Photoinduced isomerization reactions of azetidinodiazepines

THÉOPHILE TSCHAMBER, JACQUES STREITH,[1] AND HENRI STRUB
Ecole Nationale Supérieure de Chimie, Université de Haute-Alsace, F-68093 Mulhouse Cédex, France
HANS FRITZ
Zentrale Funktion Forschung Physik, Ciba–Geigy AG, CH-4002 Basel, Switzerland
AND
DAVID J. WILLIAMS
Department of Chemistry, Imperial College of Science and Technology, London SW7 2AZ, Great Britain

Received February 15, 1984

This paper is dedicated to Professor Peter Yates on the occasion of his 60th birthday

THÉOPHILE TSCHAMBER, JACQUES STREITH, HENRI STRUB, HANS FRITZ, and DAVID J. WILLIAMS. Can. J. Chem. **62**, 2440 (1984).

Ultraviolet irradiation of the azetidinodiazepines **3** leads in good yield to the expected tricyclic isomers **4** which represent potential precursors for the synthesis of 3-azacarbapenam derivatives. The rigid boat-shaped topology of the photoisomers **4** could be ascertained by detailed ^1H and ^{13}C nmr measurements, and in particular by the determination of nuclear Overhauser effects. That only the *syn* stereoisomers **4** are formed is most likely due to the conformation of the precursors **3** in which the convex side of the seven-membered ring is *syn* with respect to the β-lactam ring. Triplet sensitized irradiation of **3**, which should specifically give a $\pi^* \leftarrow n$ transition of the azetidinocarbonyl function, leads to the highly strained anti-Bredt isomers **5** whose structures were determined by ^1H and, especially, by ^{13}C nmr measurements. The structure of **5***a* was also established by an X-ray analysis which shows, in particular, that the bridgehead imine double bond is twisted out of plane by about 20°. Thermal activation of the anti-Bredt compound **5***a* leads to a mixture of the two isomers **8** and **9** which are more stable than **5***a* by about 40 kcal/mol as determined by differential scanning calorimetry.

THÉOPHILE TSCHAMBER, JACQUES STREITH, HENRI STRUB, HANS FRITZ et DAVID J. WILLIAMS. Can. J. Chem. **62**, 2440 (1984).

L'irridation ultraviolette des azétidinodiazépines **3** conduit, avec de bons rendements, aux isomères tricycliques attendus **4** qui représentent des précurseurs potentiels pour la synthèse de dérivés aza-3 carbapénames. Des mesures de rmn du ^1H et du ^{13}C et, en particulier, des mesures d'effet Overhauser nucléaire permettent d'établir que le photoisomère **4** possède une topologie de forme bateau rigide. Le fait que seuls les stéréoisomères *syn* **4** se forment est probablement dû à la conformation des précurseurs **3** dans lesquels la portion convexe du cycle à sept chaînons est en position *syn* par rapport au cycle du β-lactame. L'irradiation, sensibilisée par un triplet, du composé **3**, qui devrait conduire d'une façon spécifique à une transition $\pi^* \leftarrow n$ de la fonction azétidinocarbonyle, conduit plutôt aux isomères **5** qui sont fortement tendus et qui n'obéissent pas à la règle de Bredt; on a déterminé leurs structures en faisant appel à la rmn du ^1H et plus encore à la rmn du ^{13}C. On a également établi la structure du composé **5***a* par diffraction des rayons-X qui montre, en particulier, que la double liaison de l'imine sur la tête de pont est tordue hors du plan d'environ 20°. L'activation thermique du produit anti-Bredt **5***a* conduit à un mélange des deux isomères **8** et **9**. La calorimétrie différentielle à balayage montre que ces derniers sont plus stables que leur précurseur **5***a* d'environ 40 kcal/mol.

[Traduit par le journal]

Introduction

The pharmacologically active β-lactam antibiotics, such as penicillins, cephalosporins, or monobactams, are produced by microorganisms. Starting from these naturally occurring products, slightly modified molecules have been synthesized in the pharmaceutical industry; these play an ever-increasing role in modern medicine (1). On the other hand, medicinal chemists are focusing their attention and efforts towards the total synthesis of non-natural monocyclic or bicyclic β-lactams, which would hopefully have some antimicrobial activity.

Although to our knowledge none of the "artificial" β-lactams synthesized so far have made their way to the market, major pharmaceutical companies are striving to find new β-lactam antibiotics by total synthesis (2–5).

Azetidinodiazepines **3** can be prepared easily by cycloaddition of methylketene with the imino double bond of the corresponding 1,2-diazepines (6). We surmised that the conjugated diene moiety of **3** would undergo a facile photochemical ring closure, leading to the new tricyclic system **4**. These latter compounds represent annelated azacarbapenam derivatives whose partial structure (azetidinone and five-membered ring) is similar to that of the penicillin and the thienamycin skeleton.

We describe herein some experimental data, which agree with the above mentioned expectation, as well as some unexpected results which were obtained during photosensitized uv irradiation of the four azetidinodiazepines **3***a*–**3***d*.

Direct ultraviolet irradiation of azetidinodiazepines 3*a*–3*d*

Ultraviolet irradiation of the diazepine **1***a* has been shown to lead in moderate yield to the bicyclic isomer **2** (7). Similar results have been obtained by us (7, 8) and by others (9) during uv irradiation of a series of diazepines which gave the corresponding bicyclic isomers having the same skeleton as **2**. We expected, therefore, that the azetidinodiazepines **3** would undergo a similar disrotatory ring closure during direct ultraviolet irradiation of their conjugated diene moiety.

Ultraviolet irradiation of **3***a* through Corex glass – which permits the specific electronic excitation of the diene portion – gives the expected tricyclic isomer **4***a* in 69% yield. A minor photoisomer **5***a* also forms in this experiment (yield: 14%); the

[1]Author to whom correspondence may be addressed.

TABLE 1. 360 MHz proton magnetic resonance spectrum of compound **4***a* measured in $CDCl_3$*

H-3	H-4	H-6	H-7	H-8	Me-5	Me-8	CH_2CH_3	CH_2CH_3
5.27	5.83	3.69	3.44	3.01	1.79	1.48	4.20†	1.30

$J_{8,Me\text{-}8} = 7.5$	$J_{3,6} = 3.5$	$J_{Me\text{-}5,6} = 1$	$J_{3,8} = 0.5$
$J_{7,8} = 2$	$J_{4,3} = 0.5$	$J_{Me\text{-}5,3} = 1.5$	$J_{CH_2—CH_3} = 7$
$J_{6,7} = 6.5$	$J_{4,Me\text{-}5} = 1.5$	$J_{4,6} = 1.5$	

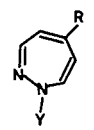
*Chemical shifts in δ (ppm) and coupling constants J in Hz.
†Center of the AB part of an ABX_3 spectrum (J_{AB} = 10.5 Hz; $\Delta\nu$(AB) = 9.4 Hz).

TABLE 2. 90.5-MHz ^{13}C magnetic resonance spectrum of the photoproduct **4***a* measured in $CDCl_3$*

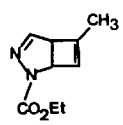
	δ	$^1J_{C,H}$	$^{n>1}J_{C,H}$
C-9	180.06		6 (Me-8); 6 (H-8); 9 (H-7)
—CO_2—	156.08		1(H-3); 3(CH_2—CH_3)
C-5	147.84		Complex coupling pattern with Me-5, H-3, H-6, and H-7; $\Sigma J = 37$
C-4	132.63	174.5	2.5 (H-3); 8 (H-6); 7 (Me-5)
C-3	67.00	159.9	3 (H-4?); 4.5 (H-6?); 1 (Me-5)
CH_2—CH_3	62.71	148.0	4.4 (CH_2—CH_3)
C-7	59.23	157.7	5 (Me-8)
C-6	53.60	146.3	2 (Me-5); 13 (H-4); 2.5, 2.5, 2.5 (H-8, H-7, H-3)
C-8	45.76	140.2	5 (Me-8)
Me-5	16.35	126.9	1.5 (H-4)
Me-8	14.87	128.9	4 (H-8); 3 (H-7)
CH_2—CH_3	14.47	127.2	2.6 (CH_2—CH_3)

*Chemical shifts in δ (ppm); coupling constants $J_{C—H}$ in Hz.

structure and the mechanism of formation of this isomer will be discussed in the next section (*vide infra*).



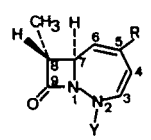
1



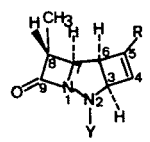
2

	R	Y
a	CH_3	CO_2Et
b	CH_3	$CONH_2$
c	CH_3	COPh
d	H	CO_2CH_2Ph

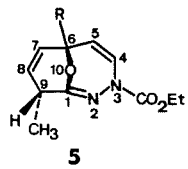
The structure and relative configuration of **4***a* follow from its spectral data. The ir spectrum shows a band at 1785 cm^{-1} which is indicative of a β-lactam ring; this means that the four-membered ring stayed intact during uv excitation. In Table 1 chemical shifts and coupling constants of the ^1H nmr spectrum of **4***a* are reproduced. We notice, in particular, that the $J_{6,7}$ coupling constant of 6.5 Hz is in favour of a *cis* configuration for H-6 and H-7, and therefore of a rigid boat-shaped topology for this tricyclic molecule. The ^{13}C nmr spectrum of **4***a* (Table 2) fits the proposed structure, although the β-lactam carbonyl function appears at an unexpectedly low field (180.06 ppm). In the starting material **3***a* the carbonyl of the β-lactam moiety appears at 164.64 ppm (6); the β-lactam carbonyls show up between 165 and 168 ppm for penicillins (10, 11), at about 165 ppm for cephalosporin (12), and at 166.1 ppm for thienamycin (13). The low-field chemical shift we observe for the β-lactam carbonyl of **4***a* clearly indicates that there is very little amide character in the four-membered ring and that the N-1 nitrogen atom is likely to have a pronounced pyramidal geometry.



3



4



5

	R	Y
a	CH_3	CO_2Et
b	CH_3	$CONH_2$
c	CH_3	COPh
d	H	CO_2CH_2Ph

The ^{13}C spectrum of **4***a* agrees well with a *syn* configuration for this tricyclic molecule: the coupling constants $J_{Me\text{-}8,H\text{-}7}$ (3 Hz) and $J_{C\text{-}6,H\text{-}8}$ (2.5 Hz) indicate that Me-8 and H-7 on the one hand, and C-6 and H-8 on the other hand, are both *cis* to each other (14). Together with the ^1H nmr data cited above, these findings are good evidence in favour of the relative configuration as shown in formula **4***a* (Table 2).

That the structure of the tricyclic compound is indeed as shown in formula **4***a* — not considering stereochemistry — is demonstrated by the $^{13}C—^{13}C$ coupling constant parameters which were obtained from satellites observed in the broad-band-decoupled ^{13}C nmr spectra of a concentrated solution of **4***a* in $CDCl_3$ (14). Table 3 gives the values of the one-bond

TABLE 3. $^1J(^{13}C-^{13}C)$ coupling constants and values for the $^{13}C-^{13}C$ isotope effects on the chemical shifts (in Hz at 90.5 MHz) for compound **4***a*

(i, j)	$J(i, j)$ Hz	$j\Delta(i)$ Hz	$i\Delta(j)$ Hz
5–4	58.4	−3.0	−2.9
5–6	35.6	−0.8	−1.1
5-Me-5	42.8	−0.4	*
4–3	39.6	−0.8	−0.9
3–6	25.5	−0.8	−1.2
6–7	38.0	−1.0	−0.9
7–8	33.0	−0.7	−1.0
8–9	40.0	−1.8	*
8-Me-8	35.0	−0.3	*

*Not measured.

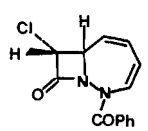
TABLE 4. Nuclear Overhauser effect measurements determined at 360 MHz by selective irradiation of several protons of compound **4***a*

Irradiated protons	Intensity enhancements observed with neighbourhood protons
H-3	H-4: +10.3%; H-6: +10.8%
H-6	H-3: +17% ; H-7: +14.9%
H-7	H-6: +13.4%; H-8: no change
Me-8	H-7: +14.6%; H-8: +19.4%
Me-5	H-4: +9.7% ; H-6: +5.8%; H-8: +15.5%

coupling constants and of the $^{13}C-^{13}C$ isotope effects on the chemical shifts.

The results obtained with nuclear Overhauser effect (nOe) measurements fully agree with the proposed relative configuration as shown in formula **4***a* (Table 4). The most pronounced nOe effects are those observed for H-8, during irradiation of the methyl group Me-5, and for H-3 and H-7 during irradiation of H-6. On the other hand, no nOe effect could be detected for H-8 when H-7 was irradiated. These data clearly indicate that H-7 and H-8 are in a *trans* configuration and that H-3, H-6, and H-7 are all three located on the convex side of the rigid boat-shaped molecule **4***a*.

The exclusive formation of stereoisomer **4***a* can be accounted for as follows. The X-ray diagram of the azetidinodiazepine **6** (15), a compound whose topology is similar to that of **3***a*, shows that the boat-shaped conformation of the seven-membered ring and the plane of the β-lactam ring are *syn*. It also shows that the H-3 and H-6 hydrogen atoms point towards the "backside" of the azetidinodiazepine. A photochemical disrotatory ring closure, starting from this *syn* conformation, would then lead to the stereoisomer **4***a*.



6

Ultraviolet irradiation of the azetidinodiazepines **3***b*–**3***d* leads likewise to the corresponding tricyclic isomers **4***b*–**4***d* (see Experimental).

Triplet-sensitized irradiation of the azetidinodiazepine 3*a*

In the above unsensitized photochemical experiments there was always formed a minor photoisomer **5** together with **4**. When the uv irradiation of **3***a* is carried out in the presence of fluorenone as triplet-sensitizer (E_T = 53.3 kcal/mol), **4***a* is no longer formed. Instead, the compound **5***a*, which was obtained as a minor by-product during the direct irradiation, is now the major photoproduct. These results show that the products **4***a*–**4***d* are most likely produced starting from an excited singlet state of the corresponding educts **3***a*–**3***d*, whereas the by-products are formed from an excited triplet state.

Determination of the structure of the by-products **5** could be achieved with the usual spectrophotometric methods, except for the relative configuration of the two asymmetric centres. The ir spectrum of **5***a* shows a strong carbonyl band at 1708 cm^{-1} which indicates the absence of a β-lactam ring in this photoproduct. The 360-MHz ^1H nmr spectrum, measured in $CDCl_3$, shows a single two-proton band at δ 5.74 ppm which could be resolved by using a solvent mixture ($CDCl_3/C_6D_6$ 1:1): these two vinylic protons have a coupling constant of 9.2 Hz. Two additional vinylic protons appear at δ 6.90 and 4.94 ppm (AB spectrum) with a coupling constant of 9.5 Hz. Clearly neither of these two pairs of olefinic protons can be attached to unsaturated five-membered rings. The ^{13}C nmr spectral data, which are reproduced in the experimental part, led us to postulate the bicyclic "anti-Bredt" structure **5***a* for this unexpected photoproduct.[2] To be noted in particular is a fully substituted sp^3 carbon atom giving rise to a singlet at δ 86.49 ppm; such a low-field chemical shift seemed to indicate that this doubly allylic carbon atom is attached to an oxygen atom. An X-ray investigation of **5***a* confirmed the postulated structure (see below) and led to the determination of the relative configuration of the two asymmetric centres.

For the time being, there is no clear-cut mechanistic interpretation for the triplet-photosensitized formation of the "anti-Bredt" isomer **5***a*. Formally, **5***a* results from a Cope-type rearrangement. Nevertheless it is obvious that this photoproduct cannot be formed in a concerted fashion, starting from **3***a* in its triplet state: Cope-rearrangements are initiated from a singlet ground state!

Whatever the real mechanism for the formation of **5***a*, a diradical intermediate of type **10** – first in its triplet state and thence in its singlet ground state – must be ruled out, since it is precisely this singlet ground state **10** which seems to be the obvious intermediate during the thermal rearrangement of **5***a* (*vide infra*).

Crystallographic analysis of 5*a*

Crystal data

$C_{12}H_{16}N_2O_3$ fw = 236.26

Monoclinic, a = 8.634(1), b = 14.853(2), c = 9.529(1) Å, β = 92.02(1)°, U = 1221 $Å^3$, Z = 4, ρ_c = 1.29 g cm^{-3}, $F(000)$ = 504, μ(Cu-$K\alpha$) = 7 cm^{-1}, space group (uniquely determined from systematic absences) $P2_1/a$. Refined unit cell parameters were obtained by centering 15 reflections on a Nicolet R3m diffractometer. 1529 independent reflections were measured ($\theta \leq 55°$) with Cu-$K\alpha$ radiation (graphite monochromator) using the ω-scan measuring technique. 1447 reflections had $|F_o| > 3\sigma(|F_o|)$ and were considered to be ob-

[2]Some so-called anti-Bredt compounds have been synthesized; some of them could be isolated at room temperature as stable entities, provided that the two-bridged cycles were sufficiently large rings, so that the bridgehead double bonds are only slightly twisted out of plane (16). For the evaluation and prediction of the stability of bridgehead olefinic compounds, see ref. 17; for a review, see ref. 18.

TABLE 5. Atom coordinates ($\times 10^4$) and temperature factors (Å^2 $\times$ 10^3) of the anti-Bredt compound **5***a*

Atom	*x*	*y*	*z*	U_{eq}
C(1)	862(2)	146(1)	3113(2)	38(1)*
N(2)	45(2)	−504(1)	2645(2)	41(1)*
N(3)	884(2)	−1081(1)	1756(1)	43(1)*
C(4)	1571(2)	−713(1)	571(2)	48(1)*
C(5)	2285(2)	77(1)	486(2)	49(1)*
C(6)	2744(2)	684(1)	1686(2)	47(1)*
C(7)	1843(2)	1553(1)	1734(2)	55(1)*
C(8)	774(3)	1696(1)	2646(2)	56(1)*
C(9)	201(2)	993(1)	3661(2)	46(1)*
O(10)	2427(1)	190(1)	2962(1)	41(1)*
C(11)	4472(2)	850(2)	1717(3)	61(1)*
C(12)	−1554(2)	1001(1)	3725(2)	56(1)*
C(13)	571(2)	−1985(1)	1789(2)	49(1)*
O(13)	1007(2)	−2504(1)	923(2)	69(1)*
O(14)	−212(2)	−2205(1)	2925(2)	58(1)*
C(15)	−507(3)	−3158(1)	3130(3)	69(1)*
C(16)	778(4)	−3596(2)	3917(3)	89(1)*

*Equivalent isotropic *U* defined as one third of the trace of the orthogonalised U_{ij} tensor.

TABLE 6. Selected torsion angles* of the anti-Bredt compound **5***a*

Atoms	Angle	Atoms	Angle
C(1)N(2)N(3)C(4)	−56.8(2)	N(2)N(3)C(4)C(5)	39.4(3)
N(3)C(4)C(5)C(6)	10.8(3)	C(4)C(5)C(6)C(7)	−111.3(2)
C(5)C(6)C(7)C(8)	105.8(2)	C(6)C(7)C(8)C(9)	−6.2(3)
C(7)C(8)C(9)C(1)	−12.2(3)	C(8)C(9)C(1)N(2)	−117.0(2)
C(9)C(1)N(2)N(3)	159.4(1)	O(10)C(1)N(2)N(3)	−10.3(2)

*With esd's in parentheses.

served. The data were corrected for Lorentz and polarisation factors. No absorption correction was applied.

The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. All the hydrogen atoms were clearly located in a difference electron density map. The hydrogen positions were idealized (C—H = 0.96 Å), assigned isotropic thermal parameters, $U(H) = 1.2U_{eq}(C)$ and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full matrix least-squares to $R = 0.040$, $R_w = 0.051$, ($w^{-1} = \sigma^2(F) + 0.00065F^2$). The maximum residual electron density in the final ΔF map was 0.17 e A^{-3}, and the mean and maximum shifts/error in the final refinement cycle were 0.03 and 0.25 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

Tables 5–7 list the fractional atomic coordinates, some selected torsion angles, bond lengths, and bond angles, respectively. The anisotropic thermal parameters, the structure factors, and the hydrogen coordinates and temperature factors (tables) have been placed in the Depository of Unpublished Data.[3]

The X-ray analysis of **5***a* has confirmed the postulated structure (Fig. 1) and showed that this highly strained arrangement can only be achieved by sacrificing the planarity of the C(1)—N(2), C(4)—C(5), and C(7)—C(8) double bonds. This is most

[3]Data are available, at a nominal charge, from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.

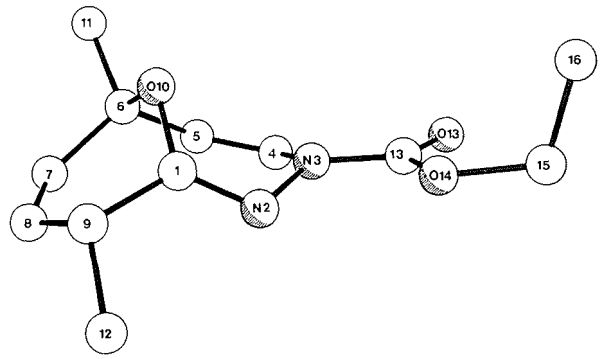
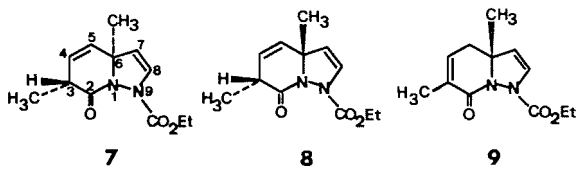


FIG. 1. Perspective view of the anti-Bredt compound **5***a* as determined by X-ray analysis.

pronounced for the bridgehead imine double bond which is twisted out of plane by 20°. This is accompanied by a pyramidal distortion of C(1) which lies 0.066 Å (in the direction of H(9)) from the plane of N(2), C(9), and O(10). N(3) is also slightly pyramidilized, being displaced 0.156 Å above the plane formed by N(2), C(4), and C(13). Table 6 lists selected torsion angles and Table 7 the bond lengths and valence angles. There are no short intermolecular contacts.

Thermal rearrangement of the anti-Bredt photoproduct 5*a*

Thermolysis of the strained photoproduct **5***a* leads to the more stable isomers **7** (85%) and **8** (7%), whose structures follow from their nmr data (see Experimental). To be noted in particular are two close peaks (δ 5.83) corresponding to H-4 and H-5 on **7**. The corresponding protons in **8** appear respectively at δ 5.60 and 5.85 ppm with a coupling constant of 9.6 Hz. The H-7 and H-8 protons show coupling constants of 4.4 Hz for **7** and 4.3 Hz for **8**; the magnitude of these coupling constants is compatible with olefinic protons in a five-membered ring.



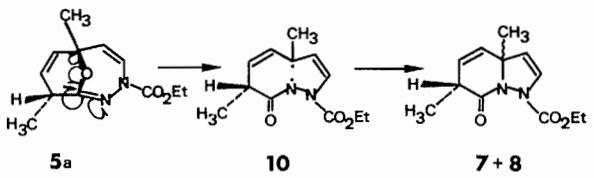
7 **8** **9**

The ^{13}C nmr spectra agree with the stereostructures which are assigned to the diastereomers **7** and **8**. For example Me-3 of **9** shows two coupling constants of 6.5 and 4.0 Hz, respectively with H-3 and with H-4, whereas Me-3 of **7** shows coupling only with H-3 (^2J = 7 Hz) but no coupling constant with H-4. The absence of any coupling with H-4 is due to the fact that the dihedral angle between the C-3—Me-3 and the C-4—H-4 bonds is close to 90°: according to the Karplus equation, ^3J for such a dihedral angle should indeed be close to zero. These data show that the two methyl groups of diastereomer **7** are located on the same side of the molecule: they are *cis* to one another. To be noted, furthermore, are the Me-3 chemical shifts of **7** (δ = 29.2) and of **8** (δ = 14.55): this large difference is not due to a so-called δ-effect between Me-3 and Me-6! It is rather the result of the steric interaction, in **8**, between Me-3 and one of the carbonyl lone electron pairs. A Dreiding model shows that the carbonyl double bond and the C-3—Me-3 bond are indeed quasi coplanar.

Differential scanning calorimetry of the reaction **5***a* → **7** + **8** gave an enthalpy of 40.5 kcal/mol for this rearrangement.

TABLE 7. Bond lengths (Å) and angles (deg) of **5***a*

Bond	Length	Bond	Length
C(1)—N(2)	1.268(2)	C(1)—C(9)	1.483(2)
C(1)—O(10)	1.366(2)	N(2)—N(3)	1.422(2)
N(3)—C(4)	1.405(2)	N(3)—C(13)	1.370(2)
C(4)—C(5)	1.329(3)	C(5)—C(6)	1.499(3)
C(6)—C(7)	1.509(3)	C(6)—O(10)	1.455(2)
C(6)—C(11)	1.511(3)	C(7)—C(8)	1.307(3)
C(8)—C(9)	1.518(3)	C(9)—C(12)	1.518(3)
C(13)—O(13)	1.200(3)	C(13)—O(14)	1.337(2)
O(14)—C(15)	1.452(2)	C(15)—C(16)	1.469(4)
Bond	**Angle**	**Bond**	**Angle**
N(2)—C(1)—C(9)	123.6(2)	N(2)—C(1)—O(10)	122.7(2)
C(9)—C(1)—O(10)	113.0(1)	C(1)—N(2)—N(3)	112.3(1)
N(2)—N(3)—C(4)	118.9(1)	N(2)—N(3)—C(13)	118.1(1)
C(4)—N(3)—C(13)	119.3(2)	N(3)—C(4)—C(5)	127.0(2)
C(4)—C(5)—C(6)	126.6(2)	C(5)—C(6)—C(7)	114.5(2)
C(5)—C(6)—O(10)	106.4(1)	C(7)—C(6)—O(10)	107.1(1)
C(5)—C(6)—C(11)	110.4(2)	C(7)—C(6)—C(11)	111.7(2)
O(10)—C(6)—C(11)	106.3(2)	C(6)—C(7)—C(8)	122.5(2)
C(7)—C(8)—C(9)	124.4(2)	C(1)—C(9)—C(8)	102.8(1)
C(1)—C(9)—C(12)	114.7(2)	C(8)—C(9)—C(12)	111.6(2)
C(1)—O(10)—C(6)	109.1(1)	N(3)—C(13)—O(13)	123.2(2)
N(3)—C(13)—O(14)	111.4(2)	O(13)—C(13)—O(14)	125.4(2)
C(13)—O(14)—C(15)	116.3(2)	O(14)—C(15)—C(16)	111.6(2)



SCHEME 1. Proposed mechanistic scheme for the thermal rearrangement of the anti-Bredt compound **5***a* to the isomers **7** and **8**.

Such a large exothermic value is to be attributed to relief of the ring strain present in the bridged anti-Bredt compound **5***a*. Treatment of the DSC (differential scanning calorimetry) curve using Ellerstein's method (19) leads to the determination of the activation energy (E_a = 31.1 kcal/mol) and the pre-exponential factor ($\ln A = 32.0\ s^{-1}$) of the Arrhenius equation for this thermal isomerization.

The mechanism of this latter ground-state rearrangement seems to be straightforward: homolytic fragmentation of the C_6—O_{10} bond leads to a singlet diradical **10** which is doubly allylic at carbon, and of the "push-pull" type (20) or of the capto-dative type (21) at nitrogen (Scheme 1). Recombination of these two delocalized radicals leads to compounds **7** and **8**, which are thermodynamically more stable than their strained precursor **5***a*.

That **7** and **8** are diastereoisomers can easily be demonstrated: both lead, after equilibration, to the same conjugated enamide **9** when treated with DBU in boiling chloroform (about 65°C) for 15 h. A similar experiment with **7** in the presence of DBU but in boiling methylene chloride (ca. 43°C), under equilibrating conditions when no **9** was formed, gave mainly **8**, suggesting that it is the thermodynamically more stable isomer of the two. Yet, in the thermolysis of **5** leading to **7** and **8**, the latter − though more stable − is the minor isomer formed.

This may indicate that the carbon radical of **10** combines with its neighbouring nitrogen radical in a very fast intramolecular process, thereby retaining to a large degree its original configuration.

Ultraviolet irradiation of the azetidinodiazepines **3***a*−**3***d* led to the expected tricyclic isomers **4***a*−**4***d* as the major photoproducts. Taking advantage of these model reactions, one should now be in a position (*i*) to attach an acid, other than carboxyl, to the nitrogen atom N-2; (*ii*) to induce a fragmentation reaction between C-3 and C-4 and between C-5 and C-6 of products having the overall structure **4**. This synthetic planning would ultimately yield 3-azacarbapenam derivatives.

The photochemical formation of the highly strained anti-Bredt isomers **5***a*−**5***d* was rather unexpected. It shows once more how specific photochemical reactions can be, when compared to thermally induced ones, provided that the proper wavelengths and spin multiplicities are chosen.

Experimental

Microanalyses were carried out by the Service Central de Microanalyses of the C.N.R.S. Melting points were taken with Büchi SMP-2 and Mettler FP5 apparatus and are not corrected. The uv spectra (λ_{max} nm (ϵ)) were recorded on a Varian Techtron 635 spectrophotometer. The ir spectra (cm^{-1}) were determined on a Perkin−Elmer 157 G spectrophotometer. The ^1H and ^{13}C nmr spectra were obtained with Varian T-60 (60 MHz), Bruker WP 80 (80 MHz), Bruker WH 360 (360 MHz), and Bruker WM 400 (400 MHz) instruments, with Me_4Si as an internal reference (δ ppm, *J* Hz). Normal ms as well as high resolution ms were measured with a MAT 311 mass spectrometer by the Centre de Mesures Physiques of the University of Rennes. Differential Scanning Calorimetry was performed with the fully automated Perkin−Elmer DSC-2C apparatus. Flash chromatographies (22) were carried out with silica gel (Merck 60; 230−400 mesh) and thin-layer chromatographies on aluminium roll (Merck 60 F_{254}). The photochemical experiments were carried out under an argon atmosphere in a Pyrex glass vessel using a water-cooled Hanovia immersion well (Corex glass) equipped with a Philips HPK 125 medium pressure mercury vapour lamp.

Synthesis of 1-benzoyloxycarbonyl 1,2-diazepine **1**d

(*i*) To a stirred solution of hydroxylamin-O-sulfonic acid at 0°C (14.13 g; 0.125 mol) in water (31 mL) are successively added potassium hydroxide (8.8 g) in water (13 mL) and pyridine (18.8 mL) over 30 min at about 5°C. After 2 days of continuous stirring at room temperature, potassium carbonate (8.75 g) is slowly added. After 2 h the precipitated solids are filtered off; ethanol is added to the solution, leading to additional precipitates which are filtered. The resulting solution is diluted with ethanol (250 mL) and stirred at 10°C. To this stirred solution potassium carbonate (25 g) and benzyl chloroformate (18 mL) are added, the latter dropwise, and the reaction mixture is kept at room temperature for 24 h and then filtered over sinter glass. The resulting solution is evaporated to dryness *in vacuo*. The resulting crude pyridinium ylide is purified by column chromatography (AcOEt/EtOH 8:2) followed by crystallization in toluene; the resulting brown crystals are further purified by dissolution in a mixture of acetone and petrol ether, whereby a brown product precipitates; after filtration, the mother liquors lead to the pure pyridinium ylide (4.60 g; 16% overall yield) as colourless crystals (toluene), mp 113°C; ir (KBr): 1630, 1605 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 312 nm (6400); ^1H nmr ($CDCl_3$ at 60 MHz) δ: 8.87 (dm, J = 7 Hz, H-2 and H-6), 7.8−7.2 (m, H-3, H-4, H-5, and H-arom.), and 5.20 ppm (s, CH_2). *Anal.* calcd. for $C_{13}H_{12}N_2O_2$ (228.24): C 68.41, H 5.30, N 12.27; found: C 68.30, H 5.25, N 12.46.

(*ii*) A solution of the above described pyridinium ylide (4.60 g; 20.2 mmol) in toluene (2.0 L) is irradiated for 7 h under nitrogen in a "falling-film" type photoreactor (23) equipped with a 700-W medium pressure mercury vapour lamp, the reaction being followed by uv spectroscopy and by tlc until complete disappearance of the pyridinium ylide absorption band. After evaporation of the solvent *in vacuo* and column flash chromatography (AcOEt/cyclohexane 3:7) of the crude reaction mixture, diazepine **1***d* is obtained as an orange oil which solidifies in the cold; mp 67−68°C (hexane); ir (KBr): 1701 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 216 nm (15 200) and 357 nm (280); ^1H nmr ($CDCl_3$ at 60 MHz) δ: 7.40 (m, H-3 and H-arom.), 6.52 (ddd, J = 11, 5, and 1 Hz, H-5), 6.24 (d, J = 7.2 Hz, H-7), 6.20 (partly hidden by H-7; resolved when determined in C_6D_6: dd, J = 11 and 3.5 Hz, H-4), 5.72 (ddd, J = 7.2, 5, 1.5 Hz, H-6), and 5.33 ppm (s, CH_2). *Anal.* calcd for $C_{13}H_{12}N_2O_2$ (228.24): C 68.41, H 5.30, N 12.27; found: C 68.32, H 5.27, N 12.17.

[7α,8α] 8-Methyl 2-benzoyloxycarbonyl 9-oxo 1,2-diazabicyclo-[5.2.0] 3,5-nonadiene **3**d

Through a solution of diazepine **1***d* (3.27 g; 14.3 mmol) in 200 mL toluene is passed the pyrolysis gas of butanone which is produced in a ketene lamp (3) for about 3 h at room temperature, until disappearance of **1***d* as shown by tlc. After evaporation of the solvent *in vacuo*, the crude reaction mixture is separated into its components by flash chromatography (AcOEt/cyclohexane 2:8), which gives mainly the expected β-lactam **3***d* (3.42 g; 84%) as a colourless solid (ether); mp 78°C; ir (KBr): 1773, 1728 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 274 nm (9600); ^1H nmr ($CDCl_3$ at 60 MHz) δ: 7.40 (s, H-arom.), 6.88 (d, J = 9 Hz, H-3), 5.93 (s, H-6), 5.87 (m, H-5), 5.27 (s, CH_2), 5.12 (ddd, J = 9, 7, and 2 Hz, H-4), 4.17 (m, H-7), 2.68 (qd, J = 7.5 and 2.0 Hz, H-8), and 1.38 ppm (d, J = 7.5 Hz, Me-8). *Anal.* calcd. for $C_{16}H_{16}N_2O_3$ (284.30): C 67.59, H 5.67, N 9.85; found: C 67.63, H 5.75, N 9.89.

[3α,6α,7α,8α] 5,8-Dimethyl 2-ethoxycarbonyl 9-oxo 1,2-diazatricyclo[5.2.0.0^{3,6}] 4-nonene **4**a *and [1α,6α,9β] 6,9-dimethyl 3-ethoxy-carbonyl 10-oxa 2,3-diazabicyclo[4.3.1] 1,4,7-decatriene* **5**a

A solution of the azetidinodiazepine **3***a* (3) (3.10 g; 13.1 mmol) in 400 mL methylene chloride is irradiated by uv light until complete consumption of the starting material, the reaction medium being monitored by tlc. Two photoproducts appear which are separated by column flash chromatography (AcOEt/cyclohexane 2:8). Compound **5***a* (435 mg; 14%), being the less polar one, is eluted first; it is followed by its isomer **4***a* (2.127 g; 69%).

Photoisomer **4**a: colourless crystals (ether/petrol ether), mp 92°C; ir (KBr): 1785, 1695 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 238 nm (770); ms: 236 (M^+; 11%); 180 (100%). *Anal.* calcd. for $C_{12}H_{16}N_2O_3$ (236.26): C 61.00, H 6.83, N 11.86; found: C 61.15, H 6.76, N 12.32.

Photoisomer **5**a: colourless crystals (*n*-hexane), mp 54°C; ir (KBr): 1708, 1700, and 1635 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 240 nm (8400); ^1H nmr ($CDCl_3$ at 360 MHz) δ: 6.90 (d, J = 9.5 Hz, H-4), 5.74 (s, H-7 and H-8), 4.94 (d, J = 9.5 Hz, H-5), 4.34 and 4.28 (two ABX systems; twice dq, J_{AB} = 11 Hz, J_{AX} = J_{BX} = 7 Hz, OCH_2CH_3), 3.31 (qd, J = 7 Hz and J < 1 Hz; H-9), 1.50 (s, Me-6), 1.35 (t, J = 7 Hz, OCH_2CH_3), 1.27 (d, J = 7 Hz, Me-9); ^1H nmr ($CDCl_3/C_6D_6$ 1:1 at 360 MHz) δ: 5.52 (d, J = 9.2 Hz, H-7) and 5.50 ppm (d, J = 9.2 Hz, H-8); ^{13}C nmr ($CDCl_3$ at 100.6 MHz) δ: ($^1J_{i,j}$) 167.40 (s, C-1), 153.90 (s, CO), 132.36 (ddq, 167 Hz, C-8), 131.86 (dm, 163 Hz, C-7), 125.91 (dd, 180.5 Hz, C-4), 115.61 (d, 162 Hz, C-5), 86.49 (s, C-6), 63.10 (tq, 149 Hz, CH_2CH_3), 35.94 (dm, 133 Hz, C-9), 28.06 (qs, 129 Hz, Me-6), 14.45 (qt, 127 Hz, CH_2CH_3), 14.45 (q, about 130 Hz, Me-9); ^{13}C nmr ($CDCl_3$ at 100.6 MHz) ^1J ($^{13}C_i-{}^{13}C_j$) coupling constants ± 0.3 Hz: J(1, 9) = 55.9 Hz; J(9, Me-9) = 35.9 Hz; J(9, 8) = 36.8 Hz; J(6, Me-6) = 39.7 Hz; J(6, 5) = 47.5 Hz; J(6, 7) = 45.3 Hz; J(5, 4) = 80 Hz; ms: 236 (M^+, 12%), 121 (100%). *Anal.* calcd. for $C_{12}H_{16}N_2O_3$ (236.26): C 61.00, H 6.83, N 11.86; found: C 61.00, H 6.89, N 11.78.

Fluorenone-sensitized formation of the bicyclic product **5**a

A stirred solution of the azetidinodiazepine **3***a* (1.416 g; 6.00 mmol) and of fluorenone (270 mg; 1.5 mmol) in 250 mL acetone is irradiated by uv light (Philips HPK 125) through Pyrex for 9 h, the disappearance of the starting material being determined by tlc. After evaporation of the solvent *in vacuo*, the crude reaction mixture is separated into its components by column flash chromatography (AcOEt/cyclohexane 1:9). The main compound proved to be the photoisomer **5***a* (1.041 g; 73%).

[3α,6α,7α,8α] 5,7-Dimethyl 2-carboxamido 9-oxo 1,2-diazatricyclo-[5.2.0.0^{3,6}] 4-nonene **4**b *and [1α,6α,9β] 6,9-dimethyl 3-carboxamido 10-oxa 2,3-diazabicyclo[4.3.1] 1,4,7-decatriene* **5**b

A solution of azetidinodiazepine **3***b* (3) (995 mg; 4.80 mmol) in 300 mL methylene chloride is irradiated by uv light for 6 h until complete disappearance of the starting material. After evaporation of the solvent *in vacuo* the crude reaction mixture is dissolved in a mixture of ethyl acetate and cyclohexane 6:4 whereby compound **4***b* (368 mg) crystallizes out. Flash chromatography of the remaining mother liquors (AcOEt/cyclohexane 6:4) leads to the successive isolation of the photoisomers **5***b* (130 mg; 13%) and **4***b* (193 mg; combined yield of **4***b*: 56%).

Photoisomer **4**b: colourless crystals (methylene chloride/petrol ether), mp 160−161°C (dec.); ir (KBr): 1779, 1690 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 241 nm (720); ^1H nmr ($CDCl_3$ at 80 MHz) δ: 5.83 (m, H-4), 5.45 (m, H-3), 3.70 (dm, H-6), 3.44 (dd, H-7), 3.07 (qd, H-8), 1.82 (m, Me-5), 1.50 (d, Me-8), 5.4 (s large, NH_2); ^1H-J (i, j) mostly determined by selective irradiation experiments: 3,6 = 3 Hz; 3, Me-5 = 1.5 Hz; 4,6 = 1.5 Hz; 4,Me-5 = 1.5 Hz; 6,7 = 7 Hz; 6,Me-5 = 1.5 Hz; 7,8 = 1.8 Hz; 8,Me-8 = 7 Hz. *Anal.* calcd. for $C_{10}H_{13}N_3O_2$ (207.23): C 57.96, H 6.32, N 20.28; found: C 57.65, H 6.18, N 20.24.

Photoisomer **5**b: colourless crystals (methylene chloride/petrol ether), mp 110−111°C (turns yellow); ir (KBr): 1695 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 243 nm (8800); ^1H nmr ($CDCl_3$ at 80 MHz) δ : 7.07 (d, J = 9.5 Hz, H-3), 5.75 (s, H-6 and H-7), 5.8 (s large, exchangeable with D_2O; NH_2), 4.91 (d, J = 9.5 Hz, H-4), 3.31 (qd, J = 7 and 1 Hz, H-8), 1.54 (s, Me-5), 1.24 (d, J = 7 Hz, Me-8). *Anal.* calcd. for $C_{10}H_{13}N_3O_2$ (207.23): C 57.96, H 6.32, N 20.28; found: C 57.97, H 6.51, N 21.07.

[3α,6α,7α,8α] 5,8-Dimethyl 2-benzoyl 9-oxo 1,2-diazatricyclo-[5.2.0.0^{3,6}] 4-nonene **4**c *and [1α,6α,9β] 6,9-dimethyl 3-benzoyl 10-oxa 2,3-diazabicyclo[4.3.1] 1,4,7-decatriene* **5**c

A solution of azetidinodiazepine **3***c* (3) (2.005 g; 7.47 mmol) in 250 mL methylene chloride is irradiated by uv light for 14 h until

complete disappearance of the starting material. After evaporation of the solvent *in vacuo*, the crude reaction mixture is separated into its components by flash chromatography (AcOEt/cyclohexane 2:8). The two isomers **5***c* (55 mg; 3%) and **4***c* (402 mg; 20%) are isolated in that order.

Photoisomer **4**c: colourless crystals (ether), mp 138−139°C; ir (KBr): 1775, 1655 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 228 nm (14 100); ^1H nmr ($CDCl_3$ at 60 MHz) δ: 7.93 (m, H-arom.), 7.47 (m, H-arom.), 5.95 (m, H-4), 5.77 (m, H-3), 3.72 (dm, J = 7 Hz, H-6), 3.37 (dd, J = 7 and 1.5 Hz, H-7), 3.07 (qd, J = 7.5 and 1.5 Hz, H-8), 1.85 (m, Me-5), 1.37 (d, J = 7.5 Hz, Me-8); ms: 268 (M^+; 4%), 105 (100%). *Anal.* calcd for $C_{16}H_{16}N_2O_2$ (268.30): C 71.62, H 6.01, N 10.44; found: C 71.50, H 5.84, N 10.41.

Photoisomer **5**c: colourless crystals (methylene chloride, petrol ether), mp 115−117°C (dec.); ir (KBr): 1670, 1640 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 280 (8000), 227 (7400), and 204 nm (14 900); ^1H nmr ($CDCl_3$ at 60 MHz) δ: 7.77 (m, H-arom.), 7.45 (m, H-arom.), 7.30 (d, J = 10 Hz, H-4), 5.78 (s, H-7 and H-8), 5.13 (d, J = 10 Hz, H-5), 3.30 (q, J = 7 Hz, H-9), 1.53 (s, Me-6), and 1.10 ppm (d, J = 7 Hz, Me-9); ms: 268 (M^+; 8%), 105 (100%). *Exact Mass* calcd. for $C_{16}H_{16}N_2O_2$ (ms): 268.121169; found: 268.1217.

[3α,6α,7α,8α] 8-Methyl 2-benzyloxycarbonyl 9-oxo 1,2-diazatricyclo[5.2.0.0^{3,6}] 4-nonene **4**d *and [1α,6α,9β] 9-methyl 3-benzyloxycarbonyl 10-oxa 2,3-diazabicyclo[4.3.1] 1,4,7-decatriene* **5**d

A solution of azetidinodiazepine **3***d* (1.11 g; 3.89 mmol) in 150 mL methylene chloride is irradiated with uv light for 9 h until consumption of the starting material. After evaporation of the solvent *in vacuo*, the crude reaction mixture is separated into its components by flash chromatography (AcOEt/cyclohexane 2:8). The two isomers **5***d* (144 mg; 13%) and **4***d* (785 mg; 71%) are isolated in that order.

Photoisomer **4**d: yellow oil; ir ($CHCl_3$): 1785, 1718 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 242 nm (770); ^1H nmr ($CDCl_3$ at 60 MHz) δ: 7.40 (s, H-arom.), 6.18 (s, H-4 and H-5), 5.45 (dm, J = 3 Hz, H-3), 5.22 (s, CH_2), 3.93 (dd, J = 6.5 and 3 Hz, H-6), 3.43 (dd, J = 6.5 and 1.5 Hz, H-7), 3.04 (qd, J = 7.5 and 1.5 Hz, H-8), 1.45 (d, J = 7.5 Hz, Me-8); ms: 284 (M^+; less than 1%), 91 (100%). *Exact Mass* calcd. for $C_{16}H_{16}N_2O_3$ (ms): 284.116083; found: 284.1153.

Photoisomer **5**d: colourless oil; ir ($CHCl_3$): 1715, 1645, 1395, 1325, 1305 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 229 (10 700) and 207 nm (13 500); ^1H nmr ($CDCl_3$ at 60 MHz) δ: 7.4 (s, H-arom.), 7.02 (dd, J = 10 and 2 Hz, H-4), 5.80 (m, H-7 and H-8), 5.37 (dd, J = 4 and 2 Hz, H-6), 5.30 (s, CH_2), 5.01 (dd, J = 10 and 4 Hz, H-5), 3.34 (qm, J = 7 Hz, H-9), and 1.27 (d, J = 7 Hz, Me-9); ms: 284 (M^+; 6%); 91 (100%). *Exact Mass* calcd. for $C_{16}H_{16}N_2O_3$ (ms): 284.116084; found: 284.1162.

[3α,6α] And [3α,6β] 3,6-dimethyl 9-ethoxycarbonyl 2-oxo 1,9-diazabicyclo[4.3.0] 4,7-nonadiene 7 and 8

The anti-Bredt compound **5***a* (2.10 g; 8.89 mmol) is heated under an argon atmosphere for 30 min at 140°C; tlc shows that the starting material has disappeared and that two new products have formed. Flash chromatography of the reaction mixture (AcOEt/cyclohexane 3:7) leads to the isolation of compound **8** (146 mg; 7%) and thence of its diasteroisomer **7** (1.78 g; 85%).

Diastereoisomer **7**: colourless crystals (ether/petrol ether), mp 68°C; ir (KBr): 1740, 1718, 1680 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 230 nm (9200); ^1H nmr ($CDCl_3$ at 80 MHz) δ: 6.79 (d, J = 4.4 Hz, H-8), 5.83 (d, J = 2.2 Hz, H-4 and H-5), 5.36 (d, J = 4.4 Hz, H-7), 4.30 (q, J = 7 Hz, CH_2CH_3), 3.04 (qt, J = 7.3 and 2.2 Hz, H-3), 1.46 (d, J = 7.3 Hz, Me-3), 1.43 (s, Me-6), 1.35 (t, J = 7 Hz, CH_2CH_3); ^{13}C nmr ($CDCl_3$ at 100.6 MHz) δ ($^1J_{C-H}$): 172.44 (s, C-2), 152.80 (s, CO_2Et), 127.24 (dd, 194 Hz, C-8), 126.98 (d, 163 Hz, C-4 or C-5), 126.96 (d, 163 Hz, C-5 or C-4), 116.22 (ddq, 181 Hz, C-7), 71.71 (sm, C-6), 62.72 (tq, 149 Hz, CH_2CH_3), 38.63 (dm, 134 Hz, C-3), 29.12 (qs, 129 Hz, Me-6), 20.52 (qd, 130 Hz, Me-3), 14.38 (qt, 128 Hz, CH_2CH_3); ^{13}C nmr ($CDCl_3$ at 100.6 Hz) ^1J ($^{13}C-^{13}C$) coupling constants ± 0.3 Hz: J(2,3) = 50.8 Hz; J(3,4) = 38.7 Hz; J(3,Me-3) = 31.6 Hz; J(6,Me-6) = 36.6 Hz; $J(CH_2,CH_3)$ = 38.3 Hz; J(6,7) = 40.2 Hz; J(7,8) = 76.8 Hz; ms: 236 (M^+; 7%); 121 (100%). *Anal.* calcd. for $C_{12}H_{16}N_2O_3$ (236.26): C 61.00, H 6.83, N 11.86; found: C 61.25, H 6.92, N 11.96.

Diastereoisomer **8**: colourless crystals (ether/petrol ether), mp 83°C; ir (KBr): 1740, 1683 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 230 nm (8800); ^1H nmr ($CDCl_3$ at 80 MHz) δ: 6.75 (d, J = 4.3 Hz, H-8), 5.85 (dd, J = 9.6 and 3.2 Hz, H-4), 5.60 (dd, J = 9.6 and 1.4 Hz, H-5), 5.27 (d, J = 4.3 Hz, H-7), 4.28 (q, J = 7 Hz, CH_2—CH_3), 3.25 (qdd, J = 7.3, 3.2, and 1.4 Hz, H-3), 1.38 (s, Me-6), 1.31 (t, J = 7 Hz, CH_2—CH_3), 1.30 (d, J = 7.3 Hz, Me-3); ^{13}C nmr ($CDCl_3$ at 20.1 MHz) δ($^1J_{C-H}$): 171.29 (sm, C-2), 152.09(st, CO_2Et), 128.20 (dm, 167 Hz, C-4 or C-5), 127.38 (ddq, 168 Hz, C-5 or C-4), 126.74 (dd, 196 Hz, C-8), 114.99 (dm, 180 Hz, C-7), 72.26 (sm, C-6), 62.29 (tq, 148.5 Hz, CH_2CH_3), 34.28 (ddq, 128 Hz, C-3), 27.31 (qs, 130 Hz, Me-6), 14.55 (qdd, 129 Hz, Me-3), 14.05 (qt, 128 Hz, CH_2CH_3); ms: 236 (M^+; 6%); 121 (100%). *Anal.* calcd. for $C_{12}H_{16}N_2O_3$ (236.26): C 61.00, H 6.83, N 11.86; found: C 60.97, H 6.79, N 12.02.

Base-catalyzed equilibration of the two diastereoisomers 7 and 8

(*i*) A solution of compound 7 (945 mg; 4.00 mmol) in 5 mL methylene chloride, to which is added DBU (0.30 mL; 2.00 mmol), is heated at reflux temperature for 90 min, the reaction being followed by tlc. After cooling to room temperature and addition of silicic acid (4 g), the solvent is evaporated *in vacuo*. Flash chromatography of the reaction mixture (AcOEt/cyclohexane 3:7) leads to the isolation of isomer **8** as the major product (530 mg; 56%) and of isomer 7 (388 mg; 41%).

(*ii*) A solution of compound **8** (590 mg; 2.50 mmol) is treated with identical reaction conditions whereby **8** is again isolated as the major product (330 mg; 56%) and 7 as the minor isomer (207 mg; 35%). In addition, compound **9** also forms in low yield (22 mg; 4%).

3,6-Dimethyl 9-ethoxycarbonyl 2-oxo 1,9-diazabicyclo[4.3.0] 3,7-nonadiene **9**

A solution of compound 7 (472 mg; 2.00 mmol) in 8 mL chloroform, to which is added DBU (0.30 mL; 2.00 mmol), is heated at reflux temperature for 15 h. The reaction is followed by tlc which shows that the equilibration between 7 and **8** occurs rapidly. After a few hours a new compound appears which is the sole product at the end of the reaction. After addition of some silicic acid (2 g) the solvent is evaporated *in vacuo* and the crude reaction mixture separated by flash chromatography (AcOEt/cyclohexane 3:7). Compound **9** is obtained (408 mg; 86%) as colourless crystals (ether/petrol ether), mp 62°C; ir (KBr): 1745, 1675, 1642, 1615 cm^{-1}; uv (MeOH) λ_{max} (ϵ): 212 (13 400) and 273 nm (1700; shoulder); ^1H nmr ($CDCl_3$ at 80 MHz) δ: 6.71 (d, J = 4.5 Hz, H-8), 6.10 (m, H-4), 5.30 (d, J = 4.5 Hz, H-7), 4.27 (q, J = 7 Hz, CH_2CH_3), 2.70 (ddq, J = 16, 2.5, and 2.5 Hz, H-5), 2.37 (dd, J = 16 and 6 Hz, H-5), 1.98 (m, Me-3), 1.39 (s, Me-6), and 1.34 ppm (t, J = 7 Hz, CH_2CH_3); ^{13}C nmr ($CDCl_3$ at 20.1 MHz) δ ($^1J_{C-H}$): 160.17 (sm, C-2), 153.61 (st, $CO_2CH_2CH_3$), 131.02 (sm, C-3), 128.24 (dm, 163 Hz, C-4), 128.10 (dd, 195 Hz, C-8), 116.35 (dm, 179 Hz, C-7), 66.84 (sm, C-6), 62.47 (tq, 149 Hz, CH_2CH_3), 33.77 (tm, 131 Hz, C-5), 25.57 (qdd, 129 Hz, Me-6), 16.24 (qdd, 128 Hz, Me-3), 13.91 (qt, 128 Hz, CH_2CH_3); ms: 236 (M^+; 13%), 82 (100%). *Anal.* calcd. for $C_{12}H_{16}N_2O_3$ (236.26): C 61.00, H 6.83, N 11.86; found: C 61.13, H 6.87, N 11.85.

Differential scanning calorimetry of the thermal isomerization of **5**a *into the mixture of 7 and 8*

The thermal rearrangement of the neat anti-Bredt compound **5***a* to its isomers **7** and **8** (melt process) was determined by DSC with a Perkin−Elmer DSC-2C apparatus coupled with a Perkin−Elmer TADS-computer. This latter permits one to memorize and to process the DSC curve according to the standard Perkin−Elmer DSC program. Measurements were determined in a dynamic mode, with a constant heating rate of 80°/min. Results: reaction enthalpy: ΔH = 169 ± 2.0 kJ/mol (40.5 kcal/mol); order of the reaction: n = 1.09 ± 0.02; activation energy: E_a = 130 ± 2.8 kJ/mol (31.1 kcal/mol); logarithm of the Arrhenius pre-exponential factor: ln (A) = 32.0 ±

0.7 (A in s^{-1}). According to the ^1H nmr (80-MHz FT) and to the tlc analysis of the reaction mixture, compound **7** is by far the major thermoisomer formed at the end of the DSC experiment with educt **5***a*.

Acknowledgements

We thank the Centre National de la Recherche Scientifique for financial support. We are also grateful to Michelle Martigneaux for her aid in preparing the diazepines **1***a*–**1***d*.

1. R. B. MORIN and M. GORMAN. Chemistry and biology of β-lactam antibiotics. Vols. 1–3. Academic Press, New York. 1982.
2. P. SAMMES. Topics in antibiotic chemistry. Vol. 4. Ellis Horwood Ltd.; Chichester, England. 1980.
3. H. R. PFAENDLER, J. GOSTELI, and R. B. WOODWARD. J. Am. Chem. Soc. **102**, 2039 (1980); V. M. GIRIJAVALLABHAN, A. K. GANGULY, P. PINTO, and R. VERSACE. J. Chem. Soc. Chem. Commun. 908 (1983).
4. A. G. BROWN. J. Antimicrob. Chemother. 15 (1981); N. IKOTA, O. YOSHINO, and K. KOGA. Chem. Pharm. Bull. **30**, 1929 (1982).
5. C. M. CIMARUSTI, H. E. APPLEGATE, H. W. CHANG, D. M. FLOYD, W. H. KOSTER, W. A. SLUSARCHYK, and M. G. YOUNG. J. Org. Chem. **47**, 179 (1982).
6. J. STREITH and T. TSCHAMBER. Justus Liebigs Ann. Chem. 1993 (1983).
7. J. P. LUTTRINGER, N. PEROL, and J. STREITH. Tetrahedron, **31**, 2435 (1975).
8. J. STREITH, J. P. LUTTRINGER, and M. NASTASI. J. Org. Chem. **36**, 2962 (1971).
9. G. KAN, M. T. THOMAS, and V. SNIECKUS. J. Chem. Soc. Chem. Commun. 1022 (1971).
10. C. R. HARRISON and P. HODGE. J. Chem. Soc. Perkin Trans. 1, 1772 (1976).
11. E. H. FLYNN. Cephalosporins and penicillins. Academic Press, New York. 1972.
12. R. MONDELLI and P. VENTURA. J. Chem. Soc. Perkin Trans. 2, 1749 (1977); J. W. PASCHAL, D. E. DORMAN, P. R. SRINIVASAN, and R. L. LICHTER. J. Org. Chem. **43**, 2013 (1978).
13. G. ALBERS-SCHÖNBERG, B. H. ARISON, O. D. HENSENS, J. HIRSHFIELD, K. HOOGSTEEN, E. A. KACZKA, R. E. RHODES, J. S. KAHAN, F. M. KAHAN, R. W. RATCLIFFE, E. WALTON, L. J. RUSWINKLE, R. B. MORIN, and B. G. CHRISTENSEN. J. Am. Chem. Soc. **100**, 6491 (1978).
14. J. L. MARSHALL. *In* Carbon–carbon and carbon–proton NMR couplings in the series stereochemical analysis. Vol. 2. *Edited by* A. P. Marchand. Verlag Chemie International, Deerfield Beach, Florida. 1983, and references cited therein.
15. R. ALLMANN and T. DEBAERDEMAEKER. Cryst. Struct. Commun. **3**, 365 (1974).
16. S. SHIOTANI, T. KOMETANI, A. KUROBE, and K. MITSUHASHI. J. Org. Chem. **41**, 4106 (1976); H. J. BESTMANN and G. SCHADE. Tetrahedron Lett. **23**, 3543 (1982); H. KATO, Y. ARIKAWA, and M. MASUZAWA. Heterocycles, **20**, 118 (1983).
17. W. F. MAIER and P. VON R. SCHLEYER. J. Am. Chem. Soc. **103**, 1891 (1981).
18. G. SZEIMIES. *In* Reactive intermediates. Vol. 3. *Edited by* R. A. Abramovitch. Plenum Publishers, New York. 1983.
19. L. W. CRANE, P. J. DYNES, and D. H. KAELBLE. J. Polym. Sci. Polymer Lett. Ed. **11**, 533 (1973).
20. A. T. BALABAN. Rev. Roum. Chim. **16**, 725 (1971).
21. H. G. VIEHE, R. MERÉNYI, L. STELLA, and Z. JANOUSEK. Angew. Chem. **91**, 982 (1979); Angew. Chem. Int. Ed. Engl. **18**, 917 (1979).
22. W. C. STILL, M. KAHN, and A. MITRA. J. Org. Chem. **43**, 2923 (1978).
23. F. BELLAMY and J. STREITH. J. Chem. Res. (S), 18 (1979).