C. A mixture of 2 mmoles of the pyridium iodide (Ia-d), 3 ml of 40% aqueous methylammonium bisulfite, and 6 ml of 34% alcoholic methylamine was heated in a sealed ampul at 150°C for 25-35 h. The mixture was extracted with benzene, and worked up as in method A.

D. A mixture of 2 mmoles of the pyridium iodide (Ia-d), 1.26 g (0.01 mole) of sodium bisulfite, and 10 ml of 34% alcoholic methylamine was heated in a sealed ampul at 175°C for 10-12 h. The mixture was worked up as in method A.

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REACTIONS OF N-(4-METHOXYBENZYLIDENE)-N,N-DIALKYLIMINIUM AND 2-(4-METHOXYPHENYL)PYRIDINIUM SALTS WITH ALIPHATIC AMINES

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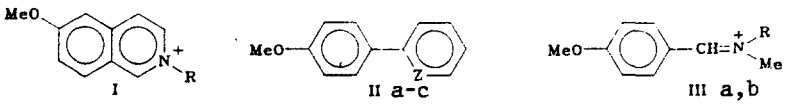
UDC 547.821.3'823'554.07

The reaction of 4-methoxybenzylideneiminium salts with methylamine and dimethylamine on heating results in replacement of the MeO group by an alkylamino-group, whereas the reaction with piperidine affords 3,5-bis-(4-methoxybenzyl)pyridine. N-Methyl-2-(4-methoxyphenyl)pyridinium iodide on treatment with methylamine undergoes dealkylation to the arylpyridine.

It is well known that the $>C=\overset{+}{N}<$ group in isoquinolinium salts activates the 6-position of the heterocyclic system, facilitating replacement of the alkoxy-group on treatment with primary aliphatic amines [1]. We have now examined the possibility of carrying out this reaction with compounds in which the $>C=\overset{+}{N}<$ group is not incorporated into the aromatic system, by treatment with nucleophiles. The compounds of this type chosen for study were the 2-(4-methoxyphenyl)pyridinium salts (IIa, b) and the N-(4-methoxybenzylidene)-N,N-dialkyliminium salts (IIIa, b), which in respect of the position of the C=N bond relative to the methoxy-group and the benzene ring is formally analogous to the isoquinoline salt (I).



II a Z=NMe+, b Z=NH+, c Z=N; III a R=Me, b R=*tert*-Bu

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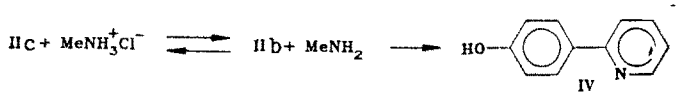
We have previously reported [2] that the MeO group in (IIIa) is replaced on treatment with primary and secondary aliphatic amines. Continuing this line of investigation, we have examined the reactions of both the salt (IIIa) and the sterically hindered salt (IIIb) with methylamine, dimethylamine, and piperidine. The required methiodides (IIIa, b) and (IIa) were obtained by reacting the appropriate Schiff's bases of methoxyphenylpyridine (IIc), obtained in one step by cross-coupling the bromopyridine and bromoanisole in the presence of a palladium catalyst, with methyl iodide.

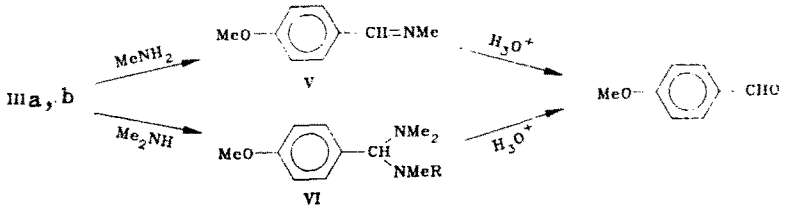
On heating the pyridinium salt (IIa) with a solution of methylamine in ethanol in a sealed ampul at 140°C for 40 h, S_N2-dealkylation of the pyridine ring takes place:

$$IIa + MeNH_2 \rightarrow IIc.$$

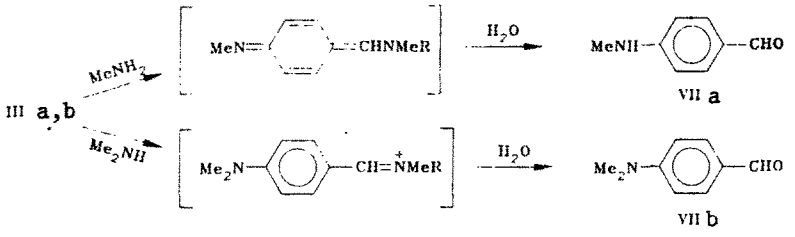
It was also found that on treatment with methylamine and methylamine hydrochloride, (IIc) undergoes dealkylation to give the hydroxyphenylpyridine (IV), a probable intermediate in the reaction being the hydrochloride (IIb)*:



The salts (IIIa, b) react with methylamine at ambient temperature, undergoing transamination to give the Schiff's base (V), while the reaction with dimethylamine affords the unstable aminals (VI) [2]. Hydrolysis of the reaction mixtures afforded in all instances a quantitative yield of anisaldehyde:

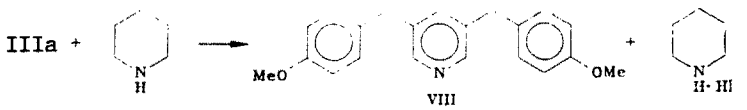


On heating the iminium salts (IIIa, b) with alcoholic methylamine or dimethylamine in sealed ampuls at 140°C, the aromatic nucleophilic substitution products were obtained, subsequent hydrolysis of the reaction mixtures giving the corresponding aldehydes (VIIa, b):



Hence, S_NAr replacement of the MeO groups in the iminium salts (III) by an alkylamino-group takes place only at elevated temperatures. At ambient temperatures only transamination occurs, with the involvement of aminals as intermediates, the aromatic ring being unaffected. It is noteworthy that the presence of the bulky tert-butyl substituent at nitrogen does not affect the course of the reaction of aliphatic amines with the iminium salts (III), and has no influence on the yields of the aromatic nucleophilic substitution reaction products.

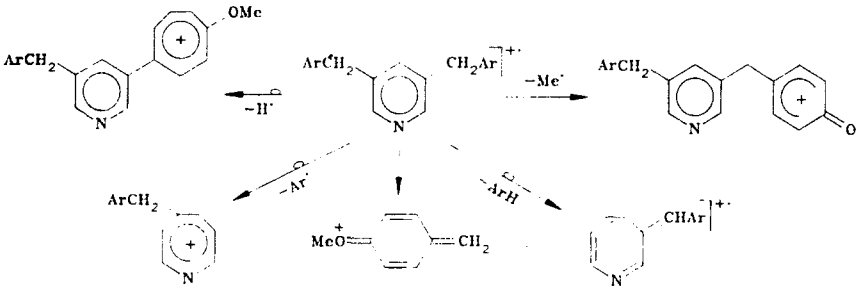
The use of piperidine as the nucleophile under similar conditions (heating in a sealed ampul in alcoholic solution) results in considerable resinification of the reaction mixture, and it was not possible to isolate any reaction products. The use of diglyme as solvent enabled resinification to be avoided, and heating the salt (IIa) with piperidine in this solvent gave the bis(methoxybenzyl)pyridine (VIII):



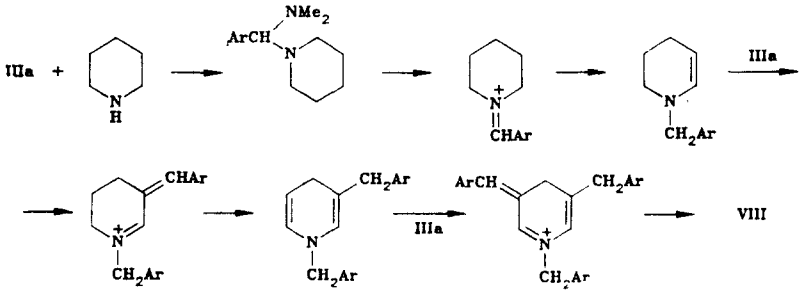
*It is, in principle, possible that this reaction occurs by an S_N2cA mechanism with the participation of an arylmethyloxonium salt corresponding to the pyridine (IIb) or (IIc).

The structure of (VIII) was confirmed by PMR, ^{13}C NMR, and mass spectroscopy. Mass-spectral fragmentation of the pyridine (VIII) involved the parallel elimination from the molecular ion of a hydrogen atom, the methyl and methoxyphenyl radicals, and a molecule of anisole, together with the formation of the methoxybenzyl cation. Noteworthy is the presence in the spectrum of strong doubly-charged ions, perhaps arising in particular from ring extension and "localization" of the two positive charges in neighboring aromatic rings.

The compound (VIII) has previously been obtained by reacting anisaldehyde with piperidine in the presence of AcHO [3]. Bearing in mind the arguments put forward earlier [2, 3], the most likely mode of formation of the pyridine (VIII) may be as follows:



Thus, the fragment $>C=\overset{+}{N}<$, when present in the para-position of the benzene ring relative to the alkoxy-group, depending on its environment (a heterocycle or an iminium salt) promotes either reactions of either the S_NAr or S_N2 types. In the case of iminium salts, depending on the amine used either aromatic substitution occurs, or redox processes leading to the formation of a 3,5-disubstituted hetarene.



EXPERIMENTAL

Nuclear magnetic resonance spectra were obtained on a Tesla BS-497 (60 MHz) or a VXR-400 (400 MHz) instrument, internal standard TMS, and IR spectra on a UR-20 spectrophotometer in Vaseline grease. The mass spectrum was obtained by N. S. Kulikov (Candidate, Chemical Sciences) on an MAT-312 (E = 100 eV) with direct sample introduction. The progress of the reactions and the purity of the products were followed by TLC on Silufol UV-254 plates.

2-(4-Methoxyphenyl)pyridine (IIc). To 1.08 g (55 mmoles) of magnesium in 45 ml of dry ether was added dropwise with stirring under argon 8.4 g (55 mmoles) of 4-bromoanisole. The resulting Grignard reagent was added dropwise under argon to a solution of 5.8 g (37 mmoles) of 2-bromopyridine and 260 mg (0.37 mmole) of $(Ph_3P)_2PdCl_2$ in 15 ml of dry ether, and the mixture stirred for 3 h and kept overnight. The mixture was then decomposed with aqueous ammonium chloride, and the ether layer decanted and the aqueous layer extracted with benzene. The combined ether and benzene extracts were dried over anhydrous $MgSO_4$, the solvents removed, and the residue chromatographed on silica gel to remove the Pd complex present. The crude product was twice recrystallized from hexane to give 4.5 g (66%) of the arylpyridine (IIc), mp 53°C (literature mp 52-53°C [4]).

N-Methyl-2-(4-methoxyphenyl)pyridinium Iodide (IIa). A mixture of 400 mg (2.16 mmoles) of the pyridine (IIc) and 5 ml of methyl iodide was heated in a sealed ampul at 100°C for 3 h. Unreacted methyl iodide was then distilled off, and the residue recrystallized from ethanol to give 610 mg (86%) of (IIa), mp 161-162°C. PMR spectrum (CD_3OD): 4.0 (3H, s, OMe), 4.3 (3H, s, NMe), 7.2 (2H, d, Ph, J = 9 Hz), 7.7 (2H, d, Ph, J = 9 Hz), 7.9-8.2 (2H, m, 3-H, 5-H), 8.4-8.8 (1H, m, 4-H), 8.9-9.1 ppm (1H, m, 2-H).

Reaction of Salt (IIa) with Methylamine. A mixture of 100 ml (3.0 mmoles) of the salt (IIa) and 30% alcoholic methylamine was heated in a sealed ampul at 140°C for 40 h. The solvent was removed, and the residue chromatographed on a column with a mixture of chloroform, ethyl acetate, and hexane (2:1:3) to give 32 mg (57%) of the arylpyridine (IIc).

Reaction of (IIc) with a Mixture of $MeNH_2$ and $MeNH_2 \cdot HCl$. A mixture of 185 mg (1 mmole) of (IIc), 135 mg (2 mmoles) of methylamine hydrochloride, and 5 ml of 30% alcoholic methylamine was heated in a sealed ampul at 140°C for 40 h. The solvent was removed, and the residue treated with 10 ml of water, neutralized with $NaHCO_3$ solution to pH 8, and extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$, the solvent removed, and the residue chromatographed on a column of silica gel (chloroform–ethyl acetate, 2:1) to give 93 mg of starting (IIc) (R_f 0.5) and 74 mg (40%) of the phenylpyridine (IV), R_f 0.2, mp 160°C (literature mp 160°C [5]).

N-(4-Methoxybenzylidene)-N-methyl-N-tert-butyliminium Iodide (IIIb, $C_{13}H_{20}INO$). N-(4-Methoxybenzylidene-tert-butylamine (19.1 g, 100 mmoles) [6] was dissolved in 100 g of methyl iodide. After 40 h, the solid was filtered off, washed with methyl iodide, and dried in vacuo to give 32.0 g (96%) of the salt (IIIb), mp 157-159°C.

4-Methylaminobenzaldehyde (VIIa). A mixture of 1 g (3 mmoles) of the salt (IIIb) and 6 ml of 30% alcoholic methylamine was heated in a sealed ampul at 140°C for 40 h. After opening the ampul, the solvent was evaporated, and the residue washed with 5 ml of 3% HCl and kept for 3 h at ambient temperature. It was then basified to pH 10 with sodium carbonate solution, and extracted with chloroform. The extract was dried over anhydrous $MgSO_4$, the solvent removed, and the residue chromatographed on a column of silica gel (hexane–ethyl acetate, 4:1) to give 122 mg (30%) of (VIIa), mp 55-57°C (hexane) (literature mp 55-57°C [7]).

4-Dimethylaminobenzaldehyde was obtained similarly, from 1 g (3 mmoles) of the salt (IIIb) and dimethylamine. Yield 143 mg (32%), mp 73°C (hexane) (literature mp 73-74°C [8]). The reaction of the salt (IIIa) with methylamine or dimethylamine (see [2]) also afforded (VIIa, b) in yields of 30-40%.

3,5-Bis(4-Methoxybenzyl)pyridine (VIII). A mixture of 873 mg (3 mmoles) of the salt (IIIa) and 255 mg (9 mmoles) of piperidine in 6 ml of dry diglyme was heated in a sealed ampul at 140°C for 40 h. After opening the ampul, the solid was filtered off and washed with ethyl acetate to give 320 mg of piperidine hydriodide. To the filtrate was added 20 ml of ethyl acetate, and the mixture extracted repeatedly with water. The organic phase was dried over anhydrous $MgSO_4$, the solvent removed, and the residue chromatographed on a column of silica gel (hexane–ethyl acetate, 4:1) to give 105 mg (40%) of the pyridine (VIII), mp 125-126°C (literature mp 125-126°C [3]). IR spectrum (Vaseline grease): 1610, 1510, 1460, 1380, 1300, 1250, 1180, 1030, 840 cm^{-1}. Mass spectrum*: 320 (34, M + 1), 319 (M^+, 100), 318 (35, M – H), 305 (10), 304 (35, M – Me), 213 (9) (9, M – C_6H_4OMe), 21 (26, M – PhOMe), 198 (23), 197 (10, M – C_6H_4OMe), 196 (14, M – PhOMe – Me), 180 (13), 169 (11), 167 (11), 159.5 (14, M^{2+}), 159 (5.5, $[M - H]^{2+}$), 154 (14), 152 (5.5, $[M - Me]^{2+}$), 131 (9), 129.5 (3), 128.5 (3), 128 (8.5), 127.5 (3), 127 (5), 122 (8), 121 (75, $MeOC_6H_4CH_2$); 120.5 (11), 111 (13), 106 (2.5, $[M - C_6H_4OMe]^{2+}$), 105.5 (6, $[M - PhOMe]^{2+}$), 101 (16), 97 (14), 91 (20), 86 (20), 78 (15), 77 (27, M – $2MeOC_6H_4CH_2$); 69 (41), 57 (27). PMR spectrum (CD_2Cl_2): 8.305 (2H, s, 2-H), 7.255 (1H, s, 4-H), 7.055 (4H, d, 2-H, ^3J = 8.6 Hz), 6.825 (4H, d, 3-H, ^3J = 8.6 Hz), 3.861 (4H, s, CH_2), 3.779 ppm (6H, s, MeO). ^{13}C NMR spectrum (CD_2Cl_2): 158.20 (4'-C); 147.91 (2-C); 136.60 (3-C + 4-C); 131.95 (1'-C); 129.76 (3'-C); 114.05 (2'-C); 55.259 (MeO); 38.067 ppm (CH_2).

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*m/z values given (in brackets, relative intensities of ion peaks, and probable assignment of signals).