GLYCOSYLAZIRIDINE DERIVATIVES

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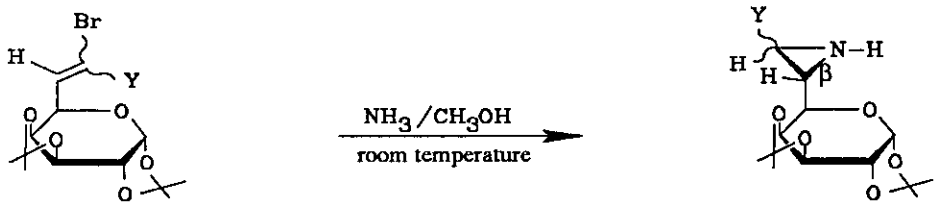
Abstract — Addition of ammonia to the bromoenoses **Ia-e** afforded the corresponding secondary dissymmetric aziridines **IIa-e** respectively. The stereochemistry of their ring opening and ring expansion to Δ^2-oxazolines has been studied and the absolute configuration of the two newly obtained asymmetric carbon atoms was established.

We describe here novel procedures of functionalization of octoenopyranoses leading to close analogs of lincosamine,[1] which is the key intermediate in the synthesis of lincomycin[2] *via* their conversion into glycosylaziridines followed by ring opening.

The conjugate nucleophilic addition of ammonia to the bromoenoses **Ia-e**[1] afforded the desired disubstituted secondary aziridines **IIa-e**,[3] generally in good yield (Scheme I), sometimes as a mixture of *Z* and *E* isomers.

Scheme I



Ia Y = CN (*E*/*Z* = 67/33)
Ib Y = $COCH_3$ (*Z*)
Ic Y = COPh (*E*/*Z* = 28/72)
Id Y = $COOCH_3$ (*Z*)
Ie Y = $COOC_2H_5$ (*Z*)
If Y = $CONH_2$ (*Z*)[a)]

IIa Y = CN	68% (*E*/*Z* = 2/3)[4]
IIb Y = $COCH_3$	65% (*E*)
IIc Y = COPh	40% (*E*)
IId Y = $COOCH_3$	84% (*E*/*Z* =16/5)
IIe Y = $COOC_2H_5$	73% (*E*/*Z* = 35/9)
IIf Y = $CONH_2$	39% (*E*)
IIg Y = CH_2OH	80% (*E*)

[a)] Obtained in 12-16% yield as a by-product of the preparation of **IId** and **IIe**.

A mixture of **IId** and **IIf** was also formed upon prolonged reaction of **Id**. The reduction of *(E)*-**IId** with $LiAlH_4$[5] afforded the corresponding *(E)*-hydroxymethylaziridine **IIg**. The ^{1}H-nmr spectra of (**IIa-g**) in $CDCl_3$ showed the N-**H** proton of the ring as an exchangeable broad singlet (δ 1.5 to 2.5 ppm). The relative configurations were established, in all cases, from the values of the coupling constants of the two methine protons of the three-membered rings ($J_{\alpha,\beta}$).[6] The obtained results are collected in Table I.

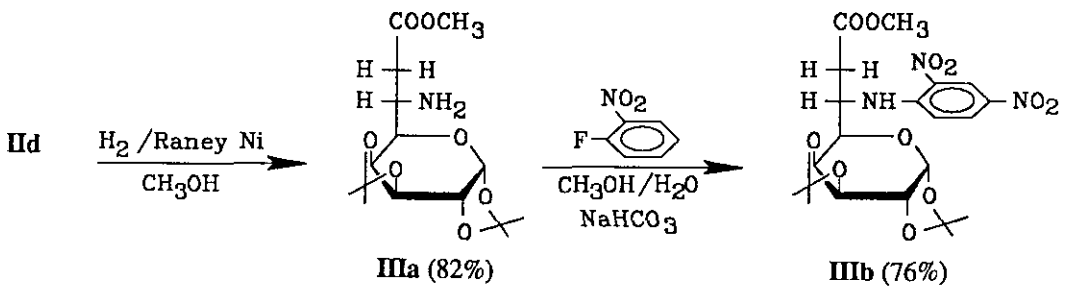
Table I. Some ^{1}H-Nmr Data of Compounds **II**.

Compounds	$\delta_{H\text{-}C\alpha}$	$\delta_{H\text{-}C\beta}$	$J_{\alpha,\beta}$	Compounds	$\delta_{H\text{-}C\alpha}$	$\delta_{H\text{-}C\beta}$	$J_{\alpha,\beta}$
(E)-**IIa**	2.56	2.69	2.7	*(Z)*-**IIa**	2.68	2.72	5.7
(E)-**IIb**	2.77	2.39	2.6	*(E)*-**IIc**	3.50	2.52	2.8
(E)-**IId**	2.57	2.66	2.9	*(Z)*-**IId**	2.77	2.68	6.5
(E)-**IIe**	2.56	2.62	2.7	*(Z)*-**IIe**	2.84	2.62	6.2
(E)-**IIf**	2.59	2.37	2.5	*(E)*-**IIg**	2.53	2.40	2.7

Variable temperature measurements (in $CDCl_3$, CCl_4, C_6D_6 or toluene-d_8) indicated the presence of a single, stable invertomer. The *cis* relationship between the proton H-C_β and the lone pair on the nitrogen was indicated by the greater value of $J_{^{13}C\beta,H}$ = 175.5 Hz, relative to $J_{^{13}C\alpha,H}$ = 172.3 Hz for *(E)*-**IId**[7] in ^{13}C-nmr.[8] This situation was favoured by the repulsion between the lone pair of the nitrogen and the pyranose ring. The ^{15}N-nmr showed a singlet at δ -350.15 ppm for both *(E)*- and *(Z)*-**IId**.[9]

Hydrogenation[10] of *(E)*- or *(Z)*-**IId** gave **IIIa** which afforded **IIIb** upon treatment with 2,4-dinitrofluorobenzene (Scheme II).

Scheme II

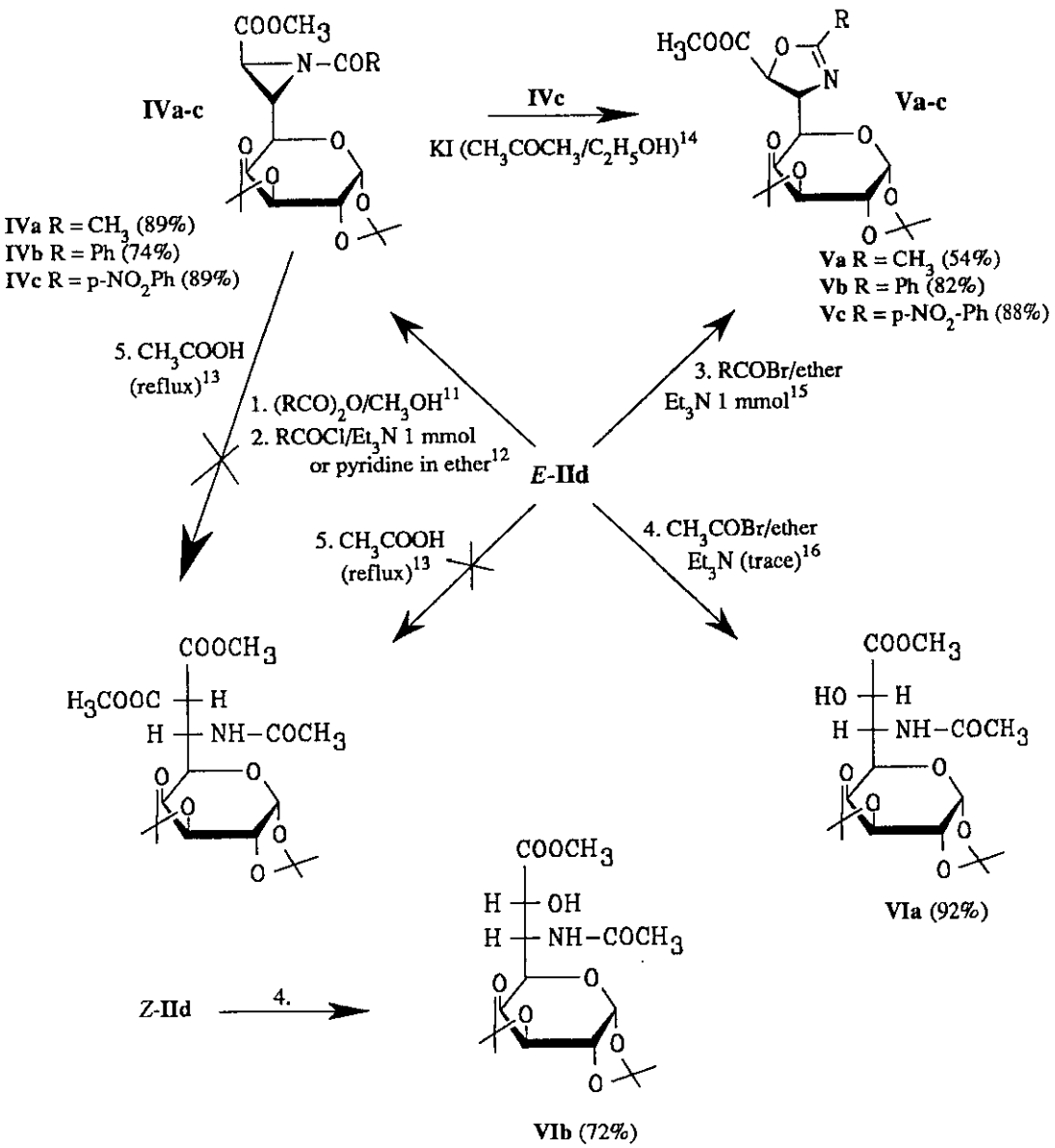


IIIa (82%) **IIIb** (76%)

The direction of the regiospecific opening of the aziridine ring (breaking of the $C_{\alpha\text{-}N}$ bond), was proved from the ^{1}H-nmr spectrum of **IIIb** (ABX system at δ 2.69, 2.98 and 4.46 ppm).

Compound *(E)*-**IId** was refractory to most traditional methods of ring opening and we had to ressort to less classical ones (Scheme III).

Scheme III



The stereospecificity of the ring opening was shown by the fact that *(Z)*-**IId** led to a compound (**VIb**) different from **VIa**.

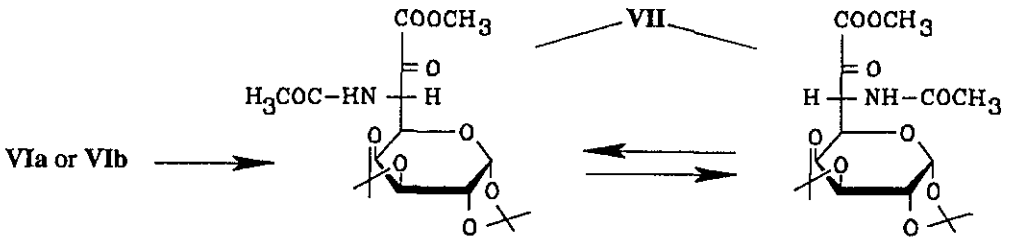
On the *N*-acylation to **IV**, the H-C_α and H-C_β protons of **II** underwent a downfield shift,[17] while the formation of **Va-c** resulted in a further deshielding of the same protons owing to the ring expansion. The attachment of the nitrogen atom at C_β was established by the comparison of ^1H and ^{13}C chemical shifts of the obtained Δ^2-oxazolines with literature data[18] and the nmr data of a positional isomer obtained by an univocal synthesis[19] (**IVd**) (Table II).

Table II. Some Nmr Data of Acylaziridines **IV** and Oxazolines **V**.

Compound	$\delta_{H\alpha}$	$\delta_{H\beta}$	$J_{\alpha,\beta}$	$\delta_{C\alpha}$	$\delta_{C\beta}$
IVa	3.14	3.21	2.5		
IVb	3.41	3.45	2.3		
IVc	3.40	3.43	2.2		
Va	5.13	4.50	6.5		
Vb	5.07	4.76	6.2	77.641	72.069
Vc	5.33	4.76	6.6	78.131	72.426
Vd	4.79	5.03	7.1	69.137	79.357

Thus, the nucleophilic attack on the aziridine ring of *(E)*-**IId** during the ring expansion, occurred regiospecifically by an abnormal mechanism[20,21] induced by the steric demand of the di-*O*-isopropylidenegalactopyranosyl group.[22] As the oxazoline **Va** could be univocally hydrolyzed (Na_2CO_3) into **VIa**, by a reaction which does not involve the asymmetric centers,[23] **VIa** should be an α-hydroxy-β-acetylamino ester in which the C_α and C_β have the same absolute configuration as the corresponding carbon atoms in **Va**, whereas **VIb** should be the α-epimer of **VIa**.

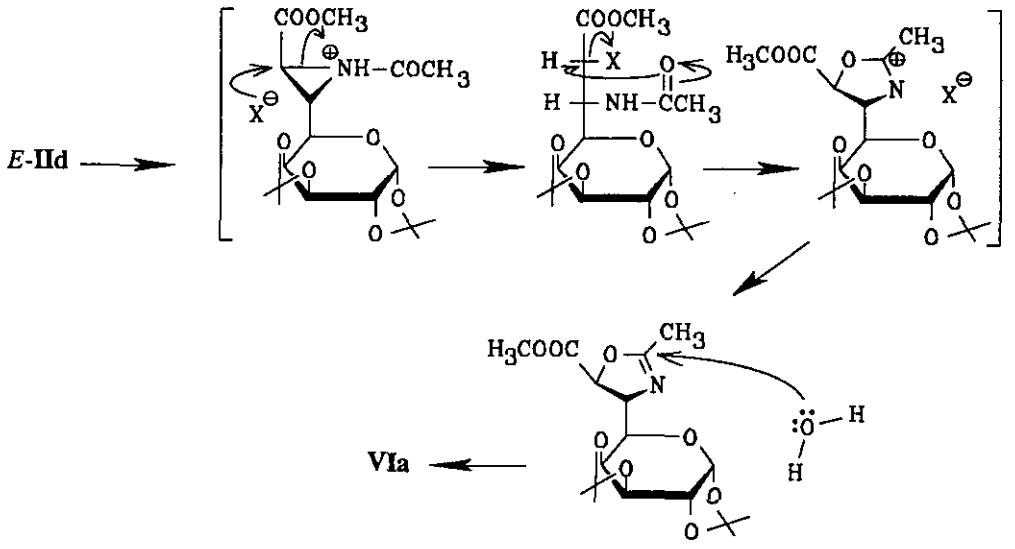
Oxidation of either **VIa** or **VIb** with Collins' reagent, gave a mixture of the α-keto-β-acetylamino esters **VII**,[24] through the epimerisation at C_β as already noted in the case of β-acetylamino ketones,[25] thus allowing access to the series epimeric at the β carbon.



The absolute configuration was determined for **IIIa** and **IIIb** by circular dichroism (cd), using the rules established for the β-amino acids,[26] where a negative sign indicated an *S* absolute configuration of the asymmetric carbon atom bearing the amino group, which corresponds to the C_β of both *(E)*- and *(Z)*-**IId**. On the other hand, the positive and the negative cd signs obtained for **VIa** and **VIb** respectively indicated[27] their absolute configuration respectively *S* and *R*, at the carbon atom bearing the hydroxyl group. The configuration of *(E)*-**IId** was established by an X-ray diffraction study[28] which confirmed also the habitual[29] $^3S_5$ conformation of the di-*O*-isopropylidene-α-*D*-galactopyranose ring.

An identical configuration could also be proposed for **IIf** and **IIg**, as their formation does not involve the asymmetric centers, while for **IIa-c** and **IIe**, the absolute configuration was established by correlation between the cd curves and the absolute configuration of both asymmetric carbon atoms constituting the aziridine ring.[30]

The ring opening of *(E)*- and *(Z)*-**IId**, as well as the ring expansion of *(E)*-**IId**, must imply two successive Walden inversions, *affording a complete retention of configuration.*



The formation of aziridines should take place by the stereospecific attack of ammonia at C_β of the bromoenoses from the *re*-side, the more favourable owing to the steric encumbrance[31] of the axial O-4 and possibly the participation of the oxygen atom of the pyranose ring.[32] The *E*/*Z* ratios of the obtained aziridines were probably kinetically controlled and governed by the electronegativity of Y groups and the steric hindrance of the *erythro* and *threo* intermediates, obtained by the reprotonation of the intermediate carbanion.[33]

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3. The ammonia gas was dried over KOH, then passed (at 30 bubles/min from a glass tube having an internal diameter of 0.3 cm) for 3 min through a solution of the appropriate bromoenose (3.0 mmol) in absolute methanol (50 ml) at room temperature. The reaction flask was then tightly closed and agitated with a magnetic stirrer for 10 min, then monitored by tlc (every 2 min). After 20 min, if the reaction was not completed, the operation was repeated. When the reaction was finished (the bromoenose having approximately disappeared), dry nitrogen gas was passed into the reaction mixture for 5 min. The solvent was then evaporated, the residue extracted with $CHCl_3$, the organic layer thoroughly washed with water, dried over $MgSO_4$ (anhydrous), evaporated under vacuum at about 30 °C and then chromatographed (ether/hexane 2:1) on a column of silica gel "60G 254 MercK". All the new compounds prepared, had elementary analyses and spectroscopic data in accordance with the proposed structure.
4. Proportions were determined on the mixture by ^{1}H-nmr using $CDCl_3$ as solvent and TMS as internal reference. Measured on a Perkin-Elmer R 32 (90 MHz).
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8. Measured at 25.2 MHz on a Varian XL100 in $CDCl_3$ as solvent, and using TMS as internal reference.
9. Measured on a Bruker WH 90 MHz (total decoupling) in $CDCl_3$ as solvent, and using NO_3^- as internal reference.
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15. Acetyl bromide (~ 1.05 mmol) was slowly added to a suspension of the *E*-**IId** (1 mmol), triethylamine (0.09 ml) in dry ether (15 ml) at 10 °C. The reaction mixture was then left tightly closed with continuous agitation at room temperature for 3 h, then filtered. The filtrate was washed with saturated $NaHCO_3$ (5 ml) at 0 °C, cold water (3x5 ml), dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed over a small column of silica gel (ether/hexane 4:1).
16. Acetyl bromide (1.05 mmol) was slowly added to a solution of *(E)*-**IId** (1 mmol), in a mixture of dry ether/CH_2Cl_2 (1:1, 30 ml) and a trace of Et_3N at 0 °C. The reaction mixture was left tightly closed with continuous agitation overnight at room temperature, then evaporated. The obtained residue was extracted with CH_2Cl_2 (30 ml), the extract was agitated with a saturated Na_2CO_3 solution (10 ml) during 1 h. The organic layer was then washed with water (3x10 ml), dried over anhydrous $MgSO_4$, filtered and evaporated to give the analytically pure product.
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