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SYNTHESIS OF TRITERPENOID SULFATES USING THE SO_3—DIMETHYL SULFOXIDE COMPLEX

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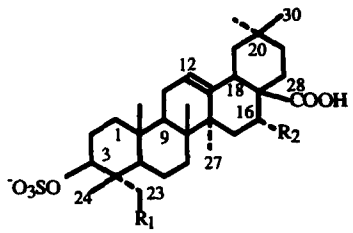
The 3-sulfates of oleanolic, echinocystic, and betulinic acids have been synthesized with the use of the SO_3—dimethyl sulfoxide sulfating complex.

The wide distribution of 3-sulfates of steroids in natural sources is generally known [1]. 3-Sulfates of triterpenoids and their glycosides have been detected in plants only recently and have been isolated from *Bupleurum rotundifolium* [2], *Patrinia scabiosaefolia* [3], *Schefflera octophylla* [4], *Hedera helix* [5]. and *Hedera taurica* [6, 7]

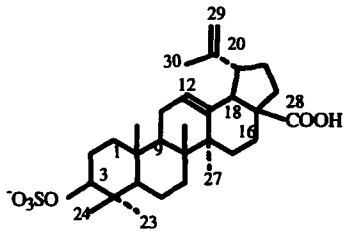
Methods proposed previously for the synthesis of sulfates of triterpenoids and steroids were based on the use of H_2SO_4 in the presence of dicyclohexylcarbodiimide [8] and commercial preparations of complexes of SO_3 with pyridine [2] and with trimethylamine [9]. However, the incompleteness of the reaction by the procedures described, in a number of cases the considerable length of the process (up to 24 h), and the heterogeneity of the reaction mixtures, necessitating stirring, have stimulated our search for new and more effective methods.

An investigation of the sulfating properties of complexes of SO_3 with 1,4-dioxane, tetrahydrofuran, and N,N-dimethyl- and N,N-diethylamines did not reveal any advantages whatever. However, on the use of a SO_3—dimethyl sulfoxide complex in dimethyl sulfoxide (DMSO), which has been proposed previously for the sulfation of cellulose [10], practically quantitative yields of the 3-sulfates (the desired products) were achieved. The sulfation process takes place smoothly in a homogeneous medium at room temperature. With a small (30—50%) excess of the sulfating reagent no more than 15—20 min is required to achieve completeness of the transformation. The working up of the reaction mixture is simple and includes dilution with ice water and extraction of the product with chloroform or butanol.

The 3-sulfates of oleanolic, echinocystic, and betulinic acids have been synthesized by the proposed method. The use of echinocystic acid as an example has shown the high selectivity of the action of the reagent on an equatorial C_3-OH group in the presence of an axial C_{16}-OH group, which is not sulfated under the condition given above.



1. R_1 = H, R_2 = H
2. R_1 = H, R_2 = OH



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EXPERIMENTAL

Preparation of the Sulfating Reagent. The complex of SO_3 with DMSO was obtained by adding liquid SO_3 (distilled from high-percentage oleum) with cooling to dry DMSO up to a concentration of about 5%. A solution of the complex in

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DMSO is stable under low-temperature (-(5÷10°C)) storage conditions for more than a month. For longer storage, the SO_3—DMSO complex can be isolated in the pure form by precipitation with dry methylene chloride, as described in [10].

The production of the sulfating reagent can be considerably simplified by the direct addition of the calculated amount of high-percentage oleum (about 60% SO_3) to DMSO with cooling. However, in this case the solution also contains H_2SO_4, which considerably lowers its stability on storage and does not exclude the possibility of the formation of by-products in the sulfation of acid-labile compounds.

Oleanolic Acid 3-Sulfate (1). A solution of 100 mg of oleanolic acid in 0.5 ml of dry DMSO was treated with 0.5 ml of the sulfating reagent, and the mixture was kept at room temperature for 15—20 min. Then it was diluted with a tenfold volume of ice water, and the product was extracted with butanol. The butanolic extract was washed with water to neutrality of the aqueous layer, evaporated to dryness, and analyzed by TLC on Silufol plates in the solvent system chloroform—methanol—water (100:30:5) or chloroform—methanol—25% ammonia (100:30:5) together with an authentic specimen of oleanolic acid 3-sulfate [6]. The product was isolated chromatographically on silica gel L with elution by water-saturated chloroform—ethanol (5:1). This gave 90 mg of pure (1), mp 158—162°C, $[\alpha]_D$ +55° (*c* 1.0; methanol), lit.: mp 161—163°C, $[\alpha]_D$ +53.7° (methanol) [2].

PMR spectrum of (1) (δ, ppm, 0-TMS, C_5D_5N): 5.25 (t, $J_{11,12}$=3.0 Hz, H-12); 4.48 (dd, $J_{2a,3}$=12.5 Hz, $J_{2e,3}$=4.5 Hz, H-3); 3.00 (dd, $J_{18,19a}$=13.0 Hz, $J_{18,19e}$=4.5 Hz, H-18); 2.60 (dd, $J_{18,19a}$=13.0 Hz, $J_{18,19e}$=4.5 Hz, H-18); 2.60 (dd, $J_{19a,19e}$=14.5 Hz, H-19e); 1.32, 1.09, 0.93, 0.83, 0.81, 0.75, 0.70 (all s, $7CH_3$); 0.7-2.2 (skeletal CH, CH_2).

The ^{13}C NMR spectrum of (1) was identical with that given in [2, 6].

Echinocystic Acid 3-Sulfate (2). The sulfation of 100 mg of echinocystic acid in a similar way to that of oleanolic acid gave 85 mg of (2), identical according to TLC with an authentic specimen of echinocystic acid 3-sulfate [7], mp 160—163°C, $[\alpha]_D$ +24° (*c* 0.5; methanol), lit. mp 162—164°C, $[\alpha]_D$ +25.2° (methanol) [2].

PMR spectrum of (2) (δ, ppm, 0-TMS, C_5D_5N): 5.47 (t, $J_{11,12}$=3.5 Hz, H-12); 4.98 (qt, $J_{15,16}$=3.5 Hz, H-16); 4.51 (dd, $J_{2a,3}$=12.0 Hz, $J_{2e,3}$=4.5, H-3); 3.35 (dd, $J_{18,19a}$=13.5 Hz, $J_{18,19e}$=4.0 Hz, H-18); 2.70 (dd, $J_{19a,19e}$=14.0 Hz, H-19e); 1.70, 1.35, 1.05, 0.98, 0.96, 0.86, 0.79 (all s, $7CH_3$); 0.7-2.5 (skeletal CH, CH_2).

The ^{13}C NMR spectrum of (2) was identical with that given in [2, 7].

Betulinic Acid 3-Sulfate (3). The sulfation of 100 mg of betulinic acid in a similar way to that of oleanolic acid gave 90 mg of (3), $[\alpha]_D$ +6° (*c* 1.0, ethanol), lit. $[\alpha]_D$ +4.3° (ethanol) [4].

PMR spectrum of (3) (δ, ppm, 0-TMS, C_5D_5N): 4.95, 4.76 (m, H-29A,B); 4.50 (m, H-3); 1.80; 1.25; 1.03; 0.98, 0.86, 0.75 (all s, $6CH_3$); 0.7-2.5 (skeletal CH, CH_2).

The ^{13}C NMR spectrum of (3) was identical with that given in [4].

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