PYRIDINIUM SALTS

III.* ALKYLATION OF 2-(PYRIDIN-2-YL)BENZAZOLES

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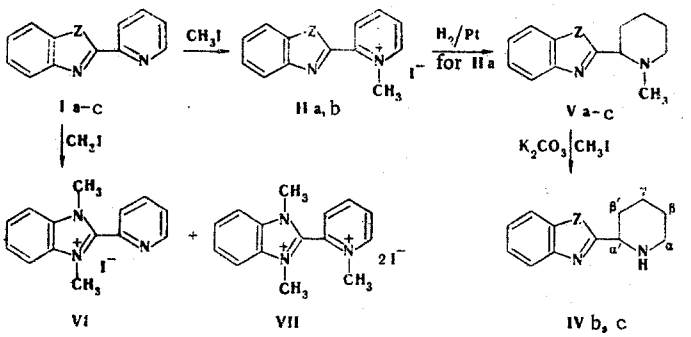
The reaction of 2-(pyridin-2-yl)benzoxazole and 2-(pyridin-2-yl)benzothiazole with methyl iodide forms the corresponding pyridinium salts. In the case of 2-(pyridin-2-yl)benzimidazole, the imidazole ring is quaternized first, and only then the pyridine ring. The catalytic hydrogenation of 2-(benzoxazol-2-yl)-1-methylpyridinium salts gives 2-(1-methylpiperidin-2-yl)benzoxazole.

It has been considered [2] that 2-(pyridin-2-yl)benzazoles are not capable of forming quaternary pyridinium salts, since they possess a low basicity. However, by the prolonged heating of 2-(pyridin-2-yl)-benzoxazole (Ia) and of 2-(pyridin-2-yl)benzothiazole (Ib) with methyl iodide in dimethylformamide we have succeeded in obtaining 2-(benzothiazol-2-yl)-1-methylpyridinium salts (IIa, b). The PMR spectrum of (IIa) in $CD_3OD + D_2O$ showed the singlet of the $N-CH_3$ protons at 4.84 ppm, a doublet of doublets at δ 9.16 ppm for the α proton, and multiplet of the β proton with its center at 824 ppm ($J_{\alpha\beta} = 6.4$ Hz), a multiplet of the γ and β' protons at 8.8 ppm, and a multiplet of the benzoxazole protons at 8.05-7.25 ppm. In the PMR spectrum of (IIb) a singlet of the $N-CH_3$ protons was observed at 4.54 ppm, a doublet of doublets with δ 9.14 ppm of the α proton, a multiplet of the β proton with its center at 8.6 ppm, and a multiplet of the benzothiazole protons at 8.2-7.5 ppm.



I, II, V a Z=O; I, II, IV, V b Z=S; I, IV, V c Z=NH

In contrast to compounds (Ia and b), 2-(pyridin-2-yl)benzimidazole (Ic) gives a mixture of the salts (III) and (IV) with methyl iodide even at an equimolecular ratio (1:1) of the reactants. Since the alkylation of (Ic) obviously begins with the imidazole ring, it is impossible to obtain compound (IIc) by the alkylation of (Ic).

The PMR spectrum of (VI) in CD_3OD showed a singlet of the $N-CH_3$ protons of the imidazole ring at 3.99 ppm, a doublet of doublets of the α proton with δ 8.91 ppm, a multiplet of the $\beta\beta'\gamma$ protons with its

*For Communication II, see [1].

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center at 8.15 ppm ($J_{\alpha\beta}$ = 4.5 Hz) and a multiplet of the benzimidazole protons at 7.85 ppm (6H). The signals of the protons of the benzimidazole and pyridine rings are shifted by 1 ppm downfield as compared with the pyridinylbenzimidazole (Ia), since, obviously, the positive charge is delocalized over the whole molecule.

In the PMR spectrum of the bisquaternary salt (VII) in $CD_3OD + D_2O$, a singlet of the $N-CH_3$ group of the imidazole ring was observed at 4.12 ppm, a singlet of the $N-CH_3$ group of the pyridine ring at 4.39 ppm (3H), a doublet of doublets of the α proton at δ 9.56 ppm, a multiplet of the $\beta\beta'\gamma$-protons at 9.19-8.38 ppm ($J_{\alpha\beta}$ = 5.4 Hz), and multiplets of the benzimidazole protons at 8.04 ppm. The signals of the protons of the benzimidazole and pyridine rings of compound (VII) are still further shifted in the downfield direction than in (VI).

In their UV spectra ($CHCl_3$), the salts (IIa and b) have their long-wave absorption maxima at 332 and 350 nm, respectively, bathochromically shifted (~30 nm) with respect to (Ia) and (Ib). Compound (VI) has its absorption maximum at 286 nm and (VII) at 272 and 286 nm.

The quaternization of compounds (Ia and b) with higher alkyl halides did not take place, apparently because of steric factors, since it can be seen on Stuart–Briegleb models that in the salts (IIa and b) even the CH_3 group is accomodated with difficulty.

The pyridinium salts (IIa and b) could not be reduced either with sodium tetrahydroborate, with pyridine–borane by Ferles' method [3], or with lithium tetrahydroaluminate [4]. Unstable resins were obtained. Catalytic reduction proved to be successful only in the case of the benzoxazolylpyridinium salt (IIa). The salt (IIb) was not reduced, which can be explained by the poisoning of the catalyst, while the reduction of (VI) and (VII) gave complex mixtures from which it was impossible to isolate individual substances. Compounds (Vb and c) were obtained only by the methylation of the 2-(piperidin-4-yl)benzazoles (IVb, c), which, in their turn, were synthesized by condensing nipecotinic acid with o-aminophenol and o-phenylenediamine.

EXPERIMENTAL

The PMR spectra were taken on a Perkin–Elmer R-12A instrument (60 MHz).

2-(Benzoxazolyl)-1-methylpyridinium Iodide (IIa). A mixture of 0.01 mole of (Ia) and 0.01 mole of methyl iodide in dimethylformamide was heated in a sealed tube at 100°C for 36 h. The solvent was evaporated off and the unchanged (Ia) was washed out with acetone. Yield 50%. Mp 217-218°C (from water). Found %: C 45.9; H 3.4; I 37.2; N 8.0. $C_{13}H_{11}IN_2O$. Calculated %: C 46.2; H 3.3; I 37.5; N 8.3.

2-(Benzothiazol-2-yl)-1-methylpyridinium iodide (IIb) was obtained similarly with a yield of 50%. Mp 232-233°C (from water). Found %: C 44.2; H 2.9; I 35.4; N 7.8. $C_{13}H_{11}IN_2S$. Calculated %: C 44.1; H 3.1; I 35.8; N 7.9.

1,3-Dimethyl-2-(pyridin-2-yl)benzimidazolium Iodide (VI) and 1,3-Dimethyl-2-(1-methylpyridinio-2-yl)benzimidazolium Diiodide (VII). The mixture of (VI) and (VII) obtained in the same way as (IIa) was crystallized from 50% ethanol. On cooling the solution to room temperature, crystals of (VI) separated out, and these were recrystallized several times. Yield 45% (with respect to the CH_3I). Mp 251-252°C. Found %: C 47.5; H 3.8; N 11.6. $C_{14}H_{14}IN_3$. Calculated %: C 47.9; H 4.0; N 12.0. Evaporation of the mother solutions gave (VII). Yield 30% (on the CH_3I). Mp 253-255°C. Found %: C 36.4; H 3.2; N 8.2. $C_{15}H_{17}I_2N_3$. Calculated %: C 36.6; H 3.5; N 8.5.

The 2-(Piperidin-2-yl)benzazoles (IVb, c). These were obtained in a similar manner to the 2-(piperidin-3-yl)benzazoles [1]. 2-(Piperidin-2-yl)benzothiazole (IVb), yield 60%, 89-90°C (from heptane). Found %: C 65.7; H 6.3; N 12.8. $C_{12}H_{14}N_2S$. Calculated %: C 66.0; H 6.5; N 12.8. PMR spectrum, δ, ppm (CCl_4): α_H 3.4-2.5 m, $\beta_H\beta'_H\gamma_H$ 2.4-1.4 m, α'_H 4.2-3.9 m, benzothiazole protons (7.95-7.1 m).

2-(Piperidin-2-yl)benzimidazole (IVc), yield 27%, mp 248-249°C (from dioxane). Found %: C 71.4; H 7.4; N 20.8. $C_{12}H_{15}N_3$. Calculated %: C 71.6; H 7.5; N 20.9. PMR spectrum (CD_3OD): α_H 3.1-2.6 m, $\beta_H\beta'_H\gamma_H$ 2.2-1.4 m, α'_H 3.94 m, benzimidazole protons 7.64-7.0 m.

2-(1-Methylpiperidin-2-yl)benzothiazole (Vb) was obtained by a method that we have described previously [1] with a yield of 89%, mp 60-61°C (from hexane). Found %: C 67.3; H 6.8; N 11.6. $C_{13}H_{16}N_2S$. Calculated %: C 67.2; H 6.9; N 12.1.

2-(1-Methylpiperidin-2-yl)benzimidazole (Vc) was obtained in a similar manner to compound (Vb) with a yield of 90%. It was crystallized from 50% propan-2-ol; it sublimed above 230°C. Found %: C 72.3; H 8.0; N 19.6. $C_{13}H_{17}N_3$. Calculated %: C 72.5; H 8.0; N 19.5.

2-(1-Methylpiperidin-2-yl)benzoxazole (Va) was obtained with a yield of 30% by the hydrogenation of the salt (IIa) with Adams catalyst in ethanol at room temperature and at atmospheric pressure, and was isolated in the form of the hydrochloride (Va · HCl), mp 172°C (from hexane). Found %: C 61.6; H 6.7; N 11.3. $C_{13}H_{16}N_2O \cdot HCl$. Calculated %: C 61.8; H 6.8; N 11.1.

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