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PREPARATION AND STEREOCHEMISTRY OF SOME INDOLE ALKALOID N-OXIDES

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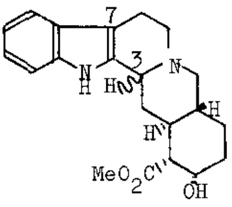
Two N-oxides were obtained from yohimbine (1) on m-chloroperbenzoic acid oxidation. The major isomer (3) was shown to possess the stable trans-quinolizidine ring system through a chemical correlation with pseudoyohimbine N-oxide (5). A similar result was obtained for N-oxidation of dihydrocorynantheine (10). A possible reaction mechanism is proposed for the conversion of 3 to 3-hydroxy-yohimbine N-oxide (7).

In general, N-oxidation of an unsymmetrically substituted tertiary base gives rise to a new center of asymmetry, and if the compound possesses the other asymmetric center(s), two kinds of diastereomeric N-oxides will be given under the absence of stereochemical restriction. In this regards, it is interesting to study the relationship between the configuration of N-oxide bond of the major isomer and the orientation of the lone pair electrons of the starting free base. Fujii et al.[1] studied N-quaternization of benzo[a]quinolizidines with methyl iodide and found that the kinetically controlled products were quaternary salts with the cis-quinolizidine ring system, which corresponded to the less stable conformer contributing only in a small extent to the parent materials. In this communication, we describe our result of preparation of several N-oxides of natural indole alkaloids which possess the indolo[a]quinolizidine ring system as the composing unit, and elucidation of the configuration of the N-oxide bonds by making use of a novel rearrangement we previously reported.$^{2)}$ As a result, we found that the major N-oxide produced from m-chloroperbenzoic acid (MCPBA) oxidation of yohimbine (1) and dihydrocorynantheine (10) maintained the original orientation which the electron pair of the starting materials occupied.

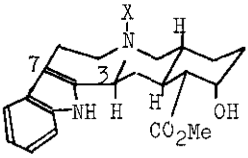
First we studied on N-oxidation of yohimbine (1) and pseudoyohimbine (2). When 1 was oxidized with MCPBA, two N-oxides were given in an approximate ratio of 10:1. Reduction of the both compounds by use of $NaHSO_3$ regenerated the starting base (1), indicating them to be stereoisomers concerning the configuration of the N-O bond. A similar oxidation of pseudoyohimbine (2) with MCPBA afforded a single product (5).

Pseudoyohimbine (2) having C-3 βH is well known to exist in the stable conformation depicted below$^{3)}$ and there is no other conformation with comparable stability. This leads to the natural assignment of the structure (5) to the sole N-oxide (5) derived thereof. On the other hand, two conformers (1a and 1b) are possible for yohimbine (1) though the former being exclusive in the ground state. Of the corresponding two possible structures, 3 and 4, the trans-quinolizidine form (3) was found to be ascribable to the major N-oxide as described below.

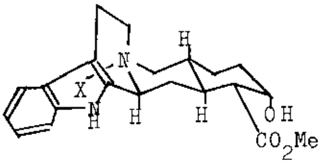
Pseudoyohimbine N-oxide (5) was chlorinated with tert-butyl hypochlorite to an unstable chloride (6), which was then treated with NaOH to give 3-hydroxy-yohimbine N-oxide (7). This compound was shown to be identical with the specimen$^{2)}$ we previously obtained from chloroindolenine N-oxide (8), which



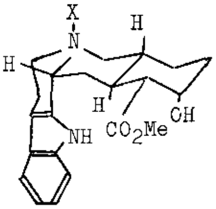
1 C-3 α H
2 C-3 β H



1a: X= electron pair
3 : X= O



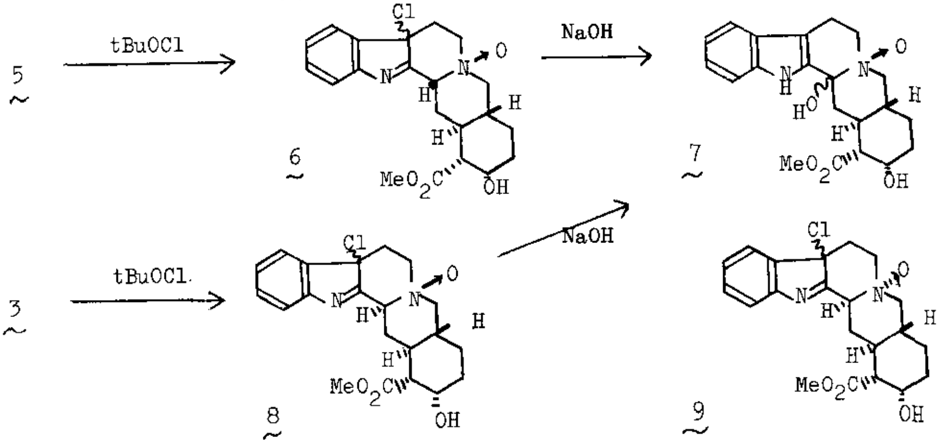
1b: X= elctron pair
4 : X= O



2: X= electron pair
5: X= O

was derived from yohimbine (1) either through one step oxidation of the hydrochloride or N-oxidation of a mixture of yohimbine chloroindolenines.4) On the other hand, the major N-oxide (3) was chlorinated to 8, which gave the same C-3 hydroxylated compound (7) on treatment with NaOH. The above observation clearly indicated that 3 possesses β configuration of the N-oxide bond, since β configuration in 5 is unequivocal and no inversion of the N-O bond is likely to occur in the above reaction sequence.

The minor N-oxide (4) gave rise to the corresponding chloroindolenine(9)

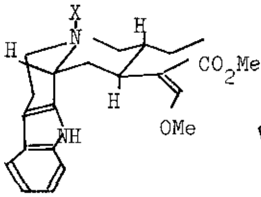


but the subsequent conversion to a C-3 hydroxy derivative was unsuccessful.

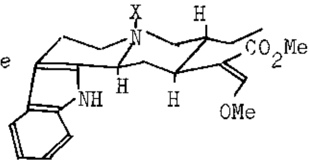
The present study indicates that the major N-oxide produced from MCPBA oxidation of yohimbine (1) is the epimer with trans-quinolizidine ring system unlike the result of N-quaternization of benzo[a]quinolizidines.1)

Next, N-oxidation of dihydrocorynantheine (10)5) and the C-3 Hβ epimer, hirsutine (11)6), was studied. Two N-oxides were obtained from 10 and only one was given from 11 on MCPBA oxidation. All of these N-oxides regenerated the starting free bases on reduction with $NaHSO_3$.

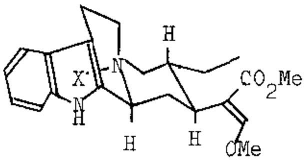
The major N-oxide (12) of dihydrocorynantheine (10) was chlorinated with tert-butyl hypochlorite and the product (15) was treated with sodium methoxide in methanol to give C-3 methoxy derivative (16). By way of the same reaction sequence, the same compound (16) was obtained from hirsutine N-oxide (14), which unambiguously possesses the cis-quinolizidine form and therefore β configuration of the N-O bond. This result again indicates that the major N-oxide resulting from MCPBA oxidation of dihydrocorynantheine (10) was the isomer with trans-quinolizidine ring system, corresponding to the energetically most stable conformation (10a) of the starting base.5) As was the case with the yohimbine derivative (4), the minor N-oxide (13) having an α N-oxide bond failed to give a corresponding C-3 substituted compound.



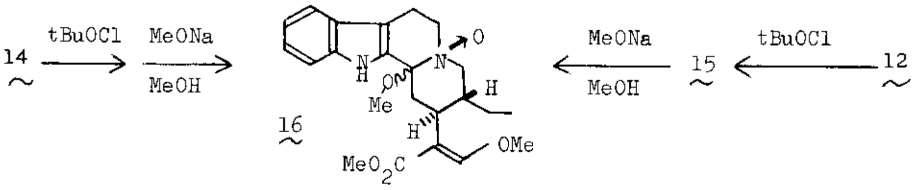
11: X= electron pair
14: X= 0



10a: X= electron pair
12: X= 0



10b: X=electron pair
13 : X= 0



Merlini et al.[7)] studied the configuration of heteroyohimbine N-oxides by means of ^{1}H-NMR spectroscopy and found that the half-width of the signal due to C-3 H is of diagnostic value. The chemical shifts and half-widths of the C-3 H signals of our N-oxides are shown in the Table 1.

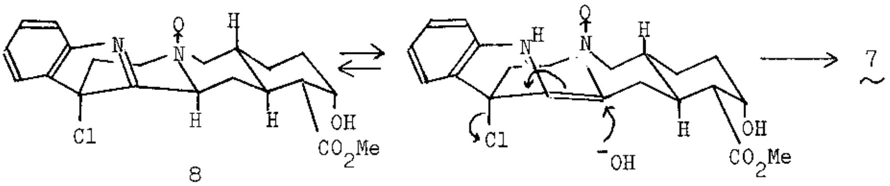
	mp.	Chemical Shift(ppm)	Half-width(Hz)
Yohimbine N-oxide			
major (3)	205-206°	4.68	17
minor (4)	208-210°	4.40	20
Pseudoyohimbine N-oxide(5)	235-237°	4.56	8
Dihydrocorynantheine N-oxide			
major (12)	188-190°	4.60	16
minor (13)	183-187°	4.20	19
Hirsutine N-oxide (14)	182-188°	4.47	10

Table 1.

As expected, pseudoyohimbine N-oxide (5) and hirsutine N-oxide (14) show smaller half-widths of the C-3 H signals than others supporting the assigned structures.

The structural proof also came from the chiroptic properties of the N-oxides. It is well known that the sign of the Cotton effect of the longest wave length reflects the C-3 configuration of indole alkaloids.[9)] In accord with this, 5 showed a negative Cotton effect, while 3 and 4 showed positive ones at around 290 nm.

Two chloroindolenine N-oxides, 8 and 9, showed approximately antipodal CD curves. On the basis of the observation reported by Finch et al. for the epimeric pairs of chloroindolenines of yohimbane series,[8)] C-7 S configuration of **8** and C-7 R configuration of **9** were deduced. The observed difference in reactivities of the two chloroindolenine N-oxides, -- while **8** gave rise to the indolic compound (**7**) under mild conditions, **9** afforded a complex mixture of uncharacterizable products--, can be explained by assuming the S_N2' mechanism, for which only the leaving group of **8** is allocated suitably.



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