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THE ACID-CATALYZED HYDROLYSIS OF 3-OXETANOLS

AN HYDROXYMETHYL GROUP MIGRATION IN THE CONVERSION OF 2,2,3-TRIMETHYL-3-OXETANOL INTO 3-METHYL-3-HYDROXYMETHYL-2-BUTANONE

J. KAGAN* and J. T. PRZYBYTEK
Chemistry Department, University of Illinois at Chicago Circle, Chicago, Illinois 60607, U.S.A.

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Abstract—The acetone photodimer 2,2,3-trimethyl-3-oxetanol was synthesized by photocyclization of isopropyloxyacetone and of 3-methyl-3-methoxy-2-butanone. The oxetanol was very sensitive to acids, and it rearranged to 3-hydroxymethyl-3-methyl-2-butanone by ring opening and migration of the hydroxymethyl group.

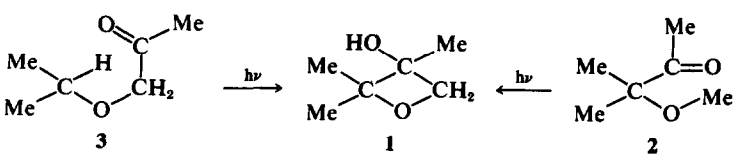
Our interest in the chemistry of 3-oxetanols originated with the isolation of 2,2,3-trimethyl-3-oxetanol (**1**) from the photolysis of acetone in liquid phase.[1] The mechanism of the reaction is unknown, but we postulated a cycloaddition of acetone with its enol, after the known cycloaddition reactions of carbonyl compounds and olefins,[2] including enol ethers and esters.[3,4] Although the spectroscopic structural proof for **1** was convincing, a direct comparison with a sample prepared by another route was desirable.

Few chemical syntheses of 3-oxetanols† have been described, and their scope has not been established. These are the benzylic acid rearrangement of a 3,4-furanedione,[5-7] the hydroxylation of a 3-methyleneoxetane,[8] the reaction of 3-oxetanones with metal hydrides[9,10] or Grignard reagents,[9,11] or the metal hydride reduction of 3-acetoxy or 3-tosyloxy oxetanes.[12] In addition, photochemical cyclizations of β-ketoethers have been reported,[11,13,14] and this approach was followed for the synthesis of **1**.

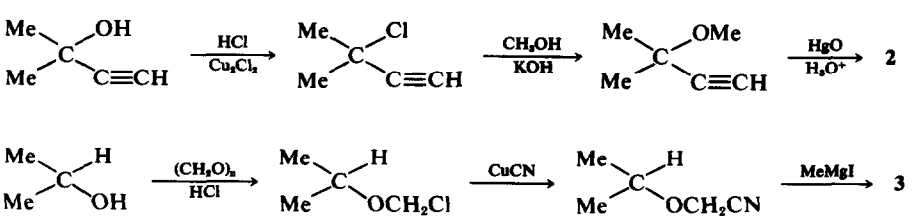
As shown in Scheme 1, two isomeric β-ketoethers, **2** and **3**, could be envisaged to lead to **1**, after a well known Norrish type-II hydrogen abstraction by the excited carbonyl, followed by ring closure.[11,13,14]

Both compounds were synthesized as shown below.

The irradiations of **2** and **3** were performed in benzene under nitrogen, and both yielded **1**. The reaction of **2** was quite clean and yielded **1** as the only major product. The photolysis of **3**, on the other hand, gave a very complex mixture, from



SCHEME 1



†The Chemical Abstracts variously described 3-oxetanols and their derivatives as substituted trimethylene oxides, oxetanes and 1,3-epoxypropanes before utilizing the entry oxetanol.

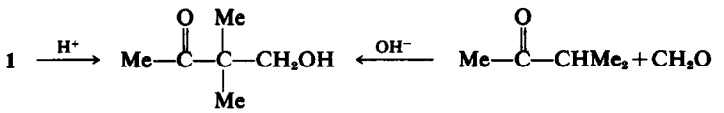
which the desired product was isolated in very low yield by preparative GLC.* The oxetanol isolated from both syntheses had the same GLC behavior, and was proved to be spectroscopically identical with the photoproduct from acetone.†

The acid-catalyzed isomerization of **1**.

Many of our initial difficulties in isolating **1** in the pure state after the photolysis of acetone were due to its facile decomposition into a carbonyl-containing product. This conversion was proved to be acid-catalyzed, yielding the isomeric 3-hydroxymethyl 3-methyl-2-butanone (**4**) which formed rapidly and quantitatively, and which was identical to an authentic sample synthesized by condensing formaldehyde with 3-methyl-2-butanone.[17]

The problem of whether the rate-determining step in the hydrolysis of oxetanes occurred without[18,19] or with solvent participation[20–25] was investigated and some work involving the acid-catalyzed hydrolysis of oxetanes,[26,27] 3-alkyloxy,[3,4,28] 3-acetoxy or 3-tosyloxyoxetanes has been recorded.[12] In all cases, the products were either postulated or proven to be simple 1,3-diols or their derivatives. Our observation of a skeletal rearrangement in the hydrolysis of **1** was therefore unusual, and a study of its mechanism was undertaken.

Two attractive mechanisms may be written for the conversion of **1** to **4**, depending upon the site of initial protonation. In mechanism 1, protonation of the OH yields a tertiary carbenium ion, possibly stabilized by interaction with the ring oxygen.[19,29]



4

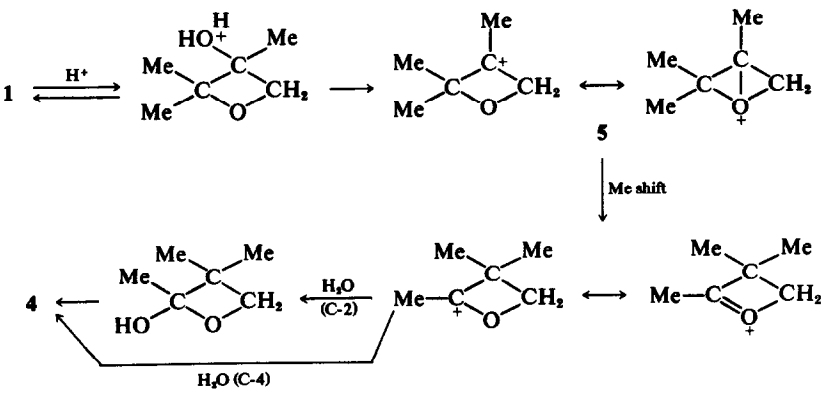
A methyl shift provides another tertiary carbenium-oxonium ion, which would be attacked by water either at C-2, to give the highly unstable hemiacetal of **4**, or at C-4 to give **4** directly.

In mechanism 2, the protonation of the ring oxygen allows relief of the oxetane strain energy by formation of an open-chain tertiary carbenium ion, which would rearrange into an even more stable ion by migration of the hydroxymethyl group, giving **4** by way of its conjugate acid.

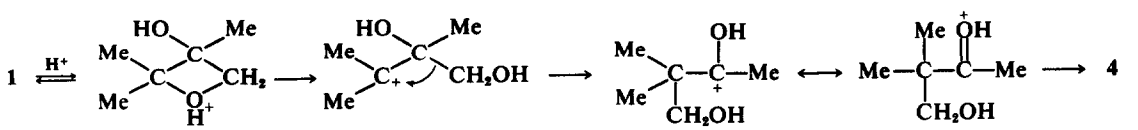
For reasons of economy, the scheme expressed

*Compound **3** is formally an acetone dimer, which might have been a precursor to **1** in its original synthesis. The photolysis of **3** in benzene led to products which were not observed in the photolyis of acetone, but a detailed study of the behavior of **3** in acetone will be required for proving or disproving its intermediacy in the conversion of acetone to **1**.

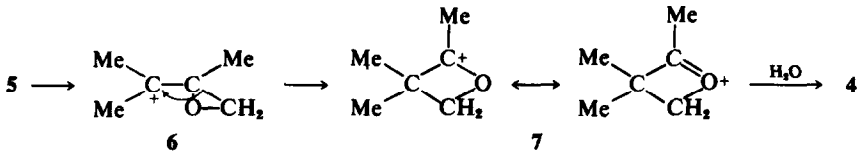
†Not surprisingly the photolysis of methoxyacetone in the gas phase led to fragmentation.[15] However, that of 2-methoxy-3-pentanone in solution did not yield any 3-oxetanol product.[16]



MECHANISM 1



MECHANISM 2



MECHANISM 3

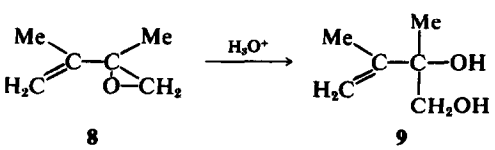
in Mechanism 2 makes no allowance for the possible intermediacy of an unrearranged 1,2,3-triol following normal hydration of the oxetane ring. If formed at all, this 2,3-dimethyl-1,2,3-butanetriol must give the same tertiary cation as shown above from **1**, in order to yield **4**. Furthermore, the cation and the triol may well be in equilibrium.

A third mechanism may be considered, which starts as in Mechanism 1 to give **5**, but then goes on to the oxirane **6** which finally rearranges into an isomeric oxetanyl cation **7**, as shown.

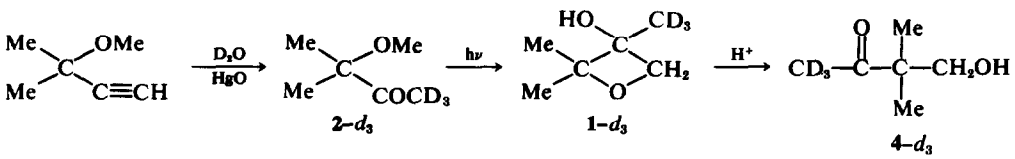
This mechanism has ample analogy with the well-known behavior of the cyclobutyl-cyclopropylcarbinyl cation. Although we have not absolutely eliminated it from consideration, we note two objections:

(a) The work of Morita and Oae[29] as well as Richey and Kinsman[30] suggests that the rearrangement of **6** to an oxetane should proceed with a carbon-oxygen (back to **5**) rather than a carbon-carbon bond migrations,[31,*] and

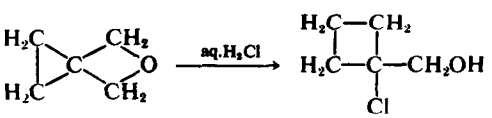
(b) The acid treatment of **8**, a logical precursor to **6**, did not yield **4**, following protonation of the double bond and rearrangement, but gave the unsaturated glycol **9** instead.



The Me group of the acetyl in **4** has a different origin whether Mechanisms 1 or 2 are followed, thus allowing an experimental distinction between them to be made. In the former it originates in one of the two C-2 methyls of **1**, while in the latter it is produced from the C-3 Me. Since the last step of our synthesis of **2** had involved the hydration of an acetylenic compound, the deuterated analog was readily available by substituting deuterium oxide. The photolysis of **2**-d_3 yielded **1** which was deuterated at the C-3 Me (**1**-d_3), and its rearrangement gave **4** which was exclusively deuterated at the acetyl position.



The result proved conclusively that Mechanism 1 did not operate, but was compatible with both Mechanisms 2 and 3. The conversion of **1** to **4** may be viewed as the equivalent of a pinacol rearrangement with hydroxymethyl migration, and it is also formally related to the acid-catalyzed rearrangement of *spiro*-3,3-dimethyleneoxetane, which occurs with migration of a group from the 3 to the 2-position.[32]

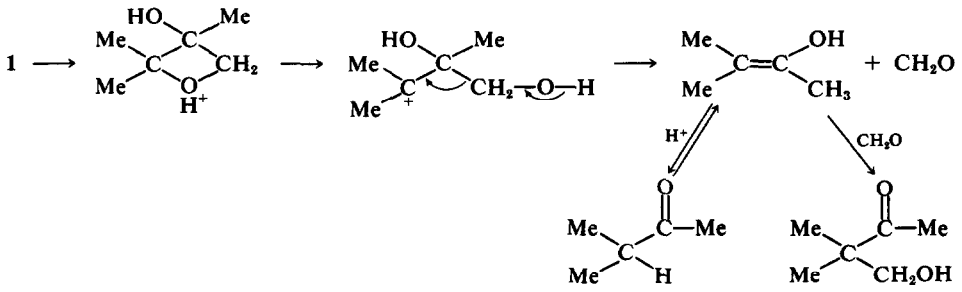


However, the rearrangement of **1** to **4** may also be formulated as a trans hydroxymethylation reaction[33] occurring by loss of formaldehyde from **5**, to give 3-methyl-2-butanone, followed by an acid-catalyzed aldol condensation reaction as shown in Mechanism 4.

There is a good precedent for the deformylation reaction postulated here in the reported isolation of tetrasubstituted olefins from the acid treatment of 2,2,3,3-tetrasubstituted oxetanes.[34]

The conversion of **1** to **4** being practically quantitative, the intermolecular process of Mechanism 4 is less attractive than the intramolecular rearrangement of Mechanisms 2 or 3. However, it may be argued that in Mechanism 4, formaldehyde is generated in the close vicinity of the enol with which it is to react, thereby allowing efficient condensation. To that extent, these mechanisms are essentially equivalent, and they cannot be readily distinguished experimentally.

*In the absence of label in the starting material, the proposed carbon-carbon bond migration in the ring contraction of 9-oxabicyclo[6.1.0] non-2-yl p-bromobenzenesulfonates is not convincing. Instead, formation 3-oxetanol through a oxabicyclobutoniun ion[32] followed by a rearrangement as described in our work, could equally well lead to the observed unsaturated aldehyde.



MECHANISM 4

EXPERIMENTAL

The NMR spectra were recorded on a T-60 or A-60A Varian spectrometer with internal TMS, and are reported on the δ-scale. The mass spectra were obtained with a Perkin-Elmer-270 GLC-mass spectrometer. The GLC analyses were performed with a Hewlett-Packard F&M 402 (analytical), or with a Varian Autoprep 711 (preparative) instrument, using columns of 15% DEGS or 15% EGSS-X on Chromosorb W (Applied Science Labs). The melting points are not corrected. The irradiations were performed under nitrogen with a 450 W Hanovia medium pressure lamp housed in a quartz immersion well.

3-Methoxy-3-methyl-2-butanone (2). The 3-methoxy-3-methylbutyne precursor was prepared from commercial 3-hydroxy-3-methylbutyne following exactly the published procedure,[35] and its NMR in CCl_4 showed singlets at 1·42 (6 H's), 2·50 (1 H) and 3·51 ppm (3 H's). A 7·3 g portion was added to a soln of 5 ml H_2O in 20 ml THF, followed by 1 g HgO and 2 drops conc H_2SO_4. After 2 hr reflux, solid Na_2CO_3 was added. The soln was diluted with 25 ml ether, washed with 20 ml H_2O, and dried over $MgSO_4$. Distillation at atm pressure yielded 80% of 2, b.p. 83–85°, NMR (CCl_4) at 1·40 (s, 6 H's) 2·12 (s, 3 H's) and 3·49 ppm (s, 3 H's). Its 2,4-DNP derivative melted at 131–133° (lit[35] m.p. 132–134°).

Photolysis of 2. The procedure was identical to that described below for 2-d_3. A single product was observed, which was isolated by prep GLC. It was identical (GLC and NMR) to the sample of 1 obtained in the photolysis of acetone.[1]

3-Methoxy-3-methyl-2-butanone-1-d_3 (2-d_3). The hydration of 3-methoxy-3-methylbutyne was performed as described for 2, using dry THF, substituting D_2O for H_2O, and protecting the system from moisture. The sharp acetyl peak at 2·12 ppm was absent in the NMR of the distilled 2-d_3. A small, broad signal at this position resulted from partial hydrogen exchange of the deuterium in the work-up procedure.

Photolysis of 2-d_3. N_2 was bubbled through a soln of 3·2 g of 2-d_3 in 250 ml C_6H_6 for 30 min before, and during a 4-hr irradiation with a 450 W Hanovia lamp, housed in a quartz immersion well. GLC showed that the starting material had almost completely disappeared and that a single product was formed, with the retention time of 1. Except for the absence of one Me absorption, the NMR of 1-d_3 purified by prep GLC was identical to that of 1.

(2-Propyl)oxyacetone (3). The reaction of (2-propyl)-oxyacetonitrile with MeMgI[36] gave 3, b.p. 41°/15 Torr, NMR (CCl_4) at 1·19 (d, 6 Hz, 6 H's), 2·13 (s, 3 H's), 3·75 (sept, 6 Hz, 1 H) and 4·10 ppm (S, 2 H's). Its phenylhydrazone had m.p. 140–142° (lit.[31] m.p. 141–142°). Its photolysis in benzene yielded a complex mixture from which a very small amount of 1 was isolated by prep GLC. This product was identical (NMR, GLC) to an authentic sample from the photolysis of acetone.

1-hydroxy-2,2-dimethyl-3-butanone (4). A mixture of 50 mg of 1 (99% pure from GLC) in 2 ml EtOH and 2 ml 10% H_2SO_4 aq was stirred overnight at room temp. It was diluted with 20 ml ether and washed with two 10 ml portions of 10% K_2CO_3 aq. After drying over $MgSO_4$ the ether layer was concentrated, and its GLC showed the disappearance of 1 and the formation of a single product, NMR (CCl_4) at 1·13 (s, 6 H's), 2·12 (s, 3 H's), 3·47 (s, 2 H's), and 2·50 ppm (br, 1 H); main peaks in the mass spec at 116 and 43. The product was identical to an authentic sample of 4 prepared from 3-methyl-2-butanone and *s*-trioxane.[17]

Acid-catalyzed isomerization of 2,2-dimethyl-3-trideuteromethyl-2-oxetanol (1-d_3). The sample of 1-d_3 from the photolysis of 2-d_3 was dissolved in 5 ml of a 1:1 mixture of EtOH and 10% H_2SO_4 aq (v/v). After 30 min of reflux, 20 ml ether was added, and the soln washed with 2 × 10 ml of 10% K_2CO_3 aq, and dried. GLC indicated complete reaction of 1-d_3 and formation of a single product. After solvent removal, its NMR showed peaks at 1·14 (s, 3 H's), 3·48 (s, 2 H's) and a broad signal at 2·60 ppm. (OH). There was no sharp acetyl peak near 2·1 ppm, but a broad signal resulting from partial exchange of D with H. The GLC-mass spectrum was similar to that of 4, the major differences being the molecular ion at *m/e* 119 and strong peaks at *m/e* 46 and 45 for CD_3CO and HCD_2CO. There was no evidence for any deuterium incorporation in the C-2 methyls.

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