PYRIDINIUM SALTS

IV.* REDUCTION OF 4-(BENZAZOL-2-YL)PYRIDINIUM SALTS WITH SODIUM TETRAHYDROBORATE IN AN ALKALINE MEDIUM

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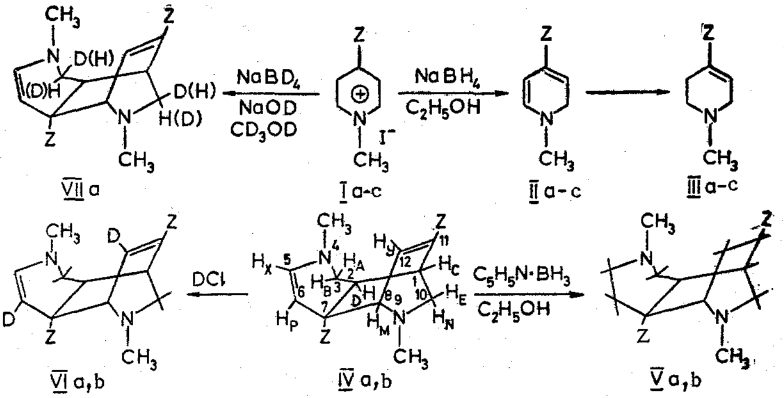
The reduction of 4-(benzoxazol-2-yl)- and 4-(benzothiazol-2-yl)-1-methylpyridinium iodides with sodium tetrahydroborate in an alkaline medium forms products of the dimerization of the corresponding 1,2-dihydropyridine derivatives. Under similar conditions, 4-(benzimidazol-2-yl)-1-methylpyridinium iodide gives a 1,2,5,6-tetrahydropyridine derivative.

We have found previously [1] that the reduction of the 4-(benzazol-2-yl)pyridinium salts (Ia-c) with sodium tetrahydroborate in a neutral medium leads to 2-(1-methyl-1,2,5,6-tetrahydropyridin-4-yl)benzazoles (IIIa-c). Continuing this work, we have performed the reduction of the same salts (Ia-c) with sodium tetrahydroborate in an alkaline medium. Generally, the reduction of pyridinium salts under these conditions gives 1,2-dihydropyridines [2]. The treatment of the benzoxazole and benzothiazole derivatives (Ia, b) with sodium tetrahydroborate in aqueous ethanolic suspension at pH ~14 gives compounds (IVa, b), the elementary analysis of which corresponded to the substituted 1,2-dihydropyridines (IIa, b). However, the molecular weights of compounds (IVa, b) proved to be double those calculated for (IIa, b).



Ia-IIa : Z = benzoxazol-2-yl
Ib-VIb : Z = benzothiazol-2-yl
Ic-IIIc : Z = benzimidazol-2-yl

It has recently been established [3] that the reduction of 4-cyano-1-methylpyridinium iodide under conditions similar to ours gives a Diels–Alder adduct: 7,11-dicyano-endo-4-endo-9-dimethyl-4,9-diazatricyclo[6,2,2,$0^{2,7}$]dodeca-5,11-diene. To determine the structures of the dimers that we had obtained, we studied the PMR spectrum of compound (IVa) (Fig. 1). In the 2.2 ppm region there are two singlets of N-methyl groups, which confirms the dimeric nature of the compound.

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*For Communication III, see [1].

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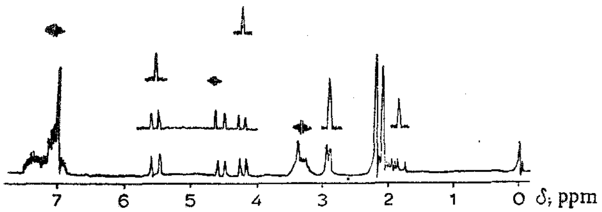

Fig. 1. PMR spectrum of 7,11-di(benzoxazol-2-yl)-endo-4-endo-9-dimethyl-4,9-diazatricyclo-$[6,2,2,0^{2,7}]$dodeca-5,11-diene in CD_3Cl.

At 5.69 and 4.53 ppm the absorption of the H_X and Hp protons is observed in the form of two doublets forming an AX system (J = 7.6 Hz). The values of their chemical shifts correspond to the usual ones for the α and β protons at an enamine double bond [4]. Part of another AX system is observed at 4.20 ppm (H_M). The second part of this system is hidden, as was shown by a double-resonance experiment (Fig. 1), by the multiplet of aromatic protons and is located at 7.3 ppm. This weak-field signal (δ 7.3 ppm) can be assigned to the H_Y proton on the double bond adjacent to a benzoxazole residue. In the 2-(1,2,5,6-tetrahydropyridin-4-yl)benzoxazoles, the signal of the vicinal proton has been found at 6.76 ppm [1].

The presence of an enamine system and of a vinyl proton in the dimer (IVa) shows the formation, as the result of a Diels–Alder reaction, of the adduct of two molecules of the 1,2-dihydropyridine (IIa). The existence of (IVa) in the more preferred endo conformation is shown by the observed long-range spin–spin coupling (SSC) of the P and D protons (J = 0.5 Hz) and the absence of such coupling between the D and the E protons. The assignment of the other signals was made on the basis of the results of experiments with double resonance (Fig. 1). The doublet at 2.97 ppm with a relative intensity of 2H can be ascribed to the A and B protons reacting identically (J = 3.2 Hz) with the D proton, which approximately corresponds to the spin–spin coupling constant usually observed [5] for a hindered conformation with dihedral angles of 60° between the A, B, and D protons. The doublet of doublets (1H) at 1.90 ppm (J = 8.72 and 1.77 Hz) must be assigned to the E proton. The multiplet at 3.6–3.2 ppm (3H) is formed by the absorption signals from the N, C, and D protons. The observed geminal spin–spin coupling constant (J_{EN} = 8.7 Hz) is in good agreement with the established SSCC constant between the protons of a methylene group adjacent to nitrogen in six-membered rings with the eclipsed conformation of the proton and the unshared electron pair of the nitrogen [6]. This is possible when there is no inversion of the N_9 nitrogen atom. A confirmation of the fixed position of the unshared electron pair of the N_9 atom is also the large difference in the chemical shifts of the geminal N and E protons (~1.5 ppm) [6, 7]. As is well known [3, 6], the cis-diaxial position of the H_N proton and the unshared electron pair of the nitrogen causes a downfield shift of the absorption signal, and the transequatorial position of the E proton and of the unshared pair of electrons causes an opposite shift. It must be mentioned that inversion of the N_9 atom must also be prevented by the voluminous benzoxazole residue at N_7, as is shown by a molecular model. The proposed structure permits an explanation of the shift of the 4-CH_3 signal in the upfield direction (δ 2.28 ppm) by the influence of the ring currents in the benzoxazole system located at C_{11}.

A further proof of the correctness of the assignment of the signals was obtained by the performance of a reaction of the salt (Ia) with $NaBD_4$. According to current ideas on the mechanism of the reduction of pyridinium salts with sodium tetrahydroborate [8], the primary reaction product must be 2-(1-methyl-2-deutero-1,2-dihydropyridin-4-yl)benzoxazole. Its dimer of structure (VIIa) must contain two deuterium atoms in positions 3 and 10. In the PMR spectrum observed for (VIIa), the intensity of the signal at 1.90 ppm had decreased to 0.5 relative units. The signal at 2.97 ppm corresponded to 1 H, and the intensity of the multiplet at 3.6–3.2 ppm to 2.5 H. The change in the intensities and the corresponding simplification of the spectrum show an equiprobable substitution of the A and B protons and also of the N and E protons. Thus, the structure of compound (IVa) that we obtained is analogous to the dimer of 4-cyano-1-methyl-1,2-dihydropyridine described previously [3]. But the conformational angles in (IVa) apparently differ somewhat from the angles of the latter, judging from the isochronicity of the A and B protons, and also their similar constants of SSC with the D proton. The action of DCl on the dimers (IVa and b) led to rapid replacement of the P and U protons by deuterium (VIa and b), as in the case of the dimer described by Liberatore et al. [3]. It appeared that a similar exchange also takes place under the action of D_2O and even in an alkaline solution (NaOD in D_2O). Consequently, the crude compound (VIIa) gives a PMR spectrum in which a ~25% replacement of the P and Y protons by deuterium is observed. The washing of the crude (VIIa) with water and with ethanol leads to deuteration at C_6 and C_{12}.

The catalytic hydrogenation of the dimers (IVa and b) takes place extremely slowly. Their reduction with pyridine–borane gives saturated compounds (Va and b) which are distinguished by thermal stability and gives the expected molecular ions with m/e 432 (Va) and 460 (Vb) in their mass spectra. It must be mentioned that on mass spectroscopy, (IVa) and (IVb) gives molecular ions with m/e 216 and 230 corresponding to tetrahydropyridine derivatives (IIIa and b). The latter are obviously formed by the thermal retrodiene reaction and the disproportionation of the 1,2-dihydropyridine formed under the experimental conditions. Decomposition of the dimers (IVa and b) is observed when they are heated briefly in solution to 40-50°C, and also on storage. Attempts to trap 1,2-dihydropyridine (IIa) on heating (IVa) with maleic anhydride or maleic acid were unsuccessful.

The dimeric structure of the benzothiazole derivative (IVb), just like that of compound (IVa), is confirmed by the presence in the PMR spectrum of the characteristic signals from two $N-CH_3$ groups at 2.32 ppm, and also by an enamine AX quartet at 5.80 and 4.53 ppm and the signal of a vinyl proton (6.99 ppm) adjacent to the multiplet of the benzothiazole residues (8.0-7.1 ppm). The deuterium derivative (VIIb) was also obtained, its properties being analogous to those of compound (VIIa).

The reduction of the benzimidazolylpyridinium salt (Ic) with sodium tetrahydroborate even in a strongly alkaline medium led to the formation of the monomeric compound (IIIc) exclusively. To explain the observed phenomenon requires additional investigations.

EXPERIMENTAL

The PMR spectra of 10% solutions in $CDCl_3$ were obtained on a Perkin–Elmer R-12A (60 MHz) instrument at 36°C. The chemical shifts δ were measured relative to TMS as internal standard with an accuracy of 0.5% of the depth of scanning.

7,11-Di(benzoxazol-2-yl)-endo-4-endo-9-dimethyl-4,9-diazatricyclo[6,2,2,$0^{2,7}$]dodeca-5,11-diene (IVa). To a mixture of 3.37 g (0.01 mole) of (Ia) and 0.4 g (0.01 mole) of NaOH in 20 ml of water and 30 ml of ethanol was added 0.76 g (0.01 mole) of sodium tetrahydroborate in portions. A vigorous reaction began. The precipitate was filtered off, washed with hot water (~30°C), and dissolved in chloroform, and the solution was passed through a layer of alumina of activity grade II according to Brockmann. Distillation of the solvent left light-yellow crystals. Yield 51%. Mp 169-170°C. Found: C 73.1; H 5.4; N 13.2%. M 423 (cryoscopy in benzene). $C_{26}H_{24}N_4O_2$. Calculated: C 73.6; H 5.7; N 13.2%. Mol. wt. 424.

7,11-Di(benzothiazol-2-yl)-endo-4-endo-9-dimethyl-4,9-diazatricyclo[6,2,2,$0^{2,7}$]dodeca-5,11-diene (IVb). This was obtained in a similar manner to (IVa). Light-yellow crystals. Yield 30%. Mp 138-140°C. Found: C 68.0; H 5.3; N 12.0%. M 455 (cryoscopy in benzene). $C_{26}H_{24}N_4S_2$. Calculated: C 68.6; H 5.3; N 12.3%. Mol. wt. 454.

7,11-Di(benzoxazol-2-yl)-endo-4-endo-9-dimethyl-4,9-diazatricyclo[6,2,2,$0^{2,7}$]dodeca-5,11-diene-3,10-D_2 (VIIa). In portions, 0.42 g (0.1 mole) of $NaBD_4$ was added to a mixture of 1.68 g (0.005 mole) of (Ia), and 0.61 g (0.01 mole) of $NaOD \cdot D_2O$ in 10 ml of D_2O and 15 ml of CD_3OD. The mixture was left overnight. Then the precipitate was filtered off and was washed with D_2O, H_2O, and C_2H_5OH. This gave 1.33 g (34%) of white crystals with mp 172-173°C. Found: C 73.0; H 6.0; N 13.3%. $C_{26}H_{22}D_2N_4O_2$. Calculated: C 73.2; H 6.1; N 13.1%.

7,11-Di(benzoxazol-2-yl)-endo-4-endo-9-dimethyl-4,9-diazatricyclo[6,2,2,$0^{2,7}$]dodecane (Va). To a suspension of 0.57 g (0.0025 mole) of (IVa) in 20 ml of ethanol was added 0.93 g (0.01 mole) of pyridine–borane, and the mixture was heated on the water bath for 20 min. During the reaction, the (IVa) dissolved completely. The solvent was evaporated, and the residue was washed with water, giving 0.97 g (90%) of a product with mp 227-228°C (from propan-2-ol). Found: C 72.7; H 6.5; N 13.1%. Mol. wt. 428 (mass spectrometry). $C_{26}H_{28}N_4O_2$. Calculated: C 72.9, H 6.6; N 12.1%. Mol. wt. 428.

7,11-Di(benzothiazol-2-yl)-endo-4-endo-9-dimethyl-4,9-diazatricyclo[6,2,2,$0^{2,7}$]dodecane (Vb). Obtained in the same way as (Va). Colorless crystals. Yield 85%. Mp 219-220°C. Found: C 67.7; H 6.1; N 12.2%. Mol. wt. 460 (mass spectrometry). $C_{26}H_{28}N_4S_2$. Calculated: C 67.8; H 6.1; N 12.2%. Mol. wt. 460.

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