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β-LACTAM DERIVATIVES FROM 1-H-1,2-DIAZEPINES

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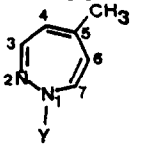
Abstract. *Trans* Azetidinodiazepines **2** were obtained when ketenes were reacted with diazepines **1**. Photoisomerization of **2** gave tricyclic isomers **5** which were cleaved to give the azacarbapenams **7**. Acylnitroso dienophiles reacted with **2** to give the pair of regioisomers **8** and **9** which were transformed to the azetidinoribose **12**, and to the 4-amino-1-deoxyribose derivative **15**, respectively. Anti-HIV activity of **15** was assessed.

Introduction. 1H-1,2-Diazepines **1** are readily obtained via photoinduced ring-enlargement of the corresponding 1-iminopyridinium ylid isomers [1]. X-Ray crystallographic analyses of diazepines **1** (Y = Ts or CO_2R) showed in particular that the C=N double bond is rather short (1.26 Å) [2]. This geometrical data led us to assume that the C=N double bond should behave as an imine, and consequently undergo the Staudinger reaction (SR). This was indeed observed since β-lactams **2** were obtained readily in a stereospecific *trans*-manner when diazepines **1** were reacted either with monosubstituted ketenes, or with monosubstituted acetyl chlorides in the presence of tertiary amines [3].



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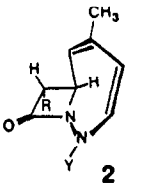

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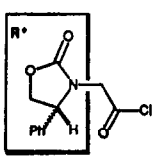
a) Y = CO_2CH_3

b) Y = $CO_2CH_2CH_2SiMe_3$

Asymmetric Synthesis of Azetidinodiazepines. Assuming the formation of a ketene intermediate when reacting an acid chloride with triethylamine, the two-step cycloaddition with (Z) imines was expected to lead stereospecifically to *trans* β-lactams [4]. In previous studies we have shown that the "Evans-Sjogren" ketene, which was generated *in situ* by a base treatment of the chiral oxazolidine-acetyl chloride **3** at low temperature, reacted with diazepine **2a** and gave the two expected *trans* diastereoisomeric β-lactams (*d.e.*: 82 %), the major cycloadduct having the absolute configuration as indicated by formule **4** [5][6].



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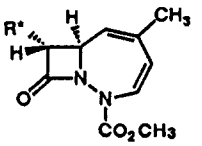

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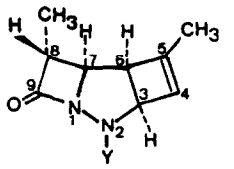
Azacarbapenam derivatives. Direct UV-irradiation of **2b** gave the tricyclic isomer **5a** in high yield. The 4π disrotatory electrocyclisation is torquospecific as a consequence of the boat-shaped conformation which is represented in formula **2** [7]. Treatment of **5a** with TBAF gave the expected N-H derivative **5b** which was transformed into its N-sulfonated ammonium salt **5c** using the SO3/DMF complex and thence tetra-n-butylammonium dihydrogenophosphate.

Microbial tests (MIC-values) of **5c** were measured with a series of pathogenic bacteria and showed that this compound did not have any antibacterial activity [7].

Next we turned our attention to the fragmentation of the cyclobutene ring of **5a** using a methodology which is seldom employed. Addition of ozone to **5a** led to a stable and crystalline secondary ozonide which was cleaved by UV-light to give the rather unstable azacarbapenem derivative **6a** (35 %), amongst other products. Catalytic hydrogenation of **6a** led to azacarbapenam derivative **7a** as a stable product. Although treatment of **7a** with TBAF obviously gave the expected compound **7b** its NH group reacted at once with the azetidino moiety of a second molecule of **7b**, leading to β-lactam ring cleavage and to the formation of an undesired amide [7].



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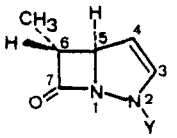

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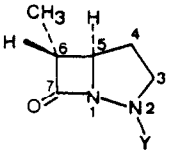

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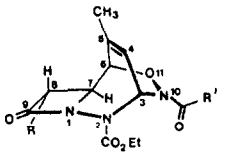
a) Y = $CO_2CH_2CH_2SiMe_3$; b) Y = H ; c) Y = $SO_3^- \cdot nBu_4N^+$

[4π + 2π]-Cycloaddition of Azetidinodiazepines 2 with Acylnitrosodienophiles. Synthesis of Aminodeoxyribose Derivatives. The *trans* azetidinodiazepines which are monosubstituted at C(7) were shown by X-ray analysis and by NMR to be in the boat conformation as indicated in the perspective view of 2 [8].



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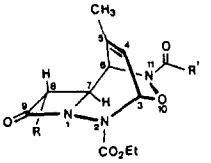
a) R = Me ; R' = O Bu

b) R = Me ; R' = Ph



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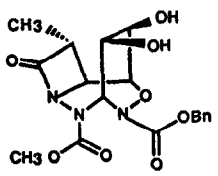

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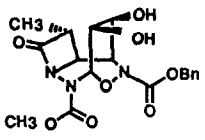

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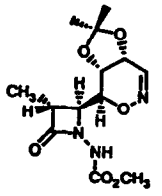

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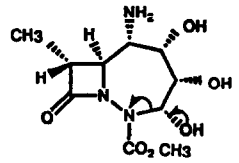

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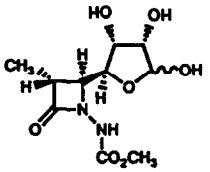

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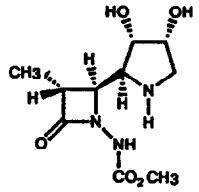

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This α-side attack was indeed observed - to the exclusion of any β-side attack - when type **2** compounds (no Me-groups at C(5)) were reacted with acylnitroso dienophiles. It led stereospecifically to type **8b** and to type **9b** regioisomers whose stereostructures were demonstrated by X-ray analyses [9].

Catalytic osmylation of **8a** and **9a** led stereospecifically to the corresponding cis-diols **10** and **13**. Hydrogenolysis (Pd/C) of the benzyloxycarbonyl moiety of **10** gave the oxazine **11** in excellent yield, the glycol being protected as an acetonide. Treatment of **11** with Raney nickel in the presence of ammonia, followed by removal of the acetonide, ultimately gave the ribose derivative**12** (two anomers), as anticipated [10].

Treated similarly (catalytic osmylation ; hydrogenolysis over Pd/C) the regio-isomer **9a** gave the dideoxyaminoribose derivative **15** via the postulated seven-membered intermediate **14** [10].

It has been known for some time that aminosugar derivatives which inhibit glycoprotein processing have potential antihuman immunodeficiency virus (HIV) activity [11]. These naturally occurring aminodeoxysugars derive either from piperidines, from pyrrolidines, from pyrrolizines, or from octahydroindolizines, and are deprived of the anomeric OH group. Compound **15** (hydrochloride), which is a derivative of (±)aminoribose, falls within the pyrrolidine group. As a consequence it was evaluated for its anti-HIV activity. This compound was evaluated in two separate experiments in duplicate in a primary screen against HIV (Strain GB 8) in JM cells (3 day assay). Activity was measured by syncytium formation [12] and cytotoxicity [13] in an MTT assay, castanospermine being the reference compound. In this assay **15** (hydrochloride) showed an antiviral activity less than that of castanospermine which was used as a reference substance (**Table 1**).

Table 1. Anti-HIV activity and cytotoxicity of compound **15**, HCl and of castanospermine.

Compounds	Antiviral activity	% Cytotoxicity at 100 μM
15,HCl	% inhibition of syncytium at 100 μM 20 and 27	0 and 32
Castanospermine	IC_{50} =7.3 μM and 8.8 μM IC_{90} = 28.2 μM and 24.5 μM	0 and 4

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References

[1] Streith J. *Pure Appl. Chem.* **1977**, *49*, 305 ; Snieckus V.; Streith J. *Acc. Chem. Res.* **1981**, *14*, 348 ; Streith J. *Chimia* **1991**, *45*, 65.

[2] Allmann R.; Frankowski A.; Streith J. *Tetrahedron* **1972**, *8*, 581.

[3] Luttringer J.P.; Streith J. *Tetrahedron Lett.* **1973**, 4163 ; Streith J.; Wolff G. *Heterocycles* **1976**, *5*, 471 ; Allmann R.; Debaerdemaeker T.; Kiehl G.; Luttringer J.P.; Tschamber T.; Wolff G.; Streith J. *Liebigs Ann. Chem.* **1983**, 1361 ; Kiehl G.; Streith J.; Tschamber T. *Liebigs Ann. Chem.* **1983**, 2141.

[4] Hegedus L.S.; Montgomery J.; Narukawa Y.; Snustad D. *J. Am. Chem. Soc.* **1991**, *113*, 5784 ; Cossio F.P.; Ugalde J.M.; Lopez X.; Lecea B.; Palomo C. *J. Am. Chem. Soc.* **1993**, *115*, 995.

[5] Muller M.; Bur D.; Tschamber T.; Streith J. *Helv. Chim. Acta* **1991**, *74*, 767.

[6] Evans D.A.; Sjogren E.B. *Tetrahedron Lett.* **1985**, *26*, 3783, and ref. cit. therein ; Ojima I.; Chen H.J.C.; Nakanishi K. *J. Am. Chem. Soc.* **1988**, *110*, 278.

[7] Tschamber T.; Henlin J.M.; Pipe D.; Streith J. *Heterocycles* **1985**, *23*, 2589.

[8] Allmann R.; Debaerdemaeker T. *Cryst. Struct. Commun.* **1974**, *3*, 365.

[9] Fritz H.; Henlin J.M.; Riesen A.; Tschamber T.; Zehnder M.; Streith J. *Helv. Chim. Acta* **1988**, *71*, 822.

[10] Muller M. PhD-thesis, Université de Haute-Alsace, July 1991, Mulhouse, France.

[11] Karpas A.; Fleet G.W.J.; Dwek R.A.; Petursson S.; Namgoong S.K.; Ramsden N.G.; Jacob G.S.; Rademacher T.W. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 9229.

[12] Craig J.C.; Duncan I.B.; Hockley D.; Grief C.; Roberts N.A.; Mills J.S. *Antiviral Res.* **1991**, *16*, 295.

[13] Craig J.C.; Duncan I.B.; Whittaker L.; Roberts N.A. *Antiviral Chem. Chemother.* **1993**, *4*, 161.