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Regiospecific Deoxygenation of the Dihydroxyacetone Moiety at C-17 of Corticoid Steroids with Iodotrimethylsilane[1)]

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Reaction of the corticoids **1**—**6** with iodotrimethylsilane in MeCN produced the regiospecifically deoxygenated products, 21-hydroxy-20-ketones **7**—**11**, in moderate to high yields. On the other hand, employment of $CHCl_3$ as a solvent resulted in lower yields of the 21-ketols **7** and **8**, accompanied by increased production of the 20-ketones **12** and **13**. The 21-ketol **7** was efficiently converted into the 20-ketone **12**, while the 17α-hydroxy isomer **14** was recovered unchanged. Rapid and quantitative conversion of the 21-iodo-20-ketone **17** into the 20-ketone **12** by this iodosilane treatment suggests that the conversion of the ketol **7** into the ketone **12** probably occurs *via* the iodide **17**.

Keywords——corticoid; dihydroxyacetone moiety; 17α-methoxy-21-hydroxy-20-keto steroid; 21-hydroxy-20-keto steroid; iodotrimethylsilane; regiospecific deoxygenation

In recent years organosilicon reagents have been used extensively in organic syntheses. Iodotrimethylsilane, one such reagent developed independently in Olah's[2)] and Jung's[3)] laboratories, has gained wide use in the cleavage of esters,[2,3a)] lactones,[4)] ethers,[3b,4)] ketals,[5)] and carbamates,[6)] as well as in the conversion of alcohols to iodides.[7)] Olah *et al.*[8)] have shown the usefulness of the iodosilane in the deoxygenation of sufoxides to sulfides. Ho[9)] has also reported the use of the iodosilane in the transformation of α-ketols to ketones. Very recently, it has also been used in the reductive removal of the *tert*-hydroxy group of α,β-unsaturated γ-*tert*-hydroxyketones.[10)]

During the course of our studies[11)] on the construction of a corticoid side-chain, we were interested in exploring the reaction of the side-chain with iodotrimethylsilane. We now report a highly regiospecific and efficient deoxygenation occurring at the C-17 position of the dihydroxyacetone moiety on iodosilane treatment.

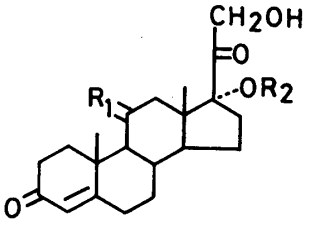
Results and Discussion

Reaction of corticoids having a dihydroxyacetone or 17-*O*-methyl ether moiety at the C-17 position with iodotrimethylsilane was initially explored. When a series of corticoids **2**—**4** was treated with 6—20 mol eq of the iodosilane in MeCN at room temperature, regiospecific deoxygenation occurred at C-17 to give the corresponding 21-hydroxy-20-ketones **7**—**9** in moderate to high yields; the dideoxygenated ketones **12** and **13** were also isolated as minor products (Table I). The 17α-methoxy compound **1**[11)] and synthetic corticoids **5** and **6** with a 1,4-dien-3-one system were also regiospecifically converted into the corresponding ketols **7**, **10**, and **11** in good yields, though the corresponding 20-ketones could not be isolated. The yields of the ketols **8** and **10** from the 11-ketones **3** and **5** were relatively low. This would be due to the increased production of the corresponding 20-ketone **13** or the formation of a complex mixture of polar by-products.[12)] Employment of a large excess of the iodosilane in the deoxygenation reaction caused increased production of the 20-ketone, resulting in lower

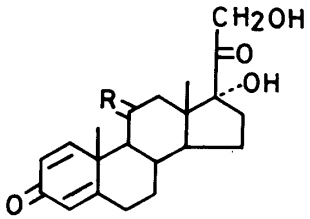
TABLE I. Deoxygenation of Corticoid Side-Chain with Iodotrimethylsilane

Substrate	Conditions			Product (Isolated yield (%))	
	Me_3SiI (mol eq)	Solvent	Time (h)	21-Hydroxy-20-ketone	20-Ketone
1	6	MeCN	3	**7** (90)	0
1	6	MeCN	24	**7** (85)	0
1	6	$CHCl_3$	24	**7** (30)	**12** (36)
2	6	MeCN	3	**7** (72)	**12** (5)
2	20	MeCN	3	**7** (52)	**12** (24)
2	6	$CHCl_3$	3	**7** (48)	**12** (38)
2	20	$CHCl_3$	3	**7** (10)	**12** (53)
3	8	MeCN	3	**8** (46)	**13** (27)
3	8	$CHCl_3$	3	**8** (10)	**13** (84)
4	6	MeCN	3	**9** (71)	0
5	4	MeCN	4	**10** (54)	0
6	4	MeCN	1	**11** (80)	0

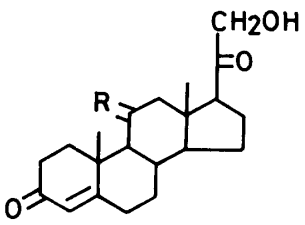
Reactions were carried out at room temperature.



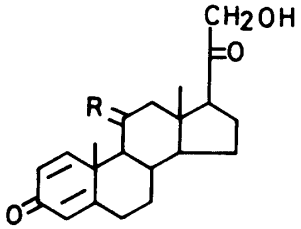
1 ; R_1 = 5α-H, R_2 = CH_3
2 ; R_1 = 5α-H, R_2 = H
3 ; R_1 = O, R_2 = H
4 ; R_1 = 5α-OH, R_2 = H



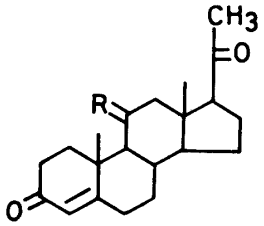
5 ; R = O
6 ; R = 5α-OH



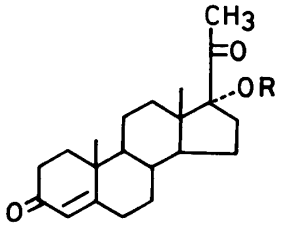
7 ; R = 5α-H
8 ; R = O
9 ; R = 5α-OH



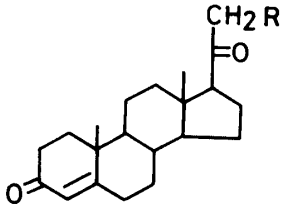
10 ; R = O
11 ; R = 5α-OH



12 ; R = 5α-H
13 ; R = O



14 ; R = H
15 ; R = CH_3



16 ; R = OSO_2Me
17 ; R = I

Chart 1

yields of the ketols.

On the other hand, employment of $CHCl_3$ as a solvent instead of MeCN in the reaction of compounds **1**—**3** caused lower yields of the ketols **7** and **8** than those given above, accompanied by markedly increased production of the 20-ketones **12** and **13** (Table I). Thus,

TABLE II. Deoxygenation of the 21- and 17α-Ketols with Iodotrimethylsilane

Substrate	Conditions			Product **12** Isolated yield (%)
	Me_3SiI (mol eq)	Solvent	Time (h)	
7	8	MeCN	4	65
7	20	MeCN	4	78
7	8	$CHCl_3$	2	59
7	20	$CHCl_3$	2	90
14	20	$CHCl_3$	4	0
15	20	$CHCl_3$	4	0

Reactions were carried out at room temperature.

the reaction conditions using $CHCl_3$ were found to be suitable for the dideoxygenation. However, the reaction of compounds **4** and **5** in $CHCl_3$ gave a complex mixture of products and the deoxygenated products could not be isolated in pure states.

It should be noted that the formation of the 21-deoxygenated derivatives, 17-hydroxy-20-ketones, could not be detected in every experiment. Moreover, when the 21-ketol **7**, 17α-ketol **14**, and 17α-methoxy-20-ketone **15** were treated with the iodosilane as above, the ketol **7** was converted into the 20-ketone **12** in good yield, while no reaction was observed with either the 17-ketol **14** or the methoxide **15** (Table II). The results indicate that the 20-ketones **12** and **13** are formed *via* the 21-hydroxy-20-ketones **7** and **8**.

It has previously been suggested that the transformation of α-ketols to ketones proceeds *via* the α-iodo ketones.[9] We therefore investigated the reaction of 21-iodo-20-ketone **17** with the iodosilane. The 21-iodide **17** was synthesized by reaction of the 21-ketol **7** with mesyl chloride, followed by treatment with NaI. When the iodide **17** was treated with 1.1 mol eq of the iodosilane in MeCN or $CHCl_3$ at room temperature for 10 min, the 20-ketone **12** was quantitatively obtained, supporting the idea that the deoxygenation of the 21-ketol **7** proceeds *via* the iodide **17**.[13]

Since the 17α-hydroxy and 17α-methoxy groups are selectively removed from the dihydroxyacetone side-chain derivatives by the iodosilane, while those of the 17α-hydroxy- and 17α-methoxy-20-ketones are not, the presence of a free 21-hydroxy group is evidently necessary for the hydrogenolysis of the C(17)-O bond. However, the exact reaction mechanism is not clear. Treatment of the dihydroxyacetone moiety with acid, usually hydrochloric acid, can result in removal of the 17α-hydroxy group *via* Mattox rearrangement to give the 21-acetal or aldehyde.[14] If zinc–acetic acid is used, the 21-acetoxy-20-ketone is obtained directly in about 35% yield.[15] However, to our knowledge, the present result is the first direct and efficient deoxygenation of a corticoid side-chain to give a 21-hydroxy-20-ketone or a 20-ketone. Related studies are in progress.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with JEOL PMX 60 (60 MHz) spectrometer using tetramethylsilane as an internal standard. High-performance liquid chromatography (HPLC) was carried out on a Waters ALC/PGC 244 liquid chromatograph equipped with a U6K injector and a differential refractometer, in which a reversed-phase μ-Bondapak C_{18} column (30 × 0.8 i.d. cm) or Radialpak C_{18} column ((10 × 0.8 i.d. cm) × 2) was used as the stationary phase and $MeOH/H_2O$ as the mobile phase.

Reaction of Steroid with Iodotrimethylsilane (TMSI)——In the reaction, freshly distilled TMSI, MeCN (over CaH_2), and alcohol free $CHCl_3$ (over P_2O_5) were used. A solution of steroid (1 mmol) and TMSI in MeCN or $CHCl_3$ (50—250 ml) was allowed to stand at room temperature for an appropriate period. The volume of the solvent depends

on the solubility of the substrate. After this time, the reaction mixture was poured into 5% $Na_2S_2O_3$ solution (20 ml) and extracted with AcOEt (300 ml). The organic layer was washed with 5% $NaHCO_3$ solution and saturated NaCl solution and dried over Na_2SO_4. After evaporation of the solvent, the residue obtained was purified by crystallization, silica gel column chromatography, or HPLC.

21-Hydroxy-4-pregnene-3,20-dione (7)——The crude product (358 mg) obtained from 21-hydroxy-17α-methoxy-4-pregnene-3,20-dione (**1**) (6 mol eq of TMSI, 3 h, 50 ml of MeCN) was crystallized from acetone–hexane to give **7** (295 mg, 90%) as colorless needles; mp 135—137 °C (lit.[16] 141—142 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 4.18 (2H, s, 21-CH_2), 5.77 (1H, s, 4-H).

21-Hydroxy-4-pregnene-3,11,20-trione (8) and 4-Pregnene-3,11,20-trione (13)——The crude product (300 mg) obtained from 17α,21-dihydroxy-3,11,20-trione (**3**) (8 mol eq of TMSI, 3 h, 180 ml of MeCN) was subjected to silica gel column chromatography (hexane : AcOEt = 3 : 1, v/v). Crystallization of the less polar fraction from acetone gave **13** (86 mg, 27%) as colorless needles; mp 172—173 °C (lit.[17] 173—175 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.65 (3H, s, 18-CH_3), 1.42 (3H, s, 19-CH_3), 2.12 (3H, s, 21-CH_3), 5.73 (1H, s, 4-H). After further purification of the more polar fraction by HPLC (Radialpak C_{18}; MeOH : H_2O = 1 : 1, v/v, 1.5 ml/min; t_R = 7.2 min), **8** (157 mg, 46%) was obtained; mp 153—157 °C (acetone) (lit.[17] mp 174—180 °C, from MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, s, 18-CH_3), 1.40 (3H, s, 19-CH_3), 4.18 (2H, s, 21-CH_2), 5.73 (1H, s, 4-H).

11β,21-Dihydroxy-4-pregnene-3,20-dione (9)——The crude product (310 mg) produced from cortisol (**4**) (6 mol eq of TMSI, 3 h, 250 ml of MeCN) was subjected to silica gel column chromatography (hexane : AcOEt = 3 : 1, v/v) and then HPLC (μ-Bondapak C_{18}; MeOH : H_2O = 3 : 2, v/v, 2 ml/min; t_R = 18.8 min) to give a solid product, which was crystallized from MeOH to afford **9** (240 mg, 71%) as colorless needles; mp 178—182 °C (lit.[18] 179—182 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, s, 18-CH_3), 1.47 (3H, s, 19-CH_3), 4.15 (2H, s, 21-CH_2), 5.67 (1H, s, 4-H).

21-Hydroxy-1,4-pregnadiene-3,11,20-trione (10)——The residue (315 mg) produced from 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione (**5**) (4 mol eq, 4 h, 75 ml of MeCN) was purified by silica gel chromatography (hexane : AcOEt = 2 : 1, v/v) and HPLC (Radialpak C_{18}; MeOH : H_2O = 3 : 2, v/v, 2 ml/min; t_R = 20.8 min). Crystallization of the crude product from MeOH gave **10** (180 mg, 54%) as colorless needles; mp 202—215 °C (lit.[19] 200—220 °C). ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 0.67 (3H, s, 18-CH_3), 1.43 (3H, s, 19-CH_3), 3.93 (2H, s, 21-CH_2), 6.10 (1H, br s, 4-H), 6.18 (1H, dd, J = 10, 2 Hz, 2-H), 7.67 (1H, d, J = 10 Hz, 1-H).

11β,21-Dihydroxy-1,4-pregnadiene-3,20-dione (11)——The crude product (350 mg) obtained from 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (**6**) was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1, v/v) and HPLC (Radialpak C_{18}; MeOH : H_2O = 1 : 1, v/v, 1.5 ml/min; t_R = 31.0 min), then crystallized from acetone to give **11** (270 mg, 80%) as colorless prisms; mp 217—218 °C (lit.[20] 227.5—230.5 °C (dec.)). ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 0.96 (3H, s, 18-CH_3), 1.48 (3H, s, 19-CH_3), 4.18 (2H, s, 21-CH_2), 6.05 (1H, br s, 4-H), 6.28 (1H, dd, J = 10, 2 Hz, 2-H), 7.40 (1H, d, J = 10 Hz, 1-H).

4-Pregnene-3,20-dione (12)——a) The crude product (320 mg) obtained from 17α,21-dihydroxy-4-pregnene-3,20-dione (**2**) (20 mol eq of TMSI, 3 h, 50 ml of $CHCl_3$) was purified by silica gel column chromatography (hexane : AcOEt = 4 : 1, v/v). Crystallization of the less polar fraction from acetone–hexane afforded **12** (167 mg, 53%) as colorless needles; mp 117—118 °C (lit.[21] 120 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 2.12 (3H, s, 21-CH_3), 5.72 (1H, s, 4-H). Compound **7** (33 mg, 10%) was also obtained from the more polar fraction.

b) Crystallization of the crude product (350 mg) obtained from **7** (20 mol eq of TMSI, 2 h, 50 ml of $CHCl_3$) from hexane–AcOEt gave **12** (287 mg, 90%); mp 114—118 °C.

Compound 7 21-Mesylate (16)——Mesyl chloride (1.5 ml) was added to a solution of compound **7** (150 mg, 0.45 mmol) in dry pyridine (3 ml) under ice-cooling with stirring. The reaction mixture was stirred for 6 h[22] and then poured into ice-water (50 ml) and extracted with AcOEt. The organic layer was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was purified by silica gel column chromatography (hexane–AcOEt). The crude product was recrystallized from acetone to afford **16** (113 mg, 62%) as colorless prisms; mp 161—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 3.20 (3H, s, 21-OSO_2CH_3), 4.78 (2H, s, 21-CH_2), 5.73 (1H, s, 4-H). IR (KBr): 1730 and 1640 (C=O), 1610 (C=C), 1350 (SO_2) cm^{-1}. *Anal.* Calcd for $C_{22}H_{32}O_5S$: C, 64.68; H, 7.89; S, 7.85. Found: C, 64.90; H, 7.57; S, 7.98.

21-Iodo-4-pregnene-3,20-dione (17)——A solution of compound **16** (63 mg, 0.16 mmol) and NaI (80 mg, 0.55 mmol) in EtOH (6 ml) was heated under reflux for 1 h. The mixture was diluted with AcOEt (100 ml) and washed with $Na_2S_2O_3$, $NaHCO_3$, and NaCl solutions and dried (Na_2SO_4). After the usual work-up, the crude product (55 mg) obtained was purified by silica gel column chromatography (hexane–AcOEt) and crystallized from MeOH to yield **17** (40 mg, 58%) as colorless prisms; mp 93—95 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 3.83 (2H, s, 21-CH_2), 5.77 (1H, s, 4-H). IR (KBr): 1710 and 1660 (C=O), 1610 (C=C) cm^{-1}. *Anal.* Calcd for $C_{21}H_{29}IO_2$: C, 57.28; H, 6.64. Found: C, 57.33; H, 6.43.

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12) The formation of polar by-products was observed by thin-layer chromatographic analysis of the reaction mixture. However, they could not be isolated in pure states by silica gel column chromatography.
13) We could not obtain 17-iodo-21-hydroxy-20-ketone derivatives because of the difficulties of their synthesis. Therefore, it is not clear whether or not the regiospecific deoxygenation of the dihydroxyacetone moiety proceeds *via* the 17-iodides.
14) For a review see: E. P. Oliveto "Organic Reactions in Steroid Chemistry," Vol. II, ed. by J. Fried and J. A. Edwards, Van Nostrand Reinhold, New York, 1972, pp. 201—217.
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