CHEMISTRY OF NUPHAR ALKALOIDS. PART IV. HOFMANN DEGRADATION OF C_{15} AND C_{30} METHIODIDES

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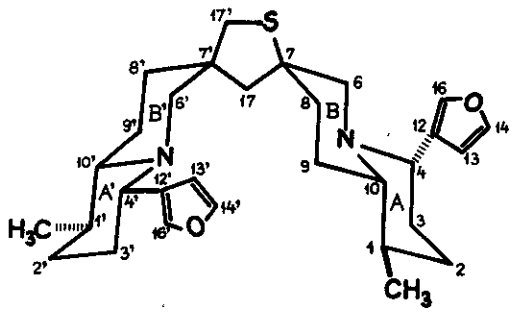
Abstract: Hofmann degradation of isomeric thiobinupharidine (TBN) monomethiodides is described. The structure and stereochemistry of the products obtained have been proposed on the basis of ^1H nmr and ^{13}C nmr spectra. Hofmann degradation products of DN- and 7EDN-methiodides have been used as model compounds.

Methylation of thiobinupharidine (TBN) 1 has been reported to result in four monomethiodides which contain quaternary nitrogen in either of the two quinolizidine rings: in A^B^(trans), 2, in A^B^(cis), 3, in AB (trans), 4, in AB (cis), 5[1,2] (Fig.1).

Presently, the chemistry of those compounds has been studied by means of Hofmann degradation using trans 7-epideoxynupharidine (7EDN) methiodide 6 and cis deoxynupharidine (DN) methiodide 7, as well as their Hofmann degradation products, as model compounds (Fig.2).

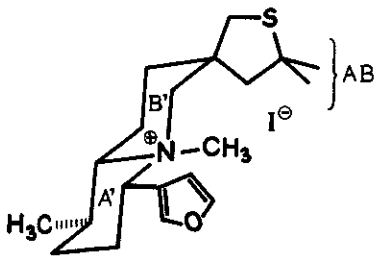
Hofmann degradation of DN methiodide 7 was previously described[3] and some characteristics of the products were given. Both methiodides 6 and 7 were treated in a standard way: first with Ag_2O in water-methanol solution and then by heating with NaOH. The reaction products - N-methyl substituted piperidines 8 and 9 (identified, among others by the presence of two olefinic protons in the ^1H nmr spectrum: δ=6.32 ppm, d, J=16 Hz and δ=6.01 ppm, m) differ only in their stereochemistry on carbon C3. Cleavage of the N-C4 bonds in both ammonium hydroxides, followed by the formation of a double bond between carbons C3 and C4 corresponds to the generally accepted mechanism of Hofmann degradation.

Cleavage of the N-C4 bond in 7EDN methiodide 6 resulted in formation of a piperidine derivative with both equatorial substituents in the ring on carbon C6 and on carbon C3 (no conformational changes were observed). Hofmann degradation



1

MeI
$(CH_3)_2CO$



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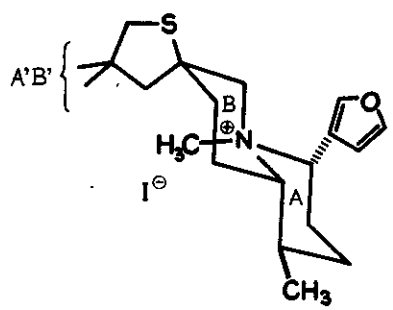

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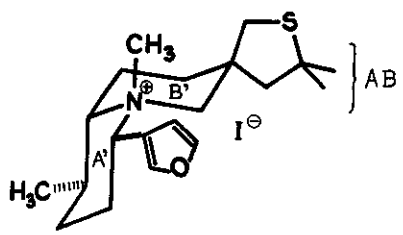

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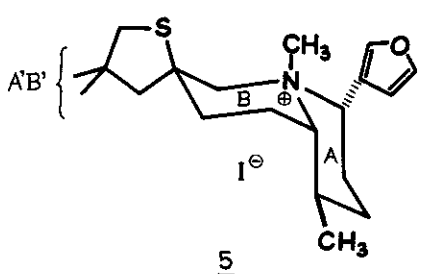


5

Fig. 1

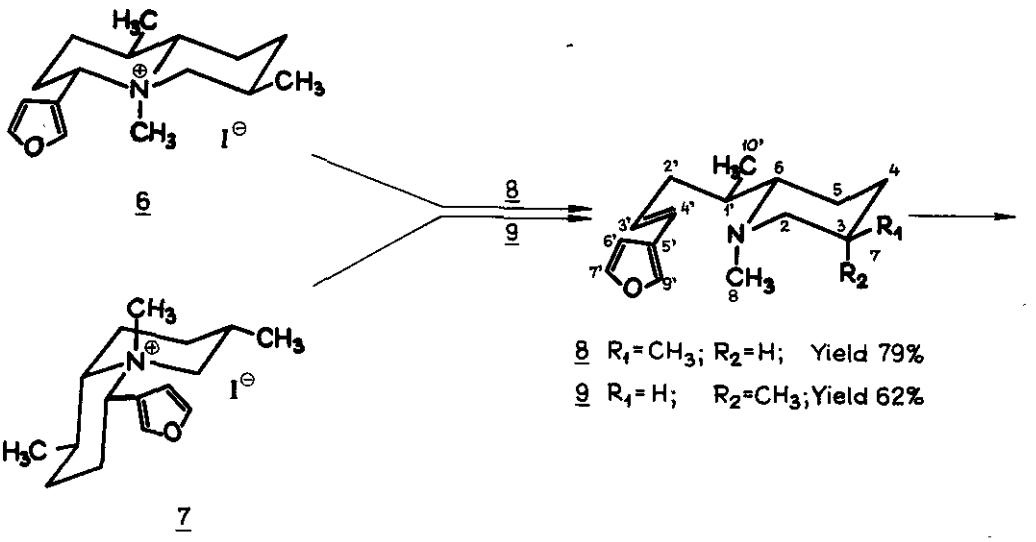
of 7 differs from this reaction course. Its first step should lead to the formation of a piperidine ring with axially situated bulky side chain with furan at carbon C6 and equatorially situated methyl group at carbon C3. This unfavorable conformation causes a spontaneous change in the stereochemistry around the piperidine ring and results in a new conformation with equatorial bulky side chain and axial methyl group. Compounds 8 and 9 differ, therefore, in the conformation of the methyl group on carbon C3. It is equatorial (^{1}H nmr δ (ppm)$_{CDCl_3}$ C3-CH_3, 0.86, d; ^{13}C nmr δ (ppm)$_{CDCl_3}$ C3-CH_3, 19.6, q) in compound 8, whereas in compound 9 it is axial (^{1}H nmr δ (ppm)$_{CDCl_3}$ C3-CH_3, 1.06, d; ^{13}C nmr δ (ppm)$_{CDCl_3}$ C3-CH_3, 18.1, q).

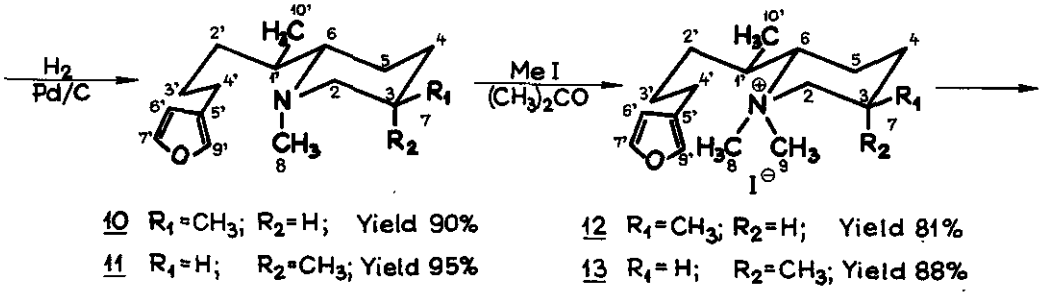
Compounds 8 and 9 were catalytically reduced over 5% Pd/C to compounds 10 and 11, respectively. This catalytic reduction confirmed the presence of trans double bonds in compounds 8 and 9. No conformational changes in the piperidine ring were observed.

Both compounds 10 and 11 were exhaustively remethylated resulting in methiodides 12 and 13. The reaction was carried out in acetone at room temperature for 3 h. The course of the reaction was monitored continuously by TLC (acid Al_2O_3; benzene:ethyl acetate:n-propanol=1:1:1; 12: R_f=0.42, 13: R_f=0.40). Quaternization did not cause any stereochemical changes in methiodides 12 and 13.

^{1}H nmr and ^{13}C nmr spectra displayed in both cases quaternization of nitrogen atom (^{13}C nmr δ (ppm)$_{CDCl_3}$ 12: $-\overset{+}{N}-(CH_3)_2$, 54.1, q, 45.0, q; 13: $-\overset{+}{N}-(CH_3)_2$, 49.8, q, 44.2, q; ^{1}H nmr δ (ppm)$_{CDCl_3}$ 12: $-N-(CH_3)_2$, 3.60, s, 3.28, s; 13: $-N-(CH_3)_2$, 3.60, s, 3.40, s).

Methiodides 12 and 13 were subjected to Hofmann degradation by heating with 50% aqueous solution of NaOH (4 h). This leads to unsaturated aliphatic amines 14 and 15 which are epimeric on carbon C3 ($[\alpha]_D^{20}$=-90.1° for compound 14 and $[\alpha]_D^{20}$=-7.9° for compound 15). In accordance with the accepted reaction mechanism the most probable is the cleavage of the N-C6 bond with formation of a double bond between carbons C5-C6 or C1'-C6. The presence of the signal of two olefinic protons at δ =5.38 ppm and δ =5.28 ppm indicated the formation of a double bond between carbons C5-C6. The AB signal (J=15 Hz), observed at δ =5.38 ppm indicates a trans substitution at the double bond. In the course of Hofmann degradation some demethylation was observed and, therefore, the reaction with methiodide 12 resulted in compounds 14 and 10, whereas that with methiodide 13 - in 15 and 11.


6
8
9
7
8 R1=CH3; R2=H; Yield 79%
9 R1=H; R2=CH3; Yield 62%


H2
Pd/C
Me I
(CH3)2CO
10 R1=CH3; R2=H; Yield 90%
11 R1=H; R2=CH3; Yield 95%
12 R1=CH3; R2=H; Yield 81%
13 R1=H; R2=CH3; Yield 88%

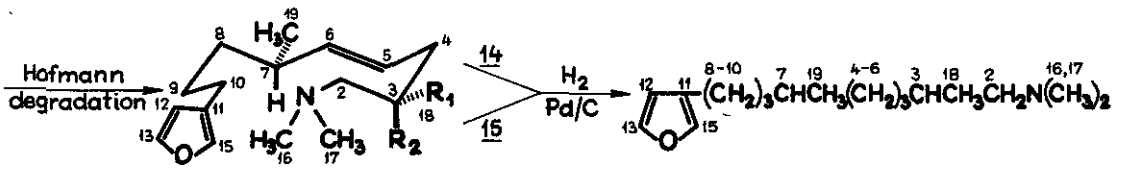

Hofmann
degradation
14
15
H2
Pd/C
16 Yield 92%
14 R1=H; R2=CH3; Yield 84%
15 R1=CH3; R2=H; Yield 77%

Fig. 2

Catalytic reduction of compounds 14 and 15 in methanol over 5% Pd/C leads to an aliphatic, N-substituted amine 16 (as evidenced by the disappearance of the signals of olefinic protons in ^{1}H nmr spectrum and of the unsaturated carbons signals in ^{13}C nmr) of the optical activity $[\alpha]_D^{20}=0.0^{o}$.

Signal of C7 and C4 carbon atoms (16) in ^{13}C nmr spectrum have been shifted diamagnetically by -4.1 ppm and -2.6 ppm, respectively. This confirms the presence of a trans double bond in compounds 14 and 15.

The full characteristics of ^{1}H nmr and ^{13}C nmr spectra of all products obtained at various degradation stages of both methiodides 6 (7EDN) and 7 (DN) has enabled the identification of the products of Hofmann degradation of TBN methiodides 2, 3, 4 and 5.

TBN monomethiodides were transformed into corresponding hydroxides (Ag_2O) and each of them was subjected to Hofmann degradation by heating for 4 h with an equivalent of NaOH in water-methanol solution. On the basis of TLC (Al_2O_3; benzene, 17: R_f=0.44, 18: R_f=0.68) and a comparison of ^{1}H nmr and ^{13}C nmr spectra it has been established that degradation of methiodides 2 and 3 leads to the same product 17, whereas degradation of methiodides 4 and 5 to the product 18 (Fig.3). This fact confirms the appropriate assignments of structures and the stereochemistry to TBN monomethiodides.

Analysis of ^{1}H nmr and ^{13}C nmr spectra of 17 and 18 has shown that the course of Hofmann degradation of methiodides 2 - 5 is the same as in the case of methiodides 6 (7EDN) and 7 (DN). In methiodides 2 and 3, A'B'quinolizidine ring has been fused and the N-C4' bond has been split with formation of a trans double bond between carbons C3' and C4' (^{1}H nmr δ (ppm)$_{CDCl_3}$ 6.32, d, J=13.5 Hz, 6.01, m, for compound 17).

Degradation of A'B'methiodide 3 with cis A'B'ring junction causes a change in conformation on carbon C7' (carbon C17' is axial in methiodide 3, whereas it is equatorial in the degradation product 17). Inversion of the conformation on carbon C7' causes a change of conformation of the side chain with furan from axial into equatorial. Conversely, degradation of methiodide 2 with a trans ring junction in the A'B'quinolizidine ring retains the configuration on carbon C7' owing to the favorable equatorial conformation of the large side chain with furan. Thus, the same degradation product 17 is formed from both methiodides 2 and 3 due to the lower stability and spontaneous ring inversion in the degradation product of 3.

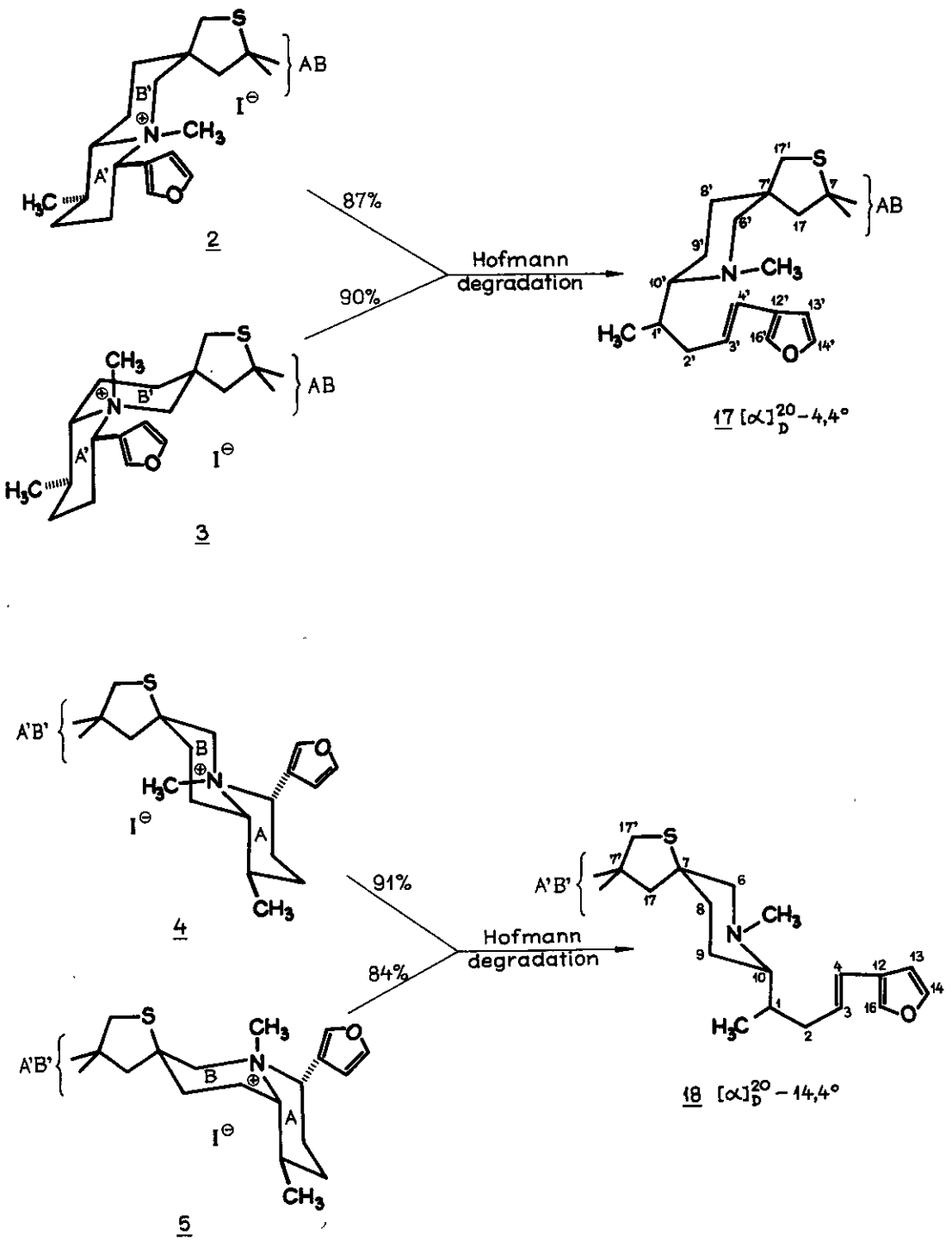

AB
I⊖
2
87%
90%
Hofmann
degradation
17 [α]D20 −4,4°
3
A'B'
91%
84%
18 [α]D20 −14,4°
4
5

Fig. 3

The stereochemistry of Hofmann degradation of methiodides 4 and 5 (AB trans and AB cis respectively) is similar to the degradation of methiodides 2 and 3. Therefore, instead of the two different configurations on carbon C7', only one corresponding to the single product, 18, is obtained. It has been established that the N-C4 bond is broken with formation of a trans double bond between carbons C3 and C4 (^{1}H nmr δ (ppm)$_{CDCl_3}$ 6.32, d, J=13.5 Hz, 6.04, m, for compound 18).

Compounds 17 and 18 were requaternized at room temperature, in acetone, with excess of MeI (Fig.4). The reaction was monitored by TLC (Al_2O_3 acid; benzene: ethyl acetate:n-propanol=1:1:1, 19: R_f=0.4, 20: R_f=0.4). These conditions prevented the nitrogen atom in one of the quinolizidine rings from quaternization which, under conditions described, is much slower than quaternization of the nitrogen in the piperidine ring.

Analysis of ^{13}C nmr spectra shows no changes in chemical shifts of carbon atoms in A'B' or AB quinolizidine rings, respectively; however, changes are observed in values of chemical shifts of carbon atoms α to nitrogen atom of the piperidine ring. Chemical shifts of $-\overset{+}{N}-(CH_3)_2$ groups (in 19: 54.8 ppm and 44.7 ppm; 20: 54.5 ppm and 44.4 ppm) have shown that compounds 19 and 20 are the respective products of quaternization of nitrogen atoms in corresponding piperidines.

Methiodides 19 and 20 were reacted with Ag_2O to form hydroxides and each of the latter was subjected to Hofmann degradation by heating with a 50% aqueous solution of NaOH for 4 h. From compound 19 a mixture of two products was obtained: compound 21 (TLC: Al_2O_3; benzene, R_f=0.32) and compound 17 - the demethylation product. From compound 20, compound 22 (TLC: Al_2O_3; benzene, R_f=0.28) and the demethylation product - compound 18 were obtained.

Analysis of the ^{1}H nmr (δ (ppm)$_{CDCl_3}$ 21: H10' 5.38, q_{AB}, J=15 Hz and H9' 5.28, t; 22: H10 5.40, q_{AB}, J=15 Hz and H9 5.28, t) and ^{13}C nmr spectra (δ (ppm)$_{CDCl_3}$ 21: C10' 125.6, d and C9' 139.0, d; 22: C10 125.3, d and C9 138.8, d) indicates that in both cases N-C10' (21) or N-C10 (22) bond was broken, respectively, whereas a trans substituted double bond was formed between carbons C9' and C10' in 21 or C9-C10 in 22.

The values of chemical shifts in ^{13}C nmr spectrum of carbon C7 in compound 21 and of carbon C7' in compound 22 show that in both these cases conformational changes do not occur (^{13}C nmr δ (ppm)$_{CDCl_3}$ 21: C7 56.00, s; 22: C7' 48.8, s).

Details of ^{13}C nmr analysis of all products disscused in this paper will be

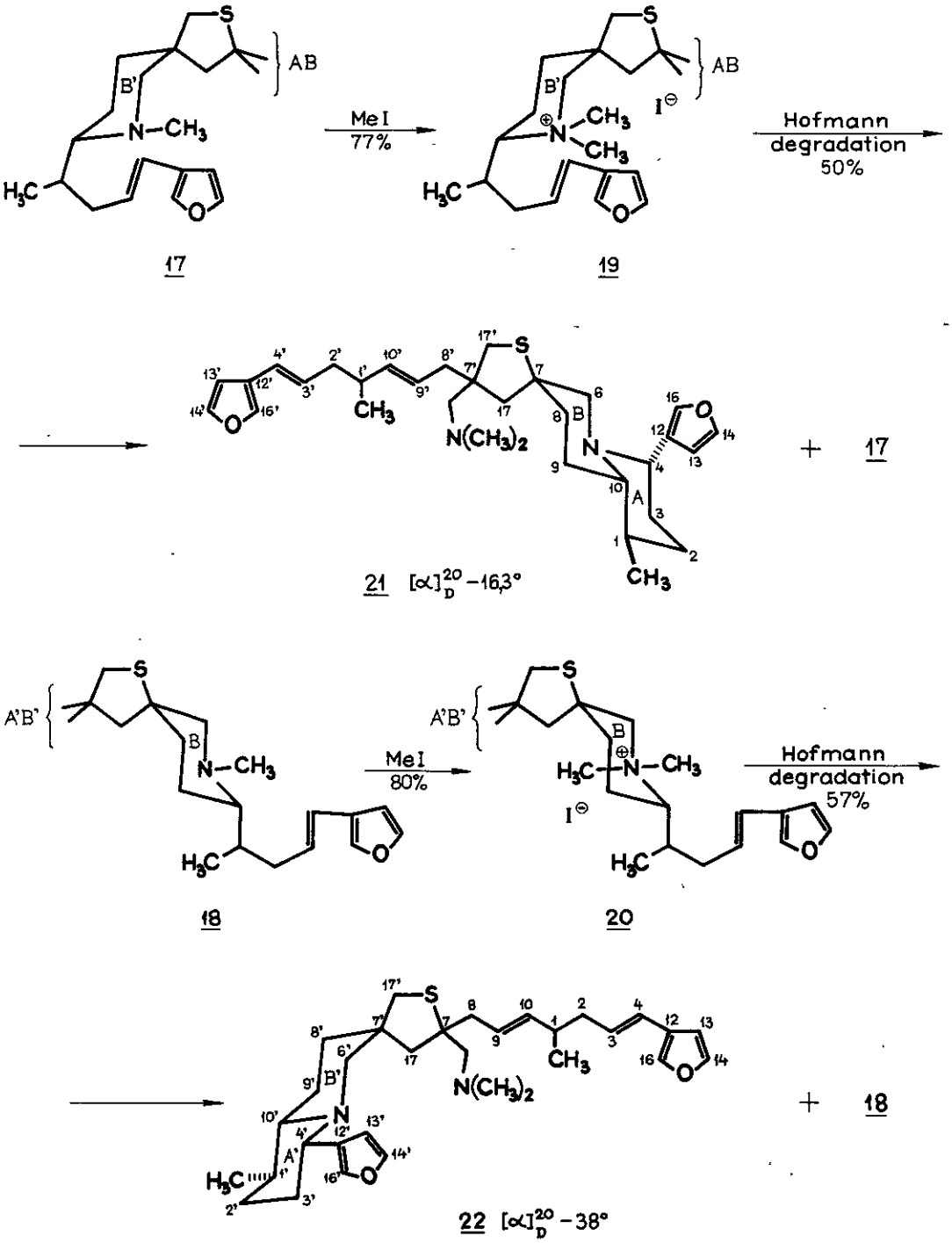

AB
B'
N–CH3
H3C
MeI
77%
I⊖
Hofmann
degradation
50%
17
19
N(CH3)2
CH3
+ 17
21 [α]D20 −16,3°
A'B'
B
MeI
80%
Hofmann
degradation
57%
18
20
+ 18
22 [α]D20 −38°

Fig. 4

published separately.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Boetius apparatus (Carl Zeiss Jena). Results of elemental analysis 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 $60F_{254}$. The column chromatography was carried out on Fluka 506C, 3 rd activity after Brockmann Al_2O_3. The solvents used in chromatography procedures were purified and distilled in conventional manner.

The first Hofmann degradation (General Procedure).- A solution of (0.002 mol) 7EDN methiodide 6, DN methiodide 7 or TBN methiodides 2, 3, 4, 5 in 10 ml of 70% methanol, moist silver oxide (prepared from 500 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 methanol (10 ml) were added and the mixture heated under reflux for 4 h. After dilution with water, the crude products were extracted with chloroform. The solvent was removed in vacuo, the residue was chromatographed on alumina using benzene as eluent. Following compounds were obtained:

8 (from 6) yield 79%; colorless oil; TLC in a benzene:chloroform (1:1) system, R_f=0.38; ^{1}H nmr ($CDCl_3$) ppm: 0.86 (d 6H J=6 Hz C3-CH_3 eq., C1'-CH_3), 2.22 (s 3H N-CH_3), 2.78 (dd 1H J=15 Hz, 3.5 Hz C6-H eq.), 6.01 (m 1H C3'-H), 6.32 (d 1H J=16 Hz C4'-H), 6.58 (s 1H β-furanyl H), 7.46 (m 2H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 12.78 (q C10'), 19.63 (q C7), 23.93 (t C5), 31.21 (d C3), 33.51 (t C4), 33.59 (d C1'), 38.27 (t C2'), 42.74 (q C8), 66.10 (t C2), 67.49 (d C6), 107.63 (d C6'), 120,41 (d C3'), 124.49 (s C5'), 129.56 (d C4'), 139.40 (d C9'), 143.25 (d C7'); ms: m/z (relative intensity) = 247 ($M^{+\cdot}$, 3), 112 (100), 70 (11).

9 (from 7) yield 62%; colorless oil; TLC in a benzene:chloroform (1:1) system, R_f=0.61; ^{1}H nmr ($CDCl_3$) ppm: 0.92 (d 3H J=6 Hz C1'-CH_3), 1.06 (d 3H J=10 Hz C3-CH_3 ax.), 2.28 (s 3H N-CH_3), 2.66 (dd 1H J=15 Hz, 3.5 Hz C6-H eq.), 6.01 (m 1H C3'-H), 6.32 (d 1H J=16 Hz C4'-H), 6.58 (s 1H β-furanyl H), 7.44 (m 2H

α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 13.61 (q C10'), 18.16 (q C7), 18.68 (t C5), 27.35 (d C3), 29.95 (t C4), 33.25 (d C1'), 37.97 (t C2'), 43.39 (q C8), 61.64 (t C2), 67.01 (d C6), 107.62 (d C6'), 120.33 (d C3'), 124.57 (s C5'), 129.73 (d C4'), 139.26 (d C9'), 143.21 (d C7'); ms: m/z (relative intensity) = 247($M^{+\cdot}$, 3), 112 (100), 70 (9).

17 (from 2 and 3) yield 88%; colorless oil; TLC in benzene, R_f=0.44; $[\alpha]_D^{20}$=-4.4°; ^1H nmr ($CDCl_3$) ppm: 0.94 (d 6H C1-CH_3, C1'-CH_3), 2.22 (s 3H N-CH_3), 2.42 (s 2H S-CH_2), 2.98 (m 2H C6'-He, C6-He), 6.01 (m 1H C3'-H), 6.32 (d 1H J=13.5 Hz C4'-H), 6.50 (s 1H β-furanyl 13H), 6.58 (s 1H β-furanyl 13'H), 7.45 (m 4H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 12.79 (q C11'), 19.07 (q C11), 21.97 (t C9'), 29.26 (t C9), 33.59 (t C2), 33.59 (d C1'), 35.02 (t C3), 35.98 (d C1), 36.50 (t C8'), 38.27 (t C2'), 40.09 (t C8), 42.48 (t C17'), 43.17 (q N-CH_3), 44.91 (t C17), 49.07 (s C7'), 56.82 (s C7), 59.64 (d C4), 65.80 (t C6), 67.79 (t, d C6', C10'), 68.57 (d C10), 107.58 (d C13'), 109.49 (d C13), 120.28 (d C3'), 124.30 (s C12'), 129.21 (s C12), 129.56 (d C4'), 139.35 (d C16'), 139.52 (d C16), 142.64 (d C14), 143.25 (d C14'); ms: m/z (relative intensity) = 508 ($M^{+\cdot}$, 12), 400 (3), 373 (100), 230 (9), 178 (8), 136 (3), 107 (18), 94 (29), 81 (10).

18 (from 4 and 5) yield 87%; colorless oil; TLC in benzene, R_f=0.68; $[\alpha]_D^{20}$=-14.4° ^1H nmr ($CDCl_3$) ppm: 0.94 (d 6H C1-CH_3, C1'-CH_3), 2.22 (s 3H N-CH_3), 2.52 (q_{AB} 2H J=12 Hz S-CH_2), 3.00 (m 2H C6'-He, C6-He), 6.04 (m 1H C3-H), 6.32 (d 1H J=13.5 Hz C4-H), 6.46 (s 1H β-furanyl 13'H), 6.62 (s 1H β-furanyl 13H), 7.48 (m 4H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 12.70 (q C11), 19.16 (q C11'), 22.63 (t C9), 28.48 (t C9'), 33.51 (d C1), 33.68 (t C2'), 35.02 (t C3'), 35.97 (d C1'), 37.80 (t C8'), 38.19 (t C2), 38.62 (t C8), 42.61 (t C17'), 42.91 (q N-CH_3), 45.16 (t C17), 49.11 (s C7'), 56.61 (s C7), 59.86 (d C4'), 62.85 (t C6'), 66.92 (d C10), 69.65 (d C10'), 71.17 (t C6), 107.58 (d C13), 109.66 (d C13'), 120.33 (d C3), 124.40 (s C12), 129.47 (s C12'), 129.47 (d C4), 139.35 (d C16), 139.48 (d C16'), 142.60 (d C14'), 143.25 (d C14); ms: m/z (relative intensity) = 508 ($M^{+\cdot}$, 9), 400 (3), 373 (100), 316 (4), 243 (3), 230 (8), 192 (3), 178 (3), 136 (4), 110 (7), 107 (18), 94 (30).

Catalytic reduction (General Procedure). - 0.0015 mol of 8, 9, 14 or 15 in 20 ml of methanol was reduced catalytically in the presence of 70 mg of 5% Pd/C. When 99% of the theoretical amount of hydrogen was absorbed, the catalyst was filtrated and the solvent removed. The residue was chromatographed on alumina using

benzene as eluent. Following compounds were obtained:

10 (from 8) yield 90%; colorless oil; TLC in a benzene:chloroform (1:1) system R_f=0.38; ^{1}H nmr ($CDCl_3$) ppm: 0.90 (d 6H J=6 Hz C3-CH_3 eq., C1'-CH_3), 2.28 (s 3H N-CH_3), 2.48 (t 2H C4'-H), 2.90 (dd 1H C6-H), 6.40 (s 1H β-furanyl H), 7.32 (m 2H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 13.00 (q C10'), 19.64 (q C7), 24.01 (t C5), 25.10 (t C3'), 28.43 (t C4'), 31.29 (d C3), 32.81 (t C4), 33.55 (d C1'), 34.42 (t C2'), 42.78 (q C8), 66.23 (t C2), 67.92 (d C6), 110.96 (d C6'), 125.13 (s C5'), 138.75 (d C9'), 142.60 (d C7'); ms: m/z (relative intensity) = 249 ($M^{+\cdot}$, 3), 112 (100), 70 (10).

11 (from 9) yield 95%; colorless oil; TLC in a benzene:chloroform (1:1) system R_f=0.61; ^{1}H nmr ($CDCl_3$) ppm: 0.90 (d 3H J=6 Hz C1'-CH_3), 1.06 (d 3H J=10 Hz C3-CH_3 ax.), 2.24 (s 3H N-CH_3), 2.42 (t 2H C4'-H), 2.70 (dd 1H J=15 Hz, 3.5 Hz C6-H), 6.38 (s 1H β-furanyl H), 7.32 (m 2H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 13.61 (q C10'), 18.03 (q C7), 18.77 (t C5), 25.14 (t C3'), 27.74 (d C3), 28.30 (t C4'), 30.08 (t C4), 32.64 (d C1'), 34.24 (t C2'), 43.39 (q C8), 62.28 (t C2), 67.92 (d C6), 111.00 (d C6'), 125.26 (s C5'), 138.75 (d C9'), 142.60 (d C7'); ms: m/z (relative intensity) = 249 ($M^{+\cdot}$,13) 235 (3), 112 (100), 70 (22).

16 (from 14 and 15) yield 92%; colorless oil; TLC in a benzene:chloroform (1:1) system, R_f=0.44; $[\alpha]_D^{20}$=0.0°; ^{1}H nmr ($CDCl_3$) ppm: 0.86 (d 3H J=6 Hz C7-CH_3), 0.92 (d 3H J=6 Hz C3-CH_3), 2.16 (d 2H J=8 Hz C2-H), 2.28 (s 6H N-$(CH_3)_2$), 2.42 (t 2H C10-H), 6.32 (s 1H β-furanyl H), 7.34 (m 2H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 18.25 (q C18), 19.64 (q C19), 24.40 (t C9), 25.10 (t C5), 27.52 (t C10), 31.03 (d C3), 32.64 (d C7), 35.46 (t C4), 36.80 (t C8), 37.23 (t C6), 45.82 (2xq C16, C17), 67.23 (t C2), 111.00 (d C12), 127.09 (s C11), 138.45 (d C15), 142.56 (d C13); ms: m/z (relative intensity) = 265 ($M^{+\cdot}$, 2), 129 (1), 81 (4), 58 (100), 55 (2).

Methylation (General Procedure). - To 0.0015 mol of compounds 10, 11, 17 or 19 in 5 ml acetone excess of methyl iodide was added and the mixture was allowed to stand overnight at room temperature (for compounds 10 and 11 - 3 h). Upon removal of excess of MeI and Me_2CO crude product was purified in each experiment chromatographically on acid Al_2O_3, using chloroform (for compounds 12,13) or chloroform:methanol (99:1) (for compounds 18 and 20) as eluent. Following compounds were obtained:

12 (from 10) yield 81%; mp 143-145°C (from acetone:ethyl acetate); TLC (acid Al_2O_3; benzene:ethyl acetate:n-propanol=1:1:1), R_f=0.42; ^1H nmr ($CDCl_3$) ppm: 1.06 (d 6H J=10 Hz C3-CH_3 eq., C1'-CH_3), 3.28 (s 3H $\overset{+}{N}$-CH_3), 3.60 (s 3H $\overset{+}{N}$-CH_3), 6.44 (s 1H β-furanyl H), 7.42 (m 2H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 16.12 (q C10'), 18.07 (q C7), 21.98 (t C5), 24.66 (t C3'), 26.83 (d C3), 27.57 (t C4'), 30.51 (t C4), 30.73 (d C1'), 36.32 (t C2'), 45.04 (q C8), 54.14 (q C9), 71.95 (t C2), 75.77 (d C6), 111.18 (d C6'), 124.57 (s C5'), 139.13 (d C9'), 142.69 (d C7').

13 (from 11) yield 88%; mp 135-136°C (from ethyl acetate); TLC (acid Al_2O_3; benzene:ethyl acetate:n-propanol=1:1:1), R_f=0.40; ^1H nmr ($CDCl_3$) ppm: 1.06 (d 3H J=8 Hz C1'-CH_3), 1.14 (d 3H J=10 Hz C3-CH_3ax.), 3.40 (s 3H $\overset{+}{N}$-CH_3), 3.60 (s 3H $\overset{+}{N}$-CH_3), 6.42 (s 1H β-furanyl H), 7.42 (m 2H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 16.77 (q C10'), 18.90 (q C7), 19.50 (t C5), 25.44 (t C3'), 27.00 (d C3), 28.43 (t C4'), 28.52 (t C4), 32.38 (d C1'), 37.41 (t C2'), 44.21 (q C8), 49.84 (q C9), 69.87 (t C2), 75.59 (d C6), 111.96 (d C6'), 125.87 (s C5'), 140.17 (d C9'), 143.77 (d C7').

19 (from 17) yield 77%; mp 240-243°C (from ethyl acetate); TLC (acid Al_2O_3; benzene:ethyl acetate:n-propanol=1:1:1), R_f=0.40; ^1H nmr ($CDCl_3$) ppm: 0.90 (d 3H C1 -CH_3), 1.08 (d 3H C1'-CH_3), 3.22 (s 3H $\overset{+}{N}$-CH_3), 3.50 (s 3H $\overset{+}{N}$-CH_3), 6.01 (m 1H C3'-H), 6.32 (d 1H J=16 Hz C4'-H), 6.40 (s 1H β-furanyl 13H), 6.70 (s 1H β-furanyl 13'H), 7.46 (m 4H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 16.21 (q C11'), 19.11 (q C11), 19.89 (t C9'), 28.74 (t C9), 31.25 (d C1'), 31.94 (t C2), 33.42 (t C8'), 34.37 (t C3), 35.85 (d C1), 39.83 (t C2'), 42.13 (t C8), 42.30 (t C17'), 44.69 (q $\overset{+}{N}$-CH_3), 46.12 (t C17), 47.94 (s C7'), 54.87 (q $\overset{+}{N}$-CH_3), 57.56 (s C7), 59.34 (d C4), 64.28 (t C6), 68.61 (d C10), 73.38 (t C6'), 74.90 (d C10'), 108.10 (d C13'), 108.86 (s C12), 109.53 (d C13), 123.31 (d C3'), 124.01 (s C12'), 126.17 (d C4'), 139.96 (d C16), 140.22 (d C16'), 142.69 (d C14), 143.47 (d C14').

20 (from 18) yield 80%; pale yellow oil; TLC (acid Al_2O_3; benzene:ethyl acetate: n-propanol=1:1:1), R_f=0.40; ^1H nmr ($CDCl_3$) ppm: 0.90 (d 3H C1'-CH_3), 1.06 (d 3H C1-CH_3), 3.30 (s 3H $\overset{+}{N}$-CH_3), 3.50 (s 3H $\overset{+}{N}$-CH_3), 6.01 (m 1H C3-H), 6.32 (d 1H J=16 Hz C4-H), 6.38 (s 1H β-furanyl 13'H), 6.70 (s 1H β-furanyl 13H), 7.48 (m 4H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 16.30 (q C11), 19.20 (q C11'), 21.41 (t C9), 28.82 (t C9'), 30.73 (d C1), 33.59 (t C2'), 34.33 (t C3'), 36.32 (d C1'), 37.27 (t C8), 39.92 (t C8'), 39.92 (t C2), 42.40 (t C17'), 44.38

($q\ \overset{+}{N}\text{-}CH_3$), 45.38 (t C17), 51.97 (s C7'), 54.48 ($q\ \overset{+}{N}\text{-}CH_3$), 54.74 (s C7), 59.55 (d C4'), 60.81 (t C6'), 70.28 (d C10'), 74.16 (d C10), 74.68 (t C6), 108.02 (d C13), 110.05 (d C13'), 123.18 (d C3), 124.01 (s C12), 126.34 (d C4), 128.82 (s C12'), 140.13 (d C16), 140.13 (d C16'), 142.64 (d C14'), 143.42 (d C14).

The second Hofmann degradation (General Procedure).- A solution of (0.001 mol) of compounds 12, 13, 19 or 20 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) and water (10 ml) was added and the mixture refluxed for 4 h. After dilution with water, the crude products were extracted with chloroform. The solvent was removed in vacuo, the residue was chromatographed on alumina using hexane:benzene (1:1) (for compounds 14 and 15) or benzene (for compounds 21 and 22). Following compounds were obtained:

14 (from 12) yield 84%; colorless oil; TLC in a benzene:chloroform (1:1) system, R_f=0.42; $[\alpha]_D^{20}$=-90.1°; ^{1}H nmr ($CDCl_3$) ppm: 0.92 (d 3H J=6 Hz C7-CH_3), 0.98 (d 3H J=6 Hz C3-CH_3), 2.24 (s 6H N-$(CH_3)_2$), 2.42 (t 2H C10-H), 5.28 (m 1H C5-H), 5.38 (q_{AB} 1H J=15 Hz C6-H), 6.30 (s 1H β-furanyl H), 7.34 (m 2H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 18.03 (q C18), 21.07 (q C19), 24.88 (t C9), 27.83 (t C10), 31.55 (d C3), 36.80 (d C7), 36.80 (t C8), 38.14 (t C4), 45.95 (2xq C16, C17), 66.62 (t C2), 111.05 (d C12), 125.58 (s C11), 126.65 (d C6), 137.84 (d C5), 138.85 (d C15), 142.56 (d C13); ms: m/z (relative intensity) = 263 ($M^{+\cdot}$, 6), 98 (1), 81 (7), 58 (100).

15 (from 13) yield 77%; colorless oil; TLC in a benzene:chloroform (1:1) system, R_f=0.42; $[\alpha]_D^{20}$=-7.9°; ^{1}H nmr ($CDCl_3$) ppm: 0.90 (d 3H J=7.5 Hz C7-CH_3), 0.96 (d 3H J=7.5 Hz C3-CH_3), 2.22 (s 6H N-$(CH_3)_2$), 2.42 (t 2H C10-H), 5.28 (m 1H C5-H), 5.38 (q_{AB} 1H J=15 Hz C6-H), 6.30 (s 1H β-furanyl H), 7.32 (m 2H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 18.03 (q C18), 21.07 (q C19), 24.88 (t C9), 27.83 (t C10), 31.55 (d C3), 36.80 (d C7), 36.80 (t C8), 38.14 (t C4), 45.95 (2xq C16, C17), 66.62 (t C2), 111.05 (d C12), 125.58 (s C11), 126.65 (d C6), 137.84 (d C5), 138.85 (d C15), 142.56 (d C13); ms: m/z (relative intensity) = 263 ($M^{+\cdot}$, 4), 126 (3), 98 (3), 58 (100), 41 (10).

21 (from 19) yield 50%; colorless oil; TLC in benzene, R_f=0.32; $[\alpha]_D^{20}$=-16.3°; ^{1}H nmr ($CDCl_3$) ppm: 0.90 (d 3H C1-CH_3), 1.02 (d 3H C1'-CH_3), 2.34 (s 6H N-$(CH_3)_2$), 2.48 (q_{AB} 2H J=12 Hz S-CH_2), 2.98 (q_{AB} 1H C6-He), 5.28 (t 1H C9'-H)

5.38 (q_{AB} 1H J=15 Hz C10'-H), 6.01 (m 1H C3'-H), 6.32 (d 1H J=16 Hz C4'-H), 6.48 (s 1H β-furanyl 13H), 6.58 (s 1H β-furanyl 13'H), 7.38 (m 4H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 19.03 (q C11), 20.46 (q C11'), 29.21 (t C9), 33.59 (t C2), 34.98 (t C3), 36.03 (d C1), 37.23 (d C1'), 39.18 (t C8'), 40.14 (t C8), 40.27 (t C17'), 40.61 (t C2'), 46.72 (t C17), 48.46 (2xq N-$(CH_3)_2$), 54.18 (s C7'), 56.00 (s C7), 59.68 (d C4), 64.93 (t C6'), 65.71 (t C6), 68.44 (d C10), 107.62 (d C13'), 109.42 (d C13), 120.62 (d C4'), 125.60 (d C10'), 128.35 (s C12), 128.35 (s C12'), 128.90 (d C4'), 138.83 (d C9'), 139.40 (d C16'), 139.57 (d C16), 142.86 (d C14'), 143.21 (d C14); ms: m/z (relative intensity) = 522 ($M^{+\cdot}$, 4), 464 (2), 415 (7), 356 (2), 230 (17), 178 (4), 149 (8), 107 (7), 94 (4), 58 (100).

22 (from 20) yield 57%; colorless oil; TLC in benzene, R_f=0.28; $[\alpha]_D^{20}$=-38°; ^{1}H nmr ($CDCl_3$) ppm: 0.92 (d 3H C1'-CH_3), 1.04 (d 3H C1-CH_3), 2.38 (s 6H N-$(CH_3)_2$), 2.50 (s 2H S-CH_2), 2.96 (q_{AB} 1H C6'-He), 5.28 (t 1H C9-H), 5.40 (q_{AB} 1H J=15 Hz C10-H), 6.02 (m 1H C3-H), 6.32 (d 1H J=16 Hz C4-H), 6.48 (s 1H β-furanyl 13'H), 6.60 (s 1H β-furanyl 13H), 7.42 (m 4H α-furanyl H); ^{13}C nmr ($CDCl_3$) ppm: 19.16 (q C11'), 20.15 (q C11), 28.17 (t C9'), 33.76 (t C2'), 35.15 (t C3'), 36.30 (d C1'), 36.97 (d C1), 36.97 (t C8'), 40.57 (t C2), 43.73 (t C8), 43.73 (t C17'), 46.42 (t C17), 48.07 (2xq N-$(CH_3)_2$), 48.76 (s C7'), 60.12 (d C4'), 62.89 (s C7), 63.24 (t C6'), 69.35 (d C10'), 69.70 (t C6), 107.75 (d C13), 109.70 (d C13'), 120.50 (d C3), 125.27 (d C10), 128.34 (d C12'), 129.04 (d C4), 129.25 (s C12), 138.76 (d C9), 139.52 (d C16), 139.52 (d C16'), 142.77 (d C14), 143.16 (d C14'); ms: m/z (relative intensity) = 522 ($M^{+\cdot}$, 3), 464 (20), 416 (2), 356 (7), 230 (3), 178 (3), 107 (8), 94 (3), 58 (100).

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