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SEMISYNTHETIC DIMERS OF ANTIPARKINSONIC ERGOT ALKALOIDS

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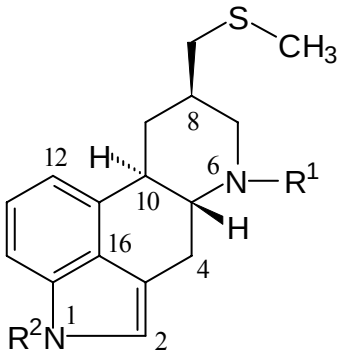
Abstract - 1,1-Linked dimers of semisynthetic ergoline alkaloids with antiparkinsonic activity were prepared in 60 - 63% yield from the parent compounds (pergolide, terguride) by action of α,ω-dihalogenalkanes in DMSO/KOH. *N*-1-ω-Halogenalkyl pergolide and terguride precursors were used for the synthesis of non-symmetric dimers. *N*-6 Alkylation was achieved (yield 18 - 28%) using 1,6-dihalogenohexane in DMF/K_2CO_3.

Many semisynthetic drugs having ergoline skeleton can be found among pharmacologically active agents.[1-3] Pergolide (8β-methylthiomethyl-6-propylergoline, **1**) is used for the treatment of Parkinson´s disease and number of hyperprolactinemia-characterized diseases.[3] It was introduced in 1989 by Eli Lilly Co. (Permax®, pergolide mesylate) and it is a constituent of other formulations (e.g., Celance, Parkotil, Pharken) produced[4] by Eli Lilly (USA) and Galena Pharm. Co. (Czech Republic). Its efficacy in this aspect is related to the postsynaptic stimulation of central dopaminergic receptors. Terguride (**2**) (6-methyl-8α-diethylcarbamoylaminoergoline, Mysalfon®, Galena Pharm. Co., Czech Rep.) is another therapeutically important antiparkinsonic drug.
Incorporation of several ligand moieties into one molecule might improve the binding to cell surface receptors.[5] Physiological effects of such compounds depend largely on the structure of multivalent molecule. The total effect is usually multiplicative, not additive. Combining two different ergot alkaloid moieties into one molecule *via* appropriate linker could bring new, entirely unexpected physiological effects.

2,2-Dimers of ergot alkaloids were obtained by $BF_3.Et_2O$/AcOH treatment of ergolines.[6] 1,1-Dimer of agroclavine-I, mixed dimer of agroclavine-I and epoxyagroclavine-I, and 1,1-bis-(6,8-dimethyl-8,9-epoxy,5a,10)ergoline were isolated from *Penicillium sizovae*.[7,8] 17-Spirooxadimer of lysergene was produced by oxidative biotransformation of lysergene.[9] However, none among these compounds has sufficient flexibility to achieve multivalency effect.

Various linkage design philosophies of these pluripotent molecules could expose different parts of the ergoline skeleton what is important for the specific interactions. Indolic moiety is required for the interaction with serotonine receptors, the exposition of rings C and D is necessary for the interaction with dopamine receptors.

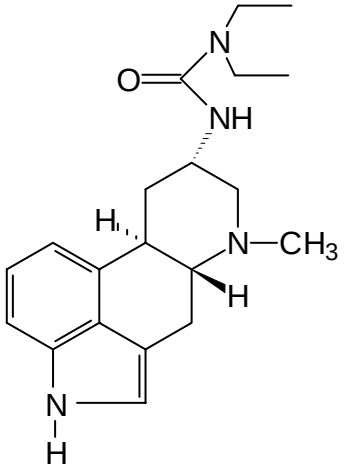
This paper describes synthesis of various pergolide dimers and a heterodimer of pergolide with terguride.



1 $R^1 = -CH_2CH_2CH_3$, $R^2 = H$

1a $R^1 = H$, $R^2 = H$

3 $R^1 = -CH_2CH_2CH_3$, $R^2 = -(CH_2)_6I$



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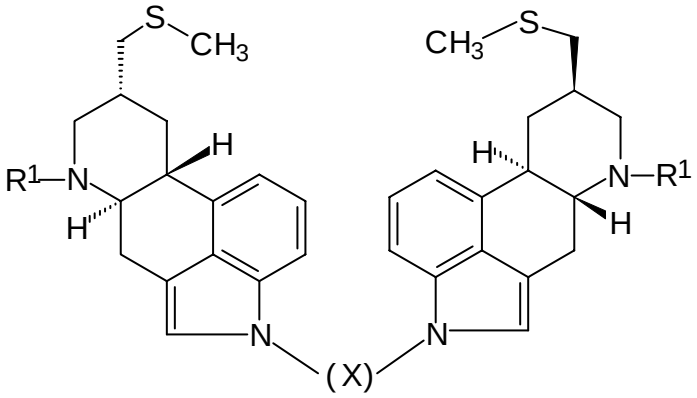
RESULTS AND DISCUSSION

Pergolide molecule (**1**) contains two reactive sites for dimerization (oligomerization), e.g., indolic nitrogen (N-1) and piperidine-type of nitrogen (N-6). There would be naturally many other places for substitution but these would change profoundly the overall molecular structure and its interaction with respective receptors could be completely changed or abolished.

Phase transfer catalysis is used mostly for industrial alkaloid N-1 methylation.[10] Some N-1-alkyl derivatives of agroclavine and festuclavine was prepared by alkylation by primary alkyl halogenides in liquid NH_3 in the presence of sodium.[11]

Bifunctional alkyl bromides (e.g., 1,6-dibromohexane) were used for alkylation of **1** under phase transfer conditions (*t*-butylammonium hydrogen sulfate/NaOH/CH_2Cl_2) but only small amount of inseparable product mixture was formed. No reaction was observed in DMF or DMSO when NaH

was used as base, however, with powdered KOH[12] fast product formation was observed in DMSO with bifunctional bromides. 1,6-Dibromohexane and *p*-bisbromomethylbenzene[13] gave excellent yields of the respective dimers (**4, 5**) within short reaction time (0.5 – 2 h). Aryl bromides did not give any reaction probably because of low reactivity. This method demonstrates feasibility of N-1 dimerization and oligomerization with polyfunctional bromo-spacers.



4 X = $-(CH_2)_6-$
R^1 = $-CH_2CH_2CH_3$

5 X = $-CH_2-C_6H_4-CH_2-$
R^1 = $-CH_2CH_2CH_3$

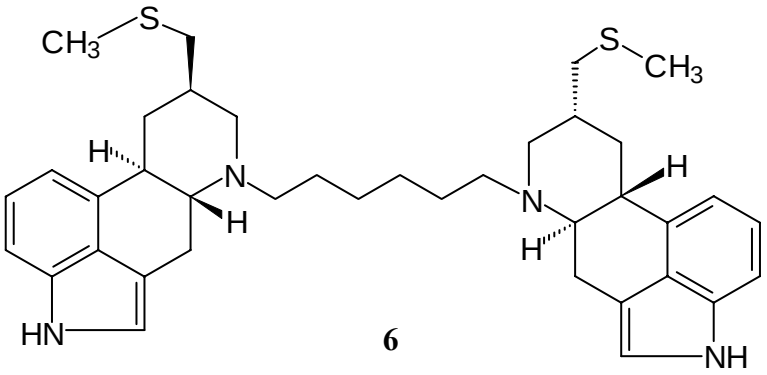
9 X = $-(CH_2)_6-$
R^1 = H

By the analogous method also pergolide with activated spacer at N-1, e.g., 1-(6'-iodohexyl)-6-propyl-8β-(methylthiomethyl)ergoline (**3**), was prepared. Here, a large excess of 1,6-diiodohexane was used. As a side product smaller amount of dimer (**4**) was also formed. Analogous reaction is feasible also with 1,6-dibromohexane[14] giving higher yield of the respective bromo derivative. In the case of iodide yields are lower than with bromide due to easy iodine elimination, but the iodide was chosen to achieve better reactivity for further coupling with less reactive N-6 of **1a**.

By an analogous method also two different alkaloids were coupled into one molecule (heterodimer). Terguride (**2**) was converted into *N*-1-ω-bromohexyl derivative[14] and this was reacted with pergolide (**1**) under above conditions yielding corresponding heterodimer (**8**). Such methodology enables combination of different ergot pharmacophors into one molecule, which could create new substances with interesting pharmacological activity.

As another target for the coupling N-6 was chosen. *nor*-Alkaloids lacking substituent at *N*-6 (methyl in the natural ergot alkaloids) can be prepared by von Braun reaction using bromocyan.[1] Direct substitution of N-6 (**1a**) with bifunctional alkyl bromides (toluene, reflux) was not feasible.

Quarternization of the N-6, which is used during pergolide production[4] with propyl iodide, was not feasible e.g, with 1,6-diiodohexane as well. We have tried reductive amination of bifunctional aldehyde (glutaraldehyde) with **2** under conditions used for industrial production of **1** from **1a**.[1]



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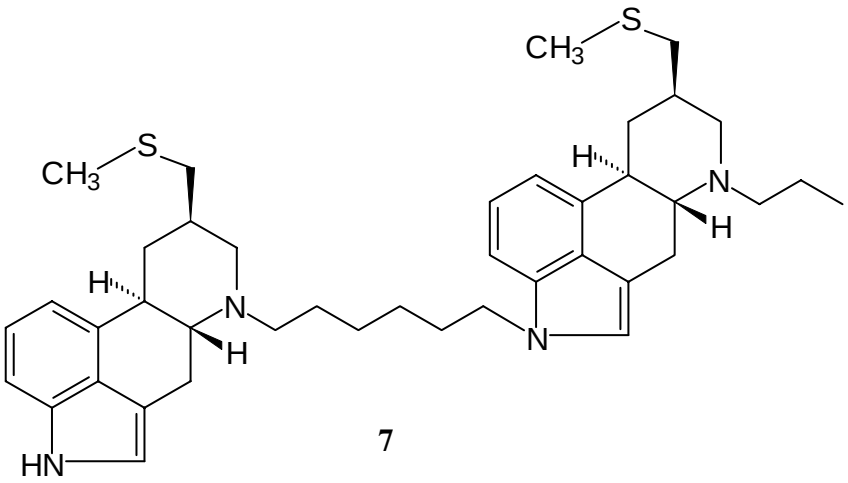

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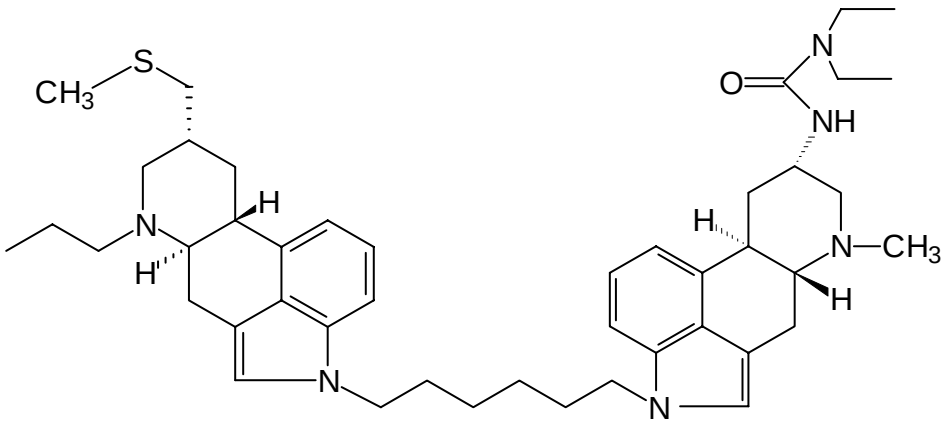

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These conditions (method A) afforded lower yield of desired product **6**. Also smaller amount of partially substituted glutaraldehyde, e.g., 6-(5'-carbonylpentyl)-8β-(methylthiomethyl)ergoline was formed. To achieve better yields an alternative method was tested using 1,6-diiodohexane with potassium carbonate in DMF (method B). Also here smaller amount of partially substituted 1,6-diiodohexane, e.g., 6-(6'-iodohexyl)-8β-(methylthiomethyl)ergoline was found. Both these side products could be used for further coupling employing the reactive groups in the molecules (aldehyde, iodide) and they could be prepared in larger yield simply using an excess of bifunctional

linkers as in the case of **3**. Dimer (**6**) has an interesting structural feature mimicking two pergolide molecules connected through each 3'-carbons.

Finally, combination of both linkage strategies, e.g., connecting N-1 and N-6 was attempted using pergolide derivative (**3**) that was reacted with *nor*-pergolide (**1a**) under above conditions (method B). This afforded moderate yield of N(1) – N(6) bound dimer (**7**).

Dimerization (N-1 substitution) is feasible also in presence of unsubstituted N-6 (e.g., **1a**). Reaction of **1a** with 1,6-dibromohexane (KOH, DMSO) yielded dimer (**9**) without affecting other reactive part of molecule (N-6).

All new compounds gave $[M+H]^+$ ions in MALDI-TOF or ESI MS spectra. Symmetric dimers (**4**, **5**, **6, 9,** and **10**) exhibited the expected symmetry of their NMR spectra (Tables 1 and 2). The attachment of a linker to N-1 was proved by heteronuclear couplings a) of the terminal methylene protons of the spacer to the pergolide C-2 and C-15; b) pergolide H-2 to the spacer CH_2. Similarly, the spacer linkage to N-6 in **6** and **7** was confirmed by couplings of the ultimate methylene protons to C-5 and C-7, and, *vice versa,* H-7 to this methylene carbon. With non-symmetric compounds (**7**) and (**8**), some distinct signals were assigned; H-2 on the substituted and unsubstituted indole ring serving as the entry point; H-8 of terguride moiety and both H-10 signals were used for compound (**8**).

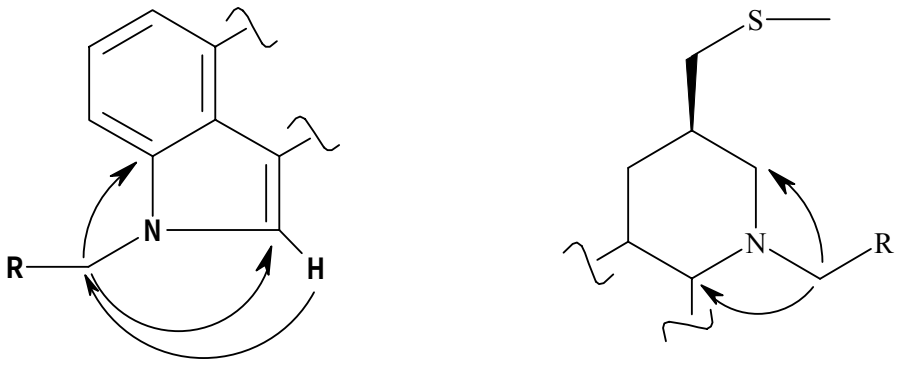

Figure 1: Diagnostic HMBC correlations used for structure confirmation

The addition of KOH to DMSO solution of **1** or **1a** causes 0.1 - 0.47 ppm upfield shifts of A and B ring protons. However, the ^{13}C NMR spectral chemical shift differences (Figure 2) clearly indicate that the indole ring is attacked in both cases. The resulting anion is then a good nucleophile for the reaction with alkyl (or aralkyl) dihalogenides. Indeed, the compound (**9**), a N1-N1 linked dimer of *nor*-pergolide was successfully prepared in 65 % yield.

Our experiments demonstrated feasibility of preparation of dimers of ergot alkaloids with different attachment of the molecule. This would allow also control an orientation of the pluripotent alkaloid molecules into respective receptors. Combination of these techniques together with the posibility of

combination of diferent alkaloids into one molecule could create entirely new entities with better tuned or entirely different biological activities. All these approaches were demonstrated on the drugs currently used in therapy.

EXPERIMENTAL

Chemicals - Pergolide, *nor*-pergolide, and terguride were kind gifts of Galena Pharmaceutical (Opava, Czech Republic).

General methods.- Reactions were monitored by TLC on silica gel F_{254} plates (Merck) using the solvent system EtOAc-MeOH-H_2O 77:13:10 (v/v). The spots were visualized by UV light and by charring with 10 % H_2SO_4 in ethanol or by the Ehrlich reagent. NMR spectra were measured on a Varian INOVA-400 spectrometer (399.91 MHz for ^1H, 100.57 MHz for ^{13}C) in $CDCl_3$ at 30 °C. Residual solvent signal (δ_H 7.265, δ_C 77.0) served as an internal reference. Signal assignment reported in Tables 1 and 2 was obtained by concerted application of COSY, TOCSY, HMQC, and HMBC experiments performed with standard manufacturer's software. 1D TOCSY obtained through Varian User Library was used to extract the exact chemical shifts of protons from overlapped spectral regions. Positive ion electrospray ionization spectra (ESI-MS) were recorded on a double-focusing instrument Finnigan MAT 95 (Finnigan MAT, Bremen, FRG) with BE geometry. Samples dissolved in MeOH-H_2O 2:1 (v/v) were continuously infused through a stainless capillary held at 3.3 kV into Finnigan ESI source *via* linear syringe pump at a flow rate of 40 μL/min. For high-resolution experiments the instrument was tuned to a resolution of about 8 000 (10% valley definition) and the measurements were carried out by the peak-matching method using a mixture of polypropylene glycols (average M_r = 725) as an internal standard. Positive ion MALDI MS spectra were measured on a Bruker BIFLEX reflectron time-of-flight mass spectrometer (Bruker-Franzen, Bremen, Germany) equipped with a multiprobe sample inlet, a gridless delayed extraction ion source and a nitrogen laser (337 nm). A saturated solution of α-cyano-4-hydroxycinnamic acid in aqueous 50% acetonitrile/0.1% TFA was used as a MALDI matrix. Spectra were calibrated externally using the monoisotopic $[M+H]^+$ ion of α-cyano-4-hydroxycinnamic acid and a peptide standard (angiotensin II, Aldrich). IR spectra were recorded on a FTIR spectrometer Nicolet 205 (Japan) in KBr.

*1-(6'-Iodohexyl)-6-propyl-8β-(methylthiomethyl)ergoline (**3**).*

Finely powdered KOH (563 mg, 10 mmol) was stirred with DMSO (3 mL) for 10 min. **1** (236 mg, 0.75 mmol) was added and the stirring was continued for another 30 min. 1,6-Diiodohexane (Aldrich) (1.52 g, 4.5 mmol, dissolved in 2 mL of DMSO) was quickly added. Reaction mixture

was poured after 1 hour into the water (40 mL), precipitate of the product was filtered of and washed with water till neutral pH and dried affording 405 mg of the crude product. Flash chromatography (silica gel, $CHCl_3$/1 % MeOH/0.1 % NH_3 sat. in anhydrous MeOH (Aldrich), 99 : 1 : 0.1) yielded **3** as brownish amorphous solid (220 mg) that was recrystallized from MeOH affording fine yellow crystals of **3** (107 mg, 27 %), MS MALDI-TOF $[M + H]^+$ (found 525.0, required 525.18 for $C_{25}H_{38}N_2IS$). Anal. Calcd for $C_{25}H_{37}N_2IS$: C, 57.2; H, 7.1; I 24.2; N, 5.3; S, 6.1; found C, 57.1; H, 7.1; I 24.4; N, 5.3; S, 6.0. IR (KBr, cm^{-1}): 3056, 2931, 2856, 2644, 2594, 2572, 1611, 1454, 747.

*1,6-Di[6'-propyl-8β'-(methylthiomethyl)ergoline-1'-yl-]hexane (**4**).*

Finely powdered KOH (370 mg, 6.6 mmol) was stirred with DMSO (2 mL) for 10 min. **1** (157 mg, 0.5 mmol) was added and the stirring was continued for another 30 min. The mixture turns green. After cooling to 10 ºC 1,6-dibromohexane (60 mg, 0.25 mmol, dissolved in 2 mL of DMSO) was slowly added in portions. Reaction was completed within 3 h as indicated by TLC: silica gel F_{254} plates (Merck), CH_3Cl-MeOH 94.5:5.5 (v/v). The spots were visualized by UV light and by charring with 10 % H_2SO_4 in ethanol where N-1-unsubstituted alkaloids gave blue spots and substituted alkaloids (dimers) gave gray spots. The product has quite similar R_f like **1**. Reaction mixture was poured in the water (40 mL) and the fine suspension was extracted 3 times with 40 mL of $CHCl_3$, combined extracts were washed with water and with brine, dried with Na_2SO_4 and evaporated to yield 167 mg of the crude product. Flash chromatography (silica gel, CH_2Cl_2 with a gradient 4 – 7 % MeOH) afforded pure **4** as amorphous yellow foam (105 mg, 60 %), MS MALDI TOF $[M + H]^+$ (found 711.2, required 711.45 for $C_{44}H_{63}N_4S_2$). Anal. Calcd for $C_{44}H_{62}N_4S_2$: C, 74.3; H, 8.8; N, 7.9; S, 9.0; found C, 74.4; H, 8.8; N, 7.9; S, 9.0. IR (KBr, cm^{-1}): 2930, 2857, 1719, 1613, 1458, 749.

*1,6-Di[8β'-(methylthiomethyl)ergoline-1'-yl-]hexane (**9**).*

The compound was prepared from **1a** (136 mg, 0.5 mmol) analogously as **4**, the same purification procedure was used except to the mobile phase 0.05 % aqueous conc. ammonia was added. Yield (97 mg, 62 %) as an amorphous yellowish foam, MS MALDI TOF $[M + H]^+$ (found 627.3, required 627.35 for $C_{38}H_{51}N_4S_2$). Anal. Calcd for $C_{44}H_{62}N_4S_2$: C, 74.3; H, 8.8; N, 7.9; S, 9.0; found C, 74.5; H, 8.6; N, 7.7; S, 9.2. IR (KBr, cm^{-1}): 2916, 2851, 1603, 1446, 746.

*1,4-Di[6'-propyl-8β'-(methylthiomethyl)ergoline-1'-yl-methyl]benzene (**5**).*

Finely powdered KOH (370 mg, 6.6 mmol) was stirred with DMSO (1 mL) for 10 min. **1** (157 mg, 0.5 mmol) was added and the stirring was continued for another 30 min. The mixture was cooled to

10 ºC and *p*-bis(bromomethyl)benzene[13] (66 mg, 0.25 mmol, dissolved in 0.5 mL of DMSO) was added in portions. Stirring was continued at the rt 2 h till the reaction is completed as indicated by TLC (CH_3Cl-MeOH 91:9). Reaction mixture was poured in the water (20 mL), precipitate of the product was filtered of and washed with water till neutral pH and dried affording 190 mg of the crude product. Recrystallization from Me_2CO / MeOH 20:1 gave fine yellow crystals of **5** (113 mg, 62 %), MS ESI $[M + H]^+$ (found 731.7, required 731.42 for $C_{46}H_{59}N_4S_2$). Anal. Calcd for $C_{46}H_{58}N_4S_2$: C, 75.6; H, 8.0; N, 7.7; S, 8.8; found C, 75.5; H, 8.0; N, 7.8; S, 8.7. IR (KBr, cm^{-1}): 3054, 2957, 2919, 2872, 1698, 1609, 1457, 748.

*1,6-Di[8β'-(methylthiomethyl)ergoline-6'-yl-]hexane (**6**).*

Procedure A: *nor*-Pergolide (**1a**) (136 mg, 0.5 mmol) was dissolved in DMF (2 mL) and at rt glutaraldehyde (Merck) (120 μL of 25 % aqueous solution, 0.3 mmol) was added. After 20 min of stirring formic acid (40 μL, 0.8 mmol) was added. After completion of the reaction (30 min) aqueous solution of NaOH (1 mL, 150 mg/mL) was added then the mixture was diluted with water (20 mL) and the product precipitate was washed with water and dried. Crude product was purified with flash chromatography (silica gel, $CHCl_3$ with 4 % MeOH plus 0.1 % conc. NH_4OH) yielding pure **6** as amorphous yellowish solid (25 mg, 16 %).

Procedure B: To the stirred mixture of *nor*-pergolide (**1a**) (136 mg, 0.5 mmol) and 1,6-dibromohexane (38 μL, 0.25 mmol) in dry DMF (2 mL), calcinated K_2CO_3 (207 mg, 1.5 mmol) was added and the reaction was quenched after 16 h (rt) with water (25 mL). The precipitate was washed with water and after drying chromatographed (method A) yielding 44 mg (28 %) of **6**. MS MALDI TOF $[M + H]^+$ (found 627.6, required 627.35 for $C_{38}H_{51}N_4S_2$). Anal. Calcd for $C_{38}H_{50}N_4S_2$: C, 72.8; H, 8.0; N, 8.9; S, 10.2; found C, 72.9; H, 8.0; N, 8.8; S, 10.3. IR (KBr, cm^{-1}): 2930, 2915, 2848, 1644, 1443, 751.

*1-[6'-Propyl-8β'-(methylthiomethyl)ergoline-1'-yl-]-6-[8β"-(methylthiomethyl)ergoline-6"-yl-]-hexane (**7**).*

To the stirred mixture of *nor*-pergolide (**2**) (44 mg, 0.16 mmol) and **3** (60 mg, 0.11 mmol) in dry DMF (0.4 mL), calcinated K_2CO_3 (85 mg, 0.5 mmol) was added and the reaction was quenched after 6 h (rt) with water (10 mL). The precipitate was filtered off and washed with water. Combined filtrates were extracted twice with $CHCl_3$ (20 mL), extracts were washed with water and the brine, dried with Na_2SO_4. The residue after evaporation was combined with the precipitate and purified with flash chromatography (silica gel, $CHCl_3$ + 1 % MeOH + 0.1 % sat. NH_3 in MeOH (Aldrich)) yielding amorphous yellowish solid of **7** (21 mg, 28 %), MS MALDI TOF $[M + H]^+$ (found 669.0,

required 669.40 for $C_{41}H_{57}N_4S_2$). Anal. calcd. for $C_{41}H_{56}N_4S_2$: C, 73.6; H, 8.4; N, 8.4; S, 9.6; found C, 73.5; H, 8.4; N, 8.5; S, 9.6.IR (KBr, cm^{-1}): 2926, 2854, 1696, 1648, 1610, 1449, 749.

*1-[6'-Propyl-8β'-(methylthiomethyl)ergoline-1'-yl-]-6-(6"-methyl-8α"-(diethylcarbamoylamino) ergoline-1"-yl)hexane (**8**).*

Finely powdered KOH (185 mg, 3,3 mmol) was stirred with DMSO (0.5 mL) for 10 min. **1** (79 mg, 0.25 mmol) was added and the stirring was continued for another 30 min. 1-(6-Bromohexyl)-6-methyl-8α(diethylcarbamoylamino)ergoline prepared analogously[11] as **3** from terguride and 1,6-dibromohexane (164 mg, 0.30 mmol, dissolved in 0.5 mL of DMSO) was slowly added at rt to the stirred mixture. The product had nearly identical R_f as **1** (TLC: silica gel F_{254} plates (Merck), solvent system CH_3Cl-MeOH 92:8 (v/v)). Reaction was quenched after 4 h with water (20 mL). The product precipitate was filtered off, washed with water and dried to give 190 mg of the crude product. Flash chromatography (silica gel, CH_2Cl_2 with 4 % MeOH plus 0.1 % conc. NH_4OH) afforded pure **8** as amorphous yellowish solid (116 mg, 63 %), MS ESI $[M + H]^+$ (found 737.8, required 737.49 for $C_{45}H_{65}N_6OS$). Anal. Calcd for $C_{45}H_{64}N_6OS$: C, 73.3; H, 8.8; N, 11.4; O, 2.2; S, 4.3; found C, 73.3; H, 8.8; N, 11.3; O 2.3; S, 4.4. IR (KBr, cm^{-1}): 2931, 2854, 2793, 1634, 1506, 1459, 746.

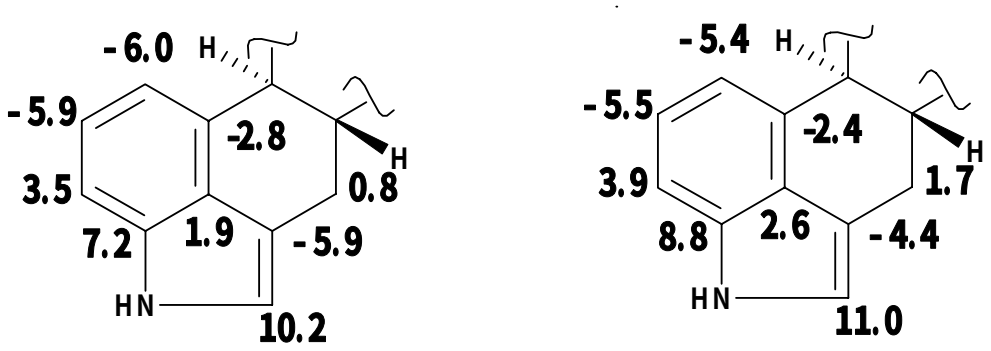

Figure 2: Selected ^{13}C chemical shift differences, $\Delta = \delta(DMSO + KOH) - \delta(DMSO)$, brought about by the addition of KOH to pergolide (**1**) and *nor*-pergolide (**1a**).

Table 1: Proton chemical shifts

Proton	**1**	**3**	**4**	**5**	**6**	**9**	**7 (N1-linked moiety)**	**7 (N6-linked moiety)**	**8 (pergolide moiety)**	**8 (terguride moiety)**
2	6.891	6.831	6.735	6.754	6.881	6.693	6.775	6.867	6.726	6.713
4*e*[1]	3.888	3.394	3.353	3.340	6.380	3.076	3.350	3.313	3.343	3.358
4*a*[1]	2.722	3.665	2.921	2.717	2.781	2.820	2.733	2.733	2.688	2.663
5	2.510	3.380	2.673	2.492	2.545	2.820	2.531	2.531	2.527	2.199
7*e*	3.250	3.755	3.351	3.243	3.269	3.431	3.256	3.256	3.242	2.798
7*a*	2.143	2.760	2.292	2.127	2.176	2.472	3.261	3.261	2.140	2.479
8	2.127	3.166	2.898	2.134	2.184	2.082	2.191	2.191	2.125	4.278
9*e*[1]	2.819	2.885	2.818	2.801	2.814	2.841	2.797	2.797	2.875	2.813
9*a*[1]	1.146	1.468	1.195	1.139	1.161	1.226	1.147	1.147	1.148	1.631
10	2.976	4.030	3.202	2.962	3.036	2.863	3.061	3.020	2.967	3.046
12	6.956	6.885	6.903	6.927	6.944	6.909	6.899	6.933	6.868	6.912
13	7.169	7.163	7.151	7.136	7.160	7.163	7.158	7.145	7.152	7.147
14	7.186	7.163	7.073	7.040	7.189	7.082	7.122	7.189	7.066	7.064
17*d*[1]	2.559	2.677	2.583	2.554	2.560	2.541	2.559	2.557	2.553	-
17*u*[1]	2.474	2.452	2.467	2.468	2.467	2.476	2.458	2.454	2.466	-
NH	6.891	-	-	-	-	-	-	8.039	-	-
S-Me	2.164	2.190	2.168	2.163	2.160	2.162	2.165	2.160	2.161	-
α	2.820	3.404	2.926	2.804	-		2.862	-	2.813	-
β	1.566	1.841	1.628	1.564	-		1.589	-	1.560	-
γ	0.924	1.060	0.955	0.914	-		0.930	-	0.918	-
1'		4.058	4.018	5.210	2.890	4.007	4.072	-	4.017	2.418[3]
2'		1.801	1.786		1.582	1.786	1.849	-	1.790	
3'		1.286	1.323	7.078[2]	1.368	1.320	1.360	-	1.331	
4'		1.403	1.323		1.368	1.320	1.386	-	1.331	
5'		1.780	1.786		1.582	1.786	1.535		1.790	
6'		3.137	4.018		2.890	4.007	2.833		4.017	

[1] *e* – equatorial, *a* – axial, *d* – downfield, *u* – upfield;
[2] 4 H;
[3] N-methyl. Underlined values in the same row for **7** or **8** might be interchanged. Additional signals - **1**: 6.981 (1 H, d, J=1.9 Hz, indole NH); **7**: 8.039 (1 H, d, J=1.8 Hz, indole NH); **8**: 1.150 (6 H, t, J=7.3 Hz, 2 x CH_3), 3.250 and 3.338 (4 H, m, 2 x CH_2); 5.527 (1 H, d, J=8.1 Hz, amine NH).

Table 2: Carbon chemical shifts

Carbon	**1**	**3**	**4**	**5**	**6**	**9**	**7 (N1-linked moiety)**	**7 (N6-linked moiety)**	**8 (pergolide moiety)**	**8 (terguride moiety)**
2	117.61	122.22	121.55	121.63	117.73	121.25	121.53	117.77	112.66	112.58
3	112.35	106.66	109.90	111.74	112.06	110.51	110.36	111.80	110.56	110.95
4	26.87	24.14	26.12	26.78	26.80	29.45	26.58	26.42	27.01	26.80
5	63.79	65.37	64.13	63.77	63.85	60.16	64.01	63.93	63.86	67.11
7	58.81	56.71	58.18	58.77	58.69	51.98	58.50	58.40	58.77	62.01
8	35.27	31.50	34.20	35.21	35.08	36.63	34.87	34.58	35.19	45.00
9	34.40	32.39	33.92	34.34	34.30	34.22	34.20	34.10	34.36	32.57
10	41.04	37.93	40.13	40.96	40.89	41.60	40.66	40.46	40.95	36.65
11	133.70	129.49	132.75	133.91	133.37	133.20	133.76	133.76	133.74	133.74
12	113.25	112.95	112.69	112.94	113.27	112.43	112.64	113.25	112.66	112.58
13	123.12	122.86	122.63	122.84	123.14	122.44	123.13	122.60	122.66	122.55
14	108.45	108.00	107.16	107.08	108.53	107.03	107.10	108.61	106.92	106.88
15	133.39	133.63	133.72	134.03	133.37	133.88	133.20	133.36	133.65	133.85
16	126.29	125.63	126.38	126.79	126.24	126.88	126.50	126.16	126.66	126.61
17	39.32	37.56	38.90	39.28	39.24	39.00	39.16	39.06	39.29	-
S-Me	16.11	16.04	16.11	16.09	16.13	16.17	16.13	16.11	16.09	-
α	55.57	54.78	55.12	55.53	-		55.23		55.52	-
β	17.06	15.16	16.61	16.96	-		16.77		17.01	-
γ	12.00	11.19	11.81	11.97	-		11.83		11.99	-
1'	-	46.36	46.35	49.83	53.45	46.18	46.41		46.30	43.41[2]
2'	-	30.26	30.45	137.36[1]	27.69	30.33	30.56		30.46	-
3'	-	25.72	26.63	127.32[1]	23.83	26.51	26.88		26.31	-
4'	-	29.72	26.63		23.83	26.51	27.28		26.31	-
5'	-	33.09	30.44		27.69	30.33	23.61		30.46	-
6'	-	6.77	46.35		53.45	46.18	53.21		46.30	-

[1] 4 C;

[2] N-methyl. Underlined values in the same row for **7** or **8** might be interchanged. Additional signals - **8** (DVK-2302): 13.90 (2 C, CH_3), 41.13 (2 C, CH_2), 156.62 (NC=O).

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REFERENCES

1 V. Křen and L. Cvak, *Ergot - Genus* Claviceps*, Medicinal & Aromatic Plants - Industrial Profiles*, Harwood Academic Publ., Ltd., Amsterodam, London 1999.

2 E. Eich and H. Pertz, *Pharmazie*, 1994, **49**, 867; E. Eich and H. Pertz, in *Ergot - Genus* Claviceps*, Medicinal & Aromatic Plants - Industrial Profiles*, ed. by V. Křen and L. Cvak, Harwood Academic Publ., Ltd., Amsterodam, London 1999, p. 411.

3 R. T. Owen, *Drugs Fut.*, 1981, **6**, 231.

4 J. W. Misner, J. H. Kennedy, and W. S. Biggs, *Org. Proc. Res. Develop.*, 1997, **1**, 77.

5 D. Page and R. Roy, *Glycoconjugate J.*, 1997, **14**, 345.

6 N. J. Bach and E. C. Kornfeld, *Tetrahedron Lett.*, 1973, 3315.

7 A. G. Kozlovsky, N. F. Zelenkova, V. M. Adanin, V. G. Sakharovskii, and M. U. Arinbasarov, *Prikl. Biokhim. Mikrobiol.*, 1995, **31**, 540.

8 N. F. Zelenkova, I. G. Vepritskaya, V. M. Adanin, V. G. Sakharovskii, M. Yu. Nefedova, and A. G. Kozlovsky, *Prikl. Biokhim. Mikrobiol.,* 1992, **28,** 738.

9 V. Křen, P. Sedmera, M. Polášek, A. Minghetti, and N. Crespi-Perrelino, *J. Nat. Prod*., 1996, **59**, 609.

10 L. Cvak, J. Stuchlík, A. Černý, J. Křepelka, and J. Spáčil, *Czechoslovak Pat. 234498*, 1987, (*Chem. Abstr*., 1997, **108**,132138); J. Šmidrkal and M. Semonský, *Collect. Czech. Chem. Commun.*, 1982, **47**, 622.

11 E. Eich, R. Sieben, and Ch. Becker, *Arch. Pharm.*, 1985, **318**, 214.

12 J. Šmidrkal and M. Semonský, *Collect. Czech. Chem. Commun*., 1982, **47**, 622; G. Marzoni and W. L. Galbrecht, *Synthesis,* 1987, 651.

13 J. Závada, M. Pánková, P. Holý, and M. Tichý, *Synthesis*, 1994, 1132.