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β-Oxo-Sulfoxide Rearrangements under Sila-Pummerer Reaction Conditions

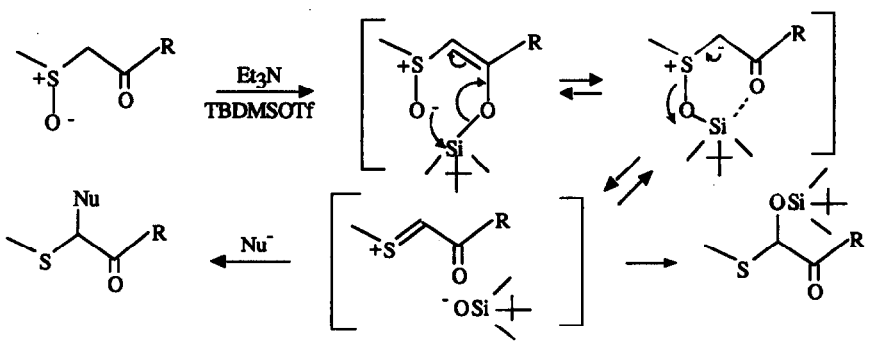
Martial Dardaine, Angèle Chiaroni, Claude Riche, Nicole Langlois*

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France

Key-Words : 1-ethyl 1-(methylsulfinyl) acetyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-a]quinolizine, trialkylsilyltrifluoromethane sulfonate, X-ray analysis.

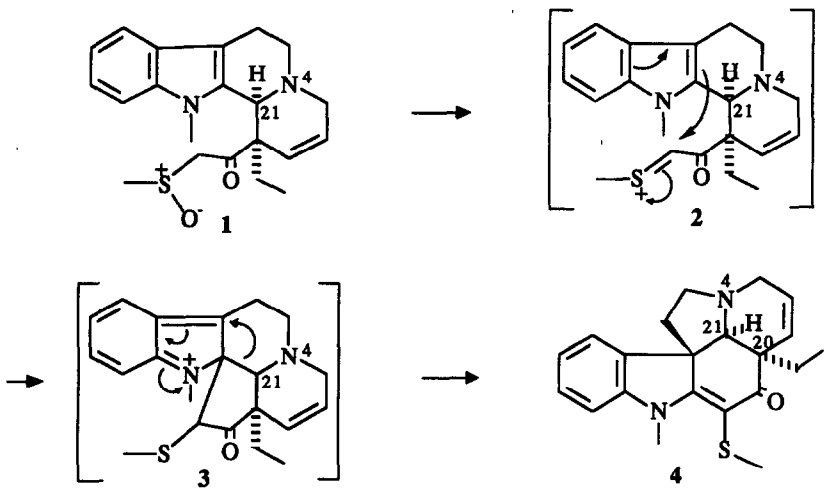
Abstract : Under sila-Pummerer reaction conditions, the β-oxo-sulfoxide 1 gave rise to a new pentacyclic compound 5. The structure of 5 was deduced from spectral data and by X-ray analysis of the sulfoxide 6 which was formed by subsequent oxidation.

Ketene silyl acetals[1-3] or trialkylsilyl trifluoromethanesulfonates[4-6] are known to induce Pummerer-type reactions in mild conditions[7] (scheme 1). We applied these reactions to the octahydro indolo[2,3-a]quinolizine **1** in order to perform its intramolecular rearrangement to the aspidospermane derivative **4** (scheme 2).[8]



Scheme 1

1-Ethoxy-1-trimethylsiloxypropene as silicon reagent and zinc iodide as catalyst were not efficient in this skeletal rearrangement, as they gave rise to **4** only in low yield. When the reaction was carried out in the presence of *t*-butyldimethylsilyl trifluoromethanesulfonate (1.3 equiv.) and triethylamine (1.3 equiv.) in dichloromethane at 0°C, product **4** was obtained in 30% yield after 4 hours, together with unreacted β-oxo-sulfoxide **1** (25%). The extension of the reaction time and the use of a larger excess of reagents, or of diisopropylethylamine[6] as base, did not significantly modify the results. In all cases a new more polar

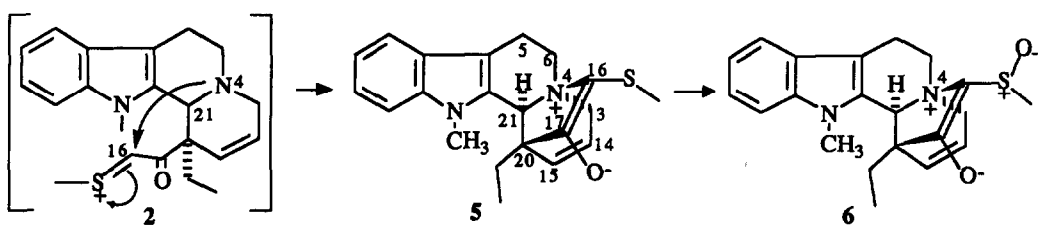


Scheme 2

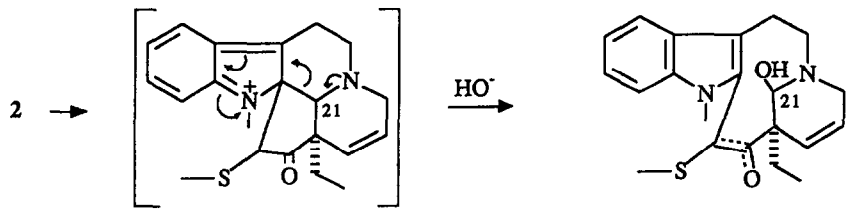
compound **5** was also isolated (c.a. 18%).[9] In order to attempt to minimize this side-reaction, it was necessary to identify product **5**.

The mass spectrum (EIMS) of **5** showed the highest peak at m/z 352 ($C_{21}H_{24}N_2OS$ by HRMS) and the base peak at m/z 305 ($C_{20}H_{21}N_2O$) is formed by the lost of a thiomethyl group ; the molecular peak was further confirmed by CIMS (isobutane) : $[M+H]^+$ at m/z =353. The UV of **5** is typical for an indolic chromophore. The carbonyl absorption at 1700 cm^{-1} in the IR of starting compound **1** disappeared almost completely in **5**, suggesting an enolization of the ketone ; the occurrence of two quaternary carbons signals in the ^{13}C NMR at 179.7 and 88.8 ppm is consistent with this hypothesis. In the HETCOR[10] experiment, the correlation between a methyl carbon at 17.2 ppm and the three proton singlet at 2.05 ppm was attributed to the thiomethyl group ; the methine carbon at 73.6 ppm was correlated with the resonance of a one proton singlet at 5.04 ppm which could be attributed to the proton in position α to N-4 (C-21-H).

On the basis of these data, several mechanisms for the formation of this new compound can be formulated, depending on the nucleophile involved. The basic nitrogen N-4, which is very close to the C-16 carbon, is a likely candidate to perform a nucleophilic attack on the thionium ion **2** or its equivalent. This should give rise to a quaternary ammonium intermediate as outlined in scheme 3. The high chemical shift observed for the proton C-21-H is compatible with this hypothesis, but also with the alternative hypothetical carbinolamine structure **7**, the formation of which could be explained by scheme 4.



Scheme 3



3 7

Scheme 4

The structure of compound **5** was unambiguously resolved by X-ray analysis. A monocrystal, obtained by several crystallizations in acetonitrile, was introduced with the solvent in a capillary in order to avoid its decomposition.

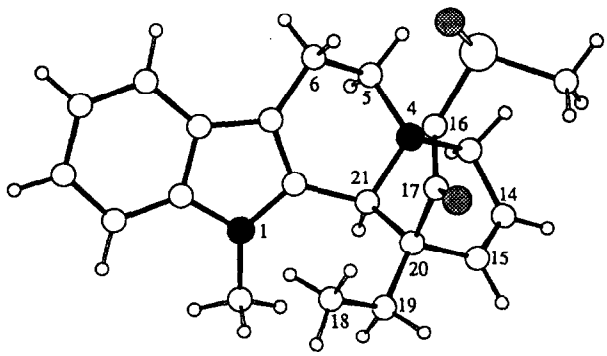


Fig. : A perspective view of the sulfoxide **6**

This X-ray analysis established fully the structure of the sulfoxide **6** (Fig.) and therefore confirmed that the nitrogen (N-4) was the nucleophile in this silicon induced-Pummerer rearrangement. The unexpected presence of the oxygen sulfur bond could be explained by the oxidation of the methyl sulfide moiety after the cyclization step. In order to verify this point, a new sample of compound **5** was submitted to three successive crystallizations in acetonitrile and the product was analyzed in FAB mass spectrometry. The observation of the highest peak at m/z 369, which was absent in the FABMS of the freshly purified **5**, indicated that indeed an oxidation occurred at sulfur during the crystallization steps.[11]

In the synthesis of vindorosine[8a], the aspidospermane derivative **4** was prepared by *p*-toluenesulfonic acid-induced Pummerer rearrangement of β-oxo-sulfoxide **1**. The pentacyclic compound **5** which would be formed by the mechanistic pathway of scheme 3 was not observed and this result could be explained by the protonation of the nitrogen (N-4) under such acidic conditions, hence prohibiting the nucleophilic attack by the N-4 electron pair.

Acknowledgements

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9. **5** : mp (dec) : 185° C ; IR : 2970, 1603 cm^{-1} ; UV (λ_{max} , CH_3OH) : 225 and 284 nm ; ^1H NMR [400 MHz, $CDCl_3$, δ = 0 ppm : TMS, J (Hz)] : 7.42 (d, 1H, J = 8), 7.28 (m, 2H, J = 8) and 7.17 (m, 1H) : H-C-9, H-C-10, H-C-11 and H-C-12), 6.53 (d, 1H, J = 10) and 5.53 (d, 1H, J = 10) : H-C-14 and H-C-15, 5.04 (bs, 1H, H-C-21), 4.10 (bd + m, 2H, Ha-C-3 and Ha-C-5), 3.96 (bd, 1H, J = 16, Hb-C-3), 3.56 (s, 3H, H_3-C-N-1), 3.02 (m, 1H, Hb-C-5), 2.90 (m, 1H, Ha-C-6), 2.52 (d, 1H, J = 16, Hb-C-6), 2.19 (m, 1H, Ha-C-19), 2.05 (s, 3H, H_3-C-S), 1.68 (m, 1H, Hb-C-19), 1.02 (t, 3H, J = 6, H_3-C-18) ; ^{13}C NMR (62.6 MHz, $CDCl_3$) : 179.7 (C-17), 140.1 and 118.7 (C-14 and C-15), 139.0, 129.2, and 126.2 : aromatic C, 122.5, 119.9, 118.4 and 109.7 : aromatic CH, 88.8 (C-16), 73.6 (C-21), 61.1 (C-3), 56.6 (C-5), 53.1 (C-20), 32.9 (H_3-C-N), 20.4 (C-19), 17.6 (C-6), 17.2 (H_3-C-S), 9.6 (C-18).) ; HRMS (m/z) = 352.1600 (15%), calc for $C_{21}H_{24}N_2OS$: 352.1609 ; 305.1647 (100%), calc for $C_{20}H_{21}N_2O$: 305.1653.
   FABMS (m/z) = 353 $[M+H]^+$, 307 $[M+H - S{=}CH_2]^+$.
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11. ^1H NMR [250 MHz, $CDCl_3$, δ = 0 ppm : TMS, J (Hz)] of sulfoxide **6** (mixture of diastereomers) : 7.52 and 7.22 (aromatic H), 6.48 and 6.41 (2d, 1H, J = 10, H-C-14 or H-C-15), 5.79 and 5.60 (2d, 1H, J = 10, H-C-15 or H-C-14), 5.07 and 4.89 (2bs, H-C-21), 4.16 (m), 3.70 and 3.59 (2s, H_3-C-N-1), 3.11 (s, H_3-C-S-O), 1.11 (t, 3H, J = 7, H_3-C-18).

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