PYRIDINIUM SALTS

I. REDUCTION OF 4-(BENZAZOL-2-YL)PYRIDINIUM SALTS IN A NEUTRAL MEDIUM

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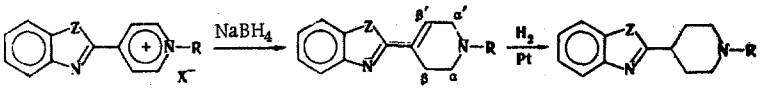
New 4-(benzazol-2-yl)pyridinium salts have been synthesized. Their reduction in a neutral medium with sodium tetrahydroborate has given 2-(1,2,5,6-tetrahydropyridin-4-yl)benzazoles. The catalytic hydrogenation of the latter leads to piperidine derivatives which have also been synthesized by an independent route.

Pyridinium salts are of interest as physiologically active substances, and they also provide the possibility of synthesizing partially and completely hydrogenated piperidine derivatives which are inaccessible by other routes. The reduction of pyridinium salts containing heterocyclic substituents has been studied only for the case of indolylpyridinium salts [1, 2]. In view of the physiological activity of azol-4-ylpyridinium salts [3] and of hydrogenated pyridylindoles [4, 5], it appeared of interest to obtain a series of benzazolylpyridinium salts and to study their reduction.

The initial pyridinium salts (I-III) were obtained by methods proposed in the literature [6, 7]. In their UV spectra, the long-wave absorption band of the benzazolylpyridinium salts has undergone a bathochromic displacement of 50-60 nm relative to the absorption band of the initial pyridinylbenzazoles. In 10^{-3} M solutions of the iodides in chloroform, a weak CTC band [8] is found at 450 nm. In the PMR spectra, the signals of the α and β protons of the pyridine ring are shifted downfield by ~1 ppm in comparison with the initial bases (in D_2O, δ 9.5-8.45 ppm).

The reduction of the salts (I-III) with sodium tetrahydroborate in a neutral medium (ethanol, water) led in all cases to 2-(1-R-1,2,5,6-tetrahydropyridin-4-yl)benzazoles (IV-VI, Table 2). The homogeneity of the reaction products was confirmed by thin-layer chromatography. The presence of a conjugated double bond in each of compounds (IV-VI) is manifested in a bathochromic shift of the long-wave absorption maxima with respect to the corresponding benzazoles (λ_{max} 290-298 nm).



I-III IV-VI VII-IX

I, IV, VII Z = O; II, V, VIII Z = S; III, VI, IX Z = NH; X = I, Br, Cl; I-IX R = Alk, $CH_2C_6H_5$, $CH_2CH_2C_6H_5$, $CH_2CH{=}CHC_6H_5$

In the PMR spectrum of compound (IVa) in $CDCl_3$ a doublet of the α' protons is observed at 3.13 ppm (J = 3.3 Hz), a multiplet of the α and β protons at 2.8-2.4 ppm, a broad triplet for the β' proton at 6.76 ppm, a multiplet of the aromatic protons of the benzoxazole system at 7.7-7.0 ppm, and a N–CH_3 singlet at 2.26 ppm. Compounds (Va) (in CCl_4) and (VIa) (in CD_3OD) give similar spectra.

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TABLE 1. 4-(Benzazol-2-yl)pyridinium Salts (I-III)

Compound	Z	R	X	Method of preparation	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
							C	H	N	X	C	H	N	X	
Ia	O	CH_3	I	A	305—307[10]	$C_{13}H_{11}IN_2O$									98
Ia	O	CH_3	Br	A	334—335	$C_{13}H_{11}BrN_2O$	53,6	3,8	9,6	27,4	53,4	3,7	9,3	27,1	21
Ib	O	C_2H_5	I	A	265—268	$C_{14}H_{13}IN_2O$	47,7	3,7	8,0	36,0	47,8	3,4	8,9	35,7	96
Ib	O	C_2H_5	Br	A	247—248	$C_{14}H_{13}BrN_2O$	55,1	4,3	9,2	26,2	55,3	4,7	8,5	26,3	20
Ic	O	C_3H_7	Br	A	249—250	$C_{15}H_{15}BrN_2O$	56,4	4,7	8,8	25,0	56,4	4,7	8,7	25,2	45
Id	O	i-C_3H_7	Br	B	256—257	$C_{15}H_{15}BrN_2O$	56,4	4,7	8,8	25,0	56,8	4,9	8,1	24,8	24
Ie	O	C_4H_9	I	B	240—243	$C_{16}H_{17}IN_2O$	50,5	4,5	7,4	33,4	50,5	4,4	7,4	33,0	70
Ie	O	C_4H_9	Br	B	244—246	$C_{16}H_{17}BrN_2O$	57,7	5,1	8,4	24,4	57,6	5,1	8,2	24,0	27
If	O	t-C_4H_9	Cl	B	300 (dec.)	$C_{16}H_{17}ClN_2O$	66,5	5,9	9,7		66,9	6,0	10,1		41
Ig	O	C_5H_{11}	Br	B	235—236	$C_{17}H_{19}BrN_2O$	51,8	4,9	7,1	32,2	51,5	4,9	6,7	32,3	46
Ih	O	$C_6H_5CH_2$	I	A	255—256	$C_{19}H_{15}IN_2O$	55,1	3,6	6,8	30,6	54,7	3,5	6,4	29,6	96
Ih	O	$C_6H_5CH_2$	Br	A	256—258	$C_{19}H_{15}BrN_2O$	62,1	4,1	7,6	21,7	62,3	4,2	7,8	21,5	94
Ih	O	$C_6H_5CH_2$	Cl	B	233—235	$C_{19}H_{15}ClN_2O$	70,7	4,7	8,7	11,0	69,7	4,6	8,5	10,5	78
Ii	O	C_9H_{19}	Br	B	200—201	$C_{21}H_{27}BrN_2O$	62,5	6,7	6,9	19,8	62,7	6,7	7,0	20,2	41
Ij	O	$C_6H_5CH_2CH_2$	Br	A	303—304	$C_{20}H_{17}BrN_2O$	63,0	4,5	7,3	21,0	63,3	4,2	7,4	20,5	52
Ik	O	$C_6H_5CH{=}CHCH_2$	Cl	B	218—220	$C_{21}H_{17}ClN_2O$	72,3	4.9	8,0	10,2	72,1	4,4	7,9	9,5	49
IIa	S	CH_3	I	A	256—257[11]	$C_{13}H_{11}IN_2S$	44,1	3,1	7.9	35,8	44,2	3,3	7,5	35,3	76
IIb	S	C_2H_5	I	A	228—229	$C_{14}H_{13}IN_2S$	45,7	3,6	7,6	34,5	45,2	3,3	7,4	34,0	46
IIc	S	C_3H_7	Br	A	225—226	$C_{15}H_{15}BrN_2S$	53,7	4,5	8,4	23,8	53,4	4,4	8,2	23,5	48
IId	S	C_4H_9	I	B	228—229	$C_{16}H_{17}IN_2S$	48,5	4,3	7,1	32,0	48,3	4,0	7,0	32,4	46
IIg	S	C_5H_{11}	I	B	235—236	$C_{17}H_{18}IN_2S$	49,9	4,4	6,8	31,0	49,9	4,3	6,8	30,6	63
IIh	S	$C_6H_5CH_2$	Cl	B	204—205	$C_{19}H_{15}ClN_2S$	67,3	4,5	8,3	10,5	67,0	4,2	8,2	10,0	54
IIh	S	$C_6H_5CH_2$	Br	A	229—300	$C_{19}H_{15}BrN_2S$	59,5	3,9	7,3	20,8	59,4	3,8	7,0	20,5	66
IIj	S	$C_6H_5CH_2CH_2$	Br	A	268—269	$C_{20}H_{17}BrN_2S$	60,5	4,3	7,0	20,1	59,0	4,1	6,5	20,4	60
IIIa	NH	CH_3	I	A	269—270	$C_{13}H_{12}IN_3$	46,3	3,6	12,5	37,6	46,1	3,5	12,4	37,2	80
IIIb	NH	C_2H_5	I	A	237—238	$C_{14}H_{14}IN_3$	47,9	4,0	12,0		47,8	3,8	11,6		70
IIIc	NH	C_3H_7	Br	A	227—228	$C_{15}H_{16}BrN_3$	56,6	5,1	13,2	25,1	56,3	5,3	12,9		69
IIIe	NH	C_4H_9	Br	B	150—151	$C_{16}H_{18}BrN_3$	57,8	5,5	12,6	24,0	57,5	5,3	12,4	24,0	59
IIIh	NH	$C_6H_5CH_2$	I	A	247—248	$C_{19}H_{16}IN_3$	55,2	3.9	10,1	30,7	54,9	3,8	10,3	31,0	94
IIIh	NH	$C_6H_5CH_2$	Br	A	240—241	$C_{19}H_{16}BrN_3$	62,3	4,4	11,5	21,8	61 8	4,3	11,2	21,5	66
IIIh	NH	$C_6H_5CH_2$	Cl	B	247—248	$C_{19}H_{16}ClN_3$	70,9	5,0	13,0	11,0	70,5	4,9	12,7	11,3	59
IIIi	NH	C_9H_{19}	Br	C	82—83	$C_{21}H_{28}BrN_3$	62,7	7,0	10.4	19,9	62,5	7,0	10,1	19,5	74
IIIj	NH	$C_6H_5CH_2CH_2$	Br	A	149—150	$C_{20}H_{18}BrN_3$	63,0	5,0	11,0	21,0	62,9	5,1	11,0	20,0	94
IIIk	NH	$C_6H_5CH{=}CHCH_2$	Cl	B	240—242	$C_{21}H_{18}ClN_3$	72,5	5,2	12,0	10,2	72,0	5,0	12,2	9,8	96

The characteristic triplet of the β'-protons at 6.8-6.5 ppm is observed in all the PMR spectra of the 2-(1-R-1,2,5,6-tetrahydropyridin-4-yl)benzazoles (IV-VI).

The catalytic hydrogenation of compounds (IVa-VIa) over Adams catalyst gave the 2-(1-methylpiperidin-4-yl)benzazoles (VII-IX), which were also obtained by the methylation of the 2-(piperidin-4-yl)benzazoles (X-XII). The direct hydrogenation of the pyridinium salts (I-III) takes place with extreme difficulty, which is explained by the poisoning of the catalyst. The replacement of the anion I^- by Cl^- does not accelerate hydrogenation. In the PMR spectra (X) (in CCl_4), multiplets of the β and β' protons at 2.4-1.5 ppm, of the α, α', and γ protons at 3.3-2.4 ppm, and of the aromatic protons at 7.7-7.0 ppm are observed. The introduction of a N-methyl group (VII) is shown by the appearance of a signal at 2.2 ppm (CCl_4) without appreciable changes of the chemical shifts of the signals of the other protons. The PMR spectra of compounds (VIII-XII) are analogous.

The treatment of compound (Ia) with pyridine-borane [9] and with lithium tetrahydroaluminate led to unstable resins, while with sodium tetrahydroborate in pyridine solution stable complexes of (IVa) and BH_3 were formed. In the PMR spectrum ($CDCl_3 + CD_3OD$) a single signal of the $N-CH_3$ protons (singlet at 2.15 ppm) is observed, which shows the formation of a single isomer, obviously the preferential N-axial complex of BH_3 [11]. Reduction with sodium tetrahydroborate in an alkaline medium led to the formation of complex products which will be described in a separate communication.

EXPERIMENTAL

The PMR spectra were taken on a Perkin-Elmer R-12A (60 MHz) instrument. Chromatography was performed with alumina of activity grade II according to Brockmann.

4-(Benzazol-2-yl)pyridinium Salts (I-III, Table 1). A. An equimolar mixture of a 2-(pyridin-4-yl)-benzazole and the appropriate alkyl halide in acetone was heated in the water bath for 30 min. After cooling, the precipitate was separated off and recrystallized from water.

B. An equimolar mixture of a 2-(pyridin-4-yl)benzazole and the appropriate alkyl halide in dimethylformamide solution was heated in a sealed glass tube at 95-100°C for 30 h. The solvent was evaporated off, and the residue was washed with acetone and was recrystallized from water.

TABLE 2. 2-(1,2,5,6-Tetrahydropyridin-4-yl)benzazoles (IV-VI)

Compound	Z	R	Mp, °C*	R_f†	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
IVa	O	CH_3	83—84	0,57	$C_{13}H_{14}N_2O$	72,9	6,6	13,1	72,4	6,5	12,7	72
IVb	O	C_2H_5	53—54		$C_{14}H_{18}N_2O$	73,7	7,1	12,3	73,6	7,0	11,9	71
IVc	O	C_3H_7	83—85	0,63	$C_{15}H_{18}N_2O$	74,4	7,5	11,6	74,1	7,1	11,2	88
IVd	O	i-C_3H_7	63—65		$C_{15}H_{18}N_2O$	74,4	7,5	11,6	74,1	7,1	11,2	75
IVe	O	C_4H_9	50—51	0,82	$C_{16}H_{20}N_2O$	75,0	7,9	10,9	74,7	8,0	10,8	72
IVg	O	C_5H_{11}	48—49		$C_{17}H_{22}N_2O$	75,5	8,2	10,4	75,5	8,2	10,4	75
IVi	O	C_9H_{19}	75—76		$C_{21}H_{30}N_2O$	77,2	9,3	8,6	77,1	9,2	8,3	80
IVh	O	$C_6H_5CH_2$	135—136	0,71	$C_{19}H_{18}N_2O$	78,6	6,2	9,6	78,8	6,2	9,7	69
IVj	O	$C_6H_5CH_2CH_2$	121—122	0,79	$C_{20}H_{20}N_2O$	78,9	6,6	9,2	78,9	6,9	9,0	92
Va	S	CH_3	96—97	0,62	$C_{13}H_{14}N_2S$	67,8	6,1	12,2	67,9	6,1	12,3	81
Vb	S	C_2H_5	67—68	0,71	$C_{14}H_{16}N_2S$	68,8	6,6	11,5	69,2	6,7	11,6	91
Vc	S	C_3H_7	80—81	0,75	$C_{15}H_{18}N_2S$	69,7	7,0	10,8	70,1	7,2	11,0	86
Ve	S	C_4H_9	52—53	0,78	$C_{16}H_{20}N_2S$	70,5	7,4	10,3	70,5	7,5	10,5	76
Vg	S	C_5H_{11}	56—58	0,81	$C_{17}H_{21}N_2S$	71,5	7,4	9,8	71,4	7,8	10,3	93
Vh	S	$C_6H_5CH_2$	114—115	0,84	$C_{19}H_{20}N_2S$	74,5	5,9	9,1	74,5	5,8	9,2	86
Vj	S	$C_6H_5CH_2CH_2$	110—111		$C_{20}H_{20}N_2S$	75,0	6,3	8,7	74,7	6,1	8,5	88
VIa	NH	CH_3	222—223	0,46	$C_{13}H_{16}N_3$	73,6	6,6	19,8	73,4	6,5	19,5	95
VIb	NH	C_2H_5	221—222		$C_{14}H_{17}N_3$	74,0	7,5	18,5	73,5	7,4	18,2	91
VIc	NH	C_3H_7	200—201	0,60	$C_{15}H_{19}N_3$	74,6	7,9	17,4	74,0	8,1	17,4	96
VIe	NH	C_4H_9	192—193	0,66	$C_{16}H_{21}N_3$	75,2	8,3	16,4	75,0	8,4	16,2	98
VIi	NH	C_9H_{19}	151—152	0	$C_{21}H_{31}N_3$	77,5	9,6	12,9	77,1	9,2	12,5	99
VIh	NH	$C_6H_5CH_2$	201—202	0,73	$C_{19}H_{19}N_3$	78,8	6,6	14,5	78,7	6,6	14,5	80
VIj	NH	$C_6H_5CH_2CH_2$	207—208	0,71	$C_{20}H_{21}N_3$	79,2	7,0	13,9	79,1	7,3	13,9	99

*Compounds (IV, V, and VI) were crystallized from 50% aqueous methanol.

†On alumina in chloroform for compounds (IV) and (V) and in the ethanol–chloroform (3:97) system for compounds (VI).

C. An equimolar mixture of a 2-(pyridin-4-yl)benzazole and nonyl bromide was heated in a sealed glass tube at 95–100°C for 30 h. The reaction product was washed with acetone and recrystallized from benzene. λ_{max} in chloroform for compound (I) was 355 nm, for compound (II) 357 nm, and for compound (III) 375 nm.

2-(1,2,5,6-Tetrahydropyridin-4-yl)benzazoles (IV-VI, Table 2). In portions, 0.76 g (0.02 mole) of sodium tetrahydroborate was added to a solution of 0.01 mole of a pyridinium salt (I-III) in ~100 ml of ethanol. The originally yellow-orange solution gradually became decolorized. The reaction mixture was left overnight and was then filtered and evaporated. Compounds (IV) and (V) were dissolved in benzene and the solution was filtered through a 1-cm-thick layer of alumina and was evaporated. The reaction products crystallized on standing in the refrigerator.

Complex of 2-(1,2,5,6-Tetrahydropyridin-4-yl)benzoxazole with BH_3. A solution of 3.37 g (0.01 mole) of the salt (Ia) in 100 ml of pyridine was treated with 0.76 g (0.02 mole) of sodium tetrahydroborate. The reaction mixture was left overnight, filtered, and evaporated. The white crystalline residue of the complex was recrystallized from methanol. Yield 1.37 g (60%), mp 209–210°C. Found %: C 68.3; H 7.5; N 12.4. $C_{13}H_{14}N_2O \cdot BH_3$. Calculated %: C 68.5; H 7.5; N 12.3.

2-(Piperidin-4-yl)benzoxazole (X). A mixture of 68.0 g (0.5 mole) of isonipecotinic acid, 54.5 g (0.5 mole) of o-aminophenol, and 200 ml of polyphosphoric acid was heated at 240–250°C for 30 min, cooled to 120°C, and poured into 1 liter of cold water, and the mixture was made alkaline to pH 8. An oil separated out which rapidly crystallized. The crystals were separated off and dissolved in chloroform, and the solution was filtered through a 1-cm layer of alumina. The chloroform was evaporated and the residue crystallized in the form of silver-white crystals. The yield of (X) was 40.4 g (40%), mp 118–119°C. Found %: C 71.0; H 6.8; N 13.5. $C_{12}H_{14}N_2O$. Calculated %: C 71.2; H 7.0; N 13.8.

2-(Piperidin-4-yl)benzothiazole (XI) was obtained similarly to (X) with a yield of 63%. Mp 100–102°C (from hexane). Found %: C 65.8; H 6.2; N 12.8. $C_{12}H_{14}N_2S$. Calculated %: C 66.0; H 6.2; N 12.8.

2-(Piperidin-4-yl)benzimidazole (XII) was obtained similarly to (X) with a yield of 63%. Mp 262–264°C (from water). Found %: C 71.3; H 7.5; N 20.6. $C_{12}H_{15}N_3$. Calculated %: C 71.6; H 7.5; N 20.9.

2-(1-Alkylpiperidin-4-yl)benzazoles (VII-IX). A. Compounds (IV-VI) were hydrogenated in ethanol at room temperature and at atmospheric pressure with Adams catalyst. 2-(1-Methylpiperidin-4-yl)benzoxazole (VIIa), mp 48–49°C (from hexane). Found %: C 71.7; H 7.7; N 12.7. $C_{13}H_{16}N_2O$. Calculated %: C 72.2; H 7.5; N 13.0. 2-(1-Benzylpiperidin-4-yl)benzoxazole (VIIh), mp 97–99°C (from hexane). Found %: C 78.1;

H 6.7; N 9.4. $C_{19}H_{20}N_2O$. Calculated %: C 78.0; H 6.9; N 9.6. 2-(1-Methylpiperidin-4-yl)benzimidazole (IXa), mp 210°C (from hexane). Found %: 72.4; H 7.2; N 19.3. $C_{13}H_{17}N_3$. Calculated %: C 72.8; H 7.5; N 19.6. 2-(1-Benzylpiperidin-4-yl)benzimidazole (IXh), mp 202-203°C (from benzene). Found %: C 78.2; H 7.1; N 14.1. $C_{19}H_{21}N_3$. Calculated %: C 78.3; H 7.3; N 14.4. 2-(1-Methylpiperidin-4-yl)benzothiazole (VIIIa), mp 73-74°C (from hexane). Found %: C 67.3; H 6.6; N 13.6. $C_{13}H_{16}N_2S$. Calculated %: C 67.2; H 6.9; N 13.8.

B. Compounds (X-XII) were heated in dimethylformamide with equimolar amounts of methyl iodide in the presence of a twofold excess of K_2CO_3 at 95-100°C for 30 h. The solutions were filtered and evaporated. This gave compounds (VII-IX), identical with those obtained by method A. The yields of (VII-IX) were 95%.

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