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DIASTEREOSPECIFIC FORMATION OF 6-N-OXIDE ERGOLINES: A ^{1}H NMR STUDY OF THE CONFIGURATION AT NITROGEN

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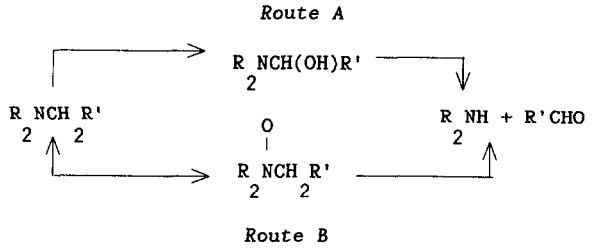
ABSTRACT. The 6-N-oxides derivatives of a series of analogous ergoline/ene derivatives were prepared and their stereochemis-try at nitrogen determined by ^{1}H NMR analysis. The factors governing the outcome of the oxidation are discussed.

Ergoline derivatives have been extensively studied over the past years in regard to their chemical, biochemical and pharmacological properties.[1-3] Their unique pharmacological profile has aroused considerable interest and a great number of structural modifications has been carried out, with the aim of finding derivatives with improved activity and specificity. In this context, studies of their metabolism were an integral part of our research program aimed at the development of new biologically active ergoline derivatives.

It is already known that the tertiary amine functionality in position 6 of the ergoline nucleus is an important chemical feature, since both its basicity and polar character play a major role in drug action as well as in drug detoxification. The metabolic fate of the tertiary amino group, leading to the formation of 6-nor-ergolines, could involve its oxidation according to two pathways (Scheme 1): oxidation at the α-carbon leads to a carbinolamine intermediate, which in general undergoes spontaneous cleavage to the secondary amine and to the corresponding carbonyl product (route A). Alternatively the tertiary amine can be oxidized to the dipolar N-oxide, which in certain cases may undergo dealkylation to the 6-nor-derivative or, alternatively, reduction to the parent drug, expecially in in vivo systems (route B).[4] Lipophilic character, steric hindrance and stereochemistry of the substrate are important in determining the extent of the latter metabolic route. The enzymatic oxidation should be totally stereospecific, leading to only one diastereoisomer at the nitrogen. Instead achiral oxidants should give both diastereoisomers, which might have different biological and pharmacological activities.

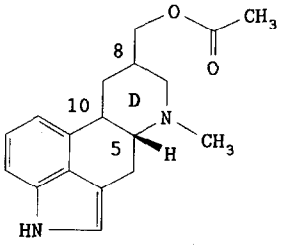
The aim of this work was thus to investigate the oxidation reaction at nitrogen using two achiral reagents of different bulk, m-chloroperbenzoic acid (MPCBA) and hydrogen peroxide,[5,6] on a series of ergolinic substrates and to determine the stereochemistry of the resulting products, in order to gain some insight into the role played by the different factors involved in this reaction, i.e. the nature of the oxidant, the stereochemistry of the substrate and its conformation in solution.

SCHEME 1

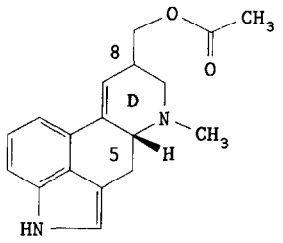


RESULTS AND DISCUSSION

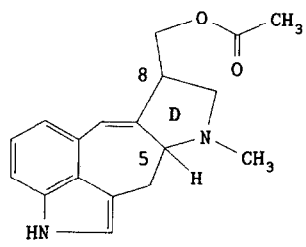
In order to rationalize the relative importance of the above mentioned factors, it was decided to perform all the experimental work on the strictly analogous substrates **1-7**, and the resulting oxidation products were analyzed by ^{1}H NMR spectroscopy to assess their stereochemistry at nitrogen. Regarding the site of attack, the N-lone pair is axial, at least in the ground state conformation of the substrate prior to attack: in all substrates considered in this work and in other numerous analogs tested in our laboratory, the N-methyl group assumes always an equatorial position, as shown by differential ^{1}H NMR nOe experiments. ^{1}H NMR data, collected for all substrates **1-7** and for the corresponding oxidation products, are reported in Tables 1-6, according to the type of substrate, in order to emphasize the differences in chemical shift values which have lead to the assigned stereochemistry.



(5R,8R,10R) : 1
(5R,8S,10R) : 2
(5R,8S,10S) : 3



(5R,8R) : 4
(5R,8S) : 5



(5R,8R) : 6
(5S,8R) : 7

Aliphatic N-oxides have been the subject of numerous spectroscopic studies concerning either the substitution effects of the N-O group and the problem of stereochemical assignment at nitrogen in asymmetric substrates, especially alkaloidal N-oxides. ^{13}C NMR spectroscopy has been used for synthetic or natural N-oxides in substitution effects studies and structural assignments, as for example in N-alkyl-piperidine derivatives[7] and in alkaloidal pyrrolizidine[8] and indoloquinolizidine[9] N-oxides.

^{1}H NMR nOe experiments have been exploited to assess the stereochemistry at nitrogen in a variety of alkaloids.[10-12] Concerning the chemical shift effects observed in ^{1}H NMR, their potential usefulness was partially exploited in stereochemical assignments, as for rhoedine[13] or pyrrolizidine[14] alkaloids and in a study of tropine oxides.[15] In early studies only the chemical shifts of the N-methyl group were used in discriminating the nitrogen stereochemistry in 6-membered ring systems.[16-19]

In this context we thought that a more systematic study of the effect of the N-O substitution in a series of homologous cyclic structures, such as the ergoline/ene derivatives here reported, should prove of general interest in the assignment of the nitrogen stereochemistry in natural and synthetic N-oxides. It must be noted that upon N-O bond formation several factors affecting the chemical shifts of the neighboring protons are at play, namely the expected deshielding substitution effect and the conjugation effect known as syn/ axial proximity effect,[20] which causes an additional deshielding of the hydrogens at the α-carbon which are in anti-periplanar relationship with the N-O bond. With regard to this effect, the N-O bond can be assimilated to an acetylenic bond, as for the S-O bond in some cyclic sulfoxides, where the proximity effect was successfully used for stereochemical assignments.[21,22] An additional factor operating in some selected substrates is the 1,3-diaxial interaction between the N-O bond and a given syn-periplanar hydrogen, resulting into a deshielding of the latter.[15,23]

(5R,10R)-6-Methyl-(8R,S)-acetoxymethyl-ergolines:

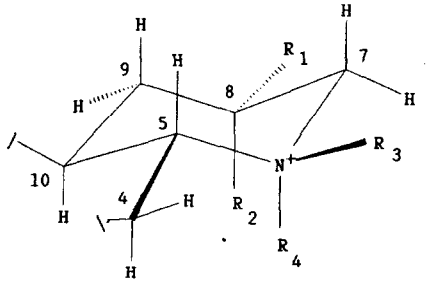
In the system of (8R,S) ergoline derivatives **1** and **2**,[24,25] the absolute stereochemistry at the 5/10 ring junction and at C-8 and the conformation of the aliphatic rings are well established[26] (Fig. 1) and can be easily deduced from the values of the coupling constants of relevant protons in a variety of solvents. Oxidation of substrate **1** (8R) with MCPBA gave **1a** as the only product, with α stereochemistry for the N-O bond: considering the data reported in Table 1, significant differences in chemical shifts between substrate **1** and product **1a** were found mainly for $H4_{ax}$, $H8_{ax}$ and H10, which are syn-periplanar to the α-N-O bond and twice removed from the site of oxidation. The large downfield shifts of the hydrogens α to the oxidation site (namely H5, $H7_{eq}$, $H7_{ax}$) are due to the substitution effect and, for those hydrogens which are also anti-periplanar to the N-O bond (H5 and $H7_{ax}$), to the syn/axial proximity effect. Oxidation with H_2O_2 afforded a mixture of N-oxides **1a** (α) and **1b** (ß) (**1a** predominant at all reaction temperatures in the following ratios α/ß: 60/40 at R.T. and 55°; 70/30, at 80°). The analysis of chemical shifts of **1b** (Table 1) was incomplete, owing to the extensive overlap with the signals of **1a**. Nevertheless the downfield shift of $H4_{eq}$ (+0.5 ppm) supported the ß stereochemistry for to the N-O bond, whereas no large downfield effect was present for the same proton in the α-N-oxide **1a**. In **1a** and **1b** the conformation of ring D was the same as in the parent compound **1**.

Substrate **2** (8S) mantained the same conformation of ring D as its (8R)-isomer (Fig.

Table 1. ^{1}H NMR Chemical Shifts of Compounds **1**, **1a**, **1b**, **2**, **2a**

H	1		1a	1b	2		2a
4e	3.69	(4.3,14.6)	3.4-3.7	4.21	3.65	(4.3,14.6)	a
4ax	2.94	(1.6,10.0, 14.6)	3.4-3.7	a	2.92	(1.9,11.0, 14.6)	3.5-3.9
5	2.46	(4.3,9.0, 10.0)	3.4-3.7	a	2.39	(4.3,9.6, 11.0)	3.5-3.9
7e	3.34	(2.2,3.3, 11.3)	3.78	a	3.67	(2.0,2.0, 11.4)	3.5-3.9
7ax	2.31	(11.3, 11.3)	3.4-3.7	a	2.65	a	3.5-3.9
8	2.55	a	3.23	a	2.50	a	2.65
9e	2.95	a	2.98	2.95	2.88	(2.0,2.0, 4.3,13.2)	3.04
9ax	1.46	(12.5,12.5, 12.5)	1.64	1.56	1.91	(5.1,13.2, 13.2)	1.96
10	3.23	(3.8,9.0, 12.5)	3.98	a	3.38	(4.3,9.6, 13.2)	4.06
NCH_3	2.75		3.58	3.38	2.66		3.51
CH_2OCO	4.31		4.41	a	4.65		4.89
$COCH_3$	2.37		2.37	2.37	2.37		2.40

[a] Not determined.



	R_1	R_2	R_3	R_4
1	CH_2OCOCH_3	H	CH_3	
1a	"	"	CH_3	O
1b	"	"	O	CH_3
2	H	CH_2OCOCH_3	CH_3	
2a	"	"	CH_3	O

Fig. 1. Conformation and configuration of **1**, **2** and their N-oxides.

1), as seen from the coupling constant values of the relevant protons. As for **1**, MCPBA oxidation was highly diastereoselective, leading to the formation of only one N-oxide **2a**, besides small amounts of deacetylated starting material. The α stereochemistry at nitrogen was supported by the large downfield shifts were observed for $H4_{ax}$, H10, H5 and $H7_{ax}$

(Table 1), similar to those found for **1a**. No change in conformation of ring D was noted. Treatment with H_2O_2 caused extensive deacetylation and severe degradation of the substrate, and the resulting reaction mixture was not analyzed.

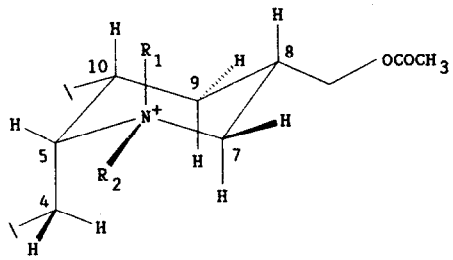
(5R,10S)-6-Methyl-(8S)-acetoxymethyl-ergoline:

In substrate **3**[27] (5/10 cis juction), shown in Fig. 2, $H9_{ax}$ has diaxial relationships with both H10 and H8, giving rise to a typical coupling pattern. Oxidation of this substrate either with H_2O_2 or MCPBA gave **3b** as the only product, to which the ß stereochemistry was assigned on consideration of the syn/axial proximity effect observed for $H7_{ax}$ and of the large downfield shifts for H8 and H10, caused by the 1,3-diaxial interaction with the syn-periplanar N-O bond (Table 2). The conformation of ring D was the same as in the substrate.

Table 2. ^{1}H NMR Chemical Shifts of Compounds **3**, **3b**

H	3		3b
4e	3.25	a	3.68
4ax	3.25	a	3.38
5	3.60	a	4.01
7e	3.04	(1.6,4.0,11.2)	3.60
7ax	2.77	(11.2,11.2)	3.60
8	2.58	a	3.30
9e	2.13	a	2.16
9ax	1.57	(12.9,12.9,12.9)	1.68
10	3.52	(4.0,4.0,12.9)	4.56
NCH_3	2.83		3.60
CH_2OCO	4.22		4.31
$COCH_3$	2.32		2.33

[a] Not determined.



	R_1	R_2
3		CH_3
3b	O	CH_3

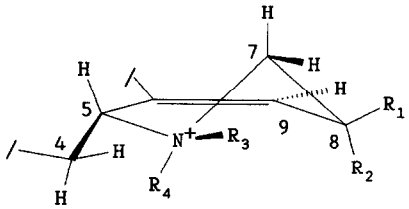
Fig. 2. Conformation and configuration of **3** and its N-oxide.

(5R)-6-Methyl-(8R,S)-acetoxymethyl-Δ 9,10-ergolenes:

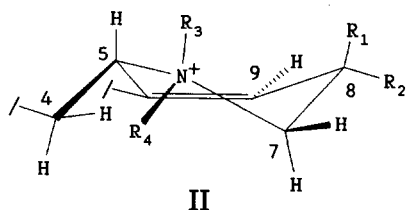
In compound **4** (8R)[24,26] the conformation adopted in solution by ring D is the half-chair (I) (Fig.3), as supported by the values of the coupling constants of H8α/H9 (<1 Hz), H5ß/H9 (2.0 Hz) and H8α/H7ß (11.8 Hz). A possible change to conformation (II)[26] can be monitored through the shape of the H9 signal, which becomes in this case a

doublet of doublets (average values J_{8-9}= 6 Hz, J_{5-9}= 1 Hz). Oxidation of **4** by MCPBA gave a mixture of α and ß N-oxides in which the α-diastereoisomer **4a** was the predominant product (95/5 ratio on the crude). When H_2O_2 was the oxidant, the ratio **4a/4b** changed to 75/25, the α-N-oxide always being the major product. In **4a**, the determining features for stereochemistry assignment were the large downfield shift (1,3-diaxial interaction) of H4α and of H8α (Table 3), together with the syn/axial proximity effect found for H5ß and H7ß. The α stereochemistry was also supported by the negligible shift of H4ß. The analysis of the data for the minor product, the ß N-oxide **4b**, was not exhaustive due to a severe signal overlap. However, in this product H4ß was found to move more downfield (+0.4 ppm) and H4α less downfield (+0.4 ppm) than in **4a**: this different behaviour is fully consistent with the stereochemical assignment given above. The conformation of ring D in **4a** and **4b** was (I) as in the parent compound.

Oxidation of compound **5** (8S),[24,28] with MCPBA gave a 30/70 mixture of α and ß N-oxides **5a** and **5b** respectively. On oxidation with H_2O_2, the ratio changed to 40/60, **5b** being always the predominant N-oxide in the reaction mixture. The analysis of the NMR data of **5a** and **5b** (Table 4) presented the additional problem of conformational mobility of



I



II

	R_1	R_2	R_3	R_4	Conformation
4	CH_2OCOCH_3	H	CH_3		I
4a	"	"	CH_3	O	I
4b	"	"	O	CH_3	I
5	H	CH_2OCOCH_3	CH_3		I
5a	"	"	CH_3	O	I
5b	"	"	O	CH_3	II
8	"	CH_2OH	CH_3		I
8a	"	"	CH_3	O	I
8b	"	"	O	CH_3	II

Fig. 3. Conformations and configuration of **4**, **5**, **8** and their N-oxides.

Table 3. ^{1}H NMR Chemical Shifts of Compounds **4**, **4a**, **4b**

H	4		4a	4b
4ß	3.82	(5.6,14.3)	3.7-3.9	4.25
4α	2.95	(1.7,11.3,14.3)	3.7-3.9	3.32
5ß	3.46	a	4.61	3.6-4.1
7ß	2.61	(11.8,11.8)	3.7-3.9	3.6-4.1
7α	3.37	a	4.03	3.6-4.1
8α	3.30	a	3.7-3.9	3.6-4.1
9	6.59	(<1,2.0)	6.73	a
NCH_3	2.85		3.70	3.46
CH_2OCO	4.38		4.50	4.54
$COCH_3$	2.38		2.35	2.37

[a] Not determined.

Table 4. ^{1}H NMR Chemical Shifts of Compounds **5**, **5a**, **5b**, **8**, **8a**, **8b**

H	5		5a	5b	8		8a	8b
4ß	3.75	(5.6, 14.3)	4.16	3.96	3.77	(5.4,14.3)	3.95	3.93
4α	2.95	a	3.42	3.28	2.91	(1.8,11.4, 14.3)	3.63	3.28
5ß	3.48	a	4.55	4.60	3.45	(1.9,1.9, 5.4,11.4)	4.57	4.57
7ß	2.95	a	a	3.6-3.8	3.04	(4.0,11.6)	3.82	3.75
7α	3.20	(4.8, 13.4)	a	3.6-3.8	3.27	(<1,2.2, 11.6)	4.00	3.75
8ß	2.95	a	a	3.75	2.76	a	3.14	3.50
9	6.62	(1.8, 4.6)	6.55	6.52	6.69	(<1,1.9, 5.4)	6.72	6.56
NCH_3	2.83		a	3.62	2.81		3.62	3.63
CH_2O	4.47		4.58	4.52	4.05		4.00	4.00
$COCH_3$	2.36		2.34	2.33				

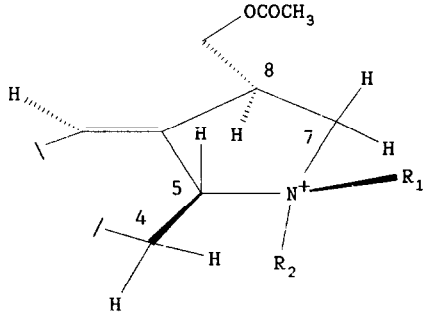
[a] Not determined.

ring D in the oxidation products. Moreover, during workup both products underwent partial deacetylation, and a severe overlap in the ^1H NMR spectrum in the 3.3-4.5 ppm range discouraged the spectral analysis of these products. Thus **5a** and **5b** were converted into their corresponding alcohols **8a** and **8b** (Fig. 3), and their NMR data were analyzed in comparison with the reference compound **8** (Table 4). Both **8** and its analog **5** assumed in solution conformation (I) for ring D, as evident from the coupling constants of H9, ($J_{9\beta-8}$= 5.4 Hz, $J_{9\beta-8}$= 1.9 Hz, $J_{>\alpha-8}$<1 Hz). Product **8a** mantained conformation (I) and appeared to be the α-N-oxide, because of the syn/axial proximity effect noted for H5ß and H7ß, and of the large deshielding effect on both H7α and H4α, syn-periplanar to the N-O bond. The second oxidation product **8b**, the ß N-oxide, underwent a conformational change to half-chair (II) (H9 signal appearing as a broad singlet) presumably to relieve the steric hindrance on the bottom face of the molecule. Because of this conformational change, no direct comparison between the chemical shift values of this product with the reference product **8** was possible, but it was argued that the extreme downfield position of H8 (3.50 δ) could only be due to a deshielding effect caused by the syn-periplanar ß N-O bond. The steric strain relieved by the said change in conformation was then caused by the 1,3-diaxial interaction between the α-substituent at C8 and the N-methyl group, as expected more severe than the interaction between the α-substituent at C8 and the N-O group in **8a**. The same pattern of chemical shift differences and of conformational preference was noted in the corresponding N-oxides **5a** and **5b**.

Table 5. ^1H NMR Chemical Shifts of Compounds **6**, **6a**

H	6		6a
4ß	3.66	(2.7,13.8)	3.73
4α	3.12	(1.6,10.5, 13.8)	3.73
5ß	3.41	(2.2,2.7, 10.5)	4.54
7ß	2.55	(8.3,10.0)	4.08
7α	3.63	b	3.82
8α	3.52	b	4.15
NCH_3	2.7		3.61
CH_2OCO	4.62		4.70
$COCH_3$	2.36		2.27

[a] Assigned by differential NOE experiment.
[b] Not determined.



	R_1	R_2
6	CH_3	
6a	CH_3	O

Fig. 4. Conformation and configuration of **6** and its N-oxide.

(5R)-5(10—>9)Abeo-6-methyl-(8R)-acetoxymethyl-Δ 9,10-ergolene :

Turning now to the class of abeo ergolenes,[29] which exhibit a severely restricted conformational mobility (Fig. 4), oxidation of substrate **6** with either H_2O_2 and MCPBA produced only **6a**. On the basis of the usual considerations, **6a** was recognized as the α N-oxide, since large downfield shifts (Table 5) were observed for H8 and H4α, syn-periplanar to the N-O bond, besides those for H5ß and H7ß (the syn/axial proximity effect).

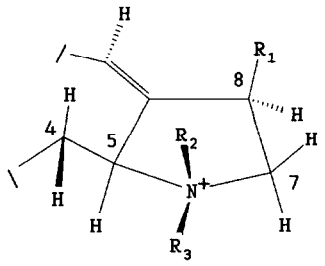
(5S)-5(10—>9)Abeo-6-methyl-(8R)-acetoxymethyl-Δ 9,10-ergolene :

Instead of testing the (5R,8S) abeo substrate, the easy availability of (5S,8R)-abeo ergolene **7** (Fig. 5), produced in the same reaction leading to **6**, was exploited: in fact **7** is the mirror image of the (5R,8S) compound,[30] and the oxidation reaction with achiral reagents must give the same relative stereochemical outcome. Oxidation of **7** with MCPBA gave **7a** as the only oxidation product, with ß stereochemistry at the N-O bond, as evident from the large downfield shift of H4ß (syn-periplanar to the N-O bond), and from the syn/axial proximity effect on H5α and H7α (Table 6). Reaction with H_2O_2 caused extensive deacetylation of the reaction mixture and afforded only one oxidation product: this was recovered as the corresponding alcohol **9a** and comparison of its data with those of the reference compound **9** (Table 6) showed that the stereochemistry at nitrogen was again ß, since the observed differences in chemical shift followed the same pattern found for the pair **7** and **7a**. Both oxidation reagents then approach the substrate from the face of the molecule opposite to the C5-H5 bond: in the mirror image of **7**, i.e. the (5R,8S) substrate, this would have given rise to the α N-oxide, as in the case of the (5R,8R) substrate **6**.

Table 6. ^{1}H NMR Chemical Shifts of Compounds **7**, **7a**, **9**, **9a**

H	7		7a	9		9a
4ß	3.08	(1.6,10.5, 13.7)	3.60	3.12	(1.5,10.5, 13.6)	3.72
4α	3.67	(2.8,13.7)	3.80	3.67	(2.8,13.6)	3.72
5α	3.3-3.4	a	4.53	3.50	(2.2,2.8, 10.5)	4.62
7ß	3.49	(9.7)	4.08	3.60	a	4.06
7α	2.91	(6.4,9.7)	4.08	2.96	(6.5,9.8)	4.37
8	3.3-3.4	a	3.60	3.19	a	3.60
NCH_3	2.80		3.58	2.82		3.64
CH_2O	4.43		4.87	3.94		4.20
$COCH_3$	2.36		2.38			

[a] Not determined.



	R_1	R_2	R_3
7	CH_2OCOCH_3		CH_3
7a	"	O	CH_3
9	CH_2OH		CH_3
9a	"	O	CH_3

Fig. 5. Conformation and configuration of **7**, **9** and their N-oxides.

CONCLUSIONS

The experimental data presented above show how the outcome of the oxidation reaction on compounds **1-7** is affected by the stereochemistry of the chiral centers present in the substrate, which determines both the conformation of the tetracyclic skeleton and the steric crowding at the site of attack. Only in some cases the outcome depends on the nature and the bulk of the oxidant, MCPBA usually performing a more diasterospecific reaction than H_2O_2. To summarize the main findings, in the case of saturated compounds **1**, **2** and **3** the diastereoselection in N-oxide formation is sharply affected by the spatial arrangement of the tetracyclic ring system: for **1** and **2** (trans 5/10 junction) the α N-oxide is predominant, regardless of the stereochemistry at C8, and the bulkier reagent (MCPBA) is more selective, with respect to H_2O_2, toward the axial α approach. For compound **3** (cis 5/10 junction) the axial ß approach is always preferred, independently of the oxidant used. For the unsaturated compounds **4** and **5**, where the tetracyclic skeleton is almost planar, the diastereoselection is determined by the stereochemistry at C8. The nature of the reagent does not play a major role, and the α N-oxide predominates when the substituent at C8 is ß, while the ß N-oxide is the preferred product when the C8 substituent is α. For the abeo ergolenes **6** and **7**, a high degree of diastereoselection towards the axial approach is observed, regardless of the oxidant and of the stereochemistry at C8, leading always to an attack opposite to the C5-H5 bond, on the least hindered face of the molecule. Playing with the above mentioned factors is then possible to direct the outcome of the oxidation reaction to prepare N-oxide ergoline/ene derivatives of selected stereochemistry at nitrogen, which could be used for further studies on the metabolic pathway of these therapeutically useful compounds. Moreover, the same N-oxide ergolines could be considered as pro-drug forms (Scheme 1), since their metabolic reduction can lead back, as mentioned before, to the parent drug. This consideration, regarding a direct pharmacological application of N-oxides obtained from biologically active ergoline/ene derivatives, was recently supported by some preliminary results,[31] which showed that the pharmacological activity present in the parent drug was still displayed in its N-oxide, although with a slower onset of the activity.

EXPERIMENTAL

^{1}H NMR spectra were obtained at room temperature at 200 MHz on a VXR-200 Varian instrument. Since 6-N-oxide ergolines have in general very poor solubility in apolar solvents, a 50\50 mixture of chloroform-d and methanol-d_4 was used, with the advantage of retaining an acceptable spread of chemical shifts in the aliphatic region, with a narrow range of blind spectrum (around 3.6 ppm) due to residual solvent lines. The central peak of the methanol multiplet was taken as internal reference at 3.60 ppm. Usually spectra were recorded on the crude reaction products, in order to quantify the relative ratios between diastereoisomers. Further NMR analysis on purified products was performed when possible. Differential ^{1}H NMR nOe experiments were performed on all substrates in $CDCl_3$ solution under the usual experimental conditions and with standard Varian software, with irradiation of the N-methyl signal. In Tables 1-6, chemical shifts of aromatic protons and coupling constants of all substituents at C8 and of all oxidation products are omitted for brevity: in the latter case the values were coincident (when determined) with those of the corresponding substrates, unless otherwise stated in the text.

The compounds used were prepared according to the following procedures: compounds **1**, **4**, and **5** were obtained by $NaBH_4$ reduction of dihydrolysergic acid methyl ester and lysergic acid methyl ester respectively. In the latter case the basicity of the medium led to a partial epimerization of the substrate, affording isolysergol. Subsequent acetylation in pyridine of the alcohols completed the preparation of compounds **1**, **4** and **5**. Compound **2** was obtained by $LiAlH_4$ reduction performed on the dihydroisolysergic acid methyl ester, obtained by epimerization of dihydrolysergic acid methyl ester, by means of lithium diisopropyl amide at low temperature and subsequent quenching with methanol. Compound **3** was obtained in highly diastereoselective manner by catalytic hydrogenation of **5** in acidic medium. Oxidative hydroboration of lysergic acid methyl ester afforded with a high degree of regio and stereo selectivity a diol, which was monoacetylated at the primary hydroxyl group. Subsequent treatment of the diol monoacetate with $POCl_3$ in pyridine gave, through a Wagner-Merwein rearrangement, the (5R,S) abeo derivatives **6** and **7**. The structure and the absolute stereochemistry of **6** and **7** were independently and fully established by chemical correlation, supported by spectroscopical and chiroptical data.[30] For the preparation of the N-oxide ergoline/ene derivatives, the two experimental methods reported below can be considered representative for all cases:

H_2O_2 oxidation: **(5R)-6-N-Oxide-6-methyl-(8R)-acetoxymethyl-Δ9,10-ergolenes (4a,4b)**: A solution of **4** (0.25 g) in i-PrOH (25 ml) and H_2O_2 (1 ml) was heated at 55° for 2 hrs. The excess H_2O_2 was then destroyed by addition of Pd/C 5% (0.1 g). After stirring for 1 hr, the solution was filtered and evaporated in vacuo to dryness, affording 0.24 g of N-oxides **4a** and **4b** (75/25 ratio in the crude mixture).

MCPBA oxidation: **(5R,10R)-6-N-Oxide-6-methyl-(8R)-acetoxymethyl-ergoline (1a)**: MCPBA 85% (0.39 g) was added portionwise to a solution of 1 (0.5 g) in CH_2Cl_2 (10 ml) cooled to 5°C. After stirring for 2 hrs, the resulting solution was treated with brine and $NaHCO_3$ (0.2 g), extracted with CH_2Cl_2/CH_3OH 9:1 (5 times 20 ml) and dried over Na_2SO_4. The solvent was removed and 0.53 g of product **1a** were recovered.

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