2,3-DIHYDRO-2-OXOERGOLENE DERIVATIVES

Ladislav CVAK[a], Josef STUCHLIK[a], Magdalena SCHREIBEROVA[a],
Petr SEDMERA[b], Vladimir HAVLICEK[b] and Miroslav FLIEGER[b]

[a] *Galena Co., 747 70 Opava-Komarov, The Czech Republic*
[b] *Institute of Microbiology,*
Academy of Sciences of the Czech Republic, 142 20 Prague 4, The Czech Republic

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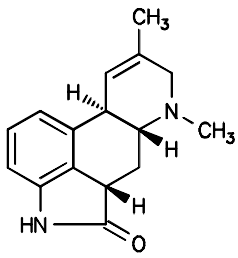
A general procedure for the preparation of 2-oxo derivatives of 8- or 9-ergolene is reported. Mass and NMR spectra of these compounds are discussed.

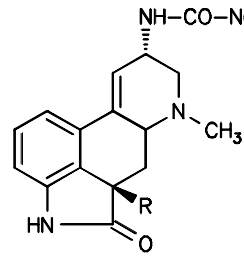
Biodegradation products of ergot alkaloids are plausible candidates in the quest for modification of these important pharmaceuticals. Oxidation at C-2 was proposed as the first step in the metabolism of semisynthetic ergolene derivatives[1]. The 2-oxo derivative of LSD was prepared by a two-step procedure in very low yield[2]. Recently, we reported the formation of 2,3-dihydro-2-oxo-α-ergokryptine and 2,3-dihydro-3-hydroxy-α-ergokryptine as the side products in bromination of α-ergokryptine[3]. An electrochemical procedure for the preparation of D-3-alkoxy-halogen-2,3-dihydro-6-methyl-2-oxoergolines was also described[4]. An optimized method for the functionalization at C-2 of both natural and semisynthetic ergot alkaloids together with the discussion of spectral properties of these compounds is presented here.

We have previously noticed that the presence of water is essential for the formation of 2,3-dihydro-2-oxoergolenes[3] during the parent alkaloid bromination. Therefore, we examined the effect of increasing water content in the reaction mixture. Originally recommended ten equivalents of water might be lowered to five providing that more bromine (1.5 – 4 equivalents) was used. The reaction is completed within few minutes at room temperature. The excess of bromine is removed by washing with aqueous sodium metabisulfite and the product is isolated[5]. With Δ^9-ergolenes, the 2-oxo derivatives prevail in the reaction mixture and could be isolated in good yields (Table I). However, the analogous compound *I* derived from agroclavine (*IX*), (Δ^8-ergolene), was obtained in much lower yield. With ergolines (i.e., 9,10-dihydro derivatives), the reaction mixture always contained bromo derivatives but according to NMR spectroscopy, the 2-oxo compounds were also present, albeit below 30%. Successful application of the method to simple ergines (agroclavine, *IX*), their semisynthetic derivatives (lisuride, *X*), lysergic acid amides (methylergometrine, *XI*), and three peptide alkaloids (ergotamine

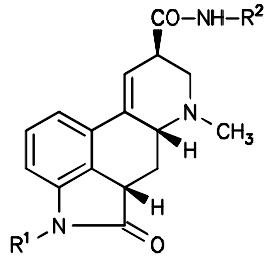
XII, ergocristine *XIII*, and α-ergokryptine *XIV*) demonstrates its general character. The new compounds now undergo basic tests and might be also used as an entry to novel modified ergolene derivatives.

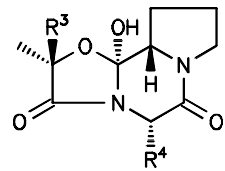


I



II, R = H
VIII, R = OH



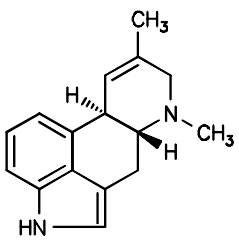


III, R^1 = H; R^2 = $CH(CH_2OH)CH_2CH_3$
IV, R^1 = CH_3; R^2 = $CH(CH_2OH)CH_2CH_3$
V, R^1 = H; R^2 = Z; R^3 = CH_3; R^4 = $CH_2C_6H_5$
VI, R^1 = H; R^2 = Z; R^3 = $CH(CH_3)_2$; R^4 = $CH_2C_6H_5$
VII, R^1 = H; R^2 = Z; R^3 = $CH(CH_3)_2$; R^4 = $CH_2CH(CH_3)_2$

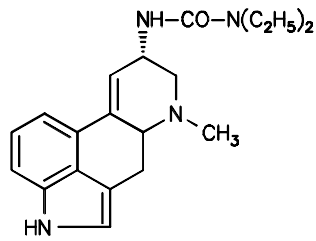
The molecular weight information on the prepared compounds (Table I) was extracted from their mass spectra. Soft ionization techniques – field desorption (FD) and chemical ionization (CI) – were needed for peptide alkaloids *V* – *VII* and 3-hydroxy derivative *VIII*. FD spectra are quite simple, besides the molecular cation-radical only the fragments corresponding to ergine-peptide bond rupture are usually observed (Scheme 1; fragmentation pattern of 2-oxoergotamine (*V*)). In contrast, the electron-impact (EI) spectra contain a wealth of fragments originating from those two ions (cf. Fig. 1). As the peptide fragmentation series is essentially identical to that described[6], it can be left aside. The remarkable feature of the ergine ion fragmentation is the retro-Diels–Alder reaction[7]. With *II* and *VII*, this fragmentation mode is especially pronounced,

producing the abundant $[M - 43]^{+\bullet}$ ions. The observation of *m/z* 43 ion as a doublet composed of $C_2H_5N^{+\bullet}$ and $C_2H_3O^+$ under high-resolution conditions indicates that the eliminated C_2H_5N species may also bear a positive charge. This deduction is further supported by the observation of neutral loss of 43 amu from the ergine ion in the appropriate linked scan. The fragmentation pathways *m/z* 283 → 240 → 223 → 195 and 283 → 239 → 237 (Scheme 1) are specific for 2-oxo derivatives of ergot alkaloids and their presence in the mass spectra might be used for diagnostic purposes.

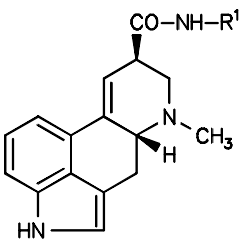
Comparison of ^{13}C NMR spectra of the reaction products (Table II) with those of parent compounds reveals two new signals – a carbonyl (177.7 – 182.2 ppm) and an aliphatic CH (38.8 – 42.9 ppm) – formed at the expense of the carbons originally constituting a trisubstituted double bond. The carbonyl chemical shifts agree well with those reported for 3β-alkoxy-2,3-dihydro-8β-(hydroxymethyl)-6-methylergoline-2-ones[4]. An



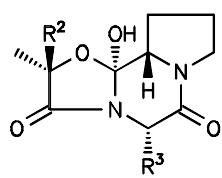
IX



X



Z =



XI, $R^1 = CH(CH_2OH)CH_2CH_3$
XII, $R^1 = Z$; $R^2 = CH_3$; $R^3 = CH_2C_6H_5$
XIII, $R^1 = Z$; $R^2 = CH(CH_3)_2$; $R^3 = CH_2C_6H_5$
XIV, $R^1 = Z$; $R^2 = CH(CH_3)_2$; $R^3 = CH_2CH(CH_3)_2$

TABLE I
Yields and physical properties of compounds *I* – *VIII*

Compound	Yield, %	M.p., °C	$[\alpha]_D^{20}$, °	*c*, $CHCl_3$	M.w.	Method
I	31	174.1 – 175.2	–275.3	1.0[a]	254[b]	EI
II	76	118.8 – 121.4	+16.5	0.5	354[c]	EI
III	61	223.2 – 224.9	–113.5	0.5	355[d]	EI
IV	82	215.2 – 216.4	–105.0	0.5	369[e]	EI
V	54	205.0 – 206.8	–64.5	0.3	597	FD
VI	70	196.0 – 196.8	–108.9	0.5	625	FD
VII	64	213.0 – 213.3	–125.0	0.5	591	FD
VIII	50	203.0 – 205.0	+278.9	0.5	371[f]	CI

[a] $CHCl_3$–MeOH 1 : 1. [b] $C_{16}H_{18}N_2O$. [c] $C_{20}H_{26}N_4O$. [d] $C_{20}H_{25}N_3O_3$. [e] $C_{21}H_{27}N_3O_3$. [f] $[M + 1]^+$.

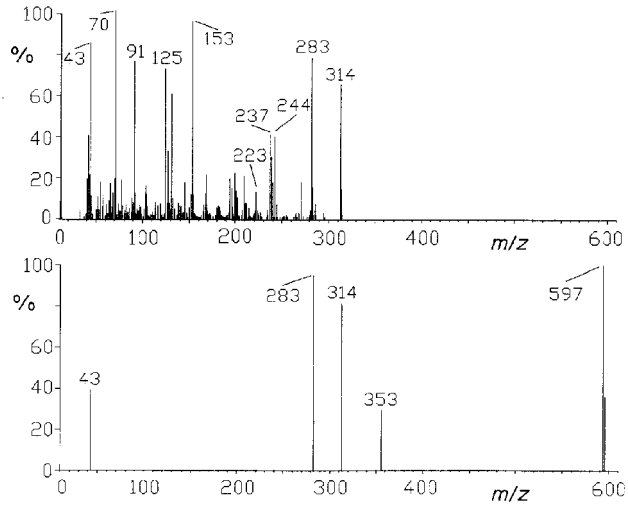
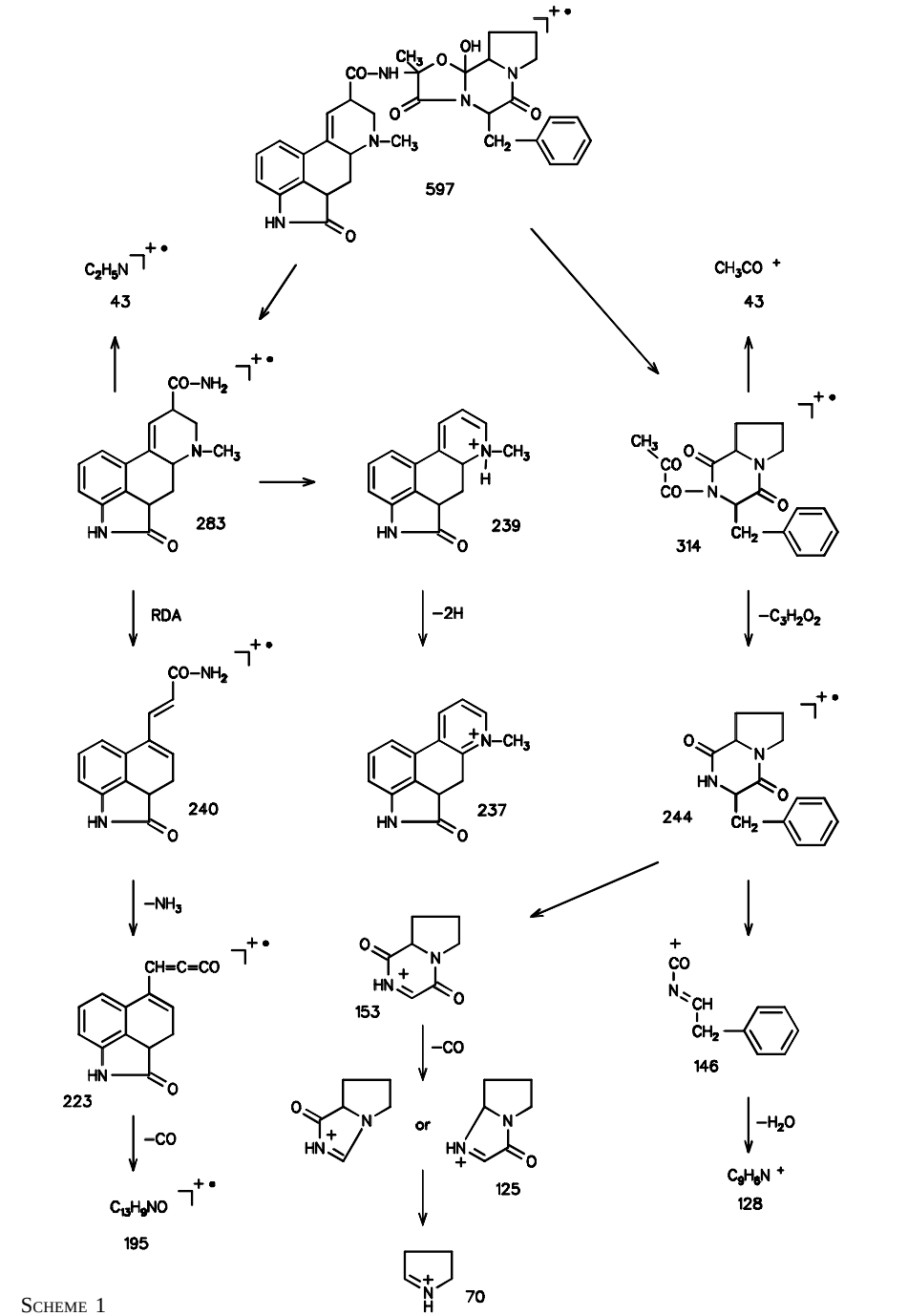


FIG. 1
Comparison of electron impact (top) and field desorption (bottom) mass spectra of 2-oxoergotamine (*V*)


597
43
43
283
239
314
RDA
−2H
−C3H2O2
240
237
244
−NH3
223
153
146
−CO
−CO
−H2O
or
125
128
195
70

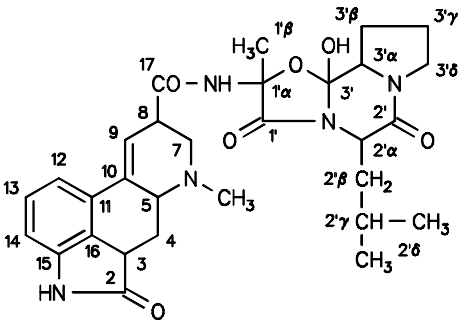
SCHEME 1

TABLE II
^{13}C NMR chemical shifts (ppm, δ-scale, 100.577 MHz, $CDCl_3$) of compounds *I – VIII;* for the numbering see formula *XV*

Atom	*I*	*II*[a]	*III*[b]	*IV*[c]	*V*	*VI*	*VII*[d]	*VIII*[e]
2	182.24	180.10	179.04	177.70	179.35	180.45	181.51	179.36
3	38.77	42.28	41.87	42.14	42.15	42.67	42.89	69.63
4	24.99	27.64	27.12	27.29	26.84	26.63	26.38	32.17
5	63.97	65.30	63.07	63.70	63.27	63.07	63.24	59.46
7	60.30	60.24	55.71	55.92	54.33	53.78	53.68	61.08
8	134.02	44.89	41.92	43.70	43.64	43.42	44.26	44.28
9	117.90	122.05	120.79	119.26	117.88	118.48	118.51	122.99
10	40.95	140.10	141.13	142.97	139.80	140.01	139.75	141.00
11	138.14	134.66	130.33	130.32	130.64	130.46	130.53	131.89
12	116.51	115.53	114.23	115.56	115.80	115.76	116.43	115.86
13	127.98	128.45	127.90	128.50	126.76	128.61	128.54	130.76
14	107.35	107.76	106.86	106.15	107.99	108.24	107.95	108.41
15	139.36	134.66	132.66	135.05	136.04	135.30	135.62	133.09
16	126.68	126.87	126.86	125.99	126.76	126.50	126.36	126.63
17	20.96	–	171.46	173.09	173.94	174.66	175.30	–
NCH_3	41.64	44.23	41.69	42.46	42.45	42.21	42.80	42.89
1′	–	–	–	–	165.80	166.05	165.33	–
1′α	–	41.07[f]	52.24	53.42	85.87	90.49	90.78	41.02[f]
1′β	–	13.73[f]	23.67	24.16	24.79	33.88	33.53	13.69[f]
1′γ_1	–	–	10.40	10.59	–	16.87	16.94	–
1′γ_2	–	–	63.03[g]	65.05[g]	–	15.38	15.26	–
2′	–	–	–	–	164.86	164.95	166.71	–
2′α	–	–	–	–	57.32	56.98	53.71	–
2′β	–	–	–	–	39.45	39.56	43.75	–
2′γ	–	–	–	–	138.30	138.57	24.99	–
2′δ	–	–	–	–	130.14[f]	129.93[f]	21.97	–
2′ε	–	–	–	–	127.98[f]	127.97[f]	23.15[h]	–
2′η	–	–	–	–	128.67	126.30	–	–
3′	–	–	–	–	103.63	104.16	104.56	–
3′α	–	–	–	–	65.40	64.14	64.34	–
3′β	–	–	–	–	26.51	26.38	27.02	–
3′γ	–	–	–	–	22.26	22.18	22.03	–
3′δ	–	–	–	–	46.27	46.20	46.10	–

[a] Additional signal: 156.66 (NCON). [b] In CD_3SOCD_3 [c] Additional signal: 26.39 (N(1)–Me). [d] Ref.[3]. [e] Additional signal: 156.78 (NCON). [f] 2 C. [g] C-1′α. [h] C-2′δ_2.

attempt to increase the solubility of studied compounds in $CDCl_3$ by addition of CD_3OD (compounds *III* and *V*) or even measuring the NMR spectra in this solvent resulted in a fast exchange of H-3 for deuterium causing a disappearance of both H-3 and C-3 signals. All couplings to H-3 were also removed from the ^{1}H NMR spectrum what was slightly misleading. Except for small changes in the chemical shifts of the ergine carbons, the remaining ones faithfully reproduced the pattern of parent compounds.



XV

The salient feature of the ^{1}H NMR spectra of compounds *I* – *VII* (Tables III and IV) are additional couplings observed on both H-4 protons and a new multiplet of H-3 around 3.5 ppm. The large coupling *J*(3,4a) (12.1 – 12.5 Hz) corresponds to an axial–axial coupling and defines the H-3 configuration as 3β. This conclusion is supported by a cross-peak between H-3 and H-5 in the ROESY spectrum[8] of *VII*. Measurable long-range coupling of H-3 to H-13 was observed in all investigated compounds (Table IV) and was confirmed by decoupling or delayed-COSY experiments[9]. A decrease in the magnitude of *J*(4a,4e) (Table IV) with respect to the parent compounds reflects the removal of the adjacent C2–C3 bond[10]. Smaller *J*(4e,5) indicates a slightly different conformation of the ring C. Chemical shifts of the aromatic protons H-12, H-13, and H-14 (Table III) are different from those of parent compounds. These signals were therefore unambiguously assigned using the NOE between H-9 and H-12 (NOESY spectra[11]). It was found that in many cases the order in which H-12 and H-14 appear in the spectrum is reversed. Since both indole N–H and amide N–H resonate as singlets in ^{1}H NMR spectra of *VI* – *VII*, again NOE between amide N–H and C-1′ side chain protons was used to differentiate among them.

There are two possible conformations of the cyclohexene ring D, flap-up and flap-down (structures *A* and *B*). Since the possibility of C-8 substituent inversion cannot be a priori ruled out in our case, another two possibilities (*C*, *D*) come into consideration. Several criteria have to be applied simultaneously to solve these conformational and configuration problems. (i) The magnitude of *J*(8,9) decides whether H-8 is pseudo-

TABLE III
^{1}H NMR chemical shifts (ppm, δ-scale, 399.95 MHz, $CDCl_3$) of compounds *I – VIII*; for numbering see formula *XV*

Proton	*I*[a]	*II*	*III*[b]	*IV*[c]	*V*	*VI*	*VII*[d]	*VIII*
3	3.579 dddd	3.465 ddd	3.524 ddd	3.508 ddd	3.521 ddd	3.504 ddd	3.520 ddd	–
4a	1.595 ddd	1.357 ddd	1.144 ddd	1.364 ddd	1.420 ddd	1.346 ddd	1.331 ddd	0.962 dd
4e	2.765 m	2.889 ddd	2.570 ddd	2.836 dddd	2.802 dddd	2.743 ddd	2.743 ddd	2.262 ddd
5	2.615 ddd	2.874 ddd	3.094 ddd	3.225 dddd	3.263 dddd	3.252 dddd	3.091 dddd	2.982 dm
7a	3.161 ddq	2.615 ddd	3.053 ddd	3.199 ddd	2.685 dd	2.679 dd	2.541 dd	2.177 m
7e	2.743 dddq	2.921 ddd	2.562 dd	2.724 dd	3.104 ddd	3.028 ddd	2.940 ddd	2.177 m
8	–	4.550 m	3.416 m	3.508 m	3.345 m	3.296 m	3.037 m	4.409 m
9	5.979 m	6.490 m	6.836 m	6.437 m	6.164 ddd	5.984 m	5.383 ddd	6.289 dd
12	6.904 ddd	7.230 dd	7.173 dd	7.246 dd	7.140 dd	6.954 dd	6.663 dd	6.713 dd
13	7.178 ddd	7.138 ddd	7.080 ddd	7.206 ddd	7.172 ddd	7.075 ddd	7.088 ddd	7.161 dd
14	6.746 ddd	6.706 dd	6.603 dd	6.650 dd	6.693 dd	6.636 dd	6.726 dd	7.130 dd
N(1)–H	8.954 s	8.818 s	10.181 s	–	7.790 s	8.993 s	9.279 s	8.326 s
N(6)–Me	2.348 s	2.485 s	2.382 s	2.513 s	2.520 s	2.475 s	2.454 s	2.079 s
CONH	–	4.992 d	7.618 d	6.096 d	7.088 s	7.921 s	7.854 s	5.779 d
1′β	–	1.097 t	–	–	1.584 s	2.225 qq	2.428 qq	1.097 t
1′γ_1	–	3.233 q	–	–	–	1.116 d	1.127 d	–
1′γ_2	–	–	–	–	–	0.914 d	0.948 d	–
2′α	–	–	–	–	4.710 dd	4.702 dd	4.571 dd	–
2′β_1	–	–	–	–	3.481 dd	3.462 dd	1.881 m	–
2′β_2	–	–	–	–	3.233 dd	3.246 dd	1.881 m	–
2′γ	–	–	–	–	–	–	1.997 m	–

TABLE III
(*Continued*)

Proton	*I*[a]	*II*	*III*[b]	*IV*[c]	*V*	*VI*	*VII*[d]	*VIII*
2′δ_1	–	–	–	–	7.422 m	7.433 m	1.109 d	–
2′δ_2	–	–	–	–	–	–	0.989 d	–
2′ε	–	–	–	–	7.262 m	7.253 m	–	–
2′η	–	–	–	–	7.183 m	7.156 m	–	–
3′α	–	–	–	–	3.562 ddd	3.712 ddd	3.707 ddd	–
3′β_1	–	–	–	–	2.133 m	2.188 m	2.151 m	–
3′β_2	–	–	–	–	1.790 m	2.138 m	2.006 m	–
3′γ_1	–	–	–	–	2.064 m	2.073 m	1.962 m	–
3′γ_2	–	–	–	–	1.812 m	1.810 m	1.828 m	–
3′δ_1	–	–	–	–	3.648 m	3.650 m	3.625 m	–
3′δ_2	–	–	–	–	3.551 m	3.558 m	3.560 m	–
3′-OH	–	–	–	–	6.556 d	7.361 d	7.506 d	–

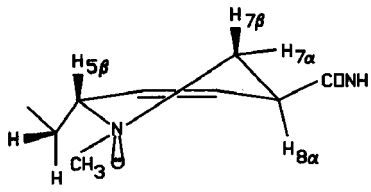
Additional signals: [a] 1.771 ddd (3 H, H-17); [b] 4.593 t (OH), 3.980 m (1′α), 3.386 dd (2 H, 1′α_1), 1.316 ddq (1′β_1), 1.572 ddq (1′β_2), 0.836 t (3 H, 1′γ); [c] 3.882 m (1′α), 3.596 dd (1′α_1), 3.696 dd (1′α_2), 3.187 s (3 H, N(1)–Me), 1.507 ddq (1′β_1), 1.623 ddq (1′β_2), 0.952 t (3 H, 1′γ). [d] Ref.[3], completed.

TABLE IV
Selected proton–proton coupling constants J, (Hz) of compounds *I* – *XIV*

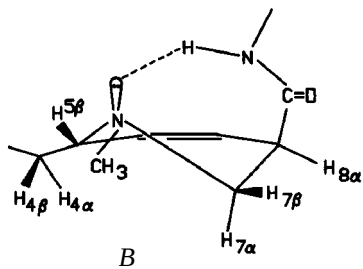
Protons	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*	*XI*	*XII*	*XIII*	*XIV*
3a,4a	–12.1	–12.3	–12.4	–12.5	–12.4	–12.3	–11.4	–	–	–	–	–	–	–
3e,4e	5.3	3.9	4.7	4.7	4.8	4.9	4.8	–	–	–	–	–	–	–
3,13	1.2	0.9	0.9	1.0	0.8	1.0	0.9	–	–	–	–	–	–	–
4a,4e	–11.6	–12.6	–11.5	–11.6	–11.6	–11.6	–11.7	–12.4	–14.4	–14.2	–14.4	–14.0	–14.1	–14.1
4a,5	11.6	12.3	11.6	11.8	11.5	11.6	12.4	12.1	11.7	11.8	11.5	12.0	12.0	12.0
4e,5	2.3	4.3	4.2	3.5	3.2	3.1	3.1	3.6	4.0	5.9	5.7	5.1	4.3	4.9
4e,9	–	–	–	0.9	0.6	–	0.6	1.4	–	0.7	–	–	–	–
5,8	–	–	–	3.5	3.5	3.0	2.7	[a]	–	2.0	3.4	1.5	1.0	1.0
5,9	–	1.3	2.2	2.5	2.4	2.4	0.6	[a]	–	2.1	2.2	2.0	1.9	2.0
7a,7e	–16.2	–12.1	–11.2	–11.7	–11.7	–11.6	–11.1	–12.3	–16.2	–13.0	–11.2	–11.9	–12.0	–12.1
7a,8	–	3.7	11.2	10.3	9.4	8.9	9.0	[a]	–	4.9	10.6	3.9	2.2	2.2
7e,8	–	1.5	6.1	6.0	5.5	5.1	4.7	[a]	–	1.2	5.0	4.0	3.6	3.5
7e,9	2.5	1.2	0.9	1.1	0.8	0.8	0.8	[a]	2.3	1.1	1.2	0.9	1.0	1.0
8,9	–	5.4	2.1	2.9	3.1	2.7	3.3	[a]	–	5.5	1.2	5.1	6.0	6.1

[a] Not determined.

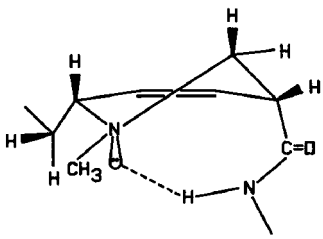
axial (small coupling) or pseudoequatorial (J = 4 – 6 Hz). (ii) The couplings of H-8 to both H-7 protons define their relative orientation. Large J means a pseudoaxial–pseudoaxial relationship, the medium one corresponds to pseudoaxial–pseudoequatorial or pseudoequatorial–pseudoaxial coupling, and small J is typical for a pseudoequatorial–pseudoequatorial orientation. (iii) Chemical shift of the amide proton of the C-8 substituent (if there is any) is large when this group is involved in hydrogen bonding (structures *B* and *C*). (iv) Chemical shift of H-5 reflects the orientation of this atom with respect to the N-6 nitrogen lone pair (*trans*-oriented protons resonate around 3.2 ppm, *gauche*-oriented ones about 3.8 ppm)[12]. (v) NOE is expected between H-5 and H-7a in structures *A* and *C*. (vi) Although NOE between N-methyl and H-4e, H-5, and H-7e occurs in all structures, it nevertheless proves the pseudoequatorial orientation of this group.



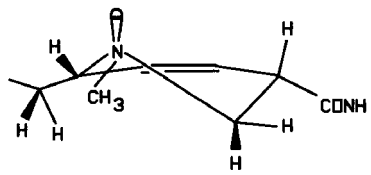
A



B



C



D

Application of these criteria to the analysis of ^{1}H NMR parameters (Table III and IV) complemented by the results of NOESY experiments reveals that with compounds *III – VII* the D-ring adopts a flap-up conformation *A*, in contrast to parent compounds *XI – XIV* existing in the flap-down conformation *B*. The conformation of the D-ring in 2-oxo derivative of lisuride *II* also differs from that of lisuride *X*, (*C* instead of *D*). According to observed coupling constants, there are also some differences in C- and D-ring conformations between agroclavine (*IX*) and its 2-oxo derivative *I*. It is known[13,14] that D-ring conformation of ergolene derivatives might be altered by protonation or solvent change (e.g., $CDCl_3$ vs CD_3SOCD_3). Our results indicate another possible driv-

ing force: conformational transmission (a change in ring B altering the conformation of the ring D).

Upon optimization of reaction conditions, the 3-(2,3,9,10-tetrahydro-2-oxo-3-hydroxy-6-methyl-8α-ergolinyl)-1,1-diethylurea (*VIII*), i.e. a lisuride derivative, was prepared in 50% yield. For its physico-chemical characterization see Table I, for spectral data see Experimental. The problem of 3-hydroxyl group configuration was solved through comparison of the CD spectra with those of (+)-2,14-dibromo-8β-(hydroxymethyl)-3β-methoxy-6-methylergolin-2-one whose structure has been determined by X-ray diffraction[4]. Strong positive Cotton effect and smaller negative one at 278 and 315 nm qualitatively agree with the reported values so that the absolute configuration of our compound *VIII* is 3*R*.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and were not corrected. Unless otherwise indicated, optical rotations were measured in chloroform. The CD spectrum (190 – 350 nm) of compound *VIII* in methanol (*c* 0.002 mol l^{-1}) was measured with a Jobin–Yvon model 5 automatic recording spectropolarimeter at ambient temperature. Mass spectra were recorded in positive ion mode with a double focusing instrument Finnigan MAT 90 (BE geometry). Electron impact: ionizing energy 70 eV, ion source temperature 250 °C, emission current 1 mA, acceleration voltage 5 kV, direct inlet. High resolution measurements were carried out by magnetic scan with perfluorokerosene as an internal standard. The products of metastable collisionally activated decompositions (helium as a collision gas, 1 . 10^{-3} Pa) in the first field-free region were analyzed by following linked scans: daughter ions – B/E = const; parent ions – B^2/E = const; neutral losses – $B^2/E^2 * (E_0 - E)$ = const, using the manufacturer's software. Chemical ionization: ammonia as a reagent gas (2 . 10^{-2} Pa), temperature 200 °C, emission current 0.2 mA. Field desorption: standard Finnigan MAT FD source was operated at an accelerating voltage 5 kV with the counter electrode kept at −7 kV. Samples were dissolved in chloroform and deposited on the emitter (standard activated 10 μm tungsten wire) by the modified syringe technique. Ion current production was controlled by total ion current and emitter heating current programmer (Linden ChroMasSpec FDF-700, F.R.G.). The molecular ion of acetone *m*/*z* 58 was used for FD source tuning.

^{1}H and ^{13}C NMR spectra (399.952 and 100.577 MHz, respectively) were measured on a Varian VXR-400 spectrometer in deuteriochloroform (except for compound *III* which was studied in hexadeuteriodimethyl sulfoxide) at 25 °C. Tetramethylsilane or residual solvent signal ($CDCl_3$: δ_H 7.265, δ_C 77.00; CD_3SOCD_3: δ_H 2.500, δ_C 39.60) were used as internal references. Spectrum width varied between 3 100 – 4 500 Hz and 18 000 – 22 000 Hz for ^{1}H and ^{13}C NMR spectra; data were collected into 64 K or 32 K memory, respectively. The digital resolution was better than 0.0003 (0.01) ppm. Proton-coupled ^{13}C NMR spectra (decoupler off during the acquisition only), APT, and DEPT GL spectra used for the determination of carbon signal multiplicity were run under similar conditions as the standard proton noise-decoupled ^{13}C NMR spectra. All 2D NMR spectra were done using the manufacturer's software.

COSY spectra. Sequence: D_1–90°–t_1-60°–t_2. Relaxation delay D_1 = 1 s, sweep width equal to that of ^{1}H NMR spectrum, identical for both F_1 and F_2. Data table 2 K × 2 K; 256 increments were acquired and zerofilled to 2 K, pseudo-echo shaped, symmetrized after FT, and presented in the absolute value mode.

Long-range COSY spectra[9]. Sequence: D_1–90°–t_1–D_2–60°–D_2–t_2. Relaxation delay D_1 = 1 s, delay D_2 = 0.2 s; other parameters were identical to that of normal COSY.

J-Resolved (HOM2DJ) spectra. Sequence: D_1–90°–$t_1/2$–180°–$t_1/2$–t_2. Relaxation delay D_1 was 1 s, spectral width in F_1 was 50 Hz; 64 increments (16 scans each) were accumulated into 4 K × 512 data points, pseudo-echo shaped, rotated, and symmetrized. Projection onto F_2 axis was used to obtain chemical shifts.

NOESY spectra. Sequence: D_1–90°–t_1–90°–tau_{mix}–90°–t_2. Relaxation delay D_1 = 1 s, mixing time 0.2 s. Quadrature detection in both dimensions, data table 1 K × 1 K, 256 increments, line broadening 0.1 Hz in both dimensions, hypercomplex Fourier transformation according to States, Habercorn and Ruben[14], phase-sensitive presentation (negative peaks only).

ROESY spectra[8]. Sequence: D_1–90°–t_1–(β-tau)$_n$–t_2. Relaxation delay D_1 = 1 s, β = 32°, mixing time 0.2 s. Other details identical to that of NOESY spectra.

^{1}H,^{13}C-COSY (HETCOR) spectra. Sequence: D_1–90°(^{1}H)–$t_1/2$–180°(^{13}C)–$t_1/2$–(1/2J)–90°(^{1}H,^{13}C)–(1/3J)–t_2. Relaxation delay D_1 = 1.5 s; optimized for direct coupling of 145 Hz, noise-decoupled during the acquisition. Spectral widths were taken from the corresponding 1D experiments; 4 K × 512 data points, pseudo-echo shaped in both dimensions, usually 64 increments (zerofilled to 512 data points), absolute value presentation.

Reported assignments (Tables II, III) are based on the extensive use of 2D NMR spectra and (in the case if quaternary carbon atoms) on the assigned ^{13}C NMR spectra of the parent compounds (by long-range HETCOR) aided by examination of the fine structure of multiplets in proton-coupled ^{13}C NMR spectra. To facilitate the comparison of different peptide alkaloids, the cyclol moiety was numbered according to the amino acids and the greek letters were used within each unit (see formula *XV*).

General Procedure for Preparation of Compounds *I – VIII*

Water (10 ml) was added to the solution of ergocristine (11.1 g, 17.7 mmol) in dichloromethane–tetrahydrofuran (2 : 1, 600 ml). Dichloromethane solution of bromine (2%, 400 ml) was added dropwise during 5 min under stirring at room temperature. The mixture was stirred 1 min, aqueous sodium metabisulfite (5%, 400 ml) was added and stirred another 5 min. The aqueous layer was extracted with dichloromethane (200 ml), combined extracts were washed with saturated aqueous sodium hydrogen carbonate and with water, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on silica gel (100 g, elution with dichloromethane). Crystallization of the crude product from acetone yielded 2,3-dihydro-2-oxo-ergocristine (*VI*) (7.7 g, 70%), m.p. 196.0 – 196.8 °C, $[\alpha]_D^{20}$ -108.9° (*c* 0.5, $CHCl_3$). Compounds *I – V* and *VII – VIII* were prepared analogously; for yields and physical constants see Table I.

Electron Impact Mass Spectra of Compounds *I – VIII*

Compound I (*m*/*z*, % rel. int.): 255 (12), 254 (70, $C_{16}H_{18}N_2O$), 253 (100), 239 (13), 238 (6), 198 (5), 197 (11), 196 (9), 183 (7), 182 (22), 108 (10), 85 (10), 83 (16), 42 (4).

Compound II (*m*/*z*, % rel. int.): 354 (1, $C_{20}H_{26}N_4O_2$), 312 (12), 311 (61), 239 (22), 238 (86), 237 (53), 211 (46), 210 (18), 209 (26), 195 (13), 182 (19), 154 (7), 100 (100), 72 (32), 58 (25), 44 (16), 42 (13).

Compound III (*m*/*z*, % rel. int.): 356 (23), 355 (100, $C_{20}H_{25}N_3O_3$), 241 (11), 240 (55), 239 (67), 238 (29), 237 (73), 225 (11), 224 (33), 223 (11), 210 (12), 209 (31), 196 (18), 195 (11), 181 (10), 168 (11), 167 (14), 154 (5).

Compound IV (*m*/*z*, % rel. int.): 370 (23), 369 (100, $C_{21}H_{27}N_3O_3$), 254 (22), 253 (80), 252 (27), 251 (85), 238 (22), 237 (10), 223 (19), 210 (10), 167 (8), 154 (5), 152 (9), 55 (11), 43 (10), 42 (11).

Compound V (*m/z*, % rel. int.): 314 (64, $C_{17}H_{18}N_2O_4$), 283 (77, $C_{16}H_{17}N_3O_2$), 244 (39, $C_{14}H_{16}N_2O_2$), 243 (26), 240 (17, $C_{14}H_{12}N_2O_2$), 239 (29, $C_{15}H_{15}N_2O$), 238 (13, $C_{15}H_{14}N_2O$), 237 (40, $C_{15}H_{13}N_2O$), 223 (13, $C_{14}H_9NO_2$), 209 (21), 200 (22), 195 (19, $C_{13}H_9NO$), 153 (95, $C_7H_9N_2O_2$), 152 (12, $C_7H_8N_2O_2$), 146 (17, C_9H_8NO), 131 (60), 128 (32, C_9H_6N), 125 (72, $C_6H_9N_2O_)$, 91 (76, C_7H_7), 77 (19, C_6H_5), 70 (100, C_4H_8N), 43 (60, C_2H_3O; 20, C_2H_5N).

Compound VI (*m/z*, % rel. int.): 342 (44, $C_{19}H_{22}N_2O_4$), 283 (50, $C_{16}H_{17}N_3O_2$), 272 (25), 244 (50), 243 (64), 240 (8), 239 (20), 237 (22), 223 (30), 153 (44), 146 (16), 131 (32), 128 (26), 125 (17), 91 (40), 71 (92), 70 (100), 43 (82).

Compound VII (*m/z*, % rel. int.): 308 (16, $C_{16}H_{24}N_2O_4$), 284 (19), 283 (100, $C_{16}H_{17}N_3O_2$), 252 (18), 240 (17), 239 (30), 238 (43), 237 (44), 210 (34), 209 (70), 196 (15), 195 (46), 168 (20), 154 (76), 71 (52), 70 (77), 43 (67), 41 (26).

Compound VIII (*m/z*, % rel. int.): 327 (54, $C_{18}H_{21}N_3O_3$), 297 (23), 254 (73), 253 (44), 237 (19), 236 (20), 227 (21), 226 (25), 225 (18), 211 (21), 209 (19), 198 (22), 154 (11), 100 (100), 72 (35), 58 (27), 44 (22), 42 (23).

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