DIAZABICYCLOALKANES WITH BRIDGEHEAD NITROGEN ATOMS.

26.* REACTIONS OF HYDROXYETHYL BENZO[b]-1,4-DIAZABICYCLO[2.2.2]OCTENES

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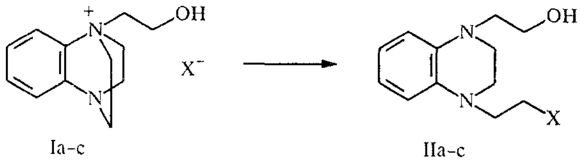
By heating 1-(2-hydroxyethyl)benzo[b]-1-azonium-4-azabicyclo-[2.2.2]octene halides in anhydrous solvents or via thermolysis, opening of the bicycle occurs with formation of the corresponding N-(2-hydroxyethyl)-N'-(2-haloethyl)-1,2,3,4-tetrahydroquinoxalines. In the presence of base, fission of the hydroxyethyl group principally occurs.

For quaternary ammonium salts containing a hydroxyalkyl group it is known [2] that intramolecular O-alkylation of the corresponding betaines (by heating above their melting points or in solvents) can give simple ethers. In this connection, there is currently interest in similar rearrangements of 1-(2-hydroxyethyl)-benzo[b]-1-azonium-4-azabicyclo[2.2.2]octene halides Ia-c.

On heating the quaternary salts Ia-c in anhydrous solvents (toluene, benzene, dioxane, acetonitrile), however, we found not O-alkylation but opening of the bicyclic fragment of I to form the corresponding N-(2-hydroxyethyl)-N'-2-(haloethyl)-1,2,3,4-tetrahydroquinoxalines IIa-c. The reaction is observed for different halide ions and different alkyl residues. Thus N-methyl-N'-(2-fluoroethyl)-1,2,3,4-tetrahydroquinoxaline (III) was obtained from 1-methyl-benzo[b]-1-azonium-4-azabicyclo[2.2.2]octene fluoride.



I, II a X=Cl, b X=F, c X=I

A similar reaction occurs on thermolysis of quaternary salts I at 120-130°C. In the solid phase, reaction occurs with weak nucleophiles (chloride and fluoride ions). This is in contrast to the previously reported reaction of quaternary ammonium salts of benzo[b]-1,4-diazabicyclo[2.2.2]octene in homogeneous solvents with strong nucleophiles (4-tert-butylthiophenolate, sodium methylate, piperidine [3]) and at high nucleophile concentrations (8.8 N HBr [4]). No change is seen when aqueous solutions of Ia-c are refluxed.

In order to exclude the presence of additional nucleophilic fragments we have tried to hydroxyethylate benzo[b]-1,4-diazabicyclo-[2.2.2]octene (IV) by heating in aprotic solvents. However, no reaction was observed in benzene or dioxane (120°C, 5 h). In chloroform solution at room temperature significant amounts of both unreacted starting materials and the products of a side reaction with dichlorocarbene (V and VI) were observed (see below).

It is known that tertiary amines cannot generate dichlorocarbene from chloroform [5]. In fact, compound IV does not react upon prolonged heating with chloroform. This points to the formation of a strongly basic betaine which leads to formation of dichlorocarbene.

Obtaining the formyl derivative V is probably connected with the ability of tertiary amines to form unstable dichlorocarbene addition compounds [5]. Subsequent hydrolysis of the ylid formed in the separation with simultaneous opening of the bicyclic fragment can then explain the formation of V.

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*For Communication 25, see [1].

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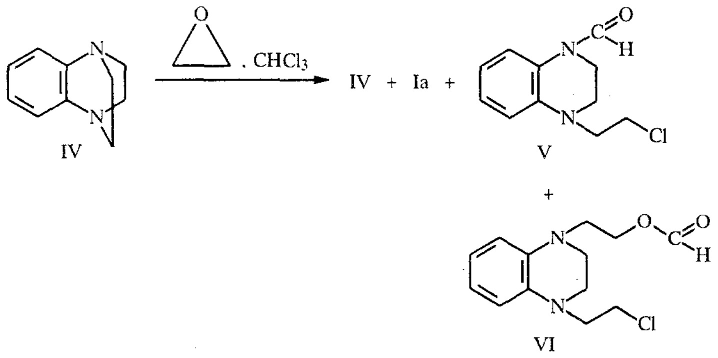
TABLE 1. Physical Constants for IIa, b, III, V, VI, and IX

Compound	Empirical formula	R_f	mp, °C	Found M$^+$ (calculated M)	IR spectrum, cm^{-1}					PMR spectrum in $CDCl_3$, chemical shift δ, ppm (spin–spin coupling, Hz)							
					C–N	C=C	C=O	C–H	C–F	HCO	aromatic protons	NCH_2CH_2N	NCH_2CH_2Cl	CH_2F	CH_3	OCH_2	other CH_2
IIa	$C_{12}H_{17}N_2ClO$	0,70	Oil	240, 1052 (240, 1029)	1048 1356	1512 1592	—	2856 2960 3008	—	—	6,67...6,51 m	3,63....3,1 m	3,63...3,1 m	—	—	3,63...3,1 m	3,63...3,1 m
IIb	$C_{12}H_{17}N_2FO$	0,65	53,4...55,0	224, 1322 (224, 1325)	1044 1356	1512 1592	—	2848 2888	1016	—	6,65...6,50 m	3,63...3,37 m	—	4,75; 4,52 dt (J_F=46, J=6)	—	3,80 t (J=6)	3,63...3,37 m
III	$C_{11}H_{15}N_2F$	0,75	Oil	194, 1222 (194, 1219)	1048 1352	1512 1592	—	2864 2952 3008	1024	—	6,70...6,40 m	3,54...3,22 sym m	—	4,76; 4,53 dt (J_F=46, J=5)	2,86 s	—	3,64; 3,54 dt (J_F=20, J=5)
VII	$C_{24}H_{32}O_2N_4$	0,95	Oil	408, 2531 (408, 2525)	1056 1356	1500 1592	—	2872	—	—	6,58...6,35 m	3,41...3,25 m	—	—	—	3,63...3,53 m	3,41...3,25 m
V	$C_{11}H_{13}N_2ClO$	0,85	90,0...91,2	224, 0726 (224, 0716)	1065 1370	1520 1602	1660	2880 2950 3010	—	8,58	7,04.6.49 m	3.9...3.2 sym m	3,6 s	—	—	—	—
VI	$C_{13}H_{17}N_2ClO_2$	0,95	Oil	268, 0979 (268, 0978)	1070 1365	1520 1592	1720	2860 2970 3020	—	8,06	6,70.. 6,50 m	3,40 s	3,65...3,52 m	— m	—	4,36 t (J=3)	3,63 t (J=3)

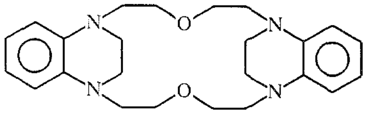


Reaction of the quaternary salt I with dichlorocarbene and subsequent opening by chloride ion or initial opening with subsequent reaction with dichlorocarbene leads to VI.

Raising the reaction temperature to 120°C (sealed ampul) gives complete consumption of IV and opening of Ia to form a mixture of IIa (60%), V (10%), and VI (5%).

Use of an equimolar amount of homogeneous base (potassium tert-butylate) in solution with the quaternary salt Ia in tert-butanol gives rise to desalkylation and principally separation of IV (up to 80%).

Among the side products there was separated ~5% of a compound with mass and PMR spectra in agreement with a dimeric product of intermolecular nucleophilic reaction (VII). The high resolution mass spectrum of VII gives a molecular ion of 408.2531 corresponding to the elemental composition $C_{24}H_{32}O_2N_4$. It also shows an ion at $[M-29]^+$ (50%), characteristic of separation of the ethylene bridge. One of the most intense IR bands is at 1116 cm^{-1} and can be assigned to a CH_2-O-CH_2 bond vibration. The PMR spectrum of VII is quite complex and consists of three multiplets in the integral ratios 1:1:2. The 6.58-6.35 ppm multiplet is assigned to the aromatic protons, that at 3.63-3.53 ppm to the OCH_2, and the highest field signal at 3.41-3.25 ppm to the NCH_2 protons. On this basis the structure below is proposed.



VII

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument in KBr and $CHCl_3$ and PMR spectra on a Bruker WP-200 spectrometer (200 MHz). Mass spectra were obtained on a Finnigan MAT-8200 spectrometer. TLC analysis was performed on Armsorb UV 254 plates in chloroform—ethanol (10:1, system A). Preparative chromatography was carried out on thin-layer silica gel in system A. The substance was visualized in UV light and bands of the corresponding R_f cut out and eluted with chloroform—methanol (1:1). The melting point was determined in a capillary in an apparatus for crystalline materials (Crystal-89, prototype design, Novosibirsk Institute of Bioorganic Chemistry).

Elemental analytical data agreed with that calculated.

1-(2-Hydroxyethyl)-benzo[b]-1-azonium-4-azabicyclo[2.2.2]octene chloride (Ia) was obtained by [1]. Fluoride Ib and iodide Ic were obtained by ion exchange of Ia on anionic Dowex 1 × 4 in the corresponding form. Similarly, the methiodide of benzo[b]-1,4-diazabicyclo[2.2.2]octene [3] gives the methofluoride.

Reaction of Quaternary Salts Ia-c. The salt (1 mmole) was refluxed in toluene (15 ml) for 4 h. The reaction mixture was evaporated and the residue distilled at 110-130°C (2 mm). The yields of quinoxalines IIa-c and III were 70-80%. Compound IIc is unstable and cannot be separated pure.

Reaction of Quaternary Salts in the Presence of Base. Tert-BuOK (1.1 mmoles) was added to the quaternary salt I (1 mmole) in absolute tert-butanol (5 ml) and refluxed. The product was filtered, evaporated, and separated by preparative chromatography. The separated fractions were distilled in vacuo at 110-130°C (2 mm) to give IV (80%) and VII (5%).

Reaction of Benzo[b]-1,4-diazabicyclo[2.2.2]octene with Ethylene Oxide in Chloroform. Ethylene oxide (3 ml) was added to IV (0.5 g, 3.1 mmoles) in $CHCl_3$ (6 ml) and held for 3 days at room temperature. The precipitate of Ia (20%) was filtered, and the reaction mixture evaporated and separated by preparative chromatography. Zones with R_f 0.95 (VI, <5%), 0.85 (V, <5%), and 0.30 (IV, 60%) were collected; b) 5 h at 120°C (ampul): the reaction mixture was also separated chromatographically to give zones with R_F 0.95 (VI, 5%), 0.85 (V, 10%), and 0.70 (IIa, 60%).

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