6- and 6′-Hydroxyneothiobinupharidine. Monohemiaminals from *Nuphar luteum* and their Possible Role in Thiaspirane Nuphar Alkaloid Biogenesis

Circular dichroism and sodium borodeuteride reduction followed by mass spectral analysis are particularly advantageous in the structure determinations of 5–10 mg quantities of thiaspirane type Nuphar hemiaminals[1]. We report herein the use of these techniques in elucidating the structures of the title α- and β-thiohemiaminals (**1** and **2** respectively) isolated as an 18 mg mixture which defied extensive separation attempts using thin layer and Alumina column chromatography.

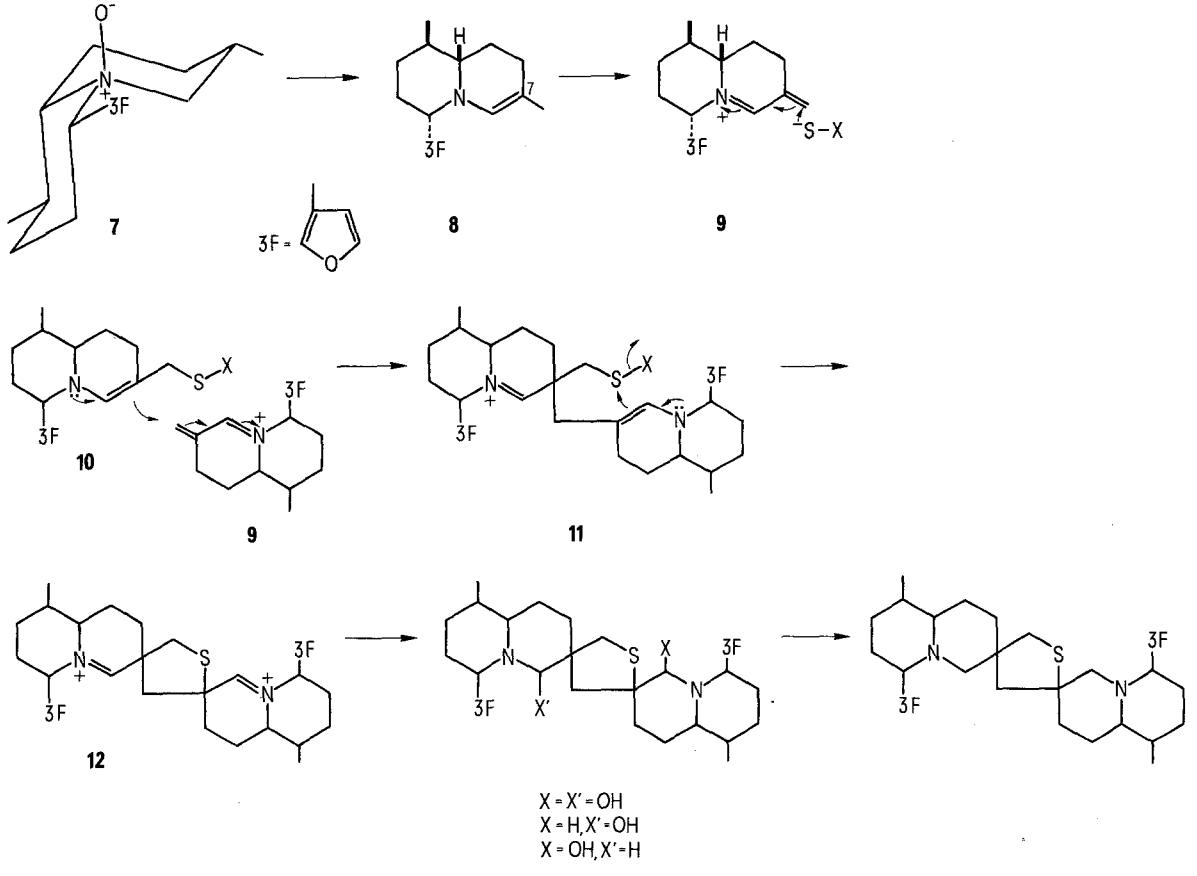
The mass spectrum (MS)[2] of the mixture gave the series of peaks *m/e* 510, 493, 492, 445, 230, 228, 178 and 176, peaks characteristic of thiaspirane C-6 or C-6′ hemiaminals. The proton magnetic resonance (PMR)[2] showed: δ 7.35 (m, 4H, αH of 3-furyl), 6.55 (m, 1H, βH of 3-furyl), 6.35 (m, 1H, βH of 3-furyl), 3.57 (m, 1H, C-4 and C-4′ H), 2.96 (q, J2 and 12 Hz, 1H, C-6′ H), 2.80 (m, 1H, C-4 H), 2.68 (ABq, J2 and 12 Hz, 2H, CH_2S), 0.88 ppm (br d, 6H, C-1 and C-1′ CH_3) but most significantly δ 4.30 and 4.10 ppm signals in a 23:77 intensity ratio. The last-named pair was assigned to C-6 and C-6′ hemiaminal carbinyl protons respectively.

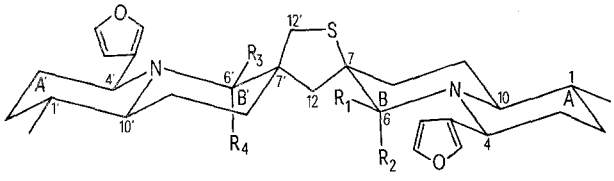
Reduction with sodium borodeuteride in methanol gave only labelled neothiobinupharidine (NTBN) [11% d_0, 86% d_1 and 3% d_2 by ms (*m/e* 495, M^+)] identical with authentic unlabelled sample (**3**) by TLC[2] (Rf 0.24) and different from thiobinupharidine[3], TLC[2] (Rf 0.58), and thionuphlutine B[3], TLC[2] (Rf 0.43). Since the reduction product was NTBN which was predominantly d_1 labelled, the single stereostructural type as well as the monohemiaminal nature of both **1** and **2** was established. The MS of the deuterated NTBN also showed 80% of *m/e* 178 was shifted to 179, a result consistent with a mixture of 78% NTBN-6-d_1 (**4**) and 22% NTBN-6′-d_1(**5**) based on the earlier finding[1] that the C-6-d_1 thiaspirane *bis*-amines gave a shift of *m/e* 178 to 179 to an extent greater than 90% whereas the C-6′-d_1 compounds gave the same shift to an extent less than 10%.

The circular dichroism (CD)[2] of the mixture in acid solution gave weak positive and strong negative bands at 245 ([Θ] + 510°) and 298 nm ([Θ] − 6760°) respectively. The latter band, whose sign, intensity and position are the same as those displayed by 6-hydroxythionuphlutine B[1], (**6**) shows the predominance of **1** in the mixture and indicates that C-7 of both **1** and **6** has the *R* configuration.

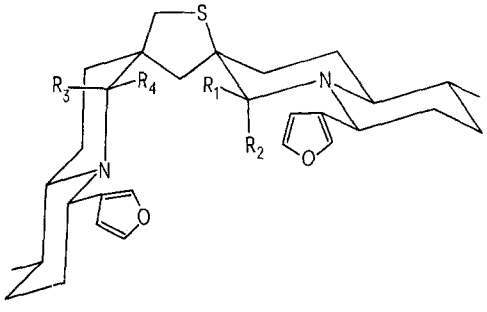
To date mono- and bishemiaminals of thiobinupharidine and thionuphlutine B series have been isolated[1,4]. The appearance of **1** and **2**, the first hemiaminals of the NTBN series, gives additional circumstantial evidence for the involvement of hemiaminals in bisamine biogenesis, our view of which is presented in the scheme below and can be described as follows. The structures of the thiaspirane

[1] R. T. LaLonde and C. F. Wong, J. org. Chem. *39*, 2892 (1974).
[2] Spectra were determined as follows: MS on a Hitachi RMU-6E mass spectrometer, 70 ev. direct inlet; PMR on a Varian A60-A in $CDCl_3$ solution; cd on a Jasco Model 5 spectropolarimeter (95% ethanol, 0.2 mg/ml). TLC was performed on 0.25 mm. Alumina GF_{254}, ether-hexane (1:4).
[3] R. T. LaLonde, C. F. Wong and W. P. Cullen, Tetrahedron Lett. *1970*, 4477.
[4] R. T. LaLonde, C. F. Wong and K. C. Das, J. Am. chem. Soc. *95*, 6342 (1973).





1, $R_1 + R_2 = H + OH$; $R_3 = R_4 = H$
2, $R_1 = R_2 = H$; $R_3 + R_4 = H + OH$
3, $R_1 = R_2 = R_3 = R_4 = H$
4, $R_1 + R_2 = H + D$; $R_3 = R_4 = H$
5, $R_1 = R_2 = H$; $R_3 + R_4 = H + D$



6, $R_1 + R_2 = H + OH$; $R_3 = R_4 = H$

alkaloids indicate incorporation of two regular sesquiterpenic units, of mevalonate origin[5], which are linked in a symmetrical fashion through carbon and a new heteroatom, sulfur. The key intermediate in the transition from C_{15} to C_{30} alkaloids would appear to be the conjugated immonium ion **9** which is formed from naturally abundant nupharidine **7** through the sequence: Polonovsky elimination by a natural anhydride (e.g. pyrophosphate) giving the enamine **8**; and allylic oxidation of the C-7 methyl giving the conjugated immonium ion **9**. Indeed, the transformation of N-oxide **7** to enamine **8** is facile in *vitro*[6].

Enamine immonium ion coupling giving dimeric structures is a well-known feature of enamine chemistry. In the present instance, such coupling involves a sulfur reagent which reacts first as a nucleophile with **9** giving **10**. In subsequent steps, enamine **10** couples with **9** giving **11** in which the newly formed enamine functions as a thiophile displacing leaving group X to give bisimmonium ion **12**. Specific reagents possessing the reactivity characteristics demanded of SX^- in this scheme can be reasonably postulated (e.g. thiosulfate). To complete the biogenesis, the bisimmonium ion **12** undergoes stepwise reduction and hydration to monohemiaminals and ultimately reduction to bisamines[7].

Résumé. Les structures des 6- et 6'-hydroxynéothiobinupharidine ont été déterminées par des études spectrales et la conversion en néothiobinupharidine-6- et 6'-d_1. Un schème de biogénèse des C_{30}, Nuphar monohémiaminals est proposé.

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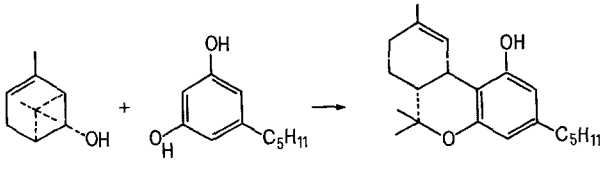
[5] H. R. SCHÜTTE and J. LEHFELDT, Arch. Pharmak. *298*, 461 (1965).
[6] R. T. LALONDE, E. AUER, C. F. WONG and V. P. MURALIDHARAN, J. Am. chem. Soc. *93*, 2501 (1971).
[7] Support of this work by the National Institutes of Health, U.S. Public Health Service (Grant No. AI 10188) is gratefully acknowledged.

A One-Step Synthesis of (−)-Δ^1- Tetrahydrocannabinol from Chrysanthenol

We have recently reported a simple one-step synthesis of (−)-Δ^1-tetrahydrocannabinol (THC) from *p*-mentha-2,8-dien-1-ol and olivetol[1]. The formation of Δ^1-THC by this method is in contrast to previously reported reaction of these reagents[2] which yielded $\Delta^{1(6)}$-THC as the major product. Two other syntheses of (−)-Δ^1-THC are from *trans*-(+)-2-carene oxide[3] and (−)-verbenol[4]. Although carene oxide is converted directly into Δ^1-THC, the route from verbenol, gives $\Delta^{1(6)}$-THC wich must be transformed to (−)-Δ^1-TCH by addition and elimination of hydrogen chloride. On mechanistic grounds, we reasoned that by virtue of the position of the double bond, verbenol can lead only to $\Delta^{1(6)}$-THC since the double bond has to migrate into that position during the ring opening of the cyclobutane ring. On the other hand, on the basis of similar arguments, we thought chrysanthenol should lead directly to Δ^1-THC. This was indeed found to be the case, albeit the yield was moderate.

Chrysanthenone[5,6] ($[\alpha]_D$ −36°) was reduced to the corresponding *cis*-chrysanthenol[5a,7] with lithium aluminum hydride in ether (0.5 h) and used without further purification in subsequent reaction. Equimolar quantities of chrysanthenol and olivetol were allowed to react in dry methylene chloride at 0° for 0.5 h in the presence of 0.1% boron trifluoride etherate. A resin containing



Chrysanthenol Olivetol Δ^1-THC

~25% (GLC)[8] Δ^1-THC was obtained and no $\Delta^{1(6)}$-THC was observed. The Δ^1-THC was separated by chromatography on thick silica gel plate (1:4 ethyl acetate/hexane) and was found to be identical to an authentic sample of (−)-Δ^1-THC (NMR, IR, TLC, GLC). The optical rotation corresponded to the % optical purity of the starting chrysanthenone. The identity of Δ^1-THC was further confirmed by its conversion to $\Delta^{1(6)}$-THC with *p*-toluenesulfonic acid in boiling benzene and comparison with an authentic sample.