CHEMISTRY LETTERS, pp. 609-612, 1988.

Photochemical Rearrangement of 16β,17β-Epoxydigitoxigenin 3-Acetate. The Formation of Cyclopropyl Ketones

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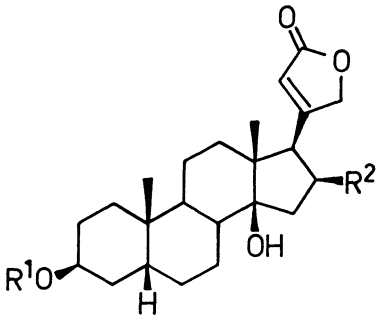
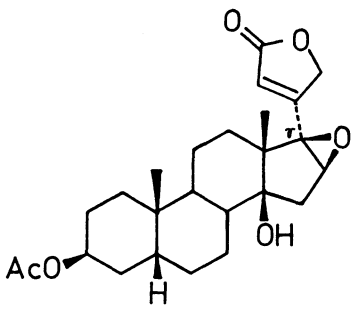
The first photochemical transformation of a cardenolide derivative was studied. The photolysis of 16β,17β-epoxydigitoxigenin 3-acetate prepared from gitoxigenin leads to cyclopropyl ketones, which are formed by oxa-di-π-methane rearrangement of the primary photoproduct, 16-oxodigitoxigenin 3-acetate.

Gitoxin (1) and digitoxin (2) are the two main cardiac glycosides of Digitalis purpurea L. leaves. In contrast to 2, 1 has not been used clinically due to its low solubility and low cardiotonic activity for heart insufficiency. Therefore, chemical transformations of 1 and its aglycone 3 have been studied to extend the utility.[1,2]

We report here the first photochemical transformation of a cardenolide derivative, 16β,17β-epoxydigitoxigenin 3-acetate (4),[3] which was prepared from gitoxigenin (3) and possessed an α,β-unsaturated γ,δ-epoxy carbonyl chromophore. The photolyses of α,β-unsaturated γ,δ-epoxy ester[4] and ketones[5] in the ionone series, e.g. 5 and 6, have been studied in great detail. From these studies, it has been known that, in general, cleavage of the C(γ),O-bond of the oxirane and/or (E/Z)-isomerization in epoxy carbonyl compounds arise from a triplet state,



1 R^1=(digitoxose)$_3$, R^2=OH
2 R^1=(digitoxose)$_3$, R^2=H
3 R^1=H, R^2=OH



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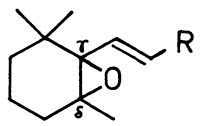
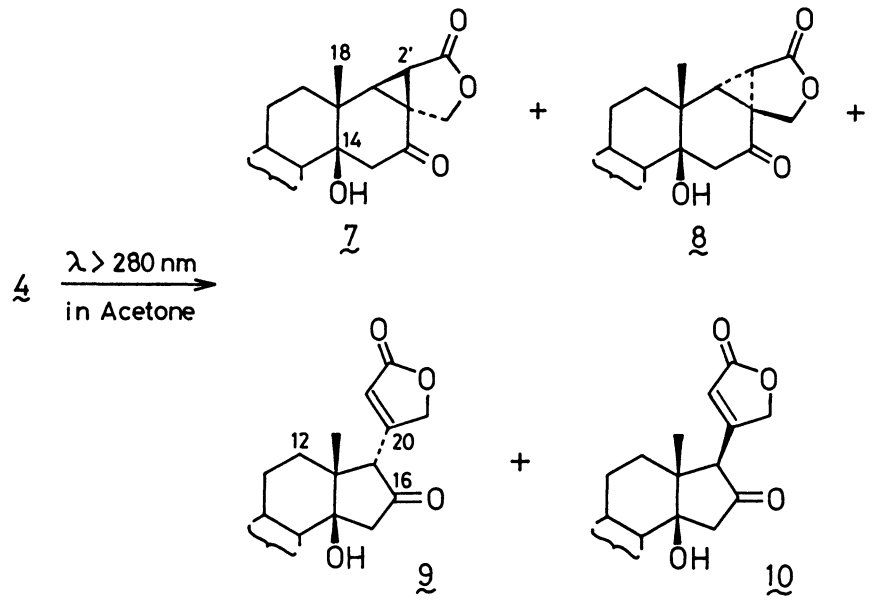


5 R=COOMe
6 R=COMe

Fig. 1.



Scheme 1.

whereas C(γ),C(δ)-bond cleavage arises from a singlet state. On the other hand, on triplet sensitization and direct irradiation of steroidal γ,δ-epoxy enones, testosterone derivatives, product formation via C(γ),O-bond cleavage is by far the main process.[6] Therefore, it was also interesting to study the influence of the 16,17-epoxy function and the butenolide moiety on photochemical cleavage of the oxirane in 4.

A 0.023 M solution of 4 in acetone was irradiated in a Pyrex vessel with a high pressure mercury lamp under argon at room temperature for 3 h (94% conversion). After the solvent had been removed, chromatography (SiO_2) of the residue gave 7 (26%[7]), 8 (20%), and 9 (49%).[8] Compound 10 could not be isolated after chromatography on SiO_2 of the photolysis mixture because of the instability. Furthermore, ^{1}H-NMR spectrum analyses of the irradiation (λ>280 nm) of 4, 9, and 10[2] in acetone-d_6 were studied (Fig. 2A, B, and C).[9] A significant difference was observed between the photoreactivity of the ketone 9 and its β-isomer 10. The

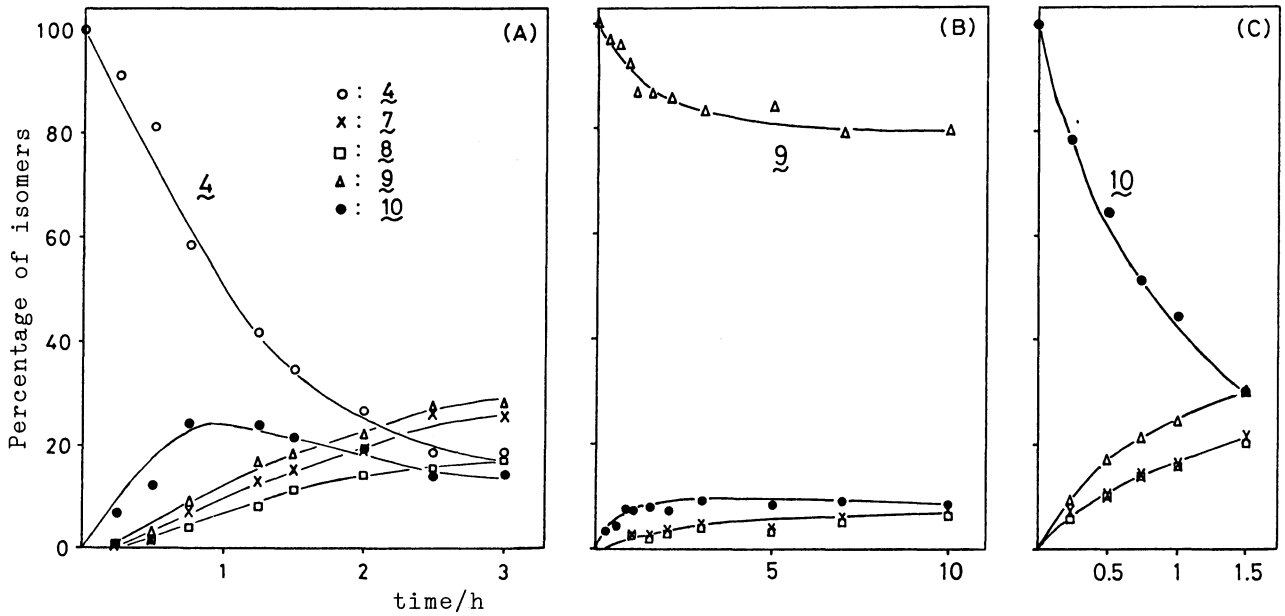


Fig. 2. Action plots of photolyses of 4, 9, and 10 in acetone-d_6.

ketone 10 was converted into cyclopropyl ketones 7 and 8 faster than 9. The results suggest that β-isomer 10 may be a reaction intermediate to furnish 7, 8, and 9.

The structure of cyclopropyl ketone 8 was deduced from the NMR spectra and determined by X-ray crystallographic analysis.[10] The molecular structure is given in Fig. 3. The structure of 7 was confirmed by comparison of the spectral data with those of 8. In particular, the ^{13}C-NMR spectrum of 7 shows a quartet (δ 19.2 ppm) due to C(18) at upper field than that of 8 (δ 22.4 ppm) because of the steric compression due to the cyclopropane ring. The ^{1}H-NMR spectrum indicated that a methine proton attached to C(2') of 7 appeared at a lower field (δ 1.02 ppm) than that of 8 due to the deshielding by the 14β-OH.

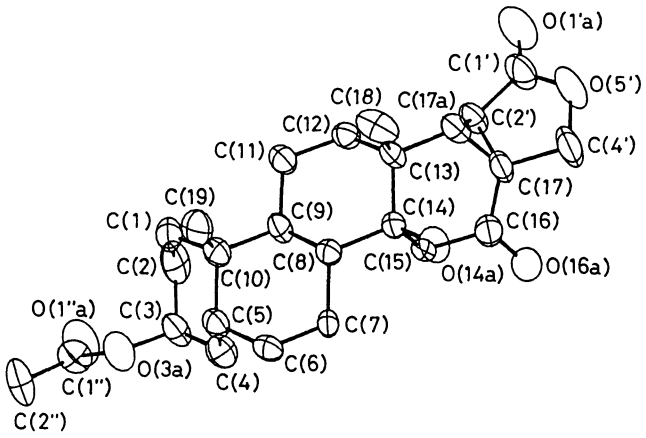
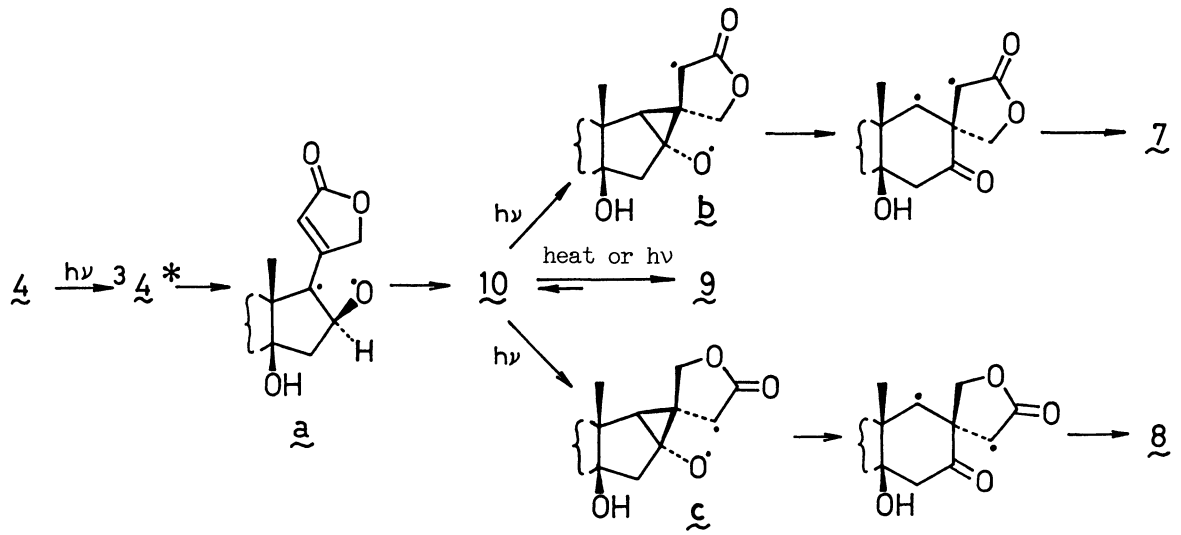


Fig. 3. Molecular structure for 8.

The proposed mechanism for the formation of 7 and 8 is shown in Scheme 2. On triplet sensitization, epoxide 4 undergoes C(γ),O-cleavage of the oxirane leading to the intermediate a followed by a [1,2]-H shift to ketone 10. The unstable β-isomer 10 is converted thermally and/or photochemically into α-isomer 9, and presumably undergoes an oxa-di-π-methane rearrangement[11] via the diradical intermediates b and c furnishing the cyclopropyl ketones 7 and 8, respectively. On the other hand, a strong steric interaction between H-C(12) and butenolide moiety may prevent the α-isomer 9 from assuming a conformation with an orbital overlap between C(16) and C(20) (from inspection of Dreiding models) suitable for the oxa-di-π-methane rearrangement.



Scheme 2.

In conclusion, triplet sensitization of epoxide 4 also shows the typical behaviour of γ,δ-epoxy enone 6[5] and corresponding ester 5[4] undergoing selective C(γ),O-bond cleavage of the oxirane leading to a, followed by a [1,2]-H shift to ketone 10. However, in contrast to the photolyses of 5, 6, and testosterone derivatives,[6] the epoxide 4 dose not afford products, e.g. aldehyde 11 (Fig. 4), arising from a [1,2]-alkyl shift via a.

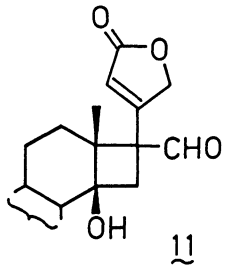


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Fig. 4.

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7) Yields are based on consumed starting material.

8) Satisfactory elemental analyses were obtained for all new compounds.

9) Yields are determined by ^{1}H-NMR analysis of the reaction mixture using bis-(trimethylsilyl)acetylene as an internal standard.

10) Crystal data for 8: $C_{25}H_{34}O_5$, M=423.48, monoclinic, space group $P2_1$, a= 16.348(8), b=7.162(5), c=9.914(6) Å, β=100.14(3)°, U=1142.6(12) Å^3, Z=2, and D_c=1.231 g/cm^3. F(000)=450. μ(Mo-K_α)=0.944 m^{-1}. Observed independent reflections of 1439 with F>6s(F) in the range 2°<2θ<50° were collected on a Rigaku four circle diffractometer AFC-6B using Mo-K_α radiation and ω-scan method and used in subsequent calculations. The structure was solved by direct methods applying MULTAN programs.[12] After refinements of non-hydrogen atoms were achieved by applying block diagonal least-squares, the hydrogen atoms were located in D-map. Furthermore, refinements were continued to the final R value of 0.106.

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(Received December 25, 1987)