N-1-TRIMETHYLSILYL DERIVATIVES OF ERGOT ALKALOIDS

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N-1-Trimethylsilyl derivatives of five different suitably protected parent ergot (clavine) alkaloids (agroclavine **1a**, elymoclavine **2a**, lysergol **3a**, lysergene **4a**, and 9,10-dihydrolysergol **5a**) were prepared in 47–94% yields by refluxing the (protected) parent compounds with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide in acetonitrile under nitrogen atmosphere.
Key words: Ergot alkaloids; Clavines; Trimethylsilyl derivatives; *N*-Glycosylation.

The reason for continued research activity in ergot alkaloid field is the broad spectrum of pharmacological effects[1–3] exhibited by these natural compounds, their derivatives and analogues. Most of therapeutically used drugs of this kind are semisynthetic derivatives. Many of them contain an alkylated nitrogen at position 1. The substitution at this site strongly influences binding parameters of resulting compounds to serotonin receptors[4–6].

Alkyl halides or tosylates were usually used as the *N*-alkylating agents in ergot alkaloids; $NaNH_2$ in liquid ammonia[7], NaOH, KOH or NaH served for the production of indolyl anion[8–11].

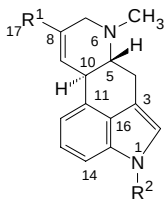
No *N*-acylation or glycosylation was achieved by this approach[12,13]. The alternative strategy, inspired by nucleotide chemistry[14,15], involves the use of *N*-silylated bases as the reactive intermediates. We present here various methods for the preparation of trimethylsilyl (TMS) derivatives of (suitably protected) clavine alkaloids (agroclavine **1a**, elymoclavine **2a**, lysergol **3a**, lysergene **4a**, and 9,10-dihydrolysergol **5a**), to be used as synthons for the construction of *N*-acylated or *N*-glycosylated ergot alkaloids.

The application of described procedure[16] (heating the base with 5–10-fold excess of hexamethyldisilazane to 160 °C in N_2 atmosphere, catalyzed by ammonium sulfate) to agroclavine **1a** produced no new compounds after one day; the alkaloid remained undissolved but only slightly decomposed. Addition of 5–10% of dry DMF to the mixture brought **1a** into solution and after 2–3 days of reflux gave **1c** in 40–50% yield. Catalysis by chlorotrimethylsilane moderately improved the yields but few days reaction time was still necessary. Some alkaloids, e.g. lysergene **4a**, decomposed significantly

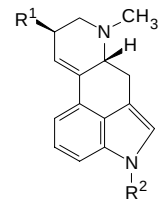
under these conditions. Also removing of last traces of DMF from the final product was rather complicated.

We have seeked alternative methods giving better yield in shorter time. It was found that *N*-TMS derivatives of investigated alkaloids could be obtained in high yield (60–90%) by short reflux (20–30 min) under nitrogen of their acetonitrile solutions with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide. Although susceptible to hydrolysis, these compounds are sufficiently stable on TLC (silica gel, $CHCl_3$–MeOH 9 : 1, visualisation by Ehrlich reagent) even in the presence of methanol. They were also spectroscopically characterized by ^1H and ^{13}C NMR (Tables I–III).

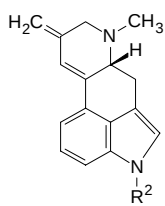
The substitution at N-1 causes a marked downfield shift (0.078–0.143 ppm) of H-14 and a slight upfield shift of H-2. However, the later is sufficient to produce separated signals needed for quantification. These H-2 signals differ in multiplicity (dd with the parent compounds, d with the TMS derivatives). The effects of TMS group on the neighbour carbons causes downfield and more pronounced shifts (C-2: 4.5–5.2 ppm,



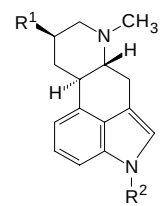
	R^1	R^2
1a	CH_3	H
1c	CH_3	$Si(CH_3)_3$
2a	CH_2OH	H
2b	CH_2OAc	H
2c	CH_2OAc	$Si(CH_3)_3$



	R^1	R^2
3a	CH_2OH	H
3b	CH_2OAc	H
3c	CH_2OAc	$Si(CH_3)_3$



4a $R^2 = H$
4c $R^2 = Si(CH_3)_3$



	R^1	R^2
5a	CH_2OH	H
5b	CH_2OAc	H
5c	CH_2OAc	$Si(CH_3)_3$

C-14: 2.0 ppm, C-15: 4.5 ppm, C-16: 3.5–3.6 ppm). No significant changes in coupling constants were observed in respective pairs parent compound – TMS derivative (Table II).

EXPERIMENTAL

Apparatus and Chemicals

NMR spectra were measured on a Varian VXR-400 spectrometer (399.95 MHz for ^{1}H, 100.58 MHz for ^{13}C) in $CDCl_3$ at 25 °C. Carbon signal multiplicity was determined by APT (Attached Proton Test), the assignment is based on COSY, delayed-COSY, and HETCOR experiments performed using the manufacturer's software and on the analysis of proton-coupled ^{13}C NMR spectra. Letters *a* and *e* (Tables I, II) denote axial and equatorial protons, *u* and *d* mean upfield and downfield resonating nonequivalent methylene protons.

TABLE I
Proton chemical shifts of compounds **1–5** in $CDCl_3$ (399.95 MHz, 25 °C, ppm, δ-scale)

Proton	**1a**[a]	**1c**	**2b**[b]	**2c**	**3b**	**3c**	**4a**	**4c**	**5b**	**5c**
2	6.899	6.865	6.830	6.876	6.902	6.877	6.938	6.903	6.886	6.871
4*a*	2.773	2.773	2.784	2.789	2.705	2.670	2.767	2.750	2.714	2.688
4*e*	3.320	3.332	3.308	3.344	3.537	3.521	3.519	3.512	3.434	3.428
5	2.513	2.527	2.580	2.574	3.156	3.122	3.623	3.292	2.175	2.152
7*a*	3.242	2.930	2.996	3.002	2.314	2.288	3.505	3.504	2.027	2.011
7*e*	3.920	3.257	3.404	3.416	3.092	3.070	3.224	3.222	3.104	3.088
8	–	–	–	–	3.058	3.036	–	–	2.314	2.311
9*a*	6.169	6.179	6.519	6.539	6.333	6.303	6.976	6.961	1.217	1.208
9*e*	–	–	–	–	–	–	–	–	2.686	2.690
10	3.738	3.738	3.803	3.802	–	–	–	–	3.008	2.990
12	6.976	7.032	6.944	7.020	[c]	7.295	7.261	7.274	6.935	6.958
13	7.154	7.161	7.133	7.166	[c]	7.168	7.203	7.190	7.183	7.172
14	7.154	7.261	7.133	7.276	[c]	7.168	7.239	7.317	7.183	7.288
17*d*	1.769	1.783	4.643	4.657	4.151	4.136	5.068	5.065	4.131	4.123
17*u*	–	–	4.555	4.573	4.078	4.066	4.964	4.960	4.000	3.997
NH	8.059	–	8.642	–	8.137	–	7.950	–	8.195	–
NCH_3	2.491	2.499	2.508	2.522	2.596	2.572	2.588	2.580	2.507	2.499
OAc	–	–	2.072	2.090	2.118	2.105	–	–	2.113	2.105
$(CH_3)_3Si$	–	0.526	–	0.528	–	0.525	–	0.538	–	0.533

[a] Ref.[18]; [b] good agreement with ref.[19], [c] overlapped signals 7.16–7.22.

TABLE II
Proton–proton coupling constants (in Hz) of compounds **1–5** in $CDCl_3$ (399.95 MHz, 25 °C)

H_i,H_j	**1a**[a]	**1c**	**2b**[b]	**2c**	**3b**	**3c**	**4a**[c]	**4c**	**5b**	**5c**
NH,2	1.9	–	1.9	–	2.0	–	2.0	–	2.0	–
2,4*a*	1.8	1.8	1.7	1.9	1.8	1.8	1.9	2.0	1.8	1.8
2,4*e*	0.8	0.6	–	–	–	–	0.5	≠0[d]	–	–
4*a*,4*e*	14.4	14.4	14.4	14.4	14.5	14.7	14.6	14.7	14.7	14.7
4*a*,5	11.6	11.5	11.6	11.7	11.4	11.5	11.4	11.4	11.1	11.1
4*e*,5	4.1	4.0	4.0	4.0	5.5	5.5	5.9	5.6	4.3	4.4
4*e*,9	0.8	0.7	–	–	–	–	≠0	≠0	–	–
5,8	–	–	–	–	3.3	[e]	–	–	–	–
5,9	–	–	–	–	2.1	[e]	2.0	2.0	–	–
5,10	9.3	9.3	9.3	9.1	–	–	–	–	9.7	9.5
7*a*,7*e*	16.2	16.2	16.4	16.3	11.9	12.5	13.2	13.3	11.3	11.3
7*a*,8	–	–	–	–	12.1	12.5	–	–	11.4	11.3
7*a*,9*a*	1.9	1.9	1.0	1.0	–	–	≠0	≠0	–	–
7*a*,10	2.4	2.5	–	–	–	–	–	–	–	–
7*e*,8	–	–	2.5	2.1	5.2	[e]	–	–	3.8	4.0
7*e*,9*e*	2.3	2.3	2.4	2.5	1.3	[e]	≠0	≠0	2.2	2.1
7*e*,10	4.0	3.9	4.2	4.2	–	–	–	–	–	–
7*a*,17*d*	1.1	≠0	0.8	≠0	–	–	≠0	≠0	–	–
7*a*,17*u*	1.1	≠0	1.0	≠0	–	–	≠0	≠0	–	–
7*e*,17*d*	≠0	≠0	≠0	≠0	–	–	1.8	1.8	–	–
7*e*,17*u*	≠0	≠0	≠0	≠0	–	–	1.8	1.8	–	–
8,9*a*	–	–	–	–	1.9	[e]	–	–	12.4	12.4
8,9*e*	–	–	–	–	–	–	–	–	3.8	[e]
8,17*d*	–	–	–	–	5.7	5.6	–	–	5.5	5.7
8,17*u*	–	–	–	–	7.3	7.3	–	–	7.3	7.2
9*a*,9*e*	–	–	–	–	–	–	–	–	12.5	12.5
9*a*,10	2.3	2.3	[e]	[e]	–	–	–	–	12.4	12.4
9*a*,17*d*	2.1	2.1	1.2	≠0	≠0	≠0	≠0	≠0	–	–
9*a*,17*u*	2.1	2.1	1.2	≠0	≠0	≠0	≠0	≠0	–	–
10,12	1.2	1.4	[e]	[e]	–	–	–	–	[e]	[e]
10,14	1.2	0.8	[e]	[e]	–	–	–	–	[e]	[e]
12,13	7.9	8.2	[f]	8.3	[f]	[f]	8.0	8.0	[f]	8.2
12,14	1.5	0.9	[f]	1.4	[f]	[f]	1.8	0.9	[f]	1.2
13,14	7.7	7.1	[f]	7.2	[f]	[f]	6.8	7.3	[f]	7.2
17*d*,17*u*	–	–	12.2	12.4	10.8	10.8	1.1	1.1	11.0	11.0

[a] Ref.[18]; [b] qualitative agreement with ref.[19]; [c] ref.[17]; [d] non-vanishing constant detected by long range COSY; [e] not determined; [f] second order multiplet, not evaluated.

Ergot alkaloids **1a–3a**, and **5a** were kindly donated by Galena Pharmaceuticals, Opava, Czech Republic. Acetates **2b**, **3b** and **5b** were prepared by acetylation with Ac_2O/Py (r.t., overnight) and purified by flash chromatography (silica gel, CH_2Cl_2–MeOH 93 : 7) affording **2b**, **3b** or **5b** in approximately 90% yield. Compound **4a** was prepared from **2a** according to the published procedure[17].

General Procedure for Prepration of *N*-1-Trimethylsilyl Derivatives of Ergot Alkaloids

Agroclavine (**1a**; 240 mg, 1 mmol) was dissolved in dry CH_3CN (20 ml) by a short reflux under nitrogen, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (280 μl, 1.5 mmol) was added and reflux continued for 25 min. The solvent was removed, dry toluene was added (two times) and evaporated. The derivative **1c** was formed in 71% yield (determined by NMR). Analogously **2c**, **3c**, **4c**, and **5c** were prepared (yield 92, 94, 76, and 47%, respectively); 60 min reflux was needed for **5c**. Reaction times longer that 1 h decrease the yields of TMS derivatives.

TABLE III
Carbon-13 chemical shifts of compounds **1–5** in $CDCl_3$ (100.58 MHz, 25 °C, ppm, δ-scale)

Carbon	**1a**[a]	**1c**	2b[a]	**2c**	**3b**	**3c**	**4a**	**4c**	**5b**	**5c**
2	117.85	123.07	118.13	123.27	118.23	122.78	118.39	122.85	117.74	122.58
3	112.16	114.37	111.54	114.10	110.92	112.92	111.09	113.11	111.77	113.82
4	26.69	26.80	26.49	26.80	27.22	27.31	27.10	27.12	26.95	27.07
5	63.85	63.82	63.49	63.64	63.23	63.16	62.45	62.37	67.13	67.17
7	60.63	60.73	56.81	57.18	56.72	56.74	58.81	58.77	60.49	60.55
8	132.25	132.28	131.05	131.53	35.93	35.95	140.62	140.57	40.33	40.43
9	119.41	119.41	124.86	124.98	120.44	120.25	121.84	121.60	30.74	30.84
10	40.95	41.07	40.57	41.01	136.31	136.41	136.36	136.45	35.51	35.58
11	132.42	132.80	131.19	131.70	128.21	128.41	127.96	128.22	133.03	133.36
12	112.62	113.13	112.41	113.05	112.14	112.50	112.61	112.90	113.06	113.47
13	122.84	122.50	122.70	122.51	123.22	123.44	123.36	123.71	123.00	123.07
14	108.51	110.49	108.81	110.73	109.51	111.47	109.82	111.81	108.56	110.55
15	133.54	137.99	133.49	138.01	133.92	138.37	133.95	138.41	133.28	137.73
16	126.33	129.82	126.19	129.77	126.17	129.64	126.45	129.94	126.12	129.58
17	20.83	20.88	66.34	66.48	66.26	66.28	111.02	110.97	67.25	67.28
NCH_3	40.85	40.97	40.59	40.98	43.90	43.90	43.02	42.90	43.26	43.31
$CH_3\mathbf{C}O$	–	–	170.88	170.89	171.14	171.13	–	–	171.12	171.12
$\mathbf{C}H_3CO$	–	–	20.84	20.95	20.93	20.94	–	–	20.91	20.93
$(CH_3)_3Si$	–	–0.03	–	–0.05	–	–0.05	–	–0.01	–	–0.04

[a] Good agreement with ref.[19].

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