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ALKALOIDS FROM NUPHAR LUTEUM. PART III. A NEW ALKALOID - NEOTHIOBINUPHARIDINE. SPECTROSCOPIC STUDIES ON THE STRUCTURE OF THIOBINUPHARIDINE AND NEOTHIOBINUPHARIDINE

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The methods previously described (1) of isolating and separating the alkaloids of the yellow water lily, based on fractionated salt crystallization, has been replaced by a new procedure based primarily on chromatographic separation of the crude bases on neutral alumina of proper activity. This made it possible to obtain a new base, m.p. 159-60°, of the empiric formula $C_{30}H_{42}O_2N_2S$ (Calc.: C, 72.84; H, 8.56; N, 5.66; S, 6.47; Found: C, 73.25; H, 8.70; N, 5.96; S, 6.27; - neither $N\text{-}CH_3$, nor OH and OCH_3 were found; $C\text{-}CH_3$ 7.95 %) (yield ca. 0.1 procent of the total crude alkaloids). We called this alkaloid (perchlorate: $C_{30}H_{42}O_2N_2S \cdot 2HClO_4$, m.p. with decomp. 320° Calc.: C, 51.79; H, 6.38; Found: C, 51.92; H, 6.52) neothiobinupharidine.

It is chemically very stable and does not yield to such reagents as $LiAlH_4$, KBH_4, and liquid NH_3/Na, von Braun's degradation, and Raney's nickel at room temperature and at 100°; it also remains unchanged on distillation with KOH, whereas distillation with zinc dust leads to an unseparable

mixture of many products. Heated in a sealed tube with CH_3J at a 100°C gives monomethiodide (m.p. 240-2°).

Potentiometric titration confirms two basic nitrogen atoms and the molecular weight computed from the analytic data.

The present paper describes our studies on the structure of neothiobinupharidine and thiobinupharidine, based on spectrometry.

Neothiobinupharidine. The UV spectrum of neothiobinupharidine in ethanol shows only the end absorption with a maximum at 210 mμ (ε = 14.750). The spectrum has no maximum at 300 mμ, due to the furane ring shown by IR and NMR spectra. This is probably because the extinction coefficient for furane is low and its absorption is masked by that of the neothiobinupharidine molecule (for neothiobinupharidine at 300 mμ, ε = 219; for furane, ε = 1.5).

However, neothiobinupharidine shows an interesting change of the spectrum in acid solution; a maximum at 284 mμ is observed (ε = 900). In alkaline solution the maximum does not appear, but there is a slight bathochromic shift of the spectrum. The maximum in point does not seem to result from chemical rearrangement, since there is no fundamental difference in I.R. spectrum between neothiobinupharidine and its chloride, except that the latter shows no maximum at 2780 cm^{-1}, which is usually attributed to the trans $\overset{\cdot\cdot}{N}\text{-}\overset{H}{\overset{|}{C}}$ system in the quinolizidine. Since deoxynupharidine shows a similar though less conspicuous change of absorption in acid solution and lupinine behaves much like neothionupharidine, we believe this to warrant the conclusion that the quinolizidine system may be present in the alkaloid.

The infrared spectra supply much more information than the ultraviolet ones. Neothiobionupharidine shows besides the already mentioned maximum suggestive of group trans $\ddot{N}-\overset{H}{\overset{|}{C}}-$ (2780 cm^{-1}) also maxima corresponding to furane (723, 757, 788, 870, 990, 1062, 1137, 1265, 1502, and 1595 cm^{-1}), with that at 788 cm^{-1} suggesting a monosubstituted furane ring. Furthermore, one may discern maxima caused by $C-CH_3$ groups (805, 1156, 1166, 1376 and 1445 cm^{-1}); the doublet 1156 and 1166 cm^{-1} and the maximum at 805 cm^{-1}, may be interpreted as indicative of two methyl groups held by a single carbon atom. The weak maximum at 3100 cm^{-1} may correspond to a double bond, or less probably, to an associated NH group. The C-S-C linkage may be recognized as a feeble maximum at 660 cm^{-1}. The fairly high frequency for the C-S linkage shows it is not conjugated with the furane ring, but may be indicative of the $-CH_2-S-$ group. Absence of a maximum in the region of 685 - 705 cm^{-1} is evidence against the group CH_3-S.

The peak of medium intensity at 1100 cm^{-1} in the neothiobinupharidine spectrum is to be ascribed to the group $C-\overset{C}{\overset{|}{N}}-C$, as follows from an analysis of the infrared spectra of desoxynupharidine, lupinine, and matrine.

The infrared spectrum of neothiobinupharidine shows a characteristic maximum at 2735 cm^{-1}. Since matrine and lupinine also show absorption within this range (2724 and 2714 cm^{-1} resp.), but have only the quinolizidine system in common, we are inclined to regard this maximum as evidence of that system in neothiobinupharidine.

In interpreting the infrared spectra range between 2600 cm^{-1} and 3000 cm^{-1}, we found very helpful the data published

by Katritzky et al. (2), who investigated the infrared absorption of quinolizidine and its methyl derivatives. From a comparison of the data it follows that the maxima at 2580, 2739, 2780, 2950, and 2920 cm^{-1} may be attributed to either quinolizidine or monomethylquinolizidine.

The data which we have gathered from the infrared spectra and the great spectral similarity between neothiobinupharidine and desoxynupharidine lend support to our view on the structural relationship between these alkaloids.

We have also obtained interesting information from NMR spectra, which has enabled us to define in more detail our views on the structure of neothiobinupharidine. The first general conclusion that may be drawn from an analysis of this spectrum is that the molecule is asymmetrical. This is suggested by the character of the signals in the region covering aromatic protons, which indicate two different β-substituted furane systems [α-protons: (2.63; 2.63 τ), (2.65; 2.71 τ), and β-protons 3.62 and 3.44 τ]. Thus, upholding the hypothesis that the molecule of neothiobinupharidine is a kind of a „dimer" of either deoxynupharidine or nufaramine $C_{30}H_{42}O_2N_2S$ = = $\left[(2 \times C_{15}H_{23}ON)-4H + S\right]$ we have to say that it cannot be a dimer of the symmetrical type.

The second group of maxima is in the range of 7 τ and covers six protons attached to carbon atoms linked directly to nitrogen (6.96; 7.06; 7.17; and 7.31 τ). The maximum at 7.31 τ suggest one N-CH_2 group. The four maxima at 8.23, 8.33, 8.42, and 8.52 τ correspond to protons not in proximity of nitrogen.

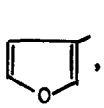
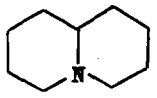
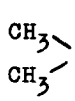
Somewhat surprising is the situation in the region of 9 τ. The strong broad signal at 9.13 τ , corresponding to nine pro-

tons, may cover two unsplit CH_3 groups, i.e., two methyl groups attached to the quoternary carbon atom. Although it is just possible that here we have the superposition of a singlet and a doublet. Hence we may conclude that we have here the system $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C<\!\!\begin{matrix} C \\ C \end{matrix}$ and CH_3CH , or $\begin{matrix} CH_3\text{-}\dot{C}\text{-} \\ CH_3\text{-}\dot{C}\text{-} \end{matrix}$ and $CH_3\dot{C}H$, whereas two $CH_3\text{-}\dot{C}H$ systems should be positively ruled out. The signal at 8.76 τ may be a singlet corresponding to one $\text{-}\dot{C}\text{-}CH_3$ group, but certainly not to two. When this range is compared with the same in the deoxynupharidine spectrum, we may see that here again the NMR spectrum fails to give conclusive results: instead of the expected two overlapping doublets (two $\dot{C}H\text{-}CH_3$ groups), we have here two signals, at 8.95 τ and at 9.07 τ , which correspond to two $\dot{C}H\text{-}CH_3$ groups in deoxynupharidine; these signals can hardly be regarded as two overlapping doublets.

Interesting also is a comparison of the NMR spectra of neothiobinupharidine and deoxynupharidine in the range of about 7 τ, i.e., of the protons next to nitrogen. In deoxynupharidine there are five signals, at 6.97, 7.05, 7.19, 7.27, and 7.4 τ , which correspond to two protons. Since in this alkaloid there are four such protons, the signals of the other two are probably shifted to a further region (8-9 τ), possibly under the influence of the π electrons of the furane ring. This surmise derives support from the signals in the NMR spectra of the protons neighbouring with nitrogen in quinolizidine and its methyl derivatives which do not show any shifts (2). If there is the same phenomenon in neothiobinupharidine, the number of protons next to nitrogen may be really eight, and not six as would appear from the spectrum. In our view this is very

likely, and we are inclined to assume in neothiobinupharidine one quinolizidine system with four protons next to nitrogen, and a system $CH\text{-}\underset{\underset{CH_2}{|}}{N}\text{-}CH$, other than quinolizidine. This is supported by the fact that the NMR spectrum of neothiobinupharidine shows a strong signal at 7.31 τ, which corresponds to one $\overset{|}{N}\text{-}CH_2$- group but is altogether absent in the spectrum of deoxynupharidine, and, therefore, cannot come from the group $-N-CH_2$ in quinolizidine attached to the furane ring. Hence the conclusion that no two quinolizidine systems exist in neothiobinupharidine.

To sum up, we hold that the following groups are incorporated in the structure of neothiobinupharidine:

2  ,  , 2 $CH_3\text{-}\overset{|}{C}\text{-}$, or  , $\overset{|}{C}H\text{-}CH_3$,

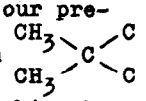
 - , and $-CH_2\text{-}S\text{-}C\text{-}$

Thiobinupharidine. In the previous paper (3) we have given a preliminary interpretation of the infrared and NMR spectra of thiobinupharidine, from which it followed that this alkaloid contains two β-substituted furane rings, two groups $CH_3\text{-}\overset{\overset{C}{|}}{C}\text{-}C$ and the system $\overset{\cdot\cdot}{N}\text{-}C\overset{H}{<}$ -trans, charakteristic for quinolizidine. On the assumption that thiobinupharidine is biogenetically related to nupharidine, we have proposed a structure that would meet the data read from the spectra.

Further investigations of the spectra enables us to be more specific about the proposed structure.

Thiobinupharidine shows in the ultraviolet only end absorption, giving in acid medium a distinct maximum at 298 mμ

(ε = 1200) (ε of the free base in ethanol is 287 at 298 mμ). This effect is much more pronounced than this in deoxynupharidine and neothiobinupharidine and suggests structural differences.

Thiobinupharidine and neothiobinupharidine are closely alike in infrared spectra, but there are some differences suggestive of structural dissimilarities. The two compounds are almost exactly alike in the part corresponding to monosubstituted furane: 717, 760, 782, 870, 987, 1065, 1135, 1268, 1500, and 1595 cm^{-1}, but differ in that corresponding to $-C-CH_3$ groups (1160 and 1375 cm^{-1}). The maxima at 805, 1166, and 1445 cm^{-1} shown by neotiobinupharidine are absent in the case of thiobinupharidine, which, consistently with our previous interpretation, suggests absence of the system  and similarity of the system of methyl groups in thiobinupharidine with that in deoxynupharidine (1147 and 1370 cm^{-1}). The maximum at 685-705 cm^{-1} is indicative of the group C-S-C, and absence of the maximum at 685-705 cm^{-1} makes the presence of CH_3-S- unlikely.

In the region of 3000 cm^{-1}, thiobinupharidine shows only a maximum at 2780 cm^{-1} (quinolizidine system), a broad maximum at 2850-2950 cm^{-1}, and a weak maximum at 3100 cm^{-1}. These maxima liken thiobinupharidine with deoxynupharidine (2800-2900 cm^{-1}) rather than with neothiobinupharidine (2580, 2739, 2780, 2850, and 2920 cm^{-1}).

From the NMR spectra we may read, in addition to the information given earlier (1), the following: to judge from the aromatic furan protons, thiobinupharidine - unlike neothiobinupharidine - should be symmetrical in molecular structure. The

signals corresponding to protons next to nitrogen cover an area corresponding to eight protons. The doublet at 7.70 τ may be due to the group $\begin{matrix} C \\ C \end{matrix}\!\!>\!N\text{-}CH_2\text{-}$. The single broad signal at 9.08 τ corresponds to 6 protons of methyl groups and may be attributed to the system $CH_3\text{-}C\text{-}CH_2N$ (9.07 τ in deoxynupharidine) or $CH_3\text{-}CH$ (9.08 τ in methylcyclohexane).

These data warrant the following conclusions:

The structure proposed earlier for thiobinupharidine seems unlikely because:

it provides for only two protons at the nitrogen, whereas NMR indicates eight;

the infrared spectrum suggests the group $-CH_2\text{-}S-$ and not the previously supposed system $-C-S-C-$; and

very likely, the system $CH_3\text{-}C\text{-}S\text{-}C$ proposed earlier in tiobinupharidine would depress considerably the frequency for the signal of the methyl group, which could then be expected in the region of 8.60 - 8.70 τ .

We may suggest, on the other hand, the following structural elements of thiobinupharidine: 2  ; 2 $CH_3\text{-}\dot{C}H$, or 2 $CH_3\text{-}\dot{C}\text{-}CH_2\text{-}N\!<$; $-CH_2\text{-}S-$, and the quinolizidine system.

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