145. Stereospecific Molecular Design. Synthesis of a New Heterotricyclic System

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(22.V.85)

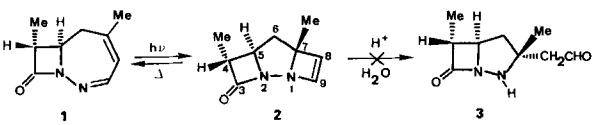
UV irradiation of the bicyclic enimine **1** led stereospecifically to the *anti*-tricyclic isomer **2** which reverted back to **1**, either by thermal activation or by acid catalysis at room temperature. Catalytic hydrogenation of **2** gave compound **4** whose configuration was fully ascertained by high-field ^{1}H-NMR measurements.

Introduction. – In [1], we described the stereospecific and high-yield synthesis of the azetidinodiazepine **1**. Since compound **1** contains a conjugated enimine function, it seemed amenable to undergo a photoinduced disrotatory [$_\pi 2_s + {}_\pi 2_s$] ring closure which was expected to give stereospecifically the tricyclic azetine derivative **2**. There is ample precedence in the literature for the photoinduced synthesis of azetines starting from the corresponding enimines [2–4].

Results and Discussion. – UV irradiation of **1** [λ_{max} (MeOH) = 299 nm (ε = 10,000)] [1] led in 75% yield to the tricyclic isomer **2** as colourless crystals. When heated at about 115°, **2** reverted back to **1** in a highly exothermal and fast-rate reaction. This latter process cannot be a concerted one, since it would violate the orbital-symmetry-conservation rule. Relief of ring-strain, when going from **2** to **1**, is mostly responsible for the exothermicity, the other energy factor being the σ-to-π bond transformation. That the tricyclic compound **2** reverts back to its isomer with a low activation energy is not surprising, since azetines are thermally not very stable entities and isomerize to the corresponding enimines [2] [5]. Differential scanning calorimetric (DSC) measurements of this thermal ring-opening permitted to determine the reaction enthalpy (ΔH = −29.0 kcal/mol). Line-shape analysis of the experimental DSC curve, according to *Freeman* and *Carroll* [8], showed that this thermal isomerisation is first-order with an activation energy of 29.2 kcal/mol.

The dihydroazete part of the photoproduct **2** contains an enamine function. Therefore, it was expected to undergo an acid-catalysed hydrolysis, leading to the corresponding azacarbapenam derivative **3**.

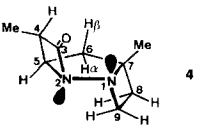
Scheme



1 **2** **3**

UV irradiation of **1** – in NMR tubes containing either CD_3OD or $CDCl_3$ as solvents – led in both cases to **2**. Thereafter, the CD_3OD solution of **2** was treated with D_2O and oxalic acid whereby **1** was formed quantitatively at room temperature. Likewise treatment of the $CDCl_3$ solution of **2** with TsOH and D_2O led to **1** at room temperature. These results were rather unexpected; quite obviously the dihydroazete part of **2** does not react as a typical enamine. So far, we were not able to secure the formation of the target azacarbapenam **3**.

Photoisomer **2** being not a stable entity – particularly in solution –, its olefinic double bond was hydrogenated over Pd, whereby compound **4** was formed in good yield (87%) as a colourless oil.



4

Structural Analysis of the Tricyclic Compound 4. – As a consequence of the repulsion of the two N non-bonding electron pairs, the photoinduced disrotatory electrocyclisation of **1** was expected to lead stereospecifically to the *anti*-isomer **2**. This is indeed the case as could be demonstrated by a high-field ^{1}H-NMR-analysis of its derivative **4**, by making use of nuclear *Overhauser* effects (NOE). The relative configuration of **4** (five asymmetric centers) could be deduced in a straightforward manner from the data from the NOE measurements (*Table*). These data permitted to demonstrate that H–C(4) and H–C(6) (the latter one appearing at 1.64 ppm) are located in an immediate vicinity. Since H–C(6) also leads to NOE when CH_3–C(7) is irradiated, it follows that the overall configuration of **4** is *anti*, as had been expected on the grounds of maximum repulsion of the two N non-bonding electron pairs. If **2** (**4**) were to be in its *syn*-configuration, the interaction of the two N non-bonding electron pairs would have been quite severe indeed: the corresponding AO's would have had close to an eclipsed topology.

Table. *Nuclear* Overhauser *Effect Measurements Determined at 400.1 MHz by Selective Irradiation of Several Protons of* **4**

Irradiated protons	Intensity enhancements observed with neighbourhood protons
CH_3–C(4)	H–C(4): +14%; H–C(5): +7%
CH_3–C(7)[a])	H–C(6): at 1.64 ppm (small); H–C(8) at 2.05 ppm (small)
H–C(6) at 1.64 ppm	H–C(4): +10%; H–C(6) at 2.42 ppm: +25%
H–C(6) at 2.42 ppm	H–C(5): +10%; H–C(6) at 1.64 ppm: +25%

[a]) In this case, NOE were indeed observed but could not be determined quantitatively.

At high-field ^{1}H-NMR all protons of **4** appear as resolved *m*'s. This is partly due to the fact that some of the protons undergo a shielding effect by the carbonyl moiety and by the N non-bonding electron pairs. To quote but one example H_β–C(6) appears at 1.64 ppm, whereas H_α–C(6) shows up at 2.57 ppm.

In the ^{13}C-NMR spectra of **2** and of **4** the carbonyl C-atoms appear at 179.17 and at 178.93 ppm, respectively. These chemical shifts are comparable to those found in very similar tricyclic compounds which we have described in [6].

We wish to thank the *Centre National de la Recherche Scientifique* for his financial support and Dr. *H. Strub* for the ^{13}C-NMR measurements and the determination of the DSC data.

Experimental Part

General. Flash chromatographies [7] were carried out with silica gel (*Merck 60*; 230–400 mesh) and TLC on alumina roll (*Merck 60 F_{254}*). M.p. were measured with a *Tottoli* apparatus *(Büchi)* and are not corrected. IR spectra (cm^{-1}) were determined on a *Perkin-Elmer-157-G* spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained with *Varian-T-60* (^{1}H-NMR only), *Bruker-WP-80-DS* and *Bruker-WM-400* instruments, with TMS as an internal reference (δ [ppm], J [Hz]). Normal and high-resolution MS were measured on a *MAT 311* spectrometer by the Centre de Mesures Physiques of the Université de Rennes.

[4α,5α,7β]-4,7-Dimethyl-1,2-diazatricyclo[5.2.0.0^{2,5}]non-8-ene-3-one (**2**). A soln. of *5,8-dimethyl-1,2-diazabicyclo[5.2.0]nona-2,4-diene-9-one* (**1**) [1] (511 mg, 3.11 mmol) in CH_2Cl_2 (125 ml) was irradiated under Ar at r.t. in a *Pyrex* glass vessel using a H_2O-cooled *Hanovia* immersion well (*Pyrex* glass) equipped with a *Philips HPK 125* medium-pressure Hg vapour lamp, until complete consumption of the starting material. After evaporation of the solvent *in vacuo*, the crude product was purified by flash chromatography (AcOEt/cyclohexane 6:4) leading thereby to **2** (385 mg, 75%) as colourless crystals (Et_2O/petrol ether), m.p. 58.5°. IR ($CHCl_3$): 1765. ^{1}H-NMR ($CDCl_3$, 60 MHz): 6.07 (*d, J* = 1.5, H–C(9)); 5.79 (*d, J* = 1.5, H–C(8)); 3.95 (*ddd, J* = 7.5, 6.5, 1.5, H–C(5)); 2.75 (*qd, J* = 7.5, 1.5, H–C(4)); 2.57 (*dd, J* = 13.5, 6.5, H_α–C(6)); 1.59 (*s,* CH_3–C(7)); 1.43 (*dd, J* = 13.5, 7.5, H_β–C(6)); 1.38 (*d, J* = 7.5, CH_3–C(4)). ^{13}C-NMR ($CDCl_3$, 20.1 MHz): 179.17 (*s,* C(3)); 143.91 (*dd, J* = 191, C(9)); 127.70 (*dm, J* = 180, C(8)); 96.36 (*sm,* C(7)); 62.42 (*dt, J* = 159, C(5)); 50.49 (*dm, J* = 140, C(4)); 39.92 (*tm, J* = 134, C(6)); 23.48 (*qd, J* = 129, *C*H_3–C(7)); 14.37 (*qt, J* = 129, *C*H_3–C(4)). MS: 164 (51, M^+), 118 (100). Mol.-wt. (MS): 164.0943 ($C_9H_{12}N_2O$), calc. 164.0950.

Thermolysis of **2**. Compound **2** (50 mg, 0.30 mmol) was gradually heated up to 115°, temp. at which a violent exothermal reaction occurred. After having been kept for about 10 min at 125°, the product is cooled to r.t. and identified with **1** by TCL, IR and ^{1}H-NMR. This thermolysis led quantitatively to **1**.

Some Thermodynamic Parameters of the Thermal **2**→**1** *Isomerisation, as Determined by DSC.* DSC measurements have been determined with a *SETARAM DSC 111* apparatus, using 8.20 mg of neat sample of **2** which was heated up at a rate of 4°/min. After a clear melting (57.7°), an exothermic peak appeared between 69.5° and 138.5°. The heating process was interrupted at 170°, and after quenching to r.t. the sample was shown by TLC and by ^{1}H-NMR (80 MHz-FT) to be composed at least of 93% of **1**. The reaction enthalpy was determined by integration: $\Delta H = -29.0 \pm 0.5$ kcal/mol. Line-shape analysis [8] led to the activation energy: $\Delta H^* = 29.2 \pm 0.5$ kcal/mol.

Reaction of **2** *in Acidic Medium. a)* A soln. of **1** (75 mg) in CD_3OD (0.5 ml) was irradiated by UV light at r.t. for 7 h, whereby **2** formed quantitatively as determined by NMR. To this soln. oxalic acid (50 mg) and D_2O (1 ml) were added. Product **1** formed back quantitatively (NMR and TLC).

b) A soln. of **1** (62 mg) in $CDCl_3$ (0.5 ml) was irradiated by UV light as described above, whereby **2** formed quantitatively (NMR). A few drops of D_2O and of CF_3CO_2H were added to the soln. of **2**. After a few min, **1** formed back quantitatively (NMR and TLC).

[4α,5α,7β]-4,7-Dimethyl-1,2-diazatricyclo[5.2.0.0^{2,5}]nonan-3-one (**4**). A stirred soln. of **2** (223 mg, 1.36 mmol) in CH_2Cl_2 (50 ml) was hydrogenated at atmospheric pressure over 5% Pd on alumina (20 mg) until complete disappearance of starting material. The solvent was evaporated and the resulting residue was purified by flash chromatography (AcOEt/cyclohexane 6:4) whereby **4** (194 mg, 87%) was obtained as a colourless oil. UV (MeOH): 237 (750, sh). IR ($CHCl_3$): 1760. ^{1}H-NMR ($CDCl_3$, 400.1 MHz): 4.00 (*ddd, J* = 7.7, 7, 2, H–C(5)); 3.74 (*ddd, J* = 10, 8.8, 5.8, H_β–C(9)); 3.10 (*td, J* = 10, 7.8, H_α–C(9)); 2.80 (*qd, J* = 7.5, 2, H–C(4)); 2.42 (*dd, J* = 13.8, 7.7, H_α–C(6)); 2.17 (*ddd, J* = 11.5, 10, 5.8, H_α–C(8)); 2.05 (*ddd, J* = 11.5, 8.8, 7.8, H_β–C(8)); 1.64 (*dd, J* = 13.8, 7, H_β–C(6)); 1.49 (*s,* CH_3–C(7)); 1.40 (*d, J* = 7.5, CH_3–C(4)). ^{13}C-NMR ($CDCl_3$, 20.1 MHz): 178.93 (*s,* C(3)); 85.06 (*s,* C(7)); 61.42 (*d, J* = 158, C(5)); 50.17 (*td, J* = 144, C(9)); 49.81 (*d, J* = 138, C(4)); 44.16 (*t, J* = 132, C(6)); 28.99 (*t, J* = 137, C(8)); 28.13 (*qm, J* = 128, *C*H_3–C(7)); 13.87 (*qt, J* = 129, *C*H_3–C(4)). MS: 166 (7, M^+), 151 (13), 139 (10), 124 (9), 111 (100). Mol-wt. (MS): 166.1118 ($C_9H_{14}N_2O$), calc. 166.1106.

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