ALKALOID N-OXIDES

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Abstract - More than 200 aliphatic and aromatic N-oxides have been individuated among natural-occurring alkaloids. The structures of these compounds as well as the role that N-oxides have in the synthesis and the chemical modification of alkaloids are reviewed.

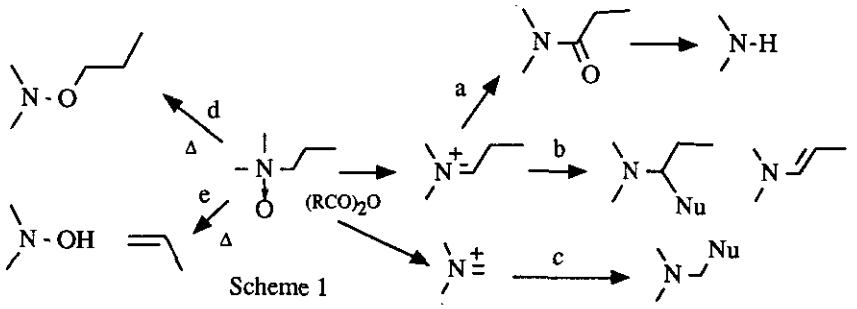
I. INTRODUCTION

The presence of N-oxides in nature is a relatively recent discovery. Thus, in 1909 it was reported that trimethylamine N-oxide is present in the muscles of a shark (Acanthus vulgaris).[1] In 1917 the structure of N-oxide was uncorrectly attributed to an alkaloid, geneserine from Physostigma venenosum[2] (this molecule was later shown to contain a tetrahydro-1,2-oxazine ring rather than a pyrazole N-oxide ring).[3] The first authentic alkaloid N-oxides, which were isolated are oxymatrine from Sophora sp.[4] and iodinine from Chromobacterium sp., were both reported in 1938.[5] The discovery of an antibiotic, aspergillic acid from Aspergillus sp.[6] fostered activity in the specific field, but for some years N-oxides remained a curiosity suspected to be an artifact (see below). After 1970, however, reports of the isolation of alkaloids N-oxides began to increase in number, and in due time they were recognized as autenthic natural products, not artefacts, and hypotheses were formulated about their role(s) in metabolism. At the same time, the chemistry of the N-oxide function was being developed, and a number of useful reactions of such compounds have been applied to alkaloid chemistry. Both these aspects will be discussed in this review. After a short outline of the general chemical properties of these compounds, of their occurrence and of the problems related to their isolation, the main classes of alkaloid N-oxides will be discussed, with regard both to the structure of the natural products isolated and to the related chemical syntheses.

Ia. Classification

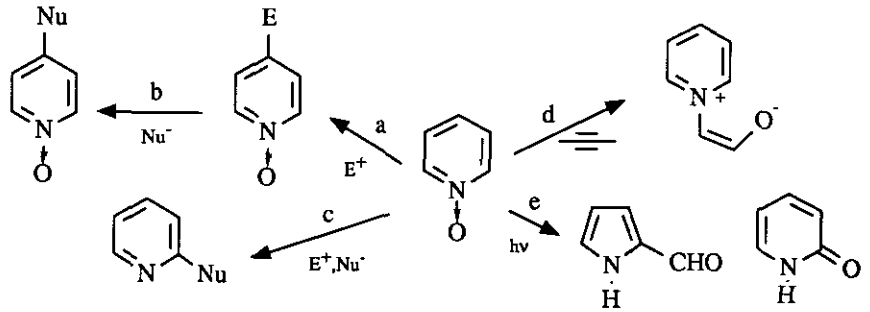
The N-oxide function ($\geq N\rightarrow O$ or $\geq N^{+}-O^{-}$) occurs in different compounds, the chemical behaviour of which

depends on the nature of the nitrogen atom. Thus, the N-oxides of aliphatic tertiary amines are very polar substances not much unlike the corresponding quaternary salts as far as solubility and chromatographic behaviour go. Aliphatic N-oxides are easily obtained from the amines, and likewise are easily deoxygenated. They ungergo a number of useful reactions (Scheme 1, Polonovski reaction with acyl anhydrides, resulting in rearrangement to amides, functionalization in the chain or cleavage of a carbon-carbon bond, paths a-c, Meisenheimer rearrangement to O-substituted hydroxylamines, path d, Cope elimination, path e).[7,8]



Scheme 1

Nitrones as well as heteroaromatic N-oxides contain a sp^2 hybridized nitrogen. The latter class of compounds is characterized by a susceptivity to electrophilic aromatic substitution much greater than for the corresponding azines (Scheme 2, path a), by the easy nucleophilic substitution (path b), by the typical deoxidative substitution occurring under *mild conditions in the presence of an auxiliary electrophile* (path c), by (cyclo)addition of dipolarophiles and photochemical rearrangement (paths d, e).[9]



Scheme 2

Nitrile oxides have a sp hybridized nitrogen. Neither these compounds nor nitrones (as well as their deoxygenated analogous, imines) are usually present among alkaloids (for an exception see Sec. Vb). A good number of heteroaromatic N-oxides have been isolated, but by far the largest part of known alkaloid N-oxides are derivatives of aliphatic amines, and usually the N→O function is located at an angular position between fused rings. Thus, this review is concerned with aliphatic and aromatic N-oxides occurring

as alkaloids in nature and with their chemistry, as well as with the use of aliphatic and aromatic N-oxides in the synthesis of alkaloids. On the other hand nitrones are not present in nature and their chemistry is markedly different from the other N-oxides. They are largely used in synthesis, including that of alkaloids, but in view of the above-mentioned difference and of the fact that their role in synthesis has been recently reviewed,[10] they are not discussed here.

Ib. Occurrence.

More than 200 individual alkaloid N-oxides have been reported so far. This figure might seem low, since it amounts to only a few percents of the known alkaloids, but it may well be that many of these compounds have gone undetected up to now (see below). In fact, the isolation and recognizment as natural products of N-oxides face two opposite sources of errors. On one hand amines are easily oxidized and their N-oxides may be formed during the extraction procedures rather than being originally present in the tissues. As an example, considerable N-oxidation occurs in chloroform solutions of strychnine or brucine on standing,[11] and uv irradiation has been found to cause N-oxidation of glaucine.[12] Such reactions are a problem of industrial significance; thus, during hydrogenation of ergot alkaloids to the pharmaceutically active 9,10-dihydro derivatives some N-oxidation occurs, and was shown to be effected by the hydroperoxides present in the dioxane used as the solvent.[13]

On the other hand, aliphatic N-oxides are easily reduced, and this also may occur during isolation. Moreover, the non-basic, water soluble N-oxides are quite different from the corresponding amines in their properties and may be overlooked when using standard extraction and partitioning procedures. Furthermore, although a complete examination should certainly reveal the $N\rightarrow O$ function (e.g. easy deoxygenation, characteristic downfield shifts of the neighboring hydrogen and carbon absorptions in the nmr spectra) and easy tests, such as the color test for indolizine N-oxides,[14] are available in some cases, a limited investigation may lead to overlook the presence of the additional oxygen or mistake its nature, since the molecular peak is usually very low or absent in the mass spectrum. As an example anadoline, which is actually a derivative of retronecine N-oxide, was initially thought to be the hydrate of a didehydro derivative of retronecine.[15] Likewise, the first proposed structure for macrodaphnine contained a tertiary alcohol rather than the N-oxide function (see Sec. Vb).[16]

In order to simplify extraction problems, in some cases the procedure has been chosen, of titrating the N-oxides present in the first extract, and then reducing them, before separation (see Sec. IVa).

Only in a limited number of cases it has been checked that the reported alkaloid N-oxides are genuine natural products. However, in view of the previously mentioned problems, their occurrence in nature might be more widespread that it appears from the present literature. The distribution of the reported N-oxides among the various classes of alkaloids is uniform, the main groups being those of indole and isoquinoline

alkaloids. Perhaps not unexpectedly, in view of the fact that the N⟶O function is most often at an angular position, an exception is found among izidine alkaloids, where the ratio of the N-oxides versus the total number of alkaloids is much larger than in the other groups, and particularly in the class of pyrrolizines where the majority of the alkaloids present in nature are N-oxides.

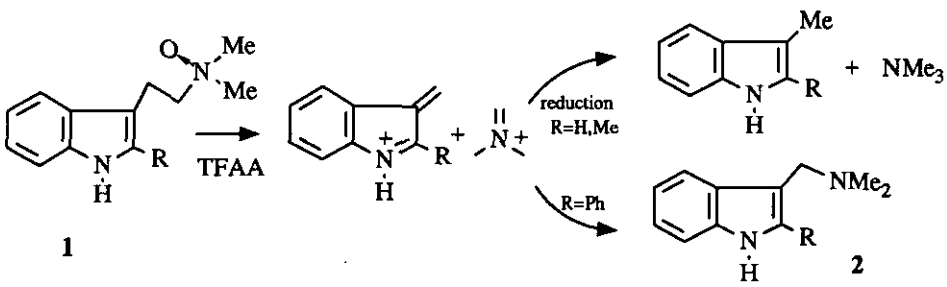
The non planarity of the N⟶O group gives rise to stereoisomerism. In most cases, a single isomer has been isolated from natural sources, though only in a few instances the stereochemistry has been determined. When both isomers have been obtained by extraction, this is mentioned in the text. Chemical oxidation of the corresponding tertiary bases usually, but not necessarily, gives a mixture of stereoisomers.

II. INDOLE ALKALOIDS

The indole nitrogen is obviously not involved in N-oxidation, which rather takes place at the other (basic) nitrogen in the molecules. Thus, these compounds are all N_b-oxides, often with the N⟶O function at an angular position.

IIa. Simple indoles and oxindoles.

N-Oxides of simple indole alkaloids occurring in nature include those of gramine from Arundo sp.,[17] 2,4,5-tribromo-1-methylgramine from Zoobotryon sp,[18] N,N-dimethyltryptamine (**1**, R=H), (as well as its 5-methoxy derivative) from Desmodium sp.[19-21] The tryptamine N-oxide (1) undergoes $C_\alpha - C_\beta$ cleavage by treatment with trifluoroacetic anhydride ("modified Polonovski reaction"), yielding skatole in low yield and with the 2-phenyl analogue the amine (2) is obtained.[22]



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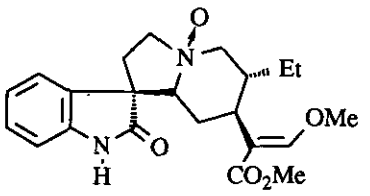
A sizeable group of N-oxides are spiro-indolizinooxindoles, such as rhynchophylline (3) and its 7-iso analogue,[23-24] rotundifoline[25] and vinylrotundifoline[26] from Mitragyna sp., as well as related alkaloids containing an additional oxygenated ring, such as the N-oxides of gelsemine from Gelsemium sp.,[27] stereoisomeric (iso)pteropodine, speciophylline and uncarine F[28] as well as mitraphylline from Uncaria sp.[29] (the third one also from Mitragyna sp.),[30] carapanaubine from Rauvolfia sp., vineridine and vinerine from Vinca sp.,[32-33] as well as the N-oxide of gardneramine (from Gardneria sp)[34] of closely related structure.

Finally, an alkaloid with spyroindoxyl structure, fluorocarpamine N-oxide (4) has been isolated from Catharanthus sp.[34]



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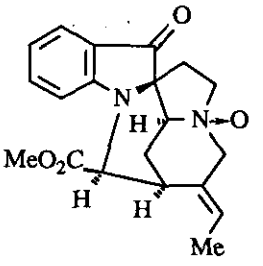

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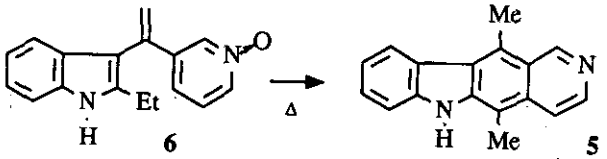
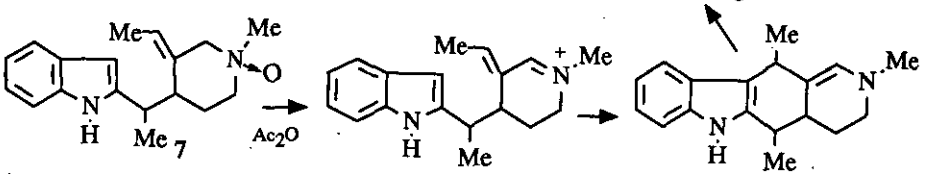
IIb. Carbazole derivatives

An aromatic N-oxide of carbazole type, ellipticine N-oxide, has been isolated from Ochrosia sp.[35] Interestingly, the corresponding base (5) can be prepared by thermolysis of the pyridine N-oxide (6) (or of the pyridinium bromide)[36c] or much better and under mild conditions from the aliphatic N-oxide (7).[36b]

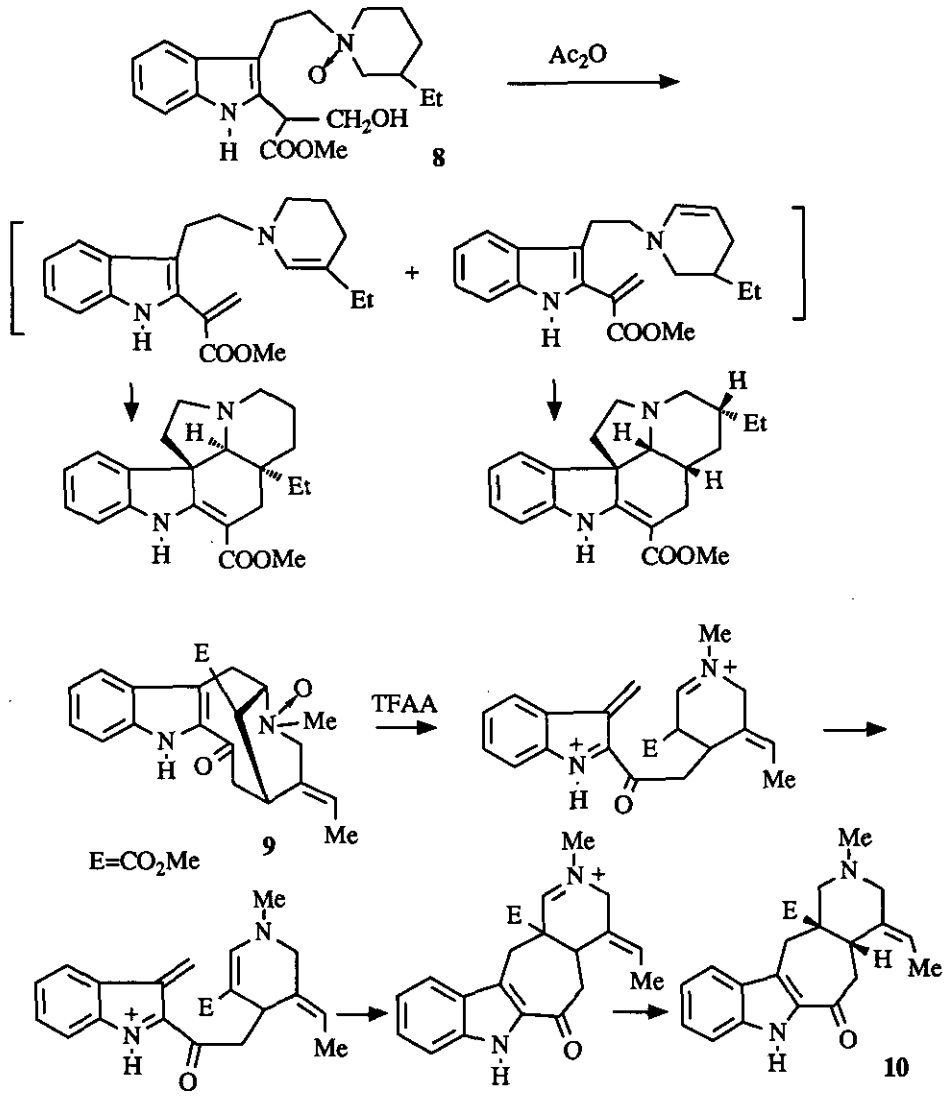




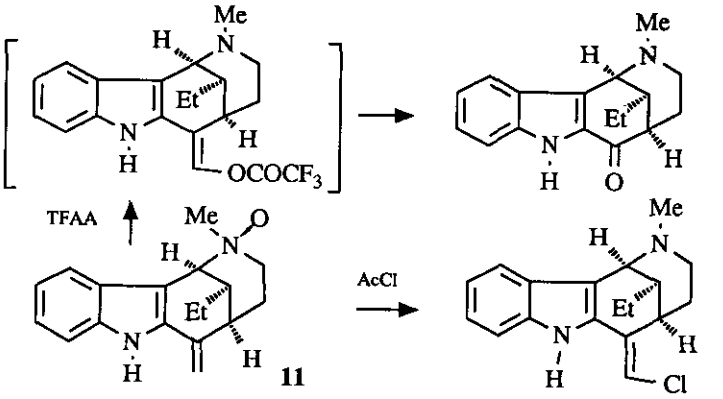
Another large group is that of indolizino[8,1-cd]carbazoles (aspidospermine alkaloids). This includes the N-oxides of vincadifformine from Amsonia sp,[37] ibophyllidine from Tabernaemontana sp.,[38] (epi)vindoline from Melodinus and Catharanthus sp.,[34,39] 1,2-dehydroaspidospermidine from Rhazya sp.,[40] (pseudo)kopsinine from Vinca sp.,[41] and kopsidasine from Kopsia sp.,[42] as well as biogenetically related alkaloids such as the N-oxides of rhazidigenine for Aspidosperma[43] and Rhazya sp.,[44] and koumine from Gelsemium sp.[27]

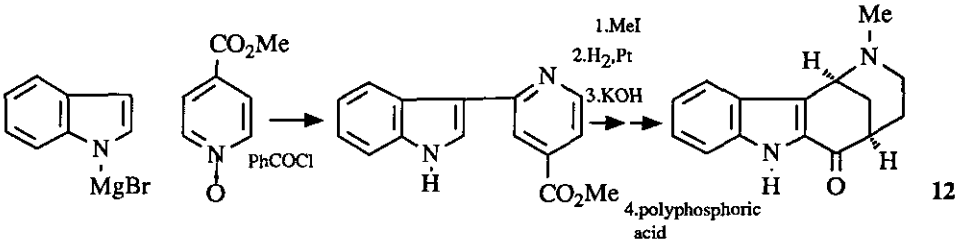
Likewise, alkaloids with the indolizino[7,1-bcd]carbazole skeleton (condylocarpine type) include the N-oxides of condylocarpine from Tabernaemontana sp.,[45] vincamine from Vinca sp.,[46] tubotaiwine from Conopharyngia[47] and Tabernaemontana sp.,[48] and retuline from Strychnos sp.[49]

A useful access to the aspidospermine skeleton is obtained by cyclization of the N-oxide (8) when submitted to the Polonovski reaction.[50]



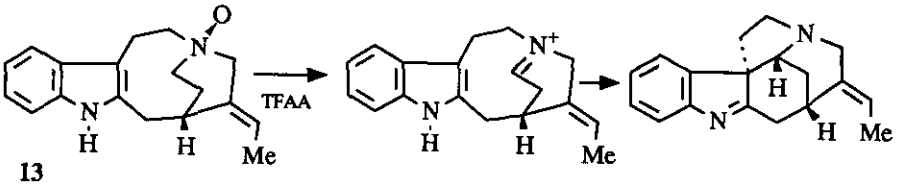
Related conditions have been used in the interesting skeleton rearrangements of vobasine and some related N-oxides (**9**) to the corresponding ervatamine derivatives (**10**).[51] The occurring of such fragmentations depends on structure however; e.g. they are not observed with uleine N-oxide (**11**), where treatment with TFAA leads to nucleophile addition onto position 13 (finally oxidized by O_2 to dasycarpidone), and treatment with AcCl to 13-chlorouleine. The corresponding 1,13-dihydro derivative when acetylated and reduced with $NaBH_4$ undergoes cleavage to an alkylhydroxylamine.[52] A synthesis leading to the uleine skeleton (e.g. deethyldasycarpidone (**12**)) involves the decoxydative addition of the methyl ester of 4-pyridinecarboxylic acid 1-oxides to indolylmagnesium bromide.[53]



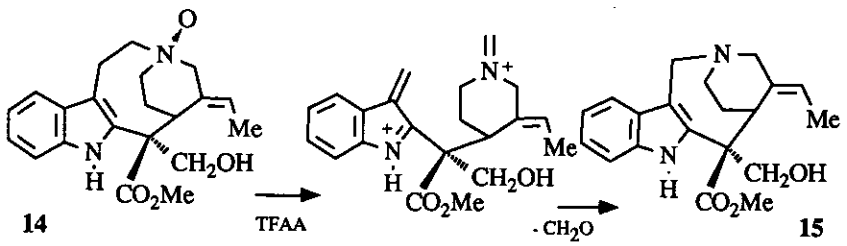


As for the Strychos group of alkaloids, the N-oxides of strychnine, brucine, icajine,[54] 12-hydroxy-11-methoxystrychnine,[55] and ß-colubrine[56a] have been isolated from Strychos sp., and the related akuammicine N-oxides from Alstonia sp.[56]

Interesting transformations of the skeleton are obtained via the N-oxides: thus a new ring is formed when the N-oxide (13) is treated with TFAA (note that only one of the possible cyclizations takes place),[57] but

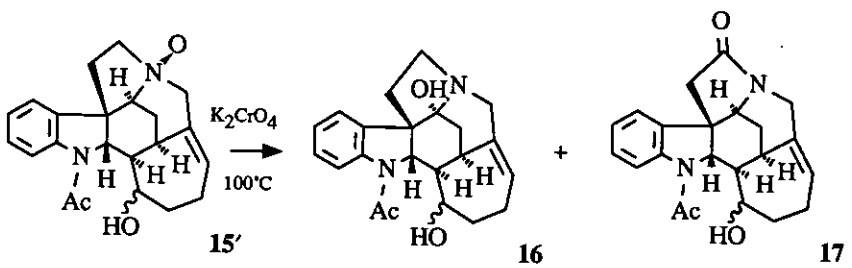


when stemmadenine N-oxide (**14**) is similarly reacted $C_\alpha - C_\beta$ bond fragmentation followed by loss of a one carbon unit and reclosure to its "nor" analogue, vallesamine (**15**) takes place. The last result arose the suggestion that this mechanism via N-oxides may be operating in nature, and that some alkaloids arising through this path should be considered" natural artifacts".[58]



14 **15**

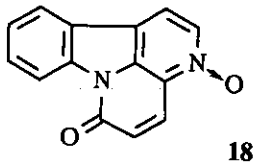
On the other hand heating diaboline N-oxide (**15'**) with K_2CrO_4 or $Fe(NO_3)_3$ converts it to naturally occurring 3-hydroxydiaboline (**16**) as the main product.[59]



15' **16** **17**

IIc. ß-Carboline derivatives

Some aromatic N-oxides pertaining to this group have been isolated from natural sources, viz those of harmine from Banisteriopsis sp.,[60] of 1-ethyl- and 1-(3-ethoxycarbonylethyl)-ß-carboline from Hannoa sp.,[61] and of canthin-6-one (**18**) from Ailanthus sp.[62] In the other cases, the aliphatic N→O function is at an angular nitrogen, generally part of a quinolizidine moiety. These include N-oxides with corynan (or related) skeleton, such as those of (epi)isositsirikine and of dihydrocorynantheol from Aspidosperma sp.,[63] (epi)pleiocarpamine from Vinca and Rauvolfia spp.,[64-65] cabucraline and 10-methoxyvincamedine from Alstonia sp.,[66-67] strictamine from Rhazya sp.,[68] and O-methylnormacusine from Rauvolfia sp.;[69] with heteroyhimbane skeleton, such as those of akuammigine (both epimers) and tetrahydroalstonine (**19**) from Uncaria sp.;[70-71] with yohimbane skeleton, such as those of reserpine from Melodinus sp.,[72] of reserpiline from Ochrosia sp.,[73] and of ß-yohimbine from Aspidosperma sp.[74]



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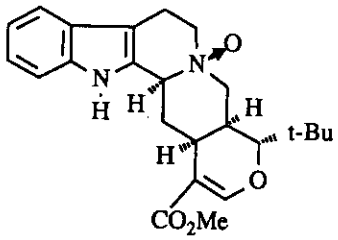

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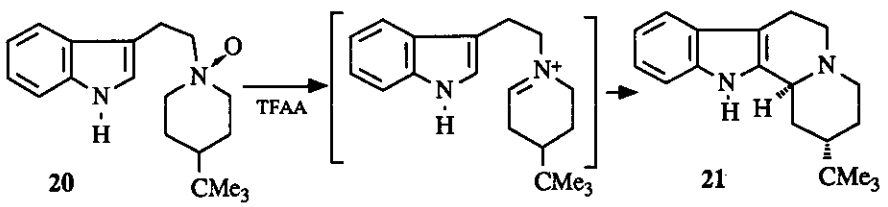
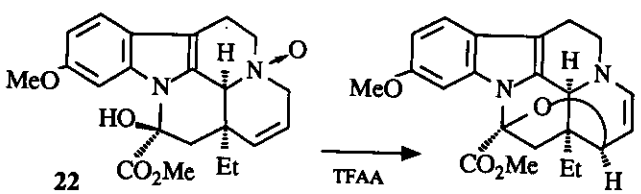
Several attempts to build up the indolo[2,3-b]quinolizine skeleton of these alkaloids by electrophilic attack of the tetrahydro(or dihydro)pyridinium ions in turn obtained from the corresponding N-oxides by Polonovski reaction have been carried out (e.g. 20, 21). The reaction can be effected also by previous conversion of the N-oxide to a α-cyanoamine and treatment of the latter with $AgBF_4$).[75-80] Altough there are other methods of generating the key imminium cation, the N-oxide approach may give some advantages in terms of regio- or stereoselectivity.



20 21

Other N-oxide based elaborations include formation of an oxygenated ring (again via trapping of the iminium cation), as in the conversion of 14,15-didehydrovincine N_b-oxide (22) into craspidospermine[80] and of demethylhirsutine N_b-oxide (23) into dihydromancunine.[81] Formation of the iminium ion and intramolecular trapping are again put to use in the conversion of vincadifformine (24a) into (16-epi)vincamine via the non-isolated hydroxyindolenine N-oxide (25);[82] in the analogous conversion of tabersonine (24b) into (epi)-14,15-didehydrovincamine a minor product is a 7,8-didehydrorhazinilam derivative, arising from the cleavage of the C_2-C_7 bond.[83]



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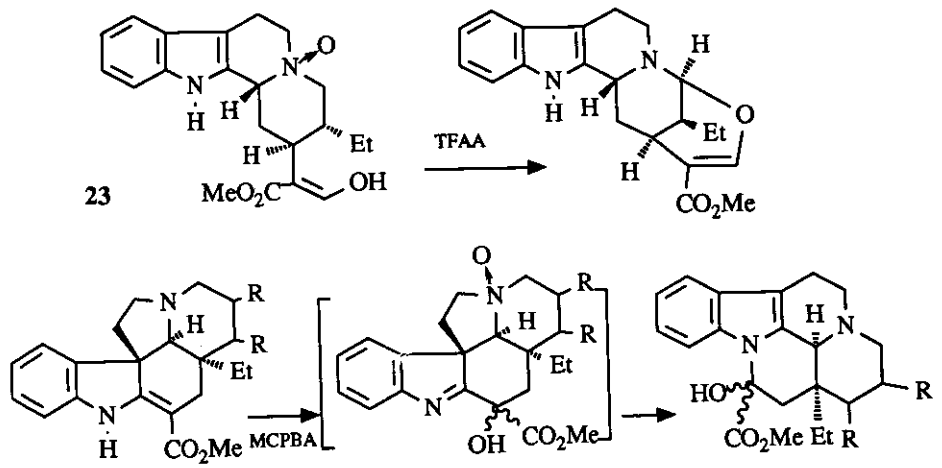


24a(R,R=H),**b**(R,R=bond) **25**

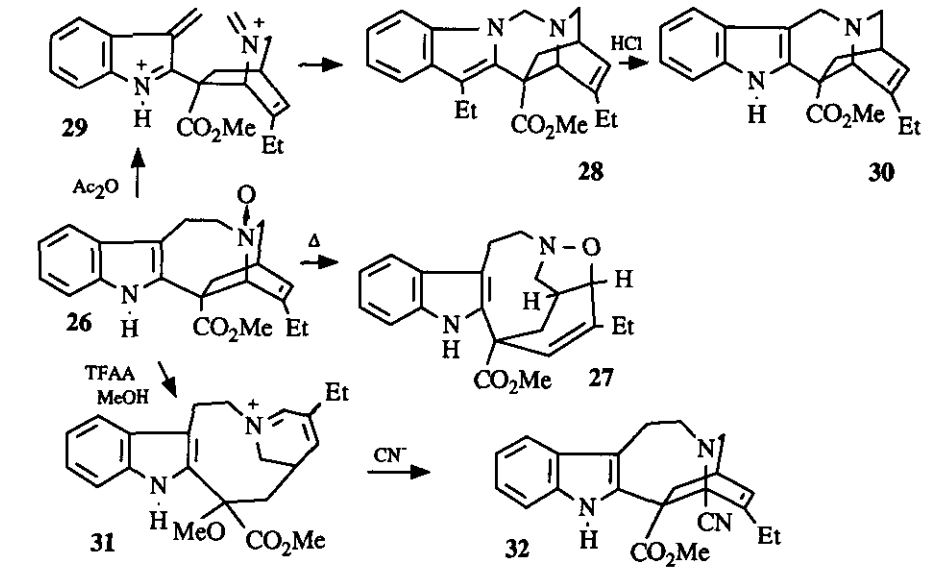
Catharanthine N-oxide (26) undergoes an interesting set of skeleton rearrangements: thus, upon heating above 40°C a Meisenheimer rearrangement takes place and leads to the isoxazoline (27)[84] (21-cyanocatharanthine, when treated with MCPA gives directly a nitrone arising from the oxidative cleavage of the corresponding isoxazoline, in turn formed from the non-isolated N-oxide).[86] Treating 26 with Ac_2O causes C_5–C_6 bond cleavage to give the pyrimidinoindole (28) (which in turn under acidic conditions reopens to the ion (29) and loses CH_2O to yield norcatharanthine (30));[85] when TFAA is used a different bond cleavage (C_{16}–C_{21}) occurs and trapping of the intermediate cation (31) with cyanide leads to 21-cyanocatharanthine (32).[86]

Finally N-oxidation and treatment with Ac_2O is useful for the introduction of a double bond between positions α and ß to a basic nitrogen as in the case of norlysergic acid derivatives.[87]

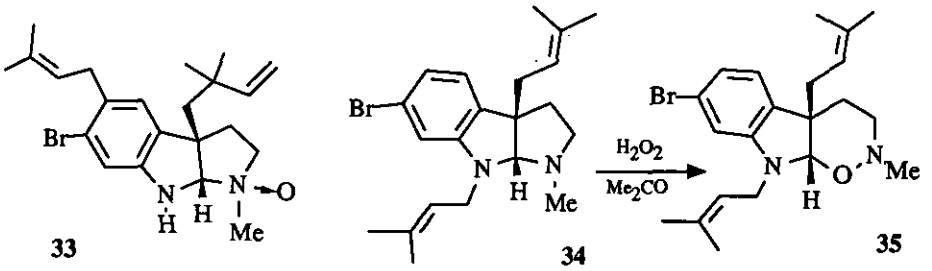
IId. Other indole derivatives.

Among monomeric alkaloid N-oxides, one should still mention pyrrolinoindoles. These include flustramine D (33) and dehydroflustramine C N-oxides from Flustra sp.[88] Flustrarines have been isolated from the same source and have an oxazinoindole structure. Treatment of compound (34) with H_2O_2 converts it to 35, reasonably via the N-oxide.[90] Flustramines and flustrarines stay in the same relation as physostigmine and geneserine; as it has been mentioned in the introduction, an N-oxide structure had been initially attributed to the latter alkaloid.[2,3]

Dimeric indole alkaloids are importat in this discussion, both because several N-oxides of such structure have been isolated from natural sources, and because important hemisynthetic methods for obtaining dimers via N-oxides have been devised. Thus, alkaloids arising from the formal coupling of two Strychnos unities include the N-oxides of longicaudatine,[91] matopensine,[92] bisnordihydrotoxiferine (mono and di-N-oxides)[93-94]

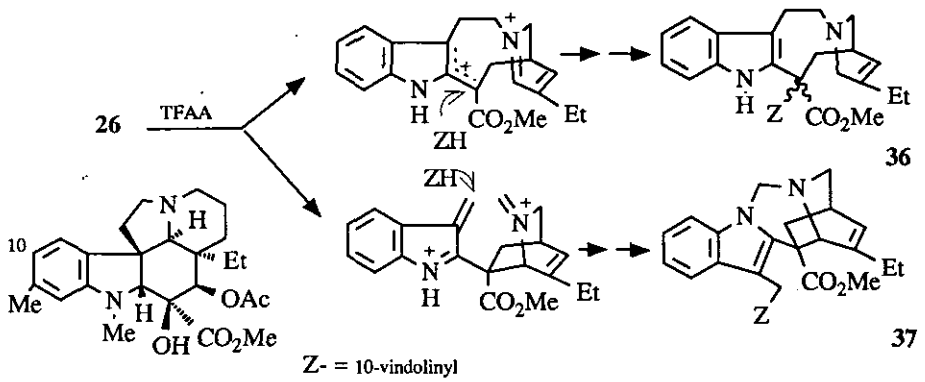


Scheme 3



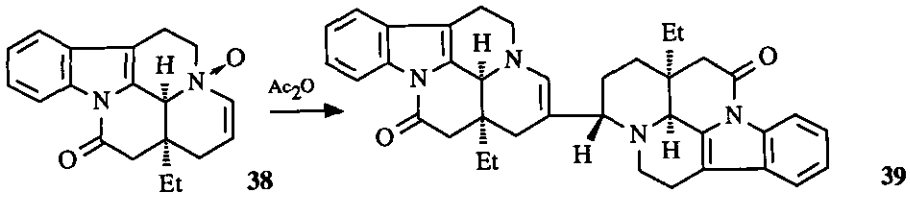
and caracurine,[95] all isolated from Strychnos sp., while the N-oxides of vobtusine (from Voacanga sp.),[96] voacamine (from Tabernaemontana sp.)[97] and leurosine (from Catharanthus sp., this one exceptionally active against melanoma B10)[98] contain indole units of the aspidospermine and (seco)- ibogamine type.

Since several dimeric alkaloids from Catharanthus sp. are in pharmacological use as antitumoral, much work has been devoted to the search of a convenient hemisynthesis from more abundant monomeric alkaloids.[8b] An important (and probably biomimetic) pathway involving N-oxides has been found. Thus, catharanthine N-oxide (26) when treated with TFAA in the presence of vindoline undergoes mainly C_{16}-C_{21} bond fragmentation (compare Scheme 3) and condensation to yield, after in situ reduction of the primarily formed immonium salts, anhydrovinblastine and its 16'R epimer (36) as the main products, along with a minor amount of the dimeric alkaloid arising from the alternative C_5-C_6 cleavage (37).[99]



This approach has been applied to several substrates including dihydrocatharanthine and other catharanthine derivatives,[100-102] e.g. 15 R-acetoxydihydrocatharanthine (in this case direct acetic acid elimination yield anhydrocatharanthine),[103] synthetic 20-deethylcatharanthine[104] and 21-cyanocatharanthine (in the last case the C_5–C_6 bond cleavage predominates).[86] Further synthetic elaboration of the obtained dimeric alkaloids[105] made available a large variety of vinblastine, vincristine and leurosidine type bisindoles. Anhydrovinblastine N_b'-oxide (36) gives the corresponding 5-nor derivative when treated with TFAA (compare 28→30 in Scheme 3).[106]

A different coupling reaction takes place from some vincamine N-oxide derivatives, e.g. 38, and yields dimers such as 39.[107]



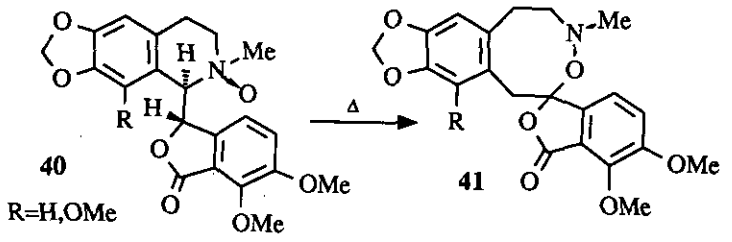
III ISOQUINOLINE ALKALOIDS

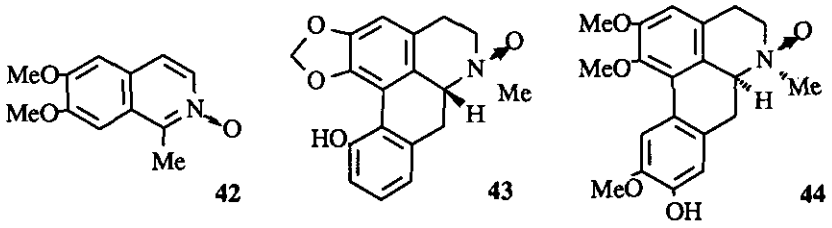
Over fifty N-oxides pertaining to this class have been reported. This is the only large alkaloid class where the N-oxide function is not at an angular position between fused rings (except for berberine and Erythrina alkaloids). Most compounds are N-oxides of N-methyltetrahydroisoquinoline derivatives.

IIIa Simple isoquinolines

This group includes an aromatic N-oxide, that of nigellimine (42) from Nigella sp.,[108] as well as various tetrahydroisoquinoline N-oxides, whether N-methyl, such as tehuanine from Pachycereus sp. and deglucopterocereine from Pterocereus sp.,[109] N-benzyl, such as sendaverine from Corydalis sp.,[110] or

1-benzyl-2-methyl, such as reticuline from Pachygone[111] and Corydalis spp.,[112] roemecarine from Roemeria sp.,[113a] and yuziphine from Corydalis sp.[110] The spirobenzylisoquinoline fumaritine N-oxide has been isolated from Fumaria sp.[113b] The phthalideisoquinoline α-narcotine N-oxide (**40**) undergoes thermal Meisenheimer rearrangement to the spiro derivative (**41**).[114]





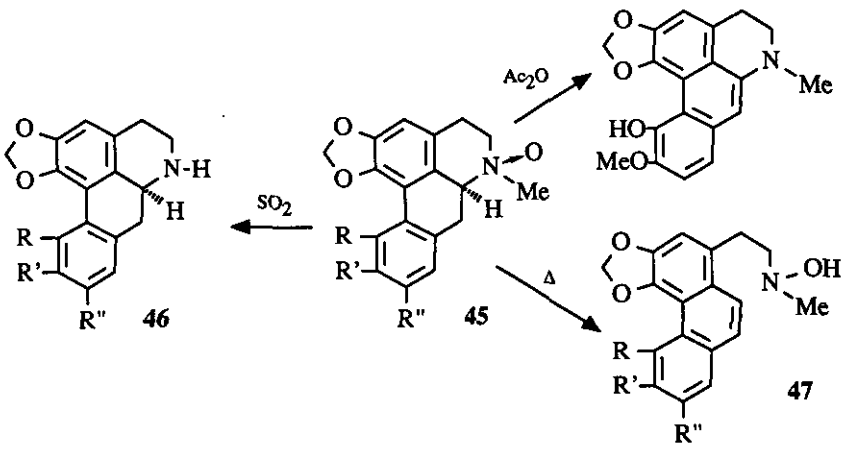
IIIb Aporphines

The largest number of known isoquinoline alkaloids N-oxides pertain to this class. Many examples have a hydroxy or methoxy function in position 7, as in the N-oxides of oliveroline and guatterine from Guatteria sp.[115] (the latter one also from Pachypodanthium sp.),[116] sukhodianine, ushinsunine, and stephadiolamine from Stephania sp.,[117] of oliverine, oliveridine, N-methylpachypodanthine, found in various Annonaceae,[118-121] in particular from Duguetia sp., a species very rich in N-oxides, where the specific N-oxides of pachyconfine, spixianine, and duguexine have been found.[122] Other aporphines are the N-oxides of corydine from Glaucium sp.,[123] isocorydine and O-methylcorydine from Berberis sp.,[124-125] remerine from Liliodendron[126] and Papaver spp.,[127] N-methyllaurotetanine (**44**) from Glossocalyx sp.,[128] pukateine (**43**) from Laurelia sp.,[129] preocoteine from Thalictrum sp.,[130] and lirinine from Liliodendron sp.[131] Related structures are present in the proaporphine trigamine N-oxide from Merendera sp.,[132a] and the homoproaporphine collutine from Colchicum sp.[132b]

Ring closure of 1-benzylisoquinolines to aporphines is conveniently obtained via the N-oxides (see Sec IIIc).[133a] Homoaporphines are analogously obtained from 1-phenylethylisoquinoline N-oxides.[133b]

Interestingly, several aporphines are demethylated by treatment of the corresponding N-oxide with SO_2 (e.g. **45** ⟶ **46**; this is a procedure that in some cases yields valuable alkaloids from largely available

precursors).[134] However, bulbocapnine N-oxide (**45**, R=OH, R'=OMe, R"=H) e.g. undergoes C_{6a}–C_7 dehydration by treatment with Ac_2O; reduction of the product has been used to obtain rac-bulbocapnine (and the (R) isomer from it) from the natural (6aS) compound.[135a] On the other hand, aporphine N-oxides undergo thermal Cope elimination to yield 4-phenanthreneethylhydroxylamines (**47**), a path which may have biomimetic significance.[135b]

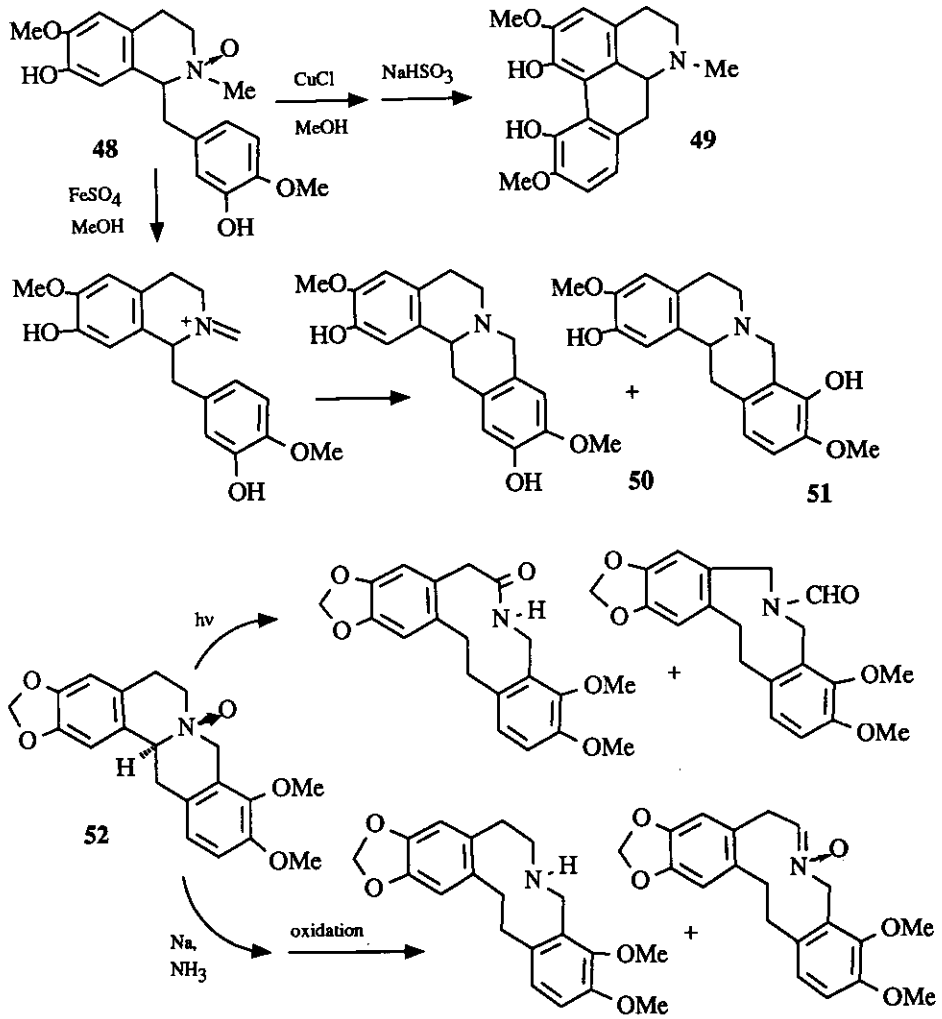


IIIc Berberines and related alkaloids

This group includes the N-oxides of xylopinine from Stephania sp.,[136a] and of tetrahydropalmatine[136b] and ophiocarpine from Corydalis sp.[137-138] Protopine N-oxide has been obtained from Bocconia sp.[139]

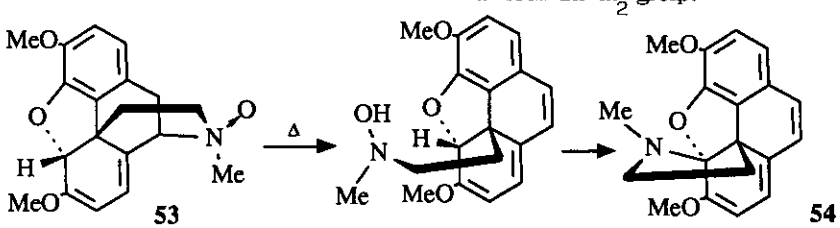
From the synthetic point of view, it may be noticed that while 1-benzyl-2-methyltetrahydroisoquinoline N-oxides cyclize to aporphines under conditions favoring phenolic coupling (e.g. reticuline N-oxide (**48**) → corytuberine (**49**)), the same substrates, when treated with $FeSO_4$ under neutral or acidic conditions undergo the alternative cyclization to berbines via iminium cation (e.g. **48** to coreximine (**50**) + scoulerine (**51**)).[133a,140]

Thermolysis or photolysis of protopine and allocryptamine N-oxides result in a Meisenheimer rearrangement as the main path, accompanied by products from Cope elimination (or secondary products from them).[141] Photolysis of trans-canadine (**52**) or trans-xylopinine N-oxide causes ring cleavage, possibly via cyclization to an oxaziridine and rearrangement.[142] Birch type reduction of the same substrates (followed by air reoxidation) leads either to ring cleavage or to simple deoxygenation.[143-144]

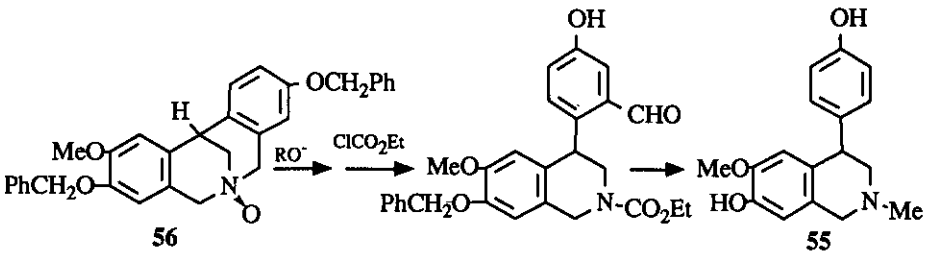


IIId Other monomeric isoquinolines

The N-oxides of morphine, thebaine, and codeine (both stereoisomers for the first two alkaloids, only one for the last one) have been isolated from Papaver sp.[145-146] One of the thebaine N-oxides (53) is thermally unstable and undergoes Cope fragmentation to finally yield 54, also present in the same species.[146] The stereoisomer of 53 is stable since the N→O function is too far from the CH_2 group.

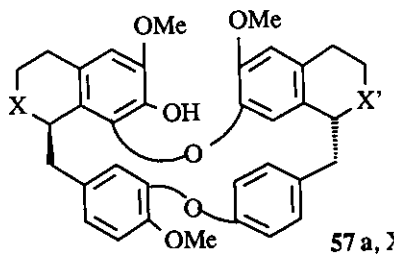


Other natural N-oxides include those of the pavines argemonine (from Argemone sp.)[147] and eschscholtzine (from Eschscholtzia sp.),[148] some Erithrina alkaloid N-oxides, viz those of erytrosine, erythrartine[149] and 11-ß-methoxyerythraline,[150] as well as the cryptaustoline jamtine N-oxide from Cocculus sp.[151] An useful approach to cherylline type alkaloids (55) has been developed, based on the regioselective Polonovski cleavage of N-oxides such as 56.[151b]

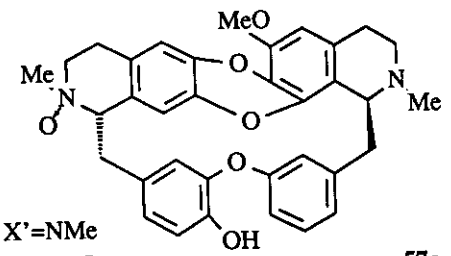


56 55

Rheadan derivatives are selectively demethylated when treated by TFAA, e.g. bicuculline N-oxide is converted to papaverrubine E.[152a] On the other hand, N-oxides of similar structure, e.g. alpinigenine N-oxide, undergo thermal ring enlargement through a Meisenheimer rearrangement.[152b]



57 a, X=NMe-O, X'=NMe
b, X=NMe, X'=NMe-O



57c

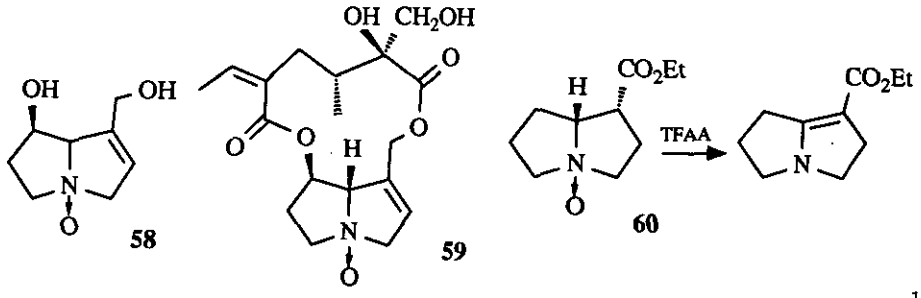
IIIe. Dimeric alkaloids

A large number of mono N-oxides of dimeric benzylisoquinoline alkaloids have been reported. These include products with a single ethereal bridge, such as the N-oxides of neothalibrine, thalrugosaminine, thaligosine, thaliphylline, and thalidasine and its 5-hydroxy derivative from Thalictrum sp.,[153] of O-methyldauricine from Popowia sp.,[154] of thalicarpine from Hernandia sp.;[155] with a C-C and one ethereal bridges, such as funiferine N-oxide from Tiliacora sp.;[156] with two ethereal bonds, such as the N-oxides of thalicmidine[130] and hernandezine from Thalictrum sp.,[157] (the former one also from Berberis sp.),[124] of berbamine[158] and calafatine (in this case both stereoisomers) from Berberis sp.,[159] of pheanthine from Pycnarrhena sp.,[160] and of cepharanthine from Stephania sp.,[161] and limacine (57a,b, the two regioisomeric N-oxides, but a single stereoisomer of each one) from Curarea sp.;[162] with a p-dibenzodioxin structure such as the N-oxides of cocsuline (57c) from Cocculus sp.,[163] isogilletine from Triclisia sp.,[164] and tiliacorine from Tiliacora sp.[165]

IV. IZIDINE ALKALOIDS

IVa. Pyrrolyzidine alkaloids

As it has been mentioned in the introduction, this is the group where the the highest ratio alkaloid N-oxides vs total alkaloid content has been found. Indeed the isolation of isatidine (58), the N-oxide of retronecine, from Senecio sp.,[166] is one of the earliest reports of N-oxides from natural sources, and the diffusion of these compounds in Senecio and other species was early recognized. From the practical point of view it may be expedient to reduce the total alkaloid fraction (this can easily be done under conditions non affecting other chemical functions present, usually by treatment with zinc,[167-170] but e.g. also with a reducing resins)[171] and then to separate the bases, thus avoiding the problems connected with the strongly polar nature of N-oxides. However, direct separation of the N-oxides can certainly be accomplished by chromatography[172-175] or droplet counter current.[176] Moreover, it has been demonstrated that extensive deoxygenation takes place during usual extraction procedures (the reaction is slow in pure solvents, but fast in the presence of the residual plant material) and the hypothesis has been advanced that all the pyrrolizidine alkaloids are present as the N-oxides, and the tertiary bases are artifacts.[174] Interest in these compounds is increased by the fact that several N-oxides show a specific and high antitumoral activity.[175,177]



Apart from some exceptions, such as 1-methylenepyrrolizidine N-oxide (from Crotalaria sp.),[178] the alkaloids of this group are either alcohols (mono- or bifunctional), with the pyrrolizidine moiety either fully reduced or containing one double bond, or esters derived from them. Alcohols are trachelanthamine N-oxide[179a] and subulacine N-oxides obtained from Heliotropium sp., where an oxetane ring is also present.[179b]

The N-oxides of several monoesters, such as heliotrine,[180-183] viridiflorine,[184-185] echinatine,[185-186] anadoline,[15] echimidine,[187] indicine,[175,177,188] europine,[189,190] intermedine,[190] heleurine,[183] lycopsamine,[172] lindelofine,[191] 9-angelylretronecine[192-193] and 9-angelylplatynecine,[194] and of diesters, such as sarracine,[195,6] heliosupine,[186,197-198] lasiocarpine,[182,183,188,199,200] asperumine,[201] and latifoline[203] have been isolated mainly from Heliotropium and Symphytum sp., and further from Senecio,

Trachelantus, Cynoglossum, Paracynoglossum, Echium, Trichodesma, Castilleja, Lindelofia, Rhesa and Hackelia sp. Absouline (from Hugonia sp.) is the N-oxide of a 1-acylaminopyrrolizidine.[203] Macrocyclic diesters of dicarboxylic acids include the N-oxides of senecionine,[176-177,204] platyphylline,[168,205] sceleratine,[171] merenskine,[171] nemorensine,[206] rosmarinine,[168] and retrorsine (**59**)[207a] from Senecio sp., again retrorsine[169] and seneciphylline[167] from Erechites sp., crosemperine[190] and monocrotaline[176,190,207b] from Crotalaria sp. (the latter one also from Senecio sp.).

As with other perhydro heterocycles, treatment of pyrrolizidine N-oxides with trifluoroacetic anhydride serves to introduce a double bond in the ring. Thus, the N-oxide (**60**), the ethyl homologue of the alkaloid chrysine, yielded the 1,7a-didehydro derivatives.[208] A general reaction for this class of alkaloid N-oxides is the transformation into pyrroles by treatment with $FeSO_4$ at room temperature (the reaction works better in the presence of fluoride ions).[209]

IVb Quinolizine and indolizine derivatives

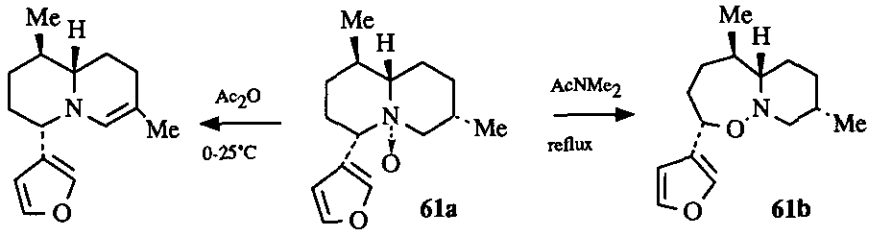
N-Oxides are largely present also among quinolizine alkaloids. Examples are found among all the structure types which form this class of alkaloids, e.g. simple quinolizines such as the N-oxides of epilupinine from Lupinus sp.,[210-11] epilambrolobine,[212] and mamanine[213] from Sophora sp.; the characteristic furylquinolizine N-oxide nuphar idine (**61**), from Nuphar sp.;[214] the tricyclic derivative cytisine N-oxide from Spartium sp.;[215] tetracyclic N-oxides both of the sparteine type, such as those of pachycarpine from Ammodendron sp.[216] and of aphylline from Anabasis sp.,[217] and of the matrine type, such as those of matrine from Sophora sp., lehmannine,[224] and 5,17-dehydromatrine from Euchresta sp.;[225] Lythraceus alkaloids such as lythrine N-oxide from Decodon sp.[226] Coccinelline, a repulsive alkaloid from Coccinella sp., is a perhydropyrido [2,1,6-de]quinolizine N-oxide.[227]

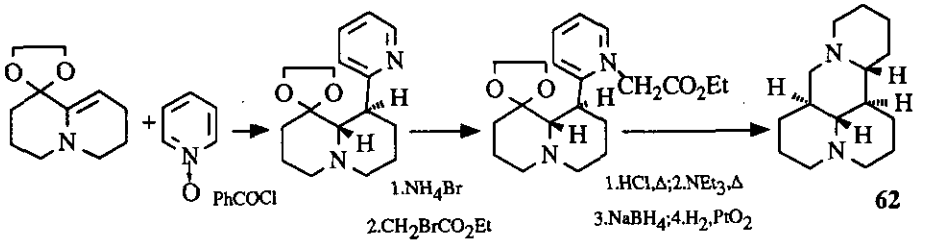
Among indolizine alkaloids, swainsonine N-oxide from Astragalus sp.[228a] and lolinine N-oxide from Lilium sp. should be mentioned.[228b]

Treatment of N-oxides with acetic anhydride has been used for introducing a double bond into the ring, e.g. for converting nuphar idine (**61a**) into dehydrodeoxynuphar idine;[229] similar reactions have been reported for lupanine N-oxide[230] and for related compounds, in view of the synthesis of lycopodinoid derivatives.[231a] On the other hand, heating nuphar idine in DMF causes a Meisenheimer rearrangement to yield **61b**.[229b] A synthesis of allomatridine (**62**) begins with a deoxidative addition to pyridine N-oxide.[231b]

V. OTHER ALKALOIDS

There are sparse examples of N-oxides among the other groups of alkaloids. For the present purpose, they are first subdivided according to the nature of the N→O function, whether aromatic or aliphatic.

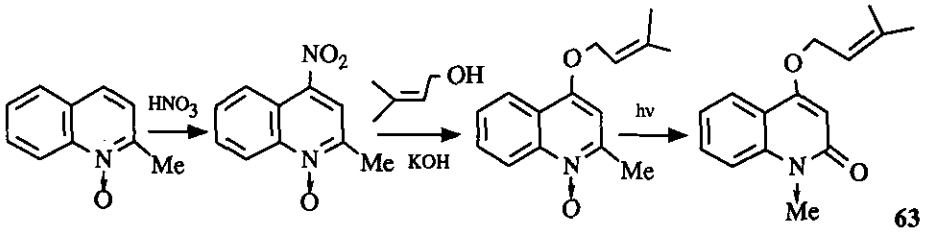




Va Aromatic N-oxides

These include various hydroxypyrazine and quinoline N-oxides (actually present as the tautomeric hydroxamic acids) such as aspergillic acid and related derivatives from Aspergillus sp.,[6,232] and the so called "Pyo" substances obtained from Pseudomonas sp.,[233] as well as the bipyridine-N-oxide orellanine from Cortinensis sp.,[234] the phenazines iodinin and mixin from Chromobacterium sp.[5] and the mono and di N-oxide of eupolauridine from Cleistopholis sp.,[235] where a naphthyridine nucleus is present.

An example of how the typical chemistry of aromatic N-oxides is exploited for the synthesis of natural products is that of revenine (63, easy nitration, nucleophilic substitution, photorearrangement).[236]



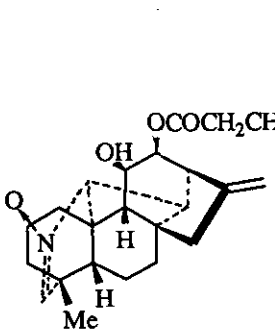
Vb Aliphatic N-oxides

This is a heterogeneous group, with alkaloids of various structure. Thus, dendrobine N-oxide (from Dendrobium sp.)[237] contains a pyrrolidine nucleus; pyrrolidine N-oxides are those of 1-methylpyrrolidine (from Vandopsis sp.),[238] ß-skytanthine (from Skytanthus sp.),[239] sibirine (from Nitraria sp.);[240] both cis and trans nicotine 1'-oxide (but not the aromatic 1-oxide) have been obtained from Nicotiana sp.[241] There

are several tropane N-oxides, such as those hyoscyamine from Atropa sp.[242] (and the 6-hydroxy derivative from Physochlaina sp.),[243] of hyoscine from Datura and Hyoscyamus sp.,[242] of 3 α-tigloyloxytropane from Physalys sp.,[244] and of convolamine from Convolvulus sp.[245] Two quinoline alkaloids, rhazicine[246] and epimeloscine N-oxides have been obtained from Melodinus sp.[247]

These are several examples among diterpene and steroidal alkaloids. The first group includes the N-oxides of anopterimine (64) from Anopterus sp. (one of the few cases where a nitrone function, rather than an aliphatic N-oxide, is present)[248] as well as of songorine,[249] napelline,[250] and zeraconine (65) from Aconitum sp.[251]

The second group is characterized by several N-oxides with a C-nor-D-homosteroidal skeleton, such as those of imperialine (66) from Petilium sp.,[252] of korsine,[253] severine,[254] and sevedine from Koralkovia sp.,[255] of veratramine from Veratrum sp.,[256] and of verticine and verticinone from Fritillaria sp.[257]



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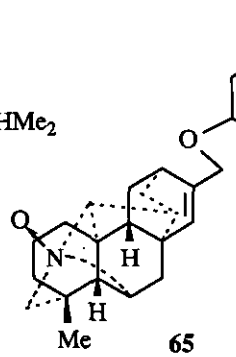

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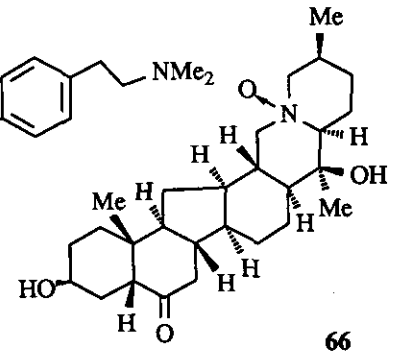

66

Alkaloids of characteristic polycyclic structure isolated from Daphniphyllum sp. include some N-oxides, viz macrodaphnine[16] and (desacetyl)daphniteijsmine.[258] A few non-heterocyclic alkaloid N-oxides are know, but they are not discussed here.

VI. CONCLUSIONS

The significance of N-oxides in biosynthesis is largely unknown, and at any rate does not come within the scope of the present discussion. However, two facts should be pointed out viz 1) that in some cases N-oxides and not the tertiary bases are the target of biochemical paths, e.g. it has been demonstrated that pyrrolizidine N-oxides are the primary product of biosynthesis in root cultures of some Senecio sp., and are accumulated as such, and 2) that N-oxides are very different from the tertiary bases in their physico-chemical properties (e.g. permeation of biological membranes)[174, 259] and thus their formation

specifically controls the translocation and storage in the cell of substances, such as the alkaloids, which have a fundamental role in life.

On the other hand, reactions via the N-oxides often affords advantageous paths in the chemical synthesis and transformation of alkaloids.

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