Tetrahedron. Vol. 29, pp. 275 to 278. Pergamon Press 1973. Printed in Great Britain

STRUCTURAL ASPECTS OF PHOTOSENSITIZED β,γ-ENONE ISOMERIZATIONS

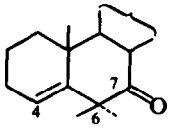
H. SATO and K. NAKANISHI
Department of Chemistry, Columbia University, New York, N.Y.

J. HAYASHI and Y. NAKADAIRA
Department of Chemistry, Tohoku University, Sendai 980, Japan

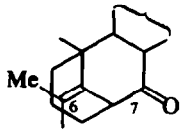
(*Received in the USA* 24 *April* 1972; *Received in the UK for publication* 1 *September* 1972)

Abstract—Sensitized irradiations of enones **5**, **9** and **11** gave the corresponding cyclopropyl ketones **6**, **10** and **12**, whereas similar irradiation of enone **1** only resulted in recovery of the starting material. Investigation of the steric course of the rearrangement of enone **11** utilizing NOE measurements and deuterio-labeled compounds **11α/11β** has shown that the overall isomerization of **11** to **12** proceeded nonstereospecifically. In addition, the positional effect of the enone moiety and influence of an additional keto group, i.e., 3-keto in enone **5**, have been investigated. These results can be rationalized and satisfactorily explained on the basis of an oxa-di-π-methane intermediate **19**.

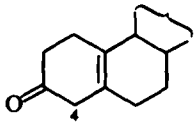
We recently discussed[1] the stereochemical and electronic factors involved in photoisomerizations of β,γ-enones which give rise to 1,3-acyl migration products and/or aldehydes,[1-3] e.g., from **1** to **2**.[1] In the following we discuss the stereochemical and structural aspects of 1,2-acyl migration reactions of β,γ-enones via triplet states, e.g., from **3** to **4**[4,5] (see also refs 6, 7).



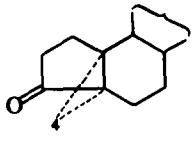
1



2



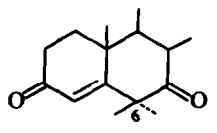
3



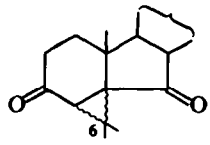
4

Irradiation of 6,6-dimethyl-cholest-4-en-7-one **1** in acetone with a 450 W high pressure Hg lamp using a Pyrex filter for 3 days afforded no photoproduct, but direct irradiation[1] gave the 1,3-acyl migration product **2**. However, acetone sensitized irradiation of 6,6-dimethyl cholest-4-en-3,7-dione **5**[8] under the same conditions gave, after TLC separation, the starting material and 15% of the cyclopropyl ketone **6**. The sluggish reactivities of **1** and **5** are presumably due to involvement of highly strained intermediates such as **19** (see below). In addition, occurrence of a singlet reaction (1,3-acyl migration) in ene-dione **5** would be unfavored because the 4-ene/7-keto interaction is decreased by the 3-oxo function.[3] This aspect is borne out by the finding of Schaffner *et al.*,[9,10] who showed that even direct irradiation (n, π*) of the ene-dione **7** in dioxane led to the triplet 1,2-acyl migration product **8a/8b** and no singlet product (aldehyde and/or 1,3-acyl migration product).

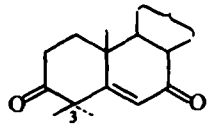
2-Oxo-1,2,3,4,9,10-hexahydrophenanthrene **9**[11] was studied next in order to examine the effect of extended conjugation of the β,γ-enone moiety. Williams, *et al.*, have reported[4,5] that direct irradiation of enone **3** in t-BuOH yielded the triplet product **4** (55%). On the other hand, we found that direct irradiation of enone **9** in t-BuOH led to a 1,3-acyl migration reaction and gave the corresponding cyclobutanone.[1] This difference can be ascribed to enhanced orbital overlap in **9** between the 2-oxo group and the double bond and stabilization of the incipient allyl radical.[1,3] In contrast, irradiation of enone **9** in t-BuOH in a Pyrex tube under acetophenone sensitization gave only the expected 1,2-acyl migration product **10** (56%). This result is similar to that obtained with an analogous acyclic compound.[6]



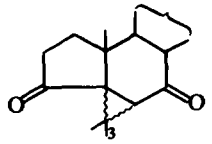
5



6

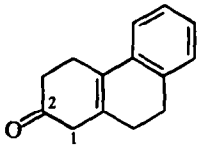


7

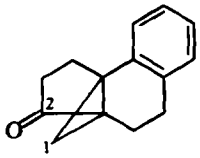


8

8a cyclopropane α
8b cyclopropane β



9



10

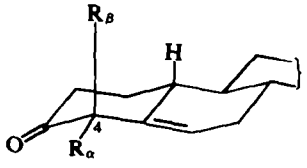
Sensitized photoirradiation of the 4,4-dimethyl-19-nor steroid **11** (see ref 12) has been reported to yield the cyclopropyl ketone **12**.[13] The stereochemical course of this reaction, however, remains unsettled and hence it was chosen as a model to clarify the configurational aspect of 1,2-acyl migrations. Although it was not feasible to determine the cyclopropyl configuration of **12** itself, the 220 MHz spectrum of its acid cleavage product **13**[13] allowed one to assign to it a β-stereochemistry. Namely, the 5-H peak at 2·57 ppm appeared as a doublet (7 Hz). This indicates that the coupling of 5-H with either 10-H or 6-H is very small. Molecular models indicated that this can only be rationalized by an A/B *cis* ring juncture having a deformed ring B (due to 1,3-diaxial repulsions among a 6β-substituent, 8β-H and 10β-H); the 5-H/6-H dihedral angle is then *ca* 90°, and this leads to stereostructure **13**.

Differentiation between the 4-R_1-Me and 4-R_2-Me groups in **12**, the other important configurational aspect ot this photo-reaction, was carried out by NMR analysis of the major sodium borohydride reduction product **14** of ketone **12**. Thus, irradiation of the 1·07 ppm Me peak resulted in a 10% increase in the integrated area of 3-H at 3·90 ppm (NOE), whereas irradiation of the 0·99 ppm Me peak caused no effect on the 3-H signal (see **14**). These results not only established that the 3-OH group was α but also led to an unambiguous assignment of the 4,4-dimethyl NMR signals.

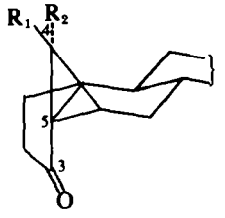
The steric course of this reaction was next investigated using deuteriomethylated compounds **11α/11β**.[14] Irradiation of a 34/66 mixture of **11α/11β** under similar conditions used for enone **11** resulted in a 53/47 mixture of **12a/12b**, as analysed from the Me signal areas of the reduction products **14a/14b**. As the products **12a/12b** would also receive triplet energy from the acetone sensitizer under the reaction conditions, thus leading to a photoequilibrium between **12a/12b**, it was not possible to determine whether the primary photochemical process was stereospecific or not.

The reactions described only occurred in sensitized photo-irradiations, and therefore they can be regarded as being triplet reactions. It has been shown that such triplets originate from π,π^* excited states.*

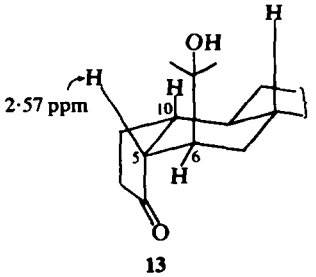
These 1,2-acyl migrations can be rationalized by one of the following mechanisms: (1) a biradical mechanism (**15** → **16** → **17/18** → **20**)[4,5] (2) a symmetry allowed concerted ($\sigma^2a+\pi^2a$) cycloaddition,[15] and (3) an oxa-di-π-methane mechanism[6,7] (**15** → **19** → **20**). The first biradical mechanism can be eliminated on the following grounds: a biradical mechanism must involve either intermediate **17** or **18**, but formation of intermediate **17** is unlikely



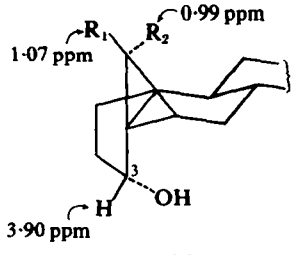
11 Rα = Rβ = Me
11α Rα = CD_3, Rβ = Me
11β Rα = Me, Rβ = CD_3



12 R_1 = R_2 = Me
12a R_1 = CD_3, R_2 = Me
12b R_1 = Me, R_2 = CD_3



13



14 R_1 = R_2 = Me
14a R_1 = CD_3, R_2 = Me
14b R_1 = Me, R_2 = CD_3

*We are grateful to a referee for bringing this point to our attention.

because of its high energy, and formation of **18**, involving attack of an acyl radical on the central carbon (β-carbon) of the allyl radical, is also chemically less favored.[6] If a biradical intermediate **16** were formed, the most plausible product would be an acyl migration product and/or an aldehyde.[1,13,15] These products, however, are only observed upon direct irradiations. A direct route leading from **15** to **18** is conceivable via spin polarization (see ref 17); however, this would be intrinsically the same as the oxa-di-π methane mechanism (see below).

The second possibility (concerted mechanism) cannot be strictly eliminated; in this case primary photochemical products are formed stereospecifically, but since a photoprimary product can also receive the triplet energy from acetone, the overall reaction would proceed in a nonstereospecific manner (**20** ⇄ **21**). However, the concerted rearrangement of electrons having a triplet nature would be energetically unfavorable. The most plausible mechanism for 1,2-acyl migrations is thus the oxa-di-π-methane mechanism. Since calculations show that π-orbital interaction between the β′-carbon (C=O) and β-carbon is favored in a triplet state,[17] formation of biradical **21** through the oxa-di-π-methane **19** is reasonable. Formation of cyclopropyl ketone **20** accompanied by spin inversion is not stereospecific (see **18** → **20**). In addition, since cyclopropyl ketone **20** can also absorb triplet energy, with the resultant formation of biradical intermediate **21**, the racemization of **20** (at 4-C) could also result from the formation of biradical intermediate **21**. Hence the oxa-di-π-methane mechanism[7] proposed by Schaffner for ene-dione **7**,[10] is also applicable to simple enones such as **9** and **11**.

This mechanism can satisfactorily explain the following differences in reactivity. Namely, the sensitized reaction of enone **5** proceeded very slowly and **1** did not proceed at all; on the other hand, enones **3** and **7** gave the rearrangement products readily and in high yields. This is presumably due to steric strain in the oxa-di-π-methane intermediate (e.g., **19**) caused by attachment of a 3-membered ring in ring-B, and participation of the reversion **19** → **15**. The relatively greater tendency for the occurrence of 1,2-acyl migration in diketone **5** as compared to **1** can also be accounted for by stabilization of the intermediate biradical such as **19** by the 3-keto group.

EXPERIMENTAL

6,6-Dimethyl cholest-5-en-7-one **1**. Compound **1** was prepared from cholest-5-en-7-one by exhaustive methylation[8] in 55% yield, m.p. 104°–105° (Lit.[8] 103°); UV (EtOH) 295 nm (ε 103).

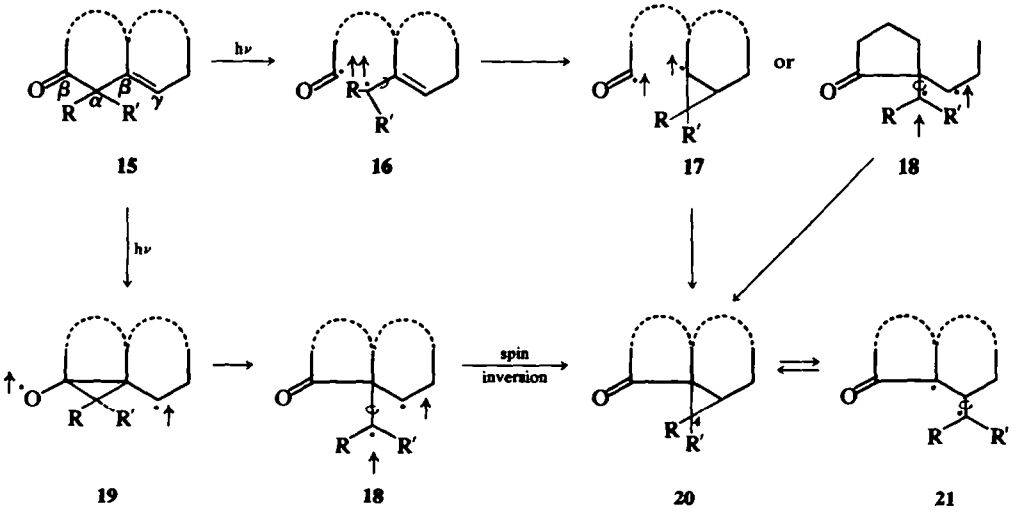
Sensitized irradiation of enone **1**. Irradiation of 30 mg of enone **1** in 10 ml of acetone for 36 hr with 450 W high pressure Hg lamp in a Pyrex tube resulted in recovery of the starting material.

6,6-Dimethyl cholest-4-en-3,7-dione **5**. Compound **5** was prepared from enone **1** by oxidation with Na_2CrO_4/AcOH in benzene[8] (52% yield); m.p. 134°–135° (Lit.[8] 133°); UV (MeOH) 240 (ε 13,000), 297 nm (ε 35).

Direct irradiation of ene-dione **5**. Irradiation of 20 mg of ene-dione **5** in 15 ml of t-BuOH with a 450 W high pressure Hg lamp in a Pyrex tube for 48 hr resulted in recovery of the starting material.

Sensitized irradiation of ene-dione **5**. A soln of 200 mg of ene-dione **5** in 35 ml acetone was irradiated at room temp with 450 W high pressure Hg lamp in a Pyrex tube for 36 hr. After removal of the solvent the residue was chromatographed on 20 g of SiO_2 ($CHCl_3$) to afford 140 mg of the starting material **5** and 30 mg of cyclopropyl diketone **6**. This was recrystallized from MeOH to give colorless cyrstals **6**; m.p. 140°; M^+ 426·3502 (calculated for $C_{29}H_{46}O_2$, 426·3498); UV (MeOH) 230 nm (ε 1,900); IR ($CHCl_3$) 1730 (5-membered ketone), 1690 cm^{-1} (6-membered ketone); NMR ($CDCl_3$) 1·25, 1·27, 1·50 ppm (3 Me's as singlets, 6,6- and 10-Me's).

2-Oxo-1-2,3,4,9,10-hexahydrophenanthrene **7**. Compound **7** was prepared by condensation of methyl vinyl



ketone with β-tetralone[11] (51% yield); m.p. 65° (Lit.[11] 67°); UV (MeOH) 224 (ε 15,400), 262 (ε 11,700), 267 (ε 11,400), 292 nm (ε 1,200).

Sensitized irradiation of enone **7**. A soln of 200 mg of enone **7** in 15 ml of t-BuOH in the presence of 5 ml acetophenone was irradiated with a 450 W high pressure Hg lamp in a Pyrex tube for 24 hr. After removal of the solvent and acetophenone by distillation *in vacuo*, the residue was separated by silica gel TLC ($CHCl_3$) to afford 123 mg of cyclopropyl ketone; oil; M^+ 198·1035 (Calc. for $C_{14}H_{14}O$), 198·1045); UV (MeOH) 225 nm (ε 7051, sh); IR ($CHCl_3$) 1720 cm^{-1} (5-membered ketone); NMR ($CDCl_3$) 1·53 (2 H, AB q 6 Hz, 1-H's), 1·8–2·8 (8 H, m, $-CH_2-$), 7·0–7·4 ppm (4 H, m, aromatic H's).

4,4-dimethyl 19-nor-testosterone acetate **11**. Compound **11** was prepared from 19-nor-testosterone by methylation;[12,13] m.p. 126°–127°; UV (EtOH) 295 nm (ε 100).

Sensitized irradiation of enone **11**. A soln of 500 mg of enone **11** in 200 mg acetone in a Pyrex tube was irradiated with a 450 W high pressure Hg lamp for 8 hr. After removal of the solvent by distillation *in vacuo*, the residue was chromatographed on 50 g of SiO_2 (benzene-EtOAc) to give 60 mg of the starting material **11** and 150 mg of cyclopropyl ketone **12**[13]. This was recrystallized from EtOH to give colorless crystals; m.p. 126°; M^+ 344 (Found C, 76·72; H, 9·44; $C_{22}H_{32}O_3$ requires: C, 76·70; H, 9·36; % mol. weight 344); UV (EtOH) 216 nm (ε 5600); CD (EtOH) Δε +9·70 (215 nm), Δε −0·83 (289 nm); IR (KBr) 1735 (—OAc), 1710 cm^{-1} (ketone); NMR (C_6D_6) 0·73 (3 H, s, 13-Me), 0·98 (3 H, s, 4-R_2-Me), 1·34 ppm (3 H, s, 4-R_1-Me); NMR ($CDCl_3$) 0·79 (3 H, s, 13-Me), 1·13 (3 H, s, 4-R_1-Me), 1·17 ppm (3 H, s, 4-R_2-Me). The assignments of 4,4-dimethyl NMR peaks in **12a/12b** were carried out by comparison of intensities with those of the corresponding alcohols **14a/14b** (see below).

Deuterio-methylation of 4-methyl-19-nor-testosterone. To an ice cold soln of t-AmOK (1·3 equiv moles to the starting ketone) in 40 ml of dry benzene was added 400 mg of 4-methyl-19-nor-testosterone in 5 ml benzene. After refluxing the mixture for 1 hr, this was cooled in an ice-water bath and 0·5 ml deuterio-methyl iodide in 2 ml dry benzene was added. The mixture was then allowed to stand over-night at room temp. This was extracted with EtOAc and the organic layer was washed with 5% HClaq water, 5% $NaHCO_3$aq, and sat NaClaq, successively. After drying the organic extract over $NaSO_4$, the solvent was removed by distillation. The residue was then acethylated with Ac_2O/pyridine. Water was added to the mixture and this was extracted with ether. The organic layer was washed with water, 5% HClaq, 5% $NaHCO_3$aq, and sat NaClaq, successively. After drying the extract over $NaSO_4$, the solvent was removed *in vacuo* by distillation. The residue was then chromatographed on SiO_2 (benzene-EtOAc) to give 220 mg of a 34:66 mixture of **11α/11β** (analysed by NMR peaks of 4,4-dimethyl group based on NOE in deuterio-benzene).[14] All physical constants were in agreement with those of enone **11** excepting the mass spectra and the IR C-D stretching frequencies (2070, 2150, and 2240 cm^{-1}).

A soln of 97 mg of 34:66 mixture of **11α/11β** in 60 ml of acetone was irradiated for 13·5 hr. Cyclopropyl ketone **12α/12β** (27 mg) was isolated by the procedure described for irradiation of enone **11**.

Reduction of cyclopropyl ketone **12** *with* $NaBH_4$. A soln of 50 mg of **12** in 1·5 ml MeOH and one drop of water was treated with 20 mg $NaBH_4$ for 3 hr at room temp. Excess borohydride was decomposed with AcOH with cooling and the mixture was extracted with ether. The ether layer was washed with water, 5% $NaHCO_3$aq, and sat NaClaq. After removal of the solvent the residue was separated by 30 g of SiO_2-TLC (EtOAc-benzene) to give 25 mg of alcohol **14** and 7 mg of its isomeric alcohol. Alcohol **14** was recrystalized from alcohol to afford colorless crystals; m.p. 96°–97°; M^+ 346 (calc for $C_{22}H_{32}O_3$, 346); IR (KBr) 3350 (-OH), 1735 cm^{-1} (-OAc); NMR ($CDCl_3$) 0·77 (3 H, S, 13-Me), 0·99 (3 H, s, 4-R_2-Me), 1·07 (3 H, s, 4-R_1-Me): the assignments of 4,4-dimethyl group were based on NOE measurements as described in the text.

Similar reduction of **12a/12b** resulted in a 53:47 mixture of **14a/14b** (based on NMR analysis of R_1/R_2 peak heights).

Acknowledgement—We are grateful to Dr. K. Kojima, Sankyo Laboratories, for a gift of compound **8**, Dr. T. Nishida, Nippon Electric Varian, for the measurements of 220 MHz NMR spectrum, and Dr. George van Lear, Lederle Laboratories, for the measurements of the high resolution mass spectra. This work was supported by the Ministry of Education, Japan, and PHS Grant CA 11572.

REFERENCES

[1]H. Sato, N. Furutachi, and K. Nakanishi, *J. Am. Chem. Soc.* **94**, 2150 (1972).
[2]R. S. Givens, W. F. Oettle, R. L. Coffin, and R. G. Carlson, *Ibid.* **93**, 3957 (1971).
[3]J. R. Williams and G. M. Sarkisian, *Chem. Commun.* 1564 (1971).
[4]J. R. Williams and H. Ziffer, *Ibid.*, 194, 469 (1967).
[5]J. R. Williams and H. Ziffer, *Tetrahedron* **24**, 6728 (1968).
[6]W. G. Dauben, M. S. Kellogg, J. I. Seeman, and W. A. Spitzer, *J. Am. Chem. Soc.* **92**, 1786 (1970).
[7]R. S. Givens and W. F. Oettle, *Ibid.*, **93**, 3963 (1971) and the refs cited.
[8]F. Lederer and G. Ourisson, *Bull. Soc. Chim. Fr.* 1078 (1962).
[9]S. Domb, G. Bozzato, J. A. Sabox and K. Schaffner, *Helv. Chim. Acta* **52**, 2436 (1969).
[10]S. Domb and K. Schaffner, *Ibid.*, **53**, 677 (1970).
[11]M. Mousseron, H. Christol and R. Salle, *C.R. Acad Sci. Paris* **245**, 1366 (1957).
[12]V. Permutti and Y. Mazur, *J. Org. Chem.* **31**, 705 (1966).
[13]K. Kojima, K. Sakai and K. Tanabe, *Tetrahedron Letters* 1925, 3399 (1969). Compound **8** was a gift from Dr. K. Kojima.
[14]Y. Nakadaira, J. Hayashi, H. Sato and K. Nakanishi, *Chem. Commun.* 282 (1972).
[15]K. G. Hancock and R. O. Grider, *Tetrahedron Letters* 4281 (1971); R. B. Woodward and R. Hoffmann, *Angew. Chem.* **81**, 797 (1969).
[16]O. P. Straus, P. J. Kozak, G. N. C. Woodal, A. G. Sherwood, and H. E. Gunning, *Canad. J. Chem.* **46**, 1317 (1968).
[17]D. I. Schuster, G. R. Underwood, and T. P. Knudsen, *J. Am. Chem. Soc.* **93**, 4304 (1971).