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A MILD METHOD OF DEPROTECTION OF CORTICOSTEROIDAL ESTERS

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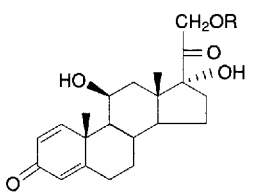
Abstract: The effect of microwave radiation and ultrasounds on the reaction of transesterification of corticosteroidal esters were investigated.

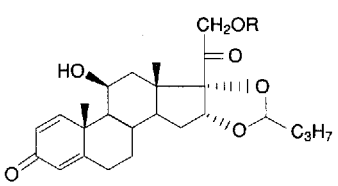
Keywords: corticosteroidal esters, deprotection, microvawes.

Hydrolysis of esters as a method of hydroxyl group deprotection is one of the most essential transformations in organic synthesis. Normally, a basic reagent, *e.g.* an aqueous methanolic solution of potassium carbonate is used (1). However in many synthetic procedures it is necessary to limit the exposure of the reactancts to basic conditions. The hydrolysis of corticosteroidal esters is often accompanied by side reactions such as an oxidation or a rearrangement of the dihydroxyacetone group (2–4). Although many useful and effective methods for cleaving the ester groups have been reported (5), a great need still exists to develop milder and more efficient synthetic procedures. The present mild and simple procedure is based on transesterification. Esters were dissolved in methanol containing a tertiary amine as a catalytic agent. Therefore, the use of an alkaline aqueous solution was avoided. Reactions were carried out at room temperature under argon or nitrogen and could be accelerated by microwave radiation or sonification. Since the use of microwaves has been recommended (6,7) it was of interest to investigate its influence on the course of reaction. A microwave radiation range is between the infrared and the radiowave radiation range (2450 MHz).

The results (Table 1) show a slow deprotection of corticosteroid esters to occur due to the transesterification catalyzed by triethylamine. This process was accelerated by microwave radiation or sonification (Table 2). Therefore, this procedure may be recommended for deprotection of sensitive compounds.



Ia/ R= CH_3CO
Ib/ R= $HOOCCH_2CH_2CO$
Ic/ R= $HOOCC_6H_6CO$



II/ R= CH_3CO

EXPERIMENTAL

Reagents and apparatus

Solvents: methanol, chloroform, acetic acid were pure (POCh Gliwice), triethylamine 99% ABCR.

HPLC was carried out on a Shimadzu LC 6AV instrument, equipped with two pumps, a Rheodyne 7125 sample injector with a 20 µl sample loop. UV detector operated at 244 nm and a CR6A data processor. A LiChrosorb RP 18 Column, particle size 10 µm, and mobile phase acetonitrilewater (45:55; v/v) were used. Flow rate, 1 ml/min. For TLC DC–Alurolle Kieselgel 60F 254 and chloroform–methanol (9:1; v/v) were used. Flash chromatography was carried out on silica gel (22 g) using chloroform–methanol (9:1) as eluent. Microwaves were emitted from a BM–1S/II Plazmatronik–Wrocław instrument at 80% of power and an operation time of 5 min. Sonification was

Table 1. Transesterification without radiation

Comp.	Time [h]	Yiedld [%]
Ia	14	49[b]
Ib	14	30[b]
Ic	14	7[a]
II	9	86[b]

Table 2. The effect of microwave and sonification

Microwaves			Sonification	
Compound	Time [min]	Yield [%]	Time [h]	Yield [%]
Ia	5	41[a]	3	46[a]
Ib	5	67[a]	3	12[a]
Ic	10	90[b]	3	18[a]
II	10	99[a]	4	99[a]

Compounds:

Ia) 21–(acetyloxy)–11β,17α–dihydroxypregna–1,4–diene–3,20–dione.

Ib) 21–(3–carboxy–1–oxopropoxy)–11β,17α–dihydroxypregna–1,4–diene–3,20–dione.

Ic) 21–[[(6–carboxy–3–cyclohexen–1–yl)carbonyl]oxy]–11β, 17α–dihydroxypregna–1,4–diene–3,20–dione.

II) 21–acetoxy–16α,17α–[butylidene–bis(oxy)]–11β–hydroxyp-regna–1,4–diene–3,20–dione.

[a] estimated *via* HPLC

[b] isolated product

carried out using a UM–05 Unitra Olsztyn instrument.

Procedure

Triethylamine (0.4 ml) was added under argon to a solution of an ester (0,5 mmol) in methanol (20 ml). The mixture was stirred at room temperature or subjected to microwaves or ultrasounds. The reaction was followed by TLC. After the reaction was completed the solution was neutralized with acetic acid. Then the solvent was removed under reduced pressure. The residue was purified by flash chromatography by using chloroform–methanol (9:1) v/v as eluent and crystallized.

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