N-Quaternary Compounds. Part LIV.* Isomerization by Flash Vacuum Pyrolysis

TORE LAERUM, TOR OTTERSEN and KJELL UNDHEIM

Department of Chemistry, University of Oslo, Oslo 3, Norway

Vacuum pyrolysis in a quartz tube at 400 °C of a dihydrothiazolo[3,2-a]pyridinium-8-olate has yielded four isomeric products. Another major product is formed from dimerisation and successive elimination reactions; the structure of this product has been verified by X-ray crystallographic structure determination.

Pyridine betaines in the vacuum of the mass spectrometer may be volatilised structurally unchanged or may initially undergo chemical transformations to uncharged volatile products; the predominant pathways depend largely on the structure of the betaine.[2] In particular,

the dihydrothiazolo[3,2-a]pyridinium-8-olate 1 is volatilised as such in the mass spectrometer.[2] Photolysis of 1 at 350 nm, however, led to rearrangements and formation of 8-methyl-dihydrothiazolo[3,2-a]pyridin-5-one 3;[3] the net outcome of the reaction is an interchange of the 5- and 8-substituents and the reaction proceeds via the valence isomeric structure 6-methyl-2-thia-5-azatricyclo[4,3,0,0¹,⁵]non-7-en-9-one 2.[3] This report describes attempts to isomerise 1 at low pressure (0.01 Torr) in the gas phase when 1 is exposed to high temperature (400 °C) for a short time. In an initial experiment it was found that 1 could be sublimed structurally unchanged at 230 °C and

* Part LIII, Ref. 1.
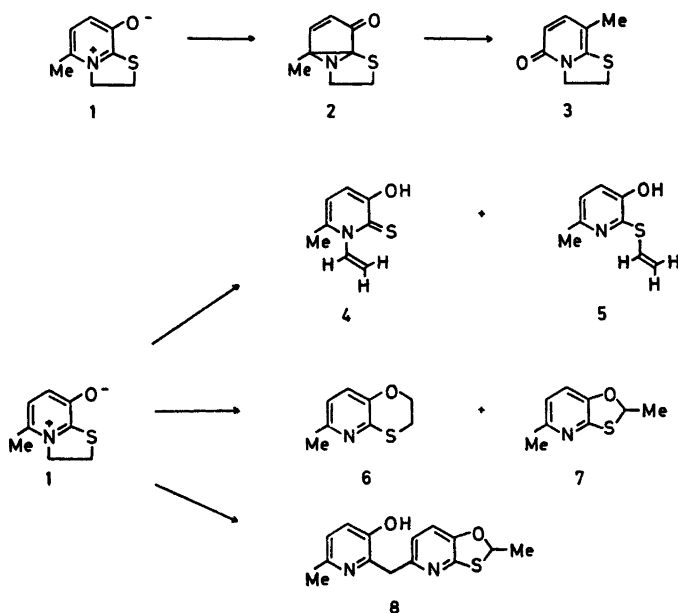
Scheme 1.

0.01 Torr. When the betaine vapour molecules, however, were passed through a narrow quartz tube enclosed by an oven at 400 °C, the product which was condensed in the tube outside the hot zone had no salt-like character.

TLC in EtOAc − benzene (1:1) gave two major spots at R_F 0.2 and 0.5 and the corresponding products were separately isolated by thick-layer chromatography. The product with the higher R_F value has been shown by TLC, GLC, MS and NMR to consist of structural isomers of *1*; *viz.* the *N*- and *S*-vinyl derivatives *4*[1] and *5*,[1] and the bicyclic structures *6*[4] and *7*. The assignment of the structures *4−6* has been verified by comparison with authentic specimens. The mass spectrum of the fourth component had molecular ion at *m/e* 167 (C_8H_9NOS) as base peak. NMR showed the presence of a new methyl group which was split by coupling with an adjacent methine proton. No methylene protons were present whereas the pyridine ring and substituents were not changed. Hence the compound was assigned

the oxathiolo[4,5-*b*]pyridin structure *7*. In order to confirm the structure assigned a separate and unambiguous synthesis of an authentic specimen of *7* has been worked out.[5]

The chromatographic band at $R_F \sim 0.2$ consisted of one major component. The base peak in the mass spectrum was the molecular ion at *m/e* 274 ($C_{14}H_{14}N_2O_2S$). The NMR spectrum contained four β,γ-pyridine protons at 6.7−7.1, one methyl group with protons coupled to an adjacent methine carbon (δ 1.75 and 6.1) as in *7*, a singlet for a methyl group at δ 2.35 and a singlet for two protons at δ 4.10. The data are consistent with structure *8* which was assigned unambiguously to the product by X-ray structure determination. A view of the molecule is given in Fig. 1. The molecular parameters are all normal within their estimated standard deviations except for the $C(2)-C(8)$ bond, which is very short, probably caused by large thermal vibrations. The angle between the two ring systems is 104.7°. The dihedral angles $C(5)-C(9)-C(2')-C(3')$
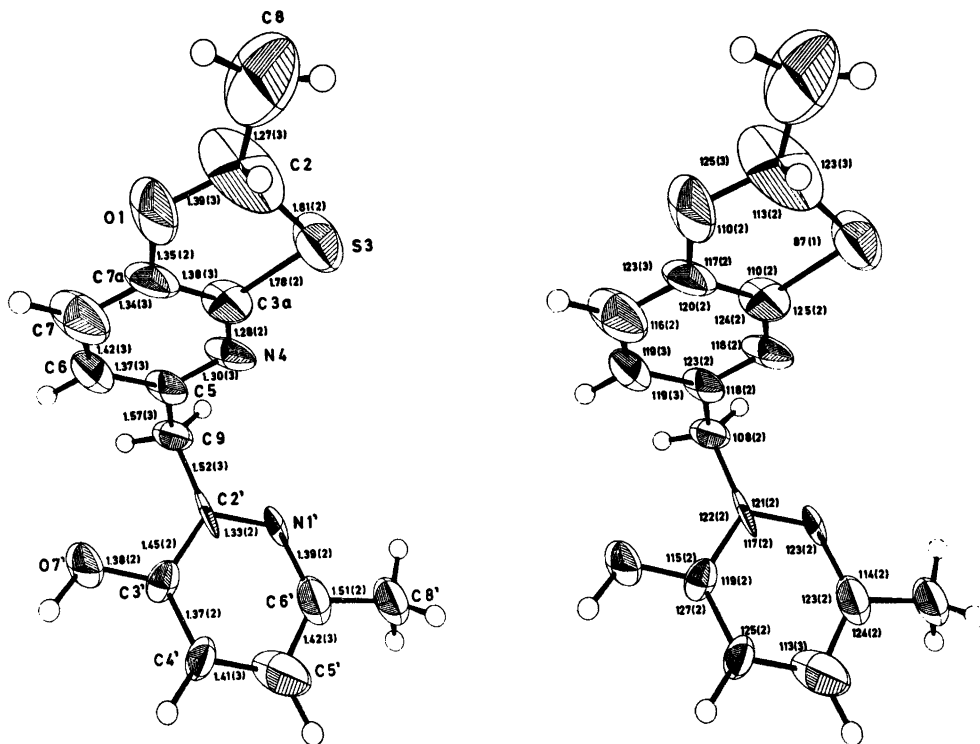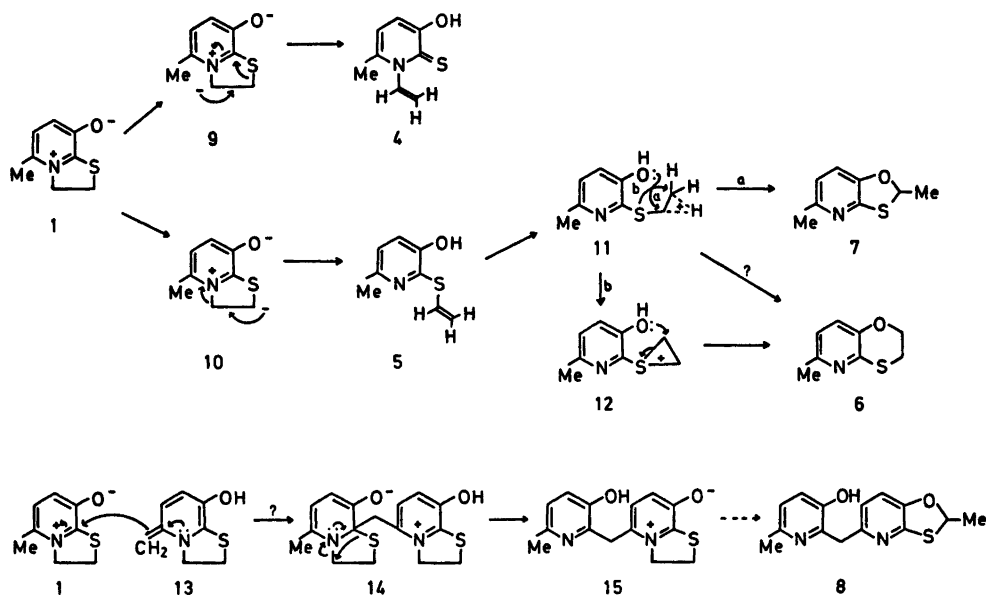

Fig. 1. Molecular geometry with bond lengths (Å) and bond angles (°).

Scheme 2.

and C(5)−C(9)−C(2′)−N(1′) are 79.4 and −101.0°, respectively, defining angles as positive in a right hand screw. N(1′)−O(7′) has an intermolecular hydrogen bond of 2.70 Å.

The percentage relative yields of products analysed by GLC on the crude reaction mixture were 23 (*4*), 18 (*5*), 4 (*6*), 29 (*7*) and 26 (*8*). Formation of the *N*- and *S*-vinyl isomers *4* and *5* can be rationalized by initial loss of a proton from C-2 or C-3 respectively. The deprotonation can occur either on the hot glass surface or by intermolecular deprotonation reactions in the gas phase. The formation of the bicyclic structures *6* and *7* are further rationalized by cyclisation of the *S*-vinyl isomer *5*. Initial protonation of the β-vinyl carbon atom is expected in the vinyl thioether *5*. Successive intramolecular addition of the oxygen nucleophile to the α-carbon results in the formation of *7*. The formation of *6* could possibly be explained by a reversal of the reaction order; alternatively protonation is accompanied by neighbouring group participation from the sulfur and ring opening of an episulfonium like intermediate *12* by the oxygen nucleophile. It thus appears that *S*-vinyl formation rather than *N*-vinyl formation is favoured by flash pyrolysis; in basic solution the predominant product is the *N*-vinyl isomer.[1]

The pathway to the condensed product *8* could possibly be initiated by a reaction between *7* and *1*. Due to the higher activation of the methyl group in *1* than in *7*, however, it seems more likely that it is the methylene isomer *13* which starts the reaction by nucleophilic substitution of the thio group as indicated in Scheme 2.

EXPERIMENTAL

Pyrolysis of 5-methyldihydrothiazolo[3,2-a]-pyridinium-8-olate 1. The apparatus was constructed from a flask (5 ml) which was connected to a quartz glass tube (1.45 cm, i.d. 4 mm) and further to a cold-trap and a vacuum pump. The quartz tube was held in a horizontal position and was enclosed by a heating mantle (length 20 cm) close to the reaction flask.

The betaine *1* (200 mg) was charged into the flask and the apparatus evacuated to 0.01 Torr. The heating mantle was operated at 400 °C. The flask was rapidly heated to 230 °C and kept at this temperature until all the compound had sublimed. The yellowish-white products condensed on the walls of the tube outside the hot zone of the oven. TLC on silica gel (EtOAc − benzene 1:1) of this product gave 2 major spots at R_F 0.2 and 0.5. The major products in these spots were isolated by thick-layer chromatography on silica gel (Merck PF 254, 2 mm thick-layer, plates 20 cm

× 20 cm) using the same developer. The desired bands were scraped off from the plate and extracted with methanol. The solutions were evaporated and the residues dissolved in chloroform to remove the silica which had been dissolved in methanol; methanol was used for the initial extraction to effect a more quantitative elution of the products from the siliga gel than was the case using chloroform. Evaporation of the chloroform solution left 77 mg of products from the faster moving band and 28 mg from the slower moving band. The compositions of the products from each band were further analysed by GLC and GLC-MS.

The GLC was run on a Varian-3700 instrument equipped with flame ionisation detectors and integrator. A column of 3 % SE-30 on Supelcoport 80 − 100 mesh (2 mm i.d. × 1.8 m) was used; flow rate 25 ml nitrogen per min. The injector and detector were at 250 °C. The samples were injected isothermally at 100 °C. After 1 min the instrument was programmed to + 10 °C/min until a temperature of 230 °C. Alternatively a GLC-instrument as above was connected to a mass spectrometer. Three of the components in the major product group have been identified from retention times and fragmention patterns, which included comparisons with authentic specimens, such as N-vinyl-3-hydroxy-6-methylpyridine-2-thione[1] 4, 2-vinylthio-3-hydroxy-6-methylpyridine[1] 5 and 6-methyl-2,3-dihydro[1,4]oxathieno[3,2-b]-pyridine[4] 6. The fourth component of the mixture was isolated by preparative GLC and has been identified as 2,5-dimethyl-[1,3]oxathiolo-[4,5-b]pyridine[5] 7; almost colourless liquid. ¹H NMR (CDCl₃) : δ 1.75 (2-Me, d, J 6 Hz), 2.30 (5-Me, s), 6.15 (2-H, q), 6.65 and 6.80 (2H-Pyr., AB, J 8 Hz). UV (0.1 M NaOH/EtOH, log ε): 315 (3.94), 243 (3.71) nm; (0.1 M HCl/EtOH): 344 (4.00), 247 (3.57) nm. MS [70 eV, m/e (% rel. int.)]: 167 (100, M), 166 (50), 152 (90), 141 (9), 139 (2), 138 (6), 134 (11).

2-Methyl-5-(3-hydroxy-6-methylpyridin-2-yl)-methyl-[1,3]oxathiolo[4,5-b]pyridine 8. The product with R_F 0.2 after preparative TLC was further purified by recrystallization from acetone: hexane, m.p. 159 − 162 °C. Anal. C₁₄H₁₄-N₂O₂S: C, H. ¹H NMR (CDCl₃): δ 1.75 (2-Me, d, J 6 Hz), 2.35 (6'-Me, s), 4.10 (5-CH₂, s), 6.1 (2H, q), 6.7-7.1 (4H-Pyr.), ca. 10.5 (3'-OH). UV (0.1 M NaOH/EtOH, log ε) 320 (4.15), 243 (4.05) nm; (0.1 M HCl/EtOH): 305 (4.00) nm. MS [70 eV, m/e (% rel. int.)]: 274 (C₁₄H₁₄N₂O₂S, 100, M), 257 (11, M-OH), 241 (11, M-SH), 185 (7, M-C₃H₄OS), 152 (27, M-C₇H₈NO).

X-Ray analysis of 2-methyl-5-(3-hydroxy-6-methylpyridin-2-yl)-methyl-[1,3]oxathiolo[4,5-b] pyridine 8. C₁₄H₁₄N₂O₂S, M = 274.35 amu, space group Pna2₁, a = 11.568 (10) Å, b = 4.794 (2) Å, c = 24.606 (22) Å, V = 1364.6 (19) Å³, Z = 4, D_calc = 1.386 g/cm³, F(000) = 576.

Structure determination. Oscillation and Weissenberg photographs indicated orthorhombic symmetry. The systematically absent reflections

were those characteristic of the space groups Pna2₁, and Pnma. The later structure determination showed the space group to be the noncentrosymmetric Pna2₁.

A computer-controlled Syntex P1̄ four circle diffractometer with graphite-monochromatized MoKα radiation was utilized in the determination of cell parameters and the collection of intensity data. The work was carried out using a plate-formed crystal of approximate dimensions 0.4 × 0.3 × 0.05 mm.

The intensity data were collected using the ω-scanning mode with scan-speed variable from 1 to 8° min⁻¹ depending on the peak intensity of the reflections. Scan area was 1.0° (ω) and background counts were taken for 0.35 (scan time) 1.0° at each side of the scan midpoint. The intensities of three standard reflections which were remeasured after every 57 reflections, showed no significant variations.

Estimated standard deviations were calculated as

$$\tau(I) = \left\{ \left[I_{int} + (B_1 + B_2)\left(\frac{\text{scan time}}{2 \times (\text{background time})}\right) \right] \times (\text{scan rate})^2 + (0.02\, I_{net})^2 \right\}^{\frac{1}{2}}$$

where $I_{net} = \left(I_{int} - (B_1 + B_2) \times \frac{\text{scan time}}{2 \times (\text{background time})} \right)$ (scan rate).

Of the 1176 reflections measured ($2\theta_{max} = 45°$), 444 had intensities greater than twice their standard deviations. These were regarded as observed reflections and the remaining were excluded from further calculations. The intensities were corrected for Lorentz and polarization effects.[6] The computer program used as well as programs subsequently employed, is part of a local library.[6] The atomic scattering factors for carbon, nitrogen, oxygen and sulfur,[7] and for hydrogen[8] were available in the literature.

The phase problem was solved by direct methods utilizing the MULTAN-77 program assembly.[9] 16 of the 22 highest peaks could be used. The last three were found by successive Fourier refinements.

The structure model was refined to an R-factor of 0.11. Introduction of anisotropic thermal parameters for all nonhydrogen atoms and least-squares refinements converged to an R of 0.086 and a weighted R_w of 0.064.

The hydrogen atoms were then placed in calculated positions and included in the structure factor calculations. Final full-matrix least-squares refinement converged to R = 0.068 and an $R_w = 0.051$.

Atomic parameters are given in Table 1. A list of observed and calculated structure

Table 1. Fractional atomic coordinates and thermal parameters for nonhydrogen atoms. The anisotropic temperature factor is given by exp {-2π²[$u_{11}(a^*h)^2 + u_{22}(b^*k)^2 + u_{33}(c^*l)^2 + 2u_{12}(a^*b^*hk) + 2u_{13}(a^*c^*hl) + 2u_{23}(b^*c^*kl)$]}. Estimated standard deviations in parentheses.

Atom	x	y	z	u_{11}	u_{22}	u_{33}	u_{12}	u_{13}	u_{23}
O1	.1880(12)	−.0019(7)	.7056(73)	.039(9)	.237(28)	.075(13)	−.048(14)	−.022(9)	.005(17)
C2	.2965(32)	−.0068(10)	.8274(130)	.171(32)	.522(98)	.042(17)	−.178(48)	−.004(21)	.135(38)
S3	.3672(5)	.0582(2)	.8731(56)	.070(4)	.116(7)	.065(4)	−.039(6)	−.044(4)	.025(6)
C3a	.2651(19)	.0846(8)	.6304(74)	.053(15)	.107(28)	.024(12)	−.005(16)	−.007(12)	.022(15)
N4	.2675(14)	.1323(6)	.5243(0)	.018(11)	.140(25)	.035(13)	.019(13)	.000(8)	.001(14)
C5	.1845(18)	.1463(8)	.3563(91)	.047(16)	.090(22)	.042(14)	.019(16)	−.003(11)	.001(19)
C6	.0969(18)	.1116(10)	.2811(89)	.040(13)	.131(36)	.064(16)	−.030(17)	.020(14)	−.008(19)
C7	.0913(17)	.0595(11)	.4079(104)	.051(15)	.190(36)	.065(18)	.011(26)	−.001(13)	.029(27)
C7a	.1779(21)	.0473(9)	.5823(88)	.039(13)	.160(32)	.027(16)	.017(19)	.015(12)	.007(18)
C9	.1922(15)	.2030(9)	.2088(70)	.017(9)	.069(20)	.044(12)	−.008(14)	.012(11)	−.004(15)
N1'	.2423(12)	.2753(7)	.5496(61)	.019(12)	.005(13)	.089(14)	−.003(10)	.010(10)	.005(12)
C2'	.1611(15)	.2462(7)	.4228(86)	.047(16)	.088(25)	.037(13)	−.034(15)	−.007(11)	.027(17)
C3'	.0417(17)	.2577(8)	.4956(73)	.035(14)	.019(18)	.052(16)	−.004(13)	−.011(12)	−.005(13)
C4'	.0200(17)	.2949(9)	.7009(73)	.051(15)	.055(20)	.077(15)	.004(15)	−.019(13)	−.036(17)
C5'	.1046(17)	.3241(8)	.8489(107)	.051(15)	.135(28)	.060(14)	.020(24)	.008(12)	−.010(23)
C6'	.2180(15)	.3144(7)	.7491(65)	.040(15)	.001(19)	.038(13)	.017(12)	.001(10)	.008(11)
O7'	−.0392(9)	.2275(4)	.3505(68)	.026(8)	.128(15)	.058(8)	.004(13)	−.013(7)	−.018(13)
C8'	.3234(17)	.3437(8)	.8564(95)	.053(13)	.118(28)	.069(16)	−.043(21)	.012(11)	−.029(23)
C8	.3447(27)	−.0514(12)	.8923(133)	.185(32)	.310(53)	.097(19)	−.095(43)	−.070(27)	.006(41)

factors, as well as a list of the hydrogen parameters used, are available upon request from: Department of Chemistry, University of Oslo, Oslo 3, Norway.

REFERENCES

1. Ulsaker, G. A., Breivik, H. and Undheim, K. *J. Chem. Soc. Perkin Trans. 1. In press.*
2. Hurum, T., Ulsaker, G. A. and Undheim, K. *Acta Chem. Scand. B 29* (1975) 1043, and references therein.
3. Laerum, T. and Undheim, K. *J. Chem. Soc. Perkin Trans. 1. In press.*
4. Undheim, K. and Hurum, T. *Acta Chem. Scand. 26* (1972) 1727.
5. Laerum, T., Ulsaker, G. A. and Undheim, K. *To be published.*
6. Groth, P. *Acta Chem. Scand. 27* (1973) 1837.
7. Doyle, P. A. and Turner, P. S. *Acta Crystallogr. A 24* (1968) 390.
8. Stewart, R. F., Davidson, E. R. and Simpson, T. *J. Chem. Phys. 42* (1965) 3175.
9. Germain, G., Main, P. and Woolfson, M. M. *Acta Crystallogr. A 27* (1971) 368.