A New Method for the Hydrolysis of Hindered Esters

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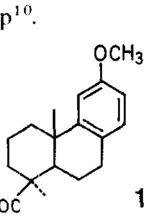
Hindered esters, such as methyl podocarpate (**1**) are usually very difficult to hydrolyse. This is a well known problem to which a great deal of solutions have been proposed, namely: use of lithium halides in dimethylformamide, collidine[1,2,3], or HMPT[4], potassium *t*-butoxide in dimethyl sulfoxide[5], lithium ethanthiolate in HMPT or dimethylformamide[6], 1,5-diazabicyclo[4.3.0]non-5-ene in xylene[7], potassium hydroxide in ethylene or diethyleneglycol, and, more recently, potassium cyanide in HMPT[4,9]. Birch reduction of aromatic compounds containing a hindered methyl ester group leads preferentially to acids[8].

Most of these methods require strictly anhydrous conditions and reagents which are not necessarily on the shelf, or may be unpleasant to handle. Moreover, side reactions may take place, such as dehydrobromination[7] and at least partial decarboxylation[4,7] or deacetylation[2].

In the course of a total synthesis of agathic acid (**2**), we have found that elimination of acetic acid from the intermediate **3** in boiling quinoline is accompanied to some extent by hydrolysis of the severely hindered methoxycarbonyl group[10].



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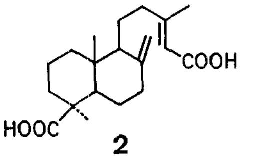

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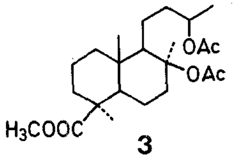

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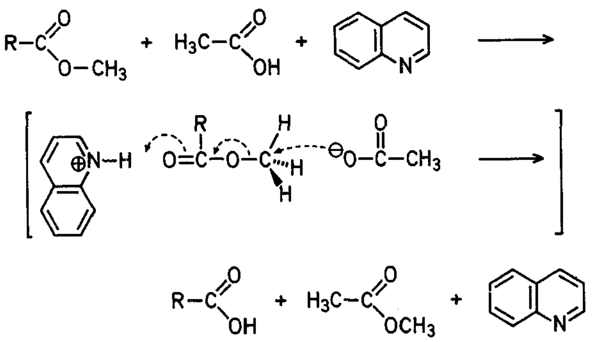
A possible mechanism for this side reaction might be the following: the eliminated acetic acid gives acetate ion and protonated quinoline (a strong acid) which react in a push-pull manner with the methyl ester, so as to afford methyl acetate and the free acid.



In fact, various hindered methyl or ethyl esters in the di- or triterpene series have been found to react slowly with acetic acid in quinoline, preferentially under a slow stream nitrogen. The course of the reaction is followed by N.M.R. (of the mixture isolated from aliquots). The yield in acid is usually good (Table 1).

Table 1. Hydrolysis of Esters

Ester (A)[a]	Acid (B)	Ratio A/B	Solvent	Reaction time (h)	Conversion of Ester to Acid[b] (%)
Methyl *O*-methylpodocarpate (**1**)	Acetic	1/2	Quinoline	32–40	85–89
	Acetic	1/4	Quinoline	36	83
	Acetic	1/2	Quinoline	20	78
	Thioacetic	1/2	Quinoline	20	82
	Hydroiodic	1/2	Quinoline	20	tars
	Acetic	1/2	Pyridine	40	Ester unchanged
	Chloroacetic	1/1	DMF	24	Ester unchanged
	Chloroacetic	1/1	DMF	23	84
	Chloroacetic	1/2	DMF	36	100
Ethyl *O*-ethylpodocarpate	Acetic	1/2	Quinoline	42	74–75
Methyl dehydroabretate	Acetic	1/2	Quinoline	33	98
	Chloroacetic	1/2	DMF	40	100
	Acetic	1/2	DMF	40	80
Methyl isopimarate	Acetic	1/2	Quinoline	40	98
Methyl 18α-glycyrrhetate	Acetic	1/4	Quinoline	40	94–95
Methyl 18β-glycyrrhetate (**4**)	Acetic	1/4	Quinoline	40	94–95
Methyl apocholate (**5**)	Acetic	1/2	Collidine	28	Ester unchanged
	Acetic	1/2	Quinoline	36	96

[a] The usual concentration of ester in the solvent is 1 *M*. For glycyrrhetates, the concentration is 0.5 *M*.

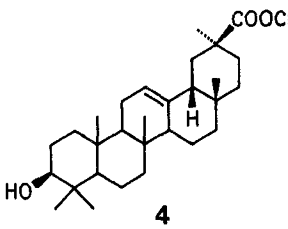
[b] The % conversion is directly measured on the N.M.R. spectrum after work-up.

Replacement of acetic acid by thioacetic acid did not improve the yield. Hydrogen iodide led to considerable formation of tars. However, if quinoline is replaced by dimethylformamide, the same reaction takes place, either with acetic or chloroacetic acid as a source of protons and nucleophiles. From a practical point of view, the quinoline/acetic system is to be preferred, since the expected product is easier to isolate and purify.

Various side reactions have been found to occur. Thus, methyl apocholate is partially acetylated (Table 2).

Table 2. Side Reactions observed in the Ester Cleavage

Esters or acetates	Conversion products
16-Acetoxymethylpodocarpane-12-one (**6**)	Acetate unchanged
Methyl 3α,7α,12α-triacetoxy-cholate (**7**)	partially desacetylated acid
Methyl apocholate (**5**) Methyl 18α-glycyrrhetate Methyl 18β-glycyrrhetate	partially acetylated acid



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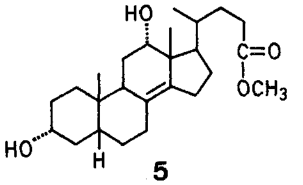

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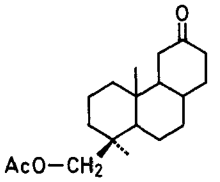

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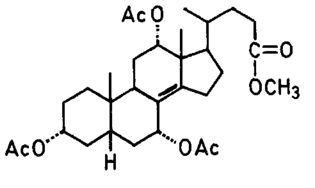

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In the case of ester acetates, for instance in the bile acids series, epimerisation of the acetate group via an S_N2 mechanism might take place. However, methyl cholate was merely transformed into cholic acid triacetate, as shown by reesterification of the isolated compound, and comparison of the latter methyl ester with the starting material (melting point, N.M.R.) (A small quantity of a mixture of unidentified olefins was also detected; purely thermal elimination of acetic acid is probably involved). In less unfavourable cases, when the S_N2 reaction is not impeded by steric hindrance, the expected formation of a mixture of two acetates has been observed.

Methyl 18α-glycyrrhetate (**4**) gives 43% of 18α-glycyrrhetic acid, 26% of its 3β-acetate, and 29% of the 3α-isomer.

Acetates of primary alcohols are not affected by prolonged heating with the quinoline acetic acid mixture.

The following procedure is of general applicability.

***O*-Methylpodocarpic Acid from Methyl *O*-Methylpodocarpate (1):** A mixture of methyl *O*-methylpodocarpate (**1**; 2.70 g), freshly distilled quinoline (9 ml), and acetic acid (1.5 ml) is refluxed for 40 h under a slow stream of nitrogen. The mixture is then allowed to cool and ether (250 ml) is added. The resulting solution is washed several times with 6*N* hydrochloric acid to remove quinoline, and then with 5*N* aqueous sodium hydroxide. The sparingly soluble sodium salt is collected; its suspension in water is acidified, and extracted with chloroform. The chloroform layer is dried and evaporated to give the acid; yield: 2.18 g (84%); m.p. 154–156° (from methanol). From the neutral ether layer, 0.42 g of **1** may be recovered.

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