DIAZABICYCLOALKANES WITH BRIDGEHEAD NITROGEN ATOMS. 28*. STEVENS REARRANGEMENT OF BENZODIAZABICYCLOALKENES

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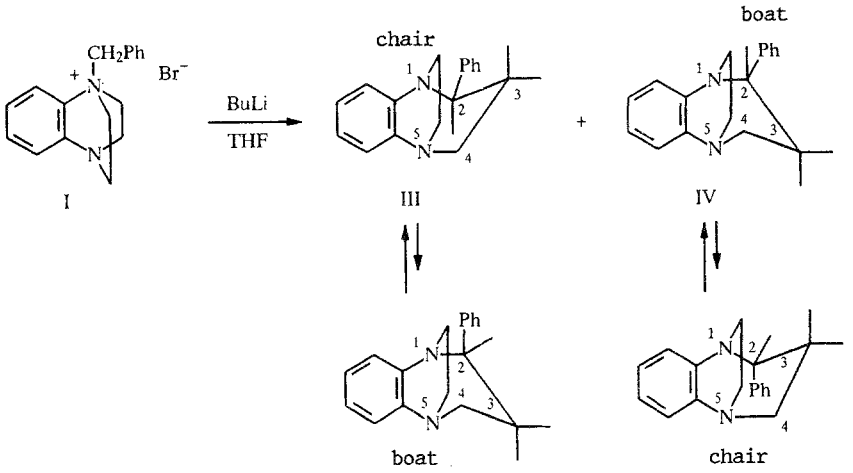
Stevens rearrangement of the benzyl bromides of benzo[b]-1,4-diazabicyclo[2.2.2]octene and benzo[f]-1,5-diazabicyclo[3.2.2]-nonene occurs with expansion of the diazabicyclic fragments to form a mixture of stereoisomers. Both the ethylene and the trimethylene bridges participate in the rearrangement of the nonene.

It is known that monophenacyl 2,3-diphenyl-1,4-diazabicyclo-[2.2.2]octanes readily undergo the Stevens rearrangement [2] in the presence of potassium tert-butylate. However, similar quaternary ammonium salts of unsubstituted diazabicycloalkanes form stable yields which can be dealkylated to the starting amines. According to [3], rearrangement of unsubstituted diazabicycloalkanes with ring expansion is observed for the corresponding benzyl bromides with butyl lithium, although only in low yields. With the aim of applying the Stevens rearrangement to quaternary salts of benzodiazabicycloalkenes with different length alkyl bridges we have studied the rearrangement of the benzyl bromides of benzo[b]-1,4-diazabicyclo[2.2.2]octene (I) and benzo[f]-1,5-diazabicyclo[3.2.2]nonene (II) in the presence of butyl lithium [3].



The starting quaternary salts I and II were prepared by the general method described in [4]. The physical parameters for the newly synthesized compounds are given in Table 1.

Reaction of salt I with butyl lithium gave an overall yield of 60% of two substances (ratio 3:1) with similar IR and UV spectra, and molecular weights corresponding to those expected. In contrast to [2, 3], we did not observe dealkylation of I to benzo[b]-1,4-diazabicyclo-[2.2.2]octene. The structures of the isomers III and IV were proved by PMR spectroscopy (Table 1). The observation of large spin–spin coupling values (J = 12 Hz) for the benzyl proton 2-H at about 4 ppm is a

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TABLE 1. Physical Parameters for II-VI

Compound	Empirical formula	R_f (A)	mp, °C	Found M^+ Calculated M^+	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum ($CDCl_3$), δ, ppm (J, Hz)			
						arom. protons	PhCH	NCH_2	$C-CH_2-C$
II	$C_{18}H_{21}N_2Br$	0,30*	169...171 decomp.	–	208 (4,2)	8,08...7,44 m, 9H	5,56 d, 1H(12) 5,10 d, 1H(12)	4,2...3,83m, 4H** 3,51...3,44m, 2H 3,27...3,20m, 2H	2,20...2,00m, 1H 1,75...1,55 m, 1H
III	$C_{17}H_{18}N_2$	0,60	50...52	250,1458 250,1470	208 (4,15) 218 (sh)	7,55 d, 2H(6) 7,38 t, 2H(6) 7,29...7,17 m, 5H	4,07 d.d 1H(12; 4)	3,58...3,36m, 3H 3,26...3,30m, 3H	2,77...2,55m, 3H 2,34...2,22m, 3H
IV	$C_{17}H_{18}N_2$	0,40	105...107	250,1460 250,1470	208 (4,12) 218 (sh)	7,30...7,16 m, 8H 6,94 d, 1H	4,11 d.d 1H(12; 4)	3,56...3,27 m, 5H 3,21...3,05 m, 1H	1,88...1,76 m, 3H 1,52...1,30 m, 3H
V	$C_{18}H_{20}N_2$	0,55	Oil	264,1617 264,1627	208 (4,42); 238 (3,97); 272 (3,47)	7,60 d, 2H(7) 7,39 t, 2H(7) 7,30...7,05 m, 5H	4,17d.d 1H(11; 4)	3,68...3,55 m, 2H 3,44...3,35 m, 1 H 3,34...3,26 m, 1H 3,16...2,98 m, 2H	2,35...2,20 m, 2H 1,70...1,62 m, 4H 1,43...1,30 m, 4H
VI	$C_{18}H_{20}N_2$	0,45	61...62	264,1615 264,1627	208 (4,2)	7,32...7,20m, 5H	4,19d.d 1H(12,5; 3,5)	3,51...3,40 m, 3H 3,29 t.d 1H 3,04...2,96 m, 2H	2,76...2,64 m, 9H 1,86...1,80 m, 3H 1,54...1,38 m, 3H, 9H

*System B.

**Signals for N^+CH_2 protons, spectrum in CD_3OD.

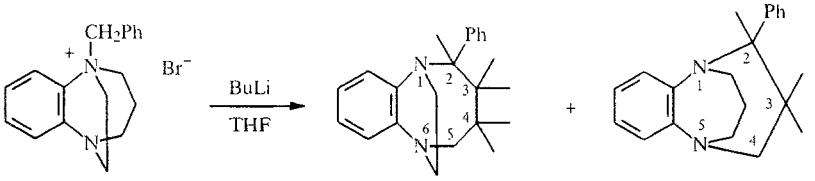
feature of axial–axial interaction and suggests, in both cases, a preferred stabilization of a conformation with the phenyl group in an equatorial position. Thus, the problem of stereoisomerism in these compounds is simplified to the question of conformations. This is resolved on the basis of the previously reported NMR conformational analysis data [5] for diazabicyclic systems as applied to the 3-H proton signals. According to this data, the highest field signal is expected for the 3a-H proton in a boat conformation due to the magnetic anisotropy of the benzene ring.

Using double resonance experiments, it was shown that the 3a-H proton (which shows a 12 Hz splitting to 2a-H) occurs as a multiplet in the spectrum of III at 2.77-2.55 ppm and to the multiplet with similar splitting at 1.52-1.30 ppm in IV. Hence III can be assigned the structure 2-*exo*-phenylbenzo[f]-1,5-diazabicyclo[3.2.2]nonene and IV 2-*endo*-phenylbenzol[f]-1,5-diazabicyclo[3.2.2]nonene.

One of the basic side products of the reaction is the expected 1-benzyl-4-hexyl-1,2,3,4-tetrahydroquinoxaline (according to mass spectrometry and PMR). It can arise through nucleophilic substitution by butyl lithium and opening of the bicyclic fragment. Such reactions have been reported for quaternary salts of diazabicycles [1, 4, 6].

The instability of III and IV under Stevens rearrangement conditions may explain the low overall reaction yield. Their mutual conversion, which might have been expected in strongly basic medium, was not observed. The structures of the reaction products from III and IV were not determined.

For the benzyl bromide II, the Stevens rearrangement can involve the ethylene or the trimethylene bridge. For the benzyl bromide of 1,5-diazabicyclo[3.2.2]nonane [3] it was reported that a single reaction product was formed involving the ethylene bridge. We have found that reaction of the quaternary salt II at room temperature leads mainly to two compounds (ratio 2:1, overall yield 55-60%) with molecular weights corresponding to expansion of the ring.



II V VI

The increase in the number of $C-CH_2-C$ proton signals (Table 1) when compared with II points to ring expansion with rearrangement. Double resonance experiments were carried out on V and VI. Irradiation of the double doublet for the benzyl proton (4.19 ppm) in the PMR spectrum of the chromatographically more mobile component leads to the disappearance of both spin–spin couplings (J = 12.5 and 3.5 Hz) only in the 2 proton multiplet at 2.31-2.20 ppm; hence it may be assigned to the 3-H proton. Irradiation of the 3-H signal changes both the benzyl proton and the nature of the splitting of the signals at 1.70-1.62 and 1.43-1.30 ppm (leading to their assignment as 4-H) and does not affect the lower field $N-CH_2$ signals (see Table 1). Only double resonance at 1.65 or 1.37 ppm changes these signals. These experiments demonstrate the presence of the $N-CHPh-CH_2-CH_2-CH_2-N$ fragment so V can be assigned the structure 2-phenylbenzo[g]-1,6-diazabicyclo[4.2.2]decene, i.e., the Stevens rearrangement product involving the trimethylene bridge.

A similar series of double resonance experiments was carried out for the second compound. It was found that the benzyl proton interacts with signals at 1.86-1.80 ppm (1H, s, J = 4 Hz) and a multiplet at 1.54-1.38 ppm (J = 11 Hz) with overall intensity 2H. Irradiation of the signals in the region of the 3-H protons causes a change in the signals for the $N-CH_2$ groups (3.51-3.40 and 3.29 ppm) but not affecting the part of the multiplet at 1.54-1.48 ppm, the protons of which are in turn connected with the protons of the $N-CH_2$ group. All of this data points to the presence of the fragments $N-CHPh-CH_2-CH_2-N$ and $N-CH_2-CH_2-CH_2-N$ and thus infers that VI is 2-phenylbenzo[f]-1,5-diazabicyclo[3.3.2]-decene, i.e., the Stevens rearrangement product involving the ethylene bridge.

The instability of V and VI in these reaction conditions does not permit measurement of an exact rearrangement product ratio and establishing the preferred participation of a particular alkyl bridge. However, it is evident that both the ethylene and the trimethylene bridges take part in the rearrangement in contrast to the report in [3]. Because the product V is slightly preferred we propose either a move favorable stereochemical situation for the rearrangement with the trimethylene bridge or a significantly higher stability of V in basic media.

Geometrical isomers can be expected for V and VI as for III and IV and the question of isomerism due to the phenyl substituent leads to a consideration of conformations. Further work would be needed to decide exactly which isomers are formed. Meanwhile, we hypothesize that compound VI occurs principally in a boat conformation (with respect to the substituted bridge) and the correspondingly phenyl group in the *endo* position. Support is given by the presence in the PMR

spectrum of VI of signals at 1.86-1.80 ppm (1H) and 1.54-1.38 ppm (part of a 2H multiplet), agreeing in position and splitting character with the 3a-H and 3e-H protons of IV.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument for KBr tablets or $CHCl_3$. UV Spectra were taken on a Specord UV-vis spectrometer using ethanol solvent and PMR spectra on a Bruker WP-200 instrument. Mass spectra were taken on a Finnnigan MAT-8200 mass spectrometer. Analysis of reaction mixtures was carried out by TLC using Armsorb TLC-KSKG-UV 254 plates in chloroform–ethanol (20:1, System A) or tert-butanol-ethylmethyl ketone-formic acid-water (8:6:3:3, System B). Preparative chromatography was performed on a Laboratorni Pristroje Praha liquid chromatograph with a 1 m × 1 cm Silasorb-600 column (20 micron) and using chloroform eluent and an analytical wavelength of 254 nm. Melting points were formed determined in a capillary using a "Crystal-89" prototype melting point apparatus for crystalline materials (Novosibirsk Institute of Organic Chemistry).

Elemental analytical data agreed with that calculated.

Reaction of the Quaternary Salts I and II. A solution of butyl lithium (2 mmole) in ether was added in one portion to a suspension of the starting salt (1 mmole) in absolute THF (20 ml) in an argon stream and held at about 20°C. The end of the reaction was signified by complete solution of the starting salt. After 3-4 h, water (5 ml) was added carefully and evaporated. The residue was dissolved in water and extracted with $CHCl_3$ (5 ×10 ml). The combined chloroform extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by preparative liquid chromatography, twice if necessary.

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