PREPARATION AND PROPERTIES OF TRIMETHYLSILYL ETHERS OF SOME STEROIDS

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A method has been given for the preparation of trimethylsilyl ethers of some steroids. Behaviour of these compounds has been investigated.

Trimethylsilyl ethers of certain steroids have been prepared by LUUKKAINEN and coworkers [1] to study their gas chromatographyc behaviours, without mentioning however the physical and chemical properties of these derivatives. They reported a method for the preparation of these compounds using hexamethyldisilazine as silylating agent and trimethylchlorosilane as catalyst. It was SJÖVALL[1], who suggested the application of trimethylsilyl diethylamine for the preparation of trimethylsilyl ethers of bile acid esters, a method earlier applied by RÜHLMANN [2] in the preparation of silyl derivatives of amino acids. Now it has been found that trimethylsilyl diethylamine is a more convenient silylating agent, since the silylation reaction does not result any nonvolatile by-product. Trimethylsilyl ethers of Δ_5-3β-hydroxy-androsten-17-one, Δ_5-3β-hydroxy-cholestene and methyl-Δ_5-3β-hydroxy-cholenate were prepared in acetone in the presence of excess trimethylsilyl diethylamine at room temperature for 4 hrs., or at elevated temperature with shorter reaction period. After the evaporation of the solvent in vacuo a crystalline product remained, which could be examined in gas chromatograph, or recrystallized for analysis without further manipulations.

These silyl ethers decompose on boiling in ethanol solution in the presence of sodium ethoxide or *p*-toluenesulphonic acid in 30 minutes, but the hydrolysis of the trimethylsilyl ether of dehydroepiandrosterone on boiling in 75% ethanol does not proceed even in 4 hrs. The reduction of the latter silyl ether by means of $LiAlH_4$ in ether, or $NaBH_4$ in tetrahydrofuran r esults $\Delta_5$3β-trimethylsilyloxy-17β-hydroxy-androstene.

A preliminary report may also be given about the selectivity of the silylation reactions. Systematic gas chromatographic investigations of the silylation product of bile acid esters show that equatorial hydroxyl groups at the 3 and 6α positions react in a few hrs. at room temperature. The silylation of OH groups at 7β position is not complete in 20 hrs. at room temperature, while the 7α-OH group is not attacked under the same conditions. The 12α-OH groups do not react even at 100°.

[1] Karolinska Institute, Institute of Chemistry, Stockholm.

Experimental

The silyl ethers were obtained either from purified trimethylsilyl diethylamine or from the crude reaction product of the preparation of trimethylsilyl diethylamine with the same results.

Trimethylsilyl ether of Δ_5-3β-hydroxy-androsten-17-one

300 mg Δ_5 – 3β-hydroxy-androstene-17-one in 2 ml acetone and 2 ml trimethylsilyl diethylamine were kept at 60° for 15 min., the mixture evaporated in vacuo and the residue crystallized from petrolether, m. p.: 158 °C. Anal.: Calc.: $C_{22}H_{36}O_2Si$ C 73,28 H 10,06; Found: C 72,84 H 9,87.

Trimethylsilyl ether of cholesterol.

It was prepared as above, m. p.: 130 °C (petrolether). Anal.: Calc.: $C_{30}H_{54}OSi$ C 78,52 H 11,86; Found: C 78,95 H 11,66.

Trimethylsilyl ether of methyl-Δ_5-3β-hydroxy-cholenate.

The compound was prepared as above and melted at 73 °C (cyclohexane). Anal.: Calc.: $C_{28}H_{48}O_3Si$ C 72,99 H 10,50; Found: C 72,64 H 10,27.

3-Trimethylsilyl ether of Δ_5-3β, 17β-dihydroxy-androstene.

A mixture of 200 mg trimethylsilyl ether of Δ_5-3β-hydroxy-androsten-17-one in 10 ml ether and 200 mg $LiAlH_4$ in 30 ml ether were stirred at 0 °C for 3 hours and a mixture of 1 ml water, 2 ml ethanol, 10 ml ether and 3 drops of acetic acid were added at the same temperature. The product was filtered, dried over Na_2SO_4 and evaporated in vacuo. The residue yielded on recrystallization from petrolether a product, m. p.: 163—164 °C. Anal.: Calc.: $C_{22}H_{38}O_2Si$ C 72,87 H 10,56; Found: C 73,00 H 10,50.

This compound gave on acidic alcoholysis Δ_5-3β-hydroxy-androsten-17-one.

Alcoholysis and hydrolysis of trimethylsilyl ether of Δ_5-3β-hydroxy-androstene-17-one.

30 mg samples of trimethylsilyl ether of Δ_5-3β-hydroxy-androsten-17-one in 5 ml abs. ethanol in the presence of traces of sodium ethoxide or benzene-sulphonic acid, or in 75% aqueous ethanol, respectively, were refluxed. Thin layer chromatography revealed the absence of starting materials in the first two cases in 30 min., while in the third case considerable amounts of starting material could be detected even in 4 hours.

ПРОИЗВОДСТВО НЕКОТОРЫХ ТРИМЕТИЛСИЛИЛ ЭФИРА СТЕРОИДОВ И ИХ СВОЙСТВА

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Был разработан метод для производства триметилсилил эфира стероидов. Было изучено свойство этих соединений.

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PREPARATION OF PREGNADIENOLONE-20-C^{14}

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$\Delta_{5,16}$-Pregnadien-3β-ol-20-on-20-C^{14} has been prepared analogously as described by BUTENANDT [1] in the case of the inactive derivative, as follows:

Δ_5-3β-acetoxy-androsten-17-one → Δ_5-3β-acetoxy-androstene-17-cyanohydrin → → $\Delta_{5,16}$-3β-hydroxy-etiocholadienic acid nitril → $\Delta_{5,16}$-3β-hydroxypregnadien-20-one.

In the first step of the reaction sequence 3,55 g $KC^{14}N$ corresponding to 2,2 μc C^{14} activity, 1 g Δ_5-3β-acetoxy-androsten-17-one, 3,5 ml glacial acetic acid and 15 ml ethanol were reacted. The final product of the reaction sequence pregnadienolon-20-C^{14} was purified in a chromatographic way on Whatman N° 3 paper in formamide-hexane system, followed by crystallization from ethyl acetate till constant specific activity.

The substance obtained this way was 72 mg, melted at 214—216°. Specific activity 43 cpm/10 μg measured with a windowended GM tube. The purity of the product was checked by thin layer chromatography running it together and parallel with inactive pregnadienolone.

The radioactive yield could be enhanced up to 25—30% by means of exchange reaction between C^{14} N ion and the previously prepared inactive Δ_5-3β-acetoxy-androstene-17-cyanohydrine, as it had been described by KOUŘIM and ZIKMUND [2] for the synthesis of C^{14}-serine.

The utilization of the compound in the synthesis of progresterone and corticosteroids, and in the solution of certain analytical problems are in progress.

ПРОИЗВОДСТВО ПРЕГНАДИЕНОЛОНА-20-C^{14}

Предворительное сообщение

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