A NOVEL STEREOSPECIFIC REARRANGEMENT OF 3-SUBSTITUTED B-HOMO-5-AZASTEROID LACTAMS TO A-NOR ANALOGUES

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<u>Summary</u>: B-Homo-5-azasteroid lactams containing nucleofugal substituents in the 3-position ($\underline{1}$ and $\underline{2}$) undergo rearrangement via stereospecific ring contractions to afford A-nor analogues $\underline{3}$ and $\underline{4}$.

As part of our studies of steroid analogues containing existing or latent reactive functional groups,¹ we wished to determine the effect of a lactam nitrogen atom at the 5-position upon the reactions of nucleofugal substituents at C-3 in compounds <u>1</u> and <u>2</u>. Neighbouring group participation by the nitrogen atom could influence the reactivity and stereochemical outcome of such processes. By analogy, nitrogen mustards [bis-(β -chloroethyl)amines] and half-mustards [β -(chloroethyl)amines] are well-known alky-lating agents where anchimeric assistance by nitrogen facilitates departure of chloride from the β -position via the formation of aziridinium ion intermediates.²

We now report that both azasteroid lactams $\underline{1}$ and $\underline{2}$ unexpectedly undergo highly stereospecific rearrangements via ring contraction to the corresponding A-nor derivatives $\underline{3}$ and $\underline{4}$, respectively, under a variety of conditions (see eq 1 and 2 and Table 1).³ These rearrangements are accompanied by competing substitution at C-3 with inversion of configuration to afford $\underline{5}$ and $\underline{6}$.



When the 3α -alcohol $\underline{1}$ (X= OH) or its tosylate (X= OTs) were treated with thionyl chloride or LiCl, respectively, the A-nor derivative $\underline{3}$ (Y= Cl) was the principal product. Similarly, the reaction of the 3α -chloride $\underline{1}$ (X= Cl) with aqueous AgNO₃ afforded chiefly the rearranged alcohol $\underline{3}$ (Y= OH). In the 3α -series, only the reaction of the alcohol $\underline{1}$ (X= OH) with triphenylphosphine and carbon tetrachloride⁴

gave predominantly the product of substitution 5 (Y= Cl). Similar results were obtained in the 3 β -series, except that the reactions were generally slower and afforded lower ratios of rearrangement vs. substitution and lower yields of rearranged products.

The substitution products $\underline{5}$ and $\underline{6}$ are presumably formed by S_N^2 processes that don't involve neighbouring group participation by the lactam nitrogen atom. On the other hand, the mechanism of the competing rearrangements must account for the highly stereospecific formation of $\underline{3}$ from $\underline{1}$ and of $\underline{4}$ from $\underline{2}$. This observation clearly rules out the formation of a carbocation intermediate $\underline{7}$ by an S_N^1 process, followed by its rearrangement, as both the α - and β -series would produce identical mixtures of isomers $\underline{3}$ and $\underline{4}$. The displacement of the amide anion by attack of Y⁻ at C-4 of $\underline{1}$ or $\underline{2}$, followed by intramolecular S_N^2 attack by the amide anion at C-3 of $\underline{8}$, would account for the observed stereochemistry. However, this N-dealkylation, N-alkylation sequence should require a relatively strong nucleophile Y⁻ and is inconsistent with the observed rearrangements of $\underline{1}$ and $\underline{2}$ (X= Cl) in aqueous AgNO₃.⁵



Neighbouring group participation by the nitrogen atom in $\underline{1}$ and $\underline{2}$ would result in the stereospecific formation of the aziridinium ion intermediates $\underline{9}$ and $\underline{10}$, leading to $\underline{3}$ and $\underline{4}$, respectively, after attack by Y at C-4. Objections to this pathway, however, arise from stereoelectronic considerations in the 3α -series (1), where the alignment of the nitrogen p-orbital with that of the axial C-X bond is unfavourable for satisfactory overlap required for the formation of the new N-C bond. We therefore propose that compounds $\underline{1}$ react via prior ring-flipping to the corresponding boat conformation, where the orientation of the equatorial C-X bond is stereoelectronically more favourable (path \underline{a} in Scheme 1). Molecular modeling calculations⁶ indicate that the boat conformations of compounds $\underline{1}$ are less stable than the corresponding chairs by 2.1, 3.7 and 3.4 kcal/mol for X= OH, OTs and Cl, respectively. Thus, ring-flipping should be relatively facile in these systems.⁷ Compounds $\underline{2}$, on the other hand, do not require prior ring-flipping, as the C-X bond is already equatorial and correctly aligned for attack by the lactam nitrogen atom. This resembles the well-known solvolyses of cholesterol derivatives containing equatorial leaving groups at C-3, where neighbouring group participation by the π -system of the Δ^5 double bond leads to stereospecific substitution with retention of configuration at C-3, or to the corresponding 6 β -substituted 3,5-cyclo-steroids⁸ (eq 3).



A final consideration involves the concertedness of the rearrangement as opposed to the formation of the discrete intermediates 9 and 10. The IR spectra of compounds 1 and 2 (X= OH, OTs, Cl) all display lactam carbonyl absorptions at the relatively low frequencies⁹ of 1616-1632 cm⁻¹, suggesting an unusually low C=O bond order and strong amide resonance. This, in turn, is expected to lower the nucleophilicity of the lactam nitrogen atom, arguing in favour of a concerted process such as shown in path <u>b</u> of Scheme 1. In the latter case, a boat conformation must again be invoked in the 3 α -series to permit the necessary antiperiplanar orientation of the C(4)-N bond with the C(3)-X bond. Further work is required to permit firm conclusions regarding the two pathways, which may vary from case to case depending on the nature of X,Y and the reaction conditions. We are also exploring the extension of this novel ring contraction to nonsteroidal lactams with varying ring sizes, as such processes would have considerable synthetic potential.



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Starting material	Conditions	Time (h)	Rearrangement product (Yield, %) ^a	Substitution product (Yield, %) ^a
<u>1;</u> X= OH	SOCI ₂ , CH ₂ CI _{2,} RT	4	<u>3;</u> Y≖ CI (72)	-
<u>2;</u> X= OH	SOCI ₂ , CH ₂ CI _{2,} RT	60	<u>4;</u> Y= CI (63)	<u>6;</u> Y= CI (14)
<u>1</u> ; X= OTs	LICI, Me ₂ C=O, t-BuOH, Δ	8	<u>3;</u> Y= Cl (67)	<u>5;</u> Y= CI (22)
<u>2;</u> X= OTs	LiCl, Me ₂ C=O, t-BuOH, Δ	48	4; Y= CI (trace)	<u>6;</u> Y= Cl (81)
<u>1;</u> X= OH	Ph ₃ P, CCl ₄ , CH ₂ Cl ₂ , RT	16	<u>3;</u> Y= Cl (13)	<u>5;</u> Y= Cl (65)
<u>2;</u> X= OH	Ph ₃ P, CCl ₄ , CH ₂ Cl ₂ , RT	48	-	<u>6;</u> Y= Cl (88)
<u>1;</u> X= Cl	AgNO ₃ (0.1 M), H ₂ O, THF, Δ	24	<u>3;</u> Y= OH (81)	-
<u>2;</u> X= CI	AgNO ₃ (0.1 M), H ₂ O, THF, Δ	168	<u>4;</u> Y= OH (44)	-

Table 1. Rearrangement of Azasterolds 1 and 2

a) Yields represent products that were purified by preparative TLC

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- 2. Steroid derivatives containing extranuclear nitrogen mustard groups have undergone clinical testing for antitumour activity. For lead references, sec: a) Dence, J.B. Steroids and Peptides; J. Wiley: New York. 1980; pp. 136-138. b) Leclercq, G.; Devleeschouwer, N.; Heuson, J.C., J. Steroid Biochem. 1983, 19, 75.
- 3. All new compounds had satisfactory IR, NMR and low resolution mass spectra, as well as elemental analyses or high resolution mass spectra. The preparation of these and related compounds will be reported elsewhere. Stereochemical assignments are based on ¹H-NMR data, in which the 3α -series $\frac{1}{3\beta}$ and $\frac{6}{5}$ showed signals for the 3-proton at lower field with smaller couplings than those for the $^{3\beta}$ -series $\frac{2}{2}$ and $\frac{5}{5}$. See: Jackman, L.M.; Sternhell, S. Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry; 2nd edition, Pergamon Press: Oxford. 1969; pp. 238-241 and pp. 286-289. The stereochemistry for the rearrangement products $\underline{3}$ and $\underline{4}$ was confirmed by the observation of NOE enhancement between the exocyclic methylene group and the angular methyl
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- 5. No rearrangement was observed in aqueous THF under similar conditions in the absence of AgNO₃.
- Molecular modeling was performed using PC Model (1.0), Serena Software Co. 6.
- 7. Since compounds in the 3α -series <u>1</u> react faster than those in the 3β -series <u>2</u>, ring-flipping does not appear to be the rate-determining step in the rearrangement of the former compounds.
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