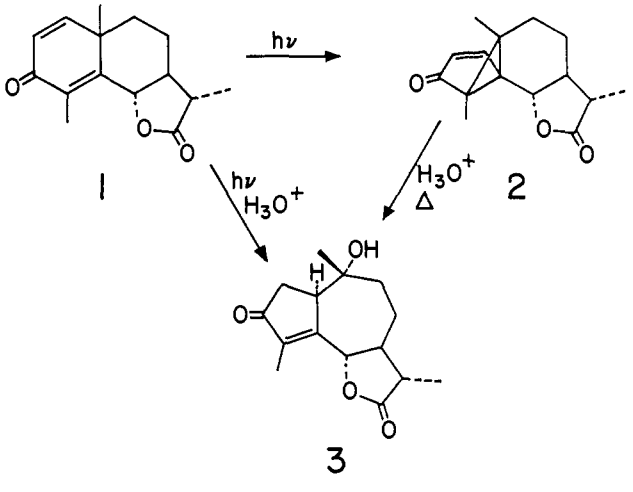
The Acid-Catalyzed Cleavage of Cyclopropyl Ketones Related to Lumisantonin

Paul J. Kropp

Contribution from The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239. *Received December 21, 1964*

As a model study for the acid-catalyzed conversion of lumisantonin (**2**) *to isophotosantonic lactone* (**3**), *the cleavage reactions of the cyclopropyl ketones* **4**, **10**, *and* **15** *in 45% acetic acid were investigated. The course of the reactions was found to be markedly influenced by the presence or absence of A-ring substituents. The unsubstituted ketone* **4** *gave predominantly spiro products* (**6**, **8**, *and* **9**), *accompanied by a small amount of the 5–7-fused ketone* **7**. *The 2-methyl ketone* **10** *gave exclusively spiro products* (**12**, **13**, *and* **14**). *In contrast, the 4-methyl analog* **15** *gave predominantly the 5–7-fused product* **17**, *accompanied by the spiro ketone* **18** *in smaller yield. Thus, only the 4-methyl ketone* **15** *gave a significant amount of 5–7-fused product. Although these substituent effects in the acid-catalyzed cleavages of the cyclopropyl ketones* **4**, **10**, *and* **15** *are reminiscent of those encountered previously in the photochemical conversions of the parent dienones* **5**, **11**, *and* **16** *to similar hydroxy ketone products, it is noted that different products and/or product ratios are obtained in these two routes. The mechanistic implications of these results are discussed. A comparison of the acid-catalyzed and light-initiated rearrangements of the cyclopropyl ketones is also made.*

The course of many photochemical transformations is highly dependent upon the nature of the solvent. One of the earliest examples to be recognized was the photochemical behavior of the sesquiterpene santonin (**1**). On irradiation in neutral media such as dioxane, santonin (**1**) undergoes isomerization to the cyclopropyl ketone lumisantonin (**2**).[1-3] However, in aqueous acidic media, such as 45% acetic acid, the formation of lumisantonin (**2**) is suppressed and the hydroazulenone isophotosantonic lactone (**3**) is the predominant product.[2,4,5]



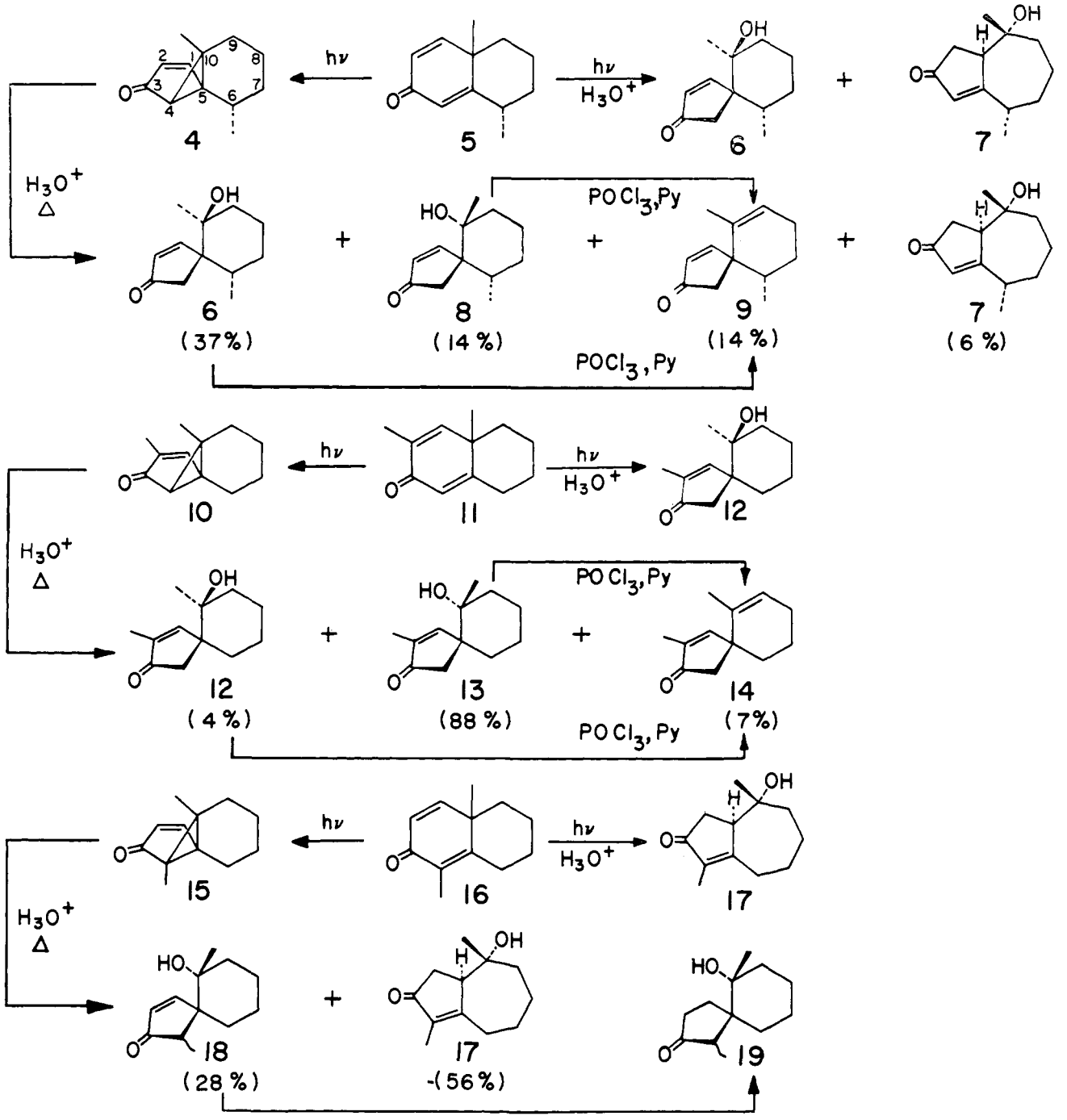
As chance would have it, this same hydroxy ketone **3** can be obtained also in a nonphotochemical fashion by the acid-catalyzed cleavage of the neutral media photoproduct, lumisantonin (**2**), with 45% acetic acid.[1,2,6] Although the photochemical formation of hydroxy ketones from santonin (**1**) and related cross-conjugated cyclohexadienones recently has received considerable mechanistic study and discussion,[7-10] relatively little attention has been devoted to the equally interesting, acid-catalyzed transformation of lumisantonin (**2**) to isophotosantonic lactone (**3**). In an effort to learn more about this reaction, the acid-catalyzed cleavages of the three model cyclopropyl ketones **4**, **10**, and **15** have been examined and are here compared with that of lumisantonin (**2**).

Results

The cyclopropyl ketone **4**,[7c] which bears no A-ring substituents, was prepared by irradiation of the dienone **5**[11] in dioxane at 2537 Å.[12] Treatment of **4** with refluxing 45% acetic acid gave principally a mixture of the two spiro ketones **6**[7c] and **8**,[7c] which are epimeric at the hydroxyl-bearing carbon. In addition, a small amount of the known 5–7-fused ketone **7**[7c] was formed. Also obtained in 14% yield was a keto olefin which is assumed to have structure **9** by analogy with the formation of the keto olefin **14** in the 2-methyl series (see below). This assignment is supported by the n.m.r. and infrared spectra; the latter has the same intriguing doublet in the carbonyl region

(1) D. H. R. Barton, P. de Mayo, and M. Shafiq, *J. Chem. Soc.*, 140 (1958).
(2) D. Arigoni, H. Bosshard, H. Bruderer, G. Büchi, O. Jeger, and L. J. Krebaum, *Helv. Chim. Acta*, **40**, 1732 (1957).
(3) D. H. R. Barton and P. T. Gilham, *J. Chem. Soc.*, 4596 (1960).
(4) D. H. R. Barton, P. de Mayo, and M. Shafiq, *ibid.*, 929 (1957).
(5) J. D. M. Asher and G. A, Sim, *ibid.*, 1584 (1965).
(6) It should be emphasized that lumisantonin (**2**) is not an intermediate in the *photochemical* conversion of santonin (**1**) to isophotosantonic lactone (**3**). The photochemical rearrangement can be effected at room temperature, whereas the acid-catalyzed cleavage of lumisantonin (**2**) requires elevated temperatures.[1] Moreover, irradiation of lumisantonin (**2**) in aqueous acid at room temperature produces photosantonic acid, not isophotosantonic lactone (**3**); see E. E. van Tamelen, S. H. Levin, G. Brenner, J. Wolinsky, and P. E. Aldrich, *J. Am. Chem. Soc.*, 81, 1666 (1959); D. H. R. Barton, P. de Mayo, and M. Shafiq, *J. Chem. Soc.*, 3314 (1958).
(7) (a) P. J. Kropp, *J. Am. Chem. Soc.*, **86**, 4053 (1964); (b) *ibid.*, **85**, 3779 (1963); (c) P. J. Kropp and W. F. Erman, *ibid.*, **85**, 2456 (1963).
(8) (a) P. J. Kropp, *J. Org. Chem.*, **29**, 3110 (1964); (b) D. Caine and J. B. Dawson, *ibid.*, **29**, 3108 (1964).
(9) (a) K. Weinberg, E. C. Utzinger, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 43, 236 (1960); (b) C. Ganter, E. C. Utzinger, K. Schaffner, D. Arigoni, and O. Jeger, *ibid.*, 45, 2403 (1962).
(10) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, 84, 4527 (1962); H. E. Zimmerman, *Advan. Photochem.*, 1, 183 (1963).
(11) S. M. Bloom, *J. Am. Chem. Soc.*, 80, 6280 (1958); *J. Org. Chem.*, 24, 278 (1959).
(12) A Hanau NK 6/20 low-pressure mercury lamp was employed which emits approximately 95% of its ultraviolet radiation at 2537 Å. The use of these conditions for the preparation of cyclopropyl ketones related to lumisantonin (**2**) is discussed in ref. 7a; see also H. Dutler, C. Ganter, H. Ryf, E. C. Utzinger, K. Weinberg, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2346 (1962).

Chart I.



(5.84 and 5.92 μ) that is exhibited by the spiro ketones **6** and **8** and a number of other cyclopentenones which are unsubstituted at the α-position.[13] The keto olefin **9** was also obtained by dehydration of either of the spiro ketones **6** or **8** with phosphorus oxychloride.

Treatment of the 2-methyl ketone **10**[7a,14] with 45% acetic acid gave two hydroxy ketones (**12** and **13**) and a keto olefin (**14**). The hydroxy ketone formed in minor amount was found to be identical in every respect with **12**, which had been obtained previously as the major product from irradiation of the dienone **11** in 45% acetic acid.[7a] Identification of the keto olefin as **14** was readily established, since it could also be obtained in good yield by the dehydration of **12** with phosphorus oxychloride.[15]

There remained the question of the identity of the major cleavage product. Unlike the products from either lumisantonin (**2**) or the cyclopropyl ketone **4**, it was not identical with the photoproduct (**12**) obtained directly from the parent dienone **11**. Nor did it appear to be a 5–7-fused ketone, as the infrared

(13) See the discussion in ref. 7c and the references cited therein; also see K. R. Varma, M. L. Maheshwari, and S. C. Bhattacharyya, *Tetrahedron*, **21**, 115 (1965).

(14) The steroid numbering system is employed in the discussion sections for dienones; positions in the cyclopropyl ketones are assigned the same number as the corresponding atom in the parent dienone.

(15) The possibility that any skeletal rearrangement occurred during dehydration is remote, since the n.m.r. spectrum (see Experimental) exhibits the absorption patterns expected for the structural assignment **14**. Furthermore, the striking similarities of the ultraviolet spectrum and the appropriate portions of the infrared and n.m.r. spectra with those of **12** and **13** testify that the cyclopentenone moiety has remained intact.

and n.m.r. spectra were almost identical with those of **12**. Indeed, the similarity with the spectra of **12** suggested that the product was the epimeric hydroxy ketone **13**. This was readily verified when it was found that dehydration gave, once again, the keto olefin **14**.

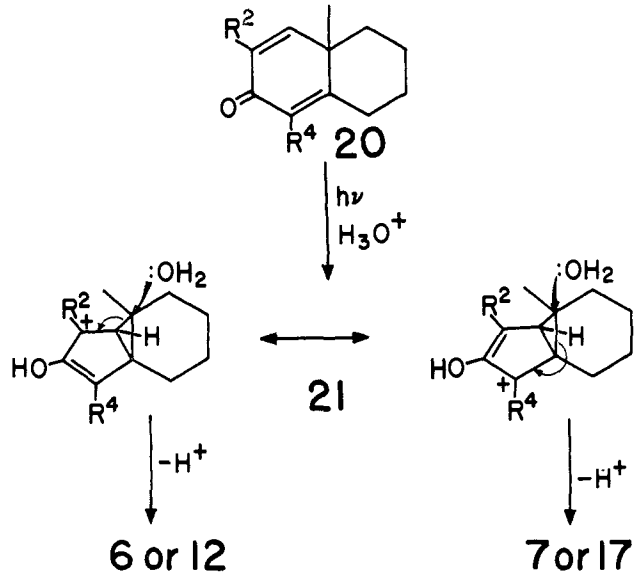
The previously unreported cyclopropyl ketone **15** was prepared in the usual manner by irradiation of the 4-methyl dienone **16**[8,16] in dioxane at 2537 Å.[12] This material exhibited the expected infrared absorption at 5.92 (carbonyl) and 6.36 μ (double bond) and ultraviolet absorption at 240 (ϵ 4650) and 272 mμ (ϵ 1950).[1,2,7,9] In the n.m.r. spectrum the olefinic protons of **15** appeared appropriately as an AB quartet consisting of doublets centered at τ 2.66 and 4.12 (J_{AB} = 10 c.p.s.), and the 4-methyl group was seen as a sharp singlet at 8.72.

Unlike the acid cleavage of lumisantonin (**2**), which is reported to give only a single product, two hydroxy ketones resulted from the treatment of **15** with 45% acetic acid. The major product was the 5–7-fused ketone **17**, which is analogous with isophotosantonic lactone (**3**) and which had been obtained earlier as the principal product from irradiation of the dienone **16** in 45% acetic acid.[8] The spiro structure **18** is proposed for the minor cleavage product. In support of this assignment, the material had infrared absorption at 5.84 (cyclopentenone carbonyl) and 6.26 μ (double bond) and ultraviolet absorption at 222 mμ (ϵ 9100). On treatment with palladium on charcoal it formed a dihydro derivative (**19**) which exhibited the typical cyclopentanone absorption at 5.76 μ. Additional support for the assignment **18** can be gathered from the n.m.r. spectrum, which shows the presence of two olefinic protons (doublets at τ 1.98 and 3.76), one proton α to the carbonyl group (quartet at τ 7.34), and two methyl groups (singlet at τ 8.70 and doublet at 8.85). Since only one stereoisomer of **18** was obtained, little information is available for establishing the configurations of the two methyl substituents. The assignment indicated by **18** at the hydroxyl-bearing carbon is suggested from mechanistic considerations (see below). Some support for this assignment is seen in the closer similarity of the spectral data of **18** with those of the spiro ketones **8** and **13** than with the isomers **6** and **12**.

The necessary control runs established that there was no interconversion between any of the hydroxy ketone products. The ketones **6** and **8** were recovered virtually unchanged from retreatment with 45% acetic acid. Retreatment of either **12** or **13** under the precise conditions of their formation from **10** resulted in 95–97% recovery of the starting hydroxy ketone, along with a trace amount (3%) of the keto olefin **14** in the case of **13**. Likewise, **17** and **18** were recovered essentially unchanged, with no indication of any interconversion. Hence it appears that all of these products arise directly from cleavage of the corresponding cyclopropyl ketones.

Discussion

The acid-catalyzed cleavage of cyclopropyl ketones related to lumisantonin (**2**) leads essentially only to spiro products unless there is a methyl substituent at C-4, in which case a 5–7-fused product predominates. This propensity of the 4-methyl system for undergoing rearrangement to a 5–7-fused product is reminiscent of a similar pattern exhibited in the alternative route to these same hydroxy ketones, namely, irradiation of the parent dienones **20** in aqueous acid, since dienones having $R^4 = CH_3$ give predominantly, if not exclusively, a 5–7-fused photoproduct (*e.g.*, **16** → **17**).[8] However, the analogy cannot be extended beyond this point, for dienones having the methyl substituent at C-2 instead give only a spiro product (**11** → **12**)[7a] and dienones lacking an A-ring substituent give approximately equal amounts of spiro and 5–7-fused products (**5** → **6** + **7**).[7c,17] In no case in the present study were the products or product ratios from the two routes identical. This difference provides a useful versatility for the synthesis of hydroxy ketones of these general types. In addition, it suggests that the various interpretations of the acid-catalyzed cleavage reactions of lumisantonin (**2**) and related compounds which have been advanced previously should be re-examined in light of the present data. Each of the previous proposals will now be considered in turn.



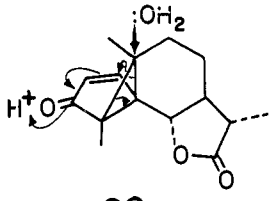
Barton and co-workers[1,18] envisioned two possible routes from lumisantonin (**2**) to isophotosantonic lactone (**3**), involving either a sequence of 1,2-shifts as illustrated by **22** or the intervention of the spiro ketone **23** as an intermediate. This latter possibility, however, was considered to be less likely in such a mildly acidic medium. It can now be confidently dismissed from consideration, since treatment of the spiro ketone **18** under similar conditions caused no detectable conversion to the 5–7-fused hydroxy ketone **17**. The alternative suggestion of a sequence of shifts such as

(16) (a) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952); (b) P. R. Hills and F. J. McQuillin, *ibid.*, 4060 (1953); (c) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956); (d) M. Yanagita, S. Inayama, M. Hirakura, and F. Seki, *ibid.*, **23**, 690 (1958); (e) L. Mandell, D. Caine, and G. E. Kilpatrick, *J. Am. Chem. Soc.*, **83**, 4457 (1961).

(17) The formation of both spiro and 5–7-fused photoproducts from dienones of type **20** has been interpreted in terms of the intervention of a common cyclopropyl intermediate **21**[7-10] which, in the absence of substituents at C-2 or C-4, suffers cleavage to the two types of product with approximately equal facility.[7] The preferred formation of a spiro or 5–7-fused product in the 2- or 4-methyl series, respectively, has been attributed to the electronic influence of the substituent on the mode of cleavage of the intermediate **21**.[7,8]

(18) D. H. R. Barton, *Proc. Chem. Soc.*, 61 (1958); *Helv. Chim. Acta*, **42**, 2604 (1959).

22 is adequate to explain the formation of both isophotosantonic lactone (3) and the hydroxy ketone **17** but, in itself, fails to account for the formation of **18** or for the marked difference in behavior exhibited by cyclopropyl ketones lacking a 4-methyl substituent.



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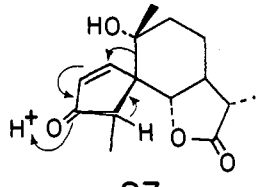
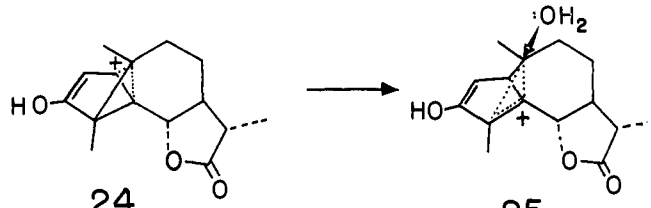


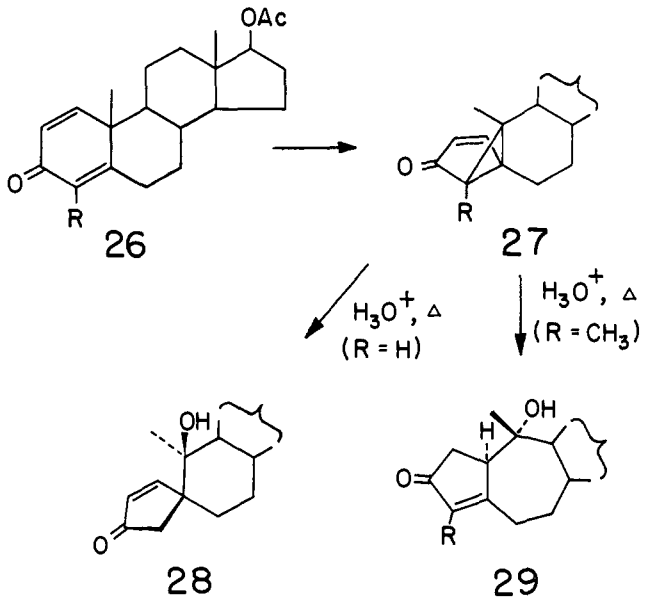
23

Jeger and collaborators[2] invoked the intervention of the nonclassical cyclopropylcarbinyl intermediate **25** in interpreting the conversion of lumisantonin (2) to isophotosantonic lactone (3). Obviously, the intervention of this intermediate alone is not generally applicable, since it too does not account for the formation of spiro products.

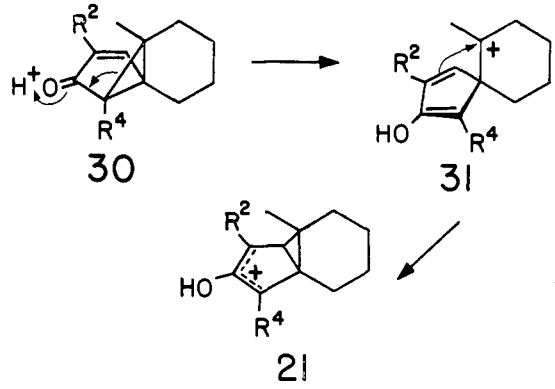


24 25

Somewhat later, an alternative mechanism was advanced by the Swiss workers.[9b] It had been found that the steroidal analogs **27** (R = H) and **27** (R = CH_3) underwent cleavage to the spiro ketone **28** and the 5–7-fused ketone **29** (R = CH_3), respectively, on acid treatment.[9] Since, by coincidence, the same ketones had been obtained as the sole products from irradiation of the parent dienones **26** (R = H) and **26** (R = CH_3) in acidic media,[9] it was proposed that the same intermediate (*i.e.*, **21**) intervenes in *both* the acid-catalyzed cleavage reactions of the cyclopropyl ketones and the photochemical rearrangements of the parent dienones.[9b] (The formation of **21** from the cyclopropyl ketones was envisioned as **30** → **31** → **21**). This conclusion was based on a false premise, however, since it has been demonstrated more recently that **26** (R = H) gives approximately equal amounts of both the spiro ketone **28** and the 5–7-fused photoproduct **29** (R = H).[7c] Moreover, the proposal as presented does not anticipate the present results, in which significantly different product compositions were obtained by the two routes. In order to assume the intervention of a common intermediate, such as **21**, in both the acid-catalyzed and photochemical pathways, it is clearly necessary to assign to it a different reactivity depending upon its mode of generation.

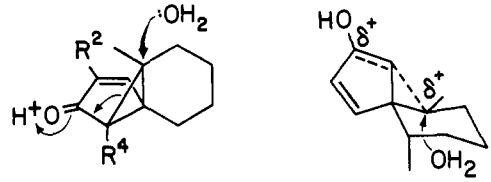


26 27 28 29



30 31 21

Although this latter possibility is not precluded by the available data,[19] neither is an alternative, perhaps somewhat more straightforward, interpretation for the acid-catalyzed cleavages which merits consideration. The data suggest that the formation of spiro products involves, quite simply, cleavage of the 4,10-cyclopropyl bond (*cf.* **32**) and nucleophilic attack by water at C-10. The attack by water might well be somewhat concerted with bond cleavage, thereby assisting cleavage and accounting for the stereospecific formation of the isomers **8**, **13**, and **18**. Since the control experiments revealed no significant dehydration of the hydroxy spiro ketone products under these conditions, whereas olefinic products were obtained in varying yields from the cleavage reactions, loss of a proton at C-9 apparently can compete with attack by water at C-10.



32 33

The cyclopropyl ketone **4** is exceptional in that it gives principally the isomer **6**, accompanied by substantial amounts of the olefinic product **9**. The different behavior of this system is probably attributable to the presence of the 6α-methyl substituent, which undoubtedly impedes the backside approach of a

(19) For example, it might be postulated that the intermediate in the photochemical route, being formed from a higher electronic state, retains a large excess of vibrational energy at the time of cleavage. Such a material would likely possess a slightly different geometry and chemical behavior than an intermediate of a similar gross structure but in the lower vibrational ground state that would be involved in the acid-catalyzed cleavages. It is interesting to note, however, that such a proposal requires the implicit assumption that a species in a higher vibrational state (*i.e.*, the intermediate in the photochemical pathway) undergoes cleavage more selectively than one possessing less vibrational energy.

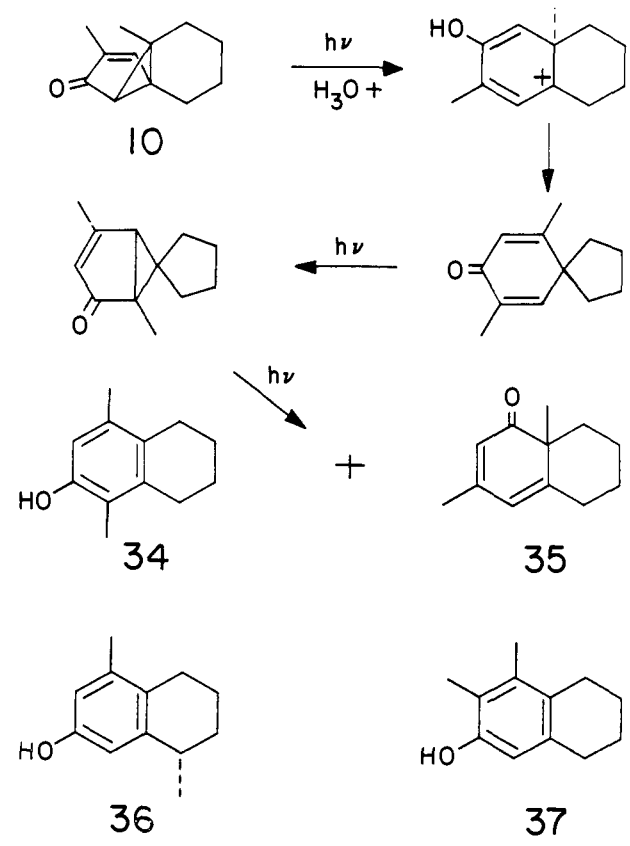
nucleophile at C-10. This interference would take the form of a 1,3-diaxial interaction in the most extreme case, in which the transition state more closely resembles product than reactant (*cf.*, **33**). Such an assumption is not unlikely for a process involving bond cleavage at a quaternary carbon. In the absence of facile backside attack by water, both olefin formation and frontside attack should become prominent.

In competition with the direct cleavage to spiro products is a rearrangement process leading to a 5–7-fused hydroxy ketone. This rearrangement might be regarded as involving either a nonclassical intermediate of type **25**[2] or a sequence of 1,2-shifts of type **22**.[1,18] In either event, this mode of rearrangement is significant only when there is substitution at C-4. This substituent effect apparently reflects a stabilization by the methyl group of either the intermediate **25** or, in the case of a mechanism of type **22**, a transition state involving double-bond formation at C_4–C_5. It is probably significant that the formation of a 5–7-fused ketone product is most important in the 4-methyl series, in which the newly formed double bond bears the methyl substituent. However, even with the stabilization imparted by the methyl group, this mode of rearrangement is not completely competitive with direct cleavage to a spiro product (**18**).[20]

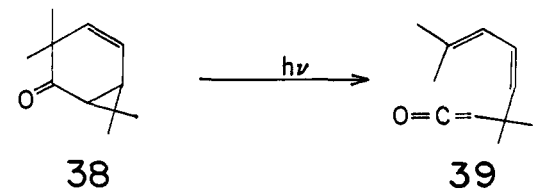
Finally, it is of interest to consider which cyclopropyl bonds undergo cleavage. In previous studies it has been found that ring opening in a cyclopropylcarbinyl cation occurs toward that carbon atom bearing substituents which can best stabilize a positive charge.[21] In the case of ketones **4**, **10**, and **15**, each cyclopropyl bond is adjacent to the carbonyl and/or β-olefinic carbon atoms, the two positions which assume positive character upon protonation of the enone system. Hence, all three bonds are available for cleavage, and since each bond could cleave toward a tertiary center (C-5 or C-10), there is little basis *a priori* for predicting the mode of cleavage of these ketones. In fact, the only reactions observed involve either direct cleavage of the 4,10-bond or cleavage of the 4,10-bond accompanied by rearrangement of the 5,10-bond.

The reason for this preferred mode of cleavage is not entirely clear. Only the orbitals of the 4,10-bond are in the proper geometrical arrangement for favorable overlap with the p-orbitals of the carbonyl groups. However, the greater accessibility of C-10 than C-5 to approach by water may also play a role in determining the mode of cleavage.[22]

There was no evidence for the formation of any products arising from acid-catalyzed cleavage of the 4,5-bond. Yet it is this bond which is cleaved in the *light-induced* rearrangements of ketones **4**, **10**, and **15** in 45% acetic acid.[7,23] Irradiation of **10**, for example, gives a mixture of the phenol **34** and the dienone **35**, a process involving the sequence of light-initiated rearrangements indicated.[7a,23b] In similar fashion, the ketones **4** and **15** give the phenols **36** and **37**, respectively.[7c,23a]



This preferred cleavage of the 4,5-bond under photochemical conditions parallels the recent report that 3-methyl-4-caren-2-one (**38**) rearranges to the ketene **39** on irradiation.[24] In this latter case it was suggested that the preferred cleavage of the one cyclopropyl bond which is contiguous with both the carbonyl group and the double bond is attributable to the possibility of continuous electronic redistribution during rearrangement, which only that particular cyclopropyl bond can provide. A similar argument can be applied in the case of **4**, **10**, and **15**. A detailed study of the effects of bond angles and substituents on the mode of both acid- and light-initiated cleavages is in progress.



Experimental[25]

5α,8aα-Dimethyl-4a,5,6,7,8,8a-hexahydro-1β,4a-cyclo-2(1H)-naphthalenone (**4**). *A. Preparation.*[12] A solution containing 808 mg. of dienone **5**[11] in 115

(20) Only 5–7-fused products have been reported from the acid-catalyzed cleavages of lumisantonin (**2**) and the 4-methyl analog **27** (R = CH_3). However, material balances were not reported, so it is not clear to what extent, if any, that spiro products analogous to **18** are formed in these cases.

(21) See H. M. Walborsky and L. Plonsker, *J. Am. Chem. Soc.*, 83, 2138 (1961).

(22) By contrast, the dihydro derivatives of **27** (R = H) and **27** (R = CH_3) lacking the 1,2-double bond are reported to give products arising from cleavage of the 4,5-bond[9]; see also W. W. Kwie, B. A. Shoulders, and P. D. Gardner, *J. Am. Chem. Soc.*, 84, 2268 (1962). For a study of the acid-catalyzed cleavage of bicyclo[3.1.0]hex-2-ene see P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, 30, 771 (1965).

(23) (a) Unpublished data from these laboratories. The irradiations were conducted at room temperature, conditions under which the cyclopropyl ketones are resistant to acid-catalyzed cleavage; (b) see also P. J. Kropp, *Tetrahedron*, in press.

(24) A. J. Bellamy and G. H. Whitham, *J. Chem. Soc.*, 4035 (1964).

(25) Ultraviolet spectra were determined in absolute ethanol with a Cary Model 14 spectrophotometer, and infrared spectra were obtained in 5% methylene chloride solution with a Perkin-Elmer Infracord

ml. of dioxane (which had been freshly distilled from lithium aluminum hydride) was irradiated for 2.5 hr. with a Hanau NK 6/20 low-pressure mercury lamp. Vigorous stirring of the reaction mixture was effected by the introduction of a stream of nitrogen through a jet opening in the bottom of the vessel. The residue obtained from removal of the solvent under reduced pressure was chromatographed on 25 g. of silica gel. Elution with 1.25 l. of 1:3 and 1.75 l. of 1:1 benzene–hexane gave 97 mg. of a yellow oil which was discarded. Continued elution with 3.75 l. of 3:1 benzene–hexane gave 479 mg. (59% yield) of a colorless oil which was identical in gas chromatographic retention time and infrared spectrum with an authentic specimen of ketone **4**.[7c]

B. Acid-Catalyzed Cleavage. A solution containing 258 mg. of ketone **4** in 25 ml. of 45% acetic acid was heated in the dark under reflux in an atmosphere of nitrogen for 6.5 hr. and was then concentrated on a rotary evaporator under reduced pressure. The last traces of acetic acid were removed by codistillation with two 100-ml. portions of toluene. Chromatography of the residue on 8.5 g. of silica gel gave, on elution with 160 ml. of benzene and 240 ml. of 1:50 ether–benzene, 56 mg. of olefinic material which was shown by gas chromatography to consist of four components. Isolation of the major component (present in 14% yield) and final purification by short-path distillation at 87–88° (0.25 mm.) gave 6,10-dimethylspiro[4.5]deca-3,6-dien-2-one (**9**) as a colorless oil: λ_{max} 5.84, 5.92, and 6.30 μ; λ_{max} 223 mμ (ϵ 8800); n.m.r. spectrum τ 2.54 and 3.78 (2d, J_{AB} 5.5, –CH=CHCO–), 4.38 (m, 1, olefinic CH), 7.58 and 7.72 (2d, J_{AB} 4, $-CH_2CO-$), 8.48 (m, 3, olefinic CH_3), and 9.10 (2d, 3, J_{AB} 6.5, CH_3CH-)[26]; mol. wt. 176.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.37; H, 9.14.

Further elution with 1.25 l. of 1:10 ether–benzene gave 20 mg. of a yellow oil which was discarded. Continued elution with 1 l. of 1:9 ether–benzene gave 98 mg. of spiro ketone **6**[7c] as colorless needles, m.p. 98–99° after recrystallization from ether–hexane. Elution with an additional 0.5 l. of 1:9 ether–benzene gave 21 mg. of a colorless oil which was shown by gas chromatography to contain both the spiro ketone **6** (22%) and the isomeric ketone **8** (45%). Further elution with 1.75 l. of 1:9 ether–benzene gave 34 mg. of spiro ketone **8** as colorless needles, m.p. 89–90° after recrystallization from ether–hexane. The yields of **6** and **8** were thus 37 and 14%, respectively. Identification of **6** and **8** was verified by direct comparison of gas chromatographic retention times and infrared spectra with authentic specimens[7c] and by mixture melting points.

Finally, elution with 0.75 l. of 1:1 ether–benzene gave 18 mg. (6% yield) of a colorless oil which was identified as the hydroxy ketone **7** by direct comparison of its gas chromatographic retention time and infrared spectrum with that of an authentic specimen.[7c]

Cleavage of 3,8a-Dimethyl-4a,5,6,7,8,8a-hexahydro-1β,4a-cyclo-2(1H)-naphthalenone (**10**). A solution of 522 mg. of cyclopropyl ketone **10**[7a] in 50 ml. of 45% acetic acid was heated under reflux in an atmosphere of nitrogen and in the dark for 9 hr. and then was concentrated on a rotary evaporator under reduced pressure. The last traces of acetic acid were removed by codistillation with two 100-ml. portions of toluene. Chromatography of the residue on 17 g. of silica gel gave on elution with 1 l. of 1:1 benzene–hexane 35 mg. (7% yield) of keto olefin **14** as a colorless oil which was identified by comparison of its infrared and n.m.r. spectra and gas chromatographic behavior with that of the material prepared by dehydration of the hydroxy ketones **12** and **13** as described below.

Continued elution with 1.7 l. of 1:19 ether–benzene gave 483 mg. (84% yield) of *3,8aβ-dimethyl-4a,5,6,-7,8,8a-hexahydro-8aα-hydroxy-1(8a → 4aβ)abeo-2(1H)-naphthalenone* (**13**). Purification by short-path distillation at 124° and 0.2 mm. gave a colorless oil: λ_{max} 2.74, 5.86, and 6.08 μ; λ_{max} 234 mμ (ϵ 9600); n.m.r. spectrum τ 2.60 (*q*, 1, J_{AB} 1.5, CH-4), 7.56 and 7.98 (2d, 2, J_{AB} 18.5, CH_2-1), 8.24 (d, 3, J_{AB} 1.5, CH_3-3), and 8.92 (s, 3, CH_3-8a); semicarbazone, colorless needles, m.p. 204.5–206°.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.87; H, 9.40.

Anal. Calcd. for $C_{13}H_{21}N_3O_2$: C, 62.12; H, 8.42; N, 16.72. Found: C, 62.34, 62.46; H, 8.39, 8.48; N, 16.94.

Finally, elution with an additional 840 ml. of 1:19 ether–benzene gave 45 mg. (8% yield) of a colorless oil which was shown by gas chromatographic analysis to consist of a 1:1 mixture of two components. Isolation of a pure specimen of each component and direct comparison of their infrared spectra and gas chromatographic retention times with those of authentic samples revealed that they were the hydroxy ketones **12** and **13**.

Dehydration Studies. A. Hydroxy Ketone **12**. A solution containing 183 mg. of hydroxy ketone **12**[7a] and 1.6 ml. of phosphorus oxychloride in 16 ml. of freshly distilled pyridine was maintained at 87° under an atmosphere of nitrogen for 1.5 hr. The resulting brown solution was cooled to room temperature, poured onto crushed ice, and extracted with three 50-ml. portions of ether. The combined ethereal extracts were washed with three 50-ml. portions of 5% hydrochloric acid and 50-ml. portions each of saturated sodium carbonate and sodium chloride solutions. Drying over anhydrous sodium sulfate and removal of the solvent gave 158 mg. of a yellow semicrystalline solid. Chromatography of the residue on 4.6 g. of silica gel gave, on elution with 150 ml. of benzene, 54 mg. (33% yield) of *3,6-dimethylspiro[4.5]deca-3,6-dien-2-one* (**14**). Further elution with 200 ml. of 1:3 ether–benzene gave 53 mg. (29% recovery) of hydroxy ketone **12**.

Short-path distillation of keto olefin **14** at 119–120° (0.3 mm.) gave a colorless oil: λ_{max} 5.88, 6.02 (sh), and 6.10 μ; λ_{max} 229 mμ (ϵ 10,400); n.m.r. spectrum

spectrophotometer. Unless otherwise stated, gas chromatographic separations were effected using a 5 ft. × 0.25 in. column containing 20% GE silicone fluid-96 over 60–80 mesh firebrick. Melting points were determined on a micro hot stage and are calibrated and corrected. Nuclear magnetic resonance spectra were obtained in deuteriochloroform solution with a Varian Model A-60 spectrometer, using tetramethylsilane as an internal standard. Molecular weights were determined using a Bendix Model 12–100 time-of-flight mass spectrometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

(26) Indicates multiplicity (s = singlet, d = doublet, q = quartet, and m = multiplet), integration, and assignment. Coupling constants given in c.p.s.

τ 2.96 (q, 1, J_{AB} 1, CH-4), 4.44 (m, 1, CH-8), 7.48 and 7.86 (2d, 2, J_{AB} 18.5, CH_2-1), 8.22 (d, 3, J_{AB} 1.5, CH_3-3), and 8.52 (m, 3, J_{AB} 2, CH_3-8a).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.31; H, 9.35.

B. Hydroxy Ketone **13**. A solution consisting of 70 mg. of hydroxy ketone **13** and 1 ml. of phosphorus oxychloride in 6 ml. of pyridine was maintained at 90–100° for 170 min. under an atmosphere of nitrogen. Isolation as described above gave 73 mg. of an amber oil. Chromatography on 3.7 g. of silica gel gave, on elution with 360 ml. of benzene, 40 mg. (64% yield) of keto olefin **14** as a colorless oil which was identified by direct comparison of its infrared and n.m.r. spectra and gas chromatographic behavior with that of the sample described immediately above.

C. Hydroxy Ketone **6**. Treatment of 31 mg. of hydroxy ketone **6** with 0.5 ml. of phosphorus oxychloride and 5 ml. of pyridine for 3 hr. at 85° gave 31 mg. of a pale yellow oil which was shown by gas chromatographic retention time and spectral data to be identical with the keto olefin **9** obtained by cleavage of cyclopropyl ketone **4**.

D. Hydroxy Ketone **8**. Similar treatment of 33 mg. of hydroxy ketone **8** gave an amber oil which was shown by gas chromatography and spectral data to consist principally of the keto olefin **9**.

1,8a-Dimethyl-4a,5,6,7,8,8a-hexahydro-1β,4a-cyclo-2(1H)-naphthalenone (**15**). *A. Preparation.* A solution containing 972 mg. of the 4-methyl dienone **16**,[8,16] prepared as previously described,[8a] in 120 ml. of dioxane was irradiated for 3 hr. as described above for the preparation of ketone **4**. The residue obtained from removal of the solvent under reduced pressure was chromatographed on 30 g. of silica gel. Elution with 6 l. of 1:1 benzene–hexane gave 679 mg. (70% yield) of a colorless oil. Further purification by preparative gas chromatography followed by short-path distillation at 115° (0.3 mm.) gave a colorless oil: λ_{max} 5.92 and 6.36 μ; λ_{max} 240 (ϵ 4650) and 272 mμ (ϵ 1950); n.m.r. spectrum τ 2.66 and 4.12 (2d, 2, J_{AB} 10, CH-4 and CH-3), 8.72 (s, 3, CH_3-1), and 8.85 (s, 3, CH_3-8a).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.89; H, 9.20.

B. Acid Cleavage. A solution of 121 mg. of cyclopropyl ketone **15** in 25 ml. of 45% acetic acid was heated under reflux in an atmosphere of nitrogen and in the dark for 3 hr. and then was concentrated on a rotary evaporator under reduced pressure. The last traces of acetic acid were removed by codistillation with two 100-ml. portions of toluene. Chromatography of the residue on 5 g. of silica gel gave, on elution with 0.5 l. of 1:9 ether–benzene, 37 mg. (28% yield) of *1,6-dimethyl-6-hydroxyspiro[4.5]dec-3-en-2-one* (**18**) as colorless prisms. Recrystallization three times from ether–hexane gave colorless prisms: m.p. 134.5–135°; λ_{max} 2.75, 5.84, and 6.26 μ; λ_{max} 222 mμ (ϵ 9100); n.m.r. spectrum τ 1.98 and 3.76 (2d, 2, J_{AB} 6, CH-4 and -3), 7.34 (q, 1, J_{AB} 7.5, CH-1), 8.70 (s, 3, CH_3-6), and 8.85 (d, 3, J_{AB} 7.5, CH_3-1).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.28; H, 9.30.

Finally elution with 600 ml. of 1:3 ether–benzene and 300 ml. of 1:1 ether–benzene gave 74 mg. (56% yield) of *3,8β-dimethyl-4,5,6,7,8,8a-hexahydro-8α-hydroxy-2(1H)-azulenone* (**17**) as a colorless oil which crystallized on seeding with an authentic sample.[8a] Recrystallization from ether–hexane gave colorless needles, m.p. 82.5–83.5°, which was not depressed on admixture with an authentic specimen.

Hydrogenation of Hydroxy Ketone **18**. A solution of 54 mg. of hydroxy ketone **18** in 10 ml. of absolute ethanol was stirred with 16 mg. of 10% palladium on charcoal in an atmosphere of hydrogen at atmospheric pressure. A total of 1.1 mole equiv. of hydrogen was absorbed. Removal of the catalyst by filtration and evaporation of the filtrate under reduced pressure gave the dihydro derivative **19** as a colorless oil which crystallized on standing. Recrystallization from ether–hexane gave colorless needles, m.p. 80–80.5°; λ_{max} 2.72 and 5.76 μ.

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.48; H, 10.08.

Control Runs. A. Hydroxy Ketone **6**. A solution prepared from 25 mg. of hydroxy ketone **6**, m.p. 98–99°, in 2.5 ml. of 45% acetic acid was heated under reflux in an atmosphere of nitrogen and in the dark for 3 hr. Isolation as described above for the cleavage of ketone **4** gave 26 mg. of a colorless oil which crystallized on seeding with a specimen of the starting material. The gas chromatographic trace of the crude product was superimposable with that of the starting material and showed no additional peaks. Neither of the ketones **7** or **8** was present.

B. Hydroxy Ketone **8**. Treatment of a solution containing 20 mg. of hydroxy ketone **8**, m.p. 89–90°, in 2.5 ml. of 45% acetic acid exactly as described above gave 21 mg. of a colorless oil which crystallized on seeding with a specimen of ketone **8**. Gas chromatographic analysis revealed that the material had been recovered unchanged.

C. Hydroxy Ketone **12**. Treatment of a solution prepared from 52 mg. of hydroxy ketone **12** in 9.5 ml. of 45% acetic acid for 4.5 hr. as described above gave 53 mg. of an amber oil, which was shown by gas chromatography to consist of a mixture of the hydroxy ketone **12** (95% recovery) and five minor components. No evidence for the presence of any of the hydroxy ketone **13** could be detected.

D. Hydroxy Ketone **13**. Treatment of a solution containing 73 mg. of hydroxy ketone **13** in 15 ml. of 45% acetic acid for 9 hr. as described above gave 72 mg. of a colorless oil which was shown by gas chromatography to be a 3:97 mixture of the keto olefin **14** and recovered hydroxy ketone **13**, respectively. None of the hydroxy ketone **12** could be detected.

E. Hydroxy Ketone **17**. Treatment of a solution of 15 mg. of hydroxy ketone **17** in 3 ml. of 45% acetic acid for 3 hr. as described above gave 15 mg. of pale yellow needles which was shown by gas chromatography to be a 92:6 mixture of recovered hydroxy ketone **17** and an unidentified product, along with a number of very minor impurities. No evidence for the formation of any of the hydroxy ketone **18** could be detected.

F. Hydroxy Ketone **18**. Treatment of a solution of 54 mg. of hydroxy ketone **18** in 10 ml. of 45% acetic

acid for 3 hr. as described above gave 59 mg. of pale yellow needles, which was shown by gas chromatography to be a 94:6 mixture of recovered hydroxy ketone **18** and an unidentified product. No evidence for the formation of any of the hydroxy ketone **17** could be detected.

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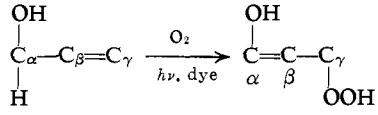
Reactivity and Geometry in Allylic Systems. VI.[1] Stereospecific Conversion of Allylic Alcohols to α,β-Epoxy Ketones by Photosensitized Oxygenation[2]

A. Nickon[3a] and W. L. Mendelson[3b]

Contribution from the Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218. *Received April 5, 1965*

In pyridine with hematoporphyrin sensitization, Δ^4- and Δ^5-steroidal olefins with an allylic hydroxyl group at C-3 and C-7, respectively, underwent photooxygenation more slowly than the parent olefins. In those cases where the allylic hydrogen on the hydroxylated carbon had (or could attain) a quasi-axial orientation, the products were the corresponding α,β-unsaturated ketone and α,β-epoxy ketone. The configuration of the epoxide group was the same as that of the allylic hydrogen abstracted. The stereospecificity is interpreted in terms of known steric and conformational factors in photosensitized oxygenations. Acetate and benzoate esters of the allylic alcohols proved essentially inert, and this deactivation is attributed to electronic factors. The proportion of enone to epoxy ketone from cholest-4-en-3β-ol was found to depend on the sensitizer.

Photosensitized oxygenation of monoolefins is a useful way to introduce an allylic oxygen function with accompanying rearrangement of the double bond.[4] Studies with steroid systems indicated that the reaction proceeds by a cyclic abstraction mechanism with rather stringent geometric requirements.[5,6] The effects of polar functional groups are not known, and the object of the present study was to examine substrates with an oxygen function (*e.g.*, OH, OCOR) on the allylic carbon. The hydroxyl group seemed of special interest because successful abstraction of the allylic hydrogen in the normal *cis* manner could generate a transient enol as shown, which could collapse to products



other than the usual allylic hydroperoxides. We now report the findings with some ring-A and ring-B allylic alcohols (and their derivatives) in the cholestane series.

Synthesis of Starting Compounds and Products

The ring-A epimeric allylic alcohols and their derivatives (partial structures **1** and **4**) were prepared as described elsewhere.[5c] We synthesized 4α,5-epoxy-5α-cholestan-3-one (**2**) from **4a** by treatment with perbenzoic acid in chloroform followed by oxidation with chromium trioxide in pyridine.[7] The epimeric epoxy ketone **5** was obtained from cholest-4-en-3-one (**3**) by treatment with alkaline hydrogen peroxide.[8] All the ring-B allylic alcohols and their esters (**8** and **9**), the related epoxy ketones (**10**), and the enones (**11**) were prepared by reported methods with the exception of cholest-5-en-7α-ol (**8b**), which was obtained conveniently from cholest-5-ene (**6a**) as follows. Photosensitized oxygenation converted **6a** to a hydroperoxide (**7a**), which was not purified but which was rearranged in chloroform to a second hydroperoxide (**8a**).[9] Reduction of the crude product with sodium iodide gave **8b** along with some cholest-5-en-7-one (**11c**), which was removed by chromatography.

Methods

Photooxygenations were conducted in pyridine solution with hematoporphyrin as sensitizer. The enone content in a crude reaction product was determined by ultraviolet spectroscopy, and the starting allylic alcohol was assayed by oxidation of an aliquot with manganese

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(2) This work was supported by the National Institutes of Health (Grant GM 09693) and an early phase of it was aided by the Alfred P. Sloan Foundation and by a grant-in-aid from the Hynson, Westcott, and Dunning Fund of The Johns Hopkins University. A preliminary communication appeared in *J. Am. Chem. Soc.*, **85**, 1894 (1963).

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