A Very Short Degradation of the Bile Acid Side Chain

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Reaction of the cholanic acid derivative (**1**) with thionyl chloride and pyridine gave, after quenching with methanol, the α-sulphine ester (**3**); treatment with acetic anhydride–sulphuric acid afforded the keto ester (**5**) which, on exposure to air in the presence of copper(II) ions and base, gave the 20-keto pregnane derivative (**9**) in excellent overall yield.

Bile acids are major raw materials for the commercial production of corticosteroids[1] and have also served in the partial synthesis of cardenolides.[2] Their synthetic utility has therefore hinged on the ease of accession to the pregnane skeleton by removing the three terminal carbons as shown in Scheme 1. To this effect, a number of procedures have been proposed,[3] but none is superior to the industrial process which is a highly optimised version of the old Meystre-Miescher method.[1]

Recently we described[4] an efficient degradation scheme based on some novel aspects of the chemistry of 3,4-dihydro-

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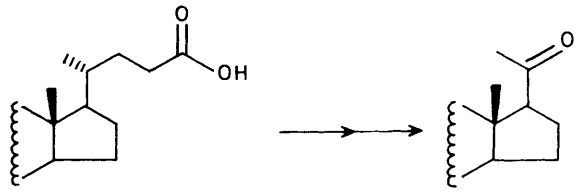
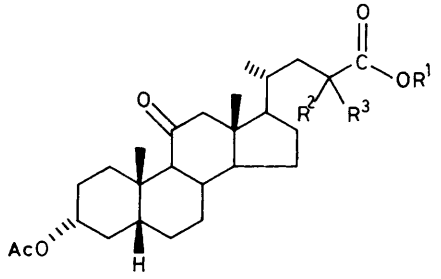
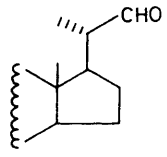


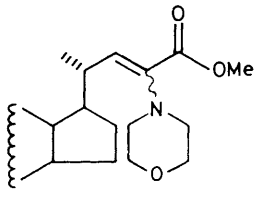
Scheme 1



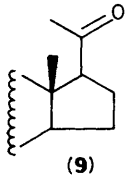
(1) $R^1 = R^2 = R^3 = H$
(2) $R^1 = H$; $R^2, R^3 = =S=O$
(3) $R^1 = Me$; $R^2, R^3 = =S=O$
(4) $R^1 = Me$; $R^2 = H$; $R^3 = -\overset{\overset{O}{\|}}{S}-OMe$
(5) $R^1 = Me$; $R^2, R^3 = =O$
(6) $R^1 = Me$; $R^2, R^3 = =NOH$



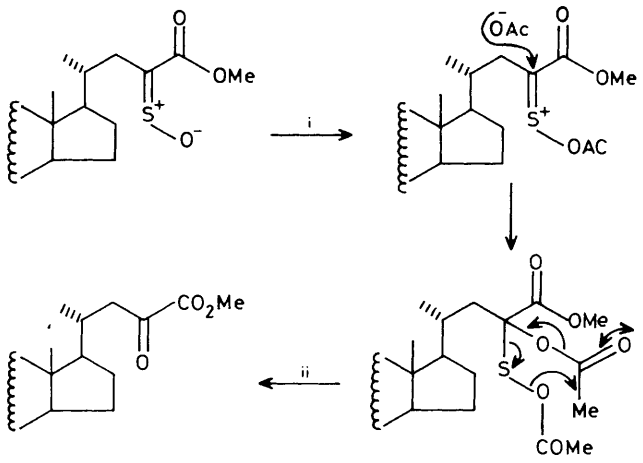
(7)



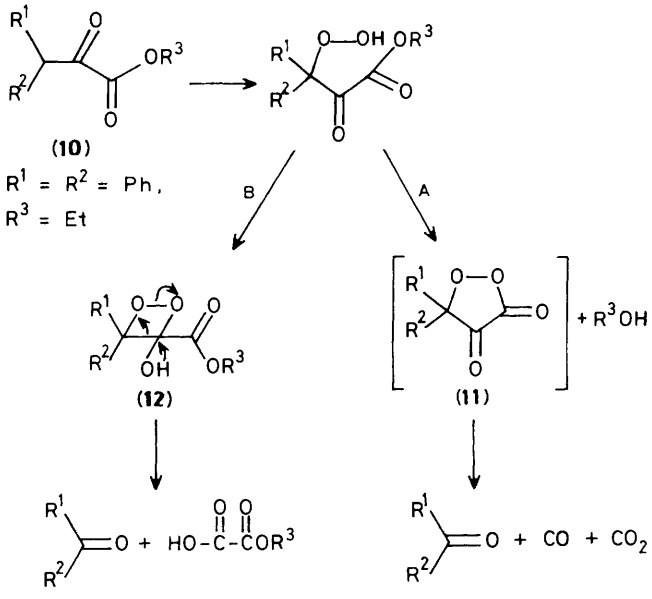
(8)



(9)



Scheme 2. i, Ac_2O, H^+; ii, $-\frac{1}{8}S_8$, $-Ac_2O$.



Scheme 3

oxazoles. However, from an industrial standpoint, this first approach is not practical because of the prohibitive cost of the phenylseleninic acid used in one of the steps. We now report a very short alternative solution to this problem using cheap, readily available reagents.

When carboxylic acids with α-hydrogens are treated with thionyl chloride in the presence of base (*e.g.* pyridine), α-substitution can occur to give, among other products, α-sulphinyl- and/or α-chlorosulphenyl acid chlorides.[5] Because of its relative complexity this reaction has seldom found synthetic use. In the case of the cholanic acid derivative (**1**), however, treatment with thionyl chloride and excess of pyridine gives cleanly, after quenching with cold water, the sulphine (**2**) (85% yield). Quenching with methanol furnishes the corresponding methyl ester (**3**) (72% yield) accompanied by small amounts of the sulphinate (**4**) (18% yield), isolated as a mixture of isomers. This reaction for obtaining the sulphine (**2**) as well as the ester (**3**) was first discovered in the research department of Roussel-Uclaf.‡ The sulphinate (**4**) may also be obtained by heating (**3**) in methanol in the presence of pyridine. The formation of (**4**) could be suppressed by neutralising the excess of pyridine with anhydrous camphorsulphonic acid before addition of methanol, increasing the yield of (**3**) to 86%.

Oxidative cleavage of the sulphine group to give the keto ester (**5**) is easily achieved with ozone[7] (95% yield) or excess of nitrogen dioxide (96% yield). It is interesting to note that if only a slight excess of nitrogen dioxide is employed, the reaction stops cleanly at the intermediate oxime (**6**) (85% yield). Other oxidants such as potassium permanganate, sodium hypochlorite, or alkaline hydrogen peroxide also effect the conversion into the desired keto ester (**5**) albeit in lower yields (70—85%). For large scale work, however, the best method is non-oxidative and involves exposing the sulphine (**3**) to acetic anhydride in dichloromethane in the presence of catalytic amounts of sulphuric acid. The keto ester (**5**) is thus obtained in >90% yield. A plausible mechanism for this apparently novel reaction is outlined in Scheme 2.

‡ The research group of Roussel-Uclaf have obtained keto-ester (**5**) from sulphines (**2**) and (**3**) by a different method. All these intermediates were degraded to ketone (**9**) using various procedures. We thank Dr. J. Buendia for a friendly exchange of information.

Although the role of the acetic anhydride is in principle catalytic, no attempts have been made at this stage to reduce the amounts used.

With a convenient access to the keto ester (**5**), we examined its autoxidation as a way of splitting off the three carbons of the side chain. When a chloroform solution of (**5**) containing morpholine and catalytic amounts of copper(I) chloride is stirred under air, the 22-aldehyde (**7**) is produced in 85% yield. Although enamine (**8**)[8] may be invoked as an intermediate in this reaction, its formation is not necessary in this case. We have observed an essentially identical result when *N*-methylmorpholine was used, in accord with a simple base catalysis, since no enamine can be formed in this instance. More importantly, the fact that the autoxidation halted at the 22-aldehyde level indicated that, at least under these conditions, the fragmentation of the keto ester is easier than that of aldehyde (**7**). Given that conditions have been described whereby similar 22-aldehydes are cleaved,[9] we envisaged the possibility of a one step degradation of the keto ester directly into the desired 20-keto steroid (**9**). In practice, exposure to air of a warm (40—50 °C) solution of the keto ester (**5**) in *N*,*N*-dimethylformamide containing catalytic amounts of DABCO (1,4-diazabicyclo[2.2.2]octane) and copper(II) acetate–2,2′-bipyridyl complex furnished ketone (**9**) in excellent yield (92%). Aldehyde (**7**) is an intermediate as indicated by t.l.c. analysis and by interrupting the oxidation halfway.

The autoxidation mechanism may involve the intermediacy of an α-keto perlactone (**11**) as indicated in Scheme 3, path A. This pathway was supported by quantitative measurement of the CO and CO_2 evolved during autoxidation of the model pyruvate (**10**) to give benzophenone. As expected from such a mechanism, one mole each of CO and CO_2 were produced per mole of pyruvate. Had the reaction proceeded through the dioxetanol (**12**) (*via* path B), neither CO nor CO_2 would have been produced since hemioxalates are stable under the reaction conditions. α-Keto perlactones have been proposed before as intermediates in the reaction of bromopyruvates with alkaline hydrogen peroxide.[10]

The degradation of the side chain is thus completed in three efficacious steps. This scheme has the added advantage of providing 22-aldehydes which are key intermediates in the synthesis of steroids with unusual side chains.[11]

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