DIAZABICYCLOALKANES WITH BRIDGEHEAD NITROGEN ATOMS.

19.* REACTIONS OF MONOQUATERNARY SALTS OF DIBENZO[b,e]-1,4-DIAZABICYCLO[2.2.2]OCTADIENE WITH NUCLEOPHILIC REAGENTS

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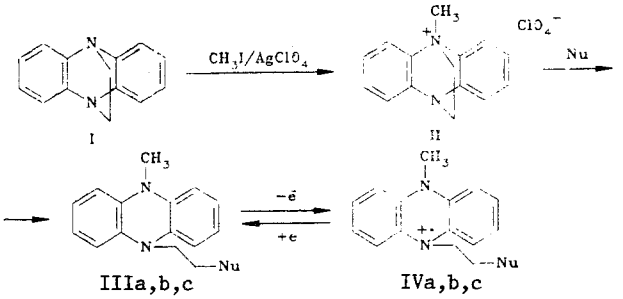
The monoquaternary salt of dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene reacts with piperidine, 1,3-propylenediamine and sodium p-nitrophenolate with the formation of N,N'-disubstituted dihydrophenazines. In its degree of reactivity level, the compound studied is comparable with a typical alkylating agent, such as methyl iodide.

It was shown [2] that monoquaternary salts of benzo[b]-1,4-diazabicyclo[2.2.2]octene react with piperidine and sodium p-tert-butylthiophenolate with the formation of mainly N,N'-disubstituted tetrahydroquinoxalines. The reactivity of monoquaternary salts was found to be much higher than that of quaternary salts of diazabicyclooctane [3]. It could therefore be expected that the reactivity would increase considerably on transition to the dibenzo[b,e]-1,4[diazabicyclo[2.2.2]octadiene (I) system.

The aim of the present work was to determine the main direction of the reaction and to evaluate quantitatively the reactivity of the quaternary salt of dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene (II) in reaction with nucleophilic reagents.

Action of methyl iodide or dimethyl sulfate on compound I under normal alkylation conditions leads to the formation, according to the TLC data, of cation-radicals of N-substituted dihydrophenazine derivatives and only a small amount of the expected quaternary salt of dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene. Compound II was obtained on a preparative scale by the action of methyl iodide in the presence of silver perchlorate on dibenzo [b,e]-1,4-diazabicyclo[2.2.2]octadiene at room temperature. In this case, cation radicals are virtually not formed and compound II is isolated in 60% yield.



III, IV a Nu=—O—C_6H_4—NO_2-p, b Nu=—$NH(CH_2)_3NH_2$, c Nu= piperidino

Boiling of the quaternary salt II in a methanolic solution of sodium p-nitrophenolate leads to a reaction mixture containing, according to the TLC and HPLC data, one component which differs from the initial one. Compound II reacts in a similar way with piperidine and 1,3-propylenediamine at room temperature. Compound I was not detected in any of the reaction mixtures, which agrees well with the results obtained under similar conditions for the quaternary salts of benzo[b]-1,4-diazabicyclo[2.2.2]octene [2], where the

*For Communication 18, see [1].

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demethylation products and ring-opening products according to the Hofmann degradation, possible for this type of reaction were also absent. The course of the reaction was monitored by comparison of the characteristic changes of the electronic spectra on transition from compound II to III, and further during the oxidation to compound IV, with the electronic spectra of N,N'-dimethyldihydrophenazine and the corresponding cation-radical [4].

During the preparative isolation of compound III, compound IV is also always formed, which makes it impossible to obtain a correct elemental analysis and qualitative PMR spectra. A detailed investigation of the reaction products was carried out using the example of the reaction of the quaternary salt II with piperidine. In the mass spectrum of the compound obtained, a peak of molecular ion of IIIc is observed. In the PMR spectrum, because of the presence of a cation-radical in the solution, signals of aromatic protons are not observed, while signals of aliphatic protons, despite their considerable broadening, can be readily identified: 2.86, 1.62 ppm – proton signals of the piperidine residue; 3.48 – of the CH_3 group; 3.62 – of the CH_2 group; 4.31 ppm – of the CH_2N^+ group. When hydrazine is added to the solution, cation radical IVc is reduced, as can be seen from the electronic spectra (the bands corresponding to the cation radical at 732, 662, 515, and 462 nm disappear; at the same time, the bands at 369 and 268 nm undergo a shift to 337 and 246 nm, respectively), and in the PMR spectrum two symmetric multiplets appear (6.67...6.57 and 6.48...6.37 ppm) which correspond to the aromatic protons of 9,10-dihydrophenazine. However, because of the presence of strong signals of hydrazine and because of the exchange with the OD group of deuteromethanol, not all the signals can be detected in the strong field. Of the observed signals we may note the singlet at 2.59 ppm, assigned to the methyl group, a triplet at 2.55 ppm, assigned to the CH_2 group of the methylene fragment and also proton signals of the piperidine residue.

Since the amount of by-products is low when the reaction was carried out without the access of atmospheric oxygen, it was possible to evaluate spectrophotometrically quantitatively the reactivity of compound II with the above enumerated nucleophiles. To make the evaluation, the differences in the electronic spectra of the quaternary salt and the reaction products were used [5]. For a more thorough comparison of the reactivity of compound II and 1-methylbenzo[b]-1-azonia-4-azabicyclo[2.2.2]octene iodide (V) in reactions with nucleophilic reagents, the rates of the reactions of compound V with sodium p-nitrophenolate were measured in a similar way as in [2].

The rate constant of the reaction of compound V with piperidine at 20°C is $K = 4.12 \cdot 10^{-6}$ liter/(mole·sec) (calculated according to the data in [2]), and with sodium p-nitrophenolate at 90°C it is $K = 2.02 \cdot 10^{-4}$ liter/(mole·sec), and the relative error in the determination of constants is not more than 10%. Under the conditions used, 1-methyl-1-azonia-4-azabicyclo[2.2.2]octane iodide practically does not react with piperidine [$K < 5 \cdot 10^{-8}$ liter/(mole·sec)].

According to the above presented data, the reactivity of the quaternary salts of diazabicyclooctane in the alkylation processes increases with increase in the number of annelated benzene rings by 4-5 orders of magnitude. In the case of the quaternary salt of dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene, the values of the reaction rate constants are 3-5 times higher than in the analogous reactions of methyl iodide [6].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets, and the UV spectra on Specord UV-Vis and Specord M-40 spectrophotometers. The kinetic measurements were carried out on Beckman-DU-8 and Specol-10 spectrophotometers. The mass spectra were obtained on an MS-902 spectrometer, and PMR spectra on a Bruker HX-90 spectrometer, using HMDS as internal standard. The chromatographic control was carried out by means of a Milichrom liquid microcolumn chromatograph and on Silufol UV-254 plates in the methanol–water (1:1) (A) and tert.–butanol–methyl ethyl ketone–formic acid–water (8:6:3:3) (B) systems.

The elemental analysis data correspond to the calculated data.

1-Methyldibenzo[b,e]-1-azonia-4-azabicyclo[2.2.2]azabicyclooctadiene perchlorate (II, $C_{15}H_{15}N_2ClO_4$). An equimolar amount of a 0.23 N solution of silver perchlorate in benzene is added to a solution of 0.2 ml of methyl iodide in 5 ml of benzene. After 30 min the solution is filtered and the filtrate is added to a benzene solution of 0.1 g (0.48 mmole) of compound I. After 12 h, the precipitate is filtered off, dissolved in methanol, and

compound II is precipitated by ether in the form of fine grey crystals. After reprecipitation by ether from methanol, 0.097 g (63%) of white crystals are obtained, which decompose at a temperature above 180°C. R_f 0.8 (B). IR spectrum: 780, 870 (=C–H); 1100 (ClO_4^-); 1470, 1490 (=C–N); 1630 cm^{-1} (–C–N). UV spectrum (in methanol), λ_{max} (log ε): 220 (3.16), 260 nm (3.74). PMR spectrum (in DMSO-D_6): 7.47...8.00 (8H, m, aromatic protons); 4.37 (3H, s, CH_3); 4.31 (2H, t, CH_2–N^+); 3.57 ppm (2H, t, CH_2).

9,10-Dihydro-9-methyl-(2-N-piperidinoethyl)phenazine (IIIc)*. An equimolar amount of piperidine is added to a solution of 0.1 g (0.31 mmole) of compound II in 10 ml of methanol, and the mixture is allowed to stand for 6 h in an argon atmosphere. The solvent is evaporated on a rotary evaporator, the dry residue is sublimed in vacuo, and 0.03 g of IIIc is obtained. The product is a white fine-crystalline precipitate which becomes rapidly green in air and on dissolution, and decomposes at a temperature higher than 157°C.

The kinetic measurements were carried out by direct spectrophotometry of the reaction mixtures in hermetically sealed thermostated 0.1...0.2 cm cuvettes. The concentration of the quaternary salt was $1 \cdot 10^{-2}$, of the nucleophile – $1 \cdot 10^{-3}$ mole/liter, the average values of the rate constants were calculated from a second order equation, based on 3-5 measurements. The rate constant of the reaction of compound III with piperidine (at 20°C) was $K = 80.16 \cdot 10^{-2}$, with 1,3-propylenediamine (at 20°C) $K = 2.09 \cdot 10^{-2}$, with sodium p-nitrophenolate (at 40°C) $K = 2.56 \cdot 10^{-2}$ liter/(mole·sec); the relative error did not exceed 10%.

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*Compounds IIIa and IIIb were not isolated in a pure state.