PYRIDINIUM SALTS

II.* REDUCTION OF 3-(BENZAZOL-2-YL)PYRIDINIUM SALTS

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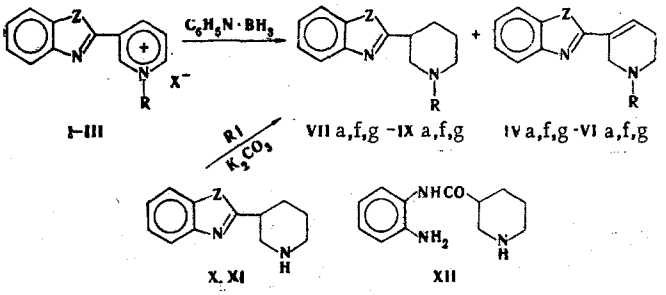
The catalytic hydrogenation and the reduction with pyridine–borane of N-alkyl-3-(benzazol-2-yl)pyridinium salts gives piperidine derivatives; other reducing agents are unsuitable.

Continuing an investigation of benzazolylpyridinium salts, we have synthesized 3-(benzazol-2-yl)pyridinium salts (I-III, Table 1) by methods described previously [1]. In the UV spectra of (I-III), the long-wave absorption band was observed in the 322-332 nm region. The bathochromic shift of the maximum of the long-wave absorption of the salts (I-III) relative to the free bases amounted to ~20 nm. In the case of the 4-substituted pyridinium salts, a greater shift was found because of the conjugation of the pyridinium ring with the benzazole aromatic system [1]. As in the case of 4-(benzazol-2-yl)pyridinium salts, in chloroform solutions (10^{-3} M) of the iodides (Ia-IIIa) a weak CTC absorption band is found at about 450 nm [2].

With sodium tetrahydroborate, the 3-(benzazol-2-yl)pyridinium salts (I-III) cause an intense red coloration of the reaction mixture. Brightly colored resinous products are formed which cannot be crystallized. It may be assumed that the reduction takes place through 1,4-dihydropyridine derivatives, which are unstable [3] and are rapidly oxidized. In the case of (Ia), nevertheless, it was possible to obtain a crystalline derivative of 1,2,5,6-tetrahydropyridine (IVa). The structure of (IVa) was confirmed by the presence of a characteristic signal of a vinyl proton δ 6.98 ppm in the PMR spectrum. Attempts to reduce compounds (I-III) by Ferles' method with lithium tetrahydroaluminate led to unstable resins.

Pyridine–borane has been used successfully in the reduction of carbonyl compounds [5]. The treatment of (Ia, f, g–IIIa, f, g) with pyridine–borane gave a mixture of two products in each case. The PMR spectra of the reduction products showed the predominance in each mixture of the piperidine derivative (VII-IX).

* For Communication I, see [1].



I-IX R = Alk, $CH_2C_6H_5$, $CH_2CH_2C_6H_5$, $CH_3-C\equiv C$, $CH_2=CHCH_2$; I, IV, VII, X Z = O; II, V, VIII, XI Z = S; III, VI, IX Z = NH; X = I, Br, Cl

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TABLE 1. 3-(Benzazol-2-yl)pyridinium Salts (I-III)

Compound	Z	R	X	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	N	X	C	H	N	X	
Ia	O	CH_3	I	295—296[7,8]	$C_{13}H_{11}IN_2O$	45,8	3,1	8,0	37,0	46,2	3,3	8,3	37,5	81
Ib	O	C_2H_5	I	254—255	$C_{14}H_{13}IN_2O$	47,4	3,6	7,5	35,5	47,7	3,7	8,0	34,5	87
Ic	O	C_3H_7	I	175—177	$C_{15}H_{15}IN_2O$	49,0	4,4	7,2	34,0	49,2	4,1	7,6	34,6	42
Ic	O	C_3H_7	Br	194—195	$C_{15}H_{15}BrN_2O$	55,9	4,5	8,5	24,5	56,4	4,7	8,8	25,0	75
Id	O	C_4H_9	I	157—159	$C_{16}H_{17}IN_2O$	49,7	4,2	7,2	32,9	50,5	4,5	7,4	33,3	79
Ie	O	C_5H_{11}	I	160—162	$C_{17}H_{19}IN_2O$	51,3	4,6	7,0	31,7	51,8	4,9	7,1	32,2	63
If	O	$C_6H_5CH_2$	Br	236—238	$C_{19}H_{15}BrN_2O$	62,1	4,1	7,6	20,9	62,1	4,1	7,6	21,7	94
Ig	O	$C_6H_5CH_2CH_2$	Br	230	$C_{20}H_{17}BrN_2O$	63,0	4,2	7,1	20,0	63,0	4,5	7,3	21,0	59
IIa	S	CH_3	I	215—216[7,8]	$C_{13}H_{11}IN_2S$	44,2	3,0	7,5	35,4	44,1	3,1	7,9	35,8	88
IIb	S	C_2H_5	I	228—229	$C_{14}H_{13}IN_2S$	44,9	3,5	7,3	34,2	45,7	3,6	7,6	34,5	92
IIc	S	C_3H_7	Br	199—201	$C_{15}H_{15}BrN_2S$	53,5	4,5	8,1	22,9	53,7	4,5	8,4	23,8	74
Id	S	C_4H_9	I	188—189	$C_{16}H_{17}IN_2S$	48,3	4,2	7,3	32,4	48,5	4,3	7,1	32,0	83
IIe	S	C_5H_{11}	I	179—180	$C_{17}H_{18}IN_2S$	49,4	4,4	6,7	30,9	49,9	4,4	6,8	31,0	69
IIf	S	$C_6H_5CH_2$	Br	213—214	$C_{19}H_{15}BrN_2S$	59,3	3,7	7,0	20,4	59,5	3,9	7,3	20,8	95
IIg	S	$C_6H_5CH_2CH_2$	Br	231—232	$C_{20}H_{17}BrN_2S$	59,9	4,2	7,2	19,9	60,5	4,3	7,0	19,7	48
IIh	S	C_9H_{19}	Br	145—146	$C_{21}H_{27}BrN_2S$	60,0	6,2	6,4	18,5	60,1	6,5	6,7	19,0	70
IIi	S	$CH_3CH{\equiv}C$	Cl	131—132	$C_{15}H_{12}ClN_2S$	62,4	3,5	9,7	12,2	62,8	3,9	9,8	12,4	74
IIj	S	C_6H_{13}	I	122—123	$C_{18}H_{21}IN_2S$	50,4	4,7	6,4	29,4	50,9	5,0	6,6	29,9	29
IIk	S	$CH_2{=}CHCH_2$	I	198—199	$C_{15}H_{13}IN_2S$	47,2	3,3	7,0	33,6	47,4	3,4	7,4	33,4	87
IIIa	NH	CH_3	I	246—247	$C_{13}H_{12}IN_3$	46,1	3,5	12,6	38,0	46,3	3,6	12,5	37,6	96
IIIb	NH	C_2H_5	I	253—254	$C_{14}H_{14}IN_3$	47,3	3,9	11,9	35,8	47,9	4,0	12,0	36,1	77
IIIc	NH	C_3H_7	Br	256—257	$C_{15}H_{16}BrN_3$	56,4	5,1	13,2	25,4	56,6	5,1	13,2	25,1	56
IIId	NH	C_4H_9	I	220—221	$C_{16}H_{18}IN_3$	50,4	4,6	11,3	33,8	50,7	4,8	11,1	33,5	64
IIId	NH	C_4H_9	Br	287—288	$C_{16}H_{18}BrN_3$	57,4	5,1	12,4	24,5	57,8	5,5	12,6	24,0	50
IIIe	NH	C_5H_{11}	I	213—214	$C_{17}H_{19}IN_3$	51,8	4,6	10,3	31,9	52,0	4,9	10,7	32,3	94
IIIf	NH	$C_6H_5CH_2$	Br	225—227	$C_{19}H_{16}BrN_3$	62,4	4,4	11,2	21,3	62,3	4,4	11,5	21,8	83
IIIg	NH	$C_6H_5CH_2CH_2$	Br	254—256	$C_{20}H_{19}BrN_3$	62,9	5,1	11,3	21,0	63,0	5,0	11,0	21,0	72
IIIh	NH	C_9H_{19}	Br	170—172	$C_{21}H_{28}BrN_3$	62,5	7,3	10,2	19,5	62,7	7,0	10,4	19,9	62

For example, in the PMR spectrum of the product of the reduction of compound (IIa) all the signals characteristic for (VIIIa) obtained by independent synthesis were observed, and also a weak signal of a vinyl proton at 6.98 ppm, which shows the presence of (Va). The amounts of tetrahydropyridines in the mixtures varied between 5 and 10%.

The benzothiazole derivatives (II) could not be catalytically reduced, while compounds (Ia, g and IIIa, e) on catalytic reduction (Pt) gave the piperidine derivatives (VIIa, g; IXa, f).

To confirm the structures of the reduction products, compounds (VIIa, VIIIa, f) were also obtained by the alkylation of the corresponding 2-(piperidin-3-yl)benzazoles (X, XI) as described previously [1]. The reaction between nipecotinic acid and o-phenylenediamine led to the formation of the amide (XII). On subsequent heating with polyphosphoric acid, no closure of the ring took place. Thus, only reduction with pyridine–borane followed by catalytic hydrogenation gives an unambiguous passage from pyridinium salts to piperidine derivatives.

EXPERIMENTAL

The PMR spectra of solutions in CCl_4 were recorded on a Perkin–Elmer R-12A (60 MHz) instrument using tetramethylsilane as internal standard.

The 3-(benzazol-2-yl)pyridinium salts (Table 1) were obtained as described previously [1] and were recrystallized from water.

2-(1,2,5,6-Tetrahydropyridin-3-yl)benzoxazole (IVa). A solution of 3.37 g (0.01 mole) of the salt (Ia) in 30 ml of ethanol and 30 ml of water was treated with 0.76 g (0.02 mole) of sodium tetrahydroborate. A vigorous reaction began and the reaction mixture acquired a red-orange color. It was left overnight and the solvent was evaporated off. The resinous residue was treated with a 30% solution of hydrochloric acid. The solution was filtered through a layer of active carbon, and 30% alkali was added to pH ~9. The oil that separated out solidified on standing. Colorless crystals with mp 64°C (from 50% ethanol). Yield 0.43 g (20%). Found %: C 72.5; H 6.5; N 12.7. $C_{13}H_{14}N_2O$. Calculated %: C 72.4; H 6.5; N 12.7.

2-(1-R-Piperidin-3-yl)benzazoles (IVa, f, g–VIa, f, g; Table 2). A. To a solution of 0.01 mole of a pyridinium salt (Ia, f, g–IIIa, f, g) in a mixture of 30 ml of methanol and 30 ml of glacial acetic acid was added 7.44 g (0.08 mole) of pyridine–borane [6] and the mixture was heated at 95-100°C for 24 h and was then evaporated, and the residue was dissolved in hydrochloric acid (1:1). The solution was treated with carbon, neutralized with alkali, and extracted with ether. The extract was dried with sodium sulfate and

TABLE 2. Hydrochlorides of 2-(1-R-Piperidin-3-yl)benzazoles (VII-IX)

Compound*	Z	R	mp, °C†	Empirical formula	Found, %			Calc., %			Yield, %		
					C	H	N	C	H	N	A	B	C
VIIa	O	CH_3	280—283 (300*)	$C_{13}H_{16}N_2O \cdot HCl$	61,9 61,7	6,6 6,5	11,3 11,4	61,8 61,8	6,8 6,8	11,1 11,1	14	75	89
VIIf	O	$C_6H_5CH_2$	228—232	$C_{19}H_{18}N_2O \cdot HCl$	69,5	6,3	8,5	69,4	6,4	8,5	21		
VIIg	O	$C_6H_5CH_2CH_2$	221—225 (255—257*)	$C_{20}H_{22}N_2O \cdot HCl$	70,3 70,2	6,6 6,6	8,1 8,2	70,1 70,1	6,8 6,8	8,2 8,2	25	70	90
VIIIa	S	CH_3	238—241 (204*)	$C_{13}H_{17}N_2S \cdot HCl$	58,3 58,0	5,4 6,2	10,4 10,0	58,1 58,1	6,4 6,4	10,4 10,4	65		73
VIIIf	S	$C_6H_5CH_2$	233—236 (207*)	$C_{19}H_{20}N_2S \cdot HCl$	66,2 65,9	5,9 6,1	8,0 8,0	66,2 66,2	6,1 6,1	8,1 8,1	44		69
VIIIg	S	$C_6H_5CH_2CH_2$	235—238	$C_{20}H_{22}N_2S \cdot HCl$	67,0	6,1	7,8	66,9	6,5	7,8	48		
IXa	NH	CH_3	270—273 (283—285*)	$C_{13}H_{16}N_3 \cdot 2HCl$	54,4 54,3	6,2 6,7	14,6 14,4	54,2 54,2	6,6 6,6	14,6 14,6	21	82	
IXf	NH	$C_6H_5CH_2$	210—213 (220—223*)	$C_{19}H_{21}N_3 \cdot 2HCl$	62,5 62,5	6,0 6,3	11,6 11,5	62,6 62,6	6,4 6,4	11,5 11,5	19	79	
IXg	NH	$C_6H_5CH_2CH_2$	260—262	$C_{20}H_{23}N_3 \cdot 2HCl$	63,2	6,4	11,0	63,5	6,7	11,1	21		

*According to the PMR spectra, samples of the hydrochlorides obtained by method A) contained about 5% of the hydrochlorides of the corresponding 2-(1-R-1,2,5,6-tetrahydropyridin-3-yl) benzazoles. The melting points of these samples are shown in parentheses.
†The 2-(1-R-piperidin-3-yl)benzazole hydrochlorides were recrystallized from isopropanol.

was saturated with HCl. The precipitate of a mixture of hydrochlorides of (VII-IX) and (IV-VI) was filtered off and was recrystallized from isopropanol.

B. A pyridinium salt (Ia, g; IIIa, f) (5 mmoles) in 40 ml of 25% aqueous methanol was hydrogenated at room temperature and atmospheric pressure with Adams catalyst.

C. The alkylation of (X) and (XI) by a method we have described previously [1] gave (VIIa · HCl) and the hydrochlorides of (VIIg) and of (VIIIa, f), identical with those described above.

Hydrochloride of 2-(Piperidin-3-yl)benzoxazole (X · HCl). The condensation of o-aminophenol with nipecotinic acid was performed as described for isonipecotinic acid [1]. The base was extracted with benzene, the solution was filtered through alumina (1 cm), and HCl was passed in. The yield of hydrochloride was 60%, mp 267-268°C. Found %: C 60.3; H 6.9; N 11.9. $C_{12}H_{14}N_2O \cdot HCl$. Calculated %: C 60.4; H 6.3; N 11.7.

The hydrochloride of 2-(piperidin-3-yl)benzothiazole (XI · HCl) was obtained in a similar manner to (X · HCl). Yield 30%, mp 226°C. Found %: C 56.4; H 6.0; N 10.6. $C_{12}H_{14}N_2S \cdot HCl$. Calculated %: C 56.6; H 5.9; N 11.0.

o-Aminoanilide of Nipecotinic Acid (XII). A mixture of 32.5 g (0.25 mole) of nipecotinic acid, 27.0 g (0.25 mole) of o-phenylenediamine, and 100 ml of polyphosphoric acid was heated at 240-250°C for 30 min. After cooling to 120°C, the mixture was poured into 500 ml of cold water and the mixture was made alkaline with concentrated caustic soda to pH 8. An oil separated out which rapidly solidified. This gave 27.0 g (54%) of (XII), mp 242-243°C (from water). Found %: C 65.4; H 7.6; N 18.9. $C_{12}H_{17}N_3O$. Calculated %: C 65.7; H 7.8; N 19.2.

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