STUDIES ON STEREOCHEMISTRY OF THIONUPHLUTINE AND NEOTHIOBINUPHARIDINE METHIODIDES AND THEIR PRODUCTS OF HOFMANN DEGRADATION

Jerzy T. WRÓBEL, Anna SCHOLL-ALEKSANDROWICZ, Jacek CYBULSKI and Krystyna WOJTASIEWICZ

Department of Chemistry, University of Warsaw, 02—093 Warsaw, Poland

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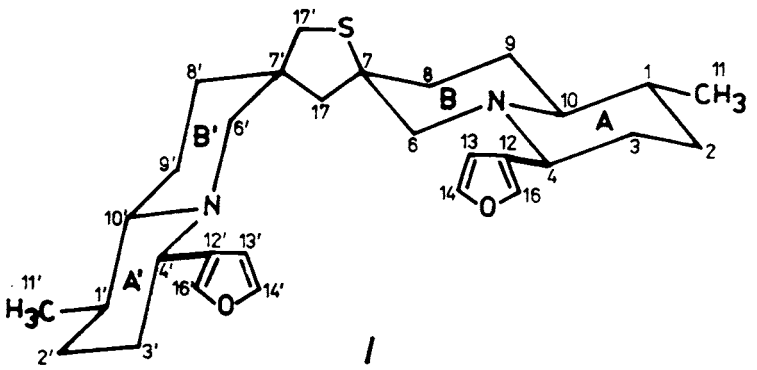
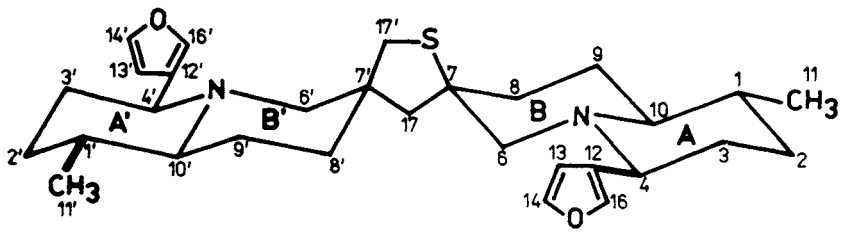
Degradation of tetrahydrothiophene ring in two isomeric Nuphar alkaloids — thionuphlutine and neothiobinupharidine has been observed during methylation under thermodynamic control. The C S bond has been cleaved and the double bond formed in the products of methylation. The structure and stereochemistry of methiodides and their products of Hofmann degradation have been determined by ^{13}C NMR spectroscopy.

The quaternization of thiobinupharidine (sulfur equatorial) was described earlier[1-3]. Two other dimeric Nuphar alkaloids thionuphlutine *I* and neothiobinupharidine *II* (in both sulfur axial) were examined in the course of the thermodynamically controlled quaternization and Hofmann degradation reaction. It was observed earlier[4] that under kinetic control thionuphlutine *I* undergoes methylation on sulfur mostly with no stereochemical changes of the molecule. It is conceivable to assume that this reaction takes place as the first step during the methylation of *I* and *II* also under thermodynamic control.

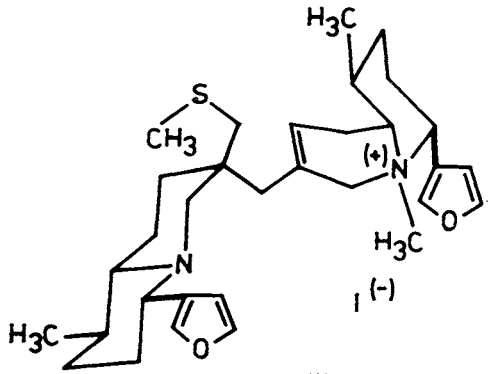


I

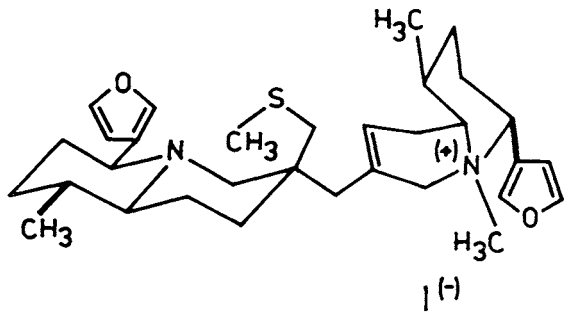


II

Quaternization of both *I* and *II* runs similarly but differs completely in comparison with the results obtained with thiobinupharidine. From *I* and *II* compounds *III* and *IV* were isolated respectively, in which the C(7)—S bond was cleaved, a double bond was formed and the *trans* AB quinolizidine moiety was converted into the *cis* configuration.

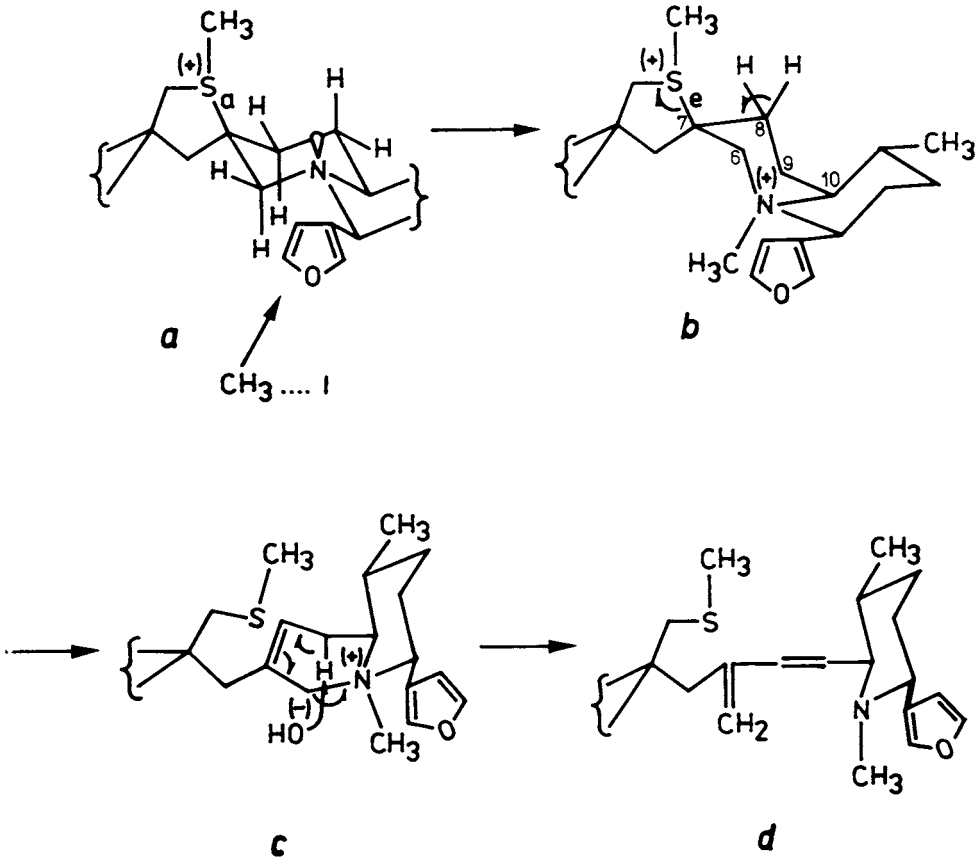


III



IV

Degradation sequence of tetrahydrothiophene ring in compounds *III* and *IV* is shown in Scheme 1. On treatment with methyl iodide thionuphlutine *I* forms N_{AB} methiodide of sulphonium salt *b* (Scheme 1). This occurs with inversion at nitrogen so as to avoid a *δ-syn*-diaxial interaction of the arising $\overset{+}{N}—CH_3$, with the C—S bond. Subsequent *syn*-elimination results in a cleavage of the C(7)—S bond and formation of the double bond between C(7) and C(8).



SCHEME 1

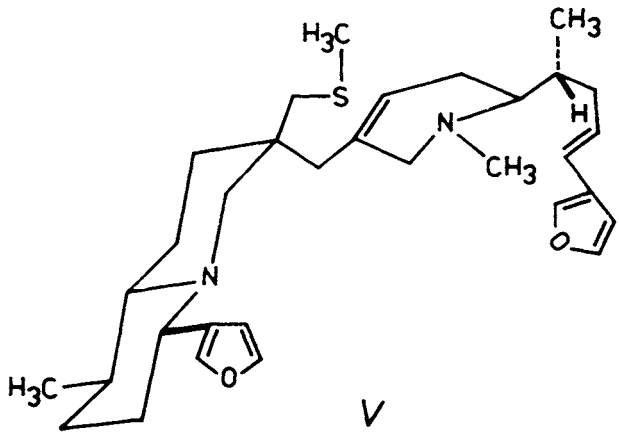
^{1}H NMR spectra of compounds *III* and *IV* are characterized by the presence of a one-proton signal (δ 6·02 ppm) indicating the presence of a double bond of the C=CH type. The presence of a three-proton singlet at δ 3·40 ppm is indicative of the presence of the $\overset{+}{N}—CH_3$ group in the *cis* quinolizidine system[5]. A three-proton singlet at δ 2·23 ppm corresponds to the S—CH_3 group. Further evidence for the structure and stereochemistry of compounds *III* and *IV* was given by ^{13}C NMR

spectra in which the order of particular carbon atoms was determined by the SFORD method.

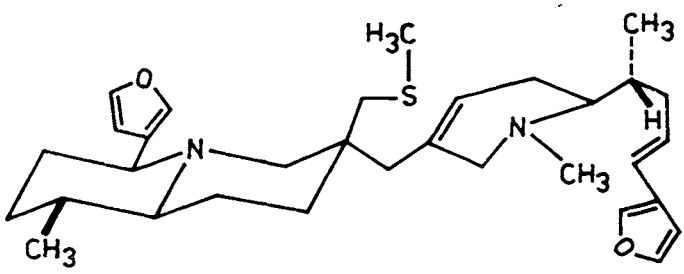
The C=C double bond in *III* and *IV* was localized between C(7) and C(8) (ref.[6]) (for the values of chemical shifts see Experimental), thus supporting the idea of the C(7)—S bond cleavage in the skeleton of *I* and *II*. Independently this cleavage was demonstrated by the presence of the primary carbon atom in the —S—CH_3 group in *III* and *IV* (^{13}C NMR data).

The *cis* conformation of AB quinolizidine ring in compounds *III* and *IV* was furnished by the following data:

- Carbon atoms C(4) in compounds *III* and *IV* are subjected to a paramagnetic shift, whereas the carbon atoms C(6) in the same compounds – to a diamagnetic shift.
- The chemical shifts values of the $\overset{+}{N}$—CH_3 groups also speak in favour of the *cis* ring junction (cf. thiobinupharidine methiodides).



V



VI

The retained *trans* ring junction in A'B' quinolizidine ring is shown by the chemical shifts of carbon atoms C(4'), C(6') and C(10') which are close to those of similar carbon atoms in compounds *I* and *II*. Different stereochemistry of the $C(17')H_2$—S—CH_3 group in A'B' quinolizidine ring of compounds *III* (equatorial) and *IV* (axial) was manifested by a paramagnetic effect of C(17') in compound *III* as compared with a similar carbon atom in compound *IV* (ref.[7]).

Compounds *III* and *IV* were subjected to Hofmann degradation under the conditions used for quaternary salts of thiobinupharidine[8]. In contrast to the previous elimination that proceeds regioselectively, we found that the Hofmann degradation goes in two directions: from compound *III*, compound *V* and *VII* and from compound *IV*, compounds *VI* and *VIII* were obtained, respectively. Compounds *V* and *VI* were formed as a result of cleavage of the N—C(4) bond with formation of a double bond between carbon atoms C(3) and C(4), as it was observed earlier for thiobinupharidine methiodides[8]. This permits to assign signals in ^{13}C NMR spectra of compounds *V* and *VI* to respective carbon atoms.

In the low field region signals of carbon atoms forming two double bonds (C(3), C(4) and C(7), C(8)) in *V* and *VI* were observed (Tables I and II). The chemical shift values of carbon atoms α to nitrogen atom in A'B' quinolizidine ring in compounds *V* and *VI* are analogous to those observed in *I* and *II*. The chemical shift values of carbon atoms α to the nitrogen atom in the piperidine ring (C(6) and C(10)), as well as those of the carbon atom in the N—CH_3 group in compounds *V* and *VI* are analogous to those observed in the products of Hofmann degradation of thiobinupharidine methiodides[8].

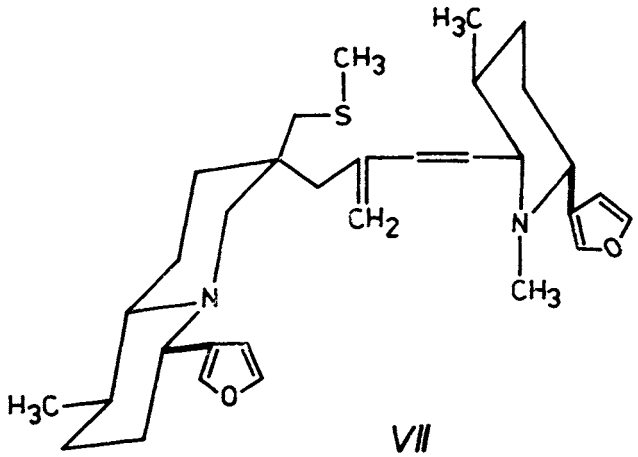
The chemical shifts of the carbon atoms C(17) and C(17') in compounds *V* and *VI* are diagnostic for the stereochemistry around C(7) and C(7') (see Tables I and II). In analogy to the ^{13}C NMR spectra obtained for compounds *III* and *IV* equatorial disposition of —$C(17')H_2$—S—CH_3 group in compound *V* and axial orientation in compound *VI* were determined.

The Hofmann degradation of methiodides *III* and *IV* results in compounds *VII* and *VIII* respectively (opening of the ring B), thus not only following 1,2-elimination as observed in products *V* and *VI* (cleavage of the N—C(4) bond). The cleavage of the N—C(6) bonds in compounds *III* and *IV*, which results in formation of conjugated double bond in molecules *VII* and *VIII*, needs some different mechanistic explanation.

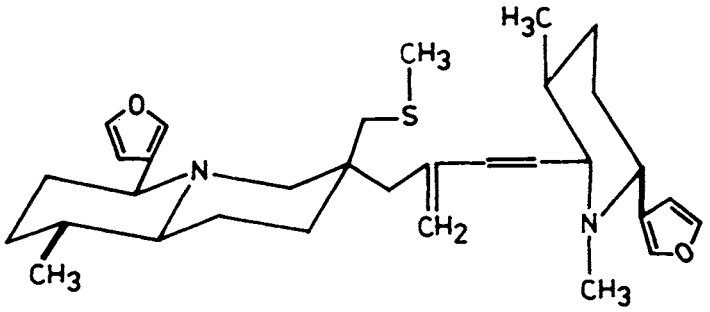
As a working hypothesis we put forward following argumentation:

The presence of the double bond at C(7) in compounds *III* and *IV* increases the acidity of allylic protons at C(9). Thus the nucleophilic attack takes place at the axial hydrogen at carbon atom C(9) and causes the cleavage of the N—C(6) bond by 1,4-allylic elimination (see Scheme 1). The conjugated double bond is formed (product *d*)[9,10]. This is the first example of a complex degradation of dimeric Nuphar alkaloids.

It is not possible by spectroscopic studies (^{13}C NMR, ^{1}H NMR) to distinguish stereochemistry around double bond (C(8)=C(9)), however the stereoelectronical rationale points out rather *cis* configuration instead of a *trans* one in compounds *VII* and *VIII*, respectively.



VII



VIII

In ^{13}C NMR spectra signals of the quaternary carbon atom C(7), the secondary carbon atom C(6) and the tertiary carbon atoms C(8) and C(9) which form double bonds are observed. The chemical shift values of carbon atoms in non-degraded A'B' quinolizidine ring, as well as of carbon atoms in the ring of substituted N-methyl-

TABLE I

^{13}C Chemical shifts and splittings of compounds *I*, *III*, *V*, and *VII*

Carbon No.	Compound											
	I			*III*			*V*			*VII*		
1,1′	35·91,	36·07	(d, d)	30·77,	36·37	(d, d)	34·19,	35·22	(d, d)	33·85,	35·20	(d, d)
2,2′	33·74,	33·74	(t, t)	26·74,	33·50	(t, t)	37·55,	33·70	(t, t)	33·72	33·46	(t, t)
3,3′	35·55,	36·42	(t, t)	29·60,	34·85	(t, t)	120·66,	36·35	(d, t)	32·46,	35·93	(t, t)
4,4′	60·09,	60·09	(d, d)	70·69,	59·50	(d, d)	129·38,	60·36	(d, d)	60·20,	60·60	(d, d)
6,6′	64·13[a],	64·33[a]	(t, t)	45·73,	62·33	(t, t)	60·20,	62·21	(t, t)	117·59,	61·98	(t, t)
7,7′	59·56,	46·74	(s, s)	138·74,	39·27	(s, s)	132·53,	38·79	(s, s)	142·64,	38·84	(s, s)
8,8′	39·30,	37·78	(t, t)	123·83,	36·97	(d, t)	123·26,	33·10	(d, t)	134·02,	36·41	(d, t)
9,9′	28·42,	29·11	(t, t)	23·58,	28·56	(t, t)	24·00,	26·93	(t, t)	133·54,	26·33	(d, t)
10,10′	69·02,	69·41	(d, d)	68·83,	69·44	(d, d)	61·77,	69·41	(d, d)	67·88,	69·37	(d, d)
11,11′	19·20,	19·20	(q, q)	18·98,	18·98	(q, q)	14·20,	19·07	(q, q)	20·11,	19·07	(q, q)
12,12′	128·71,	128·71	(s, s)	117·68,	128·60	(s, s)	124·51,	129·22	(s, s)	128·86[a],	129·25[a]	(s, s)
13,13′	109·26,	110·04	(d, d)	109·62,	110·81	(d, d)	107·65,	109·61	(d, d)	109·62,	109·62	(d, d)
14,14′	142·97,	143·38	(d, d)	145·29,	142·95	(d, d)	143·19,	142·66	(d, d)	142·43,	142·97	(d, d)
16,16′	139·50,	139·50	(d, d)	144·12,	139·70	(d, d)	139·36,	139·26	(d, d)	139·40,	139·40	(d, d)
17,17′	50·59,	42·77	(t, t)	34·85,	36·37	(t, t)	29·69,	46·05	(t, t)	41·05,	45·64	(t, t)
N^+-CH_3					53·88 (q)							
$S-CH_3$					17·81 (q)			17·93 (q)			17·81 (q)	
$N-CH_3$								39·12 (q)			41·05 (q)	

[a] Assignments may be reversed.

TABLE II

^{13}C Chemical shifts and splittings of compounds *II*, *IV*, *VI*, and *VIII*

Carbon No.	Compound											
	II			*IV*			*VI*			*VIII*		
1,1′	35·57[a],	36·15[a]	(d, d)	29·23,	36·33	(d, d)	34·02,	36·50	(d, d)	32·94,	35·63	(d, d)
2,2′	33·77,	33·77	(t, t)	26·71,	33·45[b]	(t, t)	37·45,	33·46[b]	(t, t)	33·24[a],	33·68[a]	(t, t)
3,3′	34·93,	35·80	(t, t)	28·50,	35·00	(t, t)	120·56,	35·15	(d, t)	29·69,	35·28	(t, t)
4,4′	60·24,	60·24	(d, d)	70·57,	59·61	(d, d)	129·47,	60·20	(d, d)	60·86,	60·24	(d, d)
6,6′	65·26,	63·05	(t, t)	44·21,	62·56	(t, t)	60·20,	62·42	(t, t)	117·72,	61·94	(t, t)
7,7′	57·08,	47·33	(s, s)	136·96,	39·11	(s, s)	132·50,	38·40	(s, s)	141·35,	38·45	(s, s)
8,8′	40·78,	36·52	(t, t)	124·22,	30·68	(d, t)	123·40,	39·79	(d, t)	134·37,	36·37	(d, t)
9,9′	28·16,	29·45	(t, t)	23·82,	29·44	(t, t)	23·88,	26·87	(t, t)	132·59,	26·74	(d, t)
10,10′	68·63[a],	69·29[a]	(d, d)	68·86[a],	68·74[a]	(d, d)	61·72,	69·22	(d, d)	68·16,	69·18	(d, d)
11,11′	19·12,	19·12	(q, q)	18·78,	18·78	(q, q)	14·13,	18·98	(q, q)	20·02,	19·03	(q, q)
12,12′	129·96,	130·06	(s, s)	117·53,	129·52	(s, s)	124·57,	129·26	(s, s)	128·13,	129·29	(s, s)
13,13′	109·65,	110·33	(d, d)	110·90,	109·11	(d, d)	107·62,	109·40	(d, d)	109·49,	109·66	(d, d)
14,14′	142·93,	143·31	(d, d)	145·25,	142·84	(d, d)	142·77,	143·20	(d, d)	142·73,	142·95	(d, d)
16,16′	139·51,	139·65	(d, d)	144·00,	139·06	(d, d)	139·26,	139·26	(d, d)	139·61,	139·26	(d, d)
17,17′	54,54,	39·14	(t, t)	38·90,	33·16[b]	(t, t)	33·68[b],	44·51	(t, t)	46·68,	40·83	(t, t)
$N^+—CH_3$					53·62 (q)							
$S—CH_3$					17·52 (q)			17·34 (q)			17·34 (q)	
$N·CH_3$								39·79 (q)			40·48 (q)	

[a] Assignments may be reversed; [b] one of these can be assigned to C(2′), the other to C(17′) or C(17).

piperidine are analogous to those observed in the products of Hofmann degradation of thiobinupharidine methiodide as well as in compounds *V* and *VI* (ref.[8]).

Formation of compounds *VII* and *VIII* from compounds *III* and *IV*, respectively involves the retention of configuration on carbon atom C(7') (compare ^{13}C NMR data for compounds *III*, *IV* and *V*, *VI*). Hofmann degradation products of methiodides *III* and *IV* point out that quaternization of the nitrogen atom has taken place in AB quinolizidine ring and thus give evidence for the structure of compounds *III* and *IV*.

On the basis of chemical and spectral data the following conclusions have been established:

1. Methylation of the sulfur atom and sulfonium salt formation in tetrahydrothiophene ring followed by quaternization and inversion at the nitrogen atom in the AB quinolizidine ring results in *syn*-elimination and consequently in the cleavage of the C—S bond and formation of C(7')—CH_2—S—CH_3 side chain.

2. The AB *cis* methiodides of thionuphlutine and neothiobinupharidine thus obtained differ only in configuration on carbon C(7'). In compound *III* the C(7')—CH_2—S—CH_3 group is equatorial, while in compound *IV* is axial.

3. Due to the presence of a double bond between the carbon atoms C(7) and C(8) in N-substituted quinolizidine ring (α with respect to C(6) carbon atom) as well as of a furan ring (on C(4)) Hofmann degradation does not run in one direction. Degradation products were formed as a result of a cleavage of two bonds: N—C(6) and N—C(4). Formation of compounds *VII* and *VIII* with a conjugated double bond must involve the allylic hydrogen atom on carbon C(9).

4. Hofmann degradation of *III* and *IV* proceeds with the retention of configuration on carbon C(7').

5. The products of Hofmann degradation formed as a result of the N—C(4) bond cleavage confirm the structures of the corresponding quaternary salts *III* and *IV*, respectively.

EXPERIMENTAL

The ^1H NMR spectra (δ, ppm) were recorded on a Jeol 100 MHz spectrometer and the ^{13}C NMR spectra on a Jeol FX 900 spectrometer in $CDCl_3$ solution using TMS as an internal reference. Mass spectra were registered on an LKB 2091 spectrometer. Optical rotations were measured in chloroform solution on a Perkin–Elmer polarimeter (type 241) using a 1-dm cell (*c* 0·54—0·76). The purity of the products was determined by TLC. Results of elemental analysis are given in Table III.

Methylation (General Procedure)

To 988 mg (0·002 mol) *I* or *II* in 20 ml acetone, methyl iodide (0·01 mol) was added and the reaction mixture was refluxed for ten days. Upon removal of the solvent and excess methyl

iodide, the crude reaction mixture was chromatographed on a column packed with Al_2O_3 (Fluka 506C — pH 6·0 ± 0·5, grade III). The thin-layer chromatography was conducted on glass plates coated with the alumina Woelm acid TLC. Two individual compounds were obtained from the $CHCl_3$: CH_3OH (99 : 1) fraction.

III: Pale yellow oil, yield 46·5%; ^{1}H NMR: 0·96 d, (C(1) —CH_3, C(1′)—CH_3), 1·00—3·00 m, 24 H, 2·23 s, 3 H (S—CH_3), 3·18 s, 2 H (—CH_2—S), 3·40 s, 3 H (N$^+$—CH_3), 5·12 m, 1 H (H-6e), 5·94 m, 1 H (H-4a), 6·02 br d, 1 H (C=CH), 6·32 m, 1 H (β-furanyl), 6·80 m, 1 H (β-furanyl) 7·50 m, 2 H (α-furanyl), 7·88 m, 1 H (α-furanyl), 8·00 m, 1 H (α-furanyl); TLC in benzene–ethyl acetate–1-propanol (1 : 1 : 0·5), R_F 0·26.

IV: Pale yellow oil, yield 27·5%; ^{1}H NMR: 1·00 d, 6 H (C(1)—CH_3, C(1′)—CH_3), 1·00 to 3·00 m, 24 H, 2·23 s, 3 H (S—CH_3), 3·10 s, 2 H (—CH_2—S), 3·40 s, 3 H (N$^+$—CH_3), 4·32 m, 1 H (H-6e), 5·95 m, (H-4a), 6·02 br d, 1 H (C=CH), 6·32 m, 1 H (β-furanyl), 6·88 m, 1 H (β-furanyl), 7·28 m, 1 H (α-furanyl), 7·62 m, 2 H (α-furanyl), 8·12 m, 1 H (α-furanyl); TLC (see above), R_F 0·30.

Hofmann Degradation (General Procedure)

To a solution of 0·001 mol methiodides *III* or *IV* 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.

TABLE III

Analytical data of compounds *III*— *VIII*

Compound	Formula (M.w.)	$[\alpha]_D^{25}$ *c*	Calculated/Found			
			% C	% H	% N	% I
III	$C_{32}H_{47}N_2O_2SI$	—	59·05	7·29	4·31	19·50
	(650·8)		58·92	7·20	4·42	19·68
IV	$C_{32}H_{47}N_2O_2SI$	—	59·05	7·29	4·31	19·50
	(650·8)		59·00	7·18	4·52	19·62
V	$C_{32}H_{46}N_2O_2S$	−119·7°	73·50	8·88	5·36	—
	(522·9)	0·56	73·56	8·96	5·30	
VI	$C_{32}H_{46}N_2O_2S$	−77°	73·50	8·88	5·36	—
	(522·9)	0·76	73·42	8·80	5·52	
VII	$C_{32}H_{46}N_2O_2S$	−80°	73·50	8·88	5·36	—
	(522·9)	0·63	73·36	8·68	5·50	
VIII	$C_{32}H_{46}N_2O_2S$	−141°	73·50	8·88	5·36	—
		0·54	73·38	8·66	5·42	

V: Colorless oil, yield 13·1%; ^{1}H NMR: 0·92 d, 6 H (C(1)—CH_3, C(1′)—CH_3), 1·00–2·80 m, 25 H, 2·00 s, 3 H (S—CH_3), 2·20 s, 3 H (N—CH_3), 5·54 m, 1 H (H-4), 6·00 br d, 1 H (H-8), 6·28 dd, 1 H (H-3, J = 14 Hz), 6·50 s, 2 H (β-furanyl), 7·34 m, 4 H (α-furanyl); MS (relative intensity): 522 (M^+; 6), 508 (5), 461 (2), 387 (24), 373 (10), 244 (100), 230 (63), 178 (7), 136 (6), 107 (25), 94 (29); TLC in benzene–chloroform (4 : 1) system, R_F 0·17.

VI: Colorless oil, yield 11·3%; ^{1}H NMR: 0·90 d, 6 H (C(1)—CH_3, C(1′)—CH_3), 1·00–2·80 m, 25 H, 2·12 s, 3 H (S—CH_3), 2·20 s, 3 H (N—CH_3), 5·48 m, 1 H (H-4), 6·00 br d, 1 H (H-8), 6·14 dd, 1 H (H-3, J = 15 Hz), 6·32 m, 1 H (β-furanyl), 6·54 m, 1 H (β-furanyl), 7·40 m, 4 H (α-furanyl); MS (relative intensity): 522 (M^+; 20), 508 (7), 461 (8), 387 (95), 373 (18), 244 (100), 230 (48), 178 (8), 136 (7), 107 (28), 94 (33); TLC (see above,) R_F 0·20.

VII: Colorless oil, yield 55·6%; ^{1}H NMR: 0·90 d, 6 H (C(1)—CH_3, C(1′)—CH_3), 1·00–3·00 m, 24 H, 2·00 s, 3 H (S—CH_3), 2·08 s, 3 H (N—CH_3), 5·08 d, 2 H (H-6, J = 15 Hz), 5·32 dd, 1 H (H-9, J = 13 Hz), 6·00 d, 1 H (H-8, J = 13 Hz), 6·34 s, 1 H (β-furanyl), 6·40 s, 1 H (β-furanyl), 7·50 m, 4 H (α-furanyl); MS (relative intensity): 522 (M^+; 2), 244 (3), 230 (8), 178 (3), 117 (8), 94 (6), 83 (100); TLC (see above), R_F 0·20.

VIII: Colorless oil, yield 53·6%; ^{1}H NMR: 0·94 d, 6 H (C(1)—CH_3, C(1′)—CH_3), 1·00 to 3·04 m, 24 H, 2·08 s, 3 H (S—CH_3), 2·14 s, 3 H (N—CH_3), 5·12 d, 2 H (H-6, J = 16 Hz), 5·42 dd, 1 H (H-9, J = 13 Hz), 6·05 d, 1 H (H-8, J = 13 Hz), 6·44 s, 1 H (β-furanyl), 6·56 s, 1 H (β-furanyl), 7·40 m, 4 H (α-furanyl); MS (relative intensity): 522 (M^+; 9), 475 (3), 461 (2), 387 (5), 276 (4), 244 (16), 230 (39), 107 (16), 94 (12), 85 (34), 57 (100); TLC (see above), R_F 0·24.

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