,3-dichloropropene in analogy to [3]. B.p. 69–71°/0.1 Torr, yield: 53%. – IR. (CCl_4): 1681, 1631. – NMR. (CCl_4): 6.55 (*d*, 1H); 5.80 (*d*, J=10.0, 1H); 5.10 (*s*, 1H); 5.05 (*s*, 1H); 2.65 (*AB*, J=13.0, 2H); 1.95 (*AB*, J=13.0, 2H); 1.15 (*s*, 3H); 1.12 (*s*, 3H); 1.09 (*s*, 3H). – MS.: *177* ($M^+ - Cl$).

1.7. *5-Chloro-4,4-dimethyl-2-cyclopentenone* (**15**). From **14** [2] in analogy to 1.1. After evaporation of the solvent, distillation through a 10 cm-*Vigreux* column yielded 29% **15**, b.p. 42°/0.5 Torr. – UV. (C_6H_{12}): 328 (72), 221 (13000). – IR. (CCl_4): 1741. – NMR. (CCl_4): 7.50 (*d*, 1H); 6.00 (*d*, J=6.0, 1H); 4.00 (*s*, 1H); 1.30 (*s*, 3H); 1.15 (*s*, 3H). – MS.: 144 (M^+), *109* ($M^+ - Cl$).

2. Photolyses. – The irradiations at 254 nm were carried out with a *Minerallight* PCQXI low pressure mercury lamp. The irradiations at 366 nm were carried out by filtering the light of a *Philips* HPK-125 W mercury lamp through a ($Pb(NO_3)_2$+NaBr)-solution with a cut-off at 340 nm. Intermolecular photoadditions were performed in 15 ml tubes in a merry-go-round apparatus. Intramolecular photocyclizations were performed in a conventional photochemical reactor (150 ml). All solutions were flushed with Argon before irradiation.

2.1. *Intermolecular photoadditions.* 200 mg enone and 2 ml olefin in 15 ml solvent were irradiated (λ=366 nm) for 18 h. The isolation of the photo-adducts was achieved as described below. Their yields and spectral data are summarized in Tables 1 and 3.

2.1.1. **3** *and 2,3-dimethyl-2-butene in cyclohexane.* After evaporation of the solvent the residue was chromatographed on a column (silicagel, benzene). The order of elution was **16**, **17**, **18**, and **19**.

2.1.2. **15** *and 2,3-dimethyl-2-butene in cyclohexane.* The oxetane **20** was isolated by prep. GC. (160°, 5% SE 30 on Chromosorb G-AW-DMCS).

2.1.3. **15** *and 2,3-dimethyl-2-butene in acetonitrile.* The bicycloheptanone **21** was isolated by prep. GC. (190°, same column as under 2.1.2.).

2.1.4. **3** *and isobutene in cyclohexane.* Treatment as under 2.1.1. Order of elution: **23a**, **24a** and **25a**.

2.1.5. **22a** *and isobutene in cyclohexane.* Treatment as under 2.1.1. Order of elution: **23b**, **24b** and **25b**.

2.2. *Intramolecular photoadditions.* 500 mg enone in 150 ml cyclohexane were irradiated (λ= 366 nm) for 65 h. The isolation of the photoadducts is described below. Their spectral data are summarized in *Table 4*.

2.2.1. *Irradiation of* **6**. Compound **26** was formed selectively and isolated by bulb to bulb distillation, b.p. 100°/0.2 Torr.

2.2.2. *Irradiation of* **12**. Compound **27** was formed selectively and isolated as under 2.2.1., b.p. 75°/0.1 Torr.

2.3. *Photoreduction of* **8** *and* **9** *in pentane.* 500 mg enone in 100 ml pentane were irradiated (λ= 254 nm) for 150 h in a quartz reactor. The solvent was distilled through a small *Vigreux*-column and the residue distilled at 50–90°/12 Torr. The so-obtained mixture of an unidentified C_{10}-hydrocarbon and ketone **29** was separated by prep. GC. (120°, same column as under 2.1.2.). The yield of ketone **29** from either **8** or **9** was 15–20%.

3. Quantum Yields. – These were determined by irradiating ($\lambda > 340$ nm) the compounds ($c_{enone} = 2 \cdot 10^{-1}$ mol/l) in the merry-go-round apparatus by monitoring the decrease of starting material by UV. spectroscopy and by comparing the conversion to the 'standard' 6-allyl-4,4,6-trimethyl-2-cyclohexenone (**28**) whose quantum yield had been determined independently [3].

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REFERENCES

[1] *V. Desobry & P. Margaretha*, Helv. *58*, 2161 (1975).
[2] *G. Vo Thi & P. Margaretha*, Helv. *59*, 2236 (1976).
[3] *W. Fröstl & P. Margaretha*, Helv. *59*, 2244 (1976).
[4] *T. S. Cantrell*, Tetrahedron *27*, 1227 (1971).
[5] *P. Tissot & P. Margaretha*, manuscript in preparation.
[6] *Y. G. Papulov*, J. Structural Chem. USSR *4*, 561 (1964).
[7] *Y. Chan & W. W. Epstein*, Org. Synth. *53*, 48 (1973).
[8] *M. Montury & J. Gore*, Bull. Soc. chim. France *1975*, 2622.
[9] *H. E. Zimmerman, F. X. Albrecht & M. J. Haire*, J. Amer. chem. Soc. *97*, 3726 (1975).
[10] *C. Paris, S. Geribaldi, G. Torri & M. Azzaro*, Bull. Soc. chim. France *1973*, 997.

89. Isolation and Identification of Three Major Metabolites of Retinoic Acid from Rat Feces

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Summary

Following the intraperitoneal administration of high doses of ^{14}C- and ^{3}H-labelled retinoic acid (**1**) to rats, three major metabolites and the intact compound were isolated from the feces in microgram amounts by use of column, thin-layer and high-pressure liquid chromatography. Their structures were elucidated by mass spectrometry and *Fourier* Transform ^{1}H-NMR. spectroscopy as **2** (all-*trans*-4-oxo-retinoic acid), **3** (7-*trans*-9-*cis*-11-*trans*-13-*trans*-5'-hydroxy-retinoic acid).

Hydroxylation of the 5-methyl group of the cyclohexene ring, oxidation of the cyclohexene ring in position 4 and *cis-trans* isomerisation of the nonatetraenoic acid side chain were the reactions, which produced these products from retinoic acid. The metabolites **2** and **4** each accounted for about 4% of the radioactivity administered. The metabolite **3** and the parent compound accounted for about 16% and 17% of the dose, respectively.

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