SELECTIVE REDUCTION OF PEPTIDIC ERGOT ALKALOIDS[+]

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Five 6'-deoxoergopeptines were prepared in 51–68% yield by selective reduction of parent alkaloids with lithium aluminium hydride in tetrahydrofuran at low temperature. New compounds were characterized by mass spectrometry and NMR spectroscopy. The conformation of the peptide part in starting compounds and reduced derivatives is discussed on the basis of crystal structure determination of 6'-deoxo-9,10-dihydroergotamine dihydrate butan-2-one solvate as a representative member of the series.
Key words: Indole alkaloids; Ergot alkaloids; Ergopeptines; Peptides; Reductions; NMR spectroscopy; Mass spectrometry; Crystal structure determination; X-Ray diffraction.

Despite the rather long history of ergot alkaloids involving many synthetic and semisynthetic attempts[2–4], relatively little attention was paid to the modification of peptidic alkaloids in the cyclol part. So far described examples include so-called *aci*-isomerization[5–7] at C-2', metabolic modifications of the proline residue[8–10], alkylation of the acetal hydroxyl group[11–13], pyrolysis[14], and Birch reduction[15]. Reduction of all three carbonyl groups of ergopeptines with LiAlH₄ in 4-ethylmorpholine at 70 °C was also de-

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+ In this 22nd paper on structure and polymorphism of ergot derivatives we report synthesis and crystal structure determination of ergopeptine alkaloids with an unusual modification in the cyclol part. For the preceding paper of the series see ref.[1]

scribed[16]. Our strategy for obtaining modified ergopeptine alkaloids was based on lithium aluminium hydride reduction at low temperatures[17]. This paper provides a full account of this work.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and were not corrected. Optical rotations were measured in 1% chloroform solutions.

All mass spectra were recorded in the positive-ion mode on a double focusing instrument Finnigan MAT 90 of BE geometry. Conditions for electron impact were: ionising energy 70 eV, source temperature 250 °C, emission current 1 mA, acceleration voltage 5 kV, direct inlet 190–220 °C. High-resolution measurements were carried out by HR magnetic scanning with perfluorokerosene as an internal standard. The molecular weights were obtained by FAB MS. The standard saddle field FAB gas-gun was operated at 1 mA current and 6 keV energy with xenon 4.0 ($1 \cdot 10^{-2}$ Pa) and monothioglycerol matrix (Sigma, St. Louis, U.S.A.); magnetic calibration was performed with CsI as a standard.

^1H and ^{13}C NMR spectra (399.95 and 100.58 MHz, respectively) were measured on a Varian VXR-400 spectrometer in $CDCl_3$ at 25 °C using tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. Multiplicity of carbon signals was determined by APT and DEPT; the reported assignment is based on J-resolved, COSY, LR COSY, and HETCOR experiments. A comparison of assignment of NMR signals for the parent alkaloids **1**–**5**, their 6′-deoxo-derivatives, **6**, **7**, **9**, **10**, **11**, and 6′-deoxo-ergocristinine (**8**) are summarized in Tables I–III.

Crystal Structure Determination of 6′-Deoxo-9,10-dihydroergotamine Dihydrate Butan-2-one Solvate (**11b**)

6′-Deoxo-9,10-dihydroergotamine (**11**; 70 mg) was dissolved in butan-2-one (2 ml) under short reflux and the solution was allowed to cool in an open flask overnight. The formed crystals were separated and dried in air. **11b**: $(C_{33}H_{39}N_5O_4)\cdot 2H_2O\cdot C_4H_8O$, $M_r = 677.84$, orthorhombic system, space group $C2$ (No. 5), $a = 25.615(6)$ Å, $b = 10.011(4)$ Å, $c = 17.974(4)$ Å, $\beta = 126.66(3)°$, $V = 3\,697(2)$ Å^3, $Z = 4$, $D_{calc} = 1.22$ g cm^{-3}, $\mu(CuK\alpha) = 0.687$ mm^{-1}, $F(000) = 1\,456$.

The structure of **11b** was solved by direct methods. All non-H atoms, except of butan-2-one, were refined anisotropically by full-matrix least-squares based on F-values. The hydrogen atoms were set according to the expected geometry, the O and N hydrogens were localized from the Δρ map. Data collection and refinement parameters are listed in Table IV. Consecutive numbering of individual C, N, O atoms were used as indicated in Fig. 1. Water molecules were denoted as H801–O80–H802, H901–O90–H902, and numbers C71–C74 and O75 were used for butan-2-one. The packing of molecules in the structure is shown in Figs 2a and 2b.

Reduction of Ergopeptines. General Procedure

Solution of an ergopeptine (18 mmol dissolved in 250 ml of dry tetrahydrofuran) was dropped into a LiAlH$_4$ suspension (12.0 g, 316 mmol; in 200 ml of THF) at –5 °C. The reaction was performed with α-ergokryptine (**1**), ergocristine (**2**), 9,10-dihydro-α-ergokryptine

TABLE I
^{13}C NMR chemical shifts (100.58 MHz, CDCl$_3$) of new 6′-deoxoergopeptines **6–11** and their parent compounds **1–5**

Carbon	Compound										
	1[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
2	119.07	119.14	117.91	117.91	117.87	119.28	119.11	118.42	117.91	117.88	117.93
3	110.77	110.43	111.12	111.61	111.52	109.59	110.58	109.79	111.08	111.38	111.14
4	21.55	21.73	26.71	26.98	26.87	21.95	21.78	27.50	26.83	26.91	26.77
5	59.17	59.30	66.55	66.71	66.65	59.51	59.35	62.77	66.25	66.48	66.44
7	48.04	48.26	58.86	59.20	58.94	48.81	48.53	54.61	58.51	58.87	58.73
8	44.29	44.31	43.44	44.16	42.96	43.54	44.40	43.88	43.37	43.81	43.13
9	118.94	118.52	30.08	30.51	30.57	119.28	118.69	117.76	30.14	30.43	30.25
10	139.08	139.14	39.75	40.08	39.98	137.10	139.04	137.08	39.87	40.03	39.88
11	129.70	129.42	131.84	132.13	132.11	128.68	129.51	127.27	131.82	132.01	131.93
12	112.00	111.73	113.05	113.28	113.25	118.86	111.95	112.74	112.88	113.17	113.18
13	123.36	123.13	123.10	123.26	123.18	123.03	123.25	123.22	122.96	123.10	123.04
14	110.03	110.08	108.82	108.85	108.82	110.17	110.03	110.11	108.66	108.73	108.75
15	133.82	133.81	133.32	133.41	133.38	133.66	133.84	133.84	133.27	133.30	133.29
16	126.23	126.19	125.92	126.06	126.03	125.97	126.20	126.11	125.89	125.97	125.94
17	40.89	40.88	42.82	43.04	43.57	40.86	40.99	43.24	42.95	43.00	42.83
18	176.22	176.04	175.89	175.43	175.06	175.97	176.25	176.42	175.52	175.67	175.54
2′	89.68	89.88	90.00	89.87	85.79	88.58	88.68	88.79	88.49	88.64	88.83
3′	165.76	165.63	165.97	165.04	165.63	166.16	165.82	165.34	165.78	165.23	166.26
5′	53.28	56.65	53.41	57.10	57.32	49.25	52.12	51.89	49.55	52.26	52.29
6′	166.14	165.32	165.34	165.03	164.91	55.44	52.36	52.23	55.45	52.59	52.48
8′	45.95	46.09	46.01	46.21	46.25	54.17	54.09	54.05	54.18	54.07	54.04
9′	22.08	22.20	22.05	22.28	22.23	20.55	20.81	20.81	20.64	20.83	20.78
10′	26.46	26.40	26.35	26.47	26.48	23.13	23.19	23.15	23.15	23.16	23.19
11′	64.46	64.30	64.37	64.23	65.39	70.01	69.86	69.82	70.00	69.76	71.16
12′	103.47	103.65	103.73	103.87	103.42	105.61	105.68	105.38	105.73	105.73	105.38

[a] Ref.[24] Additional signals: **1** – R^1: 34.26 d, 16.89 q, 15.35 q, R^2: 43.77 t, 25.05 d, 22.58 q, 22.19 q; **2** – R^1: 34.27 d, 16.74 q, 15.27 q, R^2: 39.55 t, 138.85 s, 129.94 d (2 C), 127.86 d (2 C), 126.14 d; **3** – R^1: 34.04 d, 16.96 q, 15.57 q, R^2: 43.47 t, 25.00 d, 22.64 q, 22.00 q; **4** – R^1: 34.26 d, 16.98 q, 15.52 q, R^2: 39.46 t, 138.52 s, 130.08 d (2 C), 127.97 d (2 C), 126.33 d; **5** – R^1: 24.83 q, R^2: 39.35 t, 138.16 s, 130.16 d (2 C), 127.94 d (2 C), 126.36 d; **6** – R^1: 34.39 d, 17.13 q, 15.44 q, R^2: 41.60 t, 24.77 d, 22.72 q, 22.46 q; **7** – R^1: 34.47 d, 17.10 q, 15.37 q, R^2: 37.95 t, 139.04 s, 129.67 d (2 C), 128.37 d (2 C), 126.23 d; **8** – R^1: 34.20 d, 17.19 q, 15.54 q, R^2: 37.79 t, 139.04 s, 129.67 d (2 C), 128.32 d (2 C), 126.15 d; **9** – R^1: 35.54 d, 17.29 q, 15.71 q, R^2: 41.61 t, 24.89 d, 22.74 q, 22.51 q; **10** – R^1: 34.39 d, 17.25 q, 15.61 q, R^2: 37.98 t, 138.83 s, 129.72 d (2 C), 126.38 d (2 C), 126.28 d; **11** – R^1: 25.27 q, R^2: 37.99 t, 138.73 s, 129.64 d (2 C), 126.28 d (2 C), 126.28 d.

TABLE II
^{1}H NMR chemical shifts (399.95 MHz, CDCl$_3$) of new 6′-deoxoergopeptines **6–11** and their parent compounds **1–5**

Proton	Compound										
	1[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
2	6.937	6.801	6.864	6.984	6.894	6.922	6.838	6.801	6.830	6.864	6.834
4a	2.851	2.715	2.652	2.671	2.769	2.836	2.705	2.571	2.615	2.626	2.598
4e	3.332	3.212	3.379	3.422	3.509	3.303	3.208	3.499	3.353	3.372	3.330
5	3.878	3.742	2.153	2.239	2.313	3.806	3.738	3.132	1.931	2.090	2.066
7a	2.963	2.713	2.340	2.418	2.488	2.882	2.838	2.641	2.169	2.312	2.290
7e	2.921	2.789	3.121	3.141	3.217	2.978	2.748	3.062	3.075	3.101	3.070
8	3.171	3.041	2.728	2.757	2.829	3.246	3.055	2.994	2.671	2.714	2.746
9a	6.374	6.275	1.516	1.697	1.743	6.281	6.280	6.480	1.137	1.478	1.502
9e	–	–	2.797	2.778	2.846	–	–	–	2.573	2.693	2.681
10	–	–	2.910	2.964	3.034	–	–	–	2.809	2.887	2.857
12	7.129	7.005	6.806	6.937	7.013	7.076	7.007	6.997	6.619	6.789	6.792
13	7.182	7.067	7.135	7.198	7.285	7.158	7.075	7.034	7.073	7.114	7.103
14	7.235	7.117	7.185	7.198	7.308	7.220	7.138	7.113	7.183	7.183	7.166
N1-H	8.138	8.318	8.231	7.977	8.282	8.294	8.323	9.268	8.657	8.269	8.457
17	2.709	2.525	2.453	2.502	2.586	2.654	2.545	2.518	2.436	2.449	2.385
CONH	9.783	9.636	6.670	6.328	6.719	9.484	9.485	9.928	6.362	6.405	9.467
5′	4.518	4.597	4.531	4.708	4.832	4.233	4.227	4.155	4.278	4.333	4.332
6′d	–	–	–	–	–	3.064	2.954	2.915	3.093	3.040	3.053
6′u	–	–	–	–	–	2.154	1.891	1.841	2.229	1.999	2.007
8′d	3.608	3.552	3.620	3.650	3.758	3.190	3.128	3.114	3.222	3.205	3.202
8′u	3.545	3.447	3.548	3.562	3.669	2.119	2.039	2.010	2.167	2.171	2.147
9′d	2.071	1.967	2.144	2.074	2.161	1.948	1.890	1.895	1.971	2.007	1.998
9′u	1.803	1.701	1.802	1.812	1.901	1.753	1.672	1.678	1.770	1.770	1.765
10′d	2.189	2.115	2.160	2.128	2.238	2.084	2.106	2.010	2.090	2.122	2.131
10′u	2.149	2.006	2.035	2.112	2.238	1.968	1.905	2.010	1.980	1.871	1.964
11′	3.659	3.586	3.686	3.698	3.651	2.055	2.022	2.033	2.122	2.148	1.998
12′-OH	7.372	7.504	7.161	7.152	6.719	7.292	7.486	7.726	6.972	7.133	6.765

[a] Ref.[24] Additional signals: **1** – R^1: 2.095 (1 H, qq), 1.025 (3 H, d, J = 6.7), 0.909 (3 H, d, J = 6.7), R^2: 1.993 (1 H, ddd, J = 13.7, 9.7, 6.0), 1.874 (1 H, ddd, J = 13.7, 7.6, 6.2), 2.078 (1 H, m), 1.048 (3 H, d, J = 6.4), 1.006 (3 H, d, J = 6.4); **2** – R^1: 1.975 (1 H, qq), 0.918 (3 H, d, J = 6.9), 0.798 (3 H, d, J = 6.9), R^2: 3.351 (1 H, m), 3.201 (1 H, m), 7.385 (2 H, m), 7.184 (2 H, m), 7.099 (1 H, m); **3** – R^1: 2.195 (1 H, qq), 0.985 (3 H, d, J = 6.7), 1.141 (3 H, d, J = 6.9), R^2: 1.968 (1 H, ddd, J = 13.4, 8.3, 5.4), 1.870 (1 H, ddd, J = 13.4, 8.1, 5.7), 2.050 (1 H, m), 0.975 (3 H, d, J = 6.5), 1.049 (3 H, d, J = 6.4); **4** – R^1: 2.130 (1 H, qq), 1.108 (3 H, d, J = 6.9), 0.948 (3 H, d, J = 6.8), R^2: 3.472 (1 H, m), 3.256 (1 H, m), 7.428 (2 H, m), 7.428 (2 H, m), 7.269 (1 H, m); **5** – R^1: 1.667 (3 H, s), R^2: 3.604 (1 H, m), 3.361 (1 H, m), 7.533 (2 H, m), 7.372 (2 H, m), 7.298 (1 H, m); **6** – R^1: 2.108 (1 H, qq), 0.918 (3 H, d, J = 6.7), 1.030 (3 H, d, J = 6.8), R^2: 2.048 (1 H, ddd, J = 13.7, 8.4, 6.0), 1.584 (1 H, ddd, J = 13.7, 7.9, 6.6), 1.726 (1 H, m), 1.025 (3 H, d, J = 6.5), 0.976 (3 H, d, J = 6.6); **7** – R^1: 2.031 (1 H, qq), 0.828 (3 H, d, J = 6.7), 0.944 (3 H, d, J = 6.8), R^2: 3.374 (1 H, dd, J = 13.3, 3.5), 2.977 (1 H, dd, J = 13.3, 3.5), 7.243 (2 H, m), 7.206 (2 H, m), 7.122 (1 H, m); **8** – R^1: 2.010 (1 H, qq), 0.824 (3 H, d, J = 6.7), 1.069 (3 H, d, J = 6.8), R^2: 3.340 (1 H, dd, J = 13.4, 11.7), 2.956 (1 H, dd, J = 13.4, 3.6), 7.205 (2 H, m), 7.217 (2 H, m), 7.094 (1 H, m); **9** – R^1: 2.198 (1 H, qq), 1.168 (3 H, d, J = 6.8), 1.052 (3 H, d, J = 6.8), R^2: 2.065 (1 H, ddd, J = 13.6, 8.3, 5.9), 1.635 (1 H, ddd, J = 13.6, 7.9, 6.7), 1.788 (1 H, m), 0.996 (3 H, d, J = 6.6), 1.045 (3 H, d, J = 6.5); **10** – R^1: 2.194 (1 H, qq), 1.131 (3 H, d, J = 6.8), 0.990 (3 H, d, J = 6.7), R^2: 3.043 (1 H, dd, J = 13.4, 11.0), 3.096 (1 H, dd, J = 13.4, 4.3), 7.333 (2 H, m), 7.286 (2 H, m), 7.199 (1 H, m); **11** – R^1: 1.633 (3 H, s), R^2: 3.423 (1 H, dd, J = 13.4, 11.0), 3.101 (1 H, dd, J = 13.4, 4.4), 7.331 (2 H, m), 7.293 (2 H, m), 7.208 (1 H, m).

Selected proton-proton coupling constants of new 6′-deoxoergopeptines **6**–**11** and their parent compounds **1**–**5**

Protons	1[a]	2	3	4	5	6	7	8	9	10	11
2,NH	1.8	2.0	1.8	1.7	1.8	1.8	1.8	1.8	1.9	1.8	2.0
2,4a	1.8	1.6	1.8	1.8	1.7	1.8	1.8	1.7	1.8	1.7	1.7
4a,4e	–14.1	–14.1	–14.8	–14.7	–14.7	–14.1	–14.1	–14.3	–14.7	–14.7	–14.8
4a,5	12.0	12.0	11.2	11.2	11.0	11.8	12.0	11.5	11.2	11.1	11.1
4e,5	4.9	4.3	4.4	4.4	4.3	4.8	4.9	5.5	4.3	4.3	4.4
5,8	1.0	1.0	–	–	–	0.8	1.4	n.d.	–	–	–
5,9	2.0	1.9	–	–	–	1.6	1.9	2.1	–	–	–
5,10	–	–	9.5	9.8	9.7	–	–	–	9.6	9.8	9.8
7a,7e	–12.1	–12.0	–11.4	–11.4	–11.4	–12.0	–12.0	–11.9	–11.5	–11.4	–11.5
7a,8	3.5	3.6	11.4	11.4	11.3	3.5	3.6	3.7	11.5	11.3	11.5
7e,8	2.2	2.2	3.3	3.6	3.5	3.0	2.1	1.2	3.8	n.d.	n.d.
7e,9e	0.7	<1	2.3	1.8	2.0	0.9	–	1.0	1.8	n.d.	2.2
8,9a	6.1	6.0	12.5	12.4	12.5	5.5	6.0	6.5	12.5	12.4	12.5
8,9e	–	–	3.4	3.5	5.2	–	–	–	3.8	n.d.	n.d.
9a,9e	–	–	–12.3	–12.8	–12.5	–	–	–	–12.5	n.d.	–12.5
9a,10	–	–	12.5	12.4	12.5	–	–	–	12.5	12.4	12.4
9e,10	–	–	3.4	3.5	3.6	–	–	–	4.0	n.d.	n.d.
10,12	–	–	1.2	n.d.	1.3	–	–	–	0.7	1.0	1.1
10,14	–	–	0.8	n.d.	n.d.	–	–	–	0.6	0.5	0.6
12,13	7.1	7.0	6.9	n.d.	7.4	7.1	7.2	7.3	7.1	7.2	7.0
12,14	1.0	1.1	0.9	n.d.	1.3	0.8	0.8	1.2	0.7	0.7	1.0
13,14	7.9	8.1	8.2	n.d.	8.1	8.0	8.0	7.6	8.2	8.2	8.2
5′,6′d	–	–	–	–	–	1.1	<0.5	<0.5	1.0	1.0	0.6
5′,6′u	–	–	–	–	–	n.d.	4.1	4.3	4.5	4.1	4.8
6′u,6′d	–	–	–	–	–	–11.3	–11.2	–11.6	–11.3	–11.4	–10.9
9′d,9′u	n.d.	n.d.	–12.3	–12.4	–12.1	–8.4	–8.4	n.d.	–8.4	–8.4	–8.5
10′d,11	9.8	9.7	9.2	9.7	7.8	8.8	n.d.	n.d.	n.d.	8.4	n.d.
10′u,11	6.3	6.0	6.8	5.9	1.8	3.0	n.d.	n.d.	n.d.	6.1	n.d.
11′,OH	1.8	1.8	1.7	1.9	1.7	1.4	1.6	1.6	1.5	1.5	1.7

Geminal couplings are reported as negative; n.d. – not determined. [a] Ref.[24]

<small>TABLE IV</small>
Data collection and refinement parameters for **11b**

Crystal dimensions, mm	$0.21 \times 0.56 \times 0.91$
Diffractometer and radiation used, Å	Enraf–Nonius CAD4, CuKα $\lambda = 1.54056$
Scan technique	$\omega/2\theta$
Temperature, K	293
No. and θ range of reflections for lattice parameter refinement, °	20; 38–40
Range of *h, k* and *l*	$-27{\rightarrow}27$, $-10{\rightarrow}10$, $-19{\rightarrow}19$
Standard reflections monitored in interval, min; intensity fluctuation, %	60; 1.28
Total number of reflections measured; 2θ range, °	4 655; 6–110
No. of observed reflections	4 536
Criterion for observed reflections	$I \geq 1.96\sigma(I)$
Function minimized	$w(|F_o| - |F_c|)^2$
Weighting scheme	Chebychev polynomial ref.[25]
Parameters refined	417
Value of *R, wR*, and *S*	0.0737, 0.0819, and 0.998
Ratio of maximum least-squares shift to e.s.d. in the last cycle	0.002
Maximum and minimum heights in final $\Delta\rho$ map, e Å^{-3}	0.83, –0.74
Source of atomic scattering factors	International Tables for X-Ray Crystallography (ref.[26])
Programs used	CRYSTALS (ref.[27]), PARST (ref.[28]), SIR92 (ref.[29])

(**3**), 9,10-dihydroergocristine (**4**), and 9,10-dihydroergotamine (**5**). According to TLC, the reaction was complete after one 1 h stirring below 0 °C giving rise the 6′-deoxo derivatives **6**, **7**, **9**, **10**, and **11**, respectively (Scheme 1). The reaction provided a single product except for ergocristine (**2**), where 6′-deoxoergocristinine (**8**) was detected as a major by-product in addition to 6′-deoxoergocristine (**7**). An excess of hydride was decomposed with water (20 ml in 200 ml of tetrahydrofuran), the suspension formed was filtered off and the filtrate was evaporated. The residue was subjected to column chromatography on silica gel (dichloromethane, TLC monitoring). Individual fractions were analysed and pooled on the basis of TLC on silica gel 60 plates (Merck; chloroform–toluene–acetone–ethanol, 5 : 3 : 2 : 1, detection by the Ehrlich reagent). Fractions containing desired 6′-deoxo derivatives were pooled, evaporated and crystallized from appropriate solvents. Crystallization of 6′-deoxo-9,10-dihydroergotamine from acetone or butan-2-one provided two crystalline forms; dihydrate acetone solvate prone to desolvation denoted as **11a** (based on NMR and assay), and dihydrate butan-2-one solvate denoted as **11b** (see crystal structure determination).

6′-Deoxo-α-ergokryptine (**6**). Yield 51%, purity 98.7% (HPLC), 98.2% (assay titration); m.p. 171–177 °C (ethyl acetate–hexane), $[\alpha]_D^{20}$ 10.9. FAB MS, *m/z*: 562 [M + H]⁺; EI MS: 295 (5), 294.1940 (23, $C_{16}H_{26}N_2O_3$), 280 (16), 279.1710 (100, $C_{15}H_{23}N_2O_3$), 267.1373 (14, $C_{16}H_{17}N_3O$), 223 (6), 221 (10), 207 (6), 197 (5), 196 (18), 195.1498 (75, $C_{11}H_{19}N_2O$), 180 (5), 111 (13), 110 (20), 97 (5), 84 (11), 83 (27), 82 (7), 71 (9), 70 (19), 69 (6), 57 (11), 55 (18), 43 (36), 42 (8), 41 (21), 27 (6), 18 (6).
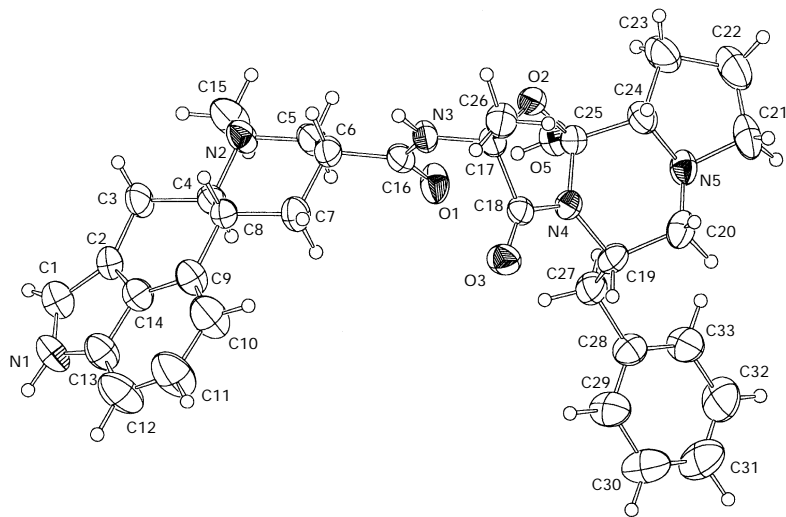

Fig. 1

Ortep[30] drawing of **11b** with the numbering system used for the X-ray data
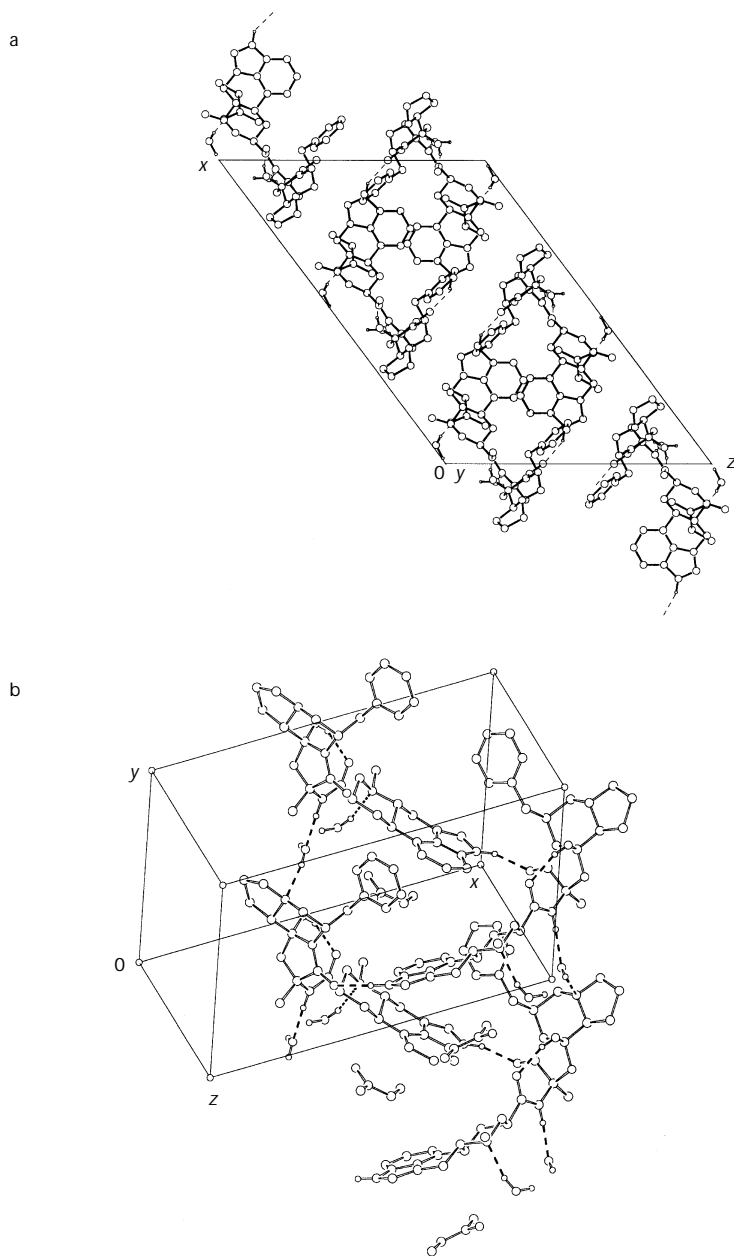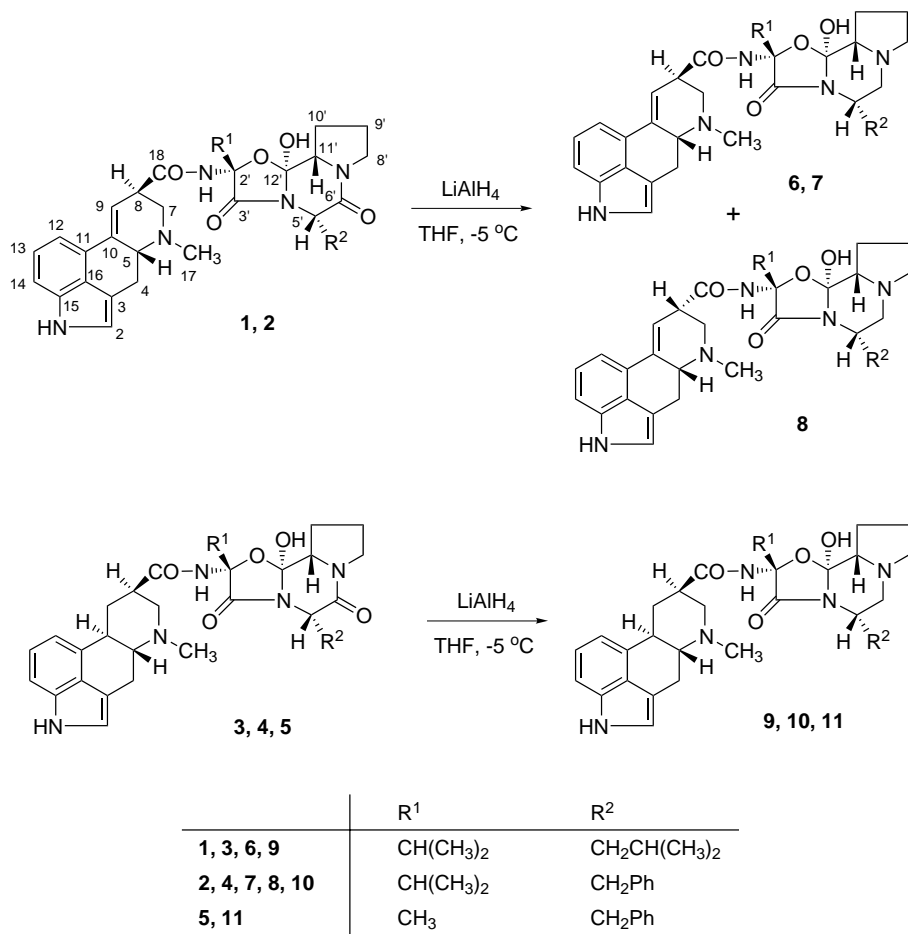
FIG. 2
Packing scheme of **11b**: a Projection along *y* axis; b detailed view of a discrete "pillar" (dashed lines represent hydrogen bonds)

6′-Deoxo-α-ergocristine (**7**). Yield 42%, purity 98.2% (HPLC), 99.1% (assay titration); m.p. 206–218 °C (acetone), $[\alpha]_D^{20}$ –177.7. FAB MS, *m/z*: 596 [M + H]$^+$; EI MS: 328.1784 (31, $C_{19}H_{24}N_2O_3$), 314 (18), 313.1535 (100, $C_{18}H_{21}N_2O_3$), 267.1370 (39, $C_{16}H_{17}N_3O$), 230 (13), 229.1330 (68, $C_{14}H_{17}N_2O$), 224 (7), 223 (10), 221 (22), 207 (16), 196 (9), 181 (8), 180 (14), 167 (6), 154 (10), 117 (12), 111 (10), 91 (25), 83 (20), 82 (13), 70 (9), 55 (11), 43 (16), 42 (9), 41 (12).

	R^1	R^2
1, 3, 6, 9	CH(CH$_3$)$_2$	CH$_2$CH(CH$_3$)$_2$
2, 4, 7, 8, 10	CH(CH$_3$)$_2$	CH$_2$Ph
5, 11	CH$_3$	CH$_2$Ph

SCHEME 1

6′-Deoxo-α-ergocristinine (**8**). Yield 24%, purity 95.0% (HPLC); m.p. 230–235 °C (acetone), $[\alpha]_D^{20}$ 360.3. FAB MS, *m/z*: 596 [M + H]$^+$; EI MS: 328.1772 (30, $C_{19}H_{24}N_2O_3$), 314 (18), 313.1553 (100, $C_{18}H_{21}N_2O_3$), 267.1372 (45, $C_{16}H_{17}N_3O$), 230 (16), 229.1330 (72, $C_{14}H_{17}N_2O$), 223 (12), 221 (25), 207 (15), 196 (11), 180 (17), 167 (7), 154 (12), 117 (14), 111 (15), 91 (28), 83 (24), 82 (13), 70 (11), 55 (12), 43 (17), 42 (10), 41 (14).

6′-Deoxo-9,10-dihydro-α-ergokryptine (**9**). Yield 68%, purity 98.4% (HPLC), 98.6% (assay titration); m.p. 188–194 °C (CH$_2$Cl$_2$), $[\alpha]_D^{20}$ 15.2. FAB MS, *m/z*: 564 [M + H]$^+$; EI MS: 294.1942 (17, $C_{16}H_{26}N_2O_3$), 280 (17), 279.1713 (100, $C_{15}H_{23}N_2O_3$), 269.1518 (30, $C_{16}H_{19}N_3O$), 223 (10), 196 (9), 195.1500 (61, $C_{11}H_{19}N_2O$), 167 (9), 154 (13), 83 (15), 82 (10), 70 (12), 55 (12), 43 (16), 41 (13).

6′-Deoxo-9,10-dihydroergocristine (**10**). Yield 66%, purity 98.7% (HPLC), 99.0 (assay titration); m.p. 222–223 °C (CH$_2$Cl$_2$), $[\alpha]_D^{20}$ –36.5. FAB MS, *m/z*: 598 [M + H]$^+$; EI MS: 329 (7), 328.1781 (32, $C_{19}H_{24}N_2O_3$), 314 (19), 313.1544 (100, $C_{18}H_{21}N_2O_3$), 270 (7), 269.1537 (33, $C_{16}H_{19}N_3O_2$), 230 (12), 229.1325 (58), 225 (6), 223 (10), 167 (7), 154 (12), 144 (7), 117 (8), 91 (15), 83 (13), 82 (7), 55 (8), 43 (9), 41 (7).

6′-Deoxo-9,10-dihydroergotamine dihydrate acetone solvate (**11b**). Yield 59%, purity 98.2% (HPLC), 85.6% (assay titration); m.p. 189–194 °C (acetone), $[\alpha]_D^{20}$ –41.5. FAB MS, *m/z*: 596 [M + H]$^+$; EI MS: 301 (11), 300.1500 (59, $C_{17}H_{20}N_2O_3$), 269.1534 (18, $C_{16}H_{19}N_3O$), 230.1400 (17, $C_{14}H_{18}N_2O$), 229.1325 (100, $C_{14}H_{17}N_2O$), 167 (4), 154 (6), 111 (10) 91 (15), 83 (15), 74 (11), 55 (13), 43 (10), 41 (13).

RESULTS AND DISCUSSION

Selective reduction of ergopeptines with LiAlH$_4$ is described. In contrast to the previously reported complete reduction of all three carbonyl groups at 70 °C in 4-ethylmorpholine[16], the reaction of ergopeptines with a LiAlH$_4$ suspension in THF at –5 °C in an inert atmosphere, decomposition of the unreacted agens with water, and chromatography of the products provided selectively 6′-deoxoergopeptines **6**, **7**, **9**, **10**, and **11**. This selectivity is a result of the low temperature only; neither the reaction time nor the amount of hydride used had any marked effect. With ergocristine (**2**), 6′-deoxo-ergocristinine (**8**) was detected as a major by-product. It should be noted, however, that ergopeptines, in contrast to 9,10-dihydroergopeptines, are prone to epimerization and thus these by-products can be expected to various extent also with other ergopeptines.

New derivatives were characterized by a combination of various spectrometric methods. Molecular cation-radicals of peptidic ergot alkaloids are usually absent in the EI spectra, but can be obtained using FAB ionization. Under EI conditions, ergot alkaloids undergo two main competitive cleavages: into ergoline and peptide parts. The whole ergoline part of the molecule in the mass spectra of 9,10-dihydro derivatives is represented by ion 269 (elemental composition $C_{16}H_{19}N_3O$); in the case of 9,10-unsaturated derivatives, the ion *m/z* 267 ($C_{16}H_{17}N_3O$) is observed. Characteristic

ergoline low-mass fragments are *m/z* 167 (composition $C_{12}H_9N$) and *m/z* 154 ($C_{11}H_8N$); see ref.[18]. Peptide parts of ergocristine, α-ergokryptine, and ergotamine derivatives are characterized by ions *m/z* 328, 294, and 300, respectively, that in turn release the $R^1CO–CO$ species (to give ions *m/z* 229, 195, and 229, respectively) and thus determine the R^1 substitution. With the exception of the ergotamine derivative, the peptide ions of all alkaloids readily eliminate the methyl radical (elimination from the acetyl group in ergotamine is not favoured). Further ions originating from the peptide parts of the molecules are *m/z* 111 (analogous to *m/z* 125 observed in spectra of parent ergopeptines[19]) and the *m/z* 70 fragment (composition $C_4H_8^+$) characterizing proline. The absence of a carbonyl group at 6′-position dramatically affected the fragmentation of the corresponding peptide ions. In contrast to α-ergokryptine showing an extensive side chain losses from the piperazine ring, the fragmentation of its 6′-deoxo derivative led predominantly to the methyl-radical loss.

Pseudomolecular ions of all new compounds **6**–**11** found in their FAB mass spectra were by 14 mass units lower than those of the parent compounds **1**–**5**. The molecular formulas (determined indirectly as the sum of elemental compositions of complementary ergoline and peptide ions) confirmed the loss of one oxygen atom. Two carbonyl signals appearing in the ^{13}C NMR spectra instead of three in the parent compounds proved this idea. Characteristic signals of two sp^3-hybridized carbons attached to two heteroatoms (C-2′, C-12′) indicated the intact cyclol system. According to COSY and LR COSY experiments, the ergoline or ergolene moieties were not affected by reduction. An exception was the case of ergocristine, where the second reaction product was found to be derived from ergocristinine through its 8-epimerization. Newly formed methylene groups (carbons resonating at 52–55.5 ppm, Table I) corresponded to a carbon of the –CH_2N– type. Protons H-6′ in compounds **6**–**11** (Table II) exhibited two additional couplings when compared with their counterparts in the parent alkaloids. The sources of these couplings were the methylene protons attached to the above mentioned carbons. Except their mutual couplings, these protons had no other coupling partners except H-6′. Therefore, the reduction took place at the second amino acid of **6**–**11**.

Protons formed as the result of the keto group reduction exhibit magnetic non-equivalence (0.864–1.074 ppm, Table II) and similar multiplicity (Table III): one small and one medium coupling. The changes at C-5′ are also reflected by the couplings of H-5′ to its neighbours in the side chain (**1**: 6.0, 7.6; **2**: 4.9, 7.0; **3**: 5.4, 8.1; **4**: 5.8, 6.1; **5**: 5.8, 6.3; **6**: 8.4, 6.6; **7**: 11.5, 3.5; **8**: 11.7, 3.6; **9**: 8.3, 6.7; **10**: 11.0, 4.3; **11**: 11.0, 4.4 Hz). The resulting

conformation is markedly different from that of parent compounds. The observed couplings correspond to one *antiperiplanar-* and one *gauche*-oriented proton. A crucial significance for the potential biological activity might have the predominant population of conformers with different orientation of the benzyl group of **7**, **10**, and **11** in solution, with respect to **2**, **4**, and **5** (see footnote to Table III). Noteworthy, the same conformation is found in the solid state (see Table V, χ_3^1, and Fig. 1). The effect of C=O group reduction is also manifested on the proline ring atoms. The most

TABLE V
Comparison of selected torsion angles in 6′-deoxo-9,10-dihydroergotamine (**11b**) and ergotamine tartrate bis(ethanol) solvate[23] (**11**)

Torsion angle[a]			**11b**	**12**
Piperazine ring	N4C19C20N5	Ψ_3	0.3(8)	–48.9(4)
	C19C20N5C24	ω_3	–1.6(9)	62.7(4)
	C20N5C24C25	θ_4	–24.6(9)	–64.8(4)
	N5C24C25N4	Ψ_4	49.0(7)	54.8(4)
	C24C25N4C19		–56.5(7)	–50.7(4)
	C25N4C19C20		31.1(8)	46.5(4)
Phenylalanine	N4C19C27C28	χ_3^1	–68.6(8)	–171.4(3)
Proline ring	C19C20N5C21		–174.8(6)	–179.9(4)
	C20N5C24C23		–150.3(5)	168.9(3)
	N5C24C23C22	χ_4^1	–37.7(7)	–30.0(4)
	C21C22C23C24	χ_4^3	38.6(7)	4.9(5)
	N5C21C22C23	χ_4^3	–24.8(8)	22.0(5)
	C22C21N5C24	χ_4^4	1.0(8)	–42.0(4)
	C21N5C24C23	χ_4^5	23.6(7)	45.1(4)

[a] Denotation of torsion angles by Greek letters refers to the usual peptide nomenclature and does not consider subsequent modification of a particular amino acid.

marked results are the large upfield shift of H-11' (1.55–1.65 ppm) and increased magnetic nonequivalence of H-8' protons (1.03–1.10 ppm) with respect to the parent compounds (0.06–0.11 ppm). Unfortunately, because of extensive signal overlap, the extraction of all vicinal coupling constants defining the proline ring conformation was not possible from the NMR data. Slight changes in the carbon chemical shifs were also found at atoms C-2' (–0.96 to –1.51 ppm) and C-12' (1.7–2.1 ppm).

Crystal structure determination of **11b** (crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-147347. Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.cam.ac.uk.), a representative member of the series, provided an additional confirmation of the molecular structure. Whereas the conformation of the ergoline moiety is nearly identical in 6'-deoxo-9,10-dihydroergotamine as well as in all other 9,10-dihydro-ergopeptines[1,20–22], reduction of the carbonyl group affected dramatically the overall conformation and puckering of the cyclol moiety. The most interesting changes are summarized in Table V in comparison with ergotamine tartrate[23]. Obviously, the different puckering of the piperazine ring is associated with the $sp^2 \rightarrow sp^3$ hybridization of the C20 atom due to the transformation of the keto group into methylene. In contrast to NMR, X-ray data make it possible to obtain also a detailed information about the proline conformation (Table V). The hydrogen bond network (Fig. 2a) forms interesting "pillars" in the *y* direction (see Fig. 2b for detail), represented by N1–H611···O3 [–*x* – 1/2, *y* – 1/2, –*z* + 1] (148° angle, 2.954(3) Å separation) and a bridge-like formation N3–H631···O80–H801···N5 [*x*, *y* – 1, *z*] (173°, 2.868(4) Å for N3–H631–O80 and 166°, 2.980(6) Å for O80–H801–N5). Note the dashed H611···O3 lines in Fig. 2a representing sets of zig-zag bonds as shown in Fig. 2b. The formation of butan-2-one solvate is expected to be responsible for the stability and growth of the crystal. Most of the compounds described in this work form unsolvated crystals not suitable for X-ray analysis. Replacing C26 with a larger substituent may also destabilize the "bridge". The second water molecule is attached to N2 *via* O90–H901···N2 (164°, 2.826(5) Å). An intramolecular hydrogen bond O5–H551···O1 (153°, 2.724(4) Å) is typical of most ergopeptines. No acceptable contact was found for butan-2-one.

The new compounds exhibited receptor activities (dopamine, serotonine, noradrenaline) similar to those of parent compounds but they were more lipophilic. A detailed study of their pharmacological properties will be reported elsewhere.

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