DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN BRIDGEHEAD POSITIONS.
25.* INFLUENCE OF 3′-SUBSTITUENTS ON THE DIRECTION OF HYDROXYETHYLATION OF BENZO[b]-1,4-DIAZABICYCLO[2.2.2]OCTENES

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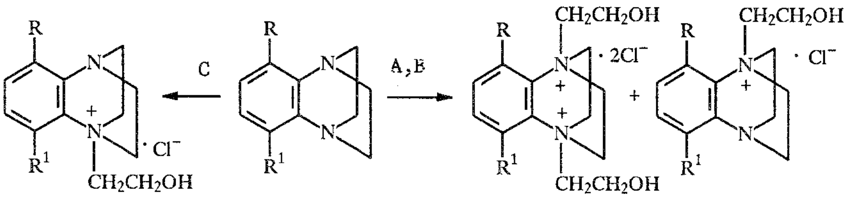
Substituents in the 3′ and 6′-positions of benzo[b]-1,4-diazabicyclo[2.2.2]octane are capable of influencing the reactivity of the nitrogen atoms in the hydroxyethylation reaction due to steric hindrances or anchimeric contribution. Depending on the reaction conditions and substituents in the aromatic ring of benzo[b]-1,4-diazabicyclo[2.2.2]octane, either mono- or bis-quaternary salts were obtained.

The m-effects of substituents in the aromatic ring of benzo[b]-1,4-diazabicyclo[2.2.2]octene (I) practically do not influence the reactivity relation of hetero atoms [2], since the rigid structure of the diazabicyclic fragment hinders the conjugation of the free electron pairs of the nitrogen atoms with the aromatic ring [3]. We studied the *ortho*-effect of the substituents on the direction of the hydroxyethylation at the $N_{(1)}$ and $N_{(4)}$ hetero atoms of 3′-substituted benzo[b]-1,4-diazabicyclo[2.2.2]octenes.

The reaction of compound I with an excess of ethylene oxide under acid activation conditions and subsequent treatment of the reaction mixture with hydrochloric acid leads to the formation of 1,4-di(2-hydroxyethyl)benzo[b]-1,4-diazoniabicyclo[2.2.2]octane dichloride (II).



VIII, IX — I, III, VI — II, IV — VII

I, II, VIII R = R¹ = H; III, IV, IX R = H, R¹ = OH; VI, VII R = H, R¹ = SiMe₃.
Reagents: A — ethylene oxide; B — HCl; C — ethylene chlorohydrin

The chromatographic monitoring showed that first a difficultly separable mixture of mono- and bis-quaternary salts of compound I is formed, and then only after 2 days compound II can be isolated in a high yield.

The reaction of 3′-hydroxybenzo[b]-1,4-diazabicyclo[2.2.2]octane (III) with ethylene oxide under similar conditions gives a bis-quaternary ammonium salt IV. 3′,6′-Bis(trimethylsilyl)benzo[b]-1,4-diazabicyclo[2.2.2]octene (V) is not alkylated under these conditions by ethylene oxide, even on prolonged holding, which can be explained by steric effect of the bulky trimethylsilyl groups. It is probable that for the same reason 3′-trimethylsilylbenzo[b]-1,4-diazabicyclo[2.2.2]octene (VI) reacts with ethylene oxide with the formation of a single quaternary salt VII, which is a product of hydroxyethylation of compound VI at the sterically unhindered $N_{(1)}$ atom.

Comparison of the PMR spectra of the quaternary salt VII and compound VI shows that the proton signal at the 6′-position of the quaternary salt VII is shifted to the weak field by approximately 0.5 ppm, while the signals of the 5′- and 4′-protons undergo a much smaller shift (about 0.1 ppm). This shift is characteristic for the 6′-proton signal during the quaternization of neighboring nitrogen atom [4] and indicate a localization of the positive change in compound VII on the $N_{(1)}$ atom. Thus, by means of a bulky substituent at the 3′-position, the hydroxyethylation reaction can be carried out selectively at the nitrogen atom at the 1-position of the diazabicyclic system of I.

Boiling of the aqueous solution of compound I with a milder alkylating agent — ethylene chlorohydrin, which in the presence of a base can serve as a source of ethylene oxide [5], leads to the formation of monoquaternary ammonium salt VIII.

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*For Communication 24, see [1].

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TABLE 1. PMR Spectra of Quaternary Salts of Benzo[b]-1,4-diazabicyclo[2.2.2]octene in CD_3OD, δ, ppm

Compound	H_{arom} (SSCC, Hz)			Aliphatic protons		
	4'-H	5'-H	6'-H	$CH_2—N^+$	$CH_2—N$, m	$CH_2—O$, m
II	7,9—8,1 4H, sym.m			4,2-4,4 4H, m 4,4-4,6 4H, m 4,7-4,9 4H, m	—	3,9-4,1 4H
IV	7,33 dd (8,0; 1,0)	7,66 t (8,0)	7,48 dd (8,0; 1,0)	4,2-4,9 12H, m	—	3,9-4,1 2H; 4,2-4,9 2H
VII*	7,57 dd (8,0; 1,0)	7,46 t (8,0)	7,67 dd (8,0; 1,0)	4,41 4H, s 4,7-4,9 2H, m	3,3-3,5 2H; 3,6-3,8 2H	2,8-3,0 2H
VIII	7,4-7,8 4H, m			4,2-4,4 6H, m	3,4-3,7 4H	3,0-3,2 2H
IX	7,08 dd (8,0; 1,0)	7,36 t (8,0)	7,14 dd (8,0; 1,0)	4,1-4,3 6H, m	3,3-3,6 4H	2,9-3,1 2H
XI	6,55 dd (8,3; 1,0)	7,07 t (8,3)	6,82 dd (8,3; 1,0)	3,9-4,3 6H, m	3,1-3,4 6H	

*In $CdCl_3$; a Me_3Si signal at 0.29 ppm, s (9H).

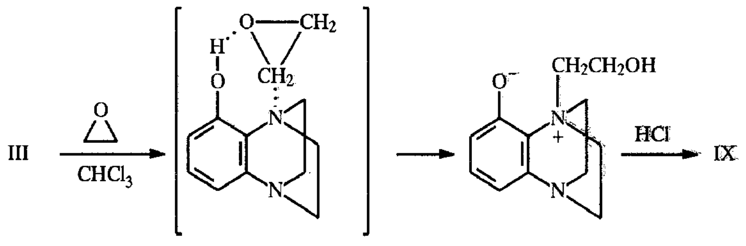
On treatment of compound III with ethylene chlorohydrin under similar conditions, a monohydroxyethyl derivative IX was isolated. In the PMR spectrum of dichloride IV a 0.4 ppm shift of the 6′-proton signal is observed to the weak field in comparison with the 6′-proton of chloride IX, which indicates the presence of the latter in the neighboring position to the tertiary $N_{(1)}$ atom.

The structure of the sole quaternary salt isolated indicates the contribution of the 3′-hydroxy group in compound III to the occurrence of the hydroxyethylation reaction at the neighboring $N_{(4)}$ atom. The result can possibly be explained by the formation of complex X, in which ethylene oxide is activated due to the presence of a hydrogen bond between the hydroxy group proton of compound III and the ethylene oxide oxygen atom. To intensify this effect, we tried to exclude the activation of ethylene oxide by the medium, by treating compound III with ethylene oxide in an aprotic solvent — chloroform.

As a result, according to the mass spectrum data, an addition product was obtained of one mole of ethylene oxide to compound III, which, according to UV and PMR spectra, has the structure of betaine XI. Treatment of this compound with one equivalent of HCl leads to the formation of chloride IX, in the PMR spectrum of which an approximately 0.3 ppm shift of the 4′- and 6′-proton signals takes place, compared with betaine XI, which indicates a localization of the negative charge on the oxygen atom of the aromatic ring (cf. [6]).

On addition of one equivalent of HCl, a shift is observed of the absorption band in the UV spectrum of betaine XI at 297 nm to the short-wave region (λ = 274 nm). A similar hypsochromic shift is observed for the transition from the phenolate anion to phenol [7].

The results obtained confirm our supposition on the contribution of the 3′-hydroxy group in compound III to the hydroxyethylation reaction at the neighboring $N_{(4)}$ atom and indicate a possible intermediate formation of complex X, in which ethylene oxide is activated due to a hydrogen bond between the hydroxy group proton of compound III and the ethylene oxide oxygen atom.



X

XI

In the mass spectrum of compound XI a molecular ion peak is observed. In the IR spectra of the quaternary salts of benzodiazabicyclooctenes obtained vibration bands are noted at 3000-2890 and 1080-1050 cm^{-1} (the C—H stretching and skeletal vibrations) and at 1490-1430, 840-805 cm^{-1} (the deformational vibrations of the CH_2 group in 1,4-diazabicyclo[2.2.2]octane fragment [8]). Moreover, less intense signals at 3030-3010 and 803-695 cm^{-1} are observed in the spectra corresponding to the C—H stretching and deformational vibrations of the aromatic ring.

In the PMR spectra of compounds II and VIII (Table 1) multiplets are observed in the 7.4-8.1 ppm region corresponding to four aromatic protons. The signals of the aromatic protons in compounds IV, VII, IX, and XI are characteristics of the 1′,2′,3′-trisubstituted benzene ring, whereby the SSCC of the protons in the 3′,5′ and 5′,6′ positions are 8.0-8.3, and in 4′,6′-positions are 1.00 Hz, which corresponds to the *ortho-* and *meta-*constants. The signals of the aliphatic protons in compounds II and IV appear in the form of multiplets at 3.9-4.9 ppm and correspond to four ethylene groups, while in compounds VII-IX and XI appear at 2.8-4.9 ppm and correspond to three ethylene groups.

EXPERIMENTAL

The IR spectra were run on a UR-20 spectrophotometer in KBr, the UV spectra on a Specord UV-VIS spectrophotometer in ethanol. The mass spectra were obtained on a Finnigan MAT-8200 mass spectrometer. The PMR spectra were recorded on a Bruker WP-200 spectrometer (200 MHz), using HMDS as internal standard. The purity of the compounds and the course of the reaction was monitored by TLC on Armsorb TLC-KSKG-UV-254 plates in a chloroform—ethanol (10:1) (A) and ter-butanol—methyl ethyl ketone—formic acid—water (8:6:3:3) (B) systems. The melting points were determined in capillaries on a Kristall-89 apparatus for the determination of melting points of crystalline compounds (an experimental model, produced at the Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Novosibirsk).

The results of the elemental analyses of the newly synthesized compounds for the carbon, hydrogen, and nitrogen content correspond to the calculated values.

Benzo[b]-1,4-diazabicyclo[2.2.2]octene (I) was obtained according to [3].

1,4-Di(2-hydroxyethyl)benzo[b]-1,4-diazoniabicyclo[2.2.2]octene Dichloride (II, $C_{14}H_{22}Cl_2N_2O_2$). A 4 ml portion (80 mmoles) of ethylene oxide was added to a solution of 1.6 g (10 mmoles) of compound I in 20 ml of acetic acid. The reaction mixture was allowed to stand for 48 h at room temperature, 5 ml of conc. HCl and 10 ml of ethanol were added, and the mixture was evaporated in vacuum. A 30 ml portion of ethanol was then added to the residue, the precipitate that separated out was filtered off, washed with ethanol, and dried in vacuum. Yield 2.8 g (87%) of compound II in the form of colorless crystals, mp 166-168°C (dec.).

1-(2-Hydroxyethyl)benzo[b]-1-azonia-4-azabicyclo[2.2.2]octene Chloride (VIII, $C_{12}H_{17}ClN_2O$). A 3 ml portion (45 mmoles) of ethylene chlorohydrin was added to a solution of 3.2 g (20 mmoles) of compound I in 10 ml of water. The mixture was boiled for 4 h and then evaporated. The residue was recrystallized from acetonitrile. Yield 2.6 g (54%) of colorless crystals, mp 145-147°C (dec.).

3′-Hydroxybenzo[b]-1,4-diazabicyclo[2.2.2]octene (III) was obtained according to [9].

1,4-Di(2-hydroxyethyl)-3′-hydroxybenzo[b]-1,4-diazoniabicyclo[2.2.2]octene Dichloride (IV, $C_{14}H_{22}Cl_2N_2O_3$). A 1 ml portion (20 mmoles) of ethylene oxide was added to a solution of 0.54 g (3 mmoles) of compound III in 5 ml of acetic acid. The reaction mixture was allowed to stand for 5 days at 20°C; then 2 ml of conc. HCl was added and the mixture was evaporated under vacuum. To the residue 10 ml of ethanol was added, and 0.4 g (40%) of colorless crystals were filtered off, mp 155-156°C (dec.).

3′,6′-Bis(trimethylsilyl)benzo[b]-1,4-diazabicyclo[2.2.2]octene (V) and 3′-trimethylsilylbenzo[b]-1,4-diazabicyclo[2.2.2]octene (VI) were obtained according to [9].

1-(2-Hydroxyethyl)-3′-trimethylsilylbenzo[b]-1-azonia-4-azabicyclo[2.2.2]octene Chloride (VII, $C_{15}H_{25}ClN_2OSi$). A 2 ml portion (40 mmoles) of ethylene oxide was added to a solution of 0.58 g (2.5 mmoles) of compound VI in 12 ml of acetic acid. The reaction mixture was allowed to stand for 3 days at 20°C to complete the reaction, and the mixture was evaporated. To the residue 0.1 ml of conc. HCl and 5 ml of ethanol were added. A 50 ml portion of ether was added to the solution obtained, the mixture was cooled to 0°C, and 0.26 g (33%) of colorless needles was filtered off, mp 158-160°C (dec.).

4-(2-Hydroxyethyl)-3′-hydroxybenzo[b]-1-aza-4-azoniabicyclo[2.2.2]octene Chloride(IX, $C_{12}H_{17}ClN_2O_2$). A solution of 0.35 g (2 mmoles) of compound III in 5 ml of water and 0.3 ml of ethylene chlorohydrin was boiled for 4 h and was then evaporated under vacuum. The residue was washed with hot toluene (2 × 20 ml) and recrystallized from 10 ml of ethanol. Yield 0.12 g (28%) of colorless crystals, mp 176-177°C (dec.).

4-(2-Hydroxyethyl)-3′-hydroxybenzo[b]-1-aza-4-azoniabicyclo[2.2.2]octene Betaine(XI, $C_{12}H_{16}N_2O_2$). A 1 ml portion (20 mmoles) of ethylene oxide was added to a solution of 0.36 g (2 mmoles) of compound III in 10 ml of dry chloroform. The reaction mixture was allowed to stand for 5 days at 20°C, the crystals that separated out were filtered off, washed with chloroform, and dried. Yield 0.3 g (68%) of colorless crystals, mp 172-174°C (dec.). Determined mass spectrometrically: M 220, 1217. $C_{12}H_{16}O_2N_2$. Calculated: M 220, 1212.

A solution of 0.3 g (1.4 mmoles) of compound XI in 2 ml of water was neutralized with 0.12 ml (1.4 mmole) of 12 N HCl, and the mixture was evaporated under vacuum. The residue was recrystallized from ethanol. Yield 0.15 g (43%) of compound IX, mp 176-177°C (dec.).

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