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STEREOCHEMISTRY OF THE POLONOVSKI REARRANGEMENT

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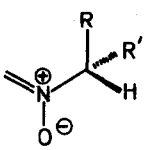
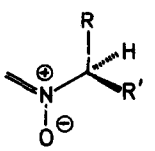
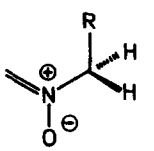
Rearrangement of heterocyclic N-oxides in the presence of reactive derivatives of carboxylic acids (halogenides, anhydrides) gave rise to the C-acylated derivatives of the parent heterocycle. This reaction was studied in detail, particularly in cases where the acyl group migrates to the trigonal carbon atom within the heterocyclic ring[1], or to the methyl group in α-position to the N-oxide function[1]. There are several explanations offered for the mechanism of this reaction based on kinetic investigations[2], on the deuterium isotope effect observed[3], as well as on reactions performed with ^{18}O-labeled acetic anhydride[4,5]. We started our stereochemical investigations of the Polonovski rearrangement on substrates having chiral (I, II) or prochiral (III) centres on a tetrahedral carbon in α-position to the N-oxide group.



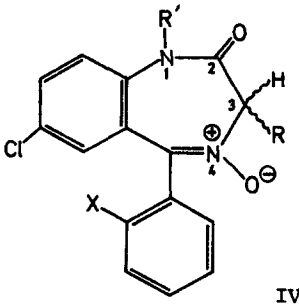


II



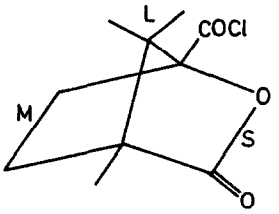
III

N^4-Oxides of 1,4-benzodiazepines (IV) were chosen as substrates, particularly because the rearrangement under investigation is of biological importance for this group of heterocycles[5].



	R	R′	X	$[\alpha]_{578}$
a	H	CH_3	H	
b	H	H	Cl	
c	CH_3	CH_3	H	+30,3°(3S)
d	CH_3	CH_3	H	-30,7°(3R)

IVa-d

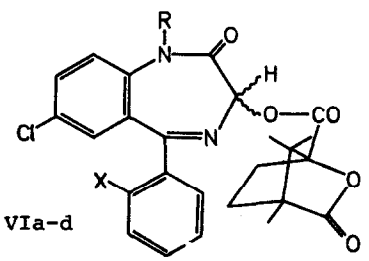


V

To distinguish between enantiotopic protons of C-3 some interaction with chiral reagent was indispensable. Therefore rearrangement of N-oxides IVa and IVb was performed using camphoyl chloride[6a,b] (V), stereochemical course of rearrangement to the prochiral centre being determined by the chiral acyl moiety (L-large, M-medium, S-small ligand).

Rearrangement of IVa and IVb with camphoyl chloride in benzene at 70° gave rise to the following ratios of diastereomers:VIa:VIb (R:S)=1.4:1.0, VIc:VId (R:S)= 1.55:1.0. Absolute configuration of the new chiral centre on C-3 in the diastereomers VIa-d was easily determined by comparison of their circular dichroism curves with those of compounds VIIIc and VIIId. The latter compounds possess known configurations on C-3 being prepared from L- and D-alanine. All diastereomers exhibited almost mirror symmetric circular dichroism curves[6b].

To determine the stereospecifity of rearrangement the reaction products VIa-d have been prepared by different procedures, and used as standards for chromatographic and nmr analysis.



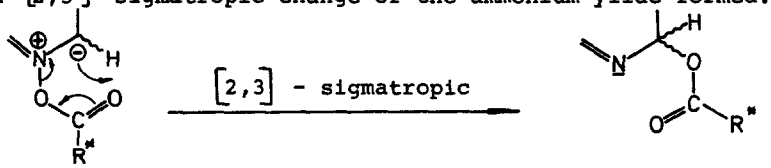
VIa-d

	R	X	Abs. configuration on C-3
a	CH_3	H	R
b	CH_3	H	S
c	H	Cl	R
d	H	Cl	S

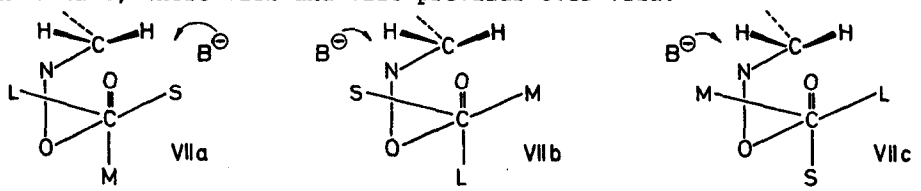
Preparation and separation of diastereomers VIa and VIb was described earlier[6b], while diastereomers VIc and VId have been prepared by the improved procedure starting from the silver salt of camphanic acid (light-stable substance,decomp. above 270°) and the 3-chloro derivative of parent 1,4-benzodiazepin-2-one (90%

yield, separation of diastereomers on silicagel column using ether-light petroleum 85:15. VIc:mp 148-150°, $[\alpha]_{578}$+62,9°, $CHCl_3$; nmr ($CDCl_3$) δ 6.17 ppm(C-3-H); mp 152-155°, $[\alpha]_{578}$-12.2°, $CHCl_3$; nmr ($CDCl_3$) δ 6.14 ppm (C-3-H).

The mechanism of rearrangement probably includes the prevously[5] postulated deprotonation at C-3 atom by the conjugate base. The second step,however,can be regarded as an [2,3] -sigmatropic change of the ammonium ylide formed.

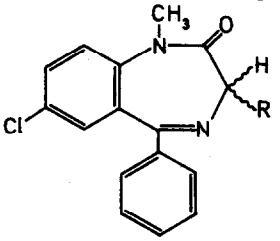


The stereochemical result of the rearrangement of IVa and IVb leading to the excess of diastereomers with R-configuration on C-3 could be explained as follows. If the reaction represents "pure" [2,3] -sigmatropic shift[7,8] (concerted reaction), then the configuration of the new chiral centre would be determined by deprotonation at C-3 which takes place from the less hindered side, and is accompanied by concerted backside formation of the C-O bond. This situation is depicted in VIIa-c, where VIIb and VIIc prevails over VIIa.



If this process is a nonconcerted elimination-addition[7], the intermediate carbonion undergoes sp^3-sp^2 rehybridization, whereas the second step. i.e. prevalent bonding of the acyl moiety to one of the two diastereotopic carbanion sides determines the stereochemical result. Models show that the first pathway should lead to the predominant formation of diastereomers with 3S configuration (VIb and d), whereas 3R diastereomers (VIa,c) should prevail if the second mechanism is operative. The result obtained with prochiral substrates IVa,b and chiral reagent supported the second possibility. Further evidence supporting nonconcerted rearrangement was obtained when chiral compounds IVc and IVd reacted with achiral acetic anhydride reagent. In both cases complete racemization on C-3 resulted giving rise to racemic 3-acetoxy derivative VIIIa, which was hydro-

lysed to VIIIb, both compounds being already described.[9]



	R	$[\alpha]_{578}$	
	a - $OCOCH_3$		
	b - OH		
VIIIa-d	c - CH_3	$+212^{o}$	(3R)
	d - CH_3	-213^{o}	(3S)

The reaction indicates that during the sigmatropic shift the carbanion loses its stereochemical specificity i.e. nonconcerted addition occurs in this rearrangement. Detailed kinetic study (glc) of this reaction as well as a study of [3,3] -sigmatropic rearrangement of heterocyclic N-oxides having a prochiral centre in β-position are in course. All new compounds described above gave satisfactory elemental analyses; their ir and nmr spectra were consistent with the structures ascribed.

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