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CHEMISTRY OF NUPHAR ALKALOIDS. PART VIII. HOFMANN DEGRADATION OF THIOBINUPHARIDINE DIMETHIODIDES

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Abstract— The two-step Hofmann degradation of thiobinupharidine dimethiodides has been carried out. The structure and stereochemistry of the obtained products have been determined by means of spectroscopic analysis.

The quaternization of thiobinupharidine (TBN) 1 (a sulfur containing C_{30} Nuphar alkaloid) results in four monomethiodides and four dimethiodides[1]. Their structure and stereochemistry have been previously established[2,3,4] using ^{13}C nmr spectroscopy. The spectral analysis has been chemically confirmed by means of the Hofmann degradation of the monomethiodides[5].

Presently, the results of a two-step Hofmann degradation of TBN dimethiodides with the following structures (ascribed on the basis of ^{13}C nmr) are reported: N,N'-dimethiodides of : 2 (A'B' trans - AB trans), 3 (A'B' trans - AB cis), 4 (A'B' cis - AB trans) and 5 (A'B' cis - AB cis).

All dimethiodides were separately treated with Ag_2O to obtain the respective ammonium hydroxides. Their one-step Hofmann degradation was carried out in 50% NaOH water-ethanol solution for 4 h. Both the spectroscopic analysis and R_f values on TLC using various adsorbents and solvent systems, showed that in each case the same product 6, was obtained.

The comparison of ^1H nmr and ^{13}C nmr spectra of 6 with those of previously obtained products from the one-step Hofmann degradation of TBN monomethiodides[5] showed that, as expected, the N-C4' and N-C4 bonds were broken in A'B' and AB rings, respectively. The evidence for this reaction course is the formation of double bonds between C3'-C4' and C3-C4 carbons (^1H nmr δ(ppm) $CDCl_3$: 6.00 m 2H

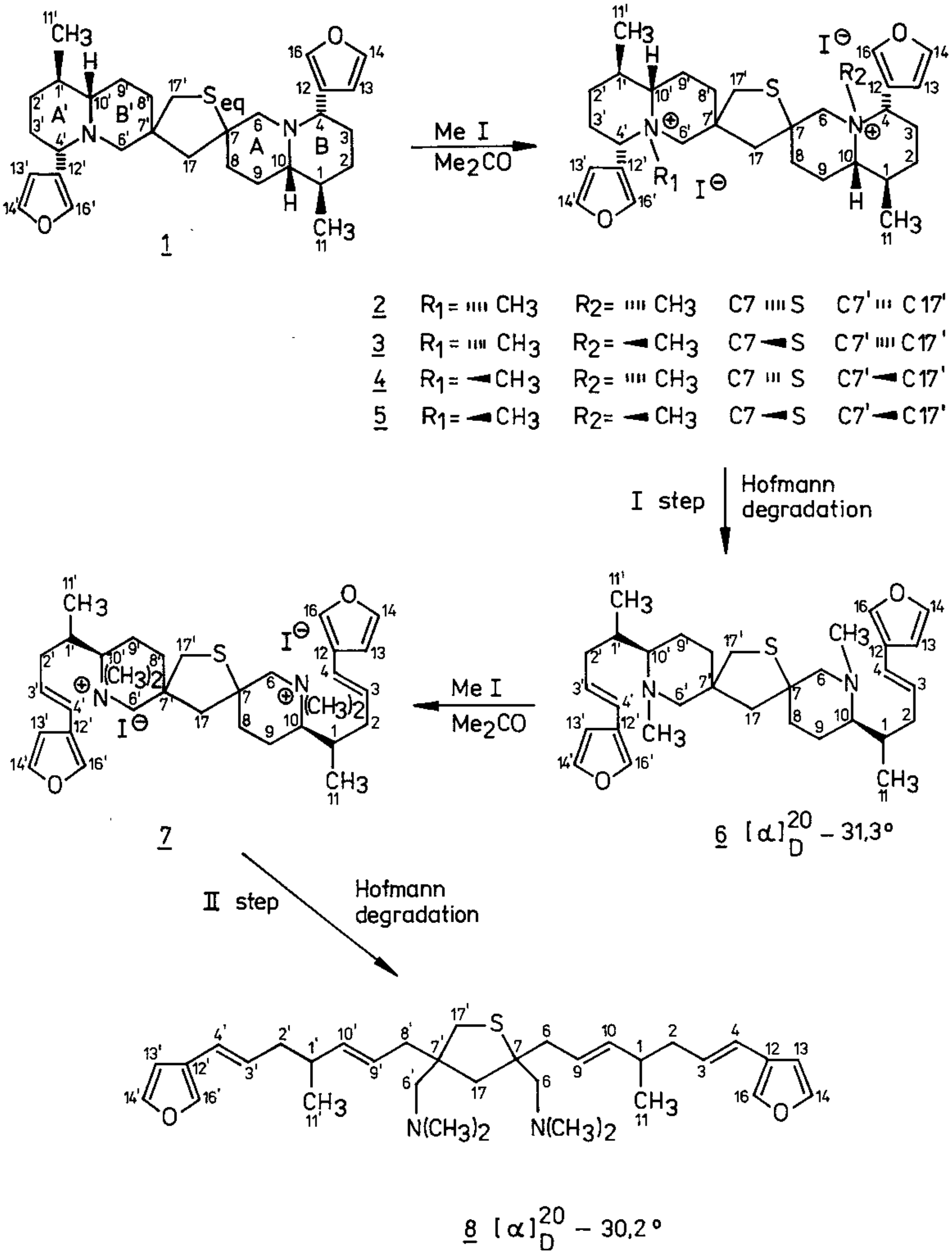
1
Me I
Me2CO
2 R1 = ···· CH3 R2 = ···· CH3 C7 ···· S C7' ···· C17'
3 R1 = ···· CH3 R2 = ◄ CH3 C7 ◄ S C7' ···· C17'
4 R1 = ◄ CH3 R2 = ···· CH3 C7 ···· S C7' ◄ C17'
5 R1 = ◄ CH3 R2 = ◄ CH3 C7 ◄ S C7' ◄ C17'
I step
Hofmann degradation
6 [α]D20 − 31,3°
Me I
Me2CO
7
II step
Hofmann degradation
8 [α]D20 − 30,2°

Fig. 1

C3-H, C3'-H, 6.32 d 2H C4-H, C4'-H; ^{13}C nmr δ(ppm) $CDCl_3$: 120.44 d C3, C3', 129.33 d C4, C4').

The chemical shifts and the character of proton signals at C3', C3,'C4' and C4 atoms in ^{1}H nmr, as well, as the chemical shifts of carbon atoms in ^{13}C nmr spectra, were similar to the values for the respective sp^2 carbons and adjacent protons, obtained for the products from the one-step Hofmann degradation of TBN monomethiodides[5]. This indicates that product 6 contains two double bonds in a trans conformation.

The chemical shifts of C7, C7', C17 and C17' (^{13}C nmr) showed that the configuration at C7 and C7' in 6 remained the same as in TBN 1. The C17 atom has a diaxial conformation with respect to both N-methylpiperidine rings formed in the reaction (^{13}C nmr δ(ppm) $CDCl_3$: C17 45.26 in TBN 1; C17 44.81 in 6).

The formation of a single product in the Hofmann degradation of TBN dimethiodides confirms the structure and stereochemistry of the original salts.

The cleavage of the N'-C4' bond in A'B' trans-quinolizidine ring (dimethiodides 2 and 3), as well as the N-C4 bond in AB trans-quinolizidine ring (dimethiodides 2 and 4) results in the formation of N-methylpiperidine with an equatorial side-chain of C10' or C10 atoms, respectively. This favorable stereochemistry of the side-chain causes no conformational changes. The cleavage of the N'-C4' bond in A'B' cis-quinolizidine ring (dimethiodides 4, 5) and of the N-C4 bond in AB cis-quinolizidine ring (dimethiodides 3, 5) resulted first in the formation of N-methylpiperidine with an axial side-chain at C10' and C10, respectively. This unfavorable stereochemistry of a large substituent causes a conformational change in the piperidine ring, accompanied by a simultaneous change of the stereochemistry of C10' and C7' or C10 and C7 rings, respectively. As a result in each case the same product is formed which contains two N-methylpiperidine rings with equatorial side-chains at C10' and C10. The C17 carbon of tetrahydrothiophene now assumes a diaxial conformation with respect to both N-methylpiperidine rings.

Product 6 was quaternised with methyl iodide. The reaction, carried out in acetone, was monitored by means of TLC. Most of the product had reacted within 24 h at room temperature (TLC Al_2O_3 acid, benzene : ethyl acetate : n-propanol =1:1:1, R_f=0.19).

The presence in 7 of both quaternary nitrogen atoms of the piperidine rings was indicated by ^{1}H nmr and ^{13}C nmr spectroscopy (^{1}H nmr δ(ppm) DMSO : $\overset{+}{N}-CH_3$, 3.25 and 3.40; ^{13}C nmr δ(ppm) DMSO : $\overset{+}{N}-CH_3$, 44.60 and 53.57). This was confirmed by the observed paramagnetic shifts of carbons α to nitrogen, as well, as by the diamagnetic shift of carbons β and γ to nitrogen in the ^{13}C nmr spectrum. Dimethiodides 7 was reacted with Ag_2O to form the corresponding ammonium hydroxide and then subjected to the second step of Hofmann degradation. This was done by heating for 4 h in 50% NaOH water-ethanol solution (TLC Al_2O_3 in benzene, R_f=0.22). Analysis of the ^{1}H nmr and ^{13}C nmr spectra has shown that the only reaction which can lead to compound 8 is the cleavage of N-C10' and N-C10 bonds with simultaneous formation of double bonds between C9'-C10' and C9-C10.

The suggested reaction course is similar to the second step of Hofmann degradation of C_{15} alkaloid methiodides and of TBN monomethiodides[5].

The comparison of ^{1}H nmr and ^{13}C nmr spectra of the products from the degradative second step of TBN monomethiodides with those of product 8 indicates that 8 contains a double bond between C9'-C10' and C9-C10 (^{1}H nmr δ(ppm) $CDCl_3$; C9-H and C9'-H, 5.50 m, C10-H and C10'-H, 5.56 dd; ^{13}C nmr δ(ppm) $CDCl_3$; C9' 139.22 d, C10' 125.53 d, C9 139.22 d, C10 125.53 d) with trans substituents.

The discussed reaction course of the second step of Hofmann degradation does not predict any inversion of configuration on carbons C7 and C7' and this is in agreement with observations based on the spectroscopic data.

The results of the two-step Hofmann degradation together with the spectral analysis of obtained products form a sound basis for structural and stereochemical conclusions.

EXPERIMENTAL

Melting point (uncorrected) was determined on a Boetius apparatus (Carl Zeiss Jena). Results of elemental analyses were within permissible error. The ^{1}H nmr spectra were recorded on a Jeol 100 MHz spectrometer and the ^{13}C nmr spectra on a Jeol FX 90Q spectrometer using TMS as an internal reference. Mass spectra were registered on a LKB 9000 spectrometer. All optical rotations were measured in chloroform solution on a Perkin - Elmer polarimeter (type 241) using a 1-dm cell. The purity of the products was determined by TLC Aluminium oxide $60F_{254}$. Column chromatography was carried out on Fluka 506C Al_2O_3 (grade III).

The first Hofmann degradation.- To a solution of 0.001 mol TBN dimethiodides 2, 3, 4 or 5 in 10 ml of 70% methanol, moist silver oxide (prepared from 400 mg of silver nitrate) was added and the mixture was shaken for 1 h. After filtration, the solvent was removed in vacuo, sodium hydroxide (10 g), water (10 ml) and ethanol (10 ml) were added and the mixture heated under reflux for 4 h. After dilution with water, the crude products were extracted with chloroform, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was chromatographed on alumina using benzene as eluent. Yield 64%; pale yellow oil; TLC in benzene : hexane = 1:1, R_f=0.43; $[\alpha]_D^{24}$=-31.3°; ^1H nmr δ(ppm) $CDCl_3$: 0.92 (d 6H C1-CH_3, C1'-CH_3), 2.20 (s 6H 2xN-CH_3), 3.00 (m 2H C6'-He, C6-He), 6.00 (m 2H C3'-H, C3-H), 6.32 (d 2H J=13.5 Hz, C4'-H, C4-H), 6.50 (s 2H β-furanyl H), 7.45 (m 4H α -furanyl H); ^{13}C nmr δ(ppm) $CDCl_3$: 12.57 (q C11) , 12.57 (q C11'), 21.72 (t C9') 22.70 (t C9), 33.48 (d C1), 33.59 (d C1'), 36.79 (t C8'), 38.20 (t C2), 38.20 (t C2'), 39.40 (t C8), 42.53 (t C17'), 42.96 (q N-CH_3), 43.18 (q N-CH_3), 44.81 (t C17), 49.25 (s C7'), 56.51 (s C7), 66.86 (d C10), 67.61 (t C6'), 67.98 (d C10'), 71.19 (t C6), 107.60 (d C13), 107.60 (d C13'), 120.44 (d C3), 120.44 (d C3'), 124.45 (s C12), 124.45 (s C12'), 129.33 (d C4), 129.33 (d C4'), 139.41 (d C16), 139.41 (d C16'), 143.31 (d C14), 143.31 (d C14'); ms: m/z (relative intensity) = 522 (M^+, 9), 508 (3), 387 (100), 373 (26), 230 (5), 192 (4), 107 (22), 94 (15).

Methylation. - To 0.0019 mol of 6 in 5 ml of acetone was added excess methyl iodide and the mixture allowed to stand overnight at room temperature. Upon removal of the excess MeI and Me_2CO the pure product was obtained directly from crystalization with acetone. Yield 88%; mp 260-263°C from Me_2CO; ^1H nmr δ(ppm) DMSO: 1.05 (d 6H C1-CH_3, C1'-CH_3, 3.25 (s 6H $\overset{+}{N}$-CH_3), 3.40 (s 6H $\overset{+}{N}$-CH_3), 6.02 (m 2H C3-H, C3'-H), 6.44 (d 2H C4-H, C4'-H), 6.86 (s 2H β-furanyl 13H, 13H'), 7.72 (m 4H α-furanyl H); ^{13}C nmr δ(ppm) DMSO: 15.77 (q C11'), 15.86 (q C11), 19.68 (t C9'), 20.02 (t C9), 29.86 (d C1), 30.04 (d C1'), 33.85 (t C8'), 36.56 (t C8), 37.02 (t C2'), 39.14 (t C2), 42.26 (t C17'), 44.04 (q $\overset{+}{N}$-CH_3), 44.60 (q $\overset{+}{N}$-CH_3), 45.29 (t C17), 49.67 (s C7'), 53.57 (q $\overset{+}{N}$-CH_3), 54.44 (q $\overset{+}{N}$-CH_3), 54.92 (s C7), 70.65 (t C6'), 73.08 (d C10),73.29 (t C6), 74.42 (d C10'), 107.80 (d C13), 107.80 (d C13'), 122.14 (d C3), 122.14 (d C3'), 123.87 (s C12), 123.87 (s C12'), 126.82 (d C4), 126.82 (d C4'), 140.04 (d C16), 140.04 (d C16'), 143.73 (d C14), 143.73 (d C14').

The second Hofmann degradation. - To a solution of 0.001 mol of 7 in 5 ml of 50% methanol moist silver oxide (prepared from 300 mg of silver nitrate) was added and the mixture shaken for 1 h. After filtration, the solvent was removed in vacuo, sodium hydroxide (10 g), water (10 ml) and ethanol (10 ml) was added and the mixture refluxed for 4 h. After dilution with water, the crude product was extracted with chloroform, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed on alumina using hexane : benzene (1:0.15). Yield 48%; pale yellow oil, TLC in benzene, R_f=0.22, $[\alpha]_D^{20}$=-30.2°; ^1H nmr δ(ppm) $CDCl_3$: 1.06 (d 6H C1'-CH_3, C1-CH_3), 2.30 (s 12H N'-$(CH_3)_2$, N-$(CH_3)_2$), 2.38 (s 2H S-CH_2), 5.50 (dt 2H C9'-H, C9-H), 5.56 (dd 2H J=15 Hz C10'-H, C10-H), 6.02 (m 2H C3'-H, C3-H), 6.32 (d 2H J=16 Hz, C4'-H, C4-H), 6.56 (s 2H β-furanyl 13'H, 13H), 7.38 (m 4H α-furanyl H); ^{13}C nmr δ(ppm) $CDCl_3$: 20.15 (q C11'), 20.37 (q C11), 37.02 (d C1'), 37.23 (d C1), 39.96 (t C8'), 40.70 (t C2'), 40.70 (t C2), 40.96 (t C17'), 44.25 (t C8), 47.11 (t C17), 48.03 (q N-$(CH_3)_2$), 48.37 (q N-$(CH_3)_2$), 54.05 (s C7'), 62.16 (s C7), 66.27 (t C6'), 69.70 (t C6), 107.88 (d C13'), 107.97 (d C13), 120.93 (d C3'), 120.93 (d C3), 125.53 (d C10'), 125.53 (d C10), 125.87 (d C4'), 125.87 (d C4), 128.99 (s C12'), 128.99 (s C12), 139.22 (d C9'), 139.22 (d C9), 139.44 (d C16'), 139.44 (d C16), 143.25 (d C14'), 143.25 (d C14); ms: m/z (relative intensity) = 550 (M^+ 3.6), 526 (3), 492 (40), 387 (8), 107 (3), 58 (100).

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