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SYNTHESIS, STRUCTURE, AND PROPERTIES OF 1-(p-R-PHENACYL)-2-(p-METHOXYBENZYLAMINO)PYRIDINIUM BROMIDES

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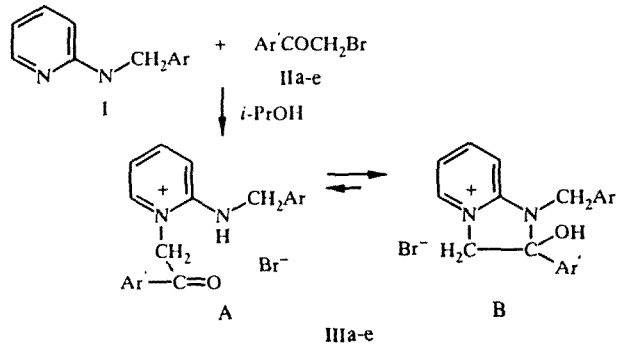
We have synthesized 2-(p-methoxybenzylamino)-1-(p-R-phenacyl)pyridinium bromides by alkylation of 2-(p-methoxybenzylamino)pyridine with substituted phenacyl bromides. Using spectral methods we have shown that the title compounds exist in the form of 1,2-diaryl-2-hydroxy-2,3-dihydroimidazo[1,2-a]pyridinium salts. We have studied their properties and suggest an alternative synthesis route.

Investigation of alkylation of 2-aminopyridine by different halocarbonyl compounds, begun by A. E. Chichibabin back in 1926 [1], led to synthesis of many compounds of practical use [2-5]. However, so far the behavior of 2-(R-amino)pyridines in this reaction has not been studied.

By alkylation of the known 2-(p-methoxybenzylamino)pyridine (I) [6] with α-haloketones (IIa-e) in 2-propanol medium, we have obtained in high yields the corresponding salts (IIIa-e), which may exist in tautomeric forms A and B [7].



I—III Ar = $C_6H_4OCH_3$-*p*, II—III Ar' = C_6H_4-R-*p*, everywhere a R = H, b R = CH_3, c R = Cl, d R = Br, e R = NO_2

Analysis of the PMR, IR, and UV spectral data is unambiguous evidence for the existence of the salts IIIa-e in the bicyclic form B. In the PMR spectrum, the protons of both methylene groups of compounds IIIa,b and the "cyclic" CH_2 group of compounds IIIc,d appear as characteristic signals of an AB-system (J = 13.6-16.6 Hz). We should note that the degree of magnetic nonequivalence of protons of the acyclic CH_2 group depends on the nature of the substituent R in the Ar′ moiety. Thus for R = Cl, Br, NO_2 (compounds IIIc-e), the signals from these protons have the form of a broadened singlet in the region 4.40-4.44 ppm. The cyclic form B also is supported by the presence in the 7.9-8.2 ppm region of a one-proton singlet signal, which we can safely say may be assigned to the hydrogen atom of the hydroxyl group in the 2 position of the imidazo[1,2-*a*]pyridine system. Upon addition of a small amount of D_2O, this signal disappears due to deuterium exchange. We observed a linear dependence of the values of the chemical shifts of the proton of the hydroxyl group on the values of the Hammett σ_{para} constants [8] of the substituents on the Ar′, which may be expressed by the equation:

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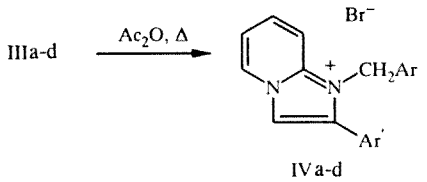
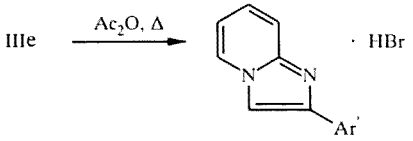
$$\delta_{OH}\ (ppm.) = 0{,}109\ \sigma para + 8{,}043\ \ (r = 0{,}95,\ S^2 = 9{,}38 \cdot 10^{-3}).$$

In the IR spectra of compounds IIIa-e (taken in KBr pellets), stretching vibrations are pronounced for the CN group in the region 1635-1645 cm^{-1} and also for the OH group in the region 3080-3170 cm^{-1}, while stretching vibratons of the CO and NH groups are missing. Consequently, in solid form the salts IIIa-e also exist in the bicyclic tautomeric form B. Additional confirmation of this is the absence in the electronic spectra of compounds IIIa-e of the characteristic benzoyl chromophore at 246 nm [9].



IVa-d



Ve

Upon brief heating of salts IIIa-d in acetic anhydride, cleavage of the water molecule occurs and the 2-aryl-1-(p-methoxybenzyl)imidazo[1,2-*a*]pyridinium bromides (IVa-d) are formed. The structure of the latter are supported by PMR spectral data. Thus in these spectra there are no signals from protons of the methylene and hydroxyl groups respectively in the 3 and 2 positions of the imidazo[1,2-*a*]pyridine system (characteristic for salts III), but there is a singlet signal at 8.68-8.75 ppm, which may be assigned to a proton in the 3 position.

In the IR spectra of the salts IVa-d, there are no bands for the stretching vibrations of the hydroxyl group (characteristic for salts IIIa-e), but there is a set of bands of characteristic stretching vibrations in the range 1650-1350 cm^{-1}, which may be assigned to vibrations of the imidazole moiety of the molecule [10].

It is interesting to note that heating the salt IIIe (R = NO_2) with acetic anhydride leads to formation of 2-(p-nitrophenyl)imidazo[1,2-*a*]pyridine hydrobromide (Ve), i.e., aromatization of the imidazole ring is accompanied by cleavage of the p-methoxybenzyl group in the 1 position of the system. Formation of the salt Ve is proven by its synthesis via a known alternate route from 2-aminopyridine and α-bromo-p-nitroacetophenone, as described in [4]. The IR spectra of salts Ve synthesized by the different methods are identical. In the PMR spectrum of salt Ve, there are no signals from protons of the p-methoxybenzyl moiety of the molecule which are characteristic for salts IVa-d.

Earlier it was shown that the transition from quaternary salts to simple salts, i.e., dequaternization of condensed imidazolium salts, occurs under rather vigorous conditions [11]. For example, cleavage of the allyl group from the 1 position of the pyrrolo[1,2-a]imidazolium system was observed at 250°C and reduced pressure [11]. The fact that upon heating compound IIIe we could not isolate the quaternary salt IVe suggests that dequaternization of the latter occurs, with cleavage of the benzyl group, under rather mild conditions. Obviously this is explained by the strong electron-acceptor properties of the p-nitrophenyl group in the 1 position of the imidazo[1,2-*a*]pyridine system.

Attempts to synthesize salts of the type IVa-d for the example of alkylation of 2-(p-chlorophenyl)imidazo[1,2-*a*]pyridine (VIc) with 4-methoxybenzyl bromide in solvents of different polarities were not successful. From the reaction mixture we isolated the hydrobromide salt of the starting imidazopyridine (Vc), which is proven by the PMR spectroscopy data (in the spectrum of the salt, after an attempt at alkylation there are no signals from protons of the p-methoxybenzyl group).

We demonstrated an alternative route for obtaining compounds of type III for the example of synthesis of the salt IIIf by reaction of 1-phenacyl-2-bromopyridinium bromide with twice as much benzylamine, occurring with considerable evolution of heat.

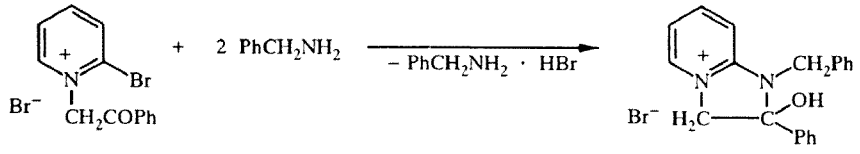


TABLE 1. Characteristics of Imidazo[1,2-*a*]pyridinium Salts IIIa-f, IVa-d

Compound	Empirical formula	Found (%) / Calculated (%)		T_{mp}, °C	UV spectrum, λ, nm (log ε)	IR spectrum, cm^{-1}	Yield, %
		Br	N				
IIIa	$C_{21}H_{21}BrN_2O_2$	19,2 19,4	6,91 6,79	177...178	333 (3,70)	1580, 1645, 3060	55
IIIb	$C_{22}H_{23}BrN_2O_2$	18,8 18,7	6,67 6,56	178...179	333 (3,64)	1575, 1640, 3170	79
IIIc	$C_{21}H_{20}BrClN_2O_2$	—	6,32 6,26	188...189	333 (3,74)	1580, 1645, 3160	72
IIId	$C_{21}H_{20}Br_2N_2O_2$	32,4 32,5	5,73 5,69	197...198	333 (3,68)	1580, 1645, 3180	82
IIIe	$C_{21}H_{20}BrN_3O_4$	17,7 17,5	8,93 9,17	210...211	333 (3,70)	1580, 1640, 3080	93
IIIf	$C_{20}H_{19}BrN_2O$	20,8 20,9	7,33 7,31	194...195	—	—	23
IVa	$C_{21}H_{19}BrN_2O$	20,2 20,3	7,18 7,09	145...146	285 (3,98)	1520, 1610, 1645	70
IVb	$C_{22}H_{21}BrN_2O$	19,6 19,6	6,88 6,85	168...169	285 (3,99)	1520, 1615, 1640	65
IVc	$C_{21}H_{18}BrClN_2O$	18,6 18,6	6,55 6,52	197...198	285 (4,19)	1515, 1610, 1635	69
IVd	$C_{21}H_{18}Br_2N_2O$	33,5 33,8	5,86 5,91	203...204	285 (4,06)	1515, 1605, 1635	68

TABLE 2. PMR Spectral Data for Compounds IIIa-f, IVa-d

Compound	Chemical shifts, δ, ppm, spin–spin coupling constant (J), Hz									
	OCH_3 s	CH_2Ar (J)	3-H_{CH2} (J) Or 3-H_{CH}*	H_{Ar}*2	H_{Ar}*3	OH s	5-H d	6-H t	7-H b	8-H*4 d
IIIa	3,70	3,85 d, 3,92 d (16,6)	4,96 d, 5,03 d (14,3)	6,81 d, 7,12 d	7,41...7,75 m	7,95	8,48	7,17	8,15	6,95
IIIb*5	3,71	4,33 d, 4,40 d (16,6)	4,94 d, 4,99 d (14,0)	6,82 d, 7,14 d	7,23 d, 7,64 d	7,88	8,49	7,16	8,10	6,91
IIIc	3,71	4,40 br. s.	4,93 d, 4,99 d (13,6)	6,81 d, 7,10 d	7,46 d, 7,76 d	8,03	8,47	7,20	8,13	7,04
IIId	3,71	4,40 br. s.	4,97 br. s.	6,81 d, 7,11 d	7,58 d, 7,70 d	8,03	8,49	7,20	8,13	6,99
IIIe	3,68	4,44 br. s.	5,03 br. s.	6,77 d, 7,08 d	8,00 d, 8,20 d	8,25	8,50	7,24	8,16	7,11
IIIf	–	4,45 d, 4,50 d (16,6)	4,97 d, 5,02 d (14,3)	7,24...7,86 m	7,40...7,76 m	7,96	8,49	7,18	8,11	6,96
IVa	3,67	5,69 s	8,76 s	6,81 d, 6,96 d	7,61 s	–	8,34	8,11	7,65	9.0[illegible]
IVb*5	3,68	5,66 s	8,68 s	6,82 d, 6,97 d	7,41 d, 7,50 d	–	8,28	8,10	7,63	9,0[illegible]
IVc	3,68	5,68 s	8,76 s	6,81 d, 6,97 d	7,63 d, 7,67 d	–	8,34	8,12	7,66	9.0[illegible]
IVd	3,68	5,68 s	8,75 s	6,81 d, 6,97 d	7,59 d, 7,80 d	–	8,33	8,11	7,65	9,0[illegible]

*For compounds IVa-d.

*2$J_{2,3} = J_{5,6} = 9$.

*3$J_{2,3} = J_{5,6} = 8$-9.

*4For compounds IIIa-f, $J_{5,6} = J_{6,5} = 6.3$, $J_{7,8} = J_{8,7} = 8.4$-8.8. For compounds IVa-d, $J_{5,6} = J_{6,5} = 9$-9.2, $J_{7,8} = J_{8,7} = 6.6$.

*5The signal from R = CH_3 protons has the form of a singlet at 2.32 ppm.

The cyclic structure of the salt IIIf is supported by PMR, IR, and UV spectral data (see Table 2).

By comparison of the PMR spectra of compounds IIIa and IIIf, we can unambiguously assign the signals from the protons of both methylene groups. Thus for the salt IIIa, both diastereotopic CH_2 groups are detected at 3.89 and 4.99 ppm while for the salt IIIf, they are detected at 4.48 and 5.00 ppm; i.e., introduction of the methoxyl group into the benzene moiety of the molecule in the case of IIIa leads to an upfield shift of the signals from the protons of the CH_2Ar group (from 4.48 to 3.89 ppm). At the same time, the signals at 4.99 ppm remained unchanged, which indicates their identical structural environment. Taking into account the fact that as a result of aromatization of the imidazole moiety of the molecule for salts IVa-d, the signals from the methylene protons of the CH_2Ar group are shifted to the region 5.66-5.69 ppm (i.e., downfield by more than 1.2 ppm), we can hypothesize that preferential localization of the positive charge in salts IIIa-f and IVa-d occurs. In salts of type III, it apparently is localized on the pyridine nitrogen, while in salts of type IV it is localized on the nitrogen atom in the 1 position of the imidazo-[1,2-*a*]pyridinium system.

EXPERIMENTAL

The IR spectra were taken on the UR-20 instrument (in KBr pellets). The electronic spectra in ethanol were obtained on the Specord M-40 instrument. The PMR spectra were recorded on the Gemini-200 instrument (200 MHz) in DMSO-D_6 solution, internal standard TMS.

The starting 2-(p-methoxybenzylamino)pyridine) was obtained from 2-aminopyridine and anisaldehyde according to the technique in [6]. 2-Bromo-1-phenacylpyridinium bromide was obtained by the familiar route from 2-bromopyridine and phenacyl bromide [12].

1-(p-Methoxybenzyl)-2-aryl-2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyridinium Bromides (IIIa-e). A solution of 2.14 g (0.01 moles) 2-(p-methoxybenzylamino)pyridine in 20 ml 2-propanol was added to a solution of 0.01 moles substituted phenacyl bromide in 10 ml 2-propanol. The reaction mixture was boiled with refluxing for 30 min and then held from 24 h at 18-20°C. The residue was filtered off and washed with ether. The products were crystallized from a mixture of 2-propanol–hexane 2:1 (IIIa, b, e), ethanol (IIIa), or 2-propanol (IIId). The characteristics of compounds IIIa-e are presented in Tables 1 and 2.

1-Benzyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium Bromide (IIIf). 0.61 ml (0.0056 moles) benzylamine was added to 1.0 g (0.0028 moles) 1-phenacyl-2-bromopyridinium bromide. After the exothermic reaction, the mixture was held for 24 h at 20°C and triturated with ether; the product IIIf was filtered off, washed with water, dried, and crystallized from a 1:1 isopropanol–hexane mixture (see Tables 1 and 2).

1-(p-Methoxybenzyl)-2-arylimidazo[1,2-*a*]pyridinium Bromides (IVa-d) and 2-(p-Nitrophenyl)imidazo[1,2-*a*]pyridine Hydrobromide (Ve). 0.01 moles of the salt IIIa-e were boiled in 30 ml acetic anhydride for 15 min. After cooling, the solvent was evaporated under vacuum, and the residue was triturated with acetone; the residue of the product IVa-d or Ve was filtered off and crystallized from 2-propanol (see Tables 1 and 2). Yield, 27%; T_{mp} 250-251°C. A mixed sample with Ve synthesized according to the technique in [4] did not give a depression of the melting point. Found (%): Br 24.9, N 13.2. $C_{13}H_9N_3O_2 \cdot HBr$. Calculated (%): Br 25.0, N 13.1. The melting point of the base Ve 261-263°C. Lit.: T_{mp} 263-264°C [13]. PMR spectrum: 7.45 (1H, t), 7.89-7.93 (2H, m), 8.22 and 8.43 (4H, d.d, $H_{AR'}$), 8.89 (1H, d), 9.00 (1H, s, 3-H). IR spectrum: 1598, 1516 cm^{-1}.

Attempts to Synthesize the Salt IVc from 2-(p-chlorophenyl)imidazo[1,2-*a*]-pyridine. 2-(p-Chlorophenyl)imidazo-[1,2-a]pyridine hydrobromide (Vc).

A. A mixture of 1.14 g (0.005 moles) 2-(p-chlorophenyl)imidazo[1,2-a]pyridine VIc, 1.0 g (0.005 moles) 4-methoxybenzyl bromide, and 20 ml 2-propanol were boiled for 1 h. The precipitate of the salt Vc falling out upon cooling was filtered off, washed with ether, and dried. Yield, 0.8 g (60%). T_{mp} 238-239°C. PMR spectrum: 7.47-7.54 (2H, m), 7.69 and 7.99 (4H, d.d, $H_{Ar'}$), 7.92-7.96 (2H, m), 7.97 (1H, s, 3-H), 8.88 (1H, s, N^+–H). Found (%): Br 25.6, N 9.04. $C_{13}H_9ClN_2$. Calculated (%): Br 25.8, N 9.05.

B. 1.0 g (0.0044 moles) imidazopyridine VIc and 0.88 g (0.0044 moles) 4-methoxybenzyl bromide were boiled in 30 ml benzene for 1 h. This was cooled, the oily residue was triturated with ether; the salt Vc was filtered off, washed with ether, and dried. Yield, 0.28 g. T_{mp} 238-239°C.

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