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METHYL DIMETHOXY ACETATE AS A CARBONYL ANION EQUIVALENT

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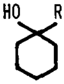
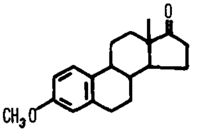
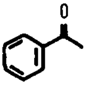
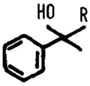
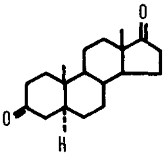
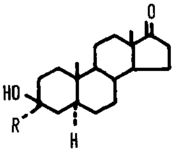
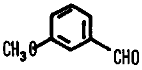
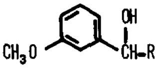
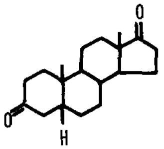
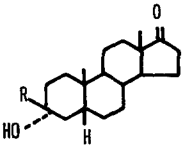
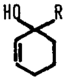
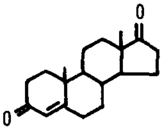
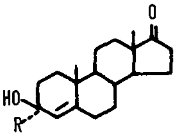
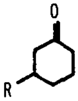
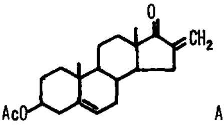
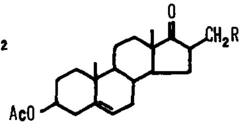
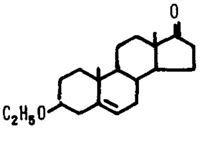
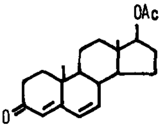
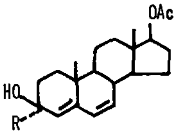
The lithium enolate of ethyl diethoxy acetate as the first fully oxygenated carbonyl anion equivalent of this type was described by Damon and Schlessinger.[1,2] The key step in their total synthesis of dl-4-isoavenaciolide was the conjugate addition of this anion to a butenolide.

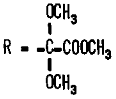
We were interested in the nucleophilic properties of the methyl analogue on a more general basis as it seemed to be an appropriate synthon both for the construction of suitably functionalized pregnane side chains and, more generally, for the formation of saturated and unsaturated α-keto esters.

We could show that the enolate of methyl dimethoxy acetate adds to simple aldehydes and ketones with excellent yields as was demonstrated in the cases of cyclohexanone, acetophenone, m-methoxybenzaldehyde, and some 3-oxo-androstane derivatives.

The transformation of the primary adducts to α-keto esters is normally achieved by dehydration, ketal hydrolysis, and hydrogenation as schematically represented below.

When dehydration of the primary adduct is not possible, ketal hydrolysis turns out to be extremely difficult. So all our attempts failed to cleave the ketal group of the benzaldehyde adduct. Whereas the unsaturated α-dimethoxy esters of type II are easily cleaved to the corresponding keto esters under mild conditions (2n-HCl, dioxane, room temp.), the saturated analogues III require essentially more drastic conditions (THF, $HClO_4$, water, 100°C), the latter being directly converted to α-keto acids.

starting material	product^c	yield % ^{d}	starting material	product^c	yield % ^{d}
		98^a		–	
		92^a			84^b
		96^a			76^b
		84^a			82^b
		14^b			93^b
	–				78^b



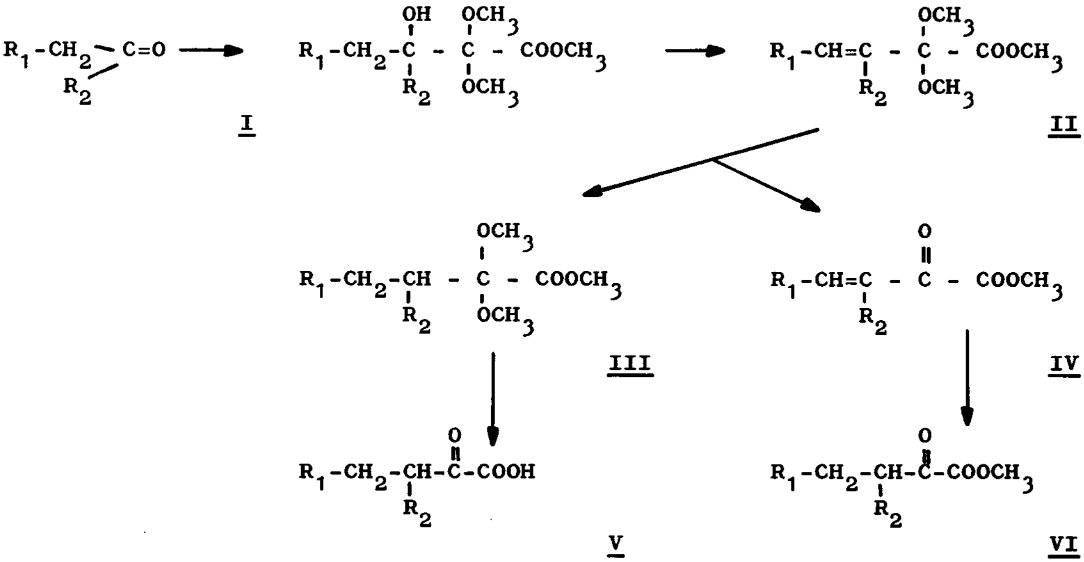
$$R = -\overset{\displaystyle OCH_3}{\underset{\displaystyle OCH_3}{\overset{|}{\underset{|}{C}}}}-COOCH_3$$

a. isolated yield by Kugelrohr distillation

b. isolated by chromatography

c. products were identified by ir and nmr spectra

d. yields refer to starting material



Our initial intention to use this anion as a synthon for pregnane side chains met with failure. The steric requirements of the reagent presumably prevent the addition to a steroid 17-keto group, which might be surprising in view of the fact that the enolate of methyl mono-methoxy acetate adds to 17-oxosteroids quite easily.[3)]

The question of 1,2- or 1,4-addition with conjugated enones was investigated in the case of cyclohexenone. We found that the enolate of methyl dimethoxy acetate adds preferentially to the carbonyl group, the product of conjugate addition being formed with less than 15% yield.

Schultz and Yee[4)] recently observed that enolates of monosubstituted acetic acid esters add reversibly to conjugated enones, the relation between 1,2- and 1,4- addition being dependent on kinetic or thermodynamic control. In the case of methyl dimethoxy acetate addition seems to be irreversible because the product distribution does not change whether the reaction is quenched at -78°C or warmed to 25°C before workup.

Conjugate addition as the exclusive reaction between methyl dimethoxy acetate and an enone could be observed only in the case of a 16-methylene-17-oxosteroid where 1,2-addition is not possible for steric reasons.

Experimental

A solution of methyl dimethoxy acetate (7,2 g, 54 mmoles) in 50 ml of THF is added dropwise to a solution of lithium diisopropylamide (54 mmoles) in 50 ml THF under on argon atmosphere at -78°C. After addition stirring is continued for 15 min at -78°C. A solution of 5α-androstane-3,17-dione (5.2 g, 18 mmoles) in 40 ml of THF is then added dropwise over a period of 15 min and stirring is continued for 10 min with cooling (-78°C). The reaction is worked up by pouring the solution into water and extraction with ethyl acetate. Crystallization from diisopropyl ether gives 6.2 g (84%) of 3α-(2.2-dimethoxy-2-methoxy carbonyl ethyl)-3ß-hydroxy-androstane-17-one, m.p. 177-180°C.

References:

1. R.E.Damon and R.H.Schlessinger, Tetrahedron Letters 1975, 4551.
2. For an excellent review on the chemistry of carbonyl anion equivalents, see: O.W.Lever, Jr., Tetrahedron 32, 1943 (1976).
3. G.Neef and U.Eder, unpublished results
4. A.G.Schultz and Y.K.Yee, J.Org. Chem. 41, 4044 (1976).