

## PREPARATION OF 1-PHENYLDIHYDROPYRIDINES POLYDEUTERATED IN THEIR HETEROCYCLIC RING\*

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The pentadeuterated quaternary salt *III* reacts with aniline to give the pentadeuterated pentamethine salt *IV* which, on action of triethylamine, gives a mixture of 1-phenylpyridinium chlorides *Va-c*. The chlorides *Va-c* are reduced with dithionite or borohydride to mixtures of 1,4- (*VIIa-c*) or 1,2-dihydropyridines (*VIIIa-c*), respectively. A procedure has been found for obtaining the 3,4,5-trideuterated or 2,3,4,5,6-pentadeuterated products.

In the context of studies of reactions of 1-phenyl-1,4-dihydropyridine (*I*), we were interested in preparation of some of its derivatives containing several deuterium atoms in the heterocyclic section of the molecules. The non-deuterated dihydropyridine *I* can be obtained by dithionite reduction of 1-phenylpyridinium halogenides in water<sup>1</sup>, and, therefore we first focused our attention on preparation of the starting quaternary salt already deuterated to a higher degree. This communication publishes the results obtained in application of the procedure<sup>2,3</sup> for preparation of the deuterated chloride *II* ( $X = \text{Cl}$ ) involving quaternization of pentadeuteriopyridine with 2,4-dinitrochlorobenzene and subsequent transformation (by action of aniline and triethylamine) to the deuterated product corresponding to the salt *II*. Moreover, isotopic structure has been examined of the dihydropyridines obtained by subsequent reductions<sup>1,4</sup> with sodium dithionite or borohydride. The presence of deuterium in the molecules investigated was followed by 100 MHz <sup>1</sup>H NMR spectra. The reaction of pentadeuteriopyridine with 2,4-dinitrochlorobenzene proceeded according to expectation without isotopic exchange and gave the salt *III*, the same being true of the subsequent pyridine ring opening by action of aniline leading to the pentamethine salt *IV*. The recyclization of the pentadeuterated product *IV* by its reaction with triethylamine was, however, accompanied by isotope exchange already, which was manifested by <sup>1</sup>H NMR spectrum of the reaction product showing the proton signal at  $\delta = 9.52$  ppm for 2- and 6-positions whose intensity was, however, only half that of the same signal in spectrum of the non-deuterated chloride *II* ( $X = \text{Cl}$ ).

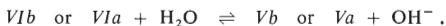
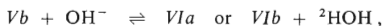
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spectrum showed chemical shifts of 4-proton ( $\delta = 2.98$  ppm) and 2- and 6-protons ( $\delta = 6.25$  ppm) with 50% signal intensity as compared with the spectrum of the non-deuterated compound *I*. The fact that the former signal has a multiplet character, whereas the latter one is singlet, indicates the presence of a mixture of deuterated 1-phenyl-1,4-dihydropyridines of the structures *VIIa-c*. The borohydride reduction of the mixture *Va-c* gave similarly mixtures of deuterated 1-phenyl-1,2-dihydropyridines *VIIIa-d* whose  $^1\text{H}$  NMR spectrum contained 2- and 6-proton signals (at  $\delta = 4.34$  and  $6.42$  ppm, respectively) of 75% and 50% intensity, respectively, as compared with the same signals of the non-deuterated 1,2-dihydro derivative *IX*.

For the both mentioned mixtures *VIIa-c* and *VIIIa-d*, the 6-proton signal intensities are higher than those expected for the presumed low isotope effect of the attack of the reducing agent on the carbon atoms bound to hydrogen or deuterium. This finding can be explained by the fact, both dithionite and borohydride reductions take place in alkaline medium, and the starting substrates can be competitively protonated as it follows:



In accordance with this presumption, it was found that heating of the mixture *Va-c* with sodium carbonate in water or deuterium oxide gave, at last, the isotopically homogeneous samples of 1-phenyl-3,4,5-trideuteriopyridinium chloride (*Va*) or 1-phenyl-2,3,4,5,6-pentadeuteriopyridinium chloride (*Vc*), this favourable result being due to shift of the reaction equilibria in the sense of the final steps  $VIa + \text{H}_2\text{O} \rightleftharpoons Va$  and  $VIb + {}^2\text{H}_2\text{O} \rightleftharpoons Vc$ . The compounds *Va* and *Vc* are suitable for preparation of the individual dihydropyridines *VIIa* or *VIIc* and 1,2-dihydro isomers *VIIIa* or *VIIIb* and/or also for preparation of the hexadeuterated isomers *VIIIc* and *VIIId* in the case of application of the deuterating reagents, *i.e.*  $\text{Na}_2\text{S}_2\text{O}_4 + {}^2\text{H}_2\text{O}$  and  $\text{NaB}^2\text{H}_4$ , respectively.

## EXPERIMENTAL

The melting points were measured with a Boetius apparatus (GDR). The  $^1\text{H}$  NMR spectra were measured with a Varian XL-100 apparatus at  $37^\circ\text{C}$ .

### 1-(2,4-Dinitrophenyl)-2,3,4,5,6-pentadeuteriopyridinium Chloride (*III*)

25 g pentadeuteriopyridine (isotopic purity: at least 99% deuterium) was added drop by drop to solution of 61 g 2,4-dinitrochlorobenzene in 150 ml toluene, and the mixture was heated

on a boiling water bath for 10 h. After cooling, the reaction product was collected by suction and recrystallized from ethanol. Yield 57 g (72%) salt *III*, m.p. 190–194°C (decomposition).  $^1\text{H}$  NMR spectrum ( $\delta$ , hexadeuteriodimethyl sulphoxide): 8.48 d (1 H, 6'-position), 8.98 d (1 H, 5'-position), 9.11 d (1 H, 3'-position);  $^4J_{3',5'} = 2.5$  Hz and  $^3J_{5',6'} = 8.5$  Hz. The non-deuterated chloride was prepared according to ref.<sup>7</sup>, m.p. 188–193°C (decomp.),  $^1\text{H}$  NMR spectrum ( $\delta$ , hexadeuteriodimethyl sulphoxide): 8.42 t (2 H, 3- and 5-positions), 8.50 d (1 H, 6'-position), 8.97 t (1 H, 4-position), 9.00 dd (1 H, 5'-position), 9.12 d (1 H, 3'-position) and 9.54 dd (2 H, 2-position);  $^3J_{2,3} = 6$  Hz,  $^3J_{3,4} = 7$  Hz,  $^4J_{3',5'} = 2.5$  Hz, and  $^3J_{5',6'} = 8.5$  Hz.

#### 1,5-Diphenylamino-1,2,3,4,5-pentadeuteriopentamethinium Chloride (*IV*)

Solution of 39 g aniline in 470 ml 80% aqueous ethanol was added drop by drop to solution of 56 g salt *III* in 470 ml of the same solvent. After 20 min, the reaction mixture was filtered to remove the red crystals formed, and this operation was repeated with the mother liquor every 10 min until yellow crystals of 2,4-dinitroaniline began to separate. At this moment the filtrations were finished, and combined red products were washed with hot acetone and recrystallized from methanol. Yield 45 g (63%) chloride *IV*, m.p. 144–146°C.  $^1\text{H}$  NMR spectrum ( $\delta$ , hexadeuteriodimethyl sulphoxide): 7.23 s (2 H, NH) and 7.42 m (10 H,  $\text{C}_6\text{H}_5$ ). The analogous chloride prepared<sup>8</sup> from the non-deuterated material had m.p. 143–145°C and  $^1\text{H}$  NMR spectrum ( $\delta$ , hexadeuteriodimethyl sulphoxide): 6.40 t (2 H, —CH—(CHNH—)), 7.23 s (2 H, —NH—), 7.84 t (1 H,  $\text{CH}=(\text{C}^2\text{HC}^2\text{H}-)_2$ ) and 8.57 d (2 H, —CH—(NH—)).

#### Reaction of Pentamethine Salt *IV* with Triethylamine

25 ml triethylamine was added drop by drop to solution of 45 g compound *IV* in 360 ml 1-butanol, and the mixture was heated at 80°C for 15 min. After cooling, the mixture was diluted with 100 ml ethyl acetate, and then 500 ml light petroleum was added drop by drop with stirring. The precipitated product was collected by suction and recrystallized from mixture 1-butanol–ethyl acetate–ether. Yield 22.4 g (66%) mixture of quaternary salts *Va–c*, m.p. 93–95°C.  $^1\text{H}$  NMR spectrum ( $\delta$ , hexadeuteriodimethyl sulphoxide): 7.7 to 8.1 m (5 H,  $\text{C}_6\text{H}_5$ ) and 9.52 s (0.5 H, 2-position or 6-position). Three hours boiling of solution of 2 g salt mixture *Va–c* and 10 mg sodium carbonate in 20 ml water and evaporation gave quantitative yield of *Va* whose  $^1\text{H}$  NMR spectrum showed, besides a multiplet 7.7 to 8.1 (5 H), a singlet 9.52 s (1 H). The reaction carried out similarly in 20 ml deuterium oxide gave the salt *Vc* whose spectrum showed exclusively the multiplet 7.7 to 8.1 m. The non-deuterated salt *II* prepared according to ref.<sup>1</sup> had m.p. 97–98°C (ref.<sup>1</sup>: m.p. 101–102°C) and  $^1\text{H}$  NMR spectrum ( $\delta$ , hexadeuteriodimethyl sulphoxide): 7.8–8.2 m (5 H,  $\text{C}_6\text{H}_5$ ), 8.46 t (2 H, 3- and 5-positions), 8.88 t (1 H, 4-position), 9.48 d (2 H, 2- and 6-positions);  $^3J_{2,3} = 6.5$  Hz and  $^3J_{4,3} = 7$  Hz.

#### Dithionite Reduction of Quaternary Salts *Va–c*

Solution of 0.4 g mixture of *Va–c* salts in 4 ml 0.05M aqueous sodium carbonate solution was added drop by drop to solution of 0.2 g sodium dithionite in 4 ml 0.5M aqueous sodium carbonate solution. After 20 min stirring at room temperature, the precipitate formed was collected by suction and dried in vacuum. Yield 0.11 g (55%), m.p. 42–44°C.  $^1\text{H}$  NMR spectrum ( $\delta$ ,  $\text{CCl}_4$ ): 2.98 m (1 H, 4-position) and 6.25 s (0.5 H, 2- or 6-positions). The non-deuterated 1,4-dihydropyridine *I* prepared according to ref.<sup>1</sup> had m.p. 45–46°C and  $^1\text{H}$  NMR spectrum ( $\delta$ ,  $\text{CCl}_4$ ): 2.98 m (2 H, 4-position), 4.52 m (2 H, 3-position), 6.24 d (2 H, 2- or 6-positions) and 7.02 m (5 H,  $\text{C}_6\text{H}_5$ ).

Borohydride Reduction of Quaternary Salts *Va-c*

Solution of 0.1 g sodium borohydride in 9 ml water was added to solution of 1.3 g salts *Va-c* and 1.6 g potassium hydroxide in 175 ml water, and the mixture was left to stand under nitrogen at room temperature for 16 h. The yellow precipitate formed was then collected by suction and recrystallized three times from methanol. Yield 0.52 g (41%) mixture of 1,2-dihydro derivatives *VIIIa-d*, m.p. 78–80°C.  $^1\text{H}$  NMR spectrum ( $\delta$ ,  $\text{CCl}_4$ ): 4.34 q (0.75 H, 2-position) and 6.42 s (0.5 H, 6-position) and 7.02 m (5 H,  $\text{C}_6\text{H}_5$ ). The non-deuterated 1,2-derivative *IX* prepared according to ref.<sup>4</sup> melted at 81–82°C (ref.<sup>4</sup>: m.p. 82–83°C),  $^1\text{H}$  NMR spectrum ( $\delta$ ,  $\text{CCl}_4$ ): 4.34 q (2 H, 2-position), 4.98 m (1 H, 5-position), 5.28 m (1 H, 3-position), 5.88 m (1 H, 4-position), 6.43 d (1 H, 6-position) and 7.02 m (5 H,  $\text{C}_6\text{H}_5$ ).

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