STRUCTURE AND STEREOCHEMISTRY OF SOME NEOTHIOBINUPHARIDINE METHIODIDES

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

Department of Chemistry, University of Warsaw, 1 Pasteur St. 02—093 Warsaw, Poland

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Quaternization of neothiobinupharidine was examined. The structure and stereochemistry of three methiodides were proposed on the basis of ^{13}C NMR and ^{1}H NMR spectroscopy and Hofmann degradation.

Compounds *II*, *III*, and *IV* obtained during the quaternization of neothiobinupharidine (*I*), were found to be: monomethiodide ($\overset{(+)}{N}5'$-CH_3)-*trans*-quinolizidine (*II*), monomethiodide ($\overset{(+)}{N}5$-CH_3)-*trans*-quinolizidine (*III*), and dimethiodide ($\overset{(+)}{N}5'$-CH_3, $\overset{(+)}{N}5$-CH_3)-*trans*-quinolizidine (*IV*). The criteria previously formulated for structural and stereochemical determinations of thiobinupharidine methiodide using ^{13}C NMR spectroscopy are shown to be applicable for the isomeric system of neothiobinupharidine methiodides.

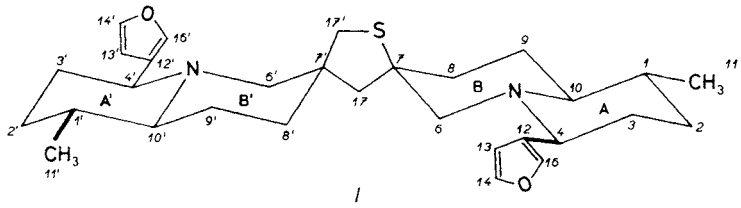
The structural and stereochemical changes occuring in the thiobinupharidine skeleton during the quaternization to methiodides have been followed by ^{13}C NMR spectroscopy and were previously described[1-3].

The aim of the present paper is to find further correlation between stereochemistry of the reaction and the stereochemistry of the spiro-tetrahydrothiophene ring in the individual free bases: thiobinupharidine, neothiobinupharidine (*I*), and thionuphlutine.

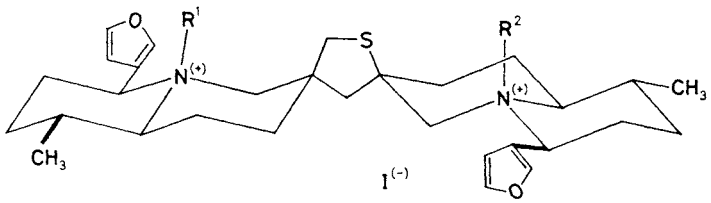
For that purpose quaternization of *I* was studied. This reaction leads to a mixture of products from which three methiodides were isolated. These compounds had chemical properties similar to those obtained by quaternization of thiobinupharidine, the reaction with resulted in derivatives of different type. Analysis of spectroscopic data (^{13}C NMR) obtained for methiodides *II*, *III*, and *IV*, and for products of their Hofmann degradation *V*, *VI*, and *VII* has demonstrated that the criteria of assigning the structure and stereochemistry are common both for thiobinupharidine and neothiobinupharidine methiodides.

RESULTS AND DISCUSSION

Compounds *II* – *VII* were studied by means of ^{13}C NMR resonance. For determining the order of particular carbon atoms the SFORD technique was used. The chemical shifts of particular carbon atoms are shown in Table I for methiodides *II*, *III*, and *IV* and in Table II for the products of Hofmann degradation *V*, *VI*, and *VII*.



I



II, $R^1 = CH_3$; $R^2 =$:
III, $R^1 =$:; $R^2 = CH_3$
IV, $R^1 = R^2 = CH_3$

The chemical shifts of carbon atoms α to nitrogen atom (in ^{13}C NMR) supplied important criteria for structure determinations of methiodiddes II, III, and IV. The paramagnetic chemical shifts for these carbon atoms, as compared with *I*, ref.[4], were as follows: in methiodide *II* in A'B' ring, in methiodide *III* in AB ring, and in methiodide *IV* in both A'B' and AB rings.

Three regions were recognized in the ^{13}C NMR spectra under study: a low-field region (signals of sp^2 carbon atoms >100 ppm), a middle-field region (80–55 ppm, signals of sp^3 carbon atoms α to nitrogen atom), and a high-field region (<55 ppm, signals of remaining sp^3 carbon atoms). Paramagnetic shifts in the low-field region were observed for carbon atoms of furan attached to: ring A'B' in compound *II* (for C(13'), C(14'), and C(16') c. 2 ppm); ring AB in compound *III* (for C(13), C(14), and C(16) c. 2 ppm); ring A'B' and AB in compound *IV* (for C(13'), C(14'), C(16'), C(13), C(14), C(16) c. 2 ppm). Signals of C(12') and/or C(12) were in all cases shifted diamagnetically (−12·2, −11·4 ppm). A similar character of the shifts was observed earlier[1] in thiobinupharidine methiodides. The middle-field region contains signals

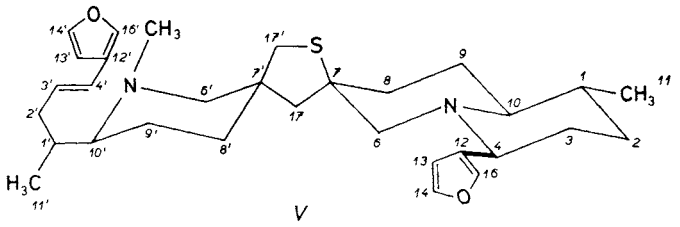
TABLE I

^{13}C chemical shifts of compound *I*–*IV*

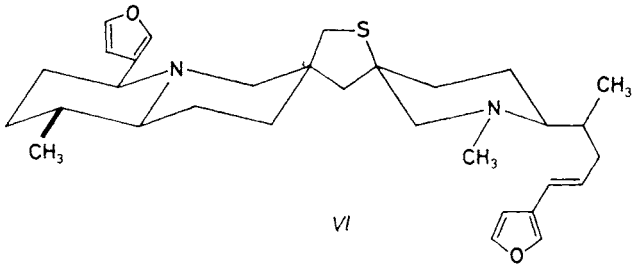
Atoms[a]	*I*[b]	*II*[b]	*III*[b]	*IV*[c]
1,1′	35·57[d], 36·15[d] (d, d)	36·24, 29·78[d] (d, d)	28·43, 35·85[d] (d, d)	31·64, 31·64 (d, d)
2,2′	33·77, 33·77 (t, t)	33·55, 31·42 (t, t)	31·38, 33·50 (t, t)	33·28, 33·28 (t, t)
3,3′	34·93, 35·80 (t, t)	35·86, 27·09 (t, t)	26·92, 35·20[d] (t, t)	28·44[d], 28·28[d] (t, t)
4,4′	60·24, 60·24 (d, d)	59·90, 68·01 (d, d)	70·82, 59·77 (d, d)	74·71, 75·04 (d, d)
6,6′	65·26, 63·05 (t, t)	64·62, 68·96 (t, t)	68·57, 62·16 (t, t)	71·57, 71·57 (t, t)
7,7′	57·08, 47·33 (s, s)	55·22, 46·08 (s, s)	53·36, 46·03 (s, s)	52·56, 43·30 (s, s)
8,8′	40·78, 36·52 (t, t)	40·62, 31·08 (t, t)	37·45, 36·54 (t, t)	38·09, 43·02 (t, t)
9,9′	28·16, 29·45 (t, t)	29·78[d], 21·58 (t, t)	22·02, 29·73 (t, t)	23·84, 22·97 (t, t)
10,10′	68·63, 69·29 (d, d)	69·61, 75·55 (d, d)	74·90, 69·39 (d, d)	79·70[e], 79·68[e] (d, d)
11,11′	19·12, 19·12 (q, q)	18·77, 18·94 (q, q)	18·68, 18·94 (q, q)	19·02, 19·02 (q, q)
12,12′	129·96, 130·06 (s, s)	129·25, 117·46 (s, s)	117·42, 129·43 (s, s)	118·36, 118·17 (s, s)
13,13′	109·65, 110·33 (d, d)	110·10, 110·88 (d, d)	109·27, 110·83 (d, d)	111·61, 111·45 (d, d)
14,14′	142·93, 143·31 (d, d)	144·12, 145·07 (d, d)	144·08, 145·07 (d, d)	146·77, 146·77 (d, d)
16,16′	139·51, 139·65 (d, d)	139·61, 142·56 (d, d)	143·04, 139·52 (d, d)	146·77, 146·77 (d, d)
17,17′	54·54, 39·14 (t, t)	54·40, 41·05 (t, t)	56·26, 41·35 (t, t)	59·87, 43·83 (t, t)
$N^{(+)}-CH_3$	—	38·32 (q)	37·64 (q)	40·69, 40·69 (q, q)

[a] In ppm from tetramethylsilane, s singlet, d doublet, t triplet, q quartet; [b] in C^2HCl_3; [c] in CF_3COO^2H (poorly soluble in chloroform); [d] assignments may be reversed; [e] one of these values can be assigned to C(10), the other to C(10′).

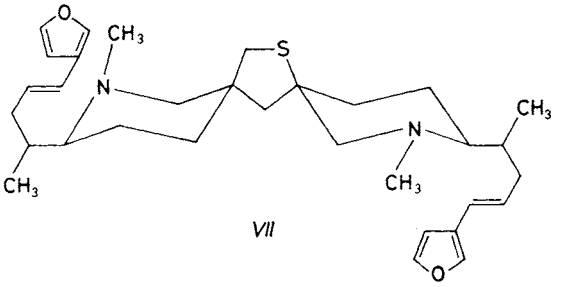
of carbon atoms α to nitrogen atom (C(10), C(10′), C(6), C(6′), C(4), C(4′)). Diagnostic atoms C(6) and C(6′) (secondary) in *I* demand special attention. They display different values of chemical shifts in the ^{13}C NMR spectra. The signal of C(6) (AB *trans*-quinolizidine ring) occurs at lower field (δ = 65·26 ppm) than the signal of C(6′) (A′B′ *trans*-quinolizidine ring) which is placed at δ = 63·05 ppm, ref.[4].



V



VI



VII

During the quaternization of the nitrogen atoms in *I*, the signals of C(6) or C(6′) (in non quaternized quinolizidine rings) showed almost the same values of chemical shifts as in *I*. In monomethiodide *II*, the signals of carbon atoms α to nitrogen atom in the A′B′ quinolizidine ring (*i.e.*, C(10′), C(6′), C(4′)) are subject to a paramagnetic shift. In monomethiodide *III* the signals of carbon atoms α to nitrogen atom in the AB quinolizidine ring (C(10), C(6), C(4)) display a paramagnetic effect. In dimethiodide *IV* the paramagnetic effect is exhibited by the signals of all carbon atoms α to nitrogen in the A′B′ and AB quinolizidine ring (Table III).

Similarly, in 7-epideoxynupharidine methiodide[1], characterized by *trans*-quinolizidine, the signals for carbon atoms α to nitrogen atom was shifted downfield relative to that of the spectrum of 7-epideoxynupharidine itself. The above data suggest that the conformation of the quinolizidine ring in *I* remains unchanged by quaternization

TABLE II

^{13}C chemical shifts of products of Hofmann degradation *V*— *VII* (in ppm from tetramethylsilane measured in C^2HCl_3)

Atoms	*V*		*VI*		*VII*	
1,1′	35·65,	33·54 (d, d)	33·70,	35·49 (d, d)	33·55,	33·55 (d, d)
2,2′	33·65,	38·09 (t, t)	38·14,	33·70 (t, t)	38·10,	38·10 (t, t)
3,3′	34·95,	120·28 (t, d)	120·34,	35·49 (d, t)	120·28,	120·28(d, d)
4,4′	60·09,	129·60 (d, d)	129·60,	60·14 (d, d)	129·51,	129·51 (d, d)
6,6′	65·07,	67·25 (t, t)	70·76,	62·60 (t, t)	70·65,	66·79 (t, t)
7,7′	56·78,	47·24 (s, s)	56·84,	47·41 (s, s)	56·65,	47·46 (s, s)
8,8′	40·91,	35·98 (t, t)	40·42,	36·46 (t, t)	40·68,	35·50 (t, t)
9,9′	29·37,	21·08 (t, t)	22·59,	29·12 (t, t)	21·15,	22·58 (t, t)
10,10′	67·24,	68·43 (d, d)	66·64,	69·13 (d, d)	66·58,	67·14 (d, d)
11,11′	19·07,	12·52 (q, q)	12·57,	19·07 (q, q)	12·53,	12·53 (q, q)
12,12′	129·60,	124·45 (s, s)	124·56,	129·60 (s, s)	124·44,	124·44 (s, s)
13,13′	109·99,	107·60 (d, d)	107·66,	109·39 (d, d)	107·58,	107·58 (d, d)
14,14′	142·60,	143·25 (d, d)	143·25,	142·98 (d, d)	143·21,	143·21 (d, d)
16,16′	139·35,	139·35 (d, d)	139·14,	139·53 (d, d)	139·35,	139·35 (d, d)
17,17′	54·50,	35·98 (t, t)	54·50,	39·17 (t, t)	54·44,	39·27 (t, t)
$N-CH_3$	43·07 (q)		43·18 (q)		40·08,	40·08 (q, q)

TABLE III

Quaternization increments (ppm) ($\Delta\delta = \delta(N^{(+)}-CH_3) - \delta(N)$) for *I* and methiodides *II*—*IV* (from tetramethylsilane)

Carbon atoms	*II*[a]	*III*[a]	*IV*[b]
4,4′	— +7·8	+10·6 —	+14·5, +14·8
6,6′	— +5·9	+3·3 —	+6.3, +8·5
10,10′	— +6·3	+6·3 —	+11·1, +10·6
$N^{(+)}-CH_3$[c]	— 38·32	37·64 —	40·69, 40·69

[a] In C^2HCl_3; [b] in CF_3COO^2H; [c] ^{13}C chemical shift.

and that structures of methiodides correspond to A'B' *trans II*, AB *trans III* and A'B' *trans*, AB *trans IV*.

In the high-field region of the *II*, *III*, and *IV* spectra, signals for carbon atoms β and γ (except for C(17) and C(17') of spiro-tetrahydrothiophene ring), were found to be shifted towards higher field. The character of the signals and the values of chemical shifts for atoms C(8) (methiodide *II*) and C(8') (methiodide *III*) is the same as in *I*. Thus the spiro-ring in these methiodides (compared with certain thiobinupharidine methiodides[1]) does not undergo deformation.

The N-methyl groups are also diagnostic for the determination of configuration of quinolizidine rings. In methiodides *II*, *III*, and *IV*, the values of the chemical shifts of N-methyl groups are similar to the value of the chemical shift of the N--methyl group in 7-epideoxynupharidine methiodide (*trans*-quinolizidine)[1].

Further evidence for the structures of *II*, *III*, and *IV* was obtained by a study of products of the Hofmann degradation of these methiodides. In each case, as expected, the methylated side of the molecule underwent degradation. Three products *V*, *VI*, and *VII* were characterized by ^{13}C NMR (Table II), ^{1}H NMR, and mass spectra.

Compound *V*, formed from *II* by the cleavage of the N–C(4') bond, has a *trans*--double bond between atoms C(3') and C(4'): ^{1}H NMR δ(ppm): 6·00 m 1 H, H-3'; 6·30 d 1 H, $J_{H-3',H-4'} = 16$ Hz. ^{13}C NMR δ(ppm): 120·28 d C(3'), 129·60 d C(4'). Mass spectrum: $m/z = 508$ (M^+). Signals of carbon atoms of the AB quinolizidine ring in the ^{13}C NMR spectrum were similar to those of *I*. Product *VI* obtained from *III* by the cleavage of the N–C(4) bond contains a *trans*-double bond between C(3)–C(4). The analogy of spectra data obtained for *V* and *VI* indicated that in the latter case the degradation had involved the AB ring (*cf.* Table II). Compound *VII*, the product of Hofmann degradation of dimethiodide *IV*, has double bonds between C(3')–C(4') and C(3)–C(4), formed by the cleavage of the N–C(4') and N–C(4) bonds, respectively. All the spectral data concerning rings A'B' and AB were similar to those obtained for *V* and *VI*. This shows that both quinolizidine ring A'B' and AB were degraded.

The N-methyl group of the piperidine ring formed in the course of the reaction is in equatorial conformation in all degradation products[5,6].

The data described above support the general diagnostic value of ^{13}C NMR spectroscopy in structural and stereochemical determinations of S-nuphar alkaloids methiodides.

For structure and stereochemistry determination of N-substituted quinolizidine ring, carbon atoms α to nitrogen, carbon atom of $\overset{(+)}{N}-CH_3$ group and atom C(17) were diagnostic.

The criteria formulted[1] for thiobinupharidine methiodides have now been extended to include determination of the structure and stereochemistry of neothiobinupharidine methiodides.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a JEOL 100 MHz spectrometer in C^2HCl_3 and ^{13}C NMR spectra on a JEOL FX 90Q spectrometer in C^2HCl_3 or CF_3COO^2H (for *IV*) using tetramethylsilane 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.

Quaternization of *I*

To 988 mg (0·02 mol) *I* in 20 cm^3 acetone, methyl iodide (0·1 mol) was added and the mixture was refluxed for ten days. Upon removal of the solvent and excess methyl iodide, the mixture was chromatographed on a column packed with Al_2O_3 (Fluka 506 C, pH 6·0 ± 0·5, grade III). Thin-layer chromatography was conducted on glass plates coated with the alumina Woelm acid TLC. Two individual compounds were obtained from the $CHCl_3$ fraction *viz.*: *II*, 188 mg, 19% yield, yellow oil; ^{1}H NMR spectrum, C^2HCl_3 δ(ppm): 0·92 (d 6 H C(1)—CH_3, C(1′)—CH_3), 1·20–3·40 (m 27 H), 3·05 (s 3 $HN^{(+)}$—CH_3), 4·18 (m 1 H C(10′)—H), 4·75 (m 1 H C(6′)—H), 5·74 (m 1 H C(4′)—H), 6·62 (s 1 H β-furanyl), 6·68 (s 1 H β-furanyl), 7·48 (m 2 H α-furanyl), 7·60 (m 1 H α-furanyl), 8·18 (m 1 H α-furanyl). *III*, 188 mg, 19% yield, yellow oil; ^{1}H NMR spectrum, C^2HCl_3 δ(ppm) 0·93 (d 6 H C(1)—CH_3, C(1′)—CH_3), 1·20–3·20 (m 27 H), 3·06 (s 3 $HN^{(+)}$—CH_3), 4·20 (m 1 H C(10)—H), 5·02 (m 1 H C(6)—H), 5·75 (m 1 H C(4)—H), 6·45 (s 1 H β-furanyl), 6·78 (s 1 H β-furanyl), 7·42 (m 2 H α-furanyl), 7·62 (m 1 H α-furanyl), 8·22 (m 1 H α-furanyl). From the $CHCl_3$–CH_3OH (97 : 3) fraction compound *IV* was obtained: 62 mg, 6% yield, m.p. 226–228°C from methanol–aceton; ^{1}H NMR spectrum, C^2HCl_3 δ(ppm): 0·92 (d 6 H C(1)—CH_3, C(1′)—CH_3), 1·16–3·30 (m 24 H), 3·05 (s 3 $HN^{(+)}$—CH_3), 3·12 (s 3 $HN^{(+)}$—CH_3), 4·20 (m 2 H C(10)—H, C(10′)—H), 4·80–5·00 (m 2 H C(6)—H, C(6′)—H), 5·82 (m 2 H C(4)—H, C(4′)—H), 6·60 (s 2 H β-furanyl), 7·64 (m 2 H α-furanyl), 8·10 (m 2 H α-furanyl). TLC (alumina Woelm acid TLC) in a C_6H_6–ethyl acetate–propanol (1 : 1 : 0·5): *II* R_F = 0·44, *III* R_F = 0·40, *IV* R_F = 0·03; in a C_6H_6–ethyl acetate–propanol (1 : 1 : 1): *IV* R_F = = 0·28.

Hofmann degradation

To a solution of 0·5 mmol methiodides *II*, *III* or *IV* in 5 ml 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 (5 g), water (5 ml) and methanol (5 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 (Fluka 506 C, grade III) using benzene as eluent. *V*, yield 30%, m.p. 119–121°C (acetone), TLC (alumina oxide) C_6H_6–$CHCl_3$ (1 : 1) R_F = 0·38; $[\alpha]_D^{25}$ = −155°; ^{1}H NMR spectrum, C^2HCl_3 δ(ppm): 0·90 (d 6 H C(1)—CH_3, C(1′)—CH_3, 1·00–2·10 (m 23 H), 2·18 (s 3 $HN^{(+)}$—CH_3), 2·60–3·10 (m 4 H S—CH_2, C(6′)—He, C(6)—He), 6·00 (m 1 H C(3′)—H), 6·30 (d 1 H $J_{H-3',H-4'}$ = 16 Hz C(4′)—H), 6·42 (s 1 H β-furanyl), 6·58 (s 1 H β-furanyl), 7·42 (m 4 H α-furanyl); mass spectrum *m/z* (relative intensity): 508 (M^+, 15), 400 (3), 373 (100), 230 (15), 192 (6), 178 (8), 110 (5), 107 (13), 94 (10), 81 (8). *VI*, yield 30%, oil, TLC (alumina oxide) C_6H_6–$CHCl_3$ (1 : 1) R_f = 0·32; $[\alpha]_D^{25}$ = −77°; ^{1}H NMR spectrum, C^2HCl_3 δ(ppm): 0·88 (d 6 H C(1)—CH_3, C(1′)—CH_3), 1·00–2·10 (m 23 H), 2·18 (s 3 H N—CH_3), 2·60–3·10 (m 4 H S—CH_2, C(6′)—He, C(6)—He), 6·00 (m 1 H C(3)—H), 6·30 (d 1 H $H_{H-3,H-4}$ = 16 Hz C(4)—H), 6·40 (s 1 H β-furanyl), 6·58 (s 1 H β-furanyl), 7·40 (m 4 H α-furanyl); mass spectrum, *m/z* (relative intensity): 508 (M^+, 15), 400 (5), 373 (100), 316 (8),

243 (2), 230 (25), 178 (33), 110 (8), 107 (16), 94 (14), 81 (8). *VII*, yield 58%, oil, TLC (alumina oxide) C_6H_6–$CHCl_3$ (1 : 1) $R_F = 0{\cdot}53$; $[\alpha]_D^{25} = -82°$; ^{1}H NMR spectrum, C^2HCl_3 δ(ppm): 0·90 (d 6 H C(1)—CH_3, C(1′)—CH_3), 1·00–2·10 (m 20 H), 2·18 (s 6 H 2 × $N^{(+)}$—CH_3), 2·60–310 (m 4 H S—CH_2, C(6′)—He, C(6)—He), 6·00 (m 2 H C(3′)—H, C(3)—H), 6·30 (d 2 H $J_{H-3',H-4'} = J_{H-3,H-4} = 16$ Hz C(4′)—H, C(4)—H), 6·58 (s 2 H β-furanyl), 7·42 (m 4 H α-furanyl); mass spectrum, *m/z* (relative intensity): 522 (M^+, 11), 508 (4), 387 (100), 373 (22), 230 (10), 192 (5), 107 (18), 94 (8).

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