

INVESTIGATIONS ON 3-HYDROXY-5-CHOLENIC ACID

MELVIN F. W. DUNKER AND BYRON RIEGEL
Northwestern University, Evanston, Illinois

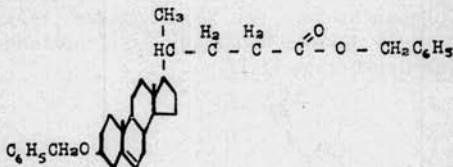
The ready availability of the bile acids makes them convenient starting materials for numerous conversions and syntheses. In the work reported in this paper, 3-hydroxy-5-choleonic acid resulting from the oxidation of cholesterol has been used. It is our purpose to study various means of building up natural compounds and of improving methods for the degradation of hydroxy bile acids to substances having possible androgenic, progestational and cortical hormone activity. 3-hydroxy-5-choleonic acid has a nuclear double bond and a secondary alcohol group that must be protected during the course of degradative or synthetic reactions on the aliphatic chain. It was thought that labile ethers, that is, ethers which could readily be removed when desired, would be the ideal means of protecting the hydroxyl group on C atom No. 3.

One of the first ethers chosen for this purpose was the trityl (triphenylmethyl) ether. The compounds were reported to be stable to alkaline reagents but easily hydrolyzed by mineral acids. This study has shown that the trityl group is replaced by the acetoxy group when the compounds are refluxed in glacial acetic acid or removed upon treatment with a Grignard reagent under even the mildest conditions.

In this work, it was found convenient to use the methyl ester since the free bile acid is highly insoluble. The methyl ester was prepared in nearly quantitative yields (averaging above 90%) upon refluxing a solution of the acid in anhydrous methanol containing 3% HCl. The trityl ether was prepared in 85-88% yields when perfectly dry methyl 3-hydroxy-5-choleolate was heated on a steam cone for 8 hours with trityl chloride in absolutely anhydrous pyridine.

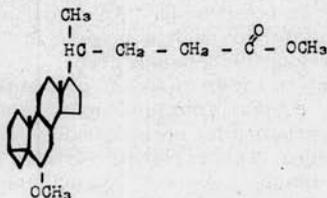
The direct benzylation of hydroxylated steroids has proven difficult. When methyl 3-hydroxy-5-choleolate was treated with benzyl chloride and pyridine under the rigorous anhydrous conditions employed in the tritylation, no benzyl ether was obtained. Likewise, the preparation of

the benzyl ether by variations of Williamson's synthesis did not prove successful. The method employed by Stoll for the preparation of the benzyl ether of cholesterol was applied to methyl 3-hydroxy-5-choleolate. Attempts to prepare the p-toluene-sulfonate of 3-hydroxy-5-choleonic acid were unsuccessful. Therefore, the methyl ester was employed. When the methyl 3-p-toluenesulfonyloxy-5-choleolate, prepared from the methyl ester, p-toluene sulfonyl chloride and pyridine at room temperature in 90-93% yields, was heated with benzyl alcohol on a steam cone for 5 hours, there were obtained 55-61% yields of



This compound exists in dimorphic forms melting 87-88° and 108.5-109.5°. The lower form can be converted to the higher melting form. This ether is stable to treatment with Grignard reagent and stable to 2 hours refluxing with glacial acetic acid.

In recent years the elucidation of the structure of the dextro or i-ethers by Stoll makes it seem that these compounds may prove useful in this work.



The 3-hydroxyl and the double bond are blocked eliminating the necessity of bromination and later debromination. The i-linkage can be broken up by refluxing with acetic acid, yielding the normal acetate which can then be saponified to liberate the hydroxyl group.