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AN IMPROVED PREPARATION OF CHENODEOXYCHOLIC ACID

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Bile acids and particularly chenodeoxycholic acid have been found to be efficacious orally in dissolving gallstones in human patients and, as such, have been the subject of intense study (1). Commercial exploitation of this discovery requires large quantities of pure material. Of the various ways in which chenodeoxycholic acid may be prepared, chemical conversion of the more plentiful bile salt, cholic acid, is economically attractive. Several reaction sequences have been recorded to effect this transformation. For example, preparation of the methyl 3α,7α-diacyloxy-12-keto-5β-cholanate from cholic acid has been described as well as its subsequent reduction to chenodeoxycholic acid (2-4). An alternative procedure involving formation of the thioketal of the 12-keto intermediate and its subsequent desulfurization has also been reported (5). Preparation of chenodeoxycholic acid via dehydration of the 12α-hydroxy group or a derivative of the 12-hydroxy group of methyl 3α,7α-diacetoxy-12α-hydroxy-5β-cholanate to form the intermediate methyl 3α,7α-diacetoxy-5β-chol-11-enate and its reduction have been reported (6-8). The subsequent reduction of the 11-enate is substantially more facile and higher yielding than the direct reduction of the 12-keto derivative.

From this work it is clear that a key intermediate is the 11-ene derivative of the 5β-cholanic acids and that it previously has been prepared only by processes that are inefficient or that have other manifest deficiencies. For example, the direct dehydration of the 12α-hydroxy group is low yielding and produces a substantial proportion of undesirable side reactions involving methyl migration or loss of other groups (6). To overcome this, one must use a process using hexamethyl phosphoric triamide (7), which is unacceptable for large-scale processes because of the established toxicity and carcinogenicity of this agent, or use alumina under high dilution (8), which is economically unfeasible because of the cost of reagents. We, therefore, undertook the examination of alternative routes for the production of methyl 3α,7α-diacetoxy-5β-chol-11-enate, which would be economically feasible and safe for application to large scale production of chenodeoxycholic acid.

An especially attractive possibility was the weak-base-catalyzed elimination of the 12α-methanesulfonate ester derivative (9,10). Accordingly, methyl-3α, 7α - diacetoxy - 12α - methanesulfonyloxy-5β-cholanate was prepared (8) and exposed to lithium chloride in dimethylformamide. The reaction mixture was warmed slowly in an oil bath with constant monitoring by tlc. A suitable rate of reaction was obtained at 125-135°; complete disappearance of starting mesylate occurred in about 8 h. The resultant product, the desired methyl 3α, 7α-diacetoxy-5β-chol-11-enate, could be purified directly from the reaction mixture in high yield by crystallization from aqueous MeOH. Of particular importance was that the reaction conditions produced the required olefin free of rearrangement products. Subsequent catalytic reduction and basic hydrolysis afforded chenodeoxycholic acid in overall 50-60% yield from cholic acid.

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EXPERIMENTAL

A mixture of LiCl (0.212 g, 5.0 mmoles) in 5.8 ml of DMF was stirred and warmed to 130° under N_2 to form a clear solution. The solution was removed from heat and methyl 3α,7α-diacetoxy-12α-methanesulfonyloxy-5β-cholante (8) (0.591 g, 1.10 mmoles) was added and the mixture was returned to 130° and stirred under N_2 for 10 h. The reaction mixture was cooled, poured onto ice (ca. 25 g) and extracted four times with Et_2O. The combined Et_2O extracts were washed with H_2O, saturated aqueous NaCl, dried over anhydrous $MgSO_4$ powder, and evaporated under vacuum. The resultant residue was recrystallized from aqueous MeOH to yield methyl 3α, 7α-diacetoxy-5β-chol-11-enate 0.39 g (80%) mp 139-140° [lit. mp 137-139° (7)].

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