8. CHEMICAL MODIFICATIONS OF ERGOT ALKALOIDS

PETR BULEJ and LADISLAV CVAK

Galena a.s., Opava 74770, Czech Republic

8.1. INTRODUCTION

Ergot alkaloids (EA) are called "dirty drugs", because they exhibit many different pharmacological activities (see Chapter 15). The objective of their chemical modifications is the preparation of new derivatives with higher selectivity for some types of receptors. The fact that many new drugs were developed by semisynthetic modification of natural precursors is a proof that this approach is fruitful.

Chemical modifications of EA were reviewed several times (Hofmann, 1964; Stoll and Hofmann, 1965; Bernardi, 1969; Semonský, 1970; Stadler and Stütz, 1975). The last and very extensive review was published by Rutschmann and Stadler (1978). Therefore, this chapter concentrates especially on derivatives described from 1978 to 1997. The papers and patents devoted to this topic, which appeared in this period, were too numerous to be included in our review. This is the reason why we selected only the most important contributions. Nevertheless, we believe that our survey covers the most important progress in this field.

Preparation of radiolabelled derivatives is also reviewed here. Total syntheses of the ergoline skeleton are not included, but they have been treated in a recent monograph (Ninomiya and Kiguchi, 1990).

8.2. CHEMICAL MODIFICATIONS IN THE ERGOLINE SKELETON

Chemical modifications of individual positions of the ergoline skeleton (Figure 1) are described below.

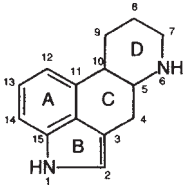

Figure 1 Ergoline numbering

8.2.1. Modifications in Position 1

Alkyiation by alkyl halogenides in liquid ammonia (Troxler and Hofmann, 1957a), acylation by ketene and diketene, hydroxymethylation by formaldehyde, Mannich type reactions and Michaels addition of acrylonitrile affording *N*-1 cyanoethyl derivatives (Troxler and Hofmann, 1957b) are the well-known modifications in this position. Most of the modifications on the indole nitrogen were used in studies of structure—activity relationships. *N*-1Hydroxymethyl or aminomethyl derivatives were used for binding to proteins in immunological methods—see Chapter 11. Protection of the *N*-1 position in multi-steps syntheses can also be the reason of its modification. Many new reactions and *N*-1 substituted ergoline derivatives have therefore been described in the last two decades.

N-1-Alkyl Derivatives

Alkyiation in the *N*-1 position significantly changes EA activity. Some of *N*-l derivatives are used in therapy (nicergoline, metergoline, methysergide). That's why many new alkyl derivatives have been prepared and new alkylation procedures were investigated. Many processes using phase-transfer catalysis were developed, mainly for industrial methylation, and are used for production of nicergoline (Ručman, 1978; Cvak *et al.,* 1983; Gervais, 1986)—see Chapter 14. Šmidrkal and Semonský (1982a) developed a new procedure for alkylation by alkyl halogenides in dimethylsulfoxide in the présence of powdered NaOH. They prepared methyl, ethyl, n-propyl and phenyl derivatives of dihydrolysergic acid and some other ergolines. All the *N*-1 alkyl ergolines were less active in the test of prolactine secretion inhibition than the basic compounds. Eich and co-workers prepared many *N*-1 alkyl derivatives (up to C_8) of agroclavine and festuclavine by alkylation by primary alkyl halogenides in liquid ammonia in the présence of a strong base—sodium or potassium amide (Eich *et al.,* 1985; Eichberg and Eich, 1985). Dehalogenation of alkyl halogenides to alkenes was observed when higher alkyl halogenides were used. The longer the alkyl chain, the more preferred was the side reaction and less alkyl ergoline was formed. The yields of higher alkyl ergolines can be improved using alkyl tosylates instead of halides. Marzoni and Garbrecht (1987) prepared *N*-1 alkyl derivatives of dihydrolysergic acid by alkylation of dihydrolysergic acid in dimethylsulfoxide in the présence of powdered KOH with yields ranging from 80–95%, even with secondary alkyl tosylates (cyclopentyl, cyclohexyl).

A different approach must be adopted for introducing a tertiary alkyl group. *tert*-Butyl ergolines were prepared by reaction of ergoline with *tert-butyl* alcohol in the présence of trifluoroacetic anhydride (Temperilli *et al.,* 1987a; Beneš and Beran, 1989). Substitution in *N*-1 position is accompanied by substitution in positions 2, 13 and 14; a complicated mixture of products is therefore often obtained.

N-1-Aryl Derivatives

Aryl derivatives of ergolines were prepared by the treatment of ergoline derivatives with the appropriate aryl halogenides under phase-transfer catalysis (Sauer *et al.,* 1987).

N-1-Acyl and Sulfamoyl Derivatives

N-1-Acyl and *N*-1-sulfamoyl derivatives are formed by the reaction of appropriate chlorides with ergolines under phase-transfer catalysis (Lončarič and Ručman, 1984, Taimr and Krěpelka, 1987). Dimethyl and diethylcarbamoyl derivatives were prepared in the same manner. *N*-1-Acetyl ergolines were also prepared by a reaction with acetic anhydride under catalysis with BF_3 etherate (Beneš, 1989). *N*-1 Formyl ergolines can be obtained by treatment with formic acid and a tertiary amine under palladium catalysis (Taimr *et al.,* 1987b).

N-1-Hydroxymethyl Derivatives

N-1-Hydroxymethyl ergolines can be prepared by refluxing the ergoline substrate with aqueous formaldehyde (Tupper *et al.,* 1993). Instead of expected 2-methoxyergolines, *N*-l-hydroxymethyl derivatives were obtained also by electrochemical reaction in methanol (Danieli *et al.,* 1983).

N-1-Carboxymethyl Derivatives

N-1-Carboxymethyl derivative resulted when dihydrolysergic acid was treated with ethyl bromoacetate and KOH in dimethylsulfoxide (Šmidrkal and Semonský, 1982b). It was further transformed to a hydroxyethyl derivative.

N-1-Trimethylsilyl Derivatives

Trimethylsilyl derivatives of EA are synthons suitable for the preparation of *N*-1 acylated or glycosylated ergolines. The trimethylsilyl group was introduced into the position 1 of some clavine alkaloids by the reaction with *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetic amide in acetonitrile or by refluxing in hexamethyldisilazane in yields of 60 to 90% (Křen and Sedmera, 1996).

N-1-Glycosides of EA

Since *N*-1-glycosides of EA can be considered as nucleosides, some interesting activities can be expected. *ß-N*-1-Ribofuranosides of clavine alkaloids were prepared by the reaction of *N*-1-trimethylsilyl derivatives with 1-O-acetyl-2, 3, 5tri-*O*-benzoyl-*ß*-D-ribofuranose in dichloromethane under $SnCl_4$ catalysis in yields of 20–40% (Křen *et al.,* 1997a). Similarly a mixture of α and *ß* anomers of *N*-1-deoxyribofuranosides of clavine alkaloids was prepared by reaction with 1-chloro-2-deoxy-3, 5-di-*O*-toluoyl-α-D-ribofuranose in acetonitrile. The two anomers were separated by preparative chromatography (Křen *et al.,* 1997b).

8.2.2. Modifications in Position 2

Position 2 of the ergoline skeleton is highly suitable for synthetic modification of EA by both electrophilic and radical substitution. Many modifications have been reviewed by Rutschmann and Stadler (1978): chlorination, bromination and iodination, nitration and reduction of nitro derivatives to amino derivatives and reaction with 2-methoxy-1, 3-dithiolane affording an intermediate which can be desulfurised to a 2-methyl derivative. Troxler and Hofmann (1959) described the oxidation of lysergic acid diethylamide (LSD) to 2-oxo-3-hydroxy-2, 3-dihydrolysergic acid diethylamide.

One of the 2-bromo derivatives, 2-bromo-α-ergokryptine (bromokryptine), is used in therapy and many processes were therefore described for its production, mainly in patent literature—see Chapter 13.

2-Acyl Derivatives

The basic procedure for the preparation of 2-acylergolines consists in acylation of ergoline compounds with carboxylic acid anhydrides under catalysis by Lewis acid (Beneš and Křepelka; 1981a,b; Taimr *et al.,* 1987a). 2-Formyl derivatives were prepared from *N*-1 protected ergolines only by a reaction with dichloromethyl methyl ether in the présence of $AlCl_3$ (Sauer and Schröter, 1991). Using this procedure 8α-(3,3-diethylureido)-6-methylergoline2-carbaldehyde (2-formyl-terguride) was prepared from *N*-1-tosylterguride. The acylation of *N*-1 protected ergolines by acyl halogenides afforded 13-acylergolines predominantly. 2-Acyl ergolines can be used for other transformations, e.g. to be subjected to aldolisation with aromatic aldehydes (Křepelka *et al.,* 1981).

2-Halogen Derivatives

The general method for introduction of a halogen group (Cl, Br, I) into the EA molecule is a reaction with *N*-halogen-succinimide (Troxler and Hofmann, 1957b). Many other processes, mainly for bromination of α-ergokryptine, have been developed: bromination by *N*-bromophthalimide, *N*-bromocaprolactam or dioxane-bromine complex in inert organic solvents (Flückiger *et al.,* 1971), usage of 3-bromo-6-chloro-2-methylimidazolo[1, 2-b]pyridazine-bromine complex, 2-pyrrollidinone-hydrotribromide or 2-piperidinone-hydrotribromide in dioxane containing peroxide or in the présence of 2, 2´-azo-bis-isobutyronitrile or dibenzoyl peroxide (Stanovnik *et al.,* 1981; Ručman *et al.,* 1983), the reaction with bromine in methylene chloride under hydrogen bromide (Börner *et al.*, 1984) or BF_3 etherate (Cvak *et al.*,1992b) catalysis. A very interesting and efficient bromination and chlorination process using dimethylsulfoxide and trimethylbromo(chloro)silane was described by Megyeri and Keve (1989). An electrochemical halogenation method was also described (Palmisano *et al.,* 1987). The selectivity of halogenation in position 2 is an important question

which must be taken into consideration. While in the case of 9, 10-didehydroergolines the regioselectivity into position 2 is high and dibrominated products are formed only when a large excess of the reagent or harsh reaction conditions are used, the parallel halogenation of s in positions 2 and 13 was observed yielding mixtures of products (Cvak, unpublished results).

Recently, 2-fluoroergolines have been prepared by an exchange reaction from 2-bromo derivatives via lithiated intermediates (Bohlmann *et al.*, 1993).

2-Hydroxymethyl Derivatives

Sauer *et al.* (1991) prepared 2-hydroxymethylergoline derivatives by treatment of terguride with paraformaldehyde under catalysis by $(CH_3)_2AlCl$.

2-Alkylthio Derivatives

The thioether group can be introduced into this position by reaction with sulfenyl chloride (Timms and Tupper, 1985; Tupper *et al.*, 1993). 2-(Methylthio)-agroclavine exhibits a strong antipsychotic effect. 2-Methylthio derivatives can be oxidised to corresponding sulfoxides and sulfones.

Electrochemical Functionalisation in Position 2

2-Alkoxyergolines were prepared by the electrolysis of EA in alcoholic solution of KOH (Seifert and Johne, 1980). The cyano group can be introduced by electrolysis of some EA in aqueous-methanolic solutions containing sodium cyanide (Seifert *et al.*, 1983). Electrochemical oxidation of dihydrolysergol in aqueous methanol containing HBr gave, at a potential of 1.1 V, 2, 13-dibromo-dihydrolysergol and at 1.6V 12, 14-dibromo-2, 3-dihydro-8*ß*(hydroxymethyl)-3*ß*-methoxy-6-methylergolin-2-one (Seifert *et al.*, 1992). Finally, the electrochemical oxidation of dihydrolysergol in acetonitrile gave a highly conjugated dimer (Figure 2) (Dankházi *et al.*, 1993). Oxidative degradation and formation of a similar type of products can underlie the darkening of EA.

Electrophilic Substitution Using 2-Lithiated s

Sauer and co-workers prepared many new 2-substituted ergolines by a process including 2-lithiated ergolines—Figure 3 (Sauer *et al.*, 1985c, 1988a). The starting

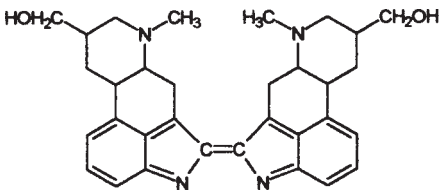

Figure 2 Ergoline dimer

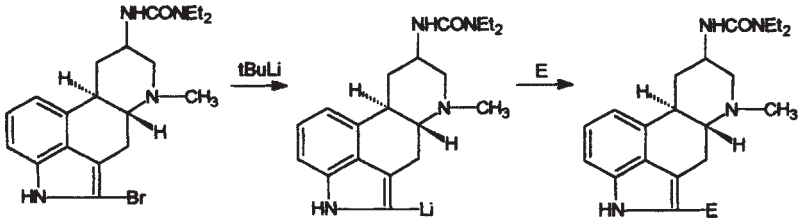

Figure 3 Electrophilic substitution of 2-lithiated ergolines

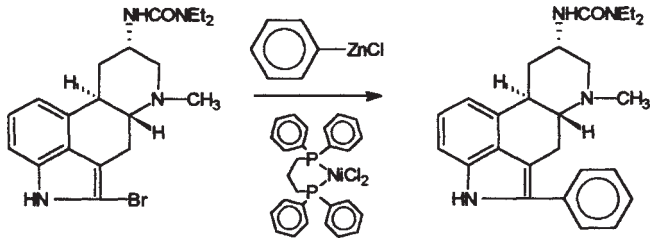

Figure 4 Nucleophilic substitution of 2-bromo derivatives

2-bromoergoline must be protected at *N*-1 position; using e.g. tert-butyldimethylsilyl group. The protected 2-bromoergoline is then transformed into a lithium derivative by tert-butyllithium and the lithiated ergoline is subjected to a reaction with an electrophilic reagent (ethylene oxide, methyl isocyanate, methyl isothiocyanate, carbon dioxide, alkyl halogenide, $(CH_3)_3Si—N=C=O$, etc.). Many derivatives of lisuride and terguride were prepared in this way.

Other Reactions Involving 2-Bromo Group Replacement—Nucleophilic Substitution

Phenyl group was introduced into position 2 by treatment of 2-bromoterguride with phenylzinc chloride under catalysis by palladium or nickel complexes—Figure 4 (Heindl *et al.*, 1989).

Oxidation in Position 2

2, 3-Dihydro-2-oxo-α-ergokryptine and 2, 3-dihydro-2-oxo-3-hydroxy-α-ergokryptine were found as the by-products in bromination of α-ergokryptine with bromine (Cvak *et al.*, 1992b). A procedure was developed for the preparation of 2-oxo derivatives of EA in 30–70% yield by treatment of EA by bromine in the présence of water (Cvak *et al.*, 1994). Also the oxidative cleavage of EA by sodium periodate giving aminoketone derivatives (Figure 5) can be considered as an oxidation in position 2. The aminoketones, prepared in this

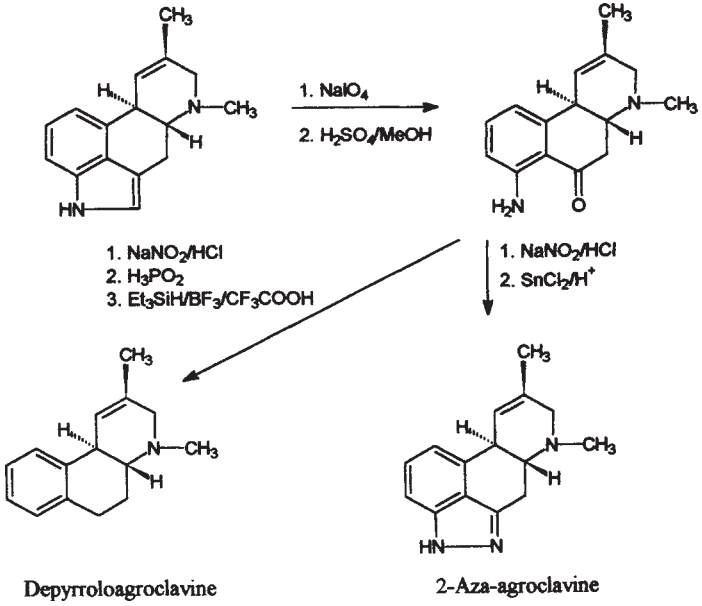

Figure 5 Oxidative cleavage of 1, 2-bond of ergoline skeleton and the use of the intermediates

way were further transformed to depyrrolo analogues of EA (Bach *et al.*, 1980) or were used for the synthesis of 2-aza analogues of ergolines (Kornfeld and Bach, 1979; Stadler *et al.*,1981). Both depyrrolo and 2-aza analogues manifested a lower dopaminergic activity than their ergoline precursors. A similar type of oxidation was observed as a side reaction during bromination of some *N*-1-acylergolines by 2-pyrrolidone hydrotribromide when water was present (Lončarič and Ručman, 1984).

8.2.3. Modifications in Position 3

All the reactions in this position affect also position 2, because they represent as a rule an addition to the 2, 3 double bond, followed in some cases by further transformation. Oxidation reactions leading to 2-oxo derivatives, in some cases substituted also in position 3, were described above.

First attempts at a direct reduction of EA in the 2, 3 position led to dimers (Bach and Kornfeld, 1973). The procedure for reduction of ergolines to 2, 3-dihydroergolines by Zn in HC1 and by $NaBH_4$ in trifluoroacetic acid was later described by Bach and Kornfeld (1976). Formation of 2, 3-dihydroergolines was also observed on hydrogenation of EA on a Raney-nickel catalyst (Cvak, unpublished results). Reduction of 2-bromoergolines by $NaBH_4$ in trifluoroacetic acid afforded 2, 3-dihydro derivatives in a high yield and without the formation of dimeric products (Sauer and Haffer, 1984).

Oxidation of 2, 3-dihydroergolines back to ergolines is an important process in some multi-step syntheses. It can be achieved by MnO_2, but this reaction is not satisfactorily reproducible and gives a poor yield. Better results were obtained with oxidation using some electrophilic reagents (*tert-butyl* hypochlorite, *N*-chlorosuccinimide, tosyl chloride, etc.) in nonpolar solvents (Sauer *et al.,* 1985a).

8.2.4. Modifications in Positions 4 and 5

Despite the considerable efforts directed at chemical transformation of these positions (especially position 4 is a challenge for many chemists), no successful example has been described. The only transformation has been the racemisation of EA occurring during their hydrazinolysis (Stoll and Hofmann, 1937 and 1943; Stoll *et al.,* 1950).

8.2.5. Modifications in Position 6

Demethylation

Classic von Braun *N*-demethylation used for the preparation of 6-norergolines consists in a reaction with BrCN followed by elimination of the cyanogen group by hydrolysis using Zn in acetic acid or KOH in diethylene glycol, or by hydrogenolysis on Raney-nickel (Rutschman and Stadler, 1978). Brumby and Sauer (1991) used organometallic reagents for CN removal, giving higher yield of 6-norergolines. An alternative process using 2, 2, 2-trichloroethyl-chloroformate as the demethylating agent was developed by Crider *et al.* (1981). Another possibility is the demethylation of *N*-6-oxides by strong bases (*n*- or *tert*-butyl lithium) in the présence of some Lewis acid (Sauer and Brumby, 1990). A very interesting, one-pot process for the synthesis of pergolide, including *N*-6 methyl group replacement as a key step, was developed by Misner (1985)—Figure 6.

N-6 Oxides

N-6-Oxides of EA were first described by Ponikvar and Ručman (1982) as by-products formed during the hydrogenation of EA in dioxane containing peroxides. They can be prepared by oxidation using hydrogen peroxide or 3-chloroperoxybenzoic acid (Mantegani *et al.,* 1988; Ballabio *et al.,* 1992).

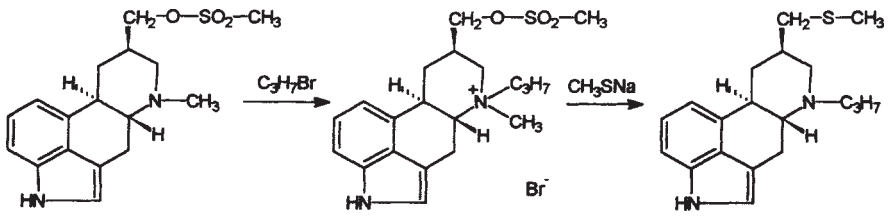

Figure 6 Pergolide manufacture

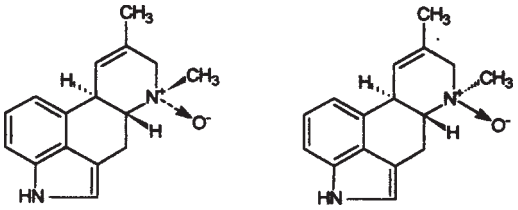

Figure 7 Diastereoisomers of agroclavine-*N*-6-oxides

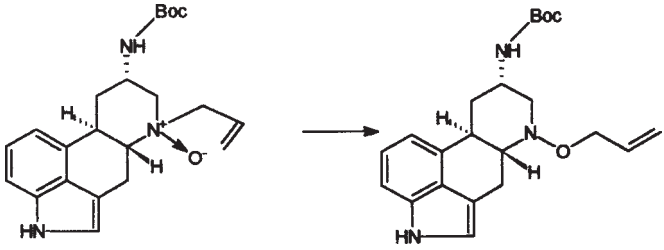

Figure 8 Meisenheimer's [2, 3]-sigmatropic rearrangement of 6-allylergoline-6-*N*-oxides

Křen *et al.* (1995) studied the chirality on *N*-6 of agroclavine and elymoclavine oxides—Figure 7. The ratio of diastereoisomers (6*R*/6*S*) was 2:3 in both cases.

Other N-6 Derivatives

N-6-Demethylated ergolines were first allylated, then oxidised to 6-allyl oxides which were subjected to rearrangement to *N*-6-allyloxy derivatives—Figure 8 (Nordmann and Gull, 1986). Nordmann and Loosli (1985) prepared *N*-6-carboxamidines from 6-cyano-6-norergolines.

8.2.6. Modifications in Position 7

The only modification in this position is formation of the $\Delta^{7,8}$ double bond (Stütz and Stadler, 1973) from *N*-6 oxides by Polonovski reaction.

8.2.7. Modifications in Position 8

Functional Derivatives of Lysergic, Isolysergic, Paspalic and Dihydrolysergic Acids

The review by Rutschmann and Stadler (1978) gives a survey of the derivatives and methods described until 1978. Only a few substantial news, particularly some new derivatives with new pharmacological activities, appeared since then. Esters of *N*-1-alkylated dihydrolysergic acid with ethylene glycol and 2,

3-butanediol were prepared by acid-catalysed esterification (Marzoni *et al.*, 1987). Another series of esters was prepared by the reaction of potassium salts of dihydrolysergic acid derivatives with cyclohexyl tosylates (Garbrecht *et al.*, 1988). In particular, *N*-1-isopropyl derivatives of these esters showed a high affinity for the $5HT_2$ receptor. Misner *et al.* (1990) prepared a new series of cyclopentyl and cyclohexyl amides of *N*-1 alkylated dihydrolysergic acid. Condensation using 1.1´-carbonyldiimidazole as the coupling reagent and condensation via acyl chlorides prepared by the reaction with $POCl_3$/DMF gave the best yields. Also in this group the *N*-1-isopropyldihydrolysergic acid derivatives showed the highest affinity for the $5HT_2$ receptor.

Anilides of both lysergic and dihydrolysergic acids were prepared using trimethylaluminium as a coupling reagent (Neef *et al.*, 1982). Technologically interesting is the direct ester preparation by acid-catalysed esterification of some lysergic and isolysergic acid amides which was described by Sauer and Haffer (1983). New sugar esters of lysergic and dihydrolysergic acids were prepared by a reaction of these acids with protected (acetylated) 1-bromosugars under silver oxide catalysis in tetrahydrofuran (Seifert and Johne, 1979).

Cabergoline (see Chapter 13), a new long lasting dopamine agonist, was selected from a group of new derivatives of dihydrolysergic acid having the structure of acylurea. These derivatives were prepared by two ways—Figure 9. The first method (Brambilla *et al.*, 1989) represents the amidation of methyl

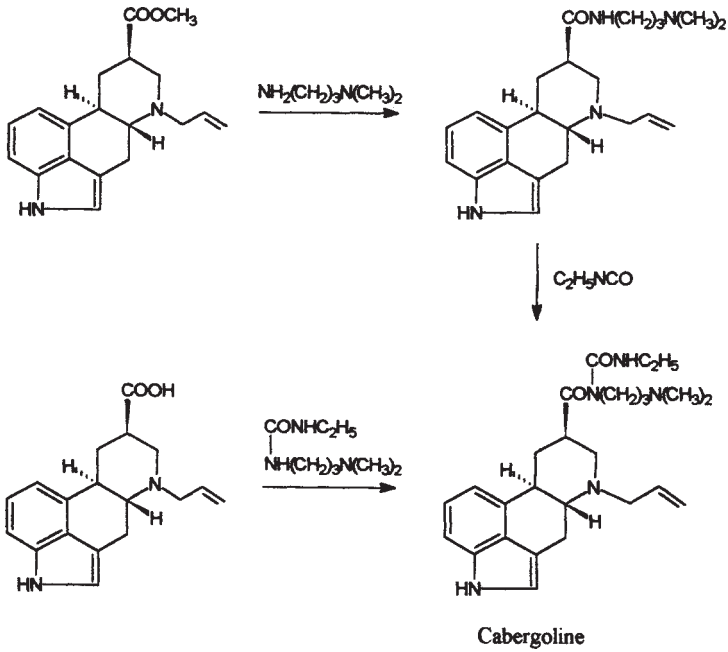

Figure 9 Two processes for cabergoline synthesis

6-(2-propenyl)-9, 10-dihydrolysergate by 3-dimethylaminopropyl-1-amine followed by the reaction with ethyl isocyanate. In the alternative method, acylurea derivatives of dihydrolysergic acid can be synthesised by a reaction of dihydrolysergic acid or its derivatives with *N*-ethyl-*N'*-(3-dimethylamino)propyl-carbodiimide in the présence of triethylamine (Salvati *et al.*, 1981).

Modification of the Side Chain in Position 8

The modifications of the side chain are the most frequently used in the studies of structure-activity relationships. The most important starting material for such syntheses is lysergol, elymoclavine and dihydrolysergol—for their industrial production see Chapter 13. They are transformed to mesylates or tosylates which are subjected to nucleophilic substitution using different nucleophilic agents. Another cheap precursor, produced by fermentation could be agroclavine, but its low reactivity prevents its wider use. Recently, Harris and Horvell (1992) described its transformation to lysergol in three steps, but the yield was not high—Figure 10. Only theoretically interesting is the preparation of agroclavine from 9, 10-didehydro-6-methylergolin-8-one (Wheeler, 1986). The starting 9, 10-didehydro-6-methylergolin-8-one was prepared from lysergic acid in five steps (Bernardi *et al.*, 1974). The last starting material for modification of the side chain can be lysergamine or dihydrolysergamine obtained by reduction of ergine or dihydroergine by $LiAlH_4$.

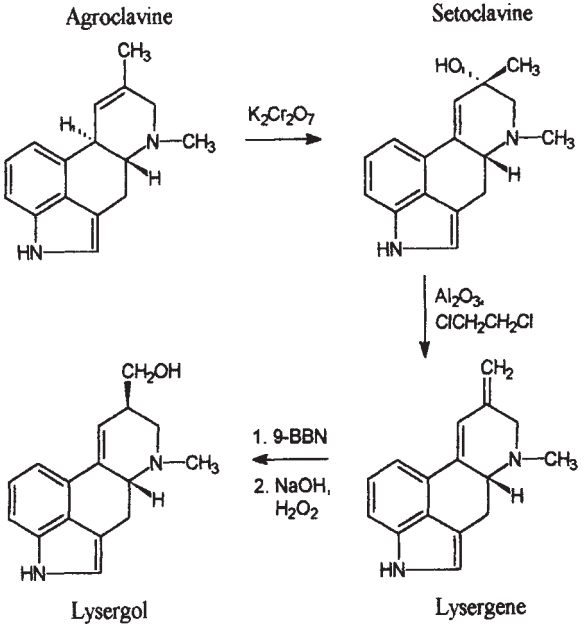

Figure 10 Agroclavine conversion to lysergol (9-BBN=9-borabicyclo[3, 3, 1]nonane)

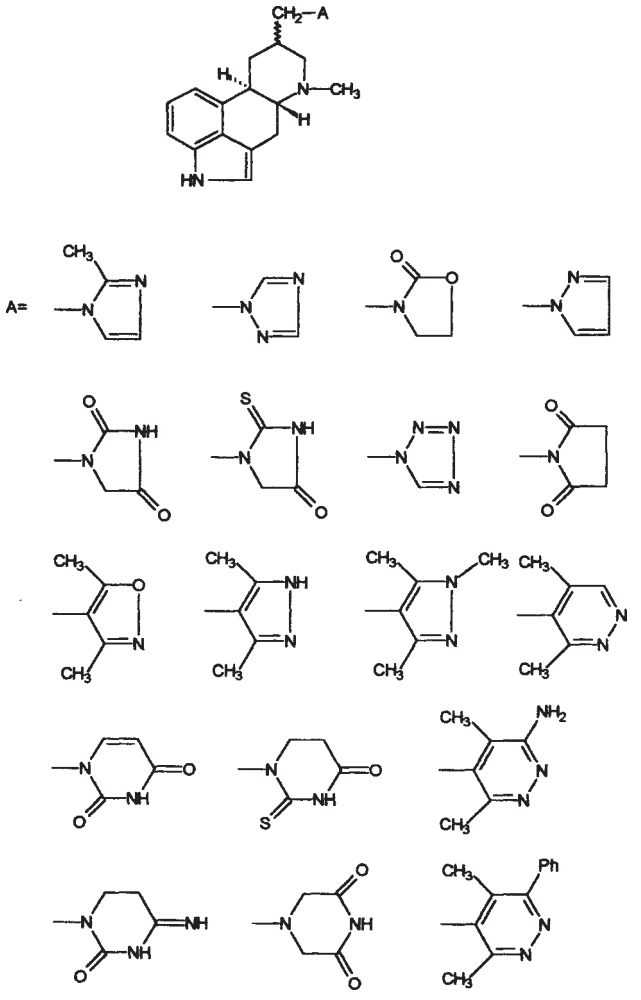

Figure 11 New ergoline derivatives containing a heterocyclic moiety bonded to methylene group in position 8

Many ergoline derivatives containing a heterocyclic moiety bonded to methylene group in position 8*ß* were described—Figure 11. Bernardi *et al.* (1983) prepared ergolines with pyrazole, isoxazole, pyrimidine, 2-amino-pyrimidine and 2-phenylpyrimidine exhibiting antihypertensive and dopaminergic activity. Other heterocyclic derivatives were prepared by Bernardi *et al.* (1984), Rettegi *et al.* (1984), Mantegani *et al.* (1986) and Seifert *et al.* (1986). Japanese authors described similar derivatives (both 8α and 8*ß*) with five-membered heterocycles (Ohno *et al.*, 1986, 1994a, b). Their syntheses use dihydrolysergol or dihydroisolysergol (8α-CH_2OH) mesylates or tosylates for further chemical

substitution. Some of their derivatives exhibited dopaminergic activity higher than bromokryptine and pergolide and are in clinical trials as antiparkinsonic agents.

Using S nucleophiles, many thiodihydrolysergol derivatives were prepared from dihydrolysergol mesylate or tosylate (Gull, 1983, Kornfeld and Bach, 1978). One of them, pergolide (Misner, 1985; Misner *et al.,* 1997), is used in the therapy (see Chapter 13). Derivatives of urea and thiourea were prepared from dihydrolysergamine or dihydroisolysergamine (8*ß*- or 8α-aminomethyl-6-methylergoline) by a reaction with isothiocyanate or dithiocarbamate derivatives (Bernardi *et al.,* 1982; Ruggieri *et al.,* 1989). A number of recent papers were devoted to glycosides of EA possessing a hydroxy group—chanoclavine, elymoclavine, lysergol, dihydrolysergol and ergometrine (Křen *et al.,* 1992, 1994, 1996, 1997c; Ščigelová *et al.,* 1994). Both chemical and enzymatic syntheses were used for their preparation.

Prolongation of the Side Chain in the Position 8

Derivatives of 6-methylergolin-8*ß*-yl-acetic and propionic acids were prepared by stepwise synthesis from dihydrolysergol mesylate or tosylate using NaCN or KCN (Beran and Benš, 1981; Brambilla *et al.,* 1983). Bernardi *et al.* (1983a) condensed dihydrolysergol tosylate with malondiamide or malondinitrile and prepared a number of 6-methylergolin-8*ß*-yl-propionic acid derivatives.

8α-Aminoergoline Derivatives

Lisuride and terguride are the therapeutically used derivatives of 8α-aminoergolene or ergoline, which were prepared by Curtius degradation of lysergic (dihydrolysergic) acid azides—see Chapter 13. Two new processes for lisuride preparation, both starting from isolysergic acid amide (erginine), were described. Sauer and Haffer (1981) used lead tetraacetate and Bulej *et al.* (1990) used iodosobenzene diacetate for erginine oxidation followed by Hofmann-like rearrangement giving 8α-isocyanate, which afforded lisuride in a reaction with diethylamine—Figure 12.

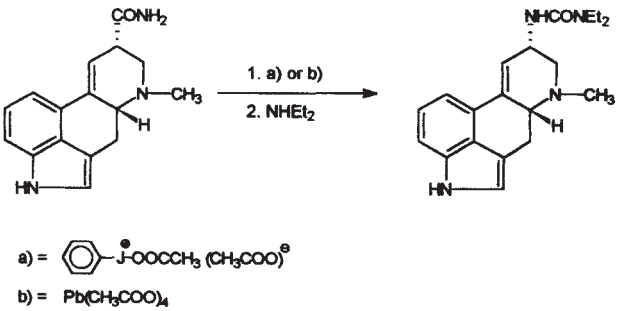

Figure 12 Conversion of erginine to lisuride

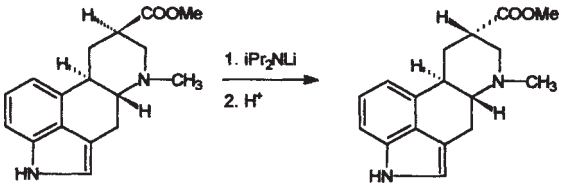

Figure 13 Isomerisation of methyl dihydrolysergate

Isomerisation in the Position 8

It is well known that derivatives of lysergic acid epimerise easily to derivatives of isolysergic acid. On the other hand, the acquisition of dihydroisolysergic acid derivatives is very complicated. That's why the new process for isomerisation of methyl dihydrolysergate described by Brich and Mühle (1981) brought a substantial progress into the synthetic modification of EA. Methyl dihydrolysergate is first deprotonated in position 8 by a strong base (lithium diisopropylamide) and the resulting anion is then hydrolysed under kinetic control giving 85% of methyl dihydroisolysergate—Figure 13.

8.2.8. Modifications in Positions 9 and 10

The ergoline structure can be easily modified in these positions via addition reactions to $\Delta^{8,9}$ or $\Delta^{9,10}$ double bond. Hydrogenation, hydroboration, addition of mercury(II) salts in methanol and photochemically initiated addition of water or alcohols can therefore be found in older literature. The industrially used photochemical methoxylation of methyl lysergate and lysergol is discussed in Chapter 13.

Hydrogenation

Mayer and Eich (1984) described a new transfer-hydrogenation of both $\Delta^{8,9}$ and $\Delta^{9,10}$ ergolenes (agroclavine, elymoclavine, lysergol, ergotamine, ergocristine), giving high yields of stereospecifically hydrogenated products.

Classic hydrogenation of 8α-substituted ergolenes requires a high pressure and affords a mixture of 5,10 *cis* and *trans* products. One such industrially used process is the hydrogenation of lisuride to terguride (*trans*-dihydrolisuride)—Figure 14. When lisuride was reduced by lithium in liquid ammonia (Birch reduction), the reduction to terguride proceeded stereochemically in a yield over 90% (Sauer, 1981; Sauer *et al.*, 1986).

Electrophilic Substitution of 10-Lithiated Ergolines and $\Delta^{8,9}$-Ergolenes

The elimination of proton from C-10 of agroclavine can be achieved by butyl lithium, giving a carbanion. Because the C-10 carbanion can tautomerise to

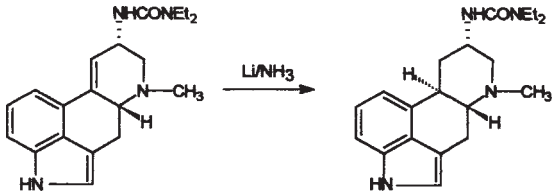

Figure 14 Birch reduction of lisuride to terguride

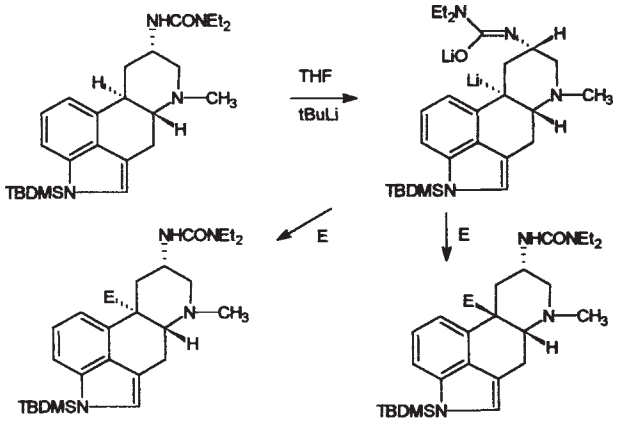

Figure 15 Electrophilic substitution of 10-lithiated terguride

C-8 carbanion, a mixture of 10 and 8 substituted derivatives was obtained after treatment with an electrophilic agent (alkyl halogenides, chloroformates, methyl isocyanate, dimethylsulfide) (Timms *et al.*, 1989).

Sauer *et al.* (1988b) studied the lithiation of terguride. Reaction with *tert*-butyl lithium afforded bis-lithiated intermediate which was further treated with different electrophiles. Depending on the electrophilic reagent 10α- or 10*ß*-substituted products or their mixture were obtained—Figure 15. The *N*-1 position must be protected, most conveniently by *tert*-butyldimethylsilyl group.

8.2.9. Modifications in Positions 12, 13 and 14

These positions on the aromatic part of the ergoline skeleton are accessible to electrophilic substitution. The most reactive position for electrophilic substitution is position 2, less reactive is position 13. Positions 14 and 12 are substituted only under harsh conditions when usually complicated mixtures of products are obtained or some special techniques must be used.

When 2, 3-dihydroergolines are subjected to substitution, position 12 reacts preferentially.

Sauer *et al.* (1985b) prepared 13-bromoterguride via 2, 13-dibromoterguride. Bromination of terguride by 2 equivalents of bromine gave 2, 13-dibromo derivative, which was then selectively debrominated by cobalt bromide (Bernardi *et al.*, 1975) or by hydrogenolysis using NaH_2PO_2 in the présence of a palladium catalyst (Boyer *et al.,* 1985). Similar approach can be used for preparation of other 13 substituted derivatives by electrophilic substitution of 2-bromoergolines and subsequent selective debromination of bromine in position 2. Many 13-acylergolines have been prepared in this way but the reaction is unfortunately accompanied by an exchange reaction giving 2-acyl-13-bromoergoline (Taimr *et al.,* 1987c).

12-Nitroergolines were prepared by Gull (1981a, b) by nitration of *N*-1 acetylated 2, 3-dihydroergolines. The nitro derivatives were further transformed to 12-amino, 12-hydroxy and 12-methoxy derivatives. The double bond was reintroduced into 2, 3 position by oxidation with air.

12-Bromoterguride was prepared by bromination of l-acetyl-2, 3-dihydroterguride. The oxidation of 12-bromo-2, 3-dihydroterguride was accomplished by *tert*-butylhypochlorite (Sauer *et al.,* 1985b).

The synthesis of clavine derivatives substituted in the C-14 position was described by Beneš and Beran (1989). A mixture of 1-*tert*-butyl-, 1-*O*-di-*tert*-butyl-, 2, 13-di-*tert*-butyl- and 2, 14-di-*tert*-butyl-elymoclavine resulted from the reaction of elymoclavine with tert-butylalcohol and trifluoroacetic anhydride. Sauer *et al.* (1990) prepared 13, 14-dibromo derivatives by bromination of 2-methyl-ergolines by different bromination reagents (bromine, pyridinehydrotribromide, pyrrolidone-hydrotribromide) in trifluoroacetic acid. When only one equivalent of bromine was used, 13-bromo derivative was preferentially formed.

The bromine in 12-bromo and 13-bromoergolines can be replaced by lithium and the lithiated ergolines subjected to further electrophilic substitution. The procedure was used to prepare 12- and 13- $CONH_2$, $COOCH_3$, CHO and OH ergolines (Sauer *et al.,* 1988a). Heindl *et al.* (1989) prepared 12- and 13- alkyl, alkenyl and alkinylergolines from the respective bromo derivatives by reaction with some organometallic compounds in the présence of a palladium catalyst.

8.2.10. Changes of the Ergoline Skeleton

5, 6- and 6, 7-Secoergolines

When quarternary ammonium salts prepared from ergoline or ergolene precursors by the treatment with alkyl halogenides were reduced, the C-N bond in the D cycle of the ergoline skeleton was cleaved—Figure 16. While the reduction with alkali metals in liquid ammonia afforded 5, 6-secoergolines (Temperilli and Bernardi, 1980a) the catalytic hydrogenation gave 6, 7-secoergolines (Temperilli and Bernardi, 1980b).

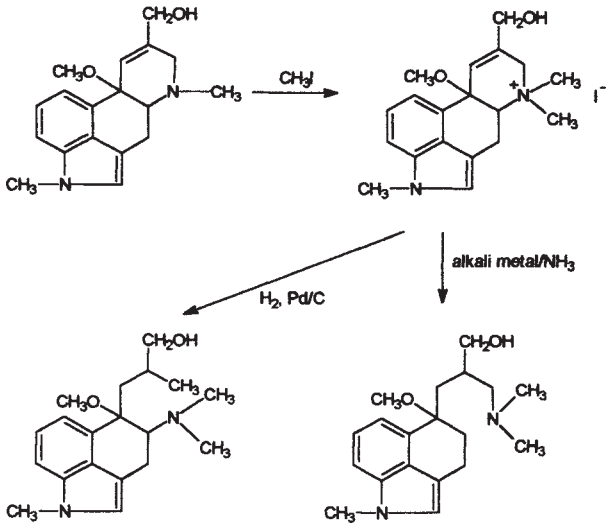

Figure 16 Synthesis of 5, 6 and 6, 7-secoergolines

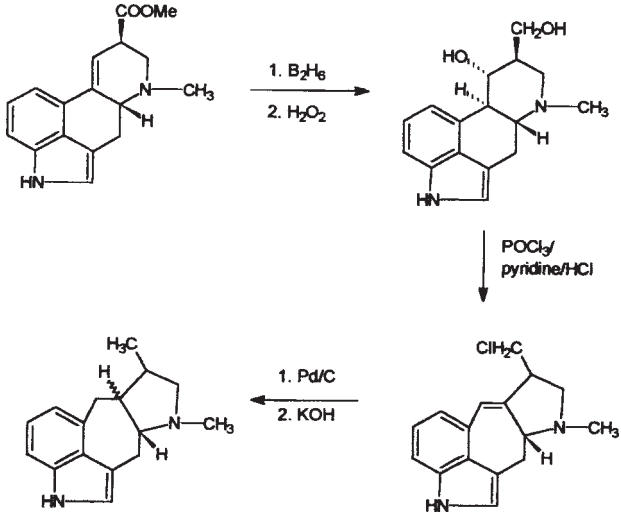

Figure 17 *5(10→9)abeo-ergolines* synthesis

5(10→9)Abeo-ergolines

Hydroboration of $\Delta^{9,10}$ ergolenes affords 9α-hydroxy-ergolines (Bernardi *et al.*, 1976). When these derivatives are treated with $POCl_3$-pyridine hydrochloride, the Merweein-Wagner rearrangement takes place and 5(10→9)*abeo-ergolines* arise—Figure 17. Temperilli *et al.* (1980, 1987b) prepared a number of such derivatives.

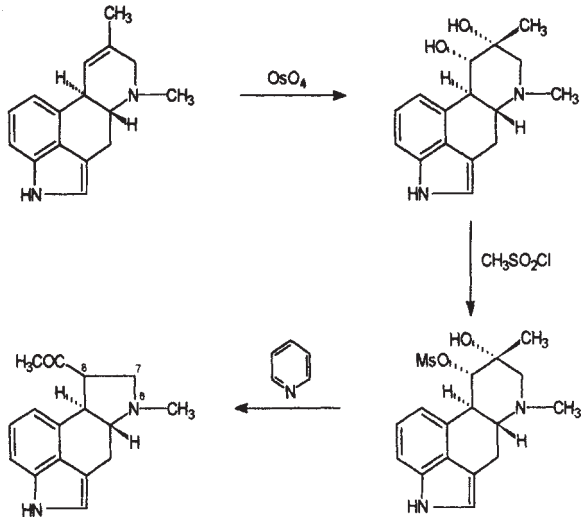

Figure 18 D-*nor*-7-ergolines synthesis

D-nor-7-Ergoline Derivatives

$\Delta^{8,9}$-Ergolenes can be oxidised by osmium tetroxide to 8*ß*, 9*ß*-dihydroxyergolines. When the 9-hydroxy group is activated (converted to a mesyloxy group) it can be eliminated under pinacol-pinacolone-like rearrangement giving D-nor-7-ergoline derivatives—Figure 18 (Hunter, 1985). A similar type of rearrangement starting from 8*ß*-hydroxy-ergolines was described by Bernardi *et al.* (1987).

8.3. CHEMICAL MODIFICATIONS IN THE PEPTIDIC MOIETY OF ERGOPEPTINES

In contrast to the ergoline part of EA, not many chemical transformations of the peptidic moiety are known. Most of the described ergopeptine (EA of a peptidic type) derivatives and analogues modified in the peptidic part were prepared by the total synthesis or by directed biosynthesis, both using modified amino acids. Many other derivatives are known as products of metabolic biotransformations—see Chapter 9. Only positions 2′, 6′ and 12′ are accessible for some types of regioselective chemical modification—Figure 19.

Aci-Derivatives

The hydroxyl group in position 12′ of natural ergopeptines is engaged in a hydrogen bond to the ergoline part of the molecule and therefore it does not exhibit its acidic properties. When the configuration in position 2′ changes, the ability to form the hydrogen bond disappears and the acidic character of the

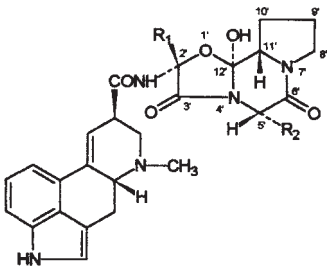

Figure 19 Ergopeptines—cyclol moiety numbering

hydroxyl is demonstrated. Such derivatives with the alkyl group in position 2′α are soluble in alkaline aqueous solutions and are called *aci*-derivatives (*aci*-ergotamine, etc.). The *aci*-derivatives are formed in acidic aqueous solutions by a mechanism started by water elimination from the protonated 12′-hydroxy group (Ott *et al.,* 1966). Because the epimerisation in position 8 of the ergoline part of ergopeptine proceeds simultaneously, a mixture of four isomeric products is obtained: ergopeptine, *aci*-ergopeptine, ergopeptinine and *aci*-ergopeptinine. The dihydroergopeptines are epimerised only on C-2′ and therefore only two products are obtained. The *aci*-derivatives of ergopeptines and dihydroergopeptines have no practical use but their occurrence must be monitored in the final products—both bulk substances and pharmaceutical products.

12′-Alkoxy-Derivatives

The mechanism of formation of 12′-alkoxy derivatives is the same as the one involved in the *aci*-rearrangement—acid-catalysed hydroxyl elimination in position 12′, here followed by an alcohol addition (Schneider *et al.,* 1977; Ručman *et al.,* 1991). Similar to the *aci*-derivatives, also the 12′-alkoxy derivatives can be present as impurities in the salts of ergopeptines.

6′-Modified Derivatives

The stereochemically less hindered carbonyl group in position 6′ can be selectively reduced. Bernardi and Bosisio (1977) prepared 6′-deoxo-$\Delta^{5'6'}$-didehydro9, 10-dihydroergopeptines by Birch reduction of dihydroergopeptines. Cvak *et al.* (1992a) prepared 6′-deoxo-ergopeptines and 6′-deoxo-9, 10-dihydroergopeptines by the selective reduction of ergopeptines or dihydroergopeptines by $LiAlH_4$.

8.4. RADIOLABELLED DERIVATIVES

Whereas the structure-activity relationship was the main target of synthetic modification of the ergoline skeleton, syntheses with labelled compounds were aimed at obtaining identical molecules using suitable labelled intermediates. In

most cases, the radiolabelled derivatives were used as tracers for the study of absorption, distribution, excretion and metabolic fate of EA. Nowadays, labelled compounds are often used also in competitive radioimmunoassays and for identification of binding sites of some neuroreceptors.

Among the numerous synthetic strategies, catalytic reduction with tritium gas of the 9, 10-double bond of EA is the simplest procedure ensuring specific activities of EA over 50 Ci/mmol. This procedure was used to prepare some dihydroergopeptines and the same method was used also for ^{3}H-terguride (Krause *et al.,* 1991), ^{3}H-mesulergine (Voges, 1985) and its derivatives (Voges, 1988). A different synthetic strategy was used for ^{3}H-pergolide (Wheeler *et al.,* 1990) and ^{3}H-cabergoline (Mantegani *et al.,* 1991) where the 9, 10-double bond was not available. ^{3}H-Pergolide was synthesised by catalytic hydrogenation of an *N*-6-allyl intermediate and, similarly, ^{3}H-cabergoline from *N*-6-propargyl derivative. Since the majority of ^{3}H-EA was synthesised for the studies of their pharmacokinetics and metabolism directly in human volunteers (Maurer and Frick, 1984; Wyss *et al.,* 1991; Krause *et al.,* 1991), it is important to note that whereas 9 and 10 positions remain intact during the metabolism of EA, oxidative dealkylation at *N*-6 by cytochrome P-450 is a common metabolic pathway of EA (see Chapters 10 and 11).

In order to achieve a better sensitivity of detection and to avoid the possible exchange or metabolism of tritium-labelled derivatives, several ^{14}C-derivatives have been prepared. In contrast to the soft tritium label, ^{14}C-EA were used solely for animal studies, biotransformations in liver perfusates, and for *in vitro* experiments. Since the total synthesis of the ergoline moiety is a complex multistep procedure, ^{14}C-label was introduced by *N*-6-dealkylation to the nor-derivative and re-alkylation with a labelled alkylhalogenide. This procedure was used, e.g., for bromokryptine (Schreier, 1976) and pergolide (Wheeler *et al.,* 1990). Since the *N*-6 position is metabolism-prone, several syntheses at the C8-atom have been described. A novel application of the ^{14}C-Wittig reagent with the 8-keto-EA intermediate has been developed for the preparation of ^{14}C-labelled 9, 10-didehydro-6, 8-dimethyl-2-methylthioergoline (Wheeler, 1988). Alternatively, the substitution of 8-mesyloxy- or 8-chlorogroups with [^{14}C]-sodium or potassium cyanides were used to introduce a series of C17 labelled derivatives (Wheeler *et al.,* 1990; Mantegani *et al.,* 1991; Angiuli *et al.,* 1997). Lisuride and proterguride were prepared by introduction of ^{14}C-label into the carbonyl group of the urea moiety in the side chain (Toda and Oshino, 1981; Krause *et al.,* 1993). 6-([^{11}C]-methyl)ergolines were prepared from corresponding 6-*nor*-derivatives by the reaction with labelled $^{n}CH_3I$ (Langström *et al.,* 1982). For special purposes, syntheses with other isotopes, leading to slight modification of original templates, have been described: ^{75}Se-pergolide (Basmadjian *et al.,* 1989) and 2-[^{125}I]-ergolines (Kadan and Hartig, 1988; Watts *et al.,* 1994; Bier *et al.,* 1996, Hartig *et al.,* 1985).

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