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NATURE OF THE REDUCING AGENT AND MECHANISM OF THE REDUCTIVE CONDENSATION OF TRICHLOROMETHYL-ARENES WITH HYDROXYLAMINE AND HYDRAZINES IN PYRIDINE

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It was shown that during the reductive condensation of trichloromethylarenes with hydroxylamine or hydrazines in pyridine the event of reduction with replacement of one chlorine atom by a hydrogen atom occurs without the participation of hydroxylamine or hydrazine. The first step of the reaction is the formation of N-(α,α-dichloroarylmethyl)pyridinium chlorides, which are converted by the action of the chloride anion or a second pyridine molecule to the corresponding 4-substituted 1,4-dihydropyridines. The latter undergo further aromatization with transfer of hydrogen from the 4-position of the dihydropyridine ring to the benzyl dichloromethylene group and the formation of N-(α-chloroarylmethyl)-4-chloropyridinium chlorides or N-(α-chloroarylmethyl)-4-(pyridino)pyridinium dichlorides, which give the corresponding aldehydes in hydrolysis or products of reductive condensation under the action of hydroxylamine or hydrazines.

Recently we discovered that in the reaction of trichloromethylarenes $ArCCl_3$ (I, a, Ar = Ph; b, Ar = 2,4-$Me_2C_6H_3$; c, Ar = 2,4,5-$Me_3C_6H_2$; d, Ar = 2,4,6-$Me_3C_6H_2$) with hydroxylamine or hydrazines in pyridine, the previously known reductive condensation reaction, leading to a number of products (oximes, nitriles, benzaldazines, hydrazones, etc.), which may be considered as derivatives of the corresponding aldehydes [1, 2], is not observed.

It was suggested [2] that the reactions include intermediate formation of the corresponding hydroximoyl or hydrazonoyl chlorides, which are further reduced by hydrazine or hydroxylamine (for precisely this reason they were used in a large excess — 5 moles or more per mole of trichloromethylarene). This hypothesis was based primarily on the fact that in the interaction of trichloromethylarenes with hydroxylamine in alcohol medium the formation of hydroximoyl chlorides was actually detected [3]. However, the new data that we obtained forced us to give up the reaction scheme discussed above and revealed the true role of pyridine in it [4, 5].

In this work we expanded the assortment of trichloromethylarenes to include 2,3,4,6-, 2,3,5,6- and 2,3,4,5-tetramethylbenzotrichlorides (Ie-g, respectively) and, on the example of the mesitotrichloride Id, studied the reactions of compounds of type I not only with pyridine (IIa) but also with its 3-substituted derivatives — β-picoline (IIb), 3-hydroxypyridine (IIc), nicotinamide (IId), ethyl nicotinate (IIe), and 3-bromopyridine (IIf). Our new results are presented below; the mechanism of the reductive condensation is discussed on the basis of these new data, as well as those obtained earlier, and the scheme of this reaction proposed in the preliminary communication [5] is detailed.

First of all we should emphasize that all the facts available to us indicate that the pyridines IIa-f or related compounds, for example, quinoline, must be present for reductive condensation to occur. Moreover, the addition of methanol or ethanol to pyridine radically changes the course of the reaction, and the interaction of trichloromethylarenes of type I with acylhydrazines [6] and thioacylhydrazines [7] leads to heterocyclization products — 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. Only the most readily reduced mesitotrichloride Id gives products of reductive condensation — N-acylhydrazones of 2,4,6-

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TABLE 1. ^{1}H NMR Spectra of Pyridinium Salts Formed in the Reaction of Pyridines with HCl (IIc-f·HCl) and Trichloromethylarenes (IIIa′, IIId″, IVa-c)*

Compound	Chemical shifts, δ, ppm (SSCC, J, Hz)						
	Pyridine ring					CHClN$^+$ or NH$^+$	Other signals
	2-H	6-H	3-H	5-H	4-H		
IIc·HCl	8,52 d (2,5)	8,31 d (5,6)	—	7,78 d. d (8,8; 5,6)	8,16 d. d (2,5; 8,8)	*2	8,90 (1H, br. s, OH)
IId·HCl	9,30 d (2,0)	9,05 br. d (5,6)	—	8,14 d. d, (8,25, 5,6)	9,01 m	11,6 br.	8,10 and 8,82 (2H, br. s, br. s, NH_2)
IIe·HCl	9,19 d (1,9)	9,07 d. d (5,3; 1,3)	—	8,03 d. d (8,2, 5,3)	8,26 d. d. d (1,3, 1,9, 8,2)	11,3 br.	1,33 (3H, t, CH_3), 4,38 (2H, q, J = 7, CH_2)
IIf·HCl	8,96 d (2,0)	8,77 d (5,1)	—	7,72 d. d (8,2, 5,1)	8,46 d. d (2,0, 8,2)	10,10 br.	—
IIIa′	9,67 m	9,67 m	8,52 m	8,52 m	9,06 m	—	7,98 (2H, m, 2- and 6-H_{Ar}), 7,73 (3H, m, 3-, 4-, 5-H_{Ar})
IIId′	8,72 m	8,72 m	7,77 m	7,77 m	—	—	2,63 (3H, s, 4-Me_{Py}), 2,68 (6H, s, 2- and 6-Me_{Ar}), 2,20 (3H, s, 4-Me_{Ar}), 6,83 (2H, s, 3- and 5-H_{Ar})
IVa	9,20 m	9,20 m	8,28 m	8,28 m	8,78 m	—	8,00 (2H, m, 2- and 6-H_{Ar}), 7,47 (3H, m, 3-, 4- and 5-H_{Ar})
IVb	8,92 m	8,92 m	8,01 m	8,01 m	8,47 m	—	7,92 (1H, d, J = 8, 6-H_{Ar}), 7,07 (1H, br. s, 3-H_{Ar}), 7,02 (1H, d, J = 8, 5-H_{Ar}), 2,52 (3H, s, 2-Me_{Ar}), 2,20 (3H, s, 4-Me_{Ar})
IVc	8,85 m	8,85 m	7,96 m	7,96 m	8,42 m	—	7,73 (1H, s, 6-H_{Ar}), 6,99 (1H, s, 3-H_{Ar}), 2,19 and 2,22 (6H, s, c, 4- and 5-Me_{Ar}), 2,62 (3H, s, 6-Me_{Ar})

*The spectra of salts IIb-f·HCl were taken in DMSO-D_6, of the salt IIIa′ in acetone-D_6, and of the remaining compounds in $CDCl_3$.

*2Overlaps with the OH signal.

trimethylbenzaldehyde — even in an alcohol—pyridine mixture. At the same time, when nitrogen-containing bases such as triethylamine or an excess of 1,1-dimethylhydrazine were used as the solvent, no products of the reaction of the trichlorides I with hydrazines could be detected.

Apparently the first step of the reaction is interaction of the trichloromethylarenes with pyridine, leading to the pyridinium salts (III). The latter can undergo two types of further conversions under the action of a second pyridine molecule.

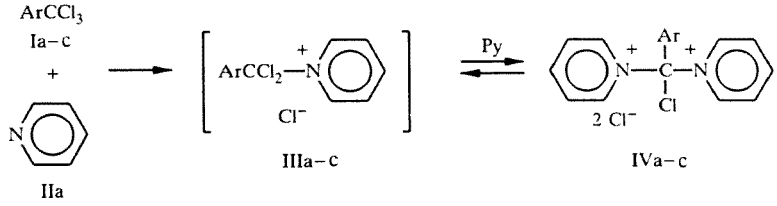
One of them (Scheme I) is nucleophilic substitution of the labile α-chlorine atom, forming a bispyridinium salt (IV). The second reaction pathway is readily implemented in the absence of steric hindrances, and, as the literature data [8-11] indicate, leads to the conversion of N-(α-haloalkyl)pyridinium salts to bispyridinium or bisonium salts. Such a conversion is also characteristic of the trichloromethylarenes Ia-c that we used (but not the o,o′-disubstituted Id-f). The formation of salts of types III and IV was considered as the initial steps of a Fujiwara reaction, proceeding in the interaction of the

TABLE 2. ^{1}H NMR Spectra of Pyridylpyridinium Salts Formed in the Reductive Condensation and after Hydrolysis of the Reaction Mixtures*

Salt	Chemical shifts, δ, ppm (SSCC, Hz)						
	Pyridylpyridinium residue					CHClN$^+$ or HN	Other signals
	2-H / 6-H	3-H / 5-H	2'-H / 6'-H	3'-H / 5'-H	4'-H		
VIId	9,77 m	8,97 m	9,77 m	8,48 m	8,99 m	8,72 s	7,09 (2H, s, 3-, 5-H_{Ar}); 2,30 (9H, br. s, 2-, 4-, 6-Me)
VIId'	10,00 m	9,21 m	9,77 m	8,70 m	9,21 m	8,56 s	7,17 (2H, s, 3-, 5-H_{Ar}); 2,35 (6H, s, 2-, 6-Me); 2,33 (3H, s, 4-Me)
VIIe	9,79 br. d (6)	8,98 br. d (6)	9,71 m	8,49 m	9,01 m	8,80 s	7,08 (1H, s, 5-H_{Ar}); 2,28 (6H, br. s, 2-, 6-Me); 2,15 (6H, br. s, 3-, 4-Me)
Xa	9,18 d (5,5)	8,47 d (5,5)	9,48 d (6)	8,37 d. d (6, 8)	8,90 t (8)	11,6 br.	—
Xb	9,04 s 8,95 d (5,6)	— 8,07 d (5,6)	9,33 s 9,23 d (6,2)	— 8,32 d. d (6,2, 8)	8,77 d (8)	9,6 br.	2,27 (3H, s, 3-Me); 2,59 (3H, s, 3'-Me)
Xc	8,86 s 8,74 d (5,7)	— 7,94 d (5,7)	9,35 d(2) 8,88 d (5,5)	— 8,16 d. d (5,5, 7)	8,48 d. d (7)	*2	9,0 (1H, br. OH)

*The spectra of the salts VIId,e and Xa,b were taken in DMSO-D_6, of the salt Xc in a mixture of $CDCl_3$ with DMSO-D_6, and of the salt VIId' in acetone-D_6.
*2Overlaps with the OH signal.

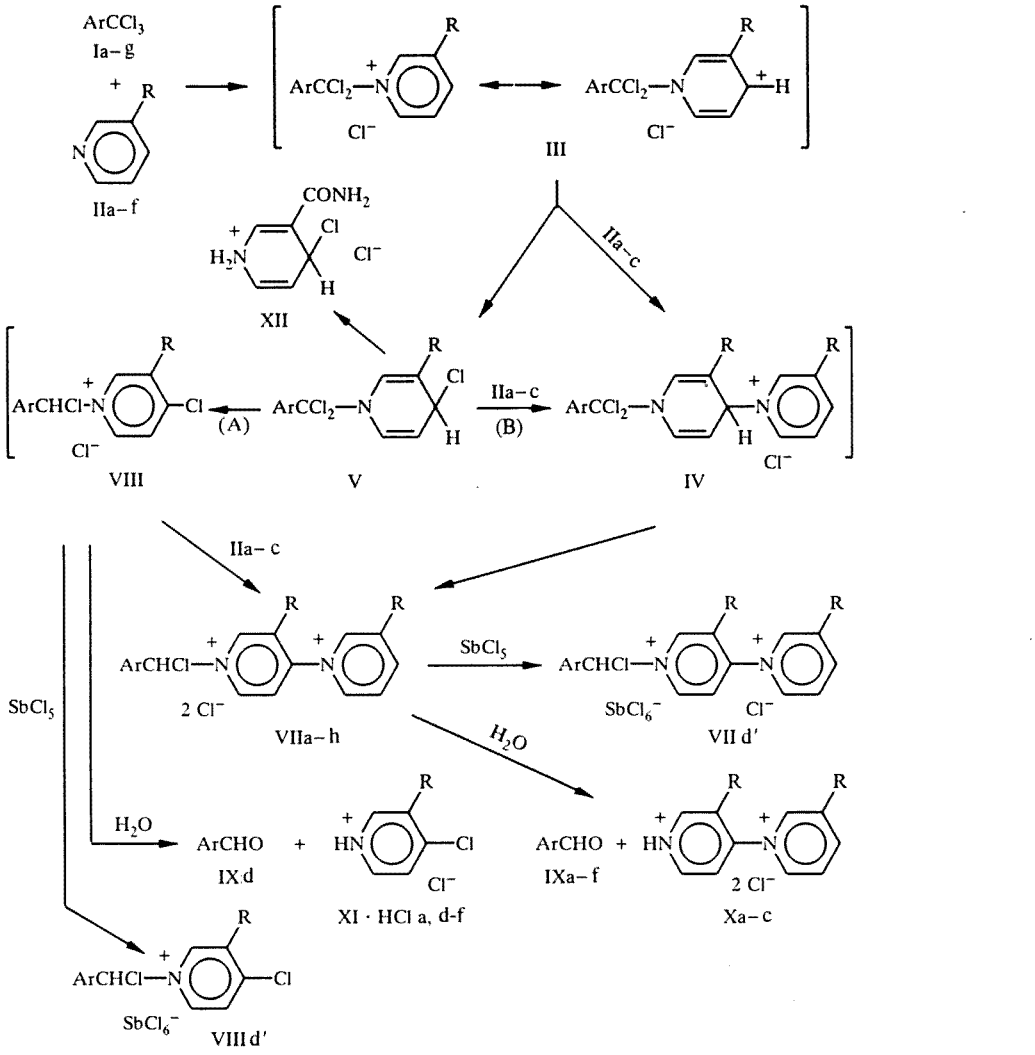
benzotrichloride Ia with pyridine and aqueous alkali [12]; however, it had not been experimentally confirmed up to now.
Scheme 1



In the reaction of trichlorides Ib and Ic with pyridine in chloroform we succeeded in obtaining good yields of the corresponding bispyridinium salts (IVb, c) (b, Ar = 2,4-$Me_2C_6H_3$; c, Ar = 2,4,5-$Me_3C_6H_2$), which were characterized by the ^{1}H NMR spectra (Table 1). We should mention that 2-methyl, 2,3- and 2,6-dimethylpyridines and 8-methylquinoline do not react with the trichlorides Ic and Id under the same conditions, evidently on account of steric hindrances. The reaction of benzotrichloride Ia with pyridine in chloroform does not occur even upon heating, but it does proceed when benzotrichloride is boiled in an excess of pyridine; the main reaction product is the bispyridinium salt IVa (Ar = Ph). The monopyridinium salt (chloride IIIa) can be detected in the form of the corresponding hexachloroantimonate IIIa' when an equivalent amount of pyridine is added to a preliminarily produced suspension of the salt $PhCCl_2{}^+SbCl_6{}^-$ in methylene chloride. The o,o'-dimethyl-substituted benzotrichlorides Id—f do not form bispyridinium salts of type IV, evidently on account of steric hindrances. These trichlorides are undoubtedly capable of forming monopyridinium salts of type III, as evidenced by our successful production of such a salt (IIId") from the chloride Id and 4-picoline. No such salts with a free 4-position can be detected, however, since they react with pyridine, which may lead not only to bispyridinium salts IV but also to essentially different products.

Another possible pathway of the conversion of monopyridinium salts III (Scheme 2) consists in nucleophilic attack by pyridine either on the sterically accessible electron-deficient 4-position of the pyridinium residue of salt III directly (carbocation site in one of the resonance forms) or on the 4-chloro-1,4-dihydropyridine (V) corresponding to it. (Similar structures were

discussed earlier as intermediates in the formation of N-(4-pyridyl)pyridinium salts [13-16], and also in the hetarylation by N-acetylpyridinium salts [17].) As a result of the variants of nucleophilic attack of pyridine discussed, N-substituted 4-(1-piperidino)-1,4-dihydropyridine (VI) should be formed; its aromatization with reduction of the dichloromethylene group of the N-substituent may lead to a N-(4-pyridyl)pyridinum salt (VII). Still another possible pathway of formation of the latter is aromatization of the dihydropyridine V to a 4-chloropyridinium salt (VIII) with further conversion to the salt VII (we should mention that the synthesis of pyridylpyridinium salts from 4-halopyridines is known [18]).



Actually, as we have established, when the reaction of o,o'-disubstituted chlorides Id-f (d, Ar = 2,4,6-$Me_3C_6H_2$; e, Ar = 2,3,4,6-Me_4C_6H; f, Ar = 2,3,5,6-Me_4C_6H) with 2 moles of pyridine in chloroform or methylene chloride is conducted, the corresponding salts VIId-f (R = H) are formed in good yields; they are readily hydrolyzed in air and, in contrast to the bispyridinium salts IV, are sparingly soluble in virtually all the usual anhydrous solvents except for dimethyl sulfoxide. On account of the high hygroscopicity of the products VII obtained, satisfactory data of elementary analysis could be obtained only for the salt VIId (synthesized in methylene chloride and isolated in an atmosphere of argon). The structure of the N-(4-pyridyl)pyridinium salts VIId,e was confirmed by the ^1H NMR spectra (in dry DMSO-D_6; see Table 2), which are in good agreement with the corresponding data for N-(α-chloroalkyl)- and N-(α-chloroarylmethyl)pyridinium salts, conducted in [10, 11, 19, 20], and for the salt VIId also by the ^{13}C NMR data (Table 3). Hydrolysis of the salts VIId-f in aqueous ethanol or aqueous DMSO leads to up to 95% yields relative to the corresponding substituted benzaldehydes (IXd-f, Ar see Id-f) and to N-(4-pyridyl)pyridinium dichloride (Xa,c R = H). The hydrolysates react smoothly with hydroxylamine, hydrazine, and its derivatives, giving the corresponding derivatives of substituted benzaldehydes.

Analogous results are also given by the reaction of the trichloride Id with excess pyridine (Id: Py = 1:4), leading to high yields of the salt VIId. This is indirect evidence that the labile chlorine atom of the benzyl fragment of the salt VIId cannot

TABLE 3. ^{13}C NMR Spectra of the Pyridylpyridinium Salt VIId and Its Hydrolysis Products

Compound	Chemical shifts, δ, ppm (SSCC, Hz)								
	Pyridylpyridinium residue			$CHClN^+$	CHO	Aryl residue			
	α'-C / α-C	β'-C / β-C	γ'-C / γ-C			i-C_{Ar}	o-C_{Ar} / o-Me	m-C_{Ar}	p-C_{Ar} / p-Me
VIId	147,9 / 146,2	124,7 / 127,7	154,3 / 144,4	79,4	—	127,4	141,7 / 20,7	130,8	137,9 / 19,9
Hydrolysis product VIId	144,8 / 149,6	119,8 / 128,1	150,8 / 147,9	—	193,3	128,1	143,2 / 20,0	129,9	140,7 / 20,7
IXd	—	—	—	—	192,9	129.6	143,2 / 19,9	130,1	140,7 / 20,0
Xa	144,9 / 150,2	120,8 / 128,8	150,8 / 148,7	—	—	—	—	—	—

be replaced by pyridine on account of obvious steric hindrances. In the hydrolysis products of the mixture formed as a result of the reaction of equimolar amounts of the mesitotrichloride Id and pyridine we detected 2,4,6-trimethylbenzaldehyde IXd, the dichloride Xa, the original trichloride Id, and also negligible amounts of pyridine hydrochloride and 2,4,6-trimethylbenzoic acid. In this case the yield of the sparingly soluble salt VIId, calculated on the basis of the original pyridine, is 76%. The data presented are evidence that even at equimolar reagent ratios the reaction does not end at the step of formation of a monopyridinium salt of type III, which evidently rather rapidly enters into further conversions with the still unreacted pyridine.

We should mention that our attempts to detect intermediates of the type of III, V, and VI in the reaction mixture in the conversions of the trichloride Id by ^1H NMR spectroscopy did not meet with success, since the formation of a precipitate of the salt VIId, sparingly soluble in $CDCl_3$ or CD_2Cl_2, is already observed 2-3 h after the reagents are mixed, and the concentrations of the indicated intermediates are probably so low that in addition to the starting materials only up to 8% of the salt VIId can be detected. It can be assumed that the limiting step of the reaction of trichloromethylarenes with pyridine is the formation of the pyridinium salts III, and subsequent steps are significantly more rapid. It is extremely probable that nucleophilic substitution of the chlorine atom of the CCl_3 group by pyridine in compounds Id-f proceeds according to an S_N1 mechanism — both on the strength of steric hindrances to substitution of another type (S_N2) and as a result of the known stability of the aryl(dichloro)methyl cations formed [21]. We should also mention that precisely an S_N1 mechanism was postulated for analogous reactions of benzyl- or diphenylmethylhalides with pyridine [22].

At the same time, the addition of antimony pentachloride to the reaction mixture during the reaction of the trichloride Id with pyridine made it possible to detect a 4-chloropyridinium salt in the form of the hexachloroantimonate (VIIId' R = H, Ar = 2,4,6-$Me_3C_6H_2$), which is evidence that the reaction under discussion proceeds through compounds V and VIII. In this case the possibility of formation of the salt VIIId through the pyridylpyridinium salt VIId is ruled out, since the latter, reacting with $SbCl_5$, is smoothly converted to the corresponding hexachloroantimonate (VIId'). We should also mention that although the mixture is subjected to hydrolysis at the early stages of the reaction when the trichloride Id is reacted with pyridine in chloroform (but not in methylene dichloride, in which the reaction proceeds appreciably more rapidly), in addition to the pyridylpyridinium salt Xa, 4-chloropyridine (XIa) and pyridine hydrochloride IIa·HCl can be detected (according to the ^1H NMR spectrum), (the ratio Xa : XIa : IIa·HCl ~4 : 1 : 1). The presence of 4-chloropyridine, and not of its hydrochloride (XIa·HCl) is apparently explained by the presence in the mixture of a still unreacted stronger base — pyridine.

We should emphasize that salts of type VII were obtained (in $CHCl_3$ or CH_2Cl_2) in good yields only for o,o'-disubstituted benzotrichlorides Id-f; however, their formation could also be detected for sterically unhindered trichlorides Ia,b. Thus, of the reaction products of the trichloride Ib with pyridine under the conditions of synthesis of the salts VIId-f, in addition to the bispyridinium salt IVb we isolated (after hydrolysis) N-(4-pyridyl)pyridinium dichloride Xa in a yield of 4%. The benzotrichloride Ia is rather inert towards pyridine at normal temperatures, as already mentioned above, and reacts with an excess of pyridine upon boiling, i.e., under conditions of reductive condensation [1-4]; in addition to the bispyridinium salt IVa, a small quantity (6%) of pyridylpyridinium dichloride Xa was isolated. These results confirm the hypothesis advanced above, that in the absence of steric hindrances nucleophilic substitution of the chlorine atom in a monopyridinium salt of type III occurs substantially more rapidly than attack by pyridine on the 4-position of this salt, and they also explain the decrease

in the yield of reductive condensation products (azines, oximes) [1-4] as we go from mesitotrichloride Id to trichloromethylarenes Ia-c.

Evidently in the course of the production of the salt VII there is also a reduction of the dichloromethyl group with replacement of one of the chlorine atoms by hydrogen. As noted above, the reaction resembles the well-known synthesis of N-(4-pyridyl)pyridinium dichloride Xa [13-15] by the action of thionyl chloride in pyridine, in the course of which, it has been suggested, the initially formed chlorosulfinylpyridinium salt is converted to N-chlorosulfinyl-4-chloro-1,4-dihydropyridine; the latter is attacked by pyridine in the 4-position, after which there is a coupled oxidation (with aromatization) of the dihydropyridinium fragment and reduction of the sulfinyl sulfur of thionyl chloride [14-16]. This analogy is quite evident in an examination of the possible pathway of the reaction of 1 mole of the trichloride Id and 2 moles of pyridine forming the salt VII (Scheme 2).

The necessary conditions for successful nucleophilic attack on pyridinium salts of type III at the 4-position are evidently, on the one hand, relatively strong acceptor properties of the substituent at the nitrogen atom, which are possessed, for example, by the chlorosulfinyl or acyl group, and on the other hand, the rather high nucleophilicity of the attacking particle, for example, pyridine or 3-methylpyridine in the syntheses of N-(4-pyridyl)pyridinium salts [13-16]. The formation of pyridylpyridinium salts VIId-f is evidence that the electron acceptor capacity of the α,α-dichlorobenzyl substituent in the monopyridinium salts IIId—f is close to that of the chlorosufinyl or acyl groups. From this it follows that in the absence of supplemental steric hindrances, we might expect the formation of N-(4-pyridyl)pyridinium salts of the VII type in the interaction of the same trichlorides Id-f with other pyridines, the nucleophilicity or strength of which as bases is not lower than that of pyridine, for example, with 3-substituted pyridines IIb,c, which carry electron donor substituents. Actually, we have shown that 3-methylpyridine IIb and 3-hydroxypyridine IIc form salts (VIIg,h, g R = Me; h, R = OH) with the trichloride Id that upon hydrolysis give 2,4,6-trimethylbenzaldehyde and N-(3-R-pyridyl-4)-3-R-pyridinium dichloride (Xb, R = Me; Xc, R = OH), respectively (Scheme 2). The structure of the salts Xb and Xc is confirmed by the ^{1}H NMR spectra (see Table 2), and in the case of the salt Xb also by the coincidence of the melting point with that described in the literature for this compound.

It was also of interest to conduct the investigated reaction with 3-R-pyridines with electron-acceptor substituents that lower the nucleophilicity of the heteroatom but increase the electrophilicity of the 4-position of the pyridine ring, which may facilitate the fixation or liberation of 1,4-dihydropyridinium intermediates of the V and VI types as a result of their stabilization by the indicated substituents. Actually, in a ^{1}H NMR investigation of products of the reaction of the trichloride Id with nicotinamide IId, the formation of 4-chloro-1,4-dihydronicotinamide hydrochloride (XII) was detected. Aromatization of the intermediate V corresponding to the indicated 1,4-dihydropyridine with replacement of one of the chlorine atoms at the benzyl carbon by hydrogen leads, after hydrolysis, to 2,4,6-trimethylbenzaldehyde IXd and 4-chloronicotinamide XId (Scheme 2, pathway A). In this case, just as in the reactions with pyridines IIe,f (see below), after hydrolysis of the reaction mixture the hydrochlorides XI·HCl are formed; however, subsequent treatment with hydrazine hydrate (to remove the aldehyde IXd in the form of an azine) converts them to the bases XI. The interaction of the trichloride Id with ethyl nicotinate, after hydrolysis, leads to 60-65% yields of the aldehyde IXd and the ethyl ester of 4-chloronicotinic acid (XIe, R = COOEt). We should mention that in both the examples discussed the corresponding N-(4-pyridyl)pyridinium salts of type X were not detected, even if a double molar amount of nicotinamide or ethyl nicotinate was used in the reactions. Such a result is easily explained considering both steric hindrances to the attack on the 4-position and the reduced (in comparison with unsubstituted pyridine) nucleophilicity of nicotinamide and 3-carbethoxypyridine. These considerations also agree with the results of the interaction of the trichloride Id with 3-bromopyridine IIf, which leads (after hydrolysis) to 3-bromo-4-chloropyridine (XIf, R = Br) and the aldehyde IXd (yield about 65%). The structure of compounds XId-f was confirmed by their ^{1}H NMR spectra (Table 4) and by comparison with the literature data available for 3-R-4-chloropyridines XIe,f (see the Experimental section).

From what has been stated it follows that the transfer of hydrogen from the dihydropyridine ring to the dichloromethylene group may occur not in pyridiniodihydropyridine salts of the VI type but in N-substituted 4-chloro-1,4-dihydropyridines V. The latter, after aromatization, may be converted to salts of the VII type in the absence of steric hindrances and sufficient nucleophilicity of the pyridine base, as is the case for pyridine IIa, 3-picoline IIb, and 3-hydroxypyridine IIc. In the case of the pyridines IId-f with voluminous substituents in the 3-position ($CONH_2$, COOMe, Br), which, moreover, decrease the nucleophilicity of the attacking pyridine, the reaction (Scheme 3, pathway A) stops at the step of N-(α-chlorobenzyl)-4-chloropyridinium salts VIII, which are converted by hydrolysis to the corresponding benzaldehyde and 3-R-4-chloropyridines XId-f, and under the action of hydroxylamine or hydrazines to products of reductive condensation. Our isolation or detection of the compounds VIIIa′, XIa,d-f, and XII and the absence of evidence for the existence of intermediates of the VI type permit us to consider the formation of pyridylpyridinium salts VII and X along pathway A through the step of 4-

TABLE 4. ^{1}H NMR Spectra of 4-Chloropyridinium (VIIId', XId·HCl) and 4-Chloro-1,4-dihydropyridinium (XII) Salts, as well as 3-R-4-Chloropyridines (XIa,d-f), Formed in the Reductive Condensation and after Hydrolysis of the Reaction Mixtures*

Compound	Chemical shifts, δ, ppm (SSCC, J, Hz)						
	Pyridine ring					$CHClN^+$ or HN^+	Other signals
	2-H	6-H	3-H	5-H	4-H		
VIIId'	9,38 m	9,38 m	8,47 m	8,47 m	—	8,33 s	7,12 (2H, s, 3-, 5-H_{Ar}); 2,32 (9H, s, 2-, 4- and 6-Me:Ar)
XId·HCl	8,98 s	8,70 d (7,0)	—	8,23 d (7,0)	—	*2	*2
XIa	8,52 d (5,5)	8,52 d (5,5)	7,40 d (5,5)	7,40 d (5,5)	—	—	—
XId	9,06 s	8,52 d (6,8)	—	7,45 d (6,8)	—	—	8,10 (2H, br., NH_2)
XIe	9,11 s	8,75 d (5,4)	—	7,61 d (5,4)	—	—	1,51 (3H, q, Me); 4,52 (2H, t, J = 7, CH_2)
XIf	8,73 s	8,41 d (5,3)	—	7,40 (5,3)	—	—	—
XII	8,09 br. s	6,63 br. s (9,0)	—	5,73 br. d (9,0)	6,16 m	*2	*2

*The spectra of the 4-chloropyridine XIa and amide XId were taken in DMSO-D_6, of the salts XII and XId·HCl in DMSO-D_6 with an addition of D_2O, of the salt VIId' in acetone-D_6, and of the remaining compounds in $CDCl_3$.

*2The proton of the NH group does not appear on account of exchange with D_2O.

chloropyridinium salts VIII as preferential, rather than the pathway B, analogous to that discussed in the literature for the production of N-(4-pyridyl)pyridinium dichloride [13-16, 22].

A key step of reductive condensation, at which the actual reduction occurs, is thus the formal transfer of a hydride ion (V → VIII, pathway A and VI → VII, pathway B). The actual transfer of hydrogen from the pyridine ring to the benzyl carbon atom is confirmed by the fact that when pyridine is replaced by deuteropyridine, the aldehyde IXd, deuterated at the formyl group, is the product of hydrolysis of the salt VIId, produced by the trichloride Id. As for the details of the mechanism of the conversions presented in Scheme 2, they are in need of additional investigation, and a brief discussion of them (see below) is constructed chiefly on the basis of the literature analogies.

We should mention that the mechanism of the formal transfer of the hydride ion from the 4-position of the 1,4-dihydropyridinium ring was and to a substantial degree still is the subject of intense debate, associated primarily with the key role of conversions of this kind in biochemical reactions involving NADH (see, for example, the reviews [23-26]). The most important conclusion from the data mentioned for the present discussion is that transfer of the hydride ion is extremely doubtful, and the selection should be made between transfer of an electron and a hydrogen atom or transfer of two electrons and a proton (in the latter case various sequences of one-electron transfers and proton transfer are possible, which will not be discussed here). At the present time the mechanism including transfer of a proton and two electrons is generally accepted, at least for biochemical processes [27]. A mechanism essentially analogous to the latter is realized in the electrochemical oxidation of 1,4-dihydropyridines [28]: At its first step there is an electron transfer, accompanied by transfer of a proton from the radical cation formed and ending with transfer of a second electron, which leads to an aromatic system. The isotope exchange of hydrogen that we observed in the reaction of 2,3,4,6-tetramethylbenzotrichloride Id with deuteropyridine in the presence of an equimolar amount of the hydrochloride C_5D_5N·HCl, the product of which proved to be a 70% nondeuterated aldehyde IXe, agrees with such a mechanism. It is important to emphasize that under the same conditions deuteroexchange of the "labile" hydrogen atom of the CHCl group of salts of type VII does not occur, as shown in a special experiment with the salt VIId. Thus, hydrogen

(deuterium) is transferred precisely in the course of a redox reaction and, moreover, in the form of a proton, not a hydride ion or a hydrogen atom.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were measured on Bruker WM-250 (250 MHz with respect to ^1H) and AM-300 (75.5 MHz with respect to ^{13}C) radiospectrometers. The spectral data and solvents are presented in the description of the syntheses of the concrete compounds and in Tables 1-4. The IR spectra were recorded on Perkin-Elmer 577 and Specord 80 instruments (pressing with KBr or solutions in chloroform). The mass spectra were obtained on a Varian MAT CH-6 instrument with direct introduction of the sample into the ion source, ionization energy 70 eV, emission current 100 μA. The melting points were measured on a Boetius microscope stage and were not corrected.

Interaction of the Benzotrichloride Ia with Pyridine. A. A mixture of 3.74 g (19.1 mmoles) of benzotrichloride and 4.54 g (57.3 mmoles) of pyridine was boiled for 1.5 h. After the excess pyridine was distilled off at reduced pressure, the residue was treated with chloroform with an addition of 2-3 drops of conc. HCl, and 0.26 g (6%) of the dichloride Xa was filtered off. Mp 172-175°C. The filtrate was diluted with dry ether; the finely divided precipitate of N,N′-(α-chlorobenzyl)bispyridinium dichloride (IVa) that formed was rapidly filtered off and washed with dry ether and acetone. We obtained 4.80 g of the salt IVa. Yield 58%. The melting point could not be determined.

B. To a solution of 5 mmoles of benzotrichloride Ia in 15 ml of dry CH_2Cl_2 at 20°C, 5 moles of $SbCl_5$ was added dropwise with mixing; after 30 min 5 mmoles of dry pyridine was added dropwise to the bright red suspension of the salt $PhCCl_2{}^+SbCl_6{}^-$ obtained, whereupon the color became dark yellow. The reaction mixture was exposed for three days at ~20°C, and the dark-yellow precipitate was filtered off; according to the ^1H NMR data it is a mixture (~1:1) of the complex $Py \cdot SbCl_5$ and (α,α-dichlorobenzyl)pyridinium hexachloroantimonate IIIa′.

Interaction of 2,4-Dimethylbenzotrichloride Ib with Pyridine. To a solution of 1.3 g (5.8 mmoles) of the trichloride Ib in 5 ml of dry methylene chloride, 0.92 g (11.6 mmoles) of dry pyridine was added with mixing. The mixture obtained was exposed for 30 days at room temperature, then boiled for 1 h. The solvent was evaporated and the residue was treated with dry ether; the precipitate was rapidly filtered off, washed with ether and hexane, and dried in a vacuum desiccator over P_2O_5. We obtained 1.79 g (81%) of N,N′-(2,4-dimethyl-α-chlorobenzyl)bispyridinium dichloride (IVb), the melting point of which could not be determined. In addition to the salt IVb, after hydrolysis of the filtrate (see above) with aqueous ethanol, the salt Xa was obtained. Yield 4%. Mp 173-175°C (cf. [13, 15]).

Interaction of 2,4,5-Trimethylbenzotrichloride Ic with Pyridine. The reaction was conducted under the conditions described above, but without boiling the reaction mixture. From 1.29 g (5.4 mmoles) of the trichloride Ic and 0.88 ml (10.8 mmoles) of pyridine in 5 ml of CH_2Cl_2 we obtained 2.01 g (93%) of N,N′-(2,4,5-trimethyl-α-chlorobenzyl)bispyridinium dichloride (IVc). The melting point could not be established on account of the high hygroscopicity of the salt.

Interaction of 2,4,6-Trimethylbenzotrichloride Id with 4-Picoline. A solution of 1.3 g (5.47 mmoles) of the trichloride Id and 0.48 g (5.47 mmoles) 4-methylpyridinium in 5 ml of dry CH_2Cl_2 was exposed at room temperature for seven days, then dry ether was added in portions, the amorphous precipitate formed was filtered off and washed with a mixture of ether, then dried under vacuum over P_2O_5, and N-(2,4,6-trimethyl-α,α-dichlorobenzyl)-4-methylpyridinium chloride (IIId″) was obtained. Yield 86%. On account of the hygroscopicity of the product, satisfactory data of elementary analysis could not be obtained, nor could the melting point be determined.

Interaction of Trichloromethylmesitylene Id with Pyridine. A. To 1.3 g (5.47 mmoles) of the trichloride Id we added a solution of 1 (0.44 ml, 5.47 mmoles), 2 (0.88 ml), or 4 (1.76 ml) molar equivalents of dry pyridine in 5 ml of dry chloroform or methylene chloride. The solution obtained was left in an atmosphere of argon at room temperature for several days. The precipitate formed was filtered off, washed with dry chloroform or methylene chloride, respectively, and dried over P_2O_5 under vacuum. In all cases N-(2,4,6-trimethyl-α-chlorobenzyl)-4-pyridylpyridinium dichloride VIId was obtained. The yields for the reaction with 1 equivalent of pyridine are equivalent to 76% pyridine (on the basis of the pyridine used); for the reaction with 2 and 4 equivalents of pyridine (on the basis of the initial chloride Id) they were 85-96%. Mp 148-152°C. Found, %: C 60.20; H 5.30; Cl 27.15; N 7.11. $C_{20}H_{21}Cl_3N_2$. Calculated, %: C 60.69; H 5.35; Cl 26.88; N 7.08. Treatment of a suspension of 0.66 g (1.67 mmoles) of the salt VIId in 20 ml of dry CH_2Cl_2 with antimony pentachloride (0.21 ml, 1.67 mmoles) with mixing leads after two days of exposure at room temperature to 1.15 g (~100%) N-(2,4,6-trimethyl-α-chlorobenzyl)-4-pyridylpyridinium chloride hexachloroantimonate VIId′. Yield 1.15 g (~100%). Mp 206-219°C. Hydrolysis

of the salt VIId here and in other cases was performed by the action of ~10 ml of water per gram of the salt at ~20°C; 2,4,6-trimethylbenzaldehyde IXd was obtained (see the preliminary communication [5]). Yield 89%. 2,4-Dinitrophenylhydrazone of IXd. Yield 88%. Mp 253-254°C. Treatment of the hydrolysis products of the salt VIId (without isolation of the aldehyde IXd) with hydroxylamine or hydrazine yielded a mixture (1:1 according to the data of the PMR spectrum) of Z- and E-isomers of 2,4,6-trimethylbenzaldoxime. Yield 68%. Mp 122-152°C (see [2]). M^+ 163; IR spectrum: 3240 (OH), 1610 cm^{-1} (C=N). In the case of analogous treatment of the products of alcoholysis of the salt VIId, 2,4,6-trimethylbenzaldazine was obtained. Yield 80%. Mp 170-171°C. Identical with a previously described sample [2]. When the reaction is conducted in chloroform for 1-3 days, up to 15% of 4-chloropyridine XIa is detected in the hydrolysis products according to the ^1H NMR spectrum (see Table 4); its spectrum agrees with that presented in [29].

B. From 1.29 g (5.43 mmoles) of the trichloride Id and 1.83 g (21.7 mmoles) pyridine-D_5 in 5 ml of dry chloroform under the conditions of the previous experiment, we obtained 0.98 g of the salt VIId. Yield 45%. Mp 151-152°C. To 0.77 g (1.9 mmoles) of the salt VIId we added 10 ml of distilled water, and the mixture obtained was extracted at 30 min intervals with chloroform. From the extract obtained over $MgSO_4$ we obtained 0.18 g (28% calculated on the basis of the initial trichloride Id) 2,4,6-trimethylbenzaldehyde IXd, deuterated at the formyl group. $M^{+\cdot}$ 149. The IR spectrum (in chloroform) contains ν_{C-D} 2128 and 2072 cm^{-1}. The PMR spectrum ($CDCl_3$) contains singlets 6.88 (H_{Ar}), 257 (2- and 6-Me), and 2.31 (4-Me), as well as a small signal at 10.40 ppm (CHO), corresponding to an ~5% admixture of the nondeuterated aldehyde IXd. From the aqueous mother liquor, after evaporation of water, we obtained 0.39 g (30%) of the deuterated N-(4-pyridyl)pyridinium dichloride Xa. Mp 178-182°C. The IR spectrum contains a band ν_{C-D} 2260 cm^{-1}. The filtrate obtained after removal of the salt VIId (see above) is evaporated; 0.5 ml of water and 5 ml of ethane are added to the residue, and then 0.2 ml of hydrazine hydrate is added, yielding 0.38 g (47%) 2,4,6-trimethylbenzaldazine, deuterated at the azomethine group. Mp 169-171°C. $M^{+\cdot}$ 294. The IR spectrum contains the band ν_{C-D} 2212 cm^{-1}. The total yield of deuterated reduction products of the trichloride Id — the aldehyde IXd and aldazine — was 75%.

C. To a solution of 1.3 g (5.47 mmoles) of mesitotrichloride Id in 6 ml of dry CH_2Cl_2, 0.88 ml (10.94 mmoles) of dry pyridine was added dropwise, exposed for 1 h at ~20°C, after which 0.70 ml (5.47 mmoles) of antimony pentachloride was added at 0°C with mixing. The mixture was exposed for 24 h at ~20°C, and 2.16 g of a precipitate, representing a complex mixture that could not be identified, was filtered off. The filtrate was partially evaporated; the precipitate that formed was filtered, washed with dry CH_2Cl_2, and 0.20 g (6%) N-(α-chloro-2,4,6-trimethylbenzyl)-4-chloropyridinium hexachloroantimonate VIIId was obtained. Mp 155-157°C.

Interaction of 2,3,4,6-Tetramethylbenzotrichloride Id with Pyridine. A. From 1.4 g (5.5 mmoles) of the trichloride Id (isolated by freezing out a mixture of the trichlorides Id-g, obtained by the action of CCl_4 on durol according to the procedure of [30]) and 11.0 mmoles of pyridine in 5 ml of chloroform, after exposure for seven days at room temperature and filtration, we obtained 2.1 g (yield 93%) of the salt VIIe. Mp 162-164°C (dec.). Hydrolysis of 0.8 g of the salt VIIe yielded 0.43 g of the pyridylpyridinium dichloride Xa and 0.31 g of the aldehyde IXe; the yields of Xa and IXe were about 90% on the basis of pyridine and the trichloride Ie. The aldehyde IXe, Literature: n_D^{20} 1.5554. Literature: n_D^{30} 1.5560 [31]. M^+ 162. ^1H NMR spectrum (DMSO-D_6): 2.07 (3H, s, 3-Me); 2.18 (3H, s, 4-Me); 2.35 (6H, s, 2- and 6-Me); 6.86 (1H, s, 5-H); 10.40 ppm (1H, s, CHO). The action of hydrazine hydrate on the aldehyde IXe yielded 2,3,4,6-tetramethylbenzaldazine. Mp 129-130°C (from alcohol). Found, %: C 82.31; H 8.73; N 8.94. $C_{22}H_{28}N_2$. Calculated, %: C 82.45; H 8.81; N 8.74.

B. Through a solution of 1.70 g (6.76 mmoles) of the trichloride Ie and 0.54 ml (6.76 mmoles) of dry deuteropyridine in 5 ml of dry $CHCl_3$, HCl was passed for 40 min, then 0.54 ml of C_5D_5N was added and the reaction mixture was exposed for 20 days at room temperature. The solvent was evaporated, 0.67 ml (15.5 mmoles) of hydrazine hydrate was added to a solution of the residue in 6 ml of ethanol and 0.5 ml of water, the mixture was exposed for 16 h at room temperature, and the precipitate formed, (0.13 g, 12%) 2,3,4,6-tetramethylbenzaldazine VIIe, was filtered off. Mp 129-130°C (from alcohol). Mass spectrum, m/z: M^+ 320, 321, and 322 (intensity ratio ~6:3:1). According to the ^1H NMR data ($CDCl_3$), the azine VIIe was 30% deuterated at the CH=N group: 2.23 (3H, s, 3-Me); 2.33 (3H, s, 4-Me); 2.48 (6H, s, 2- and 6-Me); 6.97 (1H, s, 5-H); 9.05 ppm (0.7H, s, CH=N).

C. A solution of 1.80 g (7.15 mmoles) of a mixture of 2,3,4,6-, 2,3,5,6-, and 2,3,4,5-tetramethylbenzotrichlorides (Ie:If:Ig = 52:22:26, produced by trichloromethylation of durol according to the procedure of [30]) and 1.16 ml (14.31 mmoles) pyridine in 5 ml of chloroform was exposed in an atmosphere of argon for five days at room temperature. The precipitate formed was filtered off (precipitate 1), the filtrate was evaporated, the residue was treated with aqueous methanol, the precipitate (precipitate 2) was filtered off, it was washed with the same solvent, and 0.33 g (70%) 2,3,4,5-tetramethylbenzotrichloride Ig was obtained. Mp 90-91°C, which corresponds to the data of [30]. Mass spectrum, m/z: M^+

250, 252, 254. PMR spectrum ($CDCl_3$): 7.80 (1H, s, 6-H), 2.64 (3H, s, 2-Me), 2.36 (3H, s, 4-Me), 2.29 (3H, s, 5-Me), 2.27 ppm (3H, s, 3-Me).

Precipitate 1 was washed with chloroform, dried over P_2O_5, and 0.98 g of the product was obtained. Mp 162-163°C (dec.), hydrolysis of which leads to a mixture of pyridylpyridinium dichloride Xa, 2,3,4,6- (IXe), and 2,3,5,6-tetramethylbenzaldehyde (IXf) in a ratio Xa:IXe:IXf = 4:3:1 (yields 85, 50, and 35%, respectively). The mixture was analyzed by the PMR method (in DMSO-D_6 with an addition of a small quantity of D_2O). For aldehydes $M^{+\cdot}$ 162 was also determined. The PMR spectrum of the dichloride Xa agrees with that shown in Table 2. For the PMR spectrum of the aldehyde IXe, see above. PMR spectrum of the aldehyde IXf: 10.46 (1H, s, CHO); 7.10 (1H, s, 4-H); 2.22 (6H, s, 2- and 6-Me); 2.12 ppm (6H, s, 3- and 5-Me).

Interaction of Trichloromethylmesitylene Id with 3-Picoline. To 0.55 ml (0.73 g, 3.07 mmoles) of the trichloride Id was added 0.59 ml (0.565 g, 6.14 mmoles) 3-picoline and 5 ml of chloroform. The solution obtained was exposed at room temperature for 30 days, then the solvent was evaporated; the residue was treated with 3 ml of water and extracted with ether. The extract, dried over magnesium sulfate, was evaporated; the residue (0.43 g), according to the PMR data, is a mixture (1:2) of the trichloride Id and 2,4,6-trimethylbenzaldehyde IXd. Yield of the aldehyde IXd 64%. From the aqueous layer, after evaporation and treatment of the residue with chloroform, we isolated 0.39 g (yield 49%) of N-(4-β-picolyl)-β-picolinium dichloride Xb. Mp 202-204°C. Literature: mp 202-203°C [32].

Interaction of Trichloromesitylene Id with 3-Hydroxypyridine. According to the procedure described, after exposure for 25 days, from 3.07 mmoles of Id and 6.15 mmoles 3-hydroxypyridine in 5 ml of chloroform and further treatment, we obtained a precipitate from which 2.02 moles (66%) of the aldehyde IXd was isolated by column chromatography on silica gel (eluent benzene). From an aqueous solution we obtained 0.56 g of a mixture of 3-hydroxypyridine hydrochloride (IIc·HCl) and N-(3-hydroxypyridyl-4)-3-hydroxypyridinium dichloride Xc in a 1:2 molar ratio.

Interaction of the Trichloride Id with Nicotinamide. To a solution of 0.75 ml (4.21 mmoles) of the trichloride Id in 15 ml of dry chloroform, 1.03 g (8.42 mmoles) nicotinamide was added with mixing, and the suspension formed was left for 26 days under argon at room temperature. The precipitate was filtered off, washed with dry chloroform, and 1.48 g of a substance with mp 165-168°C was obtained; a hydrolysate of it, according to the ^1H NMR data, consists of a mixture of the aldehyde IId, nicotinamide hydrochloride (IId·HCl), 4-chloronicotinamide hydrochloride (XId·HCl), and 4-chloro-1,4-dihydronicotinamide hydrochloride XII in a 1:3:1:0.8 ratio. The filtrate, according to the ^1H NMR data (DMSO-D_6), contains the initial trichloride Id and 4-chloronicotinamide XId in a 2:1 ratio.

Interaction of the Trichloride Id with Ethyl Nicotinate. Under the conditions of the preceding experiment, from 0.97 ml (5.47 mmoles) of the trichloride Id and 1.66 g (10.94 mmoles) of ethyl nicotinate, after exposure for 24 days at room temperature, we obtained 2.77 mmoles (25%) of ethyl nicotinate hydrochloride (IIe·HCl). Mp 109-113°C. Literature: mp 118-120°C [33]. After evaporation of the mother liquor and hydrolysis of the residue, the mesitoic aldehyde IXd was removed in the form of the azine (yield 61%), and then 0.64 g (64%) 4-chloro-3-ethoxycarbonylpyridine (XIe), n_D^{20} 1.5240, was isolated by chromatography (see above). Literature: n_D^{20} 1.5230 [34]. The ^1H NMR spectrum (see Table 4) agrees with those given in [34].

Interaction of Trichloromethylmesitylene Id with 3-Bromopyridine. A solution of 0.97 ml (5.47 mmoles) of the trichloride Id and 1.73 g (10.94 mmoles) 3-bromopyridine IIf in 5 ml of chloroform was exposed at room temperature for 30 days, then the solvent was evaporated, the residue was treated with ether, and the precipitate of 3-bromopyridine hydrochloride IIf·HCl formed (0.20 g) was filtered off. The filtrate was evaporated, the residue was dissolved in 4 ml of ethanol and ~0.2 ml of water, 0.6 ml of hydrazine hydrate was added to the solution obtained, and the mixture was exposed for ~16 h, after which 0.5 g (63%) of 2,4,6-trimethylbenzaldazine was filtered off. After partial evaporation of the filtrate, the precipitate of hydrazine hydrochloride that formed was filtered off. The mother liquor was evaporated, 50 ml of water was added, and the mixture was extracted with ether; the extract was dried with magnesium sulfate. The residue after evaporation of the extract was chromatographed on a column with silica gel (eluent benzene), and 0.68 g (65%) of 3-bromo-4-chloropyridine XIf was obtained. Mp 15-17°C. Lit.: mp 17.5-18.5°C [35]. The ^1H NMR spectrum of XIf corresponds to that given in [36].

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