

Synthesis and ¹H-nmr of *N*-Arylated Nitrogen-Containing Aromatic Heterocycles

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N-Arylation reaction of nitrogen-containing heterocycles such as pyridine, nicotinamide and 4,4'-bipyridine was studied. We prepared *N*-2, 4-dinitrophenyl derivatives initially by reacting the above heterocycles with 2,4-dinitrochlorobenzene in ethanol, and then treated the *N*-2, 4-dinitrophenylated heterocycles with various aniline derivatives, XC₆H₄NH₂ (X = -H, *p*-CH₃, *p*-C₂H₅, *p*-Cl, *p*-CN, *p*-OH, *p*-OCH₃, *o*-Cl, *m*-CH₃) to yield the corresponding *N*-arylated compounds in fairly good yields. H¹-nmr patterns and peak assignments of the *N*-arylated products were described.

Introduction

Nitrogen-containing aromatic heterocycles are important class of compounds in chemistry, and much efforts have been made to synthesize and derivatize those compounds. In particular, 4,4'-bipyridinium salts have attracted considerable interest over the past two decades and they have been in wide use as herbicides, oxidation-reduction indicator, electrochromic display and electron-transfer agents.^{1,2}

N-Alkylated products can be easily obtained by reacting those heterocycles with alkyl halides. The corresponding reaction with aryl halides, aromatic nucleophilic displacement reaction, is known to occur via addition-elimination pathway only when aryl halides are activated by electron-withdrawing groups at *ortho*- and/or *para*-position to the halogen.³ Therefore, introduction of various aryl groups without electron-withdrawing substituents to nitrogen cannot be achieved in a simple way.

In 1923, Konig reported the synthesis of 1,1'-diphenyl-4,4'-bipyridinium salt by reacting 4,4'-bipyridine and aniline in the presence of cyanogen bromide.⁴ In 1973, Reuss et. al. synthesized 1,1'-diphenyl-4,4'-bipyridinium salt by 4,4'-coupling of *N*-phenyl-pyridinium salt.⁵ Rather general method for preparing 1,1'-diaryl-4,4'-bipyridinium compounds was first reported by Emmert and Roh⁶ in 1925 and later patented by ICI researchers.⁷⁻⁹ The method consists of reaction between aniline derivatives and 1,1'-bis-(2,4-dinitrophenyl)-4,4'-bipyridinium salt obtained from 4,4'-bipyridine and 2,4-dinitrochlorobenzene. Russian researchers reported the synthesis of 1-arylpyridinium

salts by the similar method.¹⁰ This reaction attracted our attention in terms of its scope and adaptability to other nitrogen-containing and differently substituted aromatic heterocycles, its mechanistic reaction pathway, and characterization and application of their reaction products. Here, we wish to report a simple and general two step pathway for *N*-arylation of pyridine nucleus such as pyridine, nicotinamide and 4,4'-bipyridine.

Results and Discussion

Pyridine (Ia), nicotinamide (Ib) or 4,4'-bipyridine (Ic) was reacted with 2,4-dinitrochlorobenzene (2,4-DNCB) in ethanol to prepare *N*-2,4-dinitrophenyl derivatives, IIa, IIb or IIc, respectively. The *N*-2,4-dinitrophenylated heterocycles, II, were treated with various aniline derivatives to yield the corresponding *N*-arylated compounds, III (Scheme 1). 2,4-Dinitroaniline was obtained as a by-product.

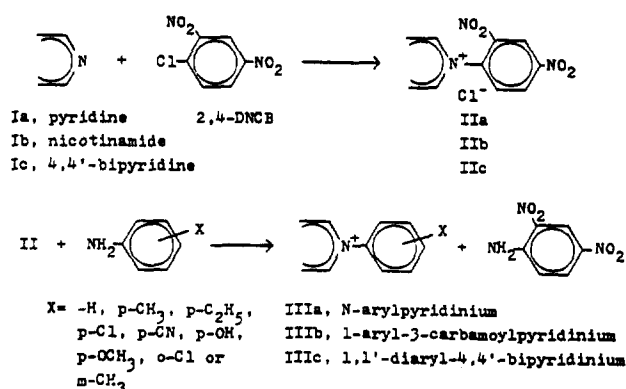


TABLE 1: Yields and Physical Properties of *N*-Arylpyridinium Chlorides, IIIa

X	Yield %	mp** °C	Chemical shift*, δ		I _r , cm ⁻¹
			Phenyl ring	X	
H	83	106-107	7.9(s,5H)		3020(m), 1640(s), 1600(m), 1490(s), 810(m)
<i>p</i> -CH ₃	75	66-67	7.7(s,4H)	2.5(s,3H)	3010(w), 2950(m), 1620(m), 1480(m) 820(s)
<i>p</i> -C ₂ H ₅	80	238-239	7.7(s,4H)	1.3(t,3H, J=7Hz) 2.8(q,2H, J=7Hz)	3020(m), 2960(m), 1620(s), 1500(m), 1460(s), 830(s)
<i>p</i> -Cl	71	200-201	7.9(s,4H)		3020(m), 1630(s), 1480(s), 880(s), 790(s)
<i>p</i> -CN	68	218-219 ^d	8.1(d,4H, J=4Hz)		3020(w), 2210(s), 1610(m), 1500(s), 780(s)
<i>p</i> -OCH ₃	78	206-207	7.3(d,2H, J=9Hz) 7.8(d,2H, J=9Hz)	4.0(s,3H)	3030(m), 2960(m), 1600(m), 1500(m) 1010(s), 850(s)
<i>p</i> -OH	66	218-220	7.1(d,2H, J=9Hz) 7.6(d,2H, J=9Hz)		3200(s), 3010(w), 1620(m), 1480(s), 760(m)
<i>m</i> -CH ₃	68	67-68	7.6(s,4H)	2.4(s,3H)	3020(w), 2960(m) 1600(s), 1500(s) 800(s)

*Chemical shifts for protons of the pyridine ring are not included. **mp for X = H, -OCH₃ and -OH were reported to be 101-102, 137 and 215-216°C respectively.¹⁰

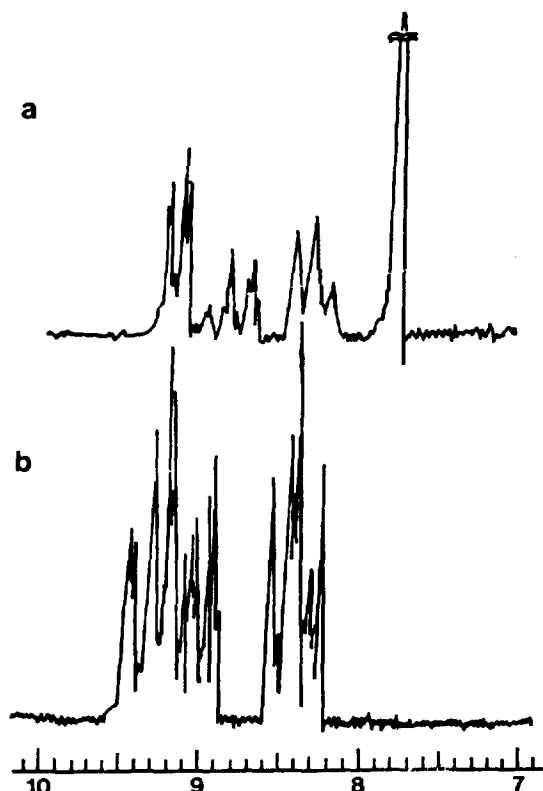


Figure 1. Pmr Spectra of 1-phenylpyridinium Chloride(a) and 1-(2,4-dinitrophenyl) pyridinium Chloride(b) in D_2O .

The products were identified by recrystallization, and the purified yields were fairly good (55-80 %) in all cases except the reaction with *o*-substituted aniline. The results obtained from pyridine, nicotinamide and 4,4'-bipyridine were summarized in Table 1, 2 and 3, respectively.

The products were identified by spectroscopic methods. The pyridine nucleus of all N-arylpiperidinium compounds obtained in this study showed the same pmr pattern. For example, the pmr spectrum of N-phenylpyridinium, IIIa(X = -H) is shown in Figure 1a. The two *ortho*-, one *para*- and two *meta*-protons to the nitrogen in the pyridine nucleus of N-arylpiperidinium compounds are appeared at δ 9.1-9.3, 8.7-9.1 and 8.2-8.6, respectively. These assignments are based on the fact that in N-heterocycles, and especially quaternary salts, the protons

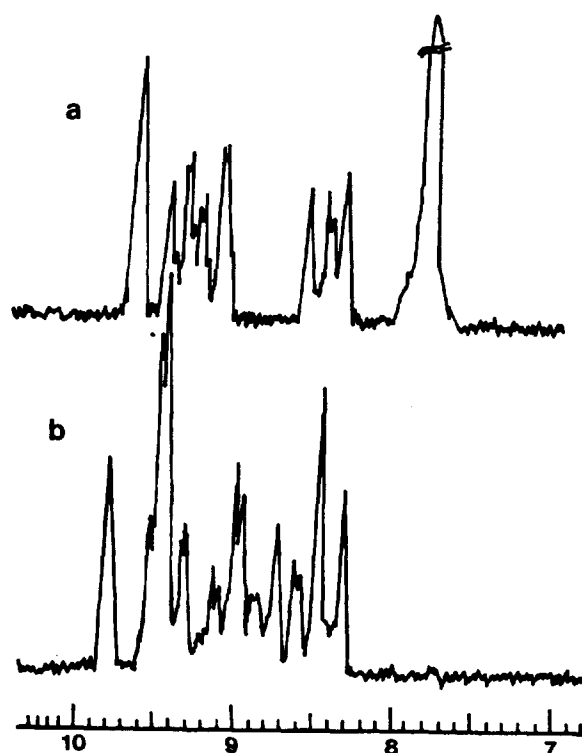


Figure 2. Pmr spectra of 1-phenyl-3-carbamoylpyridinium chloride(a) and 1-(2,4-dinitrophenyl)-3-carbamoylpyridinium chloride(b) in D_2O .

closest to the nitrogen atom are most highly deshielded and *p*-protons are more deshielded than *m*-protons to the nitrogen.¹¹ The protons of benzene nuclei showed either as singlet or as a pattern typical of *p*-disubstituted phenyl compounds. These chemical shifts are included in Table 1.

In contrast to the above N-arylpiperidinium compounds, N-(2,4-dinitrophenyl) pyridinium salt showed a rather different pmr spectrum, which is shown in Figure 1b. The pyridine nucleus of N-(2,4-dinitrophenyl) pyridinium doesn't show the same pmr pattern with those of the above N-arylpiperidinium compounds. This indicates that the substituents such as *p*-CH₃, *p*-C₂H₅, *p*-Cl, *p*-CN, *p*-OCH₃, *p*-OH and *m*-CH₃ in the phenyl ring do not shift the pmr signals of the pyridine nucleus significantly, but 2,4-dinitro substituent change those signals substan-

TABLE 2: Yields and Physical Properties of 1-Aryl-3-Carbamoyl-Pyridinium Chlorides, IIIb

X	Yield %	mp °C	Chemical shift*, δ		Ir, cm^{-1}
			Phenyl ring	X	
H	58	231	7.8(s,5H)		3320(m), 3140(m), 3080(m), 1690(s), 1640(w), 1505(w)
<i>p</i> -CH ₃	73	279	7.6(d,4H, J=2Hz)	2.5(s,3H)	3260(m), 3130(m), 3040(w), 2995(w), 1692(s), 1645(w)
<i>p</i> -C ₂ H ₅	61	234	7.7(s,4H)	2.8(q,2H, J=7Hz) 1.3(t,3H, J=7Hz)	3280(m), 3160(m) 3030(w), 2980(w), 1690(s), 1635(m)
<i>p</i> -Cl	70	295	7.9(s,4H)		3260(m), 3120(m), 3010(w), 1695(s), 1635(m), 680(m)
<i>p</i> -CN	78	301	8.2(d,4H, J=4Hz)		3280(m), 3120(m), 3010(w), 2220(m), 1700(s), 1665(w)
<i>p</i> -OCH ₃	79	274	7.3(d,2H, J=9Hz) 7.8(d,2H, J=9Hz)	4.0(s,3H)	3320(m), 3140(m) 3030(m), 1690(s), 1635(m), 1020(m)
<i>p</i> -OH	78	255	7.2(d,2H, J=9Hz) 7.7(d,2H, J=9Hz)		3560(m), 3340(m) 3160(s), 3010(m), 1700(s), 1630(m)
<i>m</i> -CH ₃	76	265	7.6(s,4H)	2.5(s,3H)	3260(m), 3130(m), 3035(w), 2995(m), 1690(s), 1640(m)
<i>o</i> -Cl	35	271	7.8(s,4H)		3260(m), 3120(m), 3010(w), 1690(s), 1630(m), 685(m)

*Chemical shifts for protons of the nicotinamide ring are not included.

TABLE 3: Yields and Physical Properties of 1,1'-diaryl-4,4'-bipyridinium Chlorides, IIIc

X	Yield %	mp °C	Chemical shift*, δ		Ir, cm^{-1}
			Phenyl ring	X	
H	61	306	7.9(<i>s</i> ,10H)		3080(<i>m</i>), 1620(<i>m</i>), 1480(<i>m</i>), 840(<i>s</i>)
<i>p</i> -CH ₃	58	300 ^d	7.7(<i>d</i> ,8H, <i>J</i> =2Hz)	2.6(<i>s</i> ,3H)	3010(<i>s</i>), 3000(<i>w</i>), 1620(<i>m</i>), 1490(<i>m</i>), 820(<i>s</i>)
<i>p</i> -C ₂ H ₅	63	300 ^d	7.8(<i>s</i> ,8H)	2.9(<i>q</i> ,2H, <i>J</i> =7Hz) 1.3(<i>t</i> ,3H, <i>J</i> =7Hz)	3010(<i>s</i>), 2940(<i>w</i>), 1625(<i>m</i>), 1490(<i>m</i>), 825(<i>m</i>)
<i>p</i> -Cl	61	300 ^d	7.9(<i>s</i> ,8H)		3040(<i>m</i>), 1620(<i>s</i>), 1480(<i>m</i>), 825(<i>m</i>), 740(<i>m</i>)
<i>p</i> -CN	62	280 ^d	8.2(<i>d</i> ,8H, <i>J</i> =2Hz)		3010(<i>s</i>), 2230(<i>w</i>), 1610(<i>s</i>), 1490(<i>m</i>), 825(<i>m</i>)
<i>p</i> -OCH ₃	55	275 ^d	7.4(<i>d</i> ,4H, <i>J</i> =8Hz) 7.9(<i>d</i> ,4H, <i>J</i> =8Hz)	4.0(<i>s</i> ,3H)	3040(<i>m</i>), 1610(<i>m</i>) 1500(<i>m</i>), 1040(<i>w</i>), 840(<i>s</i>)
<i>p</i> -OH	61	287 ^d	7.3(<i>d</i> ,4H, <i>J</i> =8Hz) 7.8(<i>d</i> ,4H, <i>J</i> =8Hz)		3500(<i>m</i>), 3080(<i>s</i>) 1620(<i>m</i>), 1480(<i>w</i>), 860(<i>m</i>)
<i>m</i> -CH ₃	77	329 ^d	7.7(<i>s</i> ,8H)	2.5(<i>s</i> ,3H)	3010(<i>s</i>), 2950(<i>m</i>), 1620(<i>m</i>), 1490(<i>m</i>), 825(<i>m</i>)
<i>o</i> -Cl	43	316 ^d	7.9(<i>s</i> ,8H)		3035(<i>m</i>), 1620(<i>m</i>), 1485(<i>m</i>), 820(<i>s</i>), 730(<i>w</i>)

*Chemical shifts for protons of the bipyridine ring are not included. ^dDecomposition temp.

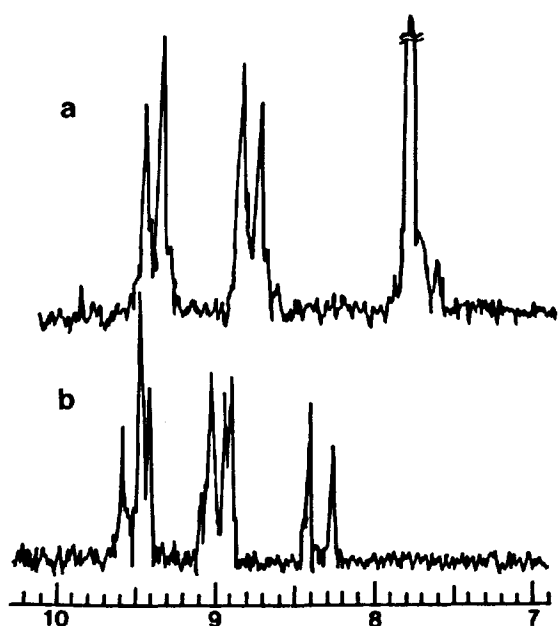


Figure 3. Pmr spectra of 1,1'-bis-(*p*-chlorophenyl)-4,4'-bipyridinium dichloride(a) and 1,1'-bis-(2,4-dinitrophenyl)-4,4'-bipyridinium dichloride(b) in D₂O.

tially. It seems to be attributed to the strong electron-withdrawing and magnetic anisotropic effect of the nitro groups.

The general characteristics in the pmr spectra of *N*-arylpyridinium salts hold also in the cases of *N*-aryl-3-carbamoylpyridinium and 1,1'-diaryl-4,4'-bipyridinium compounds. The pmr spectra of *N*-aryl-3-carbamoylpyridinium salts, IIIb, have the common peaks at δ 9.7-8.3, corresponding to the hydrogens of the nicotinamide ring. For example, the pmr spectrum of 1-phenyl-3-carbamoylpyridinium chloride, IIIb(X = -H) is shown in Figure 2a. The most highly deshielded peak at δ 9.6 is due to the hydrogen in the 2-position in the nicotinamide ring, that is, the one alpha to the nitrogen and alpha to the carbamoyl group. The protons in the 4- and 6-position of the nicotinamide ring are appeared at δ 9.1-9.5(2H). The one proton in the 5-position is at δ 8.6-8.3. The chemical shifts for protons in the phenyl groups are summarized in Table 2. The pmr spectrum of 1-(2,4-dinitrophenyl)-3-carbamoylpyridinium is shown in Figure 2b.

1,1'-Diaryl-4,4'-bipyridinium salts, IIIc, showed the same pmr pattern in a region of δ 9.7-8.8 corresponding to the hydrogens in the 4,4'-bipyridine ring, and the pmr spectrum of 1,1'-bis-(*p*-chlorophenyl)-4,4'-bipyridinium is shown in Figure 3a. The most deshielded doublet are assigned to the 2,6,2',6' protons adjacent to the quaternary nitrogens. The chemical shifts for protons in the phenyl groups of IIIc are included in Table 3. The pmr spectrum of 1,1'-bis-(2,4-dinitrophenyl)-4,4'-bipyridinium dichloride is shown in Figure 3b.

Of course, the Scheme I for the synthesis of *N*-arylated nitrogen-containing aromatic heterocycles can be applied to *N*-alkylation. For example, we obtained *N*-*n*-propylpyridinium chloride from the reaction between *N*-(2,4-dinitrophenyl)pyridinium chloride and *n*-propylamine. However, for most cases, Scheme I is not necessary for *N*-alkylation of nitrogen-containing aromatic heterocycles, because *N*-alkylation can be easily accomplished by reacting those heterocycles directly with alkyl halides. When alkyl halides are not readily available, Scheme I can be utilized for the synthesis of *N*-alkylated products, as employed for the synthesis of nicotinamide mononucleotide.¹²

The mechanism for the reaction of *N*-2,4-dinitrophenylated heterocycles, II, with aniline derivatives to yield the corresponding *N*-arylated compounds, III, is not clear at this point. Isolation of 2,4-dinitroaniline as a by-product, and our previous study¹³ about the reaction between 2,4-dinitrophenylpyridinium chloride and aqueous alkali, suggest that the nitrogen-containing heterocycles, II, are attacked by base at the C-2 position and ring opening occurs to form imine and/or aldehyde. Displacement of 2,4-dinitroaniline at some stage by aniline derivatives would be followed by ring closure to form the corresponding *N*-arylated compounds, III.

Experimental

Ir spectra were recorded on Jasco model IRA-1, and the frequencies are given in cm^{-1} . Pmr spectra were taken with a Varian Model EM-360A spectrometer, and chemical shifts are expressed as units relative to 2,2-dimethyl-2-silapentane-5-sulfonate

(DSS) in D₂O. Melting points, uncorrected, were determined on a electrothermal melting point apparatus.

Preparation of N-2,4-dinitrophenylated heterocycles (IIa, IIb or IIc). 2,4-Dinitrochlorobenzene (20 mmole) was dissolved in ethanol (20–5 ml) containing pyridine (20 mmole), nicotinamide (10 mmole) or 4,4'-bipyridine (5 mmole). The reaction mixture was refluxed for 7–15 hrs. Cooling the reaction mixtures (in cases of IIa or IIc) or addition of diethyl ether (50 ml) to the reaction mixture (in case of IIb) resulted in precipitation. The products were recrystallized from ethanol (IIa or IIb) or 50% aqueous ethanol (IIc). The purified yields were 65–75%. The pmr spectra of IIa, IIb and IIc are shown in Figure 1b, 2b and 3b, respectively. Melting points were 189–190°C for IIa, 120°C for IIb and 246–247°C for IIc.

Ir(KBr disc): IIa, 3020(w), 1600(s), 1520(s), 1330(s) and 820(m); IIb, 3350(s), 3150(s), 1690(s), 1540(s), 1500(m) and 1340(s); IIc, 3010(m), 1610(m), 1530(s), 1520(s), 1340(s) and 840(m).

Preparation of N-arylpyridinium chloride. Aniline derivative (X = -H, *p*-CH₃, *p*-C₂H₅, *p*-Cl, *p*-OCH₃ or *m*-CH₃) (12~24 mmole) was added to a solution of 2,4-dinitrophenylpyridinium chloride (IIa) (1.7 g, 6 mmole) in ethanol (25 ml) and refluxed for 3 hrs. Addition of ten-fold water (250 ml) crystallized out a by-product, 2,4-dinitroaniline. The filtrate was concentrated by rotary evaporator and the residue was recrystallized from a mixture of ethanol and diethyl ether to yield the corresponding arylpyridinium compound.

In case of X = *p*-OH or *p*-CN, the reaction was performed in a 3:1 mixture of ethanol and pyridine.

Preparation of 1-aryl-3-carbamoylpyridinium chloride. Aniline derivative (X = -H, *p*-CH₃, *p*-C₂H₅, *o*-Cl or *m*-CH₃) (10 mmole) was added to a solution of 1-(2,4-dinitrophenyl)-3-carbamoylpyridinium chloride (5 mmole, IIb) in ethanol (20 ml) and refluxed for 4–8 hrs. Cooling and addition of water (50 ml) precipitated out 2,4-dinitroaniline. After removal of 2,4-dinitroaniline and concentration of the filtrate, the residue was recrystallized from ethanol to give the corresponding 1-aryl-3-carbamoylpyridinium salt.

In case of X = *p*-Cl or *p*-CN, the product precipitated out after refluxing for 0.5–3 hrs. It was recrystallized from 50% aqueous ethanol.

In case of X = *p*-OCH₃ or *p*-OH, the reaction was performed in a 3:1 mixture of ethanol and pyridine. After refluxing for 0.5–3 hrs the product crystallized out, and it was recrystallized from 50% aqueous ethanol.

Preparation of 1,1'-diaryl-4,4'-bipyridinium dichloride.

Aniline derivative (X = -H, *p*-CH₃, *p*-C₂H₅, *p*-Cl, *o*-Cl or *m*-CH₃) (30 mmole) was added to a solution of 1,1'-bis-(2,4-dinitrophenyl)-4,4'-bipyridinium dichloride (IIc) (4.2 g, 7.5 mmole) in ethanol (42 ml) and refluxed for 3 hrs. The reaction mixture was concentrated to a half of the initial volume and then ten-fold water (210 ml) was added to precipitate out 2,4-dinitroaniline. The filtrate was treated with activated carbon. After removal of activated carbon, the filtrate was concentrated by rotary evaporator to give a residue, which was recrystallized from ethanol to get the corresponding 1,1'-diaryl-4,4'-bipyridinium dichloride.

In case of X = *p*-CN, the product precipitated out after refluxing for 3 hrs. The solid was recrystallized from 50% aqueous ethanol to give pure 1,1'-bis-(4-cyanophenyl)-4,4'-bipyridinium compound.

In case of X = *p*-OCH₃ or *p*-OH, the reaction was carried out in a 3:1 mixture of ethanol and pyridine. After refluxing for 3 hrs, the product precipitated out. It was filtered and recrystallized from 50% aqueous ethanol.

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