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Dhavadee Ponglux

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Original article

An investigation on the formation of oxindole alkaloid N oxides

Dhavadee Ponglux
Department of Pharmacognosy
Faculty of Pharmaceutical Sciences
Chulalongkorn University

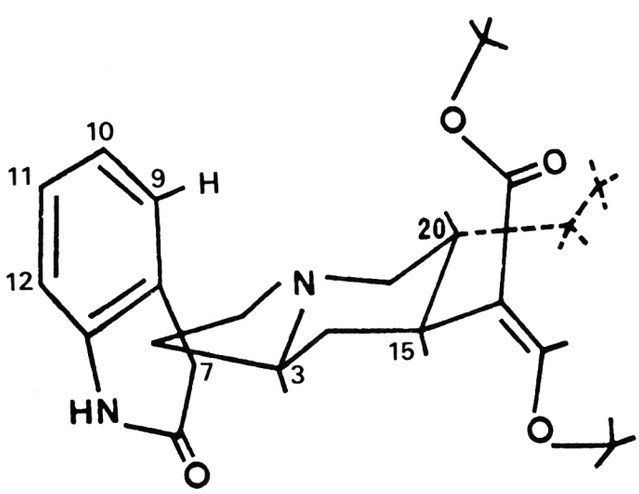
ABSTRACT:
The N-oxides of isorhynchophylline and rhynchophylline were prepared to investigate the formation of oxindole alkaloid N-oxides. The alkaloid in normal*A series (rhynchophylline) forms two N-oxides designated* anti *and and* syn *according to their conformation while alkaloid in* normal *B series (rhynchophylline) forms only one.*

A number of alkaloid *N*-oxides were isolated and prepared synthetically in the 1920's. Several reviews and textbooks have been published about this group of compounds since the publication of the review on amine oxides by Culvenor (1953). *N*-oxides of physostigmine, tropane and strychnos alkaloids were reported to have similar action to their respective tertiary amines but without their toxicity (Polonovski and Polonovski,1925). Furthermore, it was postulated that for the *N*-oxides of atropine, hyoscine, hyoscyamine, morphine and strychnine there was a continuous reduction of *N*-oxide in the body resulting in a slow release of active tertiary amine (Polonovski,1926).

Particularly interesting was the report that morphine *N*-oxide had the same action as morphine but with one-quarter of its activity, low toxicity and no addictive properties (Polonovski, Nayrac and Tiprez,1930). More recent work has shown that morphine *N*-oxide has a potencyb of 1/10 and 1/90 of that of morphine, depending on the mode of administration (Fennessy,1968).

Thus, alkaloid *N*-oxide becomes an interesting group of compounds and their formation and structures are worth studying.

During the examination of alkaloids from the leaves, stem bark and root bark of *Mitragyna tubulosa* Havil., a polar oxindole alkaloid was observed and reported, (Shellard and Rungsiyakul,1973). Establishing the identity of this new natural *N*-oxide led to the investigation on the *N*-oxide formation using isorhynchophylline (I) and rhynchophylline (II), two unsubstituted oxindole alkaloids which were available in considerable quantities.



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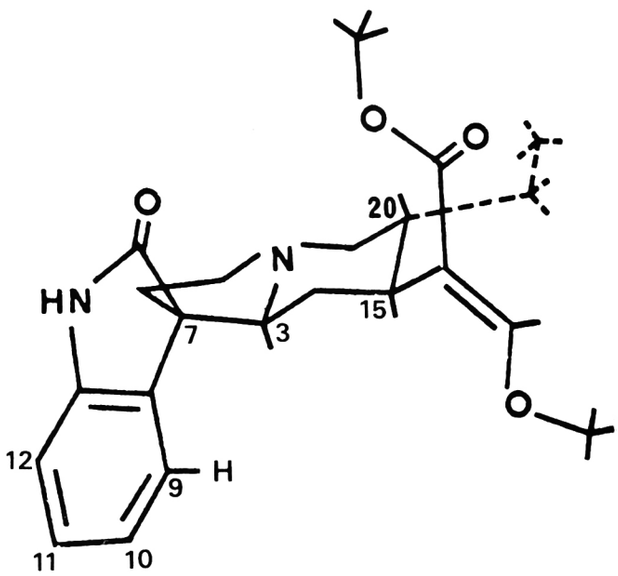


II

RESULTS AND DICUSSION

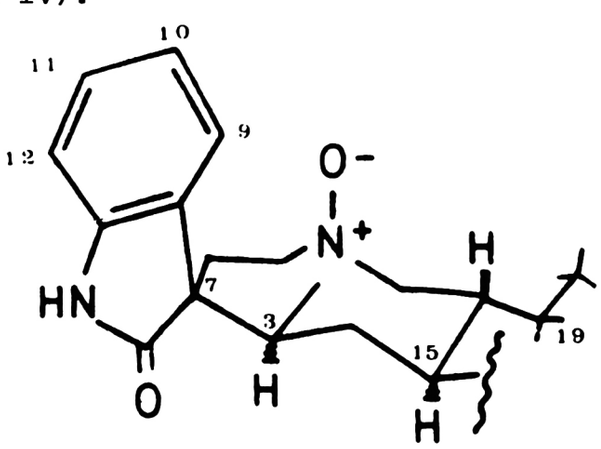
Two methods were used in the preparation of alkaloid *N*-oxides. Using *m*-chloroperbenzoic acid, only one major spot was present in each case having corresponding Rf values with previously described naturally occuring *N*-oxides (Shellard, Phillipson and Sarpong, 1971). Another method was treating the tertiary base with H_2O_2 from which three polar alkaloid spots on TLC were obtained in each case. These three compounds were separated by preparative TLC and upon reduction with H_2SO_3, the first two of them yielded isorhynchophylline, the other rhynchophylline.

Their UV spectra are identical with that of isorhynchophylline/rhynchophylline. Their mass spectra are also similar and each of them possesses the molecular-ion peak at *m/e*400, indicating the presence of one additional oxygen. Therefore, two of them are considered to be stereoisomeric *N*-oxides of isorhynchophylline and the other of rhynchophylline.

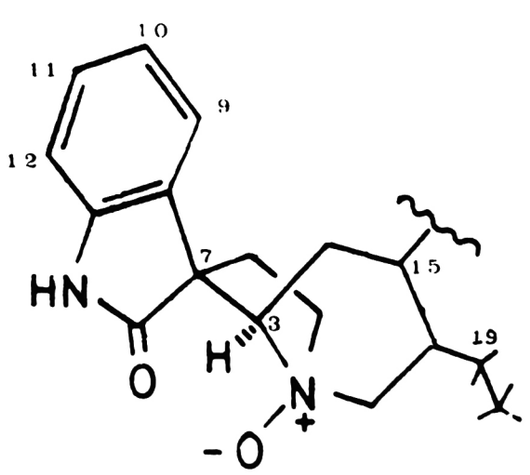
The NMR spectrum, MS and Rf values of one of the two isorhynchophylline *N*-oxides are identical with those of the isorhynchophylline *N*-oxide previously

described (Shellard, Phillipson and Sarpong, 1971); in particular, the signal for the C-9 proton appears downfield of δ8.14, indicating its close proximity to the N-4 oxygen. In the NMR spectrum of the second *N*-oxide of isorhynchophylline, this signal is absent and it is concluded that the N-4 oxygen is most likely to be on the opposite side of the molecule to the C-9 carbon. The poorly resolved three-proton triplet for the C-19 methyl group in the spectrum of isorhynchophylline *N*-oxide appears at δ0.78 and in the spectrum of the second *N*-oxide at δ0.84, showing that the relative positions of the C-19 methyl group and the N-4 oxygen are different in the two *N*-oxides.

The percentage relative abundance of the molecular ion of pentacyclic oxindole alkaloid *N*-oxides is higher for those in which the oxygen at *N*-4 is *anti* to the oxindole carbonyl than the isomers in which the *N*-4 oxygen is *syn* to the oxindole carbonyl (Phillipson and Hemingway, 1973). The percentage relative abundance of the molecular ion of isorhynchophylline *N*-oxide is 22%, contrasting with only 3% for the second *N*-oxide of isorhynchophylline. The two *N*-oxides of isorhynchophylline can therefore be represented as structures III and IV. The isorhynchophylline *N*-oxide previously described (Shellard, Phillipson and Sarpong, 1971) is now designated as *anti*-isorhynchophylline *N*-oxide (partial III) and the second *N*-oxide as *syn*-isorhynchophylline *N*-oxide (partial IV).*



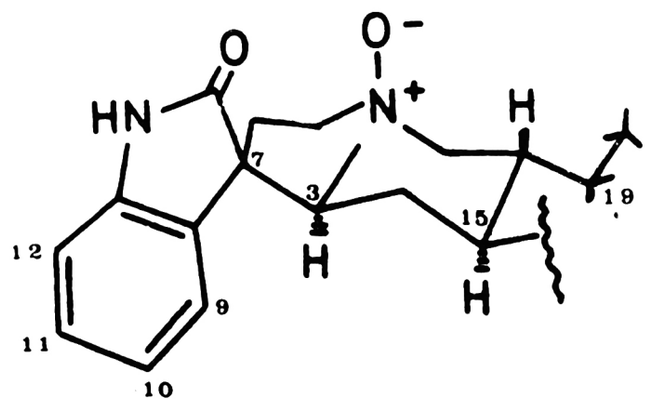
III anti-Isorhynchophylline N-oxide



IV syn-Isorhynchophylline N-oxide

* *anti* oxindole alkaloids have been defined as those alkaloids in which the pair of electrons on *N*-4 and the oxindole carbonyl are on opposite side of the molecule, when they occur on the same side of the molecule the oxindole alkaloids are defined as being *syn* (Shamma, Shine, Kompis,Sticzay, Morsingh, Poisson and Pousset,1967), the momenclature of the *N*-oxides follows that used for the corresponding tertiary bases.

The NMR spectrum, MS and Rf values of the third *N*-oxide, which was considered to be rhynchophylline *N*-oxide, are in agreement with those of reported rhynchophylline *N*-oxide (Shellard, Phillipson and Sarpong, 1971). The low percentage relative abundance of the molecular ion (11%) and the absence of a downfield aromatic proton signal in the NMR spectrum indicate that the C-9 proton is on the opposite side of the molecule to the *N*-4 oxygen, i.e. the *N*-4 oxygen and oxindole carbonyl are *syn* The signal for the C-19 mehtyl group appears at δ 0.78, i.e. it has the same chemical shift as does that of *anti* isorhynchophylline *N*-oxide, showing that the relative positions of the C-19 methyl group and the *N*-4 oxygen are very similar in both rhynchophylline *N*-oxide and *anti*-isorhynchophylline *N*-oxide. Therefore, rhynchophylline *N*-oxide can be represented by structure V.



V **Rhynchophylline N-oxide**

TABLE 1. Yields of *N*-oxides obtained using H_2O_2

N-oxide formed	% Yield of *N*-oxide from isorhynchophylline	% Yield of *N*-oxide from rhynchophylline
anti-isorhynchophylline *N*-oxide	39	18
syn-isorhynchophylline *N*-oxide	8.6	11
rhynchophylline *N*-oxide	10	24

When isorhynchophylline is treated with *m*-chloroperbenzoic acid, the major product is *anti*-isorhynchophylline *N*-oxide with only trace amounts of the other two *N*-oxides. Rhynchophylline forms only one rhynchophylline *N*-oxide with this method. The major product from isorhynchophylline and H_2O_2 is *anti*-isorhynchophylline *N*-oxide (39%) and from rhynchophylline, rhynchophylline *N*-oxide (24%). The percentage yields in Table 1 suggest that *anti*-isorhynchophylline *N*-oxide is more stable than rhynchophylline *N*-oxide which, in turn, is more stable

than *syn*-isorhynchophylline *N*-oxide. A study of Dreiding models reveals that in the two isomers in which the oxindole carbonyl is *syn* to the *N*-4 oxygen, the distance separating these two groups is 2.7 in rhynchophylline *N*-oxide (V) and 3.1 in *syn*-isorhynchophylline *N*-oxide (IV). Since these distances are sufficiently large not to give rise to any strong non-bonded interactions, the differences in stability of the two compounds is more likely to be due to the close proximity (1.5) of the C-9 carbon and the C-14 axial proton in *syn* isorhynchophylline *N*-oxide. The distance between the C-9 proton and the *N*-4 oxygen in *anti*-isorhynchophylline *N*-oxide is estimated to be 2.4, and if rhynchophylline were to form an *anti N*-oxide, the estimated distance between the C-9 proton and *N*-4 oxygen would be 1.4; the resulting interactions would probably be sufficiently strong for the compound not to be formed or only with great difficulty.

EXPERIMENTAL

The MS were determined in an AEI MS 902 high resolution mass spectrometer at 70 eV with inlet temperature between 220 and 240 . the 100 MHz NMR spectra were determined in $CDCl_3$ using TMS as internal reference.

The TLC systems used were silica gel G (Merck) with;

A, MeOH
B, EtOAc -*iso* PrOH - 5.5% NH_4OH (60:35:5)
C, EtOAc - *iso* PrOH - 5.5% NH_4OH (45:35:20)

and alumina G (Merck) with :

D, $CHCl_3$ - MeOH (1:1)
E, EtOAc - *iso* PrOH - 5.5% NH_4OH (60:35:5).

The hRf values are in Table 2.

TABLE 2 hRf values of prepared oxindole alkaloid *N*-oxides

	A	B	C	D	E
anti-isorhynchophylline *N*-oxide	62	36	72	-	-
syn-isorhynchophylline *N*-oxide	48	11	54	16	52
rhynchophylline *N*-oxide	19	4	49	18	44

Preparation of alkaloid *N*-oxides

Method 1. The alkaloid was dissolved in a few drops of EtOH, 15% H_2O_2 (1 ml per 15 mg alkaloid) added and the mixture heated on a boiling water bath for 15 minutes and then with Pt wire for 5 minutes. The solution was made alkaline with NH_4OH whrn cooled, extracted with $CHCl_3$ and the solvent evaporat to dryness and the residue was extracted with $CHCl_3$.

Isorhynchophylline (150 mg) yielded *anti*-isorhynchophylline *N*-oxide 60 mg (39%), *syn*-isorhynchophylline *N*-oxide 13 mg (8.6%) and rhynchophylline *N*-oxide 15 mg (10%).

Rhynchophylline (50 Mg) yielded *anti*-isorhynchophylline *N*-oxide 9.2 mg (18%), *syn*-isorhynchophylline *N*-oxide 5.6 mg (11%) and rhynchophylline *N*-oxide 12.7 mg (24%).

Method 2. Equimolar proportions of alkaloid and *m*-chloroperbenzoic acid were stirred in $CHCl_3$ t 0 for 3 hours (Craig and Purushothaman, 1971). The *N*-oxide were separated as described for method 1.

Isorhynchophylline (10 mg) yielded *anti*-isorhynchophylline*N* -oxide 8 mg (77%).

Rhynchophylline (10 mg) yielded rhynchophylline *N*-oxide 6.9 mg (66%).

Characterisation of prepared *N*-oxides.

Reduction of 1 mg or less of each *N*-oxide with 5% H_2SO_3, as previously described (Shellard, Phillipson and Sarpong, 1971), yielded one spot on TLC having Rf values identical with those of the corresponding tertiary base.

The hRf values of the prepared *N*-oxides are given in Table 2 and the NMR data in Table 3.

TABLE 3 NMR data on prepared alkaloid *N*-oxides

Protons	*anti*-isorhynchophylline *N*-oxide	*syn*-isorhynchophylline *N*-oxide	rhynchophylline *N*-oxide
19 CH_3	0.78 (3H, t, *J*, 7 Hz)	0.84 (3H, t, *J*, 7 Hz)	0.78 (3H, t, *J*,
CH_3 (ester)	3.62 (3H, s)	3.64 (3H, s)	3.61 (3H, s)
CH_3 (vinyl)	3.70 (3H, s)	3.78 (3H, s)	3.75 (3H, s)
CH_3 (aromatic)	-	-	-
9 H	8.14 (1H, dd, *J* 2, 7 Hz)		
10 H	7.18 (1H, t, *J* 2, 7 Hz)	6.84 - 7.32	6.85 - 7.50
11 H	7.02 (1H, t, *J* 2, 7 Hz)	(4H, m)	(4H, m)
12 H	6.92 (1H, dd, *J* 2, 7 Hz)		
17 H	7.24 (1H, s)	7.25 (1H, s)	7.29 (1H, s)

The UV spectra (EtOH) of the *N*-oxides were identical with those of the corresponding tertiary bases; λ_{max} 245, 286 nm, λ_{min} 226 nm.

The MS data are as follows:

anti-isorhynchophylline *N*-oxide, *m/e* 400 (M+ 22%), 384 (M^+-16, 60%) 382 (33%), 239 (88%), 224 (48%), 210 (31%), 208 (35%), 159 (50%), 146 (28%) 145 (27%), 144 (52%), 180 (100%), 69 (100%).

syn isorhynchophylline *N*-oxide, *m/e* 400 (M^+-16, 100%), 382 (31%), 239 (79%), 224 (43%), 210 (17%), 208 (22%), 159 (14%), 146 (12%), 145 (12%), 144 (22%), 130 (56%), 69 (93%).

rhynchophylline *N*-oxide, *m/e*400 ($M^{+\cdot}$-16, 68%), 382 (21¢), 239 (71%), 224 (53%), 210 (33%), 208 (35%), 159 (36%), 146 (33%), 145 (25%), 144 (54%), 130 (100%), 69 (100%).

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