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MECHANISTIC AND SYNTHETIC ASPECTS OF THE ACID-CATALYSED HYDROLYSIS OF 2,2-DIMETHOXY-3,4-DIHYDROPYRANS INTO 3,4-DIHYDRO-α-PYRONES AND δ-KETO ESTERS

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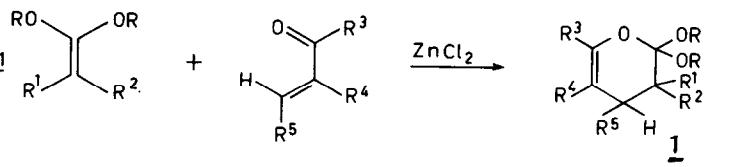
Summary: Acid-catalysed hydrolysis of 2,2-dimethoxy-3,4-dihydropyrans (1) yields mixtures of δ-keto esters (2) and 3,4-dihydro-α-pyrones (3). The amount of 3 increases with increasing alkyl substitution in the 3-, 5- and 6-position of 1 and when the hydrolysis is carried out in a two-phases system of water/dichloromethane. It is shown that 3 is formed directly from 1 whereas 2 is formed directly from 1 and by methanolysis of 3. The mechanistic and synthetic aspects of these hydrolysis reactions are discussed.

In a preceding paper[1] we reported that 2,2-dialkoxy-3,4-dihydropyrans (1) can generally be synthesized *via* $ZnCl_2$-catalysed cycloadditions of ketene acetals with α,β-unsaturated carbonyl compounds (Scheme 1).

Scheme 1



1 (1)

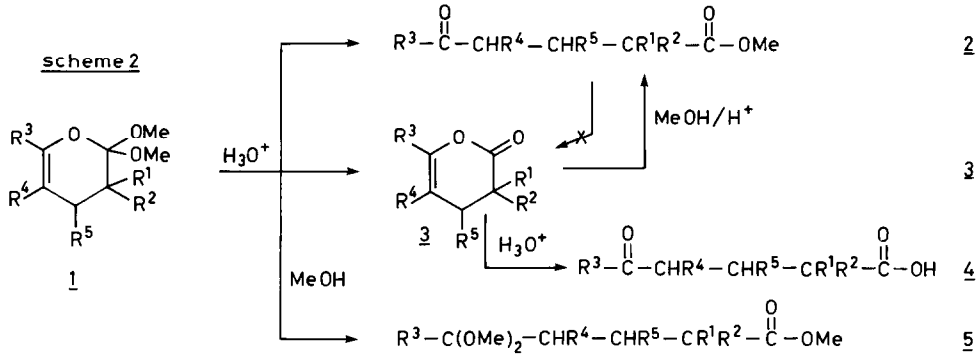
It is known[2,3] that the acid-catalysed hydrolysis of an unsubstituted 2,2-dialkoxy-3,4-dihydropyran in a homogeneous medium proceeds quite specifically, giving the corresponding δ-keto ester (2) in high yield as the only product (Scheme 2). Applying the same procedure to a series of alkyl-substituted 2,2-dimethoxy-3,4-dihydropyrans 1a-h we found that the selectivity of the reaction depends on the number and position of these substituents and also on the reaction circumstances. In several cases considerable amounts of 3,4-dihydropyrones[4] (3) appeared to be formed. We envisaged that more insight into the course of the hydrolysis might contribute to the establishment of the optimum conditions for the synthesis of either 2 or 3 from the easy available compounds 1.

To that aim we studied the hydrolysis of 1a-h under various conditions (see Scheme 2).

The acid-catalysed hydrolysis of 1a-h in the homogeneous reaction mixture water/dioxan at $[H^+] = 10^{-4}$ Mol.l^{-1} gave the δ-keto esters 2 in yields from 60-80%. Especially from the compounds 1d-h having two methyl groups (at least one in the 2-position) a 3,4-dihydro- -pyrone (3) arose as a side product even when the hydrolysis was carried out under stronger acidic conditions. In an inhomogeneous reaction mixture, *e.g.* chloroform/acidified water, the formation of 3 became more general. Moreover, other side products, *viz.* the δ-keto acids 4 and the δ-ketal esters 5 were found in the reaction mixtures.

The δ-keto esters (2) appeared quite stable under the reaction conditions, so that the products 3 do not originate from 2. On the other hand it appeared that prolonged reaction times and higher temperatures lowered the amount of 3 in favour of 4 showing that 4 arises *via* further

scheme 2



1a $R^1=R^2=R^3=R^4=R^5=H$
1b $R^1=Me, R^2=R^3=R^4=R^5=H$
1c $R^1=R^2=R^4=R^5=H, R^3=Me$
1d $R^1=R^5=Me, R^2=R^3=R^4=H$
1e $R^1=R^3=Me, R^2=R^4=R^5=H$
1f $R^1=R^4=Me, R^2=R^3=R^5=H$
1g $R^1=R^2=Me, R^3=R^4=R^5=H$
1h $R^1=R^2=R^3=Me, R^4=R^5=H$

hydrolysis of 3. The formation of 5 has to be ascribed to the occurrence of increasing amounts of methanol, liberated during the hydrolysis, in the organic phase which contains the bulk of the parent compound (1). Acid-catalysed methanolysis of 1 yields exclusively 5.

The presence of the various products was recognized from the NMR spectra of the reaction mixtures. The occurrence of 3 is obvious when one or two signals of vinylic protons are present between 4.65 and 6.70 ppm, where the other products do not show absorptions. For δ-keto esters (2) and δ-keto acids (4) the proton signal of the terminal group (CHO, CH_3CO) is characteristic and the relative amounts of 2 and 4 can be determined, when the $-COOCH_3$ signal (δ ∿ 3.60 ppm) of the δ-keto ester (2) is used as an additional datum. For the δ-keto acids, a weak COOH signal at *ca.* 11.10 ppm is visible. In the NMR spectra of the methanolysis product (5) the position of the proton signal at the terminal carbon atom ($HC(OMe)_2$- or $CH_3C(OMe)_2$) is quite different from that of the corresponding signal of 2 or 4: $HC(OMe)_2$- δ *ca.* 4.2 ppm and HCO δ *ca.* 9.5 ppm; $CH_3C(OMe)_2$- δ *ca.* 1.20 ppm and CH_3CO- δ *ca.* 2.05 ppm. Moreover, these compounds cause the occurrence of an additional singlet of the methyl protons of the acetal group at *ca.* 3.10 ppm. Based on these differences rough estimates of the product ratios were made from the NMR spectra of the reaction mixtures, obtained in the two-phase system (CH_2Cl_2/acidified water, saturated with NaCl).[5] These data are given in Table I.

Better insight into the effect of the substituents R on the product ratio 2/3 was obtained by following the hydrolysis of 1a, 1b and 1g in an NMR tube in the two-phase system $CDCl_3/D_2O$ acidified with 5 Mole % of *p*-toluene sulphonic acid. All three compounds had been completely hydrolyzed within 50 minutes. The ratio 2/3 in the $CDCl_3$ layer was continuously and in all cases roughly 1/1, at the most 3 being present in slight excess. Furthermore it appeared that on standing the ratio 2/3 increased due to methanolysis of 3 in the chloroform layer (see Scheme 2), and that faster for 1a and 1b than for 1g. So it seems that the varying ratio 2/3, [illegible] effect of the substituents R on the hydrolysis

Table I: Relative amounts of the products from the acid-hydrolysis of 2,2-dimethoxy-3,4-dihydropyrans (1) in the two-phase system dichloromethane/water, saturated with NaCl.

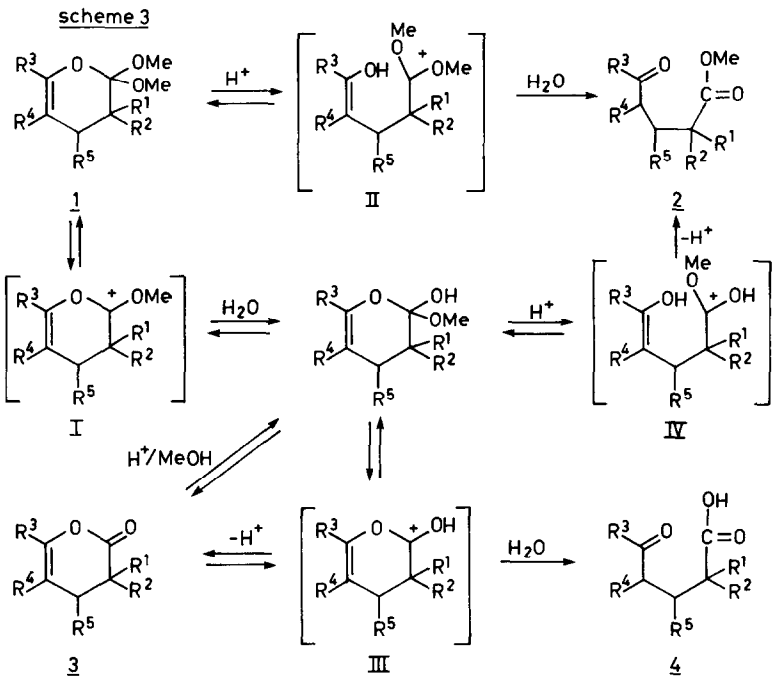
	R^1	R^2	R^3	R^4	R^5	δ-keto ester (2) (%)	α-pyrone (3) + δ-keto acid (4) (%)	δ-ketal ester (5) (%)
1a	H	H	H	H	H	100	0	0
1b	Me	H	H	H	H	75	25	0
1c	H	H	Me	H	H	100	0	0
1d	Me	H	H	H	Me	70	30	0
1e	Me	H	Me	H	H	30	70	<5
1f	Me	H	H	Me	H	30	70	<5
1g	Me	Me	H	H	H	40	50	∿10
1h	Me	Me	Me	H	H	10	70	20

In another experiment we tested whether the acid catalysed removal of the vinyloxy group from 1 in the formation of 2 leads in the first instance to vinyl alcohols, as was observed by Capon *et al.*[6] in the hydrolysis of acyclic ortho esters, bearing a vinyloxy group. To that aim the hydrolysis of 1b was followed at -20°C in a CD_3CN/D_3O^+ mixture with NMR. Within 5 minutes after addition of D_2O acidified with 5 Mol % *p*-toluene sulphonic acid 1b had disappeared. Vinyloxy proton absorptions of two new compounds had appeared. One pair belongs to 3b (5.33 and 6.52 ppm). The other could be ascribed to a Z-vinyl alcohol (4.12 and 6.33 ppm). Capon *et al.*[7] reported the corresponding protons for Z-prop-1-en-1-ol, δ = 4.15 and 6.32 ppm in the same solvent mixture. The latter pair of signals disappeared quickly when the reaction mixture was warmed up to 25°C; giving rise to the appearance of proton absorptions of 2b[8] and 5b. At -20°C the mixture consisted for about 40% of the vinyl alcohol and for about 60% of 3b. The results described above are in agreement with a mechanism for the hydrolysis of 1 as given in Scheme 3.

Our results show, however, that cyclic mono-alkenyl ortho esters in which the alkenyloxy group is part of a six membered ring behave differently from the open mono alkenyl ortho esters studied by Capon *et al* [6,7,9] as well from the 2,2-dialkoxytetrahydropyrans studied by Deslongchamps and others[10]. Capon *et al.* found that dimethyl vinyl ortho esters of the kind $R\text{-}C(OMe)_2OCH{=}CH_2$ generate only a methyl ester on hydrolysis. They showed that the vinyloxy group is liberated as a vinyl alcohol. The high selectivity of the reaction was ascribed to the much better leaving group ability of the vinyl alcohol in comparison with methanol. For the cyclic analogues 1 only 40-50% is hydrolysed in this way. Deslongchamps and others showed that 2,2-dialkoxytetrahydropyrans gave the δ-hydroxy esters as the major and sometimes as the only products. They ascribe this selectivity to stereo-electronic factors and propose a theory of stereo-electronic control in the cleavage of the tetrahedral hemiortho ester intermediate.

We could find no good arguments why stereo-electronic control[11] should oppose the better leaving ability of the vinyloxy group in the six membered ring. So it seems that the outcome of the hydrolysis of 1 is determined by entropy. The Z-vinyl alcohol in the cations II and IV (Scheme 3) has a much better chance for a retro reaction than it has in the open vinyl ortho esters where it disappears into the solvent[12] after hydrolysis. This entropy factor favors the formation of 3 *via* the cations I and III.

scheme 3



The results of above demonstrate that hydrolysis of 1 seems a less selective route to synthesize either 2 or 3. It is possible, however, to obtain exclusively 2 by first acid catalysed methanolysis of 1 followed by acid hydrolysis of the formed ketal ester 5. This hydrolysis can be carried out as a one pot process as will be published.

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5. The reaction mixtures were obtained by the following procedure: 5 mmoles of 1a-h, dissolved in 10 ml of dichloromethane were added to 10 ml of a saturated aqueous solution of NaCl, acidified to pH = 4 for 1a-e and to pH = 1 for 1f-h. The mixture was stirred vigorously for 8 hours at room temperature. Then the dichloromethane layer was separated and the water layer was extracted several times with dichloromethane. The combined dichloromethane layers were dried over Na_2SO_4 and concentrated
6. B. Capon, D.S. Rycroft, Th.W. Watson and C. Zucco, *J. Am. Chem. Soc.* 103, 1761 (1980).
7. B. Capon, A.K. Siddhanta, *J. Org. Chem.* 49, 255 (1984).
8. In the reaction mixture the aldehyde is partly converted into an unstable hemi-acetal by the methanol liberated during the hydrolysis. Therefore, the H-C=O proton absorption is very weak. The $H\text{-}C(\text{-}O\text{-})_2$ proton absorption of the hemi-acetal is observed (as expected) as a multiplet between 4.24 and 4.29 ppm.
9. It is generally accepted that the hydrolysis of trialkyl ortho esters proceeds in three steps, starting with the acid catalysed formation of a dialkoxycarbonium ion which reacts further with water to a tetrahedral hemi-ortho ester intermediate, see for example E.H. Cordes and H.G. Bull, *Chem. Rev.* 74, 581 (1974); R.A. McClelland and M. Alibhai, *Can. J. Chem.* 59, 1169 (1981).
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12. The same effect plays an important role in the mechanisme of the acid catalysed hydrolysis of cyclic ketals, see T. Fife and R. Natarajan, *J. Am. Chem. Soc.* 108, 2425 (1986).

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