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GEOMETRICAL ISOMERISM OF THE O-SUBSTITUTED OXIMES OF SOME KETO-STEROIDS

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Abstract—O-Benzyl- and/or O-iso-propyl-oximes of a number of 3-, 7- or 20-oxo-steroids and of some 3,20-dioxosteroids have been prepared. The products were characterized by their C,H,N-content and physical properties and studied by UV, ^{1}H- and ^{13}C-NMR spectroscopy. The ketoximes of 3-oxo-Δ^4-steroids were invariably found to consist of a mixture of two geometrical isomers, denominated *syn* and *anti*. In some cases both isomers could be obtained in a pure state by column-chromatography. Oximes of the 7-oxo-Δ^5-steroids were found to consist only of the *syn* isomer, whereas the 20-oximino compounds showed no isomerism.

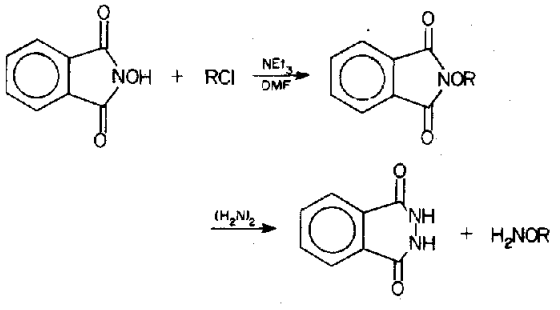
O-Substituted steroidal ketoximes are of recent interest owing to their biological activity.[1,2] O-Carboxymethyl oximes (e.g. 3 - beta - hydroxy - 17 - oxo - 5 - androsten - 7 - on - 7 - carboxymethyl oxime) bonded to proteins (e.g. bovine serum albumin, BSA) afford interesting steroid-containing antibodies.[3] Further, O-substituted oximes have been used as protecting groups of the 20-oxo-substituent during preparation of Δ^{16}-20-oxo-steroids.[4]

It has been reported,[5] that condensation of α,β-unsaturated keto-steroids with O-methylhydroxylamines, yielded a mixture of *syn* and *anti* geometrical isomeric O-methyl oximes, which could be separated by different physico-chemical procedures.[5,6] More recently,[7] a larger number of O-substituted 3-ketoximino steroids were separated into *syn* and *anti* isomers and studied by ^{1}H NMR. On the contrary, 7 - oxo - cholesterol - 3 - beta - acetate afforded only one 7-oximino derivative, to which a *syn* geometry was ascribed.[7]

In the present work we prepared a logical series of O-benzyloximes and O-iso-propyl oximes at different positions of the steroid skeleton and studied their geometrical isomerism by ^{1}H and ^{13}C NMR. The compounds examined are shown in Table 1.

RESULTS AND DISCUSSION

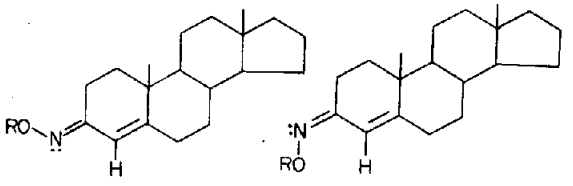
O-Substituted oximes were prepared by condensation of the keto-steroids with the appropriate O-substituted hydroxylamine. The O-substituted hydroxylamines employed for condensations were obtained[8,9] from N-hydroxyphtalimide:



We improved this procedure[9] by precipitating the O-substituted hydroxylamines as chlorohydrates, thus increasing the yields to 80–81%. The chlorohydrates were employed directly in the condensations with keto-steroids (Procedure A). An alternative condensation procedure (B) was also tried, using ethyl alcohol and sodium acetate as reaction medium; but this proved less practical owing to the limited solubility of the steroid component in ethanol.

The rate of the condensation was dependent on the position of the oxo-groups: 3-oxo groups are more easily substituted than the 7-, 12-, 17- or 20-oxo groups. Thus selective substitution at position 3 of the 3,17- or 3,20-dioxosteroids is perfectly possible by an appropriate choice of the reaction conditions. Oxo groups conjugated with skeletal double bonds are more easily substituted than their saturated counterparts. Kinetic measurements made in order to reinforce these qualitative observations will be reported elsewhere.

3-Oximino-steroids. Two components were identified by tlc in the rough condensation products obtained from reactions between O-substituted hydroxylamines and 3-oxo-Δ^4-steroids. In several cases the two components could be separated by column chromatography. As shown in Table 2, they afforded different m.ps and specific rotations, but practically the same analytical figures, thus being isomers. The position and intensity of their UV absorption maximum is also slightly but significantly different (Table 3). By analogy with the unsubstituted and O-methyl oximes[5] the *anti*-geometry (**23**) was attributed to the isomers which afford their electronic absorption maximum at shorter wavelength and higher intensity.



23 *(anti)* **24** *(syn)*

^{1}H NMR spectra proved especially valuable for studying isomerism[5–7,10–12] of 3-oximino-Δ^4- (and Δ^1)-steroids. As shown in Table 4, the olefinic proton bound to C-4 is shifted in one of the isomers about 0.65 ppm downfield from the other, which appears at nearly the same chemical shift as in the parent 3-oxo compound. (Testosterone 1 is shown in Table 4; this shift is remarkably constant in a number of 3-oxo-Δ^4-steroids (see Ref. 13). As these chemical shift values are practically not influenced by the nature of the oxime substituent R, the difference between the isomers should be ascribed to the anisotropic deshielding effect of the oxime O atom. This conclusion implies that the *syn*-geometry belongs to the isomer having the more deshielded olefinic proton at C-4. This assumption checks the above mentioned interpretation of the electronic spectra. A less pronounced but still significant difference appears between the chemical shifts of the 19-Me protons in the two isomers. ^{1}H NMR spectroscopy was also found appropriate for quantitative determination of the isomeric composition of these oximes: separate signals could be observed for the olefinic proton at C-4 as well as for the 19-Me group both in spectra of artificial mixtures of the two isomers and in spectra of the rough condensation products. The olefinic signals were used to evaluate the composition of the condensation product: it may be seen (Table 4) that the *anti*-isomer is slightly preferred.

^{13}C NMR spectra proved highly informative about geometrical isomerism in 3-oximino-Δ^4-steroids (Table 5). Using literature data[14,15] on related steroids, all carbons in our compounds could be easily identified. The influence of isomerism is shown by the chemical shifts of many carbons, but is especially evident on those situated near to the oximino-group (positions 1–5). It is interesting to note that the relative shieldings are inverse to those found for the olefinic proton and as one would expect from rudimentary theoretical consideration of the anisotropy of the oximino-oxygen atom: carbons appear more shielded when close to the oximino O atom (4, 5, 6 in the *syn*-isomer and 1,2 in the *anti*-isomer) than in their

Table 1. Steroidal ketones and oximes examined

Compd. no.	IUPAC name
1	17beta-hydroxy-4-androsten-3-one
2	17beta-hydroxy-4-androsten-3-O-benzyloxime
3	4-androsten-17beta-yl acetate-3-O-benzyloxime
4	17-oxo-4-androsten-3-O-benzyloxime
5	cholest-4-en-3-O-benzyloxime
6	17beta-hydroxy-4-androsten-3-O-isopropyloxime
7	17beta-hydroxy-4-estren-3-O-benzyloxime
8	(25d)-spirost-4-en-3-O-benzyloxime
9	cholest-5-en-3-O-benzyloxime
10	5-androsten-7-one-3beta-yl acetate, 17beta-yl benzoate
11	5-androsten-3beta-yl acetate, 17beta-yl benzoate-7-O-benzyloxime
12	cholest-5-en-3beta-yl acetate-7-O-benzyloxime
13	5alpha-cholestan-3beta-yl acetate-7-O-benzyloxime
14	17alpha-hydroxy-3,3-ethylenedioxy-20-oxo-pregna-5,9(11)dien-21-yl acetate
15	17alpha-hydroxy-3,3-ethylenedioxy-pregna-5,9(11)dien-21-yl acetate-20-O-benzyloxime
16	3,3-ethylenedioxy-pregna-5,9(11),16(17)-trien-21-yl acetate-20-O-benzyloxime
17	pregna-5,16-dien-3beta-yl acetate-20-O-benzyloxime
18	3,20-dioxo-17alpha-hydroxy-4-pregnen-21-yl acetate
19	17alpha-hydroxy-4-pregnen-21-yl acetate-3,20-di-O-benzyloxime
20	17alpha-hydroxy-pregna-4,9(11)-dien-21-yl acetate-3,20-di-O-isopropyloxime
21	pregna-4,16(17)-dien-21-yl acetate-3,20-di-O-benzyloxime
22	17beta-hydroxy-5alpha-androstan-3-O-benzyloxime

Table 2. Synthesis and characterization of the steroidal ketoximes

Compd. no.	Isomer	Procedure[a]	Yield %	m. p. °C	Analysis, % calcd. C	calcd. H	calcd. N	found C	found H	found N	Rotatory power[b]
2	syn	A	80	149-51	79.34	8.98	3.56	78.72	8.27	3.55	c
	anti			87-90				78.75	9.31	3.99	c
3	anti	B	40	106-9	77.10	8.54	3.22	77.40	8.70	3.34	c
4	syn/anti	A	70	99-103	79.79	8.49	3.92	79.75	8.85	3.62	+198°
5	syn/anti	A	85	92-4	83.10	10.85	2.86	83.03	10.93	2.92	+147°
6	syn	A	78	172-5	75.59	11.24	4.01	76.07	10.94	4.26	+221°
	anti			129				75.80	11.30	4.27	+146°
7	syn	A	85	108-10	79.17	8.76	3.71	79.13	9.48	3.51	+185°
	anti			102-3				78.84	9.41	3.61	+76.7°
8	syn/anti	A	80	151-3	79.10	9.15	2.71	79.10	9.88	2.69	+56.3°
9	d	A	60	99-104	83.37	10.48	2.86	83.04	10.85	3.21	+4.65°
12	syn	A	55	88-92	78.35	10.41	2.56	79.00	10.50	2.64	-145.5°
13	d	A	65	95-6	78.63	10.10	2.56	79.42	10.38	2.13	c
15	d	A	80	152-4	71.65	7.75	2.61	72.02	8.15	2.56	c
16	d	a	a	126-30	74.25	7.54	2.71	74.12	8.31	2.89	+62.5°
17	d	A	60	94-7	78.29	8.93	3.02	77.65	8.93	3.32	c
19	syn/anti	A	50	112-7	74.21	7.74	4.67	73.76	8.29	4.84	c
20	d	A	70	134-7	69.54	8.85	5.61	69.50	9.24	5.99	+95.2°
22	d	B	80	173-5	79.00	9.43	3.55	79.18	10.00	3.65	+51.9°

[a]See Experimental: [b]α_D in chloroforme solution at 20°C; [c]not measured; [d]no isomerism found.

Table 3. Electronic absorption maxima of the geometrical isomers of some steroid ketoximes in ethanol

Compound no.	syn wavelength (nm)	syn ε_{max} l/mole.cm	anti wavelength (nm)	anti ε_{max} l/mole.cm
2	257	18,000	252	25,900
6	257	17,600	250	26,200
7	257	14,000	250	23,000

Table 4. ^{1}H NMR Spectra of the 3-oximino-Δ^4 (and Δ^5)-steroids

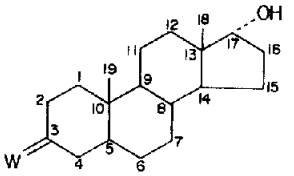
Compd. no.	Isomer	Content[a] %	Characteristic proton shifts[b] 4 =C-H	17 CH-OH[c]	18 -CH$_3$	19 -CH$_3$	other groups
1	-	-	5.78	3.70	0.80	1.20	-
2	syn	35	6.45	3.65	0.78	1.10	5.08[d]
	anti	65	5.80			1.05	5.10[d]
3	anti	100	5.80	4.85	0.81	1.05	5.10[d] 2.03[e]
4	syn	30	6.55	-	0.90	1.11	5.15[d]
	anti	70	5.88			1.08	
5	syn	44	6.48	-	0.69	0.91	5.12[d]
	anti	56	5.80				
6	syn	46	6.45	3.65	0.78	1.10	f
	anti	54	5.85	3.69		1.08	g
7	syn	-	6.50	3.65	0.78	-	5.08[d]
	anti		5.88				5.09[d]
8	syn	50	6.45	-	0.80	h	5.10[d]
	anti	50	5.80				
9	-	-	5.45[i]	-	0.69	0.90	5.10[d]

[a], determined on the rough product of the oximation reaction, using the 4-CH signals; not determined for compound 7; [b], refer to the proton shown in thick character; [c], J_{16-17} = 8.2 - 8.3 Hz; [d], 3-Ph-CH$_2$-O-N= group; [e], 17-OCOCH$_3$ group; [f], $(CH_3)_2$CH-O-N= chemical shifts: CH at 4.33, $(CH_3)_2$ at 1.23 and 1.25 ppm (diastereotopic magnetic nonequivalence), J= 6.0 Hz; [g], $(CH_3)_2$CH-O-N= chemical shifts: CH at 4.33, $(CH_3)_2$ at 1.24 ppm, J= 6.2 Hz; [h], not identified; [i], 5- =CH- group;

Table 5. ^{13}C-Chemical shifts (δ, ppm) of some O-substituted oximes of keto-steroids

Comp. no.	Isomer	Carbon no. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	-	36.0	34.2	200.1	123.9	171.9	33.2	31.9	36.0	54.4	39.0	20.8	36.8	43.2	51.0	23.6	30.6	81.6	11.2	17.6	-	-	-	-	-
22	-	35.6	27.9[a]	159.0	28.2[a]	45.6	28.8[a]	31.5	36.4	54.4	38.6	20.8	36.9	43.2	51.2	23.5	30.6	81.5	11.2	11.6	75.0	137.5	127.4[b]	127.7[b]	127.0
2	syn	36.4	24.8	159.2	111.0	153.5	33.0	32.2	36.0	54.4	39.1	20.8	36.7	43.0	50.9	23.4	30.5	81.5	11.1	18.2	75.5	138.0	127.9[a]	128.2[a]	127.5
	anti	35.0	19.8	156.9	117.9	155.7	32.7	32.0	36.2	54.4	38.2	21.2	36.9	43.2	51.2	23.6	30.7	81.9	11.1	18.0	75.9	138.6	128.4[a]	128.8[a]	128.1
6	syn	36.6	25.0	159.0	111.6	153.1	33.0	32.3	36.0	54.5	39.2	20.9	36.8	43.2	51.2	23.6	30.6	81.7	11.1	18.2	74.7	21.9	-	-	-
	anti	35.2	18.2	156.0	118.2	154.9	32.8	32.2	36.2	54.5	38.2	21.2	37.0	43.2	51.2	23.6	30.8	81.5	11.1	18.0	75.0	22.0	-	-	-

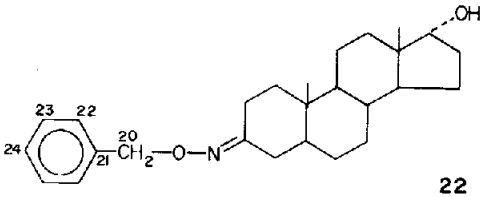
[a, b] within the group of signals marked with the same letter, assignments are not certain;



1; W: O=

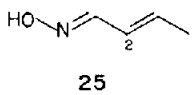
2; W: $PhCH_2-O-N=$

6; W: $(^{21}CH_3)_2{}^{20}CH-O-N=$



22

counterpart. Other factors should influence these chemical shifts, as carbon-3, bearing the oximino-substituent also shows its chemical shift dependent on this geometrical isomerism. Similar upfield shifts of the ^{13}C-signals of carbons oriented *syn* to the oxime O atom were observed[16] for simple aliphatic ketoximes and interpreted as steric compression shifts. The interpretation given[17] to the ^{13}C NMR spectra of some unsaturated aldoximes and ketoximes seems to be to some extent contradictory to that favoured in Ref. 16 and in the present paper. Thus the olefinic carbon in position 2 was found to resonate at higher field (119.8) in compound **25** than in **26** (124.8 ppm). However, the same authors[17] observed an unusually high-field resonance signal (8.3 ppm) for carbon 4 in compound **27**, thus reinforcing our interpretation.



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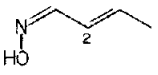

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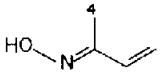

27

No isomerism was detected either by TLC or ^1H-NMR in 3-oximino steroids without the $\Delta^{4(5)}$ double bond, conjugated to the C=N (saturated (**22**) or $\Delta^{5(6)}$-compounds (**9**) were tested), although this isomerism should principally exist.

7-Oximino-steroids. One single compound was isolated from condensation between 7-oxo-steroids and O-benzylhydroxylamine. The ^1H NMR spectra of this group of substances (Table 6) indicate a *syn*-geometry for the $\Delta^{5(6)}$-derivatives **11** and **12**, if the chemical shifts of the olefinic proton at C-6 are compared to that in the parent 7-oxo compound, **10**. This finding is in accord with data reported in the literature.[7]

20-Oximino-steroids. No isomerism could be detected in the ^1H NMR spectra of these compounds (Table 7), whether their structure contains a conjugated double bond ($\Delta^{16(17)}$), or not. This is not surprising, as this time the C=N bond is situated on a side chain with at least some possibility to rotate around the C-17–C-20 single bond; thus the position of the oximino O atom against the steroid skeleton and specifically against the olefinic proton at C-16 becomes less rigorously determined.

3,20-Di-oximino-steroids. Geometrical isomerism of the 3-oximino group in these compounds can be easily followed qualitatively as well as quantitatively, when a Δ^4-unsaturation is present. On the other hand, no isomerism is detected at the 20-oximino substituent (Table 8), thus confirming previous observations on mono-oximino derivatives.

EXPERIMENTAL

Preparation of the O-substituted ketoximes

Procedure A. 1 g oxo-steroid compound was dissolved in 25 ml dry pyridine. The appropriate O-substituted hydroxylamine chlorohydrate was added in moderate excess (molar ratios up to 2:1) and the mixture stirred at room temp. until a clear soln resulted. The progress of the condensation was followed by tlc on silica gel containing 13% gyps, eluting with a 4:1 mixture of benzene-EtOAc. When no more starting oxo-steroid appeared on the tlc plate, the mixture was poured into ice-water and the resulting ppt filtered off. In some cases it was necessary to keep the mixture several days in a refrigerator in order to obtain a crystalline product.

Procedure B. 1 g oxo-steroid (e.g. testosterone-17-acetate) was dissolved in 40 ml EtOH and 0.48 g NaOAc and 0.77 g O-benzylhydroxylamine chlorohydrate was added successively. The mixture was stirred at room temp. until a clear soln resulted, then left overnight. It was then poured into ice-water and kept in a refrigerator until the product crystallized. After filtration and recrystallization from MeOH, a 40% yield of **3** was obtained.

Purification of the O-substituted ketoximes and separation of their geometrical isomers. Chromatography on a 60 cm glass-column filled with silica gel (Merck, 70–230 mesh) was used to separate the geometrical isomers of the O-substituted ketoximes **2**, **3**, **6** and **7**. Elution was performed with a 3:1 mixture of benzene–EtOAc. The eluted components were purified by evaporation to dryness and recrystallizations from MeOH until constant m.p. and rotatory power were obtained.

Syntheses

17 *α*,21 - *Dihydroxy* - *pregna* - 5,9(11) - *dien* - 21 - *acetate* - 3 - *ethyleneketal* - 20 - *one*, (**14**). 16 g 17 *α*,21 - dihydroxy - pregna - 4,9(11) - dien - 3,20 - dione - 21 - acetate were suspended in a mixture of 1200 ml benzene and 200 ml ethylene glycol, in a flask equipped with an azeotropic moisture separator. About 0.2 g *p*-toluenesulphonic acid was added and the mixture refluxed until no more water collected in the separator (10 hr). The content of

Table 6. ^1H NMR Spectra (δ, ppm) of the 7-benzyloximino-Δ^5-steroids

Compound	3 $-C\underline{H}-O$	6 $=C\underline{H}-$	17 $-C\underline{H}-O$	18 $-C\underline{H}_3$	19 $-C\underline{H}_3$
10[a]	4.9	5.78	5.00	0.96	1.25
11[a,b]	4.9	6.61	5.00	0.96	1.14
12[a,b]	4.7	6.55	-	0.68	1.10
13[a,b]	4.6	-	-	0.64	0.90

[a] $C\underline{H}_3-COO-$ in position 3 appears at 2.03 ± 0.04 ppm; [b] $=N-O-C\underline{H}_2Ph$ appears at 5.05 ± 0.02 ppm;

Table 7. ^{1}H NMR Spectra (δ, ppm) of the 20-benzyloximino-steroids

Compound	6 =C$\underline{H}$-	11 $\underline{H}$-C=	16 =C-$\underline{H}$	18 -C$\underline{H}_3$	19 -C$\underline{H}_3$	21 -C$\underline{H}_2$-
$\underline{14}$[a,b]	5.25 - 5.75		-	0.65	1.20	5.11[c] 4.87[c]
$\underline{15}$[a,d,e]	5.30 - 5.60		-	0.56	1.20	4.80
$\underline{16}$[a,f,g]	5.30 - 5.65		6.00- -6.25	0.88	1.22	4.93
$\underline{17}$[h,i]	5.25- -5.50	-	5.90- -6.10	0.93	1.05	1.95[j]

[a] -O-(C$\underline{H}_2$)$_2$-O- at 3.95 ppm; [b] C$\underline{H}_3$COO- at 2.18 ppm; [c] diastereotopic magnetic nonequivalence, J_{AB}= 18.0 Hz; [d] =N-O-C$\underline{H}_2$-Ph at 5.14 ppm; [e] C$\underline{H}_3$COO- at 2.00 ppm; [f] =N-O-C$\underline{H}_2$-Ph at 5.18 ppm; [g] C$\underline{H}_3$COO- at 2.04 ppm; [h] C$\underline{H}_3$COO- at 2.02 ppm; [i] =N-O-C$\underline{H}_2$-Ph at 5.12 ppm; [j] 21-C$\underline{H}_3$ group;

Table 8. ^{1}H NMR Spectra (δ, ppm) of the 3,20-di-oximino-steroids

Compound	Isomer	4 =C$\underline{H}$[a]-	11 =C$\underline{H}$-	16 =C$\underline{H}$-	18 -C$\underline{H}_3$	19 -C$\underline{H}_3$	21 -C$\underline{H}_2$-
$\underline{18}$	-	5.85	-	-	0.73	1.21	4.98[j] 5.20[j]
$\underline{19}$[b,c,d]	syn (30%)	6.55	-	-	0.60	1.10 -------	4.84
	anti (70%)	5.84	-	-		1.05	
$\underline{20}$[e,f,g]	syn (33%)	6.48	5.40- -5.65	-	0.65	1.20	4.83
	anti (67%)	5.87					
$\underline{21}$[b,h,i]	syn (30%)	6.55	-	6.05- -6.20	0.93	1.12 --------- 1.08	4.98
	anti (70%)	5.87					

[a] measured on rough synthetic products; isomeric compositions are included within parantheses; [b] =N-O-C$\underline{H}_2$-Ph in position 3 appears at 5.15 ppm; [c] =N-O-C$\underline{H}_2$-Ph in position 20 appears at 5.18 ppm; [d] C$\underline{H}_3$COO- at 2.02 ppm; [e] =N-O-C$\underline{H}$(CH$_3$)$_2$ in position 3 and 20 at 4.1 - 4.8 ppm; [f] =N-O-CH(C$\underline{H}_3$)$_2$ in position 3 at 1.25, in position 20 at 1.22 ppm, $J_{CH - CH_3}$ = 6.2 Hz; [g] C$\underline{H}_3$COO- at 2.08 ppm; [h] =N-O-C$\underline{H}_2$-Ph in position 20 affords two signals at 5.22 and 5.28 ppm; [i] C$\underline{H}_3$COO- affords two signals at 2.02 and 2.05 ppm; [j] diastereotopic magnetic nonequivalence, J_{AB}= 18.0 Hz;

the flask was then washed with $NaHCO_3$ aq, then with water and evaporated to obtain 13 g (70%) of **14**, m.p. 243–5°.

21 - *Hydroxy* - 5,9(11),16(17) - *pregnatrien* - 21 - *acetate* - 3 - *ethyleneketal* - 20 - O - *benzyloxime*, (**16**). A soln of 2 g (about 4 mmoles of **15**, in 50 ml dry pyridine was mixed in a flask cooled to −20°, with 3 ml (1.8 g, 15 mmoles) $SOCl_2$ diluted with 10 ml pyridine. After cooling for 2 hr, the mixture was poured into excess water. It was extracted with benzene and the solvent distilled. The residue was taken up with MeOH and the solvent evaporated. After a second dissolution in MeOH, followed by slow evaporation, 1.3 g of crystalline **16** resulted.

Spectra. Electronic spectra were recorded with a Specord Carl Zeiss Jena double beam instrument. All NMR spectra were recorded with a Bruker WP-60 FT-NMR spectrometer using a 14.1 kG magnet. For ^{1}H-measurements about 5% solns in $CDCl_3$ were used in standard 5 mm o.d. sample tubes. Proton chemical

shifts were related to internal TMS and considered accurate within ±0.01 ppm. Samples for ^{13}C-measurements were prepared by solving 0.5 g of steroid compound in 2 ml of $CDCl_3$, using standard 10 mm sample tubes. ^{13}C-Chemical shifts were also related to internal TMS and considered true within ±0.1 ppm.

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