SIDE REACTIONS IN BROMINATION OF α-ERGOCRYPTINE

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2,3-Dihydro-2-oxo-α-ergocryptine (*III*) and 2,3-dihydro-2-oxo-3-hydroxy-α-ergocryptine (*IV*) were found as the side reaction products in bromination of α-ergocryptine (*I*) with bromine in the presence of water. 2,3-Dihydro-2-oxo-3-ethoxy-α-ergocryptine (*V*) was formed in the presence of ethanol.

The first report on the reaction of ergoline compounds with elemental bromine describes a complex mixture of products[1]. On the contrary, the reaction with N-bromosuccinimide in dioxane gives 2-bromo derivatives in high yield. Other agents like N-bromophthalimide or N-bromoacetamide react similarly but the yields are lower. Because of widespread use of 2-bromo-α-ergocryptine in medicine, the bromination of ergot alkaloids was given considerable attention, mainly in the patent literature[2-5]. Most frequently treated problems are the optimization of reaction conditions and the use of different bromination agents, e.g. reaction with bromine in dichloromethane catalyzed by hydrogen bromide dissolved in glacial acetic acid[6].

We have elaborated the bromination of ergot alkaloids by elemental bromine catalyzed by Lewis acids, mainly boron trifluoride[7]. The reaction with 1·2–1·5 equivalents of bromine is carried out in dichloromethane or its mixture with tetrahydrofuran (a good solvent for majority of ergoline compounds) at −30 to 0°C; nearly complete conversion is achieved during 1 min reaction. Despite such a fast reaction, the yield of required 2-bromo derivative is high (70–90%). The proportion of highly brominated or decomposed products in the reaction mixture is usually low. However, the reaction is very sensitive to the presence of water or alcohols. For example, in the bromination of α-ergocryptine (*I*) in the presence of one equivalent of water, two unknown compounds giving characteristic yellow colour with van Urk reagent were isolated besides the required 2-bromo-α-ergocryptine (*II*).

Observation of fragmentation series[8] *m/z* 308, 209, 154, 153, 125, 86, 71, and 70 (electron impact mass spectra) and small changes in proton and carbon chemical shifts of the corresponding atoms (Tables I and II) indicate an unchanged cyclol moiety in the all reaction products.

The first members of the fragmentation ergine series in the mass spectrum of the prevailing compound, m/z 345 and 347, point to monobromination. Proton H-2 together with the couplings due to it and one olefinic methine (replaced by one quaternary sp^2-hybridized carbon) are missing in ^1H and ^{13}C NMR spectra. Changes

TABLE I
^{13}C NMR data (400 MHz, $CDCl_3$, TMS, 25°C)

Carbon	*I*	*II*	*III*	*IV*[a]	*V*[b]
2	119·07	104·28	181·51	180·57	177·49
3	110·77	110·83	42·89	70·83	74·63
4	21·55	22·05	26·38	32·83	36·24
5	59·17	58·70	63·24	58·69	54·11
7	48·04	48·04	53·68	55·51	47·78
8	44·29	44·24	44·26	42·85	43·77
9	118·94	119·48	118·51	119·98	117·06
10	139·08	138·31	139·75	141·73	139·90
11	129·70	128·54	130·53	132·58	145·79
12	112·00	112·62	116·43	116·27	117·04
13	123·36	123·40	128·54	131·13	129·48
14	110·03	109·50	107·95	109·11	115·00
15	133·82	134·18	135·62	134·42	136·40
16	126·23	126·53	126·36	127·38	119·22
17	176·22	175·99	175·30	175·82	175·97
N—CH_3	40·89	40·89	42·80	41·83	40·52
2′	89·68	89·70	90·78	91·31	89·60
3′	165·76	165·75	165·53	166·73	165·64
5′	53·28	53·31	53·71	53·92	53·22
6′	166·14	166·17	166·71	167·02	166·07
8′	45·95	46·00	46·10	46·64	45·93
9′	22·08	22·17	22·03	22·50	22·04
10′	43·47	43·46	43·75	43·97	43·41
10′a	64·46	64·44	64·34	65·00	64·43
10′b	103·47	103·48	104·56	104·25	103·43
11′	34·26	34·25	33·53	34·17	34·24
12′	16·89	16·86	16·94	17·32	16·86
13′	15·35	15·33	15·26	15·89	15·41
14′	26·46	26·43	27·02	26·79	26·41
15′	25·05	25·05	24·99	25·52	25·01
16′	22·58	22·56	23·15	22·98	22·55
17′	22·19	22·24	21·97	22·34	22·17

[a] $CDCl_3$ + CD_3OD; [b] other signals: 13·90 q, 62·74 t.

in chemical shifts of the A–C ring carbons are consistent with the expected structure *II*.

According to its mass spectrum, (M^+ ion m/z 591, first three ergine ions shifted 16 mass units to the higher masses, m/z 283 – $C_{16}H_{17}N_3O_2$), the second compound contains one additional oxygen atom in the ergine part. Comparison of ^1H and

TABLE II

^1H NMR data (400 MHz, $CDCl_3$, TMS, 25°C). Chemical shifts

Proton[a]	*I*	*II*	*III*	*IV*[b]	*V*[c]
2	6·937	—	—	—	—
3	—	—	3·520	—	—
4α	2·851	2·681	2·743	1·394	2·006
4β	3·332	3·142	1·331	2·617	2·210
5	3·878	3·826	3·091	3·909	3·778
7α	2·921	2·853	2·940	3·144	2·886
7β	2·963	2·889	2·541	2·872	2·791
8	3·171	3·114	3·037	[d]	3·125
9	6·374	6·353	5·383	6·430	6·304
12	7·129	7·109	6·663	6·712	6·631
13	7·182	7·110	7·088	7·212	7·147
14	7·235	7·152	6·726	7·235	6·982
N(1)—H	8·138	8·716	7·854	[e]	[e]
N—CH_3	2·709	2·642	2·454	2·502	2·548
N—H	9·783	9·757	9·279	[e]	9·555
5′	4·518	4·542	4·571	4·501	4·495
$8'_d$	3·608	3·623	3·625	[d]	3 614
$8'_u$	3·545	3·562	3·560	[d]	3·533
$9'_u$	1·788	1·805	[d]	[d]	1·791
$10'_d$	2·191	2·197	[d]	[d]	2·152
10′a	3·659	3·666	3·707	3·727	3·629
11′	2·096	2·112	2·428	2·171	2·067
12′	0·901	0·917	0·948	0·948	0·902
13′	1·025	1·025	1·127	1·138	1·016
$14'_d$	1·192	2·012	1·881	1·908	1·973
$14'_u$	1·184	1·893	1·881	1·841	1·846
15′	2·123	2·141	1·997	2·086	2·065
16′	1·006	1·005	0·989	0·948	0·995
17′	1·048	1·041	1·109	1·028	1·034
10′a-OH	7·372	7·320	7·506	[e]	7·249

[a] d Downfield, u upfield; [b] $CDCl_3$ + CD_3OD; [c] additional signals: 1·179 t (7·2); 4·210 dq (10·7, 7·2); 4·246 dq (10·7, 7·2); [d] not determined; [e] not observed.

^{13}C NMR spectra with that of *I* (Tables I–III) established that a trisubstituted double bond involving H-2 was replaced by one carbonyl (181·51 ppm) and one aliphatic methine (42·89 ppm). According to (^{1}H, ^{13}C)-COSY, the later carbon is directly coupled to a proton resonating at 3·520 ppm, which, in turn, is coupled to both H-4 protons. Therefore, the structure of 2-oxo derivative of α-ergocryptine, *III* was assigned to this compound. Since the coupling $J(3, 4\alpha) = 11{\cdot}4$ Hz is of similar magnitude as $J(4\alpha, 5) = 12{\cdot}4$ Hz, H-4α is *trans*- to both H-3 and H-5 so that the configuration at C-3 could be determined.

The second side product contains two additional oxygen atoms in the ergine nucleus (32 amu shift of the ergine fragments with respect to *I*). The resonance of

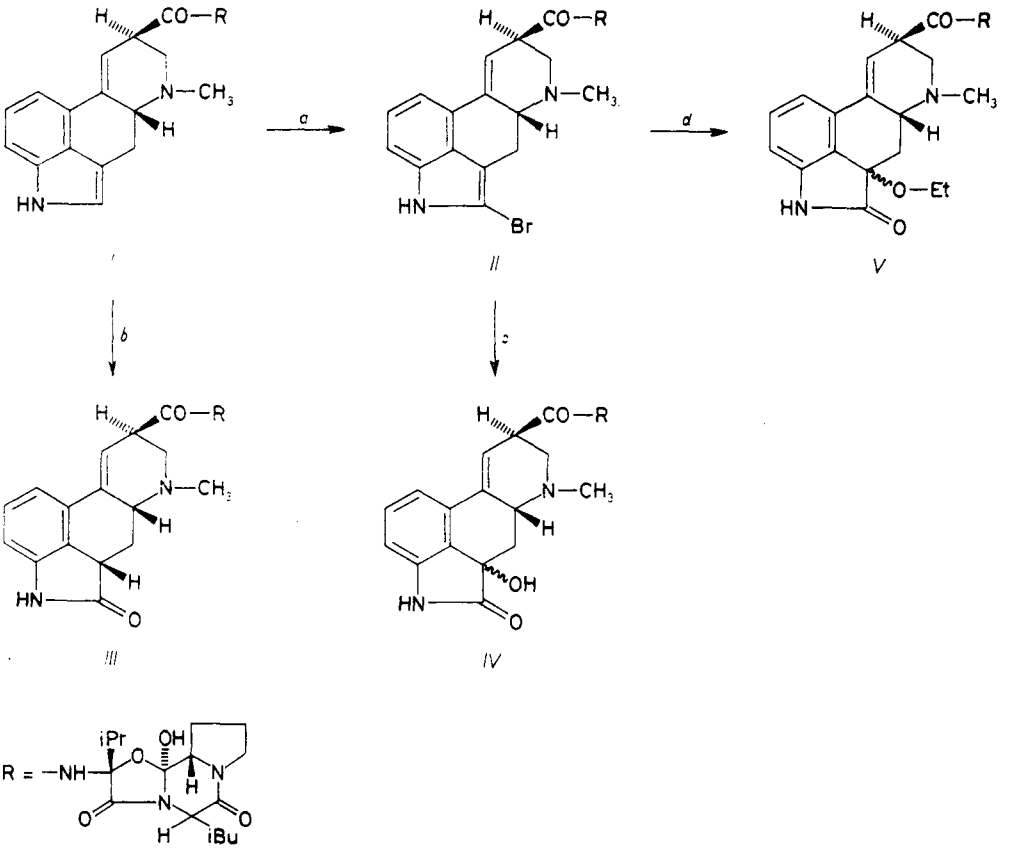
TABLE III

^{1}H NMR data (400 MHz, $CDCl_3$, TMS, 25°C). Coupling constants

H(*i*, *j*)[a]	*I*	*II*	*III*	*IV*[b]	*V*[c]
4α,4β	−14·1	−14·3	−11·7	−12·2	−12·3
4α,5	12·0	11·9	12·4	11·2	12·9
4β,5	4·9	4·9	3·1	3·8	2·9
5,8	1·0	<1	2·7	<1	0·7
5,9	2·0	1·8	0·6	2·2	1·7
7α,7β	−12·1	−12·1	−11·1	−11·7	−12·0
7α,8	2·2	2·1	4·7	6·0	1·9
7α,9	<1	<1	<1	0·9	<1
7β,8	3·5	3·3	9·0	11·0	3·6
8,9	6·1	6·1	3·3	2·5	6·4
12,13	7·1	8·3	8·1	7·0	7·8
12,14	1·0	1·8	<1	1·9	1·1
13,14	7·9	8·3	7·6	8·1	7·8
5′,14′$_d$	6·0	6·0	4·8	5·5	6·0
5′,14′$_u$	7·6	7·5	8·7	7·9	7·4
8′$_d$,8′$_u$	−9·4	−9·3	−10·0	n.d.	−9·7
8′$_d$,9′$_d$	7·9	7·9	7·5	n.d.	7·5
8′$_u$,9′$_d$	12·1	12·2	12·1	n.d.	12·1
8′$_u$,9′$_u$	2·6	2·5	2·7	n.d.	2·4
10′a,10′$_d$	9·8	9·8	9·2	7·9	9·2
10′a,10′$_u$	6·3	6·3	6·8	5·5	n.d.
10′a,OH	1·8	1·8	1·8	n.o.	1·8
11′,12′[d]	6·4	6·6	6·3	6·7	6·5
15′,16′[e]	6·7	6·7	6·8	6·4	6·8

[a] d Downfield, u upfield; [b] $J(\mathrm{NH}, 2) = 1{\cdot}8$, $J(2, 4\alpha) = 1{\cdot}8$; [c] $J(3, 4\alpha) = 11{\cdot}4$, $J(3, 4\beta) = 4{\cdot}8$, $J(3, 13) = 0{\cdot}9$; [d] $J(11', 12') = J(11', 13')$; [e] $J(15', 16') = J(15', 17')$.

H-2 is missing in ^{1}H NMR spectrum; both H-4 protons are coupled to H-5 only that requires a quaternary carbon at C-3. Instead of a trisubstituted C(2)—C(3) double bond there is one carbonyl (180·57 ppm) and one sp^3-hybridized quaternary carbon atom attached to oxygen (70·83 ppm). Therefore, the structure of 2-oxo-3--hydroxy derivative *IV* (with uncertain configuration at C-3) was assigned to this compound.



a Br_2, *b* Br_2, H_2O
c Br_2, H_2O, *d* Br_2, EtOH, H_2O

SCHEME 1

The last compound (isolated from the reaction mixture containing traces of ethanol and one equivalent of water) exhibits a pseudomolecular adduct-ion *m/z* 654 (NH_3/chemical ionization mass spectrum) and signals of an additional ethoxy

group in ^1H and ^{13}C NMR spectra (Tables I and II). Its Δ^2 double bond was replaced by one carbonyl and one –C—O type carbon. However, the downfield shift of the later signal with respect to the corresponding carbon in *IV* suggested that the ethoxy group is attached at this site. Thus, the structure *V* was obtained (configuration of C-3 uncertain).

2,3-Dihydro-2-oxo-3-hydroxyergoline derivatives are accessible by calcium hypochlorite oxidation of parent compounds[9]. Compound *IV* was mentioned as the side product in the bromination of *I* by some N-bromides[10]. 2-Ethoxydihydroergotamine has been found as the product of decomposition of ethanolic solution of dihydroergotamine methanesulfonate by heat or light action[11].

The oxidation of ergolines at C-2 was proposed as the first step of the metabolism of their semisynthetic derivatives[12]. Despite considerable effort devoted to the preparation of 2,3-dihydro-2-oxo-ergolines, only the LSD derivative was prepared in a very low yield[12]. We have found that in the presence at least 10 equivivalents of water, the compound *III* was the prevailing product (preparative yield 70%). Further experiments showed that the treatment of 2-bromo derivative *II* with bromine in the presence of water gives *IV* as the main product. However, the preparative yield was very low (about 10%), probably owing to the high polarity of *IV* and therefore difficult isolation. Attempted bromination of *III* leads to nonidentified decomposition products only. Compound *V* was also formed from *II* by reaction with bromine in the presence of water and ethanol (Scheme 1).

Experiments aimed at the extension of the described reaction to other ergot alkaloids and their semisynthetic analogues are in progress.

EXPERIMENTAL

Melting points were determined on the Kofler apparatus and were not corrected. Optical rotations were measured in chloroform. Mass spectra were measured with a Finnigan MAT-90 spectrometer (positive ions, electron impact, electron energy 70 eV, accelerating voltage 5 kV,

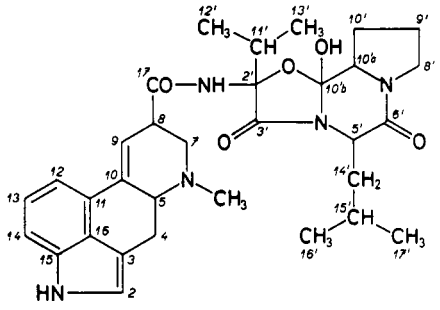


FIG. 1
Numbering of the system used

ion source temperature 250°C, direct inlet at 200°C). Ammonia was used as the reagent gas for chemical ionization mass spectra. High resolution data were obtained by manufacturer's computer routines (resolution 12 000, perfluorokerosene standard) and were accurate within 5 ppm. ^1H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were measured at 25°C on a Varian VXR-400 NMR spectrometer using tetramethylsilane as an internal standard. Signal multiplicity (^{13}C NMR) was determined from the DEPT spectra. Assignments given in Tables I—III are based on *J*-resolved, (^1H, ^1H)-COSY, delayed (^1H, ^1H)-COSY, and (^1H, ^{13}C)-COSY experiments. For the numbering see Fig. 1.

2-Bromo-α-ergocryptine *I*

$BF_3.Et_2O$ (2·1 ml, 17·4 mmol) was added to the solution of α-ergocryptine (10 g, 17·4 mmol) in dichloromethane–tetrahydrofuran mixture (2 : 1, 150 ml, water content below 0·05%) cooled to −20°C. Dichloromethane solution of bromine (8%, 42 ml, 21 mmol) was added under stirring. Aqueous sodium pyrosulfite (5%, 400 ml) was added after 1 min, the stirring was continued for another 15 min, the layers were separated and the aqueous one was extracted with dichloromethane (50 ml). The volume of the combined extracts was reduced and the residue was chromatographed on silica gel (100 g, dichloromethane). Compound *II* (9·2 g, 70% yield), m.p. 221—222°C, $[\alpha]_D^{20}$ −168° (*c* 0·1, chloroform) was obtained after recrystallization from acetone. Ref.[13] gives m.p. 202—203°C, $[\alpha]_D^{20}$ −183·4° (*c* 1·3, chloroform).

2,3-Dihydro-2-oxo-α-ergocryptine *III*

Dichloromethane solution of bromine (8%, 45 ml, 22·5 mmol) was added at room temperature to the stirred solution of α-ergocryptine *I* (10·7 g, 18·6 mmol) in dichloromethane–tetrahydrofuran mixture (2 : 1, 600 ml) containing 10 ml of water. After 1 min of stirring, aqueous sodium pyrosulfite (5%, 400 ml) was added and the stirring prolonged for 15 min. The layers were separated and the aqueous one was extracted twice with 150 ml of dichloromethane. Extracts were combined, solvents were removed, and the residue was subjected to column chromatography (silica gel, 100 g, dichloromethane). Compound *III* was obtained after crystallization from acetone (7·3 g, 62·4%), m.p. 213·0—213·5°C, $[\alpha]_D^{20}$ −125° (*c* 0·1, chloroform). For $C_{32}H_{41}N_5O_6$ (591·4) calculated: 64·97% C, 6·94% H, 11·84% N; found: 64·57% C, 6·81% H, 11·60% N.

2,3-Dihydro-2-oxo-3-hydroxy-α-ergocryptine *IV*

Dichloromethane solution of bromine (8%, 16 ml, 8 mmol) was added at room temperature to a stirred solution of 2-bromo-α-ergocryptine *II* (3·5 g, 5·3 mmol) in dichloromethane–tetrahydrofuran (2 : 1, 100 ml) containing 10 ml of water. The mixture was stirred for 10 min and then extracted with water (100 ml), aqueous layer was concentrated. The chromatography (silica gel, 50 g, chloroform) of the residue (1·2 g) yielded crude product (0·75 g), which, after crystallization from ethyl acetate gave compound *IV* (0·3 g), m.p. 185—195°C (decomposition), $[\alpha]_D^{20}$ −147° (*c* 0·1, chloroform). For $C_{32}H_{41}N_5O_7$ (607·4) calculated: 63·27% C, 6·80% H, 11·53% N; found: 62·89% C, 6·67% H, 11·29% N.

2,3-Dihydro-2-oxo-3-ethoxy-α-ergocryptine *V*

Dichloromethane solution of bromine (8%, 16 ml, 8 mmol) was added at room temperature to the stirred solution of *II* (3·5 g, 5·3 mmol) in dichloromethane–ethanol mixture (1 : 1, 100 ml) containing 5 ml of water. Upon 10 min of stirring, the aqueous solution of sodium pyrosulfite

(5%, 100 ml) was added and the mixture was stirred another 10 min. The layers were separated and the aqueous one was extracted with dichloromethane (50 ml). Organic layers were combined, and solvents were removed. Chromatography (silica gel, 50 g, dichloromethane) lead to crude product that after crystallization from diisopropylether gave compound *V* (1·1 g), m.p. 180 to 190°C (decomposition), $[\alpha]_D^{20}$ −164° (*c* 0·1, chloroform).

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