gard the values presented in Table 1 as accurately representing the conformational thermodynamic parameters of the formyl group.

Experimental

Cyclohexanecarboxaldehyde was purchased from Frinton Laboratories, South Vineland, New Jersey. Degassed 0.2 *M* solutions were employed.

Spectra were recorded with a Varian XL-100-12 n.m.r. spectrometer equipped with a variable temperature probe. The temperatures were calibrated using a dummy n.m.r. tube containing a copper–constantan thermocouple and are believed to be accurate to ± 2 °C.

To ensure that non-saturating radiofrequency conditions were employed, spectra were initially recorded at widely different r.f. powers, and the relative peak areas were measured. Final conditions were then chosen where the slope of the relative peak area *vs.* r.f. power graph was zero. Integration of the areas under the peaks was done by the cutting and weighing procedure. Each value represents an average of six determinations at a given temperature.

Least squares analysis of the data was carried out with the aid of an XDS SIGMA 6 computer. Errors in $-\Delta G^0$ were calculated from the equation $\Delta\Delta G^0 = \Delta\Delta H^0 + T\Delta\Delta S^0 + \Delta T\Delta S^0$. Contributions from the last term are negligibly small since ΔT is ± 2 °C.

The standard deviations in the equilibrium constants measured at low temperature are depicted in Fig. 2. The computer program calculated the deviations in the slopes and the intercepts by standard statistical methods (9).

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Neothiobinupharidine Sulfoxide, a New Alkaloid of *Nuphar luteum*

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A new alkaloid ($C_{30}H_{42}N_2O_3S$), isolated from *Nuphar luteum*, is shown to be neothiobinupharidine sulfoxide. The mass spectra of neothiobinupharidine and the new alkaloid are discussed.

Un nouvel alcaloïde ($C_{30}H_{42}N_2O_3S$), isolé a partir du *Nuphar luteum*, s'est avéré être le néothiobinupharidine sulfoxyde. Les spectres de masse du néothiobinupharidine et du nouvel alcaloïde sont discutés.

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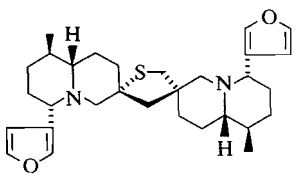
Several sulfur-containing alkaloids of Nuphar species have been described but for only one of them, neothiobinupharidine (**1**) has the structure and relative configuration been completely resolved. Neothiobinupharidine was isolated and studied in Poland (1) and some years later its structure was elucidated by X-ray analysis (2). An isomer of **1**, thiobinupharidine (3, 4), is also known. Recently, two alkaloids related in structure to **1** have been reported (5). The two alkaloids are bis-carbinolamines that on reduction give dideoxy compounds, isomeric with one

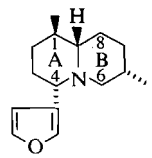
another and with neothiobinupharidine. Here we report the isolation and structure of a new sulfur alkaloid, **2**, $C_{30}H_{42}N_2O_3S$. Since only small quantities of the compound were available for structural study, physical methods, particularly mass spectrometry, was used to deduce the structure. Chemical methods were then used to confirm it.

The mass spectra of **1** and **2** were examined and compared. An earlier report of the mass spectrum of **1** appeared before its structure was established (6) and it is appropriate, therefore, to reexamine and reinterpret its spectrum in the light of the revised structure and to compare it with that of deoxynupharidine, **3** (6, 7). In the earlier report it was recognized that many of the ions present in the spectrum of deoxynupharidine were also prominent in the spectrum of **1** indicating that both alkaloids had structural features in common despite the disparity in their molecular weights.

In the high mass region of the spectrum of **1** there are peaks of low intensity corresponding to the loss of CH_3, C_2H_5, and C_3H_7 from the molecular ion just as there are in the spectrum of deoxynupharidine. Ions at *m/e* 461 and 447,



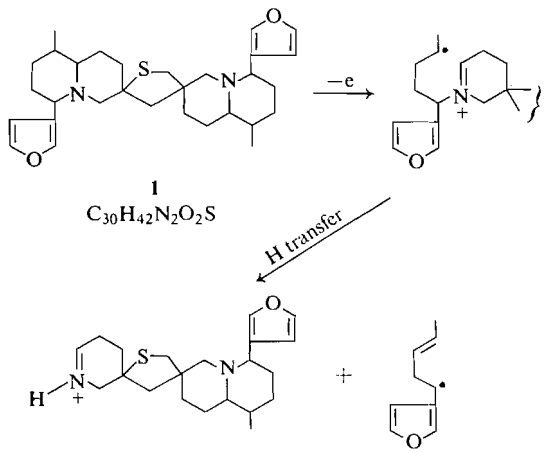
1 Neothiobinupharidine



3 Deoxynupharidine

which have no counterparts in the spectrum of **3**, owe their origin to the loss of SH and CH_2SH, respectively, from the molecular ion. An ion at *m/e* 359 formed by loss of $C_9H_{11}O$ from the molecular ion may be represented as in Scheme 1. The analogous ion in **3** appears at *m/e* 98. If hydrogen transfer does not occur and the charge remains with the furan moiety an ion at *m/e* 136 results of the same mass and composition as in the spectrum of **3**.

In the low and medium mass region the spectrum shows ions at *m/e* 230, 178, 107, and 94 besides that at *m/e* 136 already discussed. The ions at *m/e* 94 and 107 are also found in **3** and can be formed in this system in a similar way. The ions at *m/e* 230 and 178, however, deserve

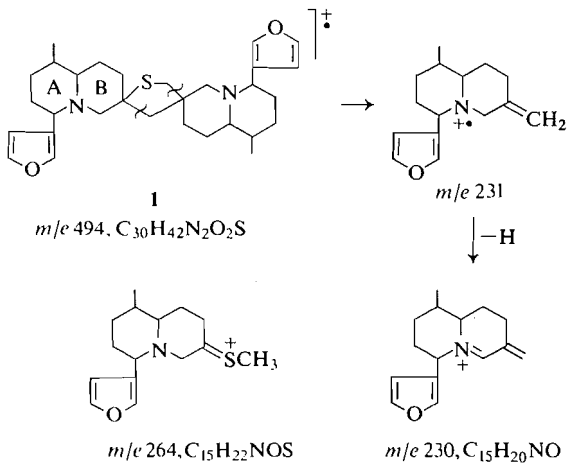


1
$C_{30}H_{42}N_2O_2S$

m/e 359, $C_{21}H_{31}N_2OS$

SCHEME 1

further comment. The former, of composition $C_{15}H_{20}NO$, can be formulated and derived as shown in Scheme 2. If a hydrogen is transferred to the sulfur-containing fragment and charge is retained on this fragment one can account for the ion observed at *m/e* 264, ($C_{15}H_{22}NOS$) which is of low intensity compared to *m/e* 230. The most intense ion of the spectrum is found at *m/e* 178 corresponding in composition to $C_{11}H_{16}NO$. A proposal for its derivation is found in Scheme 3. Charge is also carried by the residual fragment, for a peak of low intensity is also present at *m/e* 316 ($C_{19}H_{26}NOS$). An ion of *m/e* 178 is present in **3** but its intensity is



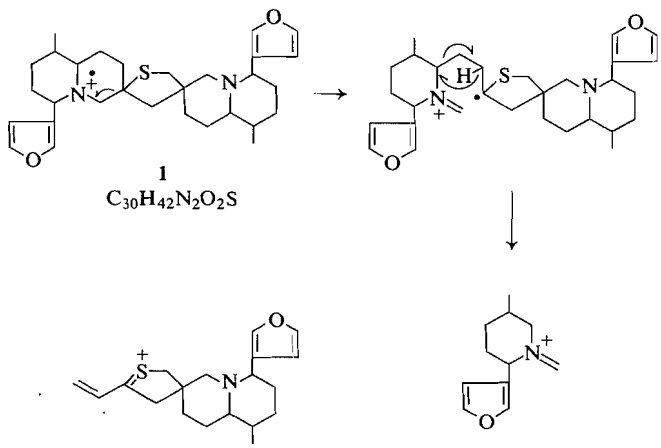
1
m/e 494, $C_{30}H_{42}N_2O_2S$

m/e 231

m/e 264, $C_{15}H_{22}NOS$

m/e 230, $C_{15}H_{20}NO$

SCHEME 2



1
$C_{30}H_{42}N_2O_2S$

m/e 316, $C_{19}H_{26}NOS$ *m/e* 178, $C_{11}H_{16}NO$

SCHEME 3

relatively weak. The quaternary center present in **1** may be responsible for promoting fission in ring B thereby leading to the formation of this ion.

In their study of the reduction products of the thionuphlutines, Lalonde *et al.* (5) came to the same conclusion regarding the derivation of the ions at *m/e* 178 and 230.

The mass spectrum of the new alkaloid **2** shows losses of SOH and CH_3SO from the molecular ion at *m/e* 461 and 447 paralleling the losses of SH and CH_2SH from neothiobinupharidine. The spectrum shows an intense peak at *m/e* 493 corresponding to the loss of OH, a transformation supported by the presence of a metastable peak. Sulfoxides are known to lose OH from the molecular ion (8) and this fact coupled with the evidence that the oxygen is lost with sulfur on electron impact suggested that the alkaloid was a sulfoxide.

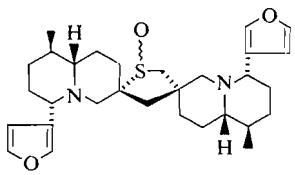
The rest of the spectrum of **2** is similar to that of neothiobinupharidine. Thus, the peaks at *m/e* 230, 178, 136, 107, and 94 are all present and have compositions identical with those found in the spectrum of **1**. Ions of low intensity are also present at *m/e* 280 ($C_{15}H_{22}NO_2S$), 262 (280-H_2O), 375 ($C_{21}H_{31}N_2O_2S$), and 357 (375-H_2O). The *m/e* 280 ion is cognate to *m/e* 230 while *m/e* 375 is cognate to *m/e* 136-H. Thus the mass spectral evidence indicates that the new alkaloid is a sulfoxide of a compound related in structure to neothiobinupharidine.

Chemical studies have confirmed that the new alkaloid is neothiobinupharidine sulfoxide for it has been both prepared from and converted to **1**. The configuration at sulfur has not been established, however, by these studies.

When **1** was treated with H_2O_2 in glacial acetic acid it yielded a compound identical with the natural base **2**. Their identity was established by comparison of their i.r., p.m.r., and mass spectra, their melting points, and a mixture melting point determination. The i.r. spectrum showed a band at 1020 cm^{-1} which is just below the region reported for sulfoxides (9) but considerably above that reported for *N*-oxides (10). An *N*-oxide structure is unlikely on the basis of the mass spectral evidence. The mass spectrum of deoxynupharidine is very different from its *N*-oxide, nupharidine (7), whereas the spectra of **1** and **2** are similar. Compound **2** is remarkably stable to reducing agents which argues further against its being an *N*-oxide. For example it is recovered unchanged after treatment with Zn in acetic acid, sulfur dioxide in aqueous solution, and sodium borohydride in alcohol. Nupharidine is converted, however, to deoxynupharidine with aqueous SO_2.

The natural base yielded **1** upon treatment with phosphorus trichloride in ethyl acetate, a reagent known to convert sulfoxides to sulfides (11). Thus, there seems little doubt that the new compound is a sulfoxide. It is the first representative of its class among the sulfur-containing

alkaloids of Nuphar species. Its structure is represented in **2** below.



2

$C_{30}H_{42}N_2O_3S$

Experimental

Apparatus, Methods, and Materials

Mass spectra were determined on a C.E.C. 21-110B double-focusing mass spectrometer. Samples were introduced through a direct inlet system. The high resolution mass spectra (h.r.m.s.) were recorded on Ilford Q-2 photographic plates, which were developed in the usual manner. The spectra were then recorded on magnetic tape, using a Gaertner comparator-densitometer linked to a Datex system. They were processed on a CDC-6400 computer using a modified version of the HIRES program of Tunnicliff and Wadsworth (12). The composition of all ions discussed in this paper was established by high resolution measurements and agreed with calculated values within the limits, ±5 milli mass units.

A Perkin–Elmer 337 grating i.r. spectrometer was used to record i.r. spectra.

Melting points were determined on a Kofler hot stage and are uncorrected.

Isolation of Neothiobinupharidine Sulfoxide

The crude bases extracted from the rhizomes of *N. luteum* were adsorbed on neutral alumina (activity III) and the column eluted progressively with benzene, ether, chloroform, and methanol. The chloroform fraction was rechromatographed on a cellulose column using a citrate–acetate buffer of p*H* 4 and 1-butanol.[1] The sulfoxide, after separation from other bases, was recrystallized from methanol–acetone yielding colorless crystals melting at 240–242°.

Anal. Calcd. for $C_{30}H_{42}N_2O_3S$ (mol. wt. 510.291): C, 70.6; H, 8.2; N, 5.5. Found (510.286 (h.r.m.s.)): C, 70.2; H, 8.3; N, 5.3.

Mass spectrum (relative intensities in brackets): 511(5), 510(15), 495(10), 494(30), 493(66), 492(3), 461(2), 447(3), 375(1), 357(5), 280(1), 262(4), 231(20), 230(100), 179(4), 178(24), 136(5), 107(15), 94(31).

[1]Full details of the isolation procedure will be published elsewhere.

Oxidation of Neothiobinupharidine

A solution of neothiobinupharidine (110 mg) in glacial acetic acid (4 ml) was treated with 30% hydrogen peroxide (54 mg) at 20° for 1.5 h. The mixture was poured into water (20 ml), made alkaline with potassium hydroxide, and extracted repeatedly with benzene. Evaporation of the benzene gave a colorless oil which showed three spots on t.l.c. The mixture was separated by chromatography on alumina (25 g). The column was eluted successively with benzene–chloroform (9:1), followed by benzene–chloroform (1:1). The first solvent system gave neothiobinupharidine (22 mg) and the second gave first an oil (20 mg), not further investigated, and then a crystalline fraction (70 mg), m.p. 240–242°, identical with natural neothiobinupharidine sulfoxide.

Treatment of Neothiobinupharidine Sulfoxide with Phosphorus Trichloride

A solution of **2** (4 mg) in ethyl acetate (4 ml) was treated with PCl_3 (3–4 drops) and the mixture heated under reflux for 15 min, poured into water (5 ml), and made alkaline with aqueous KOH. The organic layer was separated and evaporated, and the crystalline residue obtained proved to be identical with an authentic sample of neothiobinupharidine.

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