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SYNTHESIS OF HALOGENOPYRIDINES (REVIEW)

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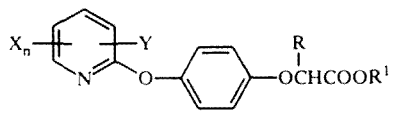
Published data on the synthesis of derivatives of pyridines containing halogen atoms directly at the carbon atoms of the pyridine ring are reviewed.

INTRODUCTION

Halogen-substituted pyridines are of great interest as starting materials for the synthesis of compounds having a wide range of biological activity. Among these compounds, the investigators have paid greatest attention to pyridine bases, which exhibit high herbicidal, insecticidal, acaricidal, fungicidal, biocidal, and growth-regulating activity. For example, it is possible to mention various auxin-type herbicides, including lanthrel, tordone, gardone, and the esters of α-substituted carboxylic acids with the general formula [1]:



X = halogen; Y = halogenoalkyl

In the last 20-30 years numerous publications have appeared on various methods for the synthesis of derivatives of pyridine containing halogen atoms at the carbon atoms of the pyridine ring and their transformations. In 1961 there was a monograph [2], followed in 1974 by a supplement [3], on methods for the synthesis of halogen-substituted pyridines and their transformations. In 1990 two articles summarizing the principal published data on this subject up to 1987 were published [1, 4].

For this reason the present review as a rule covers data on the synthesis of the chlorine derivatives of pyridine that appeared in the literature after 1985. Data on the synthesis of the fluorine, bromine, and iodine derivatives of pyridine that appeared in the literature after 1973 are included in the review.

1. SYNTHESIS OF HALOGENOPYRIDINES BY THE SUBSTITUTION OF ATOMS OR GROUPS IN THE PYRIDINE RING BY HALOGEN ATOMS

1.1. Substitution of Hydrogen by Halogen

The substitution of hydrogen atoms in the pyridine ring by halogen atoms takes place by a radical or electrophilic mechanism, depending on the reaction conditions (the employed pyridine base, the nature of the halogenating reagent, the temperature, and the catalyst).

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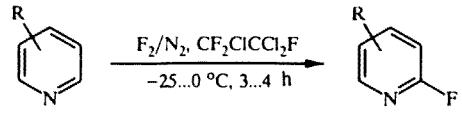
During the action of a gaseous mixture of fluorine and nitrogen on derivatives of pyridine (I) the hydrogen atom at position 2 is substituted by a fluorine atom [5, 6].

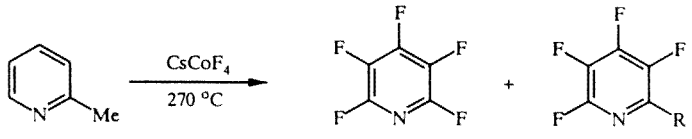


I

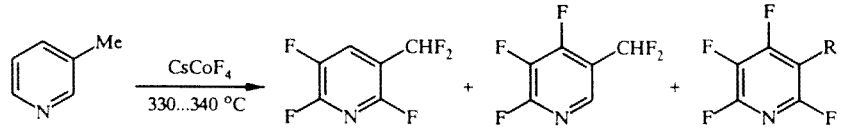
R = 4-Et (32%) [5, 6]; 4-Me (31%); 4-Me_2CH (47%); 4-$PhCH_2$ (25%); 3-Me (43%); 3,5-Me_2 (37%); 2,5-Cl_2 (46%); 4-Ac (26%); 4-COOMe (61%); 3-COOMe (36%) [6]

2-Fluoropyridine is formed with a 22% yield from pyridine in acetonitrile in the presence of $Me_4NF \cdot 2HF$ during electrolysis (2.5 V) with a platinum electrode [7].

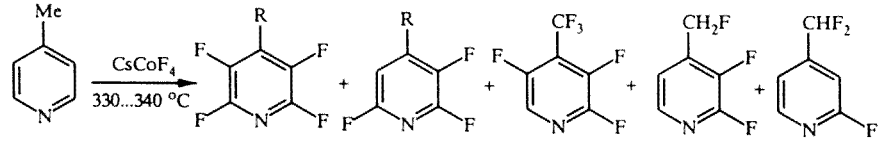
The fluorination of pyridine [8] and picolines [9] was achieved by treatment with cesium tetrafluorocobaltate. The reaction with pyridine was conducted under various conditions: a) at 395-405°C for 25-30 min (the products contained 14.9% of pentafluoropyridine and other fluorine derivatives); b) at 310°C for 3.5 h (the products contained 6.8% of pentafluoropyridine, 1.5% of 2,3,4-trifluoropyridine, 2% of 2,3,6-trifluoropyridine, 1.6% of 2,5-difluoropyridine, 1.6% of 2,3-difluoropyridine, and 1.2% of 2,6-difluoropyridine) [8]. The reaction of picolines with $CsCoF_4$ for 2.5 h gave a mixture of fluorination products [9]:



R = CF_3, CHF_2, CH_2F

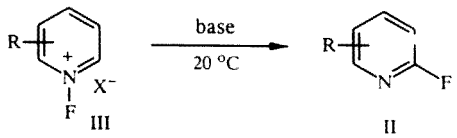


R = Me, CH_2F, CHF_2



R = CHF_2, CF_3

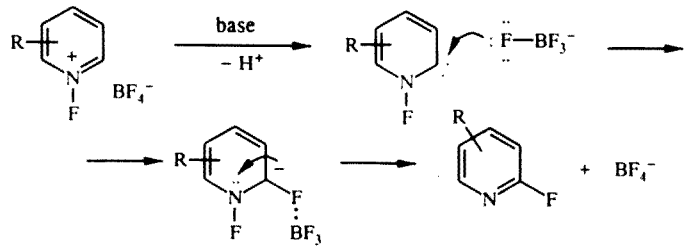
A large number of 2-fluoro derivatives (II) were obtained by treating the salts (III) with bases at 20°C for 5 min [10]; the best results were obtained with ten equivalents of the base [10]:



For X = BF_4: R, base , yield of II (%): H, Et_3N, 79; H, C_5H_5N, 58; H, KF, 26; H, $Bu_4^+F^-$, 80; 4-Me, Et_3N, 80; 3,5-Me_2, Et_3N, 87; 3,5-Me_2, C_5H_5N, 30; 4-Me_3C, Et_3N, 91; 4-Me_3C, C_5H_5N, 24; 2-MeO, Et_3N, 75; 2-MeO, C_5H_5N, 10; 4-Ph, Et_3N, 40; 4-COOMe, Et_3N, 69; 4-COOMe, C_5H_5N, 49; 3-COOEt, Et_3N, 48; 2-Cl, Et_3N, 72; 3,5-Cl_2, Et_3N, 62; 3,5-Cl_2, C_5H_5N, 70; 3,5-Cl_2, Et_2NH, 73; 3,5-$(CF_3)_2$, Et_3N, 99; 3-CN, Et_3N, 51; 3-CN, C_5H_5N, 49; 2-CN, C_5H_5N, 79; 4-NO_2, Et_3N, 21; 4-CN, C_5H_5N, 31. If the base was Et_3N: R, X, yield of II (%): H, SbF_6, 78; H, PF_6, 74; 6-Cl, OSO_2CF_3, 19; H, OSO_2CF_3, 21.

for R = 3,5-$(CF_3)_2$, X = OSO_2CF_3, base C_5H_5N, yield of II — 31%

In the opinion of the authors [10] the reaction takes place by a carbene mechanism:

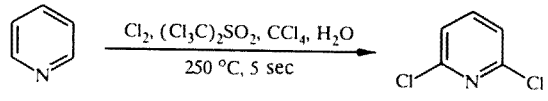


As a rule the direct action of chlorine on pyridine leads to 2-chloropyridine (yields 20-61%) and 2,6-dichloropyridine (yields 29-41%) [11-16], although there are reports of the exclusive production of 2-chloropyridine (yields 31-41%) [17-19]. The chlorination of pyridine is conducted at 75-170°C in the presence of water with UV irradiation.

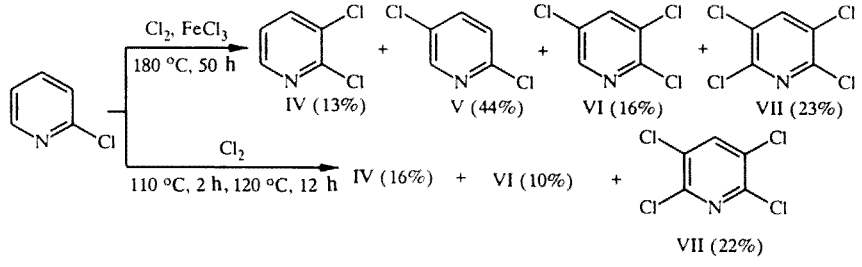
Various conditions have been proposed for the photochlorination of 2-chloropyridine to 2,6-dichloropyridine [20, 21]. Realization of the reaction for 60-75 min at 75-76°C with 59.6-94.4% yields of 2,6-dichloropyridine was reported. Other authors have conducted the reaction at 140-150°C in the presence of benzophenone for 93 min (yield 84.2%) [22] and in the presence of succinimide [23] or N-chlorosuccinimide [24] for 93 min (yields 92.8% or 90.1% respectively). The yield of 2,6-dichloropyridine under these conditions without the succinimide amounted to 46.2% [23].

2-Chloropyridine was also obtained with a yield of 72.8% by the action of chlorine on pyridine hydrochloride at 400°C [25].

The transformation of pyridine into 2,6-dichloropyridine with 78% selectivity and 100% conversion was described [26]:



As a result of the chlorination of 2-chloropyridine, Japanese workers obtained mixtures of products with various degrees of chlorination (IV-VII) [27, 28]:

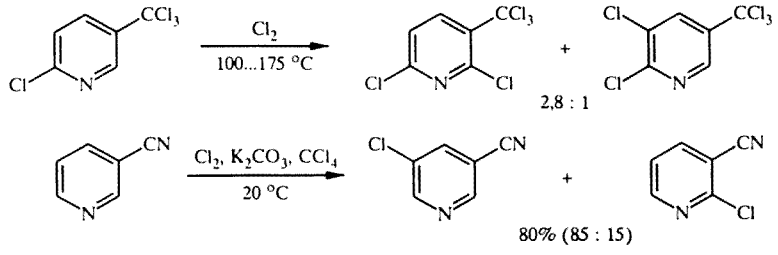


The composition of the products from the chlorination of 2,6-dichloropyridine depends on the process temperature: At 410°C 3.9% of 2,3,6-trichloropyridine, 5.1% of 2,4,6-trichloropyridine, and 0.5% of 2,3,5,6-tetrachloropyridine are obtained [29]; at 520°C pentachloropyridine is mainly formed (yield 83%). The latter was also produced by the chlorination of 2,3,6-trichloropyridine or 2,3,5,6-tetrachloropyridine [30].

The chlorination of 3,5-trichloropyridine at 140°C for 15 h under the influence of UV light leads to a mixture of 2,3,4-trichloropyridine (yield 69.4%) and 2,3,5,6-tetrachloropyridine (yield 4.8%) [31].

2,3,6-Trichloropyridine is transformed into 2,3,5,6-tetrachloropyridine with a yield of 15.7% by the action of chlorine at 410°C for 0.49 sec [29].

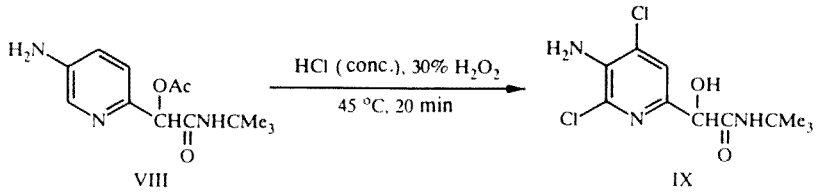
The reaction of chlorine with 2-chloro-5-trichloromethylpyridine [32] or with 3-cyanopyridine [33] in each case results in the formation of two compounds:



The chlorination of 2-hydroxy-5-trifluoropyridine (50°C in chloroform) leads to the formation of 3-chloro-2-hydroxy-5-trifluoropyridine [34], while the reaction of 3-amino-4-alkyl(C_1-C_3)pyridines with chlorine (5-30°C, 0.5-2 h, pH 0.01-2) gives 2-chloro-3-amino-4-alkylpyridines [35].

During the action of chlorine on 2,3-dimethylpyridine in the vapor phase, chlorination takes place not only in the ring but also at the methyl group, and 2-chloro-5,6-di(chloromethyl)pyridine is formed [36].

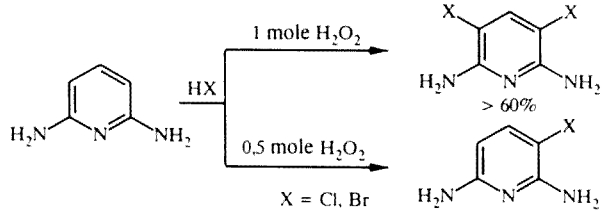
In reaction with concentrated hydrochloric acid and hydrogen peroxide under mild conditions the amine is converted into compound (IX) with a yield of 50% [37]:



VIII IX

In the reaction of 3-hydroxynicotinic acid with concentrated hydrochloric acid and hydrogen peroxide at 20-35°C for 15 h, only one hydrogen atom is substituted, and 5-chloro-2-hydroxynicotinic acid is formed with a yield of 30% [38].

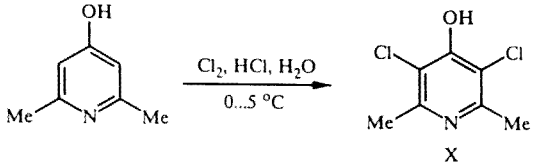
By the action of hydrochloric acid or hydrobromic acid and hydrogen peroxide it is possible to introduce one or two halogen atoms into the molecule of 2,6-diaminopyridine [39]:



2,6-Diamino-3-chloropyridine was converted by the action of hydrobromic acid and hydrogen peroxide into 2,6-diamino-5-bromo-3-chloropyridine. The latter was also obtained during the treatment of 2,6-diamino-3-bromopyridine (X = Br) with hydrochloric acid and hydrogen peroxide [39].

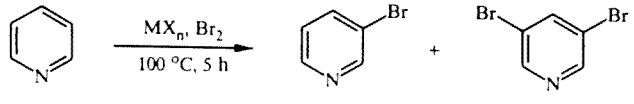
2-Hydroxy-5-nitropyridine was converted into 3-chloro- and 3-bromo-2-hydroxy-5-nitropyridine with yields of 93% and 91% respectively by the action of hydrochloric acid or hydrobromic acid and potassium chlorate in water at 50-60°C for 15 min [40].

A method was patented for the introduction of two chlorine atoms into the molecule of 4-hydroxy-2,6-dimethylpyridine by the action of chlorine and hydrochloric acid at 0-5°C and pH 3; the yield of the reaction product (X) was 70% [41]:



X

The production of bromine derivatives of pyridine bases by the direct action of bromine has been studied in a fair amount of detail. The reaction of pyridine with bromine in the presence of various Lewis acids MCl_n (M = B, Al, Fe, Co, Ni, Cu, Zn, Zr, In, Sn, Sb, Te, Hg, or Bi and also $BiBr_3$) at 100°C with a reaction time of 5 h was investigated systematically.



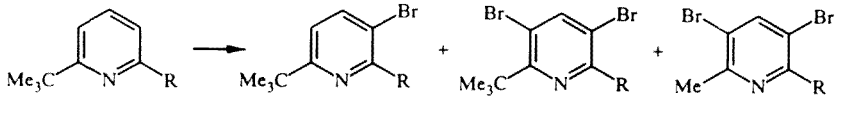
The bromination products were not obtained when boron trifluoride, ferric chloride, zinc chloride, and bismuth tribromide were used. Only 3,5-dibromopyridine is formed with a small yield in the reaction with bromine in the presence of $2C_5H_5N \cdot SnCl_4$, and mixtures of 3-bromopyridine and 3,5-dibromopyridine are formed in other cases with yields of 3.8-28.2%

and 0.7-43.1% respectively. The highest yield of 3-bromopyridine was obtained when the $2C_5H_5N \cdot CuCl_2$ complex was used, and the highest yield of 3,5-dibromopyridine was obtained when the $2C_5H_5N \cdot InCl_3$ complex was used [42]. This process was also studied with catalytic amounts of Lewis acids at 100, 150, and 200°C with the pyridine and bromine in ratios of 1:1 and 1:2. It was found that the yields of 3,5-dibromopyridine become significantly higher with increase in temperature, while the yields of 3-bromopyridine vary in a disordered manner [42].

The reaction of 3-fluoropyridine with bromine at 590°C for 30 sec leads to the formation of mixtures of 2-bromo-3-fluoropyridine with 2-bromo-5-fluoropyridine (yield 15%, ratio 1:1) and of 2,4,6-tribromo-3-fluoropyridine with 2,5,6-tribromo-3-fluoropyridine (yield 25%, ratio 1:2) and also to the formation of 2,6-dibromo-3-fluoropyridine (yield 40%) [43].

The bromination of pyridine bases was carried out in the presence of oleum. During the bromination of 2-methylpyridine in the presence of 65% oleum in ampuls at 90°C for 7 h, a mixture of 3-bromo-2-methylpyridine and 5-bromo-2-methylpyridine was formed with a total yield of 40-57% [44].

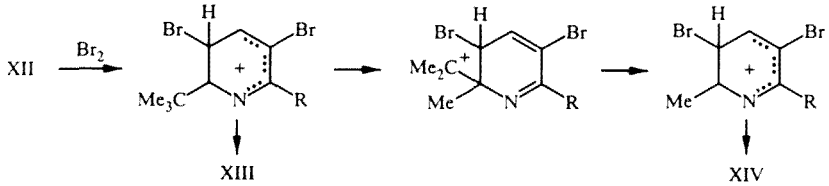
The reaction of alkylpyridines (XI) with bromine in 65% oleum (55°C, 5 h, ampul) gave mixtures of compounds (XII, XIII, XIV) in various ratios, depending on the position of the alkyl substituents in the pyridine ring [45]:



XI XII XIII XIV

Formed with R = H: XII (60...65%) and XIII (2...3%); with R = Br — XIV (1...2%) and XIII (10...15%). Formed with R = Me XII (10...15%), XIII (30...35%) and XIV (25...30%); with R = CMe_3 — XII (15...20%), XIII (30...35%) and XIV (10%).

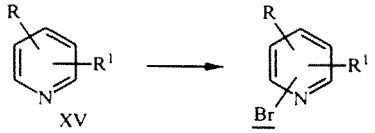
The authors in [45] consider that compound (XIV) is formed as a result of a rearrangement involving the *tert*-butyl radical:



XIII XIV

Various mixtures of products were obtained as a result of the reactions of ethyl-substituted pyridines with bromine in the presence of 65% oleum. 3-Bromo-2-ethylpyridine (20%) and 4-bromo-2-ethylpyridine (52%) were obtained from 2-ethylpyridine; 4-bromo-3-ethylpyridine and 2-bromo-3-ethylpyridine were obtained from 3-ethylpyridine; 3-bromo-2,5-diethylpyridine (26%) and 2,5-dibromo-3,6-diethylpyridine (21%) were obtained from 2,5-diethylpyridine [46].

Other authors brominated derivatives of pyridine (XV) in 20% oleum at 185-190°C for 18 h in the presence of mercuric sulfate [47] or at 155-175°C for 20-24 h [48]:

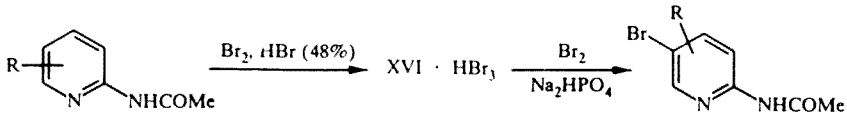


XV

R, R^1, position of Br, yield (%): H, 4-Me, 3,59 [47]; 2-Me, 6-Me (3,9 + 3,5-Br_2, 61); 2-Me, 4-Me (5,11 + 3,17 + 6, 63); 2-Me, 5-Me (3,63 + 6,4 + 3,6 25); 2-Me, 3-Me (5,37 + 5,6-Br_2, 33); 3-Me, 4-Me (5,44 + 5,6-Br_2, 47); 3-Me, 5-Me (2,34 + 2,6-Br_2, 49) [48]

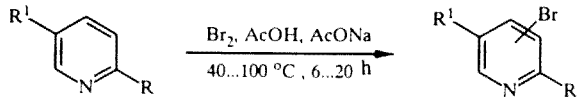
During treatment with bromine in the presence of 48% hydrobromic acid, 2,4-dihydroxypyridine is converted into 3-bromo-2,4-dihydropyridine [49].

The 2-acetyl derivative (XVI) is converted with good yields into the bromination products (XVII) when treated with HBr_3 ($HBr + Br_2$) in the presence of Na_2HPO_4 or AcONa; the authors [50] consider that the active particles are $Br^+NaHPO_4^-$ or $Br^+CH_3COO^-$:



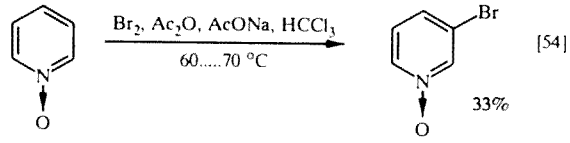
5-Bromo-2-aminopyridine was obtained with a yield of 86% when 2-aminopyridine was treated with bromine in glacial acetic acid at 20°C for 1.5 h [51].

Bromine was introduced into the pyridine ring by the action of bromine in acetic acid [52, 53] or in acetic anhydride in the presence of sodium acetate:



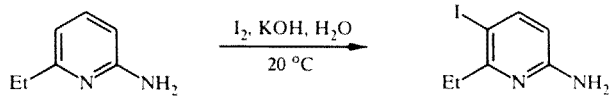
R, R^1, position of Br, yield (%): OMe, H, 5, 41; OMe, CHO, 3, — [52]; OMe, Cl, 3, 74; OMe, Cl, 3,5-Br_2, 71 [53]

The bromination of pyridine N-oxide has also been described:



[54]

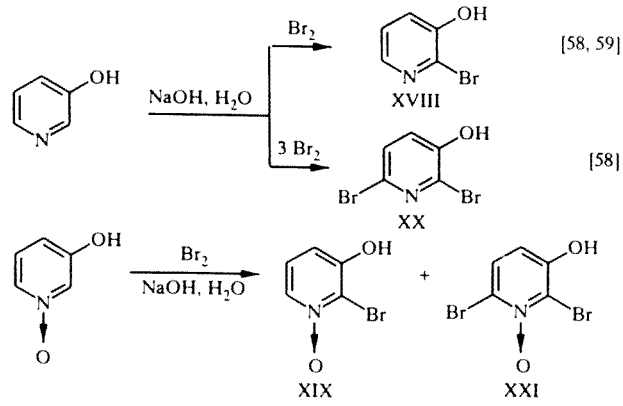
The action of iodine on 2-amino-6-ethylpyridine in an alkaline medium gives 2-amino-5-iodo-6-ethylpyridine [55]:



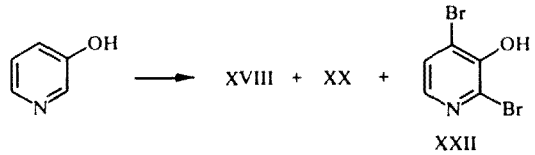
During the action of iodine on 3-hydroxypyridine in the presence of sodium carbonate in water at 20°C for 0.5 h, the nature of the iodination products depends on the ratio of the halogenating agent and the base; with I_2:Na_2CO_3 = 1:2, 2-iodo-3-hydroxypyridine is mainly formed (yield 85%); with I_2:Na_2CO_3 = 2:3 the main product is 2,6-diiodo-3-hydroxypyridine (yield 94%); in a second reaction, 2,4,6-triiodo-3-hydroxypyridine was obtained (yield 4%) [56].

Numerous examples of the introduction of halogen atoms into the pyridine ring by the action of various halogen-containing reagents have been described. The transformation of 2-hydroxypyridine into 3,5-dichloro-2-hydroxypyridine by heating the former with HCl in DMFA for 1 h has been patented [57].

When treated with bromine in 10% aqueous sodium hydroxide, 3-hydroxypyridine and its N-oxide form the monobromination products (XVIII, XIX) or the dibromo derivatives (XX, XXI) with yields of 60% [58] and 30-35% [59] or 44% [58]:

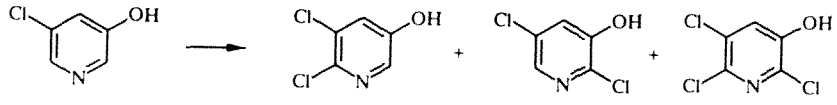


More recently it was shown that 2,4-dibromo-3-hydroxypyridine (XXII) is also formed from 3-hydroxypyridine under analogous conditions in addition to compounds (XVIII, XX) [56]:

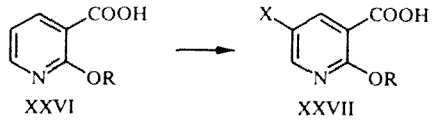


Moles of Br_2, time (h), yield (%) of (XVIII, XX, XII): 1, 3, 87, 5, 3; 2, 0.5, 43, 39, 18).

5-Chloro-3-hydroxypyridine also forms three compounds (XXIII, XXIV, XXV) after 1 h with NaOCl in aqueous sodium hydroxide [40]:

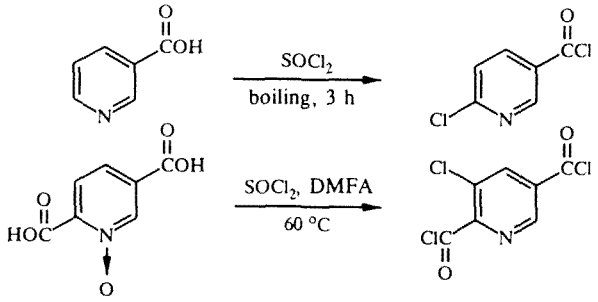


Nicotinic acid derivatives (XXVI) are converted with good yields (61-84%) into compounds (XXVII), containing chlorine or bromine atoms at position 5, by the action of sodium hypochlorite or hypobromite for 16-48 h at 20°C [38, 60-62].

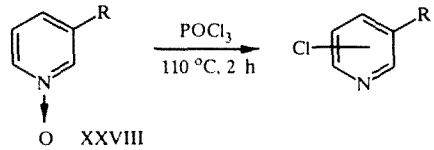


X = Cl, Br; R = H, Me, Et

Together with substitution of the hydrogen atoms in the ring by chlorine atoms, the action of heat on nicotinic acid derivatives in the presence of thionyl chloride converts the —COOH group into a —COCl group [63, 64]:



In addition to chlorination in the heterocyclic ring, deoxidation of the initial compounds takes place during the action of phosphorus oxychloride on derivatives of pyridine N-oxide [65, 66]:

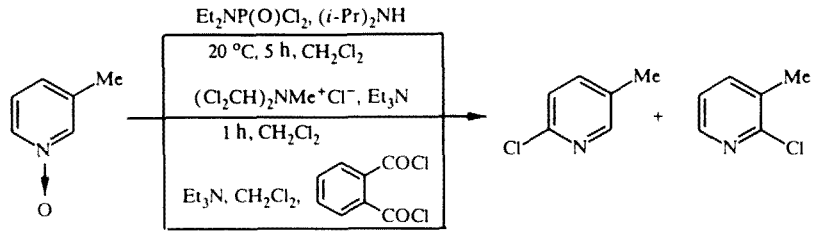


R, total yield (%), position of Cl, yield on total (%): H, 82, 2, 70, 4, 30; CN, 83, 2, 88, 6, 10, 4, —; COOH, 75, 2, 86, 6, 14; $CONH_2$, 69, 2, 86, 6, 12, 4, 2; $CONEt_2$, 93, 2, 80, 6, 20; COOEt, 93, 2, 80, 6, 20; NO_2, 68, 2, 73, 6, 27; Cl, 74, 2, 47, 6, 38, 4, 15; Br, 77, 2, 64, 6, 46, 4, 8; Me, 77, 2, 30, 6, 27, 4, 43; Ph, 84, 2, 32, 6, 46, 4, 22; Me_2, 80, 2, 34, 6, 47, 4, 19 [65]; Me, 2, 15, 6, 81 (in CH_2CH_2 at −10°C, 2.5 h in the presence of i-Pr_2NH) [66]

2-Amino-3-cyano-5-(4-pyridyl)pyridine N-oxide was converted by the action of phosphorus oxychloride in DMFA into 6-chloro-2-amino-3-cyano-5-(4-pyridyl)pyridine [67].

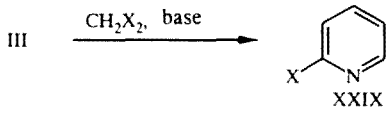
The introduction of a chlorine atom and the removal of an oxygen atom are observed during the treatment of 3-methylpyridine N-oxide with the acid chloride CF_3SO_2Cl in the presence of triethylamine in methylene chloride, when 5-chloro-3-methylpyridine is formed with a yield of 48% [68].

Several methods have been described for the transformation of 3-methylpyridine N-oxide into a mixture of 2-chloro-5-methylpyridine and 2-chloro-3-methylpyridine, i.e., by the action of $Et_2NP(O)Cl_2$ (total yield 83%, ratio of isomers 85:15) [69], by reaction with $(Cl_2CH)_2NMe_2{}^+Cl^-$ (total yield 80%, ratio of isomers 77:23) [70], and by treatment with phthaloyl chloride (total yield 85%, ratio of isomers 84:16) [71]:



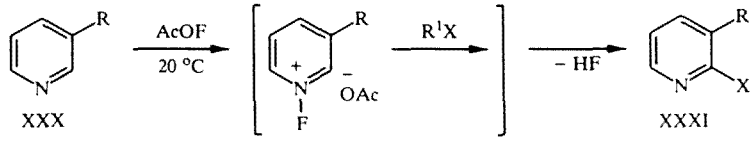
2-Bromopyridine was obtained with a 10% yield by the reaction of pyridine with F_3CBr in the presence of iodine at 600°C [72].

An unusual method for the introduction of chlorine or bromine atoms is the treatment of N-fluoropyridinium triflate (III) with bases in the respective dihalogenomethane at 20°C for 5-10 min, as a result of which 2-halogenopyridines (XXIX) were obtained [73]:



Base, X, yield (%): Et_3N, Cl, 62; Et_2NH, Cl, 63; MeONa, Cl, 25; Me_3COK, Cl, 35; $PhCH_2N^+Me_3OH^-$ (3 h), Cl, 34; Et_3N, Br, 60

In another original method for the transformation of pyridine derivatives containing substituents at position 3 (XXX) into the 2-halogeno-substituted compounds (XXXI), acetyl hypofluorite (formed *in situ* from F_2 and sodium acetate) and alkyl halides are used as reagents [74, 75]:



R, R^1X, yield (%): H, CH_2Cl_2, 70; 4-Me, CH_2Cl_2, 70; 3-Me, CH_2Cl_2, 15 (+15% 6-Cl); 3-Cl, CH_2Cl_2, 80; 3-PhO, CH_2Cl_2, 80; 3-COOMe, CH_2Cl_2, 60; 3-F, CH_2Cl_2, 40; H, CH_2Br_2, 60; 3-Cl, CH_2Br_2, 80; 4-MeO, CH_2Br_2, 60 [74]; H, CH_2Cl_2, 70; Me_3CCl, 20; H, CH_2Br_2 (or CH_3Br), 50...60; 4-Me, CH_2Cl_2, 60; 3-Cl, CH_2Br_2, 80 [75]

The course of these reactions is affected by the basicity of the pyridine derivatives, the solvent (alkyl halide), and by steric effects. The halogenated products were not obtained when chloroform, carbon tetrachloride, and butyl chloride were used as alkyl halides. The reaction does not occur with compounds (XXX) where R = 2-CN, 2-Cl, or 3,5-Cl_2. It is not possible to use methyl iodide or methylene iodide in this process — oxidation processes with the release of iodine occur [75].

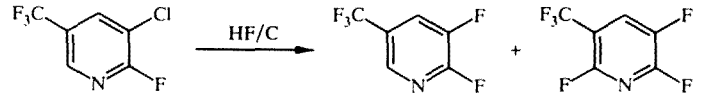
The reaction of pyridine with AcOF in a mixture of methylene chloride and methylene bromide gave a 1:1 mixture of 3-chloropyridine and 3-bromopyridine. (There are two competing factors, i.e., the small size of CH_2Cl_2 and the strength of the bonds: C—Cl > C—Br.) The reaction of pyridine with AcOF in chlorobromomethane leads to a 2:3 mixture of 3-chloropyridine and 3-bromopyridine. In this case a major role is played by the fact that the C—Cl bond is stronger than the C—Br bond [75].

1.2. Exchange of Halogens in Halogenopyridines

The substitution of halogens directly attached to the carbon atoms of the pyridine ring by other halogens has either a radical mechanism (at high temperatures) or a nucleophilic mechanism (promoted by the use of polar solvents).

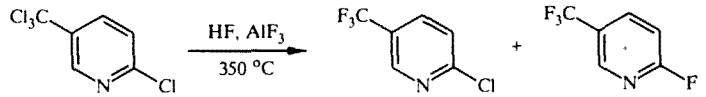
Processes involving the substitution of chlorine atoms by fluorine atoms have been worked out in greatest detail. 2-Chloropyridine was converted into 2-fluoropyridine with a 94% yield by heating with hydrogen fluoride in γ-collidine at 150-200°C while the released hydrogen chloride was removed [76]. The reaction of 2-chloropyridine with potassium fluoride in benzonitrile in the presence of tetraphenylphosphonium bromide at 200°C in an autoclave for 10 h gave 2-fluoropyridine with 88% selectivity and 82% conversion [77].

The chlorine derivative (XXXII) was converted by the action of hydrogen fluoride over active carbon at 508°C for 12-15 sec into compound (XXXIII) with a yield of 15.3% [78]. At 525°C and with a considerably longer reaction time (5.5 h) the chlorine derivative (XXXII) reacts with hydrogen fluoride in the presence of active carbon to form a mixture of compounds (XXXIII) (yield 20.7%) and (XXXIV) (yield 9.4%) [79].



XXXII XXXIII XXXIV

2-Chloro-5-(trichloromethyl)pyridine treated with hydrogen fluoride in the presence of aluminum trifluoride gives a mixture of compounds (XXXV, XXXVI) in a ratio of 71.4:28.6 with an overall yield of 89.6% [80]:

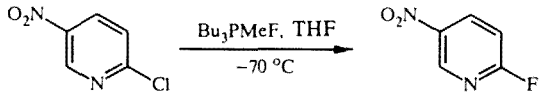


XXXV XXXVI

If potassium fluoride is used instead of hydrogen fluoride in the reaction with 2-chloro-5-(trichloromethyl)pyridine, only compound (XXXVI) is obtained with a yield of 77% (reaction temperature 142°C, time 8 h, in the presence of $Me_3N^+C_{16}H_{33}Br^-$) [81].

The transformation of 3-fluoro-2,5-dichloropyridine into 2,3-difluoro-5-chloropyridine takes place with a yield of 88% in reaction with potassium fluoride in the presence of cesium fluoride in sulfolane at 140°C [82].

An unusual fluorinating agent was used by the authors in [83] for the production of 5-nitro-2-fluoropyridine:



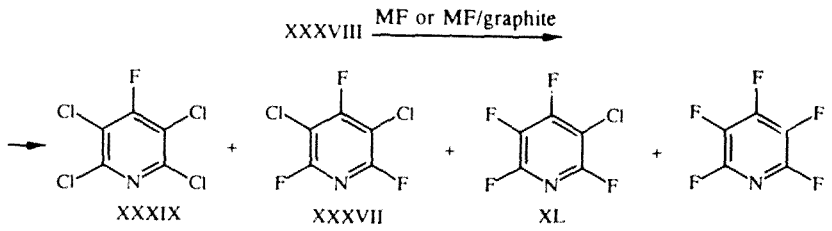
The synthesis of 2,4,6-trifluoro-3,5-dichloropyridine was conducted under various conditions with the use of potassium fluoride [84, 85] or hydrogen fluoride [86]:

XXXVIII XXXVII

Conditions, yield (%): (complex of acetonitrile with 18-crown-6, potassium fluoride, boiling, 2 h in acetonitrile under nitrogen), 60 [84]; KF ($FeCl_3$, 300°C, 5h), 88.7 [85]; HF (220°C in N-methyl-2-pyrrolidone, under pressure), [86].

A mixture containing 83% of compound (XXXVII) and 4% of 2,4,5,6-tetrafluoro-3-chloropyridine was obtained as a result of the reaction of (XXXVIII) with potassium fluoride in the presence of ferric chloride at 300°C in an autoclave under nitrogen for 16 h [87].

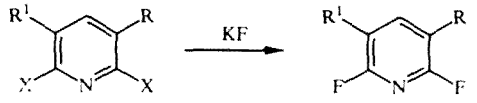
While studying the reaction of (XXXVIII) with potassium fluoride, cesium fluoride, potassium fluoride/graphite, or cesium fluoride/graphite, the authors in [88] established that only compound (XXXIX) (yield 8%) is formed when potassium fluoride is used; a mixture of compounds (XXXIX) and (XXXVII) (yields 32% and 5%) is formed with potassium fluoride/graphite; compounds (XXXIX, XXXVII, XL) and pentafluoropyridine (yields 39%, 4%, 9%, and 2% respectively) are formed with cesium fluoride/graphite:



M = K, Cs

The synthesis of pentafluoropyridine with a 75.8% yield by heating pentachloropyridine with potassium fluoride without a solvent at 330°C for 5 h is described in the patent [89].

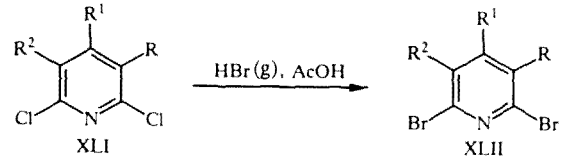
The substitution of the chlorine or bromine atoms by fluorine atoms [90] in the presence of potassium fluoride was studied in detail. As a rule the product yields were high during the substitution of chlorine by fluorine (200°C); the yield of the product from the substitution of a bromine atom by a fluorine atom (100°C) was significantly lower [90]:



X, R, R^1, reaction time (h), yield (%): Cl, Cl, Cl, 5, 77; Cl, H, Cl, 7, 72; Cl, H, Me, 328, 33; Cl, Cl, Me, 34, 69; Cl, H, CF_3, 1,5, 83...94; Br, H, NO_2, 24, 14

A case of the substitution of a fluorine atom in fluoropyridines by chlorine or bromine atoms by the action of calcium chloride or calcium bromide in sulfolane at 210°C was described [91].

The substitution of chlorine atoms by bromine atoms in compounds (XLI) by the action of hydrogen bromide at 80-120°C in acetic acid was investigated systematically, and the dibromo derivatives (XLII) were obtained (yields 70-93%) [91]:

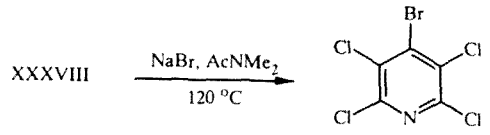


R, R^1, R^2, time (h): H, H, H, 9; Cl, H, H, 14; Cl, H, Cl, 12; NO_2, H, H, 4; NO_2, H, Cl, 4; CHO, H, H, 1,5; CHO, H, Cl, 6; COOH, H, H, 6; COOH, H, Cl, 6; CF_3, H, H, 4,5; NH_2, H, Cl, 12

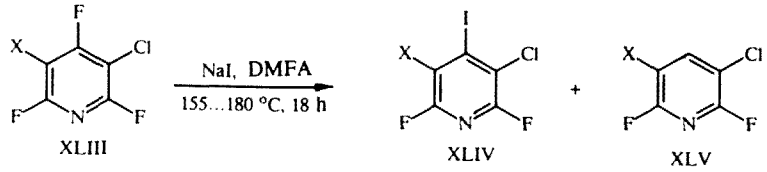
In one case 3,5-dichloro-2,4,6-tribromopyridine was obtained from compound (XXXVIII) (110°C, 21 h) with a yield of 72%. In the reaction of compounds (XLI) (R = CH_2Cl, R^1 = R^2 = H; R = CH_2Cl, R^1 = H, R^2 = Cl; R = CH_2Cl, R^1 = H, R^2 = NO_2, 110°C, 6-11 h) compounds (XLII), where R = CH_2Br, R^1 = R^2 = H, R = CH_2Br, R^1 = H, R^2 = Cl and R = CH_2Br, R^1 = H, R^2 = NO_2, are formed with yields of 95%, 94%, and 98% respectively [91].

2,6-Dichloropyridine was converted into a mixture of 2-chloro-6-bromopyridine (yield 5.5%) and 2,6-dibromopyridine (93.8%) by the action of hydrogen bromide in glacial acetic acid at 110°C for 7 h [92].

In pentachloropyridine heated with sodium bromide in DMAA at 120°C, one chlorine atom is substituted by a bromine atom (yield 39.7%, selectivity 96.7%) [93]:



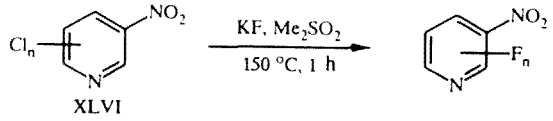
The reaction of perhalogenopyridines (XLIII) with sodium iodide in DMFA gives a mixture of two compounds: (XLIV) (the fluorine atom is substituted by an iodine atom) and (XLV) (the fluorine atom is substituted by a hydrogen atom) [94]:



XLIII XLIV XLV

X, yields (%) of (XLIV) and (XLV): F, 63 and 6; Cl, 65 and 4

The substitution of the chlorine atoms by fluorine atoms in chloronitropyridines (XLVI) heated with potassium fluoride in dimethyl sulfone gives yields of 55-85% [95]:

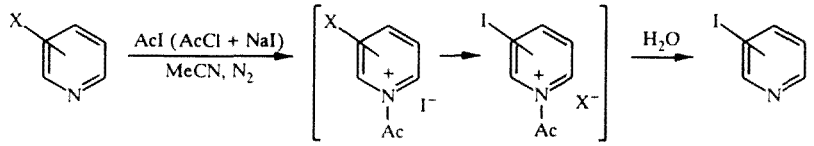


XLVI

Cl_n, F_n: 2,4-Cl_2, 2,4-F_2; 2,6-Cl_2, 2,6-F_2; 4,6-Cl_2, 4,6-F_2, 2,4,6-Cl_3, 2,4,6-F_3

In the case of compound (XLVI) (Cl_n = 2,5-Cl_2) 2-fluoro-2-chloropyridine is formed with an 80% yield [95].

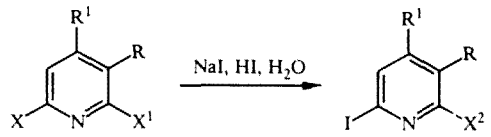
The chlorine or bromine atoms in the pyridine ring can be substituted by iodine atoms by the action of acetyl iodide (formed *in situ* from acetyl chloride and sodium iodide) [96]:



X, position of iodine, reaction time (h), yield (%): 2-Cl, 2, 24, 55; 2-Br, 2, 3, 64; 2,4-Cl_2, 2,4-I_2, 24, 35

This reaction could not be carried out with 2,6-dichloropyridine, 2-chloro-3-methoxypyridine, or 2-bromo-5-ethoxycarbonylpyridine [96].

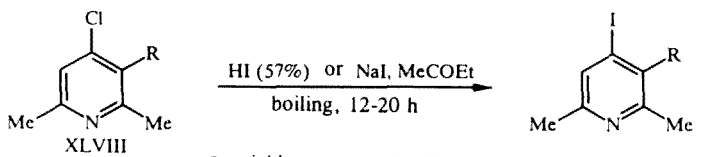
In the pyridine derivatives (XLVII) the chlorine or bromine atoms at positions 2 and 6 are substituted by iodine atoms when the compounds are boiled with a solution of sodium iodide in concentrated hydriodic acid [97]:



XLVII

X, X^1, R, R^1, X^2, yield (%): Cl, Cl, COOH, H, 51; Cl, H, COOH, H, H, 45; Br, Br, H, H, I, 55; Cl, CF_3, H, H, CF_3, 43; Cl, Cl, CF_3, H, H, 39; Cl, Cl, H, CF_3, I, 37

The chlorine atom at position 4 of compound (XLVIII) is substituted by an iodine atom when the compound is boiled with hydriodic acid or with sodium iodide in MEK [98, 99]:



XLVIII

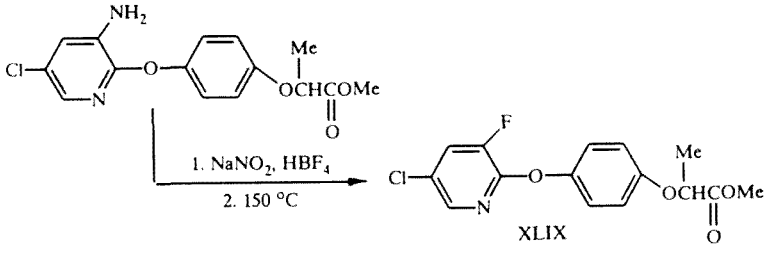
R, yield (%): NO_2, 83; COOEt, 62

As seen from the data in section 1.2, methods have been developed for the conversion of fluoropyridines into chloro-, bromo-, and iodopyridines, of chloropyridines into fluoro-, bromo-, and iodopyridines, and of bromopyridines only into iodopyridines.

1.3. Substitution of Amino Groups by Halogen Atoms

The substitution of amino groups situated directly at a pyridine ring by halogen atoms is achieved by the action of halogen-containing inorganic compounds on the diazonium salts formed as a result of the diazotization of the initial aminopyridines. An amino group at any position of the pyridine ring can be substituted by a fluorine atom by the action of sodium nitrite and fluoroboric acid. Thus, under these conditions 4-aminopyridine was converted into 4-fluoropyridine [100], and 2-amino-6-methylpyridine was converted into 2-fluoro-6-methylpyridine [101].

Compound (XLIX), which is a potential effective herbicide, was obtained with a 67% yield by substitution of an amino group by a fluorine atom [102]:

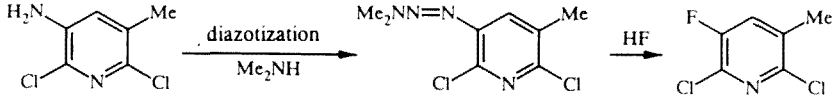


XLIX

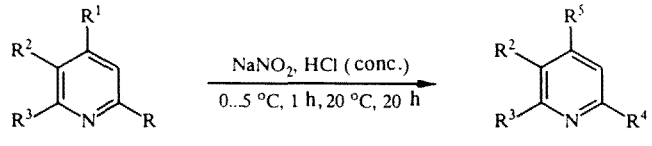
2-Bromo-3-fluoropyridine was obtained with a 15% yield by treating 2-bromo-3-aminopyridine with sodium nitrite, concentrated hydrochloric acid, and HPF_6 at −5-0°C [103].

3-Amino-2,5-dichloropyridine is converted into 3-fluoro-2,5-dichloropyridine with a higher yield (85%) by reaction with sodium nitrite and hydrofluoric acid in water [82].

An unusual method for the substitution of an amino group by a fluorine atom was patented in 1986 [104]:



Compounds (LI) containing two or three chlorine atoms were obtained with yields of 45-53% by the action of sodium nitrite and concentrated hydrochloric acid on the amino derivative (L) [95]:



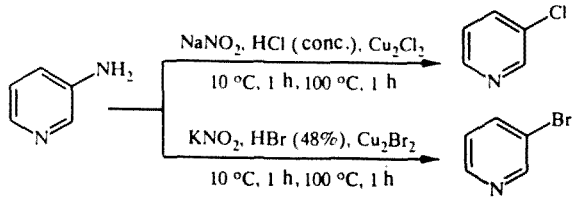
L LI

R, R^1, R^2, R^3, R^4, R^5: NH_2, Cl, NO_2, H, Cl, Cl; NH_2, H, Cl, H, Cl, H; Cl, NH_2, H, Cl, Cl, Cl

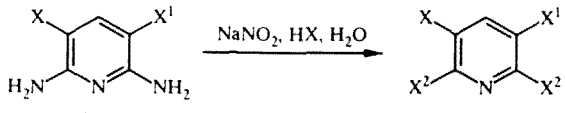
Under analogous conditions in the presence of metallic copper powder, 2-chloro-5-amino-3-methylpyridine was converted into 2,5-dichloro-3-methylpyridine (yield 62%), and 2-bromo-5-amino-3-methylpyridine and 2-bromo-3-amino-5-methylpyridine were converted into 2-bromo-5-chloro-3-methylpyridine or 2-bromo-3-chloro-5-methylpyridine with yields of 60% and 53% respectively [105, 106].

The treatment of 2-amino-5-methylpyridine with NOCl in water saturated with hydrogen chloride gives 5-methyl-2-chloropyridine (yield 94%) [107]. The latter was obtained from the same aminopyridine with a yield of 87% by the action of methyl nitrite or ethyl nitrite and hydrogen chloride in chlorobenzene [108] or with a yield of 86.1% by the action of methyl nitrite and hydrogen chloride in methanol [109].

3-Aminopyridine was converted into 3-chloropyridine (82-87%) or 3-bromopyridine (73-84%) with high yields by diazotization followed by treatment in the presence of copper salts [110]:



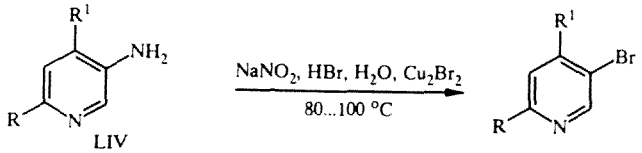
2,3,5,6-Tetrahalogenopyridines (LII) were obtained by the treatment of 2,6-diamino-3,5-dihalogenopyridines (LIII) with sodium nitrite and the respective hydrohalic acids [39]:



LIII LII

X, X^1, X^2, yield (%): Cl, Cl, Cl, 45; Cl, Cl, Br, —; Cl, Br, Br, —; Br, Br, Br, 65; Br, Br, Cl, —; Br, Cl, Cl, —; H, Cl, Cl, —

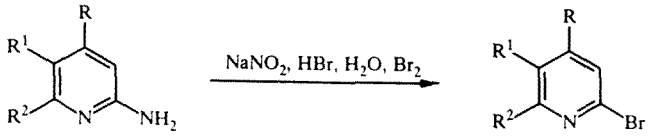
The amino group in 3-aminopyridines (LIV) was substituted by bromine by the action of sodium nitrite and hydrobromic acid in the presence of Cu_2Br_2 [99, 111]:



LIV

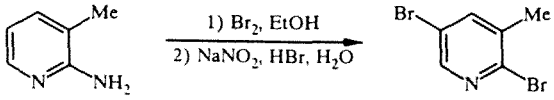
R, R^1, yield (%): COOH, H, 82 [111]; Me, Me, 56 [99]

During the diazotization of aminopyridines with sodium nitrite and hydrobromic acid in the presence of bromine, only substitution of the amino group by a bromine atom is observed [111, 112]:

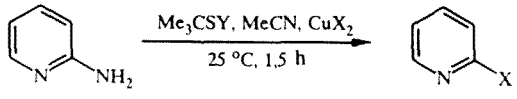


R, R^1, R^2, yield (%): H, NO_2, H, 67 [111]; Me, H, Me, — [112]

2-Amino-3-methylpyridine was converted into 2,5-dibromo-3-methylpyridine in two stages, i.e., by the action of bromine in alcohol followed by treatment of the bromination product with sodium nitrite and hydrobromic acid [113]:

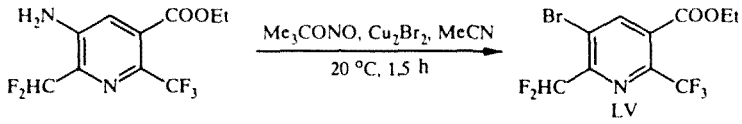


Japanese investigators developed an original method for the substitution of an amino group by halogen atoms by the action of Me_3CSNO or Me_3CSNO_2 in acetonitrile in the presence of copper salts in an atmosphere of argon [114]:



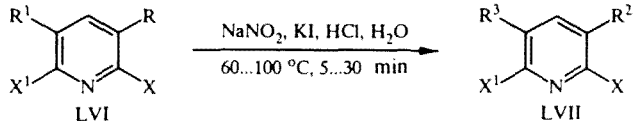
Y, X, yield (%): NO, Cl, 35; NO, Br, 7; NO_2, Cl, 64; NO_2, Br, 13

Other authors [115] used Me_3CONO instead of Me_3CSNO; the yield of the reaction product (LV) here was 91%:



LV

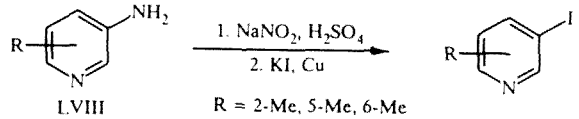
A series of derivatives of 3-aminopyridine (LVI) were converted into the corresponding 3-iodo derivatives (LVII) with yields of 62-92% by reaction with sodium nitrite and potassium iodide in the presence of hydrochloric acid [98, 105, 106, 111]:



LVI LVII

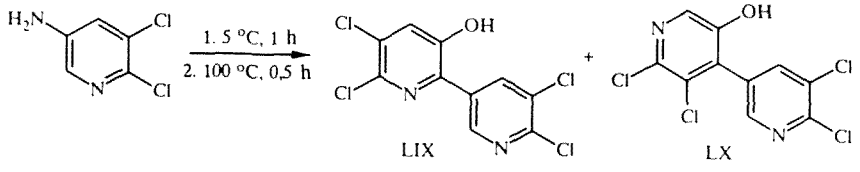
X, X^1, R, R^1, R^2, R^3: Cl, H, NH_2, H, I, H [98]; Cl, H, Me, NH_2, Me, I; H, Cl, Me, NH_2, Me, I [105]; Br, H, Me, NH_2, Me, I; H, Br, Me, NH_2, Me, I [106]; COOH, H, H, NH_2, H, I [111]

The amino group in the amino derivatives of picolines (LVIII) is substituted by an iodine atom during diazotization with sodium nitrite and sulfuric acid followed by treatment of the obtained diazonium salts with potassium iodide in the presence of copper (yields 16-45%) [116]:



LVIII R = 2-Me, 5-Me, 6-Me

Derivatives of bipyridyl (LIX, LX) were obtained in a ratio of 3:2 with an overall yield of 74% by the successive treatment of 5-amino-2,3-dichloropyridine first with sodium nitrite in water and sulfuric acid under argon, and then by the action of sulfuric acid (water) and copper sulfate [40]:



LIX LX

1.4. Substitution of Oxygen-Containing Functional Groups by Halogen Atoms

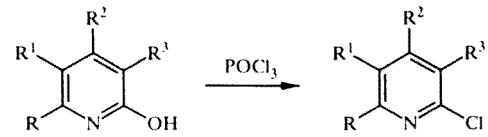
A fairly widely used method for the production of halogenopyridines is substitution of hydroxyl or alkoxyl groups at a pyridine ring by the action of the halogen derivatives of sulfur or phosphorus.

Substitution of a hydroxyl group by a chlorine atom in the pyridine ring can be achieved by the action of thionyl chloride in DMFA. Thus, the hydroxyl group in 5-chloro(bromo)-2-hydroxynicotinic acid [38] or in 2-hydroxy-3-cyano-4-methoxymethyl-5-nitro-6-methylpyridine [117] is easily substituted by a chlorine atom by the action of thionyl chloride in DMFA.

2-Hydroxy-5-nitro-3-methylpyridine is converted by the action of phosphorus tribromide at 130°C into 2-bromo-4-nitro-3-methylpyridine with a yield of 37.9% in 2 h [63].

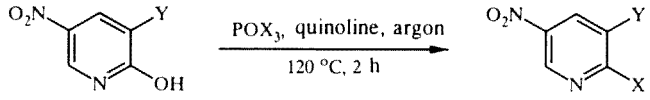
The most widely used method for the substitution of oxygen-containing functional groups by a chlorine atom in the pyridine ring is by the action of phosphorus oxychloride [57, 65, 118-123]. This transformation can be achieved by boiling with phosphorus oxychloride [65, 120] or by heating with phosphorus oxychloride at 190°C in sealed tubes for 4 h; the yields are 70-91% [121-123].

2,3,5-Trichloropyridine was obtained with a yield of 89.9% by heating 3,4-dichloro-2-hydroxypyridine with phosphorus oxychloride in DMFA at 150°C for 1 h [57].



R, R^1, R^2, R^3: H, COOH, H, H [65]; H, Ph, Ph, H [120]; H, Cl, H, Cl [121]; Me, Cl, H, Cl; Et, Cl, H, Cl; Pr, Cl, H, Cl [122]; H, Cl, H, Me; Me, H, H, Me [123]

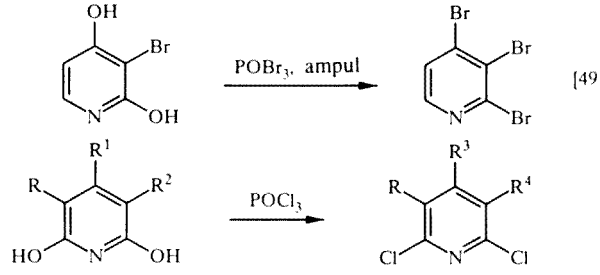
Phosphorus oxybromide has been used as well as phosphorus oxychloride for the substitution of a hydroxyl group by halogen [40]:



X, Y, yield (%): Cl, Cl, 98; Br, Cl, 90; Cl, Br, 94

2-Hydroxy-5-nitro-3,4-dimethylpyridine is converted into 2-chloro-5-nitro-3,4-dimethylpyridine with a yield of 81.5% in the reaction with phosphorus oxychloride and phosphorus pentachloride at 110-120°C for 8 h [63].

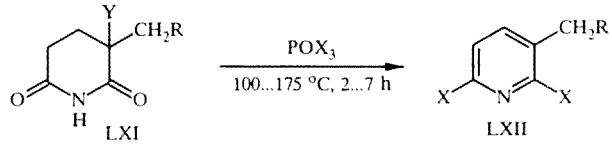
It is possible to substitute two or three hydroxyl groups by halogen atoms by the action of POX_3 (X = Cl, Br) [35, 49, 124]:



[49]

R, R^1, R^2, R^3, R^4, conditions: H, Cl_{1-3} alkyl, $CONH_2$, C_{1-3} alkyl, CN, 110-180°C, 6-24 h [35]; F, OH, $COOR^5$, H, COCl, in the presence of lithium phosphate [124]

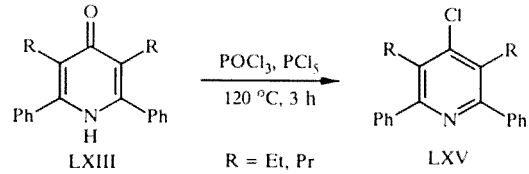
The action of POX_3 (X = Cl, Br) on compounds (LXI) with heat leads to aromatization at the same time as substitution of the oxygen atoms by halogen atoms; as a rule, the yields of the reaction products LXII are good [125-128]:



LXI LXII

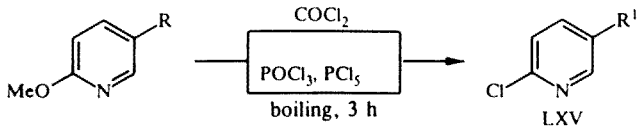
R, X, Y: Cl, Cl, Cl [125]; Br, Br, Br [126]; Ph, Cl, Cl [127, 128]; 4-MeC_6H_4, Cl, Cl; 4-$MeOC_6H_4$, Cl, Cl; 4-ClC_6H_4, Cl, Cl; 4-FC_6H_4, Cl, Cl; 3-$CF_3C_6H_4$, Cl, Cl; 4-$O_2NC_6H_4$, Cl, Cl; 2-MeOOC, Cl, Cl; 2,5-$Cl_2C_6H_3$, Cl, Cl; 3,4-$Cl_2C_6H_3$, Cl, Cl; 2-Me, 4-$NO_2C_6H_4$, Cl, Cl; 2-CF_3, 5-$NO_2C_6H_4$, Cl, Cl; 3-O_2N, 4-ClC_6H_4, Cl, Cl; 3-pyridyl , Cl, Cl; 2-Cl- 3-pyridyl , Cl, Cl; 2,6-Cl_2- 3-pyridyl , Cl, Cl; 2-MeOOC-3- 2-thienyl Cl, Cl [128]

The transformation of γ-pyridones (LXIII) into chloropyridines (LXIV) was achieved by heating with a mixture of phosphorus oxychloride and phosphorus pentachloride; the yields were 85-90% [129]:



LXIII R = Et, Pr LXV

The possibility of substituting alkoxyl radicals in the pyridine ring by chlorine atoms by the action of either phosgene [130, 131] or a mixture of phosphorus oxychloride and phosphorus pentachloride [132] with the formation of compounds (LXV) was reported.

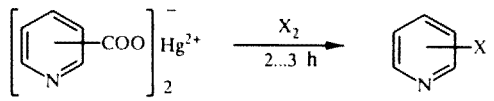


LXV

R, R^1, yield (%): CH_2OH, CH_2Cl, — [130]; CHO, $CHCl_2$, 80 [131]; CH_2OMe, CH_2Cl, 45 [132]

5,6-Dichloronicotinic acid is decarboxylated in reaction with bromine in the presence of mercuric oxide, and the reaction product is 3-bromo-5,6-dichloropyridine [133].

When heated with bromine or iodine, the mercury salts of pyridinecarboxylic acids undergo decarboxylation with the formation of the corresponding bromopyridines or 3-iodopyridines [134]:



LXVI

X = Br, I

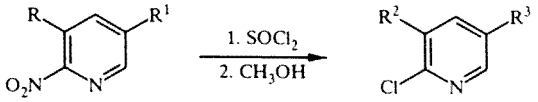
The reaction of a salt of nicotinic acid with bromine at 180-185°C gave a 27% yield of 3-bromopyridine, while reaction for 17 h gave a yield of 48%. A salt of nicotinic acid and bromine at 150-160°C gave 2-bromopyridine with a yield of 3%.

In the reaction of nicotinic acid with bromine or iodine in the presence of mercuric oxide in nitrobenzene (180-185°C, 15 h) the yields of 3-bromopyridine and 3-iodopyridine were 21% and 50% respectively. With the thallium salts of nicotinic acid, the yield of 3-bromopyridine amounted to 8% (165°C, 2 h), and the yield of 3-iodopyridine amounted to 9% (180-185°C, 2 h). The reaction does not occur with isonicotinic acid [134].

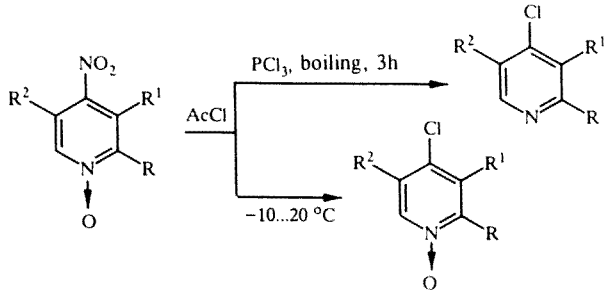
1.5. Substitution of Other Groups by Halogen

The reaction of 2,5-dichloro-3-nitroaminopyridine with boron trifluoride in acetic acid or with boron trifluoride etherate results in the formation of 2,5-dichloro-3-fluoropyridine [135].

A nitro group in the pyridine ring can be substituted by a chlorine atom by the action of thionyl chloride [63] or acetyl chloride [65, 136]:

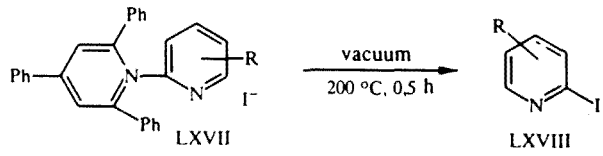


R, R^1, R^2, R^3, yield (%): Me, COOH, Me, COOMe, 26,7; COOH, Me, COOMe, Me 13,8 [63]



R, R^1, R^2, yield (%): H, $CONEt_2$, H, 94 [65]; Me, Me, Me, — [136]

When the salt (LXVII) is heated the pyridinium radical is substituted by an iodine atom, and the iodine derivative (LXVIII) is formed [137]:

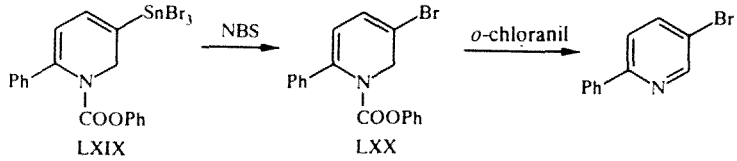


LXVII LXVIII

R, yield (%): H, 75; 3-Me, 71; 4-Me, 62

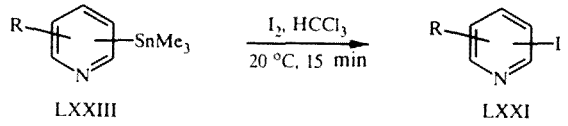
An original method for the synthesis of pentabromopyridine, patented in 1975, involves heating the pentahydrate of the pentasulfopyridine sodium salt with phosphorus pentabromide at 210-220°C for 4 h [138].

The treatment of compound (LXIX) with N-bromosuccinimide followed by aromatization of the obtained product (LXX) with *o*-chloranil gave an 87% yield of 3-bromo-6-phenylpyridine [139]:



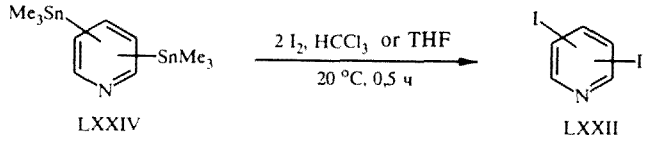
LXIX LXX

A series of monoiodo derivatives (LXXI) (yields 75-78%) or diiodo derivatives (LXXII) (yields 80-91%) were obtained by the action of iodine on mono(trimethylstannyl)-substituted (LXXIII) or bis(trimethylstannyl)-substituted (LXXIV) pyridine bases [140].



LXXIII LXXI

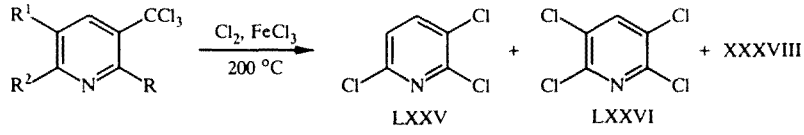
R, position of $SnMe_3$(I): H, 2; H, 3; H, 4; 2-Me, 4; 2,6-Me_2,



LXXIV LXXII

Positions of $SnMe_3$(I): 2,3; 2,4; 2,5; 2,6; 3,4; 3,5

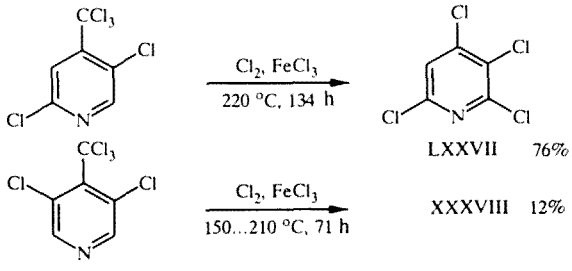
The CCl_3 group situated at position 3 of the pyridine ring can be substituted by a chlorine atom by the action of chlorine in the presence of ferric chloride with the formation of trichloropyridine (LXXV), tetrachloropyridine (LXXVI), and pentachloropyridine (XXXVIII) [141-143]:



LXXV LXXVI

R, R^1, R^2, yield (%) LXXV, LXXVI and XXXVIII: Cl, H, Cl, —, 40,5 [141]; Cl, Cl, H, mixture of Cl, Cl, H+H, H, Cl + Cl, Cl, Cl, 38,1, 40,1, 4,7 [142]; H, H, H, —, —, — [143]

A CCl_3 group at position 4 of the pyridine ring can be substituted by the action of chlorine in the presence of ferric chloride under analogous conditions. Thus, 2,5-dichloro-4-trichloromethylpyridine and 3,5-dichloro-4-trichloromethylpyridine are converted into compounds (LXXVII) and (XXXVIII) respectively [144]:



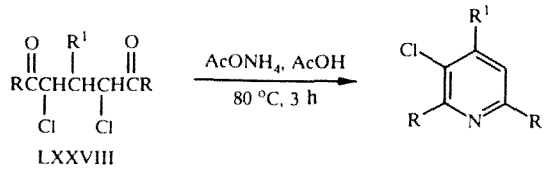
LXXVII 76%

XXXVIII 12%

2. SYNTHESIS OF HALOGENOPYRIDINES BY CYCLIZATION REACTIONS

One of the classical methods for the synthesis of compounds of the pyridine series is the cyclization of bifunctional compounds containing these functions at specific mutual positions — dicarbonyl compounds, ketonitriles, dinitriles, and certain other compounds.

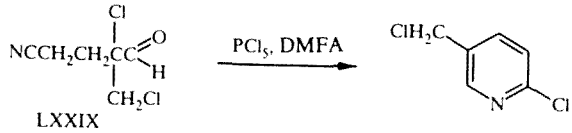
Derivatives of pyridine containing a chlorine atom at position 3 are obtained with high yields (80-92%) by heating compound (LXXVIII) with ammonium acetate in acetic acid [145]:



LXXVIII

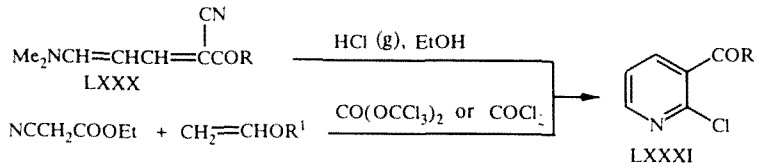
R, R^1: Ph, H; 4-ClC_6H_4, H (45 h); Ph, Me; Ph, Ph

The aldehyde (LXXIX) undergoes cyclization to 2-chloro-5-chloromethylpyridine when treated with phosphorus pentachloride in DMFA [146]:



LXXIX

The functionally substituted dienes (LXXX), which are the products from the reaction of β-(dimethylamino)acrolein with $NCCH_2COOEt$ [147] or $NCCH_2CONMe_2$ [148], were converted by the action of hydrogen chloride into the pyridine derivatives (LXXXI) with yields of 88% or 72%; compound (LXXXI) (R = COOEt) was also obtained from $NCCH_2COOEt$ and $CH_2{=}CHOR^1$ in a single stage with a yield of 69% [148]:

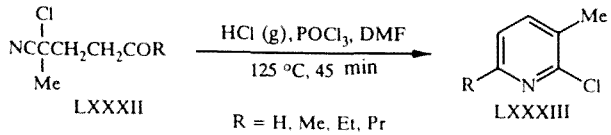


LXXX

LXXXI

R = COOEt [147], $CONMe_2$ [148]; R^1 = Et, Me_2CHCH_2 [148]

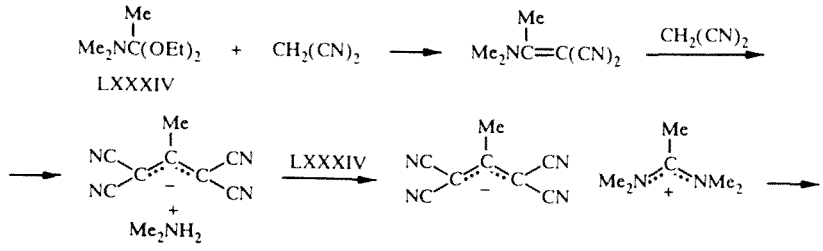
The oxonitriles (LXXXII) undergo cyclization to the pyridine derivatives (LXXXIII) (yields 76-88%) when treated with hydrogen chloride and phosphorus oxychloride in DMFA at 125°C [123]:

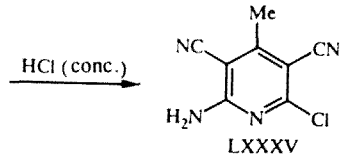


LXXXII

LXXXIII

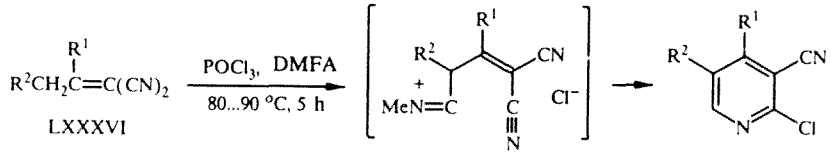
The reaction of the acetal (LXXXIV) with malononitrile in the presence of concentrated hydrochloric acid results in the formation of compound (LXXXV) with a yield of 94% [149]:





LXXXV

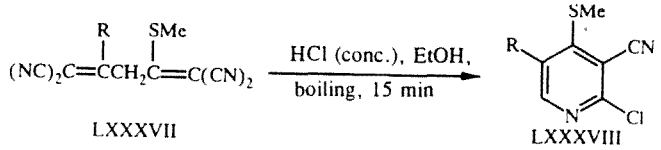
The corresponding derivatives of pyridine were obtained with 15-23% yields when the dinitriles (LXXXVI) were heated with phosphorus oxychloride in DMFA [150]:



LXXXVI

R^1, R^2 = H, Me; H, Et; Me, Me; Et, Me

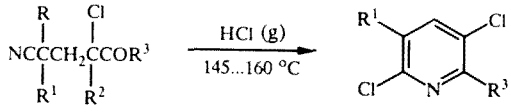
The cyclization of the tetranitriles (LXXXVII) takes place readily and smoothly with the formation of compound (LXXXVIII) (yields 61-81%) when they are boiled with concentrated hydrochloric acid in alcohol [151].



LXXXVII LXXXVIII

R: Ph, 4-ClC_6H_4, 4-MeC_6H_4

The chlorine-substituted pyridines (LXXXIX) were synthesized by the cyclization of the ketonitriles (XC) with gaseous hydrogen chloride [123, 152-154]:

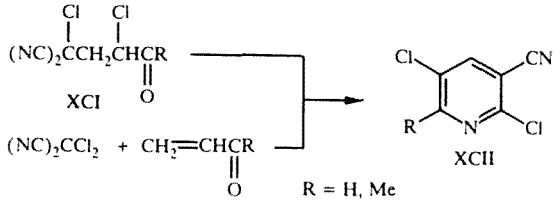


XC LXXXIX

R, R^1, R^2, R^3, yield (%): H, H, Cl, Me, 50 [152]; H, H, Cl, Me, — [153]; Cl, COOMe, H, H, 42; Cl, COOMe, H, Me, 50; Cl, COOEt, H, H, 35; Cl, COOEt, H, Me, 58 [154]; Cl, Me, H, H, 83; Cl, Me, H, Me, 90; Cl, Me, H, Et, 79; Cl, Me, H, Pr, 82 [123]

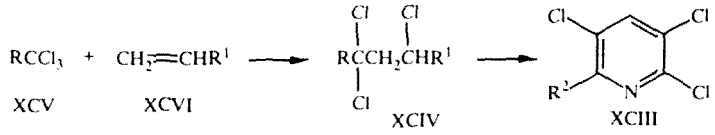
The cyclization can be conducted in alcohol [151] and DMFA [123]; the highest yields of the cyclization products were obtained in the presence of phosphorus oxychloride [123].

During distillation the adduct (XCI) (R = H), obtained from $(NC)_2CCl_2$ and acrolein, is converted into 2,5-dichloro-3-cyanopyridine (XCII) (R = H) with a yield of 37%; the adduct (XCI) (R = Me) undergoes cyclization to 2,5-dichloro-3-cyano-6-methylpyridine with a yield of 58% when gaseous hydrogen chloride is passed into it in the presence of phosphorus oxychloride in DMFA at 115°C for 15 min. The same pyridine derivatives are formed with yields of 31% and 51% when mixtures of $(NC)_2CCl_2$ and acrolein or methyl vinyl ketone are heated at 100°C in acetonitrile in the presence of Cu_2Cl_2 [155]:



XCII

A convenient method for the synthesis of 2,3,5-trichloro-6R-pyridines (XCIII) (yields 79-95%) is the cyclization of the adducts (XCIV), formed from the trichloro derivatives (XCV) and the unsaturated compounds (XCVI) [121, 122, 156, 157]:

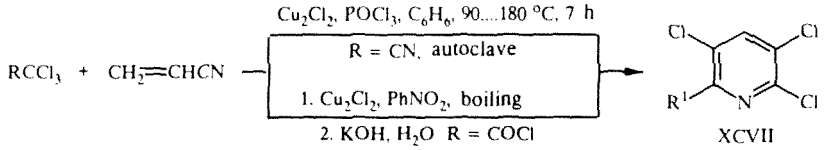


XCV XCVI XCIV XCIII

R, R^1, R^2: CN, Ac, Me; CN, EtCO, Et; CN, PrCO, Pr [122]; CN, CHO, H [121]; Ac, CN, Me; Cl_3CO, CN, CCl_3, [90]; PhCO, CN, Ph; 4-HOC_6H_4CO, CN, 4-HOC_6H_4 [156]; ArOCO, CN, ArO [157]

The cyclization of the adducts (XCIV) was conducted by the action of gaseous hydrogen chloride in organic solvents at 0-130°C for 45-60 min [156, 157] and, in some cases, in the presence of phosphorus oxychloride [121, 122] or phosphorus pentoxide [122].

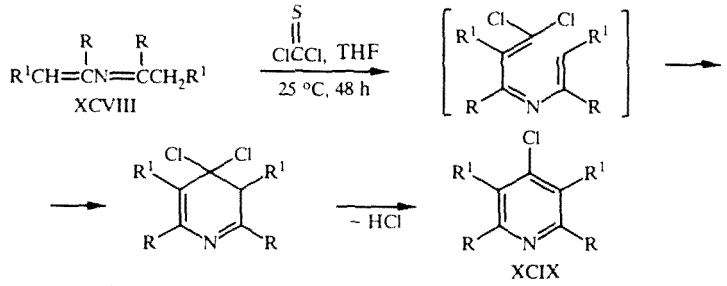
The synthesis of the pyridines (XCVII) (yields 62.5-95%) was realized directly from the trichloro derivatives (XCV) (R = CN, COCl) and acrylonitrile under the conditions indicated below [121, 158, 159]:



XCVII

R, R^1: CN, H [121]; COCl, OH [158]; COCl, OH [159]

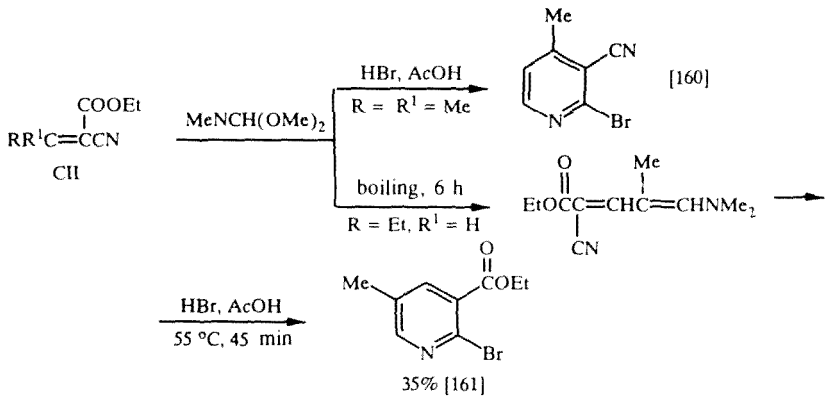
The reaction of the heterodienes (XCVIII) with thiophosgene in THF at normal temperature gave 57-62% yields of the derivatives of 4-chloropyridine (XCIX) [129]:



XCVIII XCIX

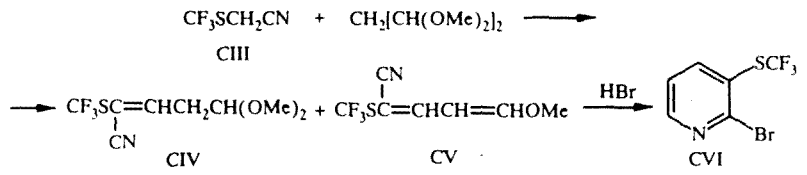
R, R^1: Ph, Me; Ph, Et; 4-MeC_6H_4, Me; Ph, $CH_2{=}CH(CH_2)_2$; Ph, Ph

Various compounds (C, CI) are formed from the alkylidene derivatives of cyanoacetic ester (CII) and DMFA dimethyl acetal using compounds (C) with various R and R^1 groups [160, 161]:



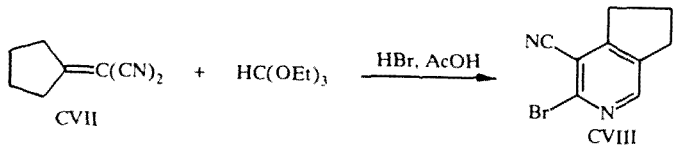
CII [160] 35% [161]

The reaction of the nitrile (CII) with malonaldehyde gives two unsaturated compounds (CIV, CV), which are converted by the action of HBr into one and the same product (CVI) with a yield of 16% [162]:

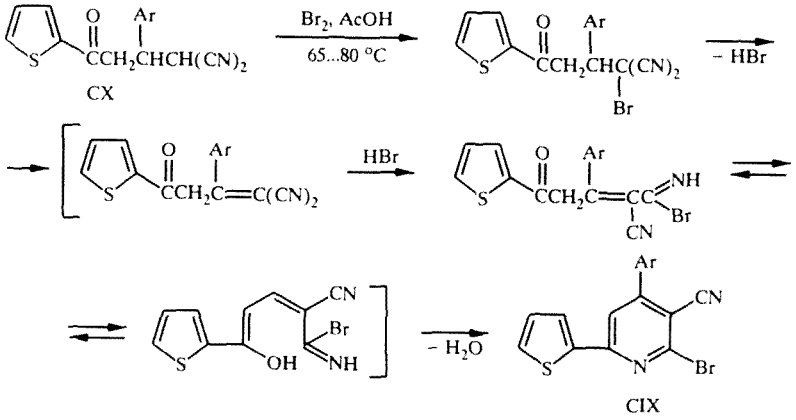


In some papers, gem-dinitriles were used as starting compounds in the synthesis of monobromo derivatives of the pyridine series.

During the condensation of the dinitrile (CVII) with the ortho ester $HC(OEt)_3$ in the presence of HBr in acetic acid, the bicyclic compound (CVIII) is formed with a yield of 15% [163]:

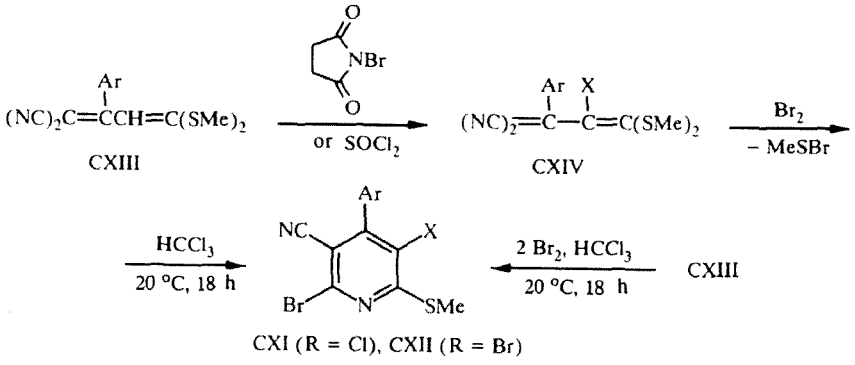


Derivatives of *o*-bromo-2-(2-thienyl)pyridine (CIX) were synthesized (with yields of 69-86%) by heating the dinitrile (CX) with bromine in acetic acid. The authors [163] propose the following scheme for this process:



Ar: Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$

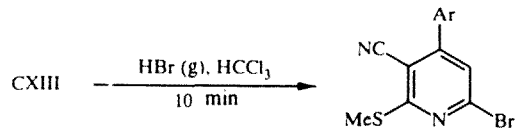
A series of chlorine and bromine derivatives (CXI, CXII) were obtained by the cyclization of dienes containing two geminal cyano groups (CXIII, CXIV) under the influence of bromine [164, 165] or hydrogen bromide [166]. The authors [164, 165] describe the process by the following scheme:



CXI (R = Cl), CXII (R = Br)

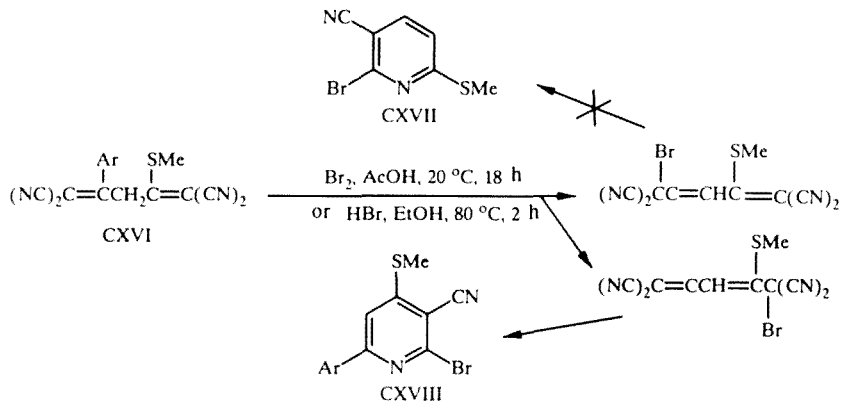
Ar, X, yield (%) from CXIII and CXIV: Ph, Cl, 44 and 69; Ph, Br, 73 and 51; 4-ClC_6H_4, 70 and 79; 4-$MeOC_6H_4$, Br, 39 and — [164]; Ph, Br, — and 73; 4-ClC_6H_4, Br, — and — [165]

Gaseous hydrogen bromide was used for the cyclization of the dienes (CXIII). As a result compounds (CXV), differing from (CXI) and (CXII), were obtained with yields of 85-96% [166]:



Ar : Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$

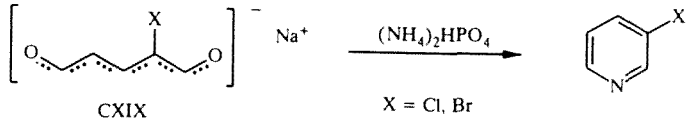
The formation of two types of compounds (CXVII) or (CXVIII) could be expected in the reaction of the tetracyanodienes (CXVI) with bromine or HBr. By using ^{13}C NMR spectroscopy, the authors [151] established that only compound (CXVIII) was formed:



R, yield (%), with Br_2 and HBr: Ph, 64 and 39; 4-ClC_6H_4, 85 and —; 4-MeC_6H_4, — and 26

The reaction of the dienes (CXVI) in boiling concentrated hydrochloric acid for 15 min leads to the corresponding 2-chlorine derivatives with yields of 61-81% [151].

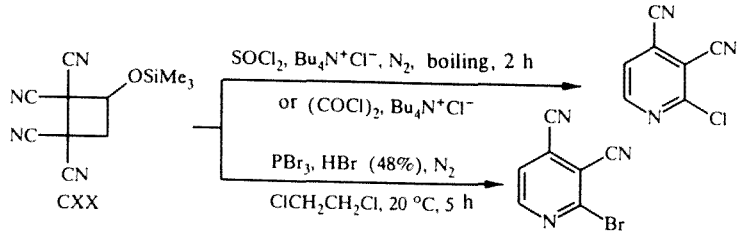
Steam distillation of the sodium salts (CXIX) in the presence of diammonium hydrogen phosphate gave 3-chloropyridine (yield 31%) or 3-bromopyridine (yield 17%) [167]:



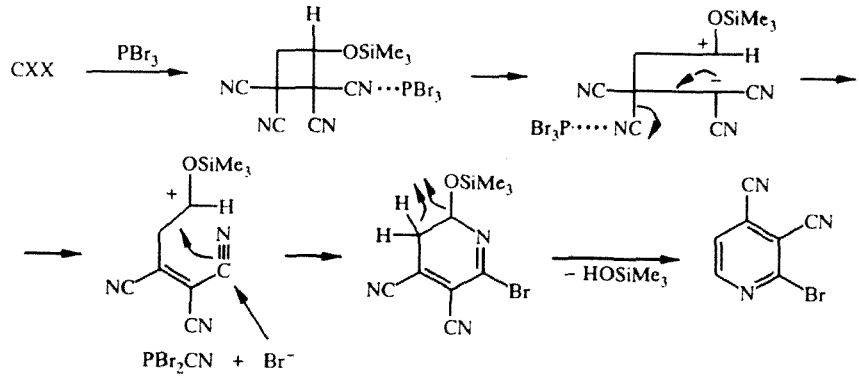
Published data on the synthesis of chloropyridines based on trichloroacetonitrile were summarized in the review [168].

3. SYNTHESIS OF HALOGENOPYRIDINES BY RECYCLIZATION REACTIONS

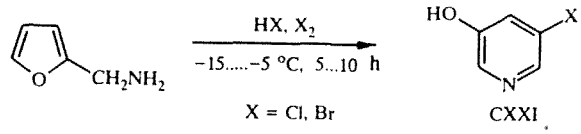
In reaction with $SOCl_2$ or $(COCl)_2$ under the conditions of phase-transfer catalysis, the cyclobutane derivatives (CXX) are converted into 2-chloro-3,4-dicyanopyridine (yield 40%), while under the influence of phosphorus tribromide and concentrated hydrobromic acid they give 2-bromo-3,4-dicyanopyridine (yield 45%) [169, 170]:



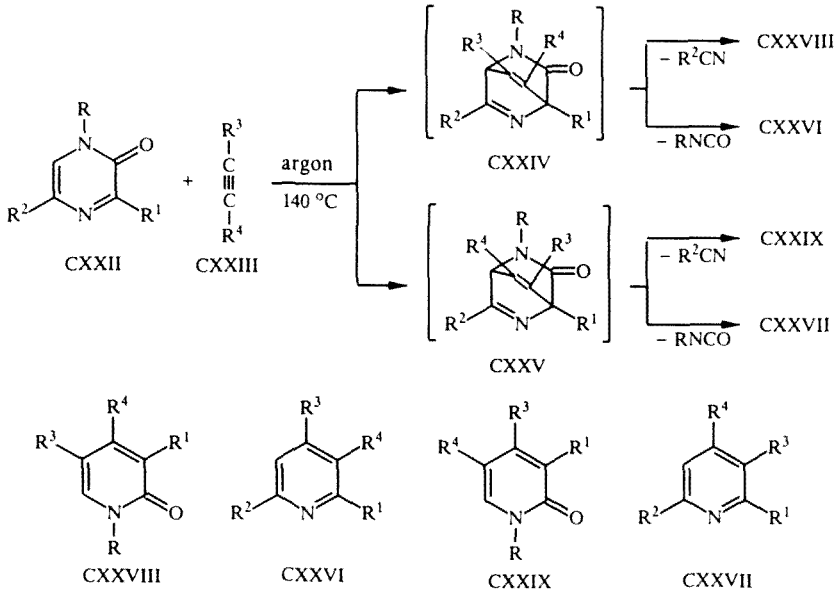
For the case of the reaction with phosphorus tribromide, the following scheme was proposed for the transformation of compound (CXX) into pyridine derivatives [169]:



During the slow addition of hydrohalic acids and halogens to 2-aminomethylfuran at low temperature 3-halogeno-5-hydroxypyridines (CXXI) are formed with yields of 70-80% [171]:



As a result of the diene synthesis of cyclic heterodienes (CXXII) with the alkynes (CXXIII), the adducts (CXXIV) or (CXXV) are formed. Under the reaction conditions they dissociate and give compounds of the pyridine series (CXXVI) or (CXXVII) and the pyridone series (CXXVIII) or (CXXIX) [172]:

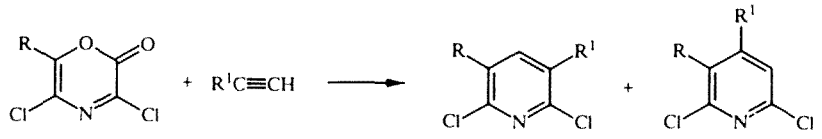


R, R^1, R^2, R^3, R^4, total yield (%), ratio of (CXXVI + CXXVII) : (CXXVIII + CXXIX):
Ph, CN, Cl, H, Ph, 99, 2,5 : 1; Ph, Cl, Cl, H, Ph, 75, 1,6 : 1; Ph, OMe, Cl, H, Ph, 36, 0,55 : 1; Ph, CN, Cl, H, COOEt, 95, 3,7 : 1; Ph, OMe, Cl, H, COOEt, 69, 0,5 : 1; Ph, CN, Cl, COOMe, COOMe, 75, 30 : 1; Ph, Cl, Cl, COOMe, COOMe, 83, 5 : 1; Ph, OMe, Cl, COOMe, COOMe, 92, 5,5 : 1; Me, CN, Cl, COOMe, COOMe, 59, 0,8 : 1

In [173] the same authors continued their research in this region and brought the heterodienes (CXXI[I]) (where R = Me, Ph, 4-MeC_6H_4, R^1 = Cl, CN, OMe, R^2 = Cl) into reaction with dimethyl acetylenedicarboxylate, ethyl propiolate, and phenylacetylene. Compounds (CXXVI-CXXIX) were obtained with total yields of 27-91%.

In reaction with acetylene with or without a solvent, the derivatives of 1,4-oxazin-2-one (CXXX) undergo recyclization and are converted into the dichloro derivatives (CXXXI, CXXXII). The authors [174, 175] used two methods: 1) heating a

mixture of equivalent amounts of the initial compounds in toluene at 80°C for 2.5-72 h (yields 85-98%); 2) heating compounds (CXXX) with an excess of $R^1C{\equiv}CH$ at 80°C for 1.5-16 h (yields 89-95%).

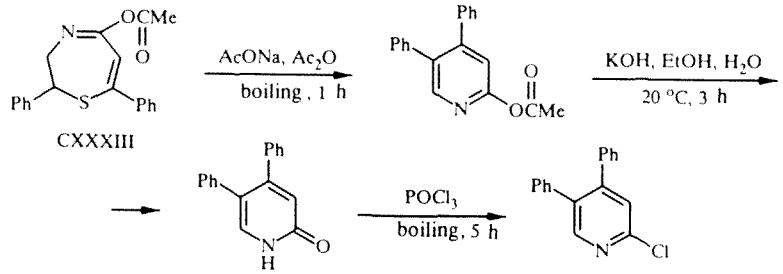


CXXX CXXXI CXXXII

R, R^1, method, (CXXXI):(CXXXII) ratio, reaction time (h): H, CH_2Br, 1), >20 : 1, 3; Me, CH_2Br, 1), 20 : 1, 6; Et, CH_2Br, 1), >20 : 1, 7; Me_2CH, CH_2Br, 1), >20 : 1, 9; $PhCH_2$, CH_2Br, 1), 20 : 1, 6; $CHCl_2$, CH_2Br, 1), 20 : 1, 2,5; CH_2Cl, CH_2Br, 1), 7 : 2, 3; Me, Me, 1), 20 : 1, 14; Me, $PhCH_2CH_2$, 1), 20 : 1, 15; Me, Me_3C, 1), >20 : 1, 72; Me, COOEt, 1), 1 : 1, 24; Me, COOEt, 2), 4 : 1, 3; Me, OEt, 1), 2 : 1, 16; Me, Ph, 1), 4 : 1, 18; Me, Ph, 2), 6 : 1, 2; Me, 3,4,5-$(MeO)_3C_6H_2$, 1), 10 : 1, 4; H, Ph, 2), 20 : 1, 1,5; $PhCH_2$, Ph, 2), >20 : 7; CH_2Cl, Ph, 2), 10 : 1, 7; $CHCl_2$, Ph, 2), >20 : 1, 1,7; H, COOEt, 2), 3 : 1, 1,5; $CHCl_2$, COOEt, 2), 4 : 1, 3; COOMe, COOEt, 2), 4 : 1, 6 [175]

2,6-Dibromo-3-methyl-5-phenylpyridine was obtained with a 65% yield by the reaction of 3,5-dibromo-2-methyl-1,4-oxadiazine with phenylacetylene at 80°C for 20 h [174].

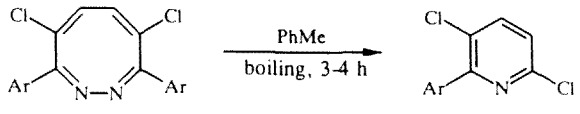
Japanese researchers [120] have described the production of 2-chloro-4,5-diphenylpyridine starting from the 1,4-thiazepine derivative (CXXXIII):



CXXXIII

When the 4,7-dichloro derivatives of 1,2-diazocine are heated, they undergo thermal recyclization, resulting in the formation of 2,5-dichloropyridine [176-178].

When boiled in dry toluene or heated at 160-165°C without a solvent the symmetrically substituted 1,2-diazocines (CXXXIV) are converted into 2,5-dichloro-6-arylpyridines (CXXXV) [176]:

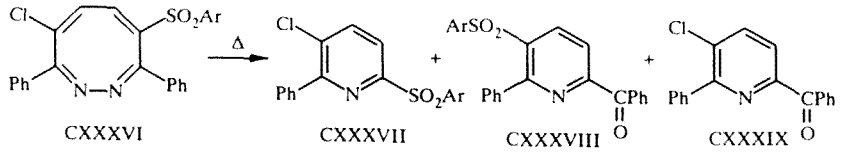


CXXXIV CXXXV

Ar, yield (%): Ph, 70 (without PhMe, 82%); 4-MeC_6H_4, 41,5; 4-ClC_6H_4, 70

If the diazocine (CXXXIV) (Ar = Ph) is boiled in moist toluene, 3-chloro-2-phenyl-6-benzoylpyridine (yield 25%) is formed together with 2,6-dichloro-5-phenylpyridine (yield 16%).

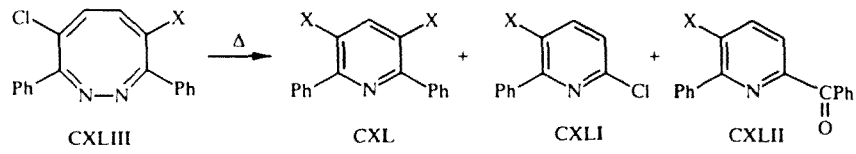
A mixture of three compounds (CXXXVII, CXXXVIII, CXXXIX) in various ratios was obtained as a result of boiling the 1,2-diazocine derivatives (CXXXVI) in toluene for 5 h [177]:



CXXXVI CXXXVII CXXXVIII CXXXIX

Ar, yield (%) CXXXVII, CXXXVIII and CXXXIX: Ph, 16,27 and 18; 4-MeC_6H_4, 19,12 and 22; 4-ClC_6H_4, 16,34 and 30

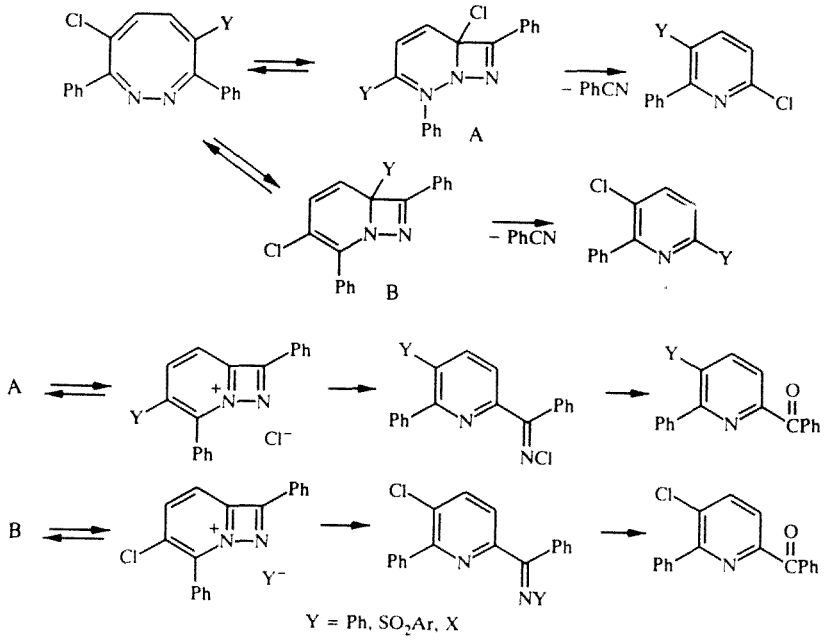
Likewise, three compounds each (CXL, CXLI, CXLII) are formed when solutions of the 1,2-diazocine derivatives (CXLIII) in xylene are boiled for 5 h [178]:



CXLIII CXL CXLI CXLII

X, yield of (CXL< CXLI, CXLII) (%): 1-succinimidyl, 35, 15, 8; 1-phthalimidyl,–, 42, 30; 1,2-$SO_2NCOC_6H_4$, 29, 9, 11 (+17% of 2,5-dichloro-6-phenylpyridine and 5% of 3-chloro-2-phenyl-6-benzoylpyridine)

The authors [177] suggest that the formation of all the compounds can be represented in the following way:



Y = Ph, SO_2Ar, X

After analysis of the presented material and also of the data in the reviews [1-4] it is possible to come to the unequivocal conclusion that the introduction of halogen atoms into the pyridine ring by substitution of the hydrogen atoms with various halogenating agents is the most widely used method for the synthesis of halogenopyridines. However, it should be noted that such reactions are often not regioselective and in most cases lead to mixtures of products. On the other hand, the method for the synthesis of halogenopyridines by the cyclization of bifunctional compounds is regioselective. By this method it is possible to synthesize compounds with the halogen atoms and other substituents at strictly specific positions in the pyridine ring. In contrast to other methods for the synthesis of halogenopyridines, acyclic compounds can be used in these reactions. An interesting and promising method for the synthesis of halogenopyridines is the recyclization of alicyclic and heterocyclic compounds with various ring sizes.

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