EXPERIMENTAL METHOD

UV spectra were measured on a Unicam SP-800 spectrophotometer and IR spectra were taken in KBr disks in a Perkin-Elmer 337 instrument. PMR was measured on a Tesla-BS-487C (80 MHz) in $CDCl_3$ and $[\alpha]_D$ was measured on a Hilger-Watts M511 instrument.

17α-Trimethylsilylhydroxypregn-4-ene-3,20-dione. To a solution of 1.5 g 17α-hydroxyprogesterone in 7.5 ml absolute pyridine were added 6 ml N,O-di-TMS-acetamide and 1.2 ml trimethylcholorisilane and the mixture was heated for 6 h at 60°C. The reaction mixture was evaporated to dryness (40°/15 mm), acetamide was distilled off (60°/0.04 mm), the residue was dissolved in 50 ml methylene chloride, the solution was filtered through 70 g Al_2O_3 (neutral, activity grade II), and the filtrate evaporated. A clear oil (1.4 g) was obtained which crystallized on trituration with hexane. The yield of 17α-hydroxyprogesterone TMS-ether was 1.2 g (70%), mp 168-170°; $[\alpha]_D^{18}$ + 89° (concn. 1.19, dioxan); λ_{max} (hexane) 231.5 nm (log ε 4.19); λ_{max} (alcohol) 241 nm; ν_{max} cm^{-1}: 1710 (20-C-O), 1670, 1620 (C-CC-O), 1260, 1104, and 842 ($OSiMe_3$); δ ppm: 0.05 (singlet, 9H, $OSi(CH_3)_3$), 0.52 (singlet, 3H, 18-CH_3), 1.09 (singlet, 3H, 19-CH_3), 2.05 (singlet, 3H, 21-CH_3), 5.68 (broad singlet, 1H, 4-H). Found, %: C 71.49; H 9.52; Si 6.66. $C_{24}H_{38}O_3Si$. Calculated, %: C 71.60; H 9.46; Si 6.96.

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SYNTHESIS AND HORMONAL ACTIVITY OF TRIMETHYLSILYL ETHERS OF 17β-HYDROXY STEROIDS

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The esterification of hydroxyl groups of testosterone and its modified derivatives with carboxylic acids, especially higher ones, has been applied widely in the search for preparations with high and prolonged hormonal activity [1, 2]. Other esters of hydroxyandrostanes are used at present. There are reports on the high hormonal activity of tetrahydropyranyl, cyclopentenyl, and a series of α-alkoxyalkyl ethers of modified testosterones [3, 8].

Silylation of hydroxyl groups has found wide application as a method of obtaining easily chromatographed, especially in the gas phase, derivatives and has found even more application for the protection of hydroxyl groups in organic synthesis [9]. Less is known on the use of silylation for the modification of the hormonal activity of steroids. There are patent reports on the hormonal activity of silyl ethers of estrogens [10], 21-hydroxypregnanes [11], and certain hydroxyandrostanes [12]. Trimethylsilyl mono- and di-ethers of testosterone possess prolonged androgenic and anabolic activity [13, 14].

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TABLE 1. Trimethylsilyl Ethers of Hydroxy Steroids

Compound	Method of synthesis	Yield, %	Mp, °C*	$[\alpha]_D$ in degrees†	Found, %			Emperical formula	Calculated, %		
					C	H	Si		C	H	Si
IV	A	86	119,5—20	+46	73,06	10,15	7,93	$C_{21}H_{34}O_2Si$	72,77	9,89	8,10
	B	92									
V	A	100	74—4,5	—210	73,20	9,30	8,10	$C_{21}H_{32}O_2Si$	73,20	9,36	8,14
VII	B	95	132—3	+94							
VIII	B	100	82—3,5	+137	72,98	10,0	—	$C_{21}H_{36}O_2Si$	72,77	9,89	—
IX	C	93	110—1	+66	73,63	10,13	7,55	$C_{23}H_{38}O_2Si$	73,79	10,15	7,50
XII	C	96	127—8	+15	73,99	9,68	7,49	$C_{23}H_{36}O_2Si$	74,19	9,67	7,54
XIV	C	89	115—6	+45	75,90	10,95	7,91	$C_{22}H_{38}O\,Si$	76,22	11,04	8,11
XV	—	86	102—3	+44	69,06	10,55	13,14	$C_{25}H_{46}O_2Si_2$	69,11	11,21	12,91

*Compound (VIII) was distilled at 70° (0.03 mm), (V) was crystallized from hexane and the remainder from acetone at —30°.

†Optical rotations were measured in dioxan (concentration 0.7-1). Literature data [12]: for (IV) mp 118-120°; for (VII) mp 133-135°, $[\alpha]_D$ + 69° (in chloroform); for (XI) mp 104-111°.

TABLE 2. Hormonal Activity, Myotropic Index, and Prolongation Indexes of Trimethylsilyl Ethers of 17β-Hydroxy Steroids

Compound	Relative activity			MI*	Prolongation indexes	
	myotropic, on LA	androgenic			on LA	mean of SV and VP
		on SV	on VP			
Testosterone†	100	100	100	1,00	1,6	1,7
Fenobolin	285	225	140	1,60	1,4	2,15
IV	151	58	77	2,24	5,3	3,6
V	175	106	112	1,61	1,9	1,9
VII	181	246	131	0,96	3,6	3,6
XI	34	27	77	0,65	0,9	1,1
XII	12	4	36	0,60	0,8	1,0
XIV	3	30	45	0,08	1,9	2,0

*Myotropic index (MI) = $\frac{\text{relative myotropic activity}}{\text{mean relative androgenic activity}}$.

†Standard compound.

We have undertaken a more detailed study of the hormonal activity of silyl ethers of certain hydroxy steroids. The present communication concerns the synthesis and hormonal activity of trimethylsilyl (TMS) ethers of 17β-hydroxyandrostanes.

Many methods are known for obtaining silyl ethers of hydroxy steroids, but the majority of them have been studied only on a micro scale with the aim of preparing volatile derivatives for gas—liquid chromatography [15, 16]. Silylation with a mixture of hexamethyldisilazane and trimethylchlorosilane in pyridine [12, 15] in the case of the readily enolizable keto steroids testosterone (I), estr-4-en-17β-ol-4-one (II), or estra-4,9-dien-17β-ol-3-one (III) is accompanied by the formation of side products, namely the silyl ethers of the enol forms of the ketones, which complicate isolation and purification. The application of the same reagents in benzene or acetone (method A) occasionally gives better results. This method was used for obtaining the TMS ethers (IV) and (V) of 19-nortestosterone (II) and the dienone (III) respectively. The optimum method, particularly in the case of steroids unstable to acid (for example estr-5(10)-en-17β-ol-3-one, VI), proved to be the application of the more powerful silylating agent N,O-bis(trimethylsilyl)acetamide in the presence of catalytic amounts of trimethylchlorosilane (method B). The application of this silylating agent did not require aqueous treatment of the reaction mixture which is a virtue when working with readily hydrolyzable TMS ethers of secondary alcohols such as the ethers (IV), (VII), and (VIII). The hydroxy steroids with tertiary hydroxyl groups, 17α-methyltestosterone (IX) and 17α-methylandrosta-1,4-dien-17β-ol-3-one (X), were silylated only slowly and incompletely by methods A and B. Consequently, a mixture of hexamethyldisilazane and trimethylchloro-

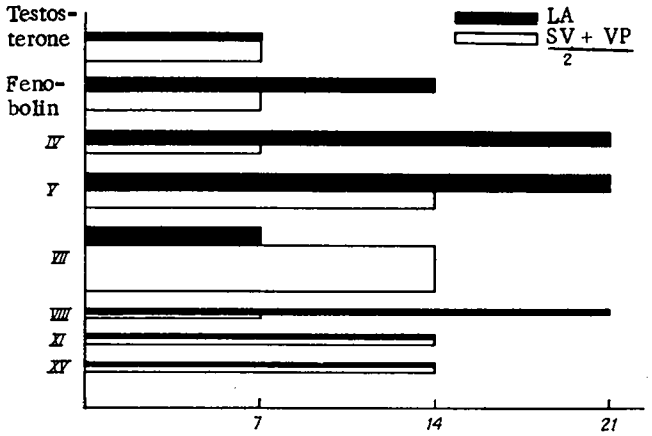
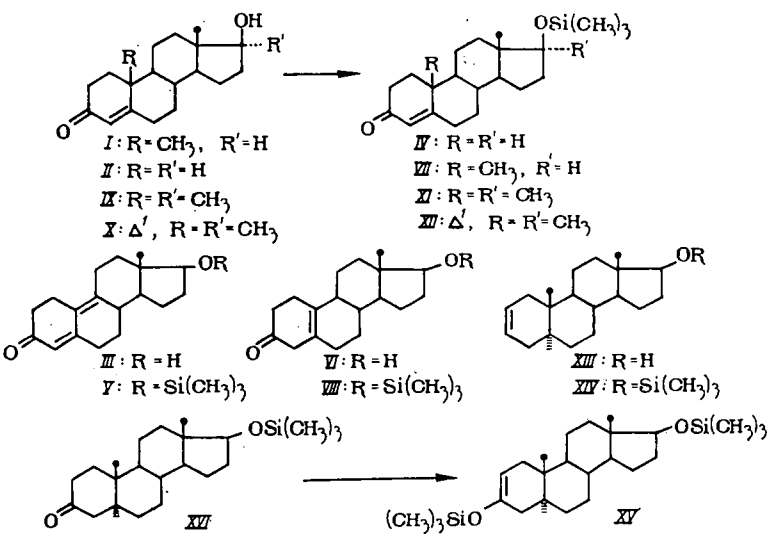


Fig. 1. Prolonged hormonal activity of trimethylsilyl ethers of 17β-hydroxy steroids. The time of onset of maximal effect (in days) is given on the abscissa; the maximal effect of preparations (weight increase of organs) is given on the ordinate proportional to the width of the column, the scale being 1 mm = 10 mg.

silane in dimethylformamide was used for the preparation of the corresponding TMS ethers (XI) and (XII) [17-19] (method C). 5α-Androst-2-en-17β-ol (XIII) formed TMS ether (XIV) by method C also without complications.

In connection with the report on the androgenic activity of the bis-TMS ether of the enolic form of testosterone [14] we also prepared the bis-TMS ether (XV) of the enolic form of 5α-dihydrotestosterone, the true androgen of animals, by silylating the TMS ether of 5α-dihydrotestosterone (XVI) under strongly acid conditions.

High yields of TMS ethers were achieved for all the studied steroids, which are shown in Table 1 together with the constants of the synthesized substances.



In Table 2 results are shown of the investigation of the hormonal activity of the TMS ethers of hydroxy steroids with the aid of a modified Hershberger test [20]. The androgenic activity of the 17-methylated ethers (XI) and (XII) and of ether (XIV) having no oxygen function in ring A was significantly reduced in comparison with testosterone, and the myotropic (anabolic) activity to the same or to an even greater extent so that the ratio of the two forms of activity, the myotropic index (MI), for them was less than 1. The opposite picture was observed for the TMS ethers (V) and (VII) of the steroid secondary alcohols which possessed high levels of activity and of MI. Analogous characteristics were obtained

by us previously [21] for ether (V) with the aid of the usual variant of the Hershberger test. The TMS ether (IV) of nortestosterone, in which androgenic activity was reduced and myotropic activity was increased, is also worthy of mention.

In contrast to the ethers of tertiary alcohols all the TMS ethers of secondary alcohols shown in Table 2 also possessed increased (in comparison with testosterone) prolongation indexes. These roughly estimate the extension of the hormonal action of a preparation in time. This was confirmed by the testing data for prolonged hormonal activity given in Fig. 1. All the investigated ethers proved to have a more extended action than testosterone. The effect on myotropic and androgenic activity was usually different for the TMS ethers both in the size and in the duration of the effect; the more marked the activity the more the intrinsic activity of the initial steroid. The best among the TMS ethers in this test was once again the TMS ether (IV) of 19-nortestosterone which surpassed the β-phenylpropionate of the same steroid (known under the names durabolin, fenobolin [1, 2]) both in MI and in prolongation of action.

EXPERIMENTAL METHOD

IR spectra were recorded in KBr disks on a Perkin-Elmer 337 instrument; angles of rotation were measured on a Hilger-Watts-270 MA-511 instrument.

The myotropic and androgenic properties of substances were studied with the aid of a modified Hershberger test: single injection to rats of 5 mg substance in oil (0.2 ml), recording effects on the 3rd and 7th and on the 14th and 21st days in the prolongation test. The increase in weight compared to control of the levator ani muscle (LA) served as a measure of the myotropic activity, and the increase of the seminal vesicles (SV) and the ventral prostate (VP) of androgenic activity. Calculation of activity in the 3-7 day test was carried out by the method in [20]. The ratio of the effect on day 7 after injection to the effect on day 3 served as an index of prolongation; at an index of less than 1 the maximal effect of a preparation was exerted on the 3rd to 5th day and at an index of greater than 1, on the 7th or subsequent days. The results of testing are given in Table 2 and in Fig. 1.

Trimethylsilyl Ethers of 17β-Hydroxy Steroids. A. To a solution of 1.5 ml hexamethyldisilazane and 0.37 ml trimethylchlorosilane in 25 ml benzene was added 500 mg steroid (II) or (III), and the mixture was stirred for 5 h at 20°. After 16 h the solution was diluted with hexane and filtered through 5 g aluminum oxide (activity grade II). The TMS ether was isolated by evaporating the filtrate in vacuum. B. Steroid (I), (II), or (III) (1 g) was added to 10 ml 10% solution of N,O-bis(trimethylsilyl)acetamide(bp 157.5-159.3°) containing traces (0.1-0.3%) trimethylchlorosilane, the mixture was boiled for 1 h or stored for 48 h at 20° after which it was evaporated to dryness in vacuum and acetamide was distilled from the residue at 80° (0.1 mm). C. A solution of 1 g steroid (IX), (X), or (XIII), 3 ml hexamethyldisilazane and 1 ml trimethylchlorosilane in 10-25 ml dimethylformamide was kept for 30 min at 20°, and poured into water. The TMS ether was isolated by filtration or extraction with ether with subsequent evaporation, washing with water, and drying in vacuum.

The TMS ethers of steroids were purified if necessary by recrystallization or distillation in high vacuum. Constants of analytically pure specimens are given in Table 2. The UV spectra of the TMS ethers were identical with the spectra of the starting steroids and the IR spectra had intense absorption bands for the $OSi(CH_3)_3$ grouping at 1250-1260, 1095-1110, 897-910, and 840 cm^{-1}.

3,17β-Bis-trimethylsilyloxy-5α-androst-2-ene (XV). A mixture of 600 mg (XVI), 1.8 ml trimethylchlorosilane, 5.42 ml triethylamine, and 15 ml dimethylformamide was boiled for 14 h, 1 ml N,O-bis(trimethylsilyl)acetamide added, the mixture boiled a further 30 min, and after 18 h was diluted with hexane. The solution was washed twice with saturated sodium bicarbonate solution, 1.5 N hydrochloric acid, once again with bicarbonate solution, and with water, dried with sodium sulfate, and evaporated. Crystals (620 mg) of (XV) were obtained (see Table 1).

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SYNTHESIS AND NEUROTROPIC PROPERTIES OF NITROGEN DERIVATIVES OF o-CARBORANE AND (3)-1,2-DICARBAUNDECABORATE

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The introduction of a bulky lipophilic adamantyl substituent into a molecule of a potentially biologically active compound changes the penetration and distribution of a preparation, the conditions of its interaction with receptors, and leads to the appearance of new biological effects [1, 2]. A whole series of adamantane derivatives has been obtained possessing antiviral, antibacterial, and neurotropic properties [3-5].

It seemed of interest to study the pharmacological activity of preparations containing highly lipophilic and bulky carborane and dicarbaundecaborane radicals. There are only isolated reports on the biological activity of o-carborane derivatives, these concern a study of the distribution of carborane-containing preparations between tumor and healthy tissue [6-8].

A slightly distorted eicosahedron forms the basis of the structure of o-carborane. The dicarbaundecaborate ion is an eicosahedral fragment formed from an o-carborane nucleus by the action of alkaline agents [9, 10]. Their structures are shown in Fig. 1.

The present communication is devoted to a study of the toxicity and neurotropic activity of carborane aminoalcohols, their esters and N-aminoacyl derivatives, dialkylamides of dicarbaundecarboranylacetic acids, 1-alkylcarboranyl-2-(N,N-dialkylamino)ethanes, internal

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