Thermolysis of Pentasubstituted 3-Hydroxy-1,2-dioxolanes

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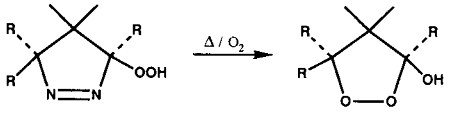
Received July 9, 1992

A series of pentasubstituted 3-hydroxy-1,2-dioxolanes, **1a-e**, was synthesized by oxygen trapping of β-keto radicals formed during α-azo hydroperoxide decomposition. Thermolysis of the pentasubstituted 3-hydroxy-1,2-dioxolanes (hemiperketals) in benzene proceeded cleanly and yielded pairs of ketones and carboxylic acids. Two of the hemiperketals yielded only one pair of products while the others produced two sets of products. One of each pair of fragmentation products had undergone skeletal rearrangement. Only methyl migrations were observed when in competition with phenyl groups from the same position. The activation parameter data for **1d** [$\Delta H^{\ddagger} = 24.3$ kcal/mol, $\Delta S^{\ddagger} = -8.4$ eu, $\Delta G^{\ddagger} = 27.1$ kcal/mol, $k_{60°} = 3.1 \times 10^{-5}\ s^{-1}$] were consistent with O-O bond scission as the rate-determining-step. A likely mechanism for this thermolysis is initial peroxy bond homolysis to the 1,5-oxygen diradical followed by β-scissions with rearrangements.

J. Heterocyclic Chem., **29**, 1781 (1992).

Introduction.

The 1,2-dioxolanes, five-membered cyclic peroxides, and related ring systems are of mechanistic and synthetic interest [1-4]. 3-Hydroxy-1,2-dioxolanes (hemiperketals) and related compounds have been found as natural products [2,5]. The 3-hydroxy-1,2-dioxolane system has been generated [6] by ene-reaction of singlet oxygen or Michael-type addition of hydrogen peroxide to α,β-unsaturated carbonyl compounds followed by ring closure. Recently, we have developed [7] a new route for the synthesis of highly-substituted 3-hydroxy-1,2-dioxolanes **1** *via* oxygen-trapping of intermediates from the thermolysis of cyclic α-azohydroperoxides (reaction 1). Thermolysis of 1,2-dioxolanes and related systems has been shown [3,8] to be an excellent source of 1,5-oxygen diradicals. The thermolysis of 3-hydroxy-1,2-dioxolanes should allow the generation of α-hydroxy substituted 1,5-diradicals, a system that has not been investigated extensively. We report here the first study of the homolytic thermolysis of a series of 3,4,4,5,5-pentasubstituted-3-hydroxy-1,2-dioxolanes, **1a-e**, to generate 1,5-diradicals which underwent β-scission with interesting rearrangements that showed a high preference for alkyl *vs* phenyl migration.

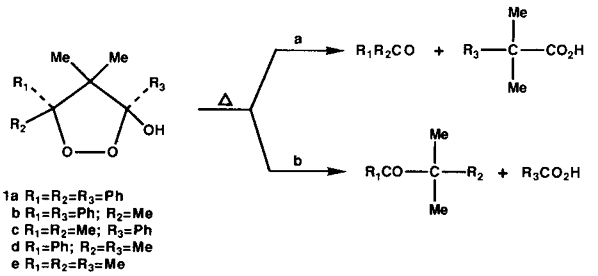


(1)

1

Results and Discussion.

The pentasubstituted 3-hydroxy-1,2-dioxolanes, **1a-e**, were synthesized [7] by the trapping of β-keto radicals with oxygen. The thermal decomposition of hemiperketals **1a-e** in benzene-d_6 at 80° for approximately 8-10 hours resulted in clean fragmentation to ketone and carboxylic acid products (reaction 2). For example, thermolysis of **1a** yielded benzophenone and phenyldimethylacetic acid (16 ±2% respectively) as well as benzoic acid and phenyl phenyl-2-propyl ketone (84 ±2% respectively). Thermolysis of **1b** yielded benzoic acid and phenyl *t*-butyl ketone in quantitative yields. Compound **1c** yielded only one pair of ketone/carboxylic acid products while compounds **1d,e** yielded two pairs (see Table 1). The products were isolated and characterized by standard methods. The mass balance for these thermolysis was found to be 90 ±5% (isolated yields). Thus, the products were formed in (essentially) quantitative yields. The results are summarized in Table 1.



$$R_1R_2CO + R_3-C(Me)_2-CO_2H$$

$$R_1CO-C(Me)_2-R_2 + R_3CO_2H$$

(2)

1a $R_1=R_2=R_3=Ph$
b $R_1=R_3=Ph$; $R_2=Me$
c $R_1=R_2=Me$; $R_3=Ph$
d $R_1=Ph$; $R_2=R_3=Me$
e $R_1=R_2=R_3=Me$

The data (Table 1) were indicative of two routes of fragmentation (reaction 2). For each route, two products are formed from the original hemiperketal: one of which had undergone skeletal rearrangement (R group migration). Route **a** yielded a rearranged carboxylic acid and a ketone while **b** yielded a rearranged ketone and a carboxylic acid. Route **b** was found to be the sole pathway for decomposition of **1b,c** and the major pathway for **1a,d,e**. Route **a** was observed as the minor pathway for decomposition of **1a,d,e**. For thermolysis of hemiperketals **1b-d**, no phenyl migration was observed when in competition with methyl migration. The results for **1a** showed that phenyl migration was possible for this system and that the ratio of route **a/b** products was essentially identical to that for **1e** in which two sets of methyl migrations were observed.

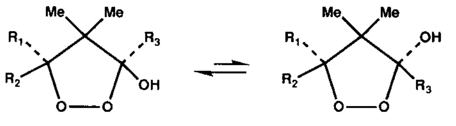
Table 1

Product Yields [a] for the Thermolysis of **1a-e** in Benzene-d_6 at ~80°C

Hemiperketal	R_1	R_2	R_3	R_1R_2CO R_3-CMe_2-CO_2H	R_1CO-CMe_2-R_2 R_3CO_2H
1a	Ph	Ph	Ph	16%	84%
1b	Ph	Me	Ph	-	100%
1c	Me	Me	Ph	-	100%
1d	Ph	Me	Me	44%	56%
1e	Me	Me	Me	18%	82%

[a] Determined by ^1H nmr spectroscopy (±2%). All products isolated by chromatographic methods in yields that were at least 85% of those determined by the nmr method.

The thermolysis of **1a-e** was found to be of the first order. The rate constants (k_1) were determined by thermolysis of the hemiperketals in chlorobenzene by ^1H nmr techniques. All five compounds underwent thermolysis with similar k_1 values. Epimerization of **1b,d** (reaction 3) was noted under the thermolysis conditions. Equilibrium was established in less than 60 minutes at 59° presumably *via* an acyclic intermediate. The epimers of **1b,d** were the minor components in both cases with K values of 0.36 ±0.05 and 0.52 ±0.06 for **1b** and **1d** respectively. The rate constants for the thermolysis of **1d** were determined in chlorobenzene over a 40° range. The activation parameters were calculated to be: $\Delta H^\ddagger = 24.3 \pm 0.6$ kcal/mol, $\Delta S^\ddagger = -8.4$ eu; $\Delta G^\ddagger = 27.1 \pm 0.6$ kcal/mol; $k_{60^\circ} = 3.1 \times 10^{-5}$ s^{-1}. The product distribution changed slightly over the temperature range. The percentage of route **a** products was found to increase from 42% at ~50° to 50% at ~90°. However, the magnitude of this small trend is close to that of the experimental error. The kinetic data are summarized in Table 2.



1b,d

(3)

Table 2

First-order Rate Constant [a] for the Thermolysis of **1a-e** in Chlorobenzene

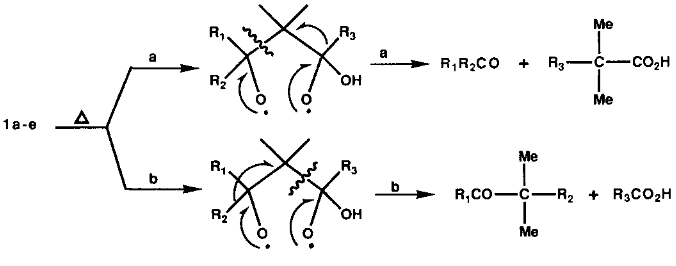
Hemiperketal	$k_1 s^{-1}$	Temperature (°C)
1a	5.6×10^{-5}	58.9°
1b [b]	1.6×10^{-4}	58.9°
1c	5.7×10^{-5}	58.9°
1d [b]	9.3×10^{-6}	49.8°
	2.8×10^{-5}	58.9°
	8.8 x 10-5	69.7°
	2.3 x 10-4	79.0°
	6.2×10^{-4}	88.2°
1e	5.1×10^{-5}	58.9°

[a] Error in k_1 is ±10% of value. [b] Epimerization observed.

The activation parameter data seem indicative of a homolytic process. The $\Delta G^\ddagger$ value is similar to those (27-28 kcal/mol) for tetrasubstituted β-peroxylactones which have been shown [1c] to proceed *via* 1,5-diradical intermediates. However, in contrast to the activation parameter data [1c] for β-peroxylactones, the $\Delta S^\ddagger$ value for **1d** of −8 eu is quite different from those (~ +1 eu) for thermolysis of β-peroxylactones while the $\Delta H^\ddagger$ value is lower than that of $\Delta G^\ddagger$. The compensating effects observed for **1d** in the $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values could be indicative of anchimeric assistance and/or involvement of the hydroxy group in the rate-determining step. A concerted ionic process appears unlikely because of the high preference of methyl *vs* phenyl migration. Intramolecular hydrogen-bonding of the hydroxy proton to one of the peroxy oxygen would be expected to lower the $\Delta H^\ddagger$ value and yield a negative $\Delta S^\ddagger$ value for a homolytic process. Thus, the rate-determining step for thermolysis of **1** appears to be O-O bond scission to yield 1,5-diradicals.

The pattern of fragmentation and rearrangement products is somewhat similar with those of β-peroxylactone-related systems [3,8]. Studies on the thermolysis of β-peroxylactones [3] observed a 5.6 to 1 preference of alkyl *vs* phenyl migration. Thermolysis of 3,3,5,5-tetrasubstituted 1,2-dioxolanes were found to show variable preference for alkyl *vs* phenyl migration. For decomposition of hemiperketals **1a-e** no phenyl migration was detected when in competition with methyl migration. Since little effect of structure on hemiperketal stability (k_1's) was found, the data are indicative of processes which are occurring after the rate-determining step. A mechanism consistent with the results is shown in Scheme 1. Initial homolysis of the peroxy bond yields 1,5-diradical intermediates. The observed product distributions would result from fragmentations of the 1,5-diradical: β-scission with rearrangement (R group migration). The fragmentation process may be concerted since the overall reaction is clean with no discoloration or detectable side-products.

Scheme 1



EXPERIMENTAL

All solvents were of reagent grade. Benzene was distilled, from over calcium hydride, before use. The synthesis of the hemiperketals [4] has been reported. The ^1H and ^{13}C nmr spectra were recorded on a JEOL GX-270 NMR spectrometer. The ir spectra were recorded on a Bomem-Michelson 100-FT-IR spectrometer. Melting points were taken in a Thomas Hoover Uni-melt apparatus and are uncorrected. Combustion analyses were performed by Atlanta Microlabs, Atlanta, Georgia. The ms data were obtained at the Georgia Institute of Technology.

Product Studies.

The following general procedure was employed for the thermolysis of 3,5,5-trisubstituted-3-hydroxy-1,2-dioxolanes **1a-e**. A 0.1 to 0.2 *M* solution of hemiperketal in benzene-d_6 was heated at ~80° (bath) in a sealed nmr tube until complete disappearance of the starting material (8-10 hours). The ^1H nmr spectrum was recorded and the relative peak intensities were determined. The products were isolated by chromatographic methods and identified by comparison of physical and spectral (ir, nmr, ms) data with those of authentic samples. Isolated yields were 85 ±5% of those determined by ^1H nmr spectroscopy in all cases. For **1a**, the products were isolated employing a chromatatron (petroleum ether-ether 5% gradient for the ketones and 40% methanol-ethyl acetate for the carboxylic acids). Conversion of the carboxylic acids to methyl esters by treatment of the reaction mixture with diazomethane improved the isolated yields for the "acids" by reducing loss on the solid support. For **1b** and **1c**, the volatile components were removed by distillation. Recrystallization of the solid residue yielded benzoic acid in quantitative yields. Volatile ketones were separated by gc procedures and by conversion to the DNP derivatives. For **1d** and **1e** volatile products including acetic acid were isolated by gc methods.

Kinetic Studies.

The kinetic experiments were carried out by the following general procedure. A 10-15 mg sample of pure hemiperketal was weighed into a 5 mm nmr sample tube. Five milligrams of anisole (internal standard) and 0.500 ml of chlorobenzene (Aldrich) were added. The sealed nmr tube was heated in a constant temperature water bath (T ±0.2°). Reaction progress was followed by monitoring the disappearance (^1H nmr electronic integration) of the most upfield methyl group signal *vs* internal standard. The nmr sample was placed in ice after removal from the constant temperature bath as well as before and after nmr analysis. Reaction time was taken as the composite of time spent in the constant temperature bath. First order plots were linear for, at least, three half-lives (r = 0.99). Variation between duplicate runs was less than 10% of the value of k_1. Product yields were within experimental error (±2%) of those observed for thermolysis in benzene-d_6.

Acknowledgement.

Acknowledgement is made to the National Science Foundation (CHE-9017230) for support of this research. The nmr instrumentation was obtained, in part, by an NSF Equipment Grant (CHE-8409599).

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