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Studies on Dimethyl-*tert*-butylsilyl Ethers of Steroid[1]

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In order to obtain the more precise knowledge on the nature of the dimethyl-*tert*-butylsilyloxy linkage, several steroid silyl ethers were prepared. The rate of acid-catalyzed hydrolysis was determined with the typical steroid derivatives. Convenient syntheses of 3β-hydroxy-4-androsten-17-one have also been described.

A tetrahydropyranyl function has been widely used for the purpose of protecting various hydroxyl groups. Despite of its high utility for the steroid chemistry the ether is generally obtained as a mixture of diastereoisomers. Recently, 4-methoxy-5,6-dihydro-2H-pyran has been devised to overcome this disadvantage.[3] The resulting ether is much less stable to acid than the tetrahydropyranyl ether. In 1972 Corey and his co-worker reported that dimethyl-*tert*-butylsilyl group might be used as an alternative to the tetrahydropyranyl group, being particularly advantageous in that it does not possess a chiral center, and also in that its derivatives are nicely crystalline and suitable for gas chromatography and mass spectral measurements.[4] In the previous papers the use of dimethyl-*tert*-butylsilyl chloride for the selective protection of dioxygenated steroid was demonstrated.[5] From the similar point of view Ogilvie, *et al.* have also proposed the utility of this reagent in the nucleoside chemistry.[6] The present paper deals with the basic studies and some applications of the silyl ethers in the field of steroids.

In order to obtain the more precise knowledge on the nature of the dimethyl-*tert*-butylsilyl ether, the derivatives of estrone, estradiol, 2-hydroxyestrone, testosterone, androsterone, isoandrosterone, 19-hydroxy-4-androstene-3,17-dione, 5α-androstane-3β,17β-diol, 5α-androstane-3α,17β-diol, 4-androstene-3β,17β-diol, cholesterol, and 4-cholesten-3β-ol were prepared by treatment with dimethyl-*tert*-butylsilyl chloride in dimethylformamide in the presence of imidazole.[4] The silyl ethers were all obtained in the crystalline state and almost quantitatively. Derivatization into the silyl ethers often allows an epimeric mixture to be separated each other by means of thin-layer (TLC) or column chromatography. For instance, it is somewhat difficult to separate epimeric 5α-androstane-3,17β-diols or their diacetates, but the chromatographic separation was readily attained when these C-3 epimers were transformed into the disilyl ethers.

The silyloxy linkage of the steroid derivatives resisted to cleavage with acetic acid to a certain extent, as compared with that of the prostaglandin derivatives[4] and hence the more acidic conditions, such as hydrochloric acid or trifluoroacetic acid in acetone, were required in some cases. The rate of acid-catalyzed hydrolysis was determined with the silyl ethers of estrone, dehydroisoandrosterone, and testosterone. As can be seen in Table I the reaction

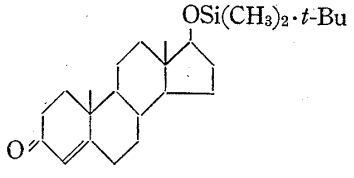
1) Part CI of "Studies on Steroids" by T. Nambara; Part C: T. Nambara, S. Ikegawa, and M. Kato, *Chem. Pharm. Bull.* (Tokyo), **23**, 2164 (1975).
2) Location: *Aobayama, Sendai.*
3) C.B. Reese, R. Saffhill, and J.E. Sulston, *Tetrahedron*, **26**, 1023 (1970).
4) E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
5) *a*) H. Hosoda, D.K. Fukushima, and J. Fishman, *J. Org. Chem.*, **38**, 4209 (1973); *b*) H. Hosoda and J. Fishman, *Chem. Commun.*, **1974**, 546; *c*) *Idem*, *J. Am. Chem. Soc.*, **96**, 7325 (1974).
6) K.K. Ogilvie, *Can. J. Chem.*, **51**, 3799 (1973); K.K. Ogilvie, K.L. Sadana, E.A. Thompson, M.A. Quilliam, and J.B. Westmore, *Tetrahedron Letters*, **1974**, 2861; K.K. Ogilvie, E.A. Thompson, M.A. Quilliam, and J.B. Westmore, *ibid.*, **1974**, 2865.

Table I. Acid-Catalyzed Hydrolysis of Steroid Dimethyl-*tert*-butylsilyl Ethers at 20° [a]

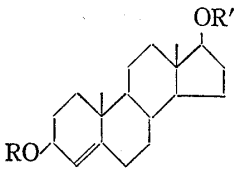
Steroid	$t^{1/2}$ (min)
Estrone	480
Dehydroisoandrosterone	6.5
Testosterone	110

a) One twentieth millimole each of steroid dimethyl-*tert*-butylsilyl ether was hydrolyzed with 5N HCl (200 μl) in acetone (20 ml), whereby pseudo-first-order kinetics were observed in all the cases.

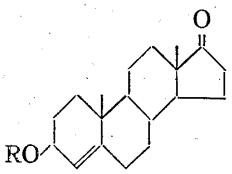
rate of dehydroisoandrosterone derivative is 17 times as fast as that of testosterone derivative. In addition, when 5α-androstane-3β,17β-diol bis(dimethyl-*tert*-butylsilyl) ether was hydrolyzed for 30 min under the same conditions, selective removal of the silyl group at C-3 took place to give the 17-monosilyl derivative in 72% yield. Furthermore, the 3α-silyloxy group of axial nature was found to be approximately 30 times stable as much as the 3β-equatorial. The steric factor, therefore, appears to be effective for hydrolysis of the silyloxy group. It is also to be noted that the silyl ether of phenol is more stable to acid than that of alcohol. On the other hand, the silyl ether is known to be stable to base under the usual conditions employed for saponification of the acetate.[4] Indeed, this was the case in the alcoholic ethers of steroid. In contrast the phenolic ether was susceptible to the basic conditions at room temperature.



1



2: R=H, R'=Si(CH$_3$)$_2$·*t*-Bu
3: R=Ac, R'=Si(CH$_3$)$_2$·*t*-Bu
4: R=Ac, R'=H
7: R=H, R'=H
8: R=Si(CH$_3$)$_2$·*t*-Bu, R'=H



5: R=Ac
6: R=H
9: R=Si(CH$_3$)$_2$·*t*-Bu

Chart 1

It was reported that the dimethyl-*tert*-butylsilyl ether was easily cleaved to the corresponding alcohol by treatment with tetra-*n*-butylammonium fluoride in tetrahydrofuran at 25°.[4] This procedure was found to be unsuitable for the α,β-unsaturated keto or phenolic steroids due to the formation of by-products, but applicable to the acid-unstable steroids having allylic alcohol. For example, 3β-hydroxy-4-androsten-17-one (**6**) could be synthesized much more conveniently than by the hitherto known methods. Reduction of testosterone dimethyl-*tert*-butylsilyl ether (**1**) with lithium tri(*tert*-butoxy)aluminum hydride afforded 4-androstene-3β,17β-diol 17-silyl ether (**2**), which on usual acetylation was led to the 3-acetate (**3**). Upon exposure to tetra-*n*-butylammonium fluoride in tetrahydrofuran, **3** underwent cleavage of the 17-silyloxy bond to afford 4-androstene-3β,17β-diol 3-monoacetate (**4**) in a fairly good yield. Subsequent oxidation with chromic anhydride-pyridine complex under the mild conditions provided 3β-acetoxy-4-androsten-17-one (**5**), which in turn was hydrolyzed with methanolic potassium hydroxide yielding the desired allylic alcohol (**6**).

Alternatively, preparation of **6** from 4-androstene-3β,17β-diol (**7**) by the more facile route involving selective silylation was undertaken. Reaction of **7** with a limited amount of dimethyl-*tert*-butylsilyl chloride in dimethylformamide in the presence of imidazole furnished 4-androstene-3β,17β-diol 3-monosilyl ether (**8**) in 74% yield. Oxidation with chromic anhydride-pyridine complex gave 3β-dimethyl-*tert*-butylsilyloxy-4-androsten-17-one (**9**), which on treatment with tetra-*n*-butylammonium fluoride in tetrahydrofuran was led to the desired

compound (**6**). It is evident that these two synthetic methods employing the readily available starting material are much more convenient than the known methods.[7,8]

It has proved that dimethyl-*tert*-butylsilyl chloride is promising as a derivatizing agent used for purification and identification in the biosynthetic studies as well as in the chemical synthesis of steroids, because of its favorable properties, *i.e.* the ease of silylation and desilylation under the mild conditions. In addition, the silyl ether was found to be advantageous for the use of a lantanide shift reagent in the nuclear magnetic resonance (NMR) spectral studies, and the results will be published elsewhere in the near future.

Experimental[9]

Gas Chromatography——The apparatus used was a Shimadzu Model GC-3BF gas chromatograph equipped with a hydrogen flame ionization detector and a "silanized" glass column (2 m×3 mm I.D.). The column was packed with 3% SE-30 on Shimalite W (60—80 mesh). The detector and flash heater were kept at 280°, while the column temperature was 250°. Nitrogen was used as carrier gas at a flow rate of 44 ml/min.

General Procedure for Preparation of Dimethyl-*tert*-butylsilyl Ether——To a solution of steroid (0.1 mmole) in dimethyl formamide (DMF) (2 ml) were added dimethyl-*tert*-butylsilyl chloride (1—3 mmole) and imidazole (3—5 mmole), and the solution was allowed to stand at room temperature for 2 hr. The reaction mixture was diluted with ether, washed with H_2O, and dried over anhydrous Na_2SO_4. The solvent and excess reagent were removed by evaporation under reduced pressure. The product was purified, if necessary, by preparative TLC, and recrystallized from MeOH.

Estrone Dimethyl-*tert*-butylsilyl Ether——Colorless needles. mp 172—173°. $[\alpha]_D^{22}$ +133.7° (c=0.10). *Anal.* Calcd. for $C_{24}H_{36}O_2Si$: C, 74.95; H, 9.44. Found: C, 74.72; H, 9.50.

Estradiol Bis(dimethyl-*tert*-butylsilyl) Ether——Colorless needles. mp 127—128°. $[\alpha]_D^{20}$ +32.1° (c=0.12). *Anal.* Calcd. for $C_{30}H_{52}O_2Si_2$: C, 71.94; H, 10.47. Found: C, 71.80; H, 10.41.

2-Hydroxyestrone Bis(dimethyl-*tert*-butylsilyl) Ether——Colorless needles. mp 172—174°. $[\alpha]_D^{14}$ +102.0° (c=0.10). *Anal.* Calcd. for $C_{30}H_{50}O_3Si_2$: C, 69.99; H, 9.79. Found: C, 70.24; H, 9.77.

Testosterone Dimethyl-*tert*-butylsilyl Ether (1)——Colorless plates. mp 139—140.5°. $[\alpha]_D^{22}$ +84.9° (c=0.11). *Anal.* Calcd. for $C_{25}H_{42}O_2Si$: C, 74.57; H, 10.51. Found: C, 74.88; H, 10.88.

Androsterone Dimethyl-*tert*-butylsilyl Ether——Colorless needles. mp 69—71°. $[\alpha]_D^{15}$ +58.2° (c=0.18). *Anal.* Calcd. for $C_{25}H_{44}O_2Si$: C, 74.20; H, 10.96. Found: C, 74.39; H, 11.05.

Isoandrosterone Dimethyl-*tert*-butylsilyl Ether——Colorless leaflets, mp 162—163°. $[\alpha]_D^{14}$ +71.0° (c=0.10). *Anal.* Calcd. for $C_{25}H_{44}O_2Si$: C, 74.20; H, 10.96. Found: C, 74.57; H, 11.06.

19-Dimethyl-*tert*-butylsilyloxy-4-androstene-3,17-dione——Colorless leaflets. mp 157—158°. $[\alpha]_D^{22}$ +182.0° (c=0.10). *Anal.* Calcd. for $C_{25}H_{40}O_3Si$: C, 72.07; H, 9.68. Found: C, 72.17; H, 9.86.

5α-Androstane-3β,17β-diol Bis(dimethyl-*tert*-butylsilyl) Ether——Colorless leaflets. mp 152—153.5°. $[\alpha]_D^{15}$ +19.6° (c=0.10). *Anal.* Calcd. for $C_{31}H_{60}O_2Si_2$: C, 71.47; H, 11.61. Found: C, 71.40; H, 11.59.

5α-Androstane-3α,17β-diol Bis(dimethyl-*tert*-butylsilyl) Ether——Colorless plates. mp 124—125°. $[\alpha]_D^{15}$ +18.9° (c=0.10). *Anal.* Calcd. for $C_{31}H_{60}O_2Si_2$: C, 71.47; H, 11.61. Found: C, 71.09; H, 11.50.

4-Androstene-3β,17β-diol Bis(dimethyl-*tert*-butylsilyl) Ether——Colorless needles. mp 102—104°. $[\alpha]_D^{22}$ +31.3° (c=0.11). *Anal.* Calcd. for $C_{31}H_{58}O_2Si$: C, 71.75; H, 11.27. Found: C, 71.78; H, 11.30.

Cholesterol Dimethyl-*tert*-butylsilyl Ether——Colorless plates. mp 153.5—155°. $[\alpha]_D^{15}$ −31.6° (c=0.13). *Anal.* Calcd. for $C_{33}H_{60}OSi$: C, 79.13; H, 12.07. Found: C, 78.97; H, 12.26.

4-Cholesten-3β-yl Dimethyl-*tert*-butylsilyl Ether——Colorless needles. mp 111.5—112.5°. $[\alpha]_D^{22}$ +30.0° (c=0.15). *Anal.* Calcd. for $C_{33}H_{60}OSi$: C, 79.12; H, 12.07. Found: C, 79.53; H, 11.96.

4-Androstene-3β,17β-diol 17-Dimethyl-*tert*-butylsilyl Ether (2)——To a solution of LiAl(*tert*-BuO)$_3$H freshly prepared from $LiAlH_4$ (0.34 g) and *tert*-BuOH (3 ml) in dry ether (35 ml) was added testosterone dimethyl-*tert*-butylsilyl ether (**1**) (300 mg) in dry ether and the solution was stirred at room temperature for 30 min. After addition of moistened AcOEt and 25% Rochelle salt solution, the mixture was extracted

7) *a*) L. Ruzicka, W. Fischer, and J. Meyer, *Helv. Chim. Acta*, **18**, 1483 (1935); *b*) B. Löken and M. Gut, *Steroids*, **5**, Suppl. I, 39 (1965); *c*) P.D. Klimstra and F.B. Colton, *Steroids*, **10**, 411 (1967).

8) P.Z. Thomas and R.I. Dorfman, *J. Biol. Chem.*, **239**, 766 (1964); M.G. Ward, J.C. Orr, and L.L. Engel, *J. Org. Chem.*, **30**, 1421 (1965).

9) Melting points were measured on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$. Infrared (IR) spectra were obtained on a JASCO Model IR-S spectrometer. NMR spectra were run on a Hitachi H-60 spectrometer at 60 MHz using tetramethylsilane (TMS) as an internal standard. Abbreviation used s=singlet, t=triplet, and m=multiplet. For preparative TLC Silica gel H (E. Merck AG, Darmstadt) was used as an adsorbent.

with AcOEt. The organic phase was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was recrystallized from MeOH to give **2** (190 mg) as colorless leaflets. mp 140—141°. $[\alpha]_D^{22}$ +59.9° (c=0.10). NMR ($CDCl_3$) δ: 0 (6H, s, Si-CH_3), 0.71 (3H, s, 18-CH_3), 0.87 (9H, s, *tert*-C_4H_9), 1.05 (3H, s, 19-CH_3), 3.51 (1H, t, J=7 Hz, 17α-H), 4.10 (1H, m, 3α-H), 5.24 (1H, s, 4-H). *Anal.* Calcd. for $C_{25}H_{44}O_2Si$: C, 74.20; H, 10.96. Found: C, 74.40; H, 11.22.

3β-Acetoxy-4-androsten-17β-yl Dimethyl-*tert*-butylsilyl Ether (3)——Treatment of **2** (190 mg) with Ac_2O and pyridine, followed by recrystallization from MeOH gave **3** (190 mg) as colorless needles. mp 137—138°. $[\alpha]_D^{17}$ +27.0° (c=0.15). NMR ($CDCl_3$) δ: 0 (6H, s, Si-CH_3), 0.71 (3H, s, 18-CH_3), 0.87 (9H, s, *tert*-C_4H_9), 1.05 (3H, s, 19-CH_3), 2.04 (3H, s, 3β-OCOCH_3), 3.54 (1H, t, J=7 Hz, 17α-H), 5.21 (1H, s, 4-H), 5.03—5.40 (1H, m, 3α-H). *Anal.* Calcd. for $C_{27}H_{46}O_3Si$: C, 72.60; H, 10.38. Found: C, 72.62; H, 10.38.

4-Androstene-3β,17β-diol 3-Acetate (4)——To a solution of **3** (132 mg) in tetrahydrofuran (THF) (4 ml) was added (n-$C_4H_9)_4NF$ (2 g) and the solution was allowed to stand at room temperature for 10 hr. The reaction mixture was diluted with AcOEt, washed with H_2O, and dried over anhydrous Na_2SO_4. After usual work-up the crude product was purified by preparative TLC using hexane–AcOEt (5: 1) as developing solvent. Recrystallization of the eluate from hexane gave **4** (91 mg) as colorless needles. mp 98—99°. $[\alpha]_D^{15}$ 0° (c=0.15). NMR ($CDCl_3$) δ: 0.77 (3H, s, 18-CH_3), 1.08 (3H, s, 19-CH_3), 2.04 (3H, s, 3β-OCOCH_3), 3.62 (1H, t, J=8 Hz, 17α-H), 5.20 (1H, s, 4-H), 5.02—5.41 (1H, m, 3α-H). *Anal.* Calcd. for $C_{21}H_{32}O_3 \cdot 1/2H_2O$: C, 73.86; H, 9.74. Found: C, 74.01; H, 9.98.

3β-Acetoxy-4-androsten-17-one (5)——To a solution of **4** (50 mg) in pyridine (2 ml) was added CrO_3–pyridine complex (1: 10 w/v) (1 ml) and allowed to stand at room temperature for 5 hr. The reaction mixture was diluted with ether, washed with 10% AcOH, 5% $NaHCO_3$, and H_2O, successively and dried over anhydrous Na_2SO_4. After usual work-up the crude product was purified by preparative TLC using hexane–AcOEt (4: 1) as developing solvent. Recrystallization from MeOH gave **5** (46 mg) as colorless needles. mp 105—106° (lit. mp 124—126.5°).[7b] NMR ($CDCl_3$) δ: 0.87 (3H, s, 18-CH_3), 1.07 (3H, s, 19-CH_3), 2.03 (3H, s, 3β-OCOCH_3), 5.22 (1H, s, 4-H), 5.02—5.41 (1H, m, 3α-H).

4-Androstene-3β,17β-diol 3-Dimethyl-*tert*-butylsilyl Ether (8)——To a solution of **7** (42 mg) in DMF (1 ml) were added dimethyl-*tert*-butylsilyl chloride (150 mg) and imidazole (160 mg) and the solution was allowed to stand at room temperature for 30 min. The reaction mixture was diluted with ether, washed with H_2O, and dried over anhydrous Na_2SO_4. After usual work-up the crude product was purified by preparative TLC using hexane–AcOEt (5: 1) as developing solvent. Recrystallization of the eluate from MeOH gave **8** (43 mg) as colorless needles. mp 145—147°. $[\alpha]_D^{15}$ +18.5° (c=0.14). NMR ($CDCl_3$) δ: 0.08 (6H, s, Si–CH_3), 0.76 (3H, s, 18-CH_3), 0.90 (9H, s, *tert*-C_4H_9), 1.05 (3H, s, 19-CH_3), 3.62 (1H, t, J=8 Hz, 17α-H), 4.14 (1H, m, 3α-H), 5.19 (1H, s, 4-H). *Anal.* Calcd. for $C_{25}H_{44}O_2Si \cdot 1/2\ H_2O$: C, 72.58; H, 10.96. Found: C, 72.96; H, 11.18.

3β-Dimethyl-*tert*-butylsilyloxy-4-androsten-17-one (9)——To a solution of **8** (40 mg) in pyridine (1.2 ml) was added CrO_3–pyridine complex (1: 10 w/v) (1 ml) and allowed to stand at room temperature for 20 hr. The reaction mixture was diluted with ether, washed with 10% AcOH, 5% $NaHCO_3$, and H_2O, and dried over anhydrous Na_2SO_4. After usual work-up the crude product was purified by preparative TLC using hexane–AcOEt (5: 1) as developing solvent. Recrystallization of the eluate from MeOH gave **9** (32 mg) as colorless plates. mp 122—123.5°. $[\alpha]_D^{17}$ +71.2° (c=0.16). NMR ($CDCl_3$) δ: 0.08 (6H, s, Si–CH_3), 0.87 (3H, s, 18-CH_3), 0.91 (9H, s, *tert*-C_4H_9), 1.06 (3H, s, 19-CH_3), 4.18 (1H, m, 3α-H), 5.21 (1H, s, 4-H). *Anal.* Calcd. for $C_{25}H_{42}O_2Si$: C, 74.56; H, 10.51. Found: C, 74.36; H, 10.71.

3β-Hydroxy-4-androsten-17-one (6)——i) Saponification of **5**: The 3-acetate (**5**) (40 mg) was dissolved in 5% methanolic KOH (2 ml) and allowed to stand at room temperature for 1 hr. The reaction mixture was diluted with AcOEt, washed with H_2O, and dried over anhydrous Na_2SO_4. After usual work-up the crude product was recrystallized from hexane to give **6** (30 mg) as colorless prisms. mp 135—136° (lit. mp 135—137°).[7b] NMR ($CDCl_3$) δ: 0.87 (3H, s, 18-CH_3), 1.07 (3H, s, 19-CH_3), 4.12 (1H, m, 3α-H), 5.28 (1H, s, 4-H).

ii) Desilylation of **9**: The 3-silyl ether (**9**) (16 mg) was treated with (n-$C_4H_9)_4NF$ in the same manner as described in **4**. Purification of the crystalline product by preparative TLC, followed by recrystallization from hexane gave **6** (11 mg) as colorless prisms. mp 137—138°. Mixed melting point on admixture with the sample obtained in i) showed no depression and IR spectra of two samples were entirely identical.

Selective Desilylation of 5α-Androstane-3β,17β-diol Bis(dimethyl-*tert*-butylsilyl) Ether——To a solution of 5α-androstane-3β,17β-diol bis(dimethyl-*tert*-butylsilyl) ether (20 mg) in acetone (20 ml) was added 5N HCl (200 μl) and allowed to stand at room temperature for 30 min. The reaction mixture was diluted with AcOEt and washed with 5% $NaHCO_3$, H_2O, and dried over anhydrous Na_2SO_4. After usual work-up the crude product was purified by preparative TLC using hexane–AcOEt (5: 1) as developing solvent. Recrystallization of the eluate from MeOH gave 5α-androstane-3β,17β-diol 17-dimethyl-*tert*-butylsilyl ether (11 mg) as colorless plates. mp 161—163°. $[\alpha]_D^{14}$ +15.3° (c=0.21). *Anal.* Calcd. for $C_{25}H_{44}O_2Si$: C, 73.83; H, 11.40. Found: C, 73.79; H, 10.90.

Determination of Hydrolysis Rate of Steroid Dimethyl-*tert*-butylsilyl Ethers——To each solution of 0.05 mmole of dimethyl-*tert*-butylsilyl ether of estrone, testosterone or dehydroisoandrosterone[5a] in acetone

(20 ml) was added 5N HCl (200 μl) and the solution was stirred at 20°. One ml aliquot of the reaction mixture was taken up and transferred to a test-tube. To this solution were added 5% $NaHCO_3$ (0.5 ml) and cholesterol (500 μg), an internal standard, dissolved in AcOEt (1 ml) and extracted with AcOEt (3 ml). The organic phase was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue was redissolved in AcOEt (0.1 ml) and injected into the gas chromatograph. For the quantitative analysis of the samples, calibration curves were constructed by plotting the ratio of peak area of each silyl ether to cholesterol against the weight ratio of these two, whereby good linearity was observed. Relative retention times of the silyl ethers to cholesterol were 0.63 for estrone, 0.78 for testosterone, and 0.58 for dehydroisoandrosterone. The hydrolysis half-times ($t^{1/2}$) of estrone, testosterone, and dehydroisoandrosterone silyl ethers were found to be 480, 110, and 6.5 min, respectively.

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