# Germylated steroids
## 2.* Synthesis of steroid germatranes

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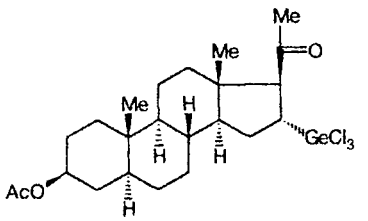
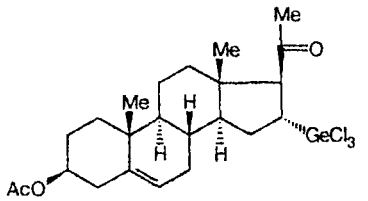
Steroid germatranes were synthesized by a two-stage procedure from 16-trichlorogermylated steroids.

**Key words:** organogermanium compounds, steroids, germatranes.

Previously,[1] we have synthesized 3β-acetoxy-16α-trichlorogermyl-5α-pregnan-20-one (**1**), 3β-acetoxy-16α-trichlorogermylpregn-5-en-20-one (**2**), and their 16β-isomers by hydrogermylation of steroid 16-en-20-ones.




**1**

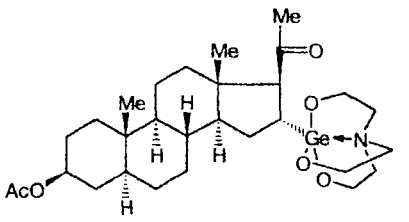



**2**

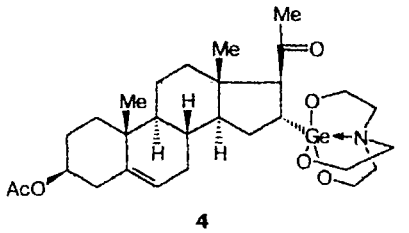
The subsequent transformation of the steroid skeleton with the aim of accessing active germylated steroids required the conversion of the trichlorogermyl substituent containing the readily hydrolyzable Ge—Cl bond into a more stable group, for example, into a trialkylgermyl, germoxane, or germatrane function. However, the selective replacement of chlorine atoms by alkyl groups, for example, under the action of Grignard reagents, presents difficulties due to the presence of the carbonyl and ester groups. As expected, hydrolysis of trichlorogermyl steroids afforded poorly soluble sesquioxides, which makes their use difficult.

Compounds **1** and **2** were successfully converted into stable steroid germatranes containing the coordination N→Ge bond. Taking into account that germatranes are biologically active compounds,[2] we believe that this property can extend the spectrum of pharmacological activity of germylated steroids.

The most convenient and versatile procedure for the preparation of germatranes involves transalkoxylation, which proceeds under mild conditions in the absence of catalysts. For this purpose, the corresponding organyltrihalogermane is preliminarily converted into the trialkoxygermyl derivative, which is then converted into the germatrane. Steroid germatranes **3** and **4** were synthesized according to this procedure from trichlorogermylated steroids **1** and **2** by reaction with MeOH and then with $N(CH_2CH_2OH)_3$. The structures of germatranes **3** and **4** were confirmed by the $^1H$ NMR spectra, which have signals typical of steroid and atrane fragments.




**3**




**4**

Attempts to prepare germatranes from 16β-isomers of compounds **1** and **2** under the same conditions were unsuccessful due, apparently, to steric hindrances

* For Part 1, see Ref. 1.

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and, in addition, because of the presence of the coordination O→Ge bond in these compounds.[3] Therefore, germatranes **3** and **4** can be prepared with the use of mixtures of 16α- and 16β-isomers as such, which are formed as a result of hydrogermylation of steroid enones. Taking into account that hydrogermylation at low temperature afforded predominantly 16α-isomers,[1] the use of mixtures of isomers as such without their separation can substantially simplify the preparation of germatranes. Thus, hydrogermylation of 3β-acetoxypregna-5,16-dien-20-one (**5**) at −50 °C followed by treatment of the resulting mixture of steroid **2** and its 16β-isomer (in a ratio of 3 : 1) with methanol and triethanolamine afforded germatrane **4** in a total yield of 42%.

The resulting germatranes can be converted into the known steroid drugs (gestagens, corticosteroids, *etc.*) containing the germatrane group at position 16.

## Experimental

The $^1$H NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) in $CDCl_3$. The completion of the reactions was monitored by TLC. The ratios of the isomers were determined by integration of the signals of the 21-Me groups in the $^1$H NMR spectra.

**3β-Acetoxy-16α-(1-germatranyl)-5α-pregnan-20-one (3).** Methanol (0.2 mL) and then triethylamine (0.3 g) were added to a solution of germylated steroid **1** (360 mg) in dry benzene (2 mL). The precipitate that formed (triethylamine hydrochloride) was filtered off and the filtrate was concentrated. The oily residue (410 mg) was refluxed with triethanolamine (0.13 mL) in dry benzene (3 mL) for 2 h. The solvent was evaporated and the residue was triturated with ether. The finely crystalline precipitate that formed was filtered off. 3β-Acetoxy-16α-(1-germatranyl)-5α-pregnan-20-one (**3**) was obtained in a yield of 340 mg (88%), m.p. 283–285 °C (from MeOH). Found (%): C, 59.95; H, 8.07; Ge, 12.58; N, 2.55. $C_{29}H_{47}GeNO_6$. Calculated (%): C, 60.23; H, 8.18; Ge, 12.56; N, 2.42. $^1$H NMR, δ: 0.53 (s, 3 H, 18-Me); 0.78 (s, 3 H, 19-Me); 1.97 (s, 3 H, AcO); 2.02 (s, 3 H, 21-Me); 2.75 (t, 6 H, $NCH_2$); 3.60 (t, 6 H, $OCH_2$); 4.60 (m, 1 H, 3-H).

**3β-Acetoxy-16α-(1-germatranyl)-pregn-5-en-20-one (4).** ***A.*** 3β-Acetoxy-16α-(1-germatranyl)-pregn-5-en-20-one **4** was prepared from trichlorogermyl derivative **2** (300 mg) under conditions of the synthesis of germatrane **3** in a yield of 310 mg (95%), m.p. 273–276 °C (from MeOH). Found (%): C, 60.02; H, 8.01; Ge, 12.70; N, 2.56. $C_{29}H_{45}GeNO_6$. Calculated (%): C, 60.45; H, 7.82; Ge, 12.61; N, 2.43. $^1$H NMR, δ: 0.50 (s, 3 H, 18-Me); 1.00 (s, 3 H, 19-Me); 1.98 (s, 3 H, AcO); 2.03 (s, 3 H, 21-Me); 2.75 (t, 6 H, $NCH_2$); 3.60 (t, 6 H, $OCH_2$); 4.43 (m, 1 H, 3-H); 5.33 (m, 1 H, CH=).

***B.*** Trichlorogermane etherate (1.3 g, 4 mmol) was added at −50 °C to a solution of enone **5** (1.1 g, 3 mmol) in chloroform (3 mL). The reaction mixture was kept for 1 h and the solvent was evaporated. The oily residue containing (according to the $^1$H NMR spectral data) a mixture of 16α-trichlorogermyl derivative **2** and its 16β-isomer (3 : 1) was dissolved in benzene (3 mL) and treated successively with MeOH (in the presence of triethylamine) and triethanolamine under conditions of the synthesis of **3**. Germatrane **4** was isolated in a yield of 750 mg (42% calculated for two stages). The melting point and the $^1$H NMR spectrum of the resulting compound are identical with the corresponding characteristics of compound **4** prepared according to method *A*.

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