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REGIO-AND STEREOSELECTIVITY IN β-PARTICIPATION OF A VINILOGOUS-AMIDE NITROGEN

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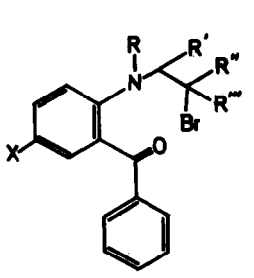
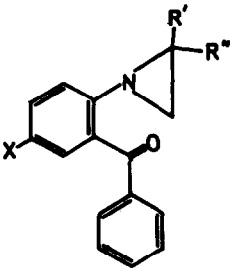
We wish to report on the first stereochemical evidence for β-participation of a weakly basic nitrogen, constitutive of a vinilogous-amide group. In β-participation of nitrogen atoms, aziridines and aziridinium ions arise as transition forms[1,2] prone to ring enlargement through various intra- or intermolecular transformations[3]. Compounds of types A and B (below) are, therefore, convenient models for styding β-participation mechanisms involving a vinilogous-amide nitrogen atom.



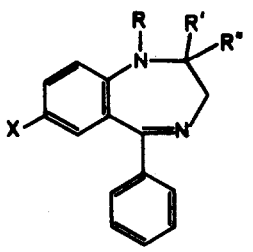
A



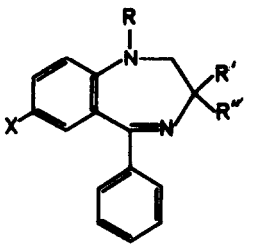
B

		R	R'	R"	R"'	X	Abs.conf.
A:	1	CH_3	H	D	D	Cl	-
	2	CH_3	H	CH_3	H	Cl	(R,S)
	3	H	C_2H_5	H	H	NO_2	(S)
B:	4	-	H	H	-	Cl	-
	5	-	H	H	-	NO_2	-
	6	-	H	C_2H_5	-	NO_2	(S)

They can be induced by treatment with hexamethylentetramine or ammonia to undergo ring closure or recyclization into prochiral and chiral 7-membered heterocycles (C and D, respectively, 7-12). Compounds of these types are encountered in our current research of chiral 1,4-benzodiazepines active on central nervous system[4,5]. The stereochemistry of these reactions, however, is also interesting from a general mechanistic aspect.



C



D

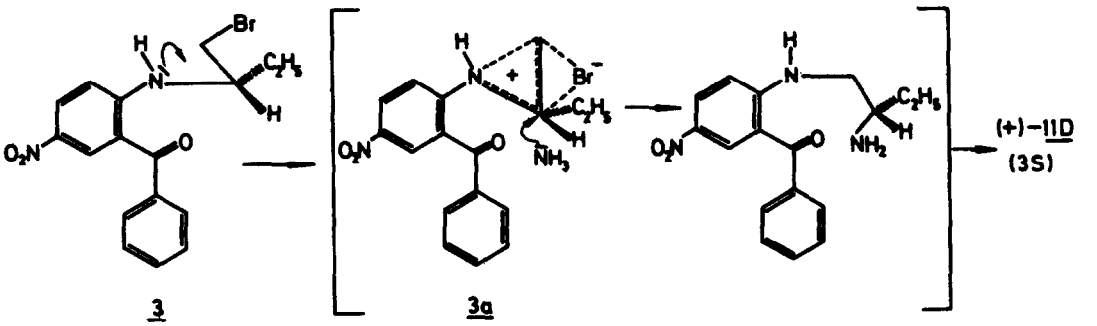
	R	R'	R''	X	Abs.config.
7C,7D	CH_3	D	D	Cl	-
8	H	H	H	Cl	-
9	H	H	H	NO_2	-
10C,10D	CH_3	H	CH_3	Cl	-
11C	H	H	C_2H_5	NO_2	(S)
11D	H	H	C_2H_5	NO_2	(R and S)
12D	CH_3	H	C_2H_5	Cl	(S)

In regioselectivity investigations, initial experiments were made with a deuterium-labelled precursor 1[6]. Treatment of 1 with an ethanolic ammonia solution (saturated at 0°) in a sealed tube at 130°C gave a 75 % - yield of a 45:55 mixture of compounds 7C and 7D. The product ratio was determined by measurement of nmr-signal intensities at 3.63 and 3.46 ppm for the methylenic protons in 7C and 7D, respectively. The above ratio shows that an aziridine ring must have arisen as an intermediate form, and that its opening was of low regioselectivity. In parallel experiments, the unlabelled aziridines 4 and 5 were recyclized into benzodiazepines 8 and 9 with yields of 78 % and 71 % , respectively. The racemic precursor 2 gave 10C and 10D in a total yield of 71 % . Ratio determination by careful separation of products on a silica column gave the value 57:43 (confirmed by glc), which indicates that the regioselectivity was low again.

The stereoselectivity of β-participation was examined with compounds 3 and 6 as starting materials. These compounds were prepared from S-(+)-2-aminobutanol, preventing an attack at the chiral centre. When 3 was treated as described for 1 , compounds 11C and 11D were obtained in the ratio 92:8 (detn. of components by glc; tot. yield 70 %). Under similar conditions, 6 gave the same products in the ratio 76:24 (tot. yield 76 %). Absolute configurations for 11C and 11D were assessed by relating the chiroptical properties ($[\alpha]_D$ in $CHCl_3$, and characteristic extremes of CD-curves-nm, $[\theta]x10^3$ - are given) of these compounds to those of 12D, prepared by an independent procedure, having 3(S)-configuration ($[\alpha]_D$+290.5°, CD:268,+10.8; 243, -10.6). Product 11C, 2-ethyl-1,4-benzodiazepi-

ne, resulting from either 3 or 6, possessed S-configuration, since in its formation no bond breaking occured between the chiral carbon and the adjacent nitrogen (11C:$[\alpha]_D$+321°). Formation of 11D, in contrast, took different stereochemical courses depending on the starting compound. From the acyclic precursor 3, it was formed with retention of configuration ($[\alpha]_D$+227°, CD:292, +4.8; 240, -11.75), whereas the aziridine 6 formed 11D with a high incidence of inversion of configuration ($[\alpha]_D$-271°, CD:292, -1.6;246, +17.6).

The following mechanistic scheme would account for these results:



3 3a

/3-Patticipation in 3 leads to the tightly bound ion-pair interme - diate 3a in which the bromine situated at the rear side of the aziridinium ring stabilizes a partial change on the chiral secondary carbon. This intermediate cannot therefore, suffer a back-side attack, but must be attacked from the front side by ammonia, which results in ring opening and recyclization into 11D with retention of configuration. In contrast to the aziridinium ion, aziridine 6 is open to back-side nucleophilic attack, and inversion of configuration takes place in recyclization to 11D.

Front-side attack on aziridines is well-established mode of nucleophilic-ring opening in intra[7,8] as well as intermolecular reactions[9-10]. The former might be the path taken by benzophenone imine derivative, likely to originate from both, types A and B compounds, in responde to our conditions of ammonia treatment[12]. Such ring openings, however, should go without inversion of configuration. Since inversion of configuration actually occured in reaction with compound 6, probably no benzophenone imine intermediates were involved.

Finally, the higher incidence of "normal" ring openings with 3 than with 6 indicates a predominance of the S_N2 mechanism, as front-side S_N2 attack is more selective at the less hindered primary carbon in 3a than in 6. S_N1-type attack should lead to a higher incidence of "abnormal" ring openings through the more stable secondary carbonium ion, as was reported for acid-catalyzed aziridine cleavage[13,14]. The racemic product 11D should therefore be expected to result from compound 3, undergoing transformation by the S_N1 mechanism - this prediction was not borne out by the experimental results presented here.

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