SELECTIVE CATALYTIC HYDROGENATION OF THE PYRIDINE RING IN ARYLPYRIDINES AND CONDENSED PYRIDINE SYSTEMS (REVIEW)

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Data are summarized concerning selective hydrogenation of the pyridine ring in arylpyridines, including those containing silicon, and in annelated pyridines. An effective catalyst, rhenium heptasulfide, has been found, which makes it possible to reduce the pyridine ring without affecting the benzene rings.

The hydrogenation of aromatic heterocycles has not lost its importance for organic synthesis. One of the key problems in this field is selective hydrogenation of condensed nitrogen-containing heterocyclic compounds. The molecules of many alkaloids (narcotine, emetine, salsoline, tylophorinine, etc.), contain a completely or partially hydrogenated pyridine ring. For their preparation, a strategy often providing simpler routes of synthesis of the corresponding completely aromatic compounds with subsequent selective hydrogenation of the specific nitrogen-containing ring appears very attractive. However, such an approach has virtually not had a methodological basis.

As a result of a systematic study of the catalytic properties of various sulfides carried out in the N. D. Zelinskii Institute of Organic Chemistry of the Russian Academy of Sciences [1], hydrogenating and N-alkylating (in the presence of alcohols) activity of rhenium heptasulfide with respect to pyridine [2], α-, β-, and γ-picolines, and 2,3-, 2,4-, 2,5-, 2,6-, and 3,5-lutidines [3-5] has been observed.

In the Russian University of People's Friendship, new syntheses of a number of physiologically active substances of various actions containing a pyridine ring have been developed [6, 7]; selective hydrogenation of these substances could afford some alkaloids and their analogs.

In the present review, we summarize the results obtained from our investigations and show that rhenium heptasulfide is an effective catalyst for selective hydrogenation of aryl-substituted pyridines, isoquinolines, indeno[2,1-c]pyridines, benzo- and dibenzoindolizines, and dihydrosilaazaanthracenes. Together with hydrogenating activity in the presence of alcohols, N-alkylation occurs on rhenium heptasulfide at the same time.

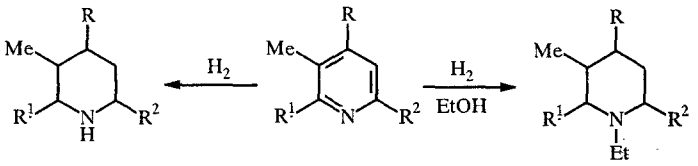
HYDROGENATION OF PHENYL-, BENZYL-, AND TRIORGANOSILYLPYRIDINES

The substances of the investigation were 2,5-dimethyl-4-phenyl- (I), p-methylbenzyl- (III), p-ethylbenzyl- (IV), triphenylsilyl- (VI), 3-methyl-2,6-diphenyl-4- (II), and 3-methyl-4-(dimethylphenylsilyl)pyrimidines (V). Hydrogenation was carried out in benzene in an autoclave under a hydrogen pressure of 130-200 atm at 200-280°C for 3-5 h in the presence of rhenium heptasulfide (5-10% with respect to the substance being hydrogenated). The hydrogenation products were recovered from the reaction mixture chromatographically. 2,5-Dimethyl-4-phenyl- (VII), p-methylbenzyl- (IX), p-ethylbenzyl- (X), and 3-methyl-2,6-diphenyl-4-benzylpiperidines (VIII) were obtained in 69-80% yields [8-13].

N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913. Russian University of People's Friendship, Moscow, 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1443-1450, November, 1992. Original article submitted January 23, 1992.

0009-3122/92/2811-1229$12.50

TABLE 1



VII-XII I-VI XIII, XIV

Starting compound	R	R^1	R^2	Solvent	mp, °C	P_{H_2}	Time, h	Reaction product	Yield, %*	Literature
I	Ph	H	Me	C_6H_6	270	95	6	VII	70	[9]
II	CH_2Ph	Ph	Ph	C_6H_6	240	135	6	VIII	69	[10]
III	$CH_2C_6H_4Me$-*p*	H	Me	C_6H_6	270	105	6	IX	69	[9]
IV	$CH_2C_6H_4Et$-*p*	H	Me	EtOH	250	120	6	X	78	[9]
V	$(Me)_2SiPh$	H	H	C_6H_6	250	130	6	XI	70	[13]
		H	H	EtOH	250	130	6	XIII	80	[13]
VI	$(Ph)_3Si$	H	Me	C_6H_6	250...300	140...260	5	XII	16	[13]
		H	Me	EtOH	300	140	3	XIV	80	[12]

*In presence of 10% Re_2S_7.

For the case of hydrogenation of pyridine base III, it was determined that with increasing temperature from 180 to 250°C, the yield of substituted piperidine IX increased from 69 to 99%. A significant effect on the yield of the hydrogenation products was exerted by the amount of the catalyst taken in the reaction. In the hydrogenation of compound III, the yield of piperidine IX was 38% in the presence of 1% catalyst and almost quantitative in the presence of 10% catalyst.

Platinum sulfide was found to be an active catalyst, but inferior to rhenium heptasulfide, for selective hydrogenation of pyridine III, and palladium sulfide was found to be significantly less active. In the series of these catalysts, Re_2S_7, PtS, and PdS, the yield of compound IX (hydrogenation under identical conditions) was 99, 92, and 39% [9].

In hydrogenation of 3-methyl-4-(dimethylphenylsilyl)pyridine (V), piperidine base XI was obtained in 70% yield. The recovery of 1,1,3,3-tetramethyl-1,3-diphenyldisiloxane in this case (20%) indicates simultaneous hydrogenolysis of the $Si-C_4$ bond.

The PMR spectrum of 3-methyl-4-(dimethylphenylsilyl)piperidine (XI) contained two singlet peaks of methyl groups bonded to the silicon atom at 0.28 and 0.33 ppm (ratio 1:1.5) and also two doublets at 0.75 and 1.03 ppm (ratio 1:1.5) of protons of methyl groups in the 3 position. This indicates that two isomers of 3-methyl-4-(dimethylphenylsilyl)piperidine (XI) were formed in the hydrogenation of the pyridine ring of compound V [13].

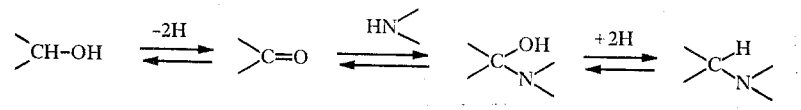
The hydrogenation of 2,5-dimethyl-4-(triphenylsilyl)pyridine (VI) at 250-300°C and a hydrogenation pressure of 260 atm (conditions under which pyridine bases I-IV are hydrogenated almost completely) occurred with difficulty. The starting compound was recovered from the reaction mixture in 75% yield, and 2,5-dimethyl-4-(triphenylsilyl)piperidine (XII) was obtained in 16% yield. It is possible that the stability of this substituted pyridine base under catalytic hydrogenation condition was related to steric factors due to the triphenylsilyl group and also to a decrease of the basicity of the pyridine ring in the presence of the electronegative effect of that group [13].

During reduction of pyridine, picolines [4, 5], and their silylated derivatives V and VI [11-13] in alcohols in the presence of rhenium heptasulfide, N-alkylation occurred at the same time as hydrogenation of the pyridine ring. 3-Methyl-1-ethyl-4-(dimethylphenylsilyl)- (XIII) and 2,5-dimethyl-1-ethyl-4-(triphenylsilyl)piperidines (XIV) were obtained in quantitative yields. According to data of PMR spectra, compound XIV was formed as a mixture of two geometric isomers. The N-alkylation reactions occurred similarly on PtS and PdS, but they were much less effective than Re_2S_7 [11-13].

Special attention has been devoted to investigation of this reaction, which has made it possible to obtain the corresponding N-alkylpiperidines in high yields from pyridine, picolines, and lutidines [5]. The presence of one or two substituents in the 2 and 6 positions virtually does not hinder the introduction of methyl and ethyl radicals at the nitrogen atom. This, in fact, should have been expected because it is known that the basicity of substituted pyridines increases in the presence of electron-donor groups. Steric factors begin to affect the alkylation of lutidines and picolines by secondary alcohols.

Approximately equal amounts of N-isopropyl-α-pipecoline (~52%) and its unsubstituted analog (48%) form during reductive alkylation of α-picoline in isopropyl alcohol. At the same time, isopropylation of β- and γ-picolines occurs virtually completely. It should be emphasized that the mentioned reactions could not be carried out in the presence of platinum and palladium sulfides.

The most probable mechanism of reductive alkylation of amines by alcohols in the presence of Re_2S_7 is redox according to the following scheme:



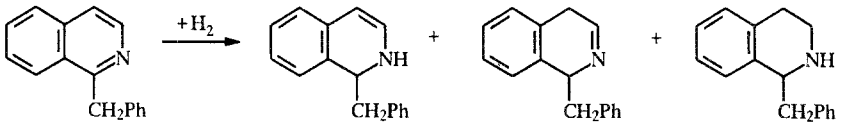
The stated assumption was confirmed by experiments in which the alkylating agent was tert-butyl alcohol. As expected, it was not possible to introduce an alkyl radical in α-, β-, and γ-picolines under those conditions. The possibility of reductive alkylation of p-phenylenediamine by ketones with formation of monoalkylation products in the presence of Re_2S_7 under close conditions was shown in [14].

2,5-Dimethyl-4-(triphenylsilyl)pyridine, having a bulky substituent in the 4 position, is hydrogenated with difficulty (10-15%), but it gives the corresponding N-ethylpiperidine (XIV) in 80% yield in ethanol. This result can also be considered as confirmation of the above-presented redox reaction scheme in the presence of alcohols.

Thus, rhenium heptasulfide is an effective catalyst for hydrogenation of the pyridine ring to a piperidine ring and reductive N-alkylation by alcohols in uncondensed systems containing pyridine and benzene fragments.

HYDROGENATION OF BENZYL(PHENYL)ISOQUINOLINES AND INDOLIZINES

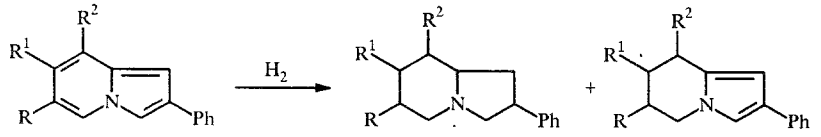
Hydrogenation of 2-benzylisoquinoline (XV) on Re_2S_7 occurs via a step of formation of 1,2- (XVI) and 1,4- (XIII) dihydro-1-benzylisoquinolines with preservation of the phenyl fragment of the benzyl substituent [15]. The position of the double bond in compounds XVI and XVII was determined according to PMR data.



XV XVI 2% XVII 13% XVIII 35%

For the cases of hydrogenation of 6-methyl-2-phenyl-7-benzyl- (XIX), 3,4-dimethylphenyl- (XX), and 3,4,5-trimethylphenylindolizines (XXI) and 2,8-diphenylindolizine (XXII), it was determined that only the indolizine system was

TABLE 2



XIX-XXII XXIII-XXV XXVI-XXVIII

Starting compound	R	R^1	R^2	Reaction product	Yield, %
XIX	Me	CH_2Ph	H	XXIII	40
XX	Me	3,4-$(Me)_2C_6H_3$	H	XXIV	1,8
			H	XXVI	14,0
XXI	Me	3,4,5-$(Me)_3C_6H_2$	H	XXVII	11,5
			H	XXV	3,4
XXII	H	H	Ph	XXVIII	71

Note. Conditions: 250°C, P_{H_2} 150 atm, time 4 h, and 10% Re_2S_7 [16].

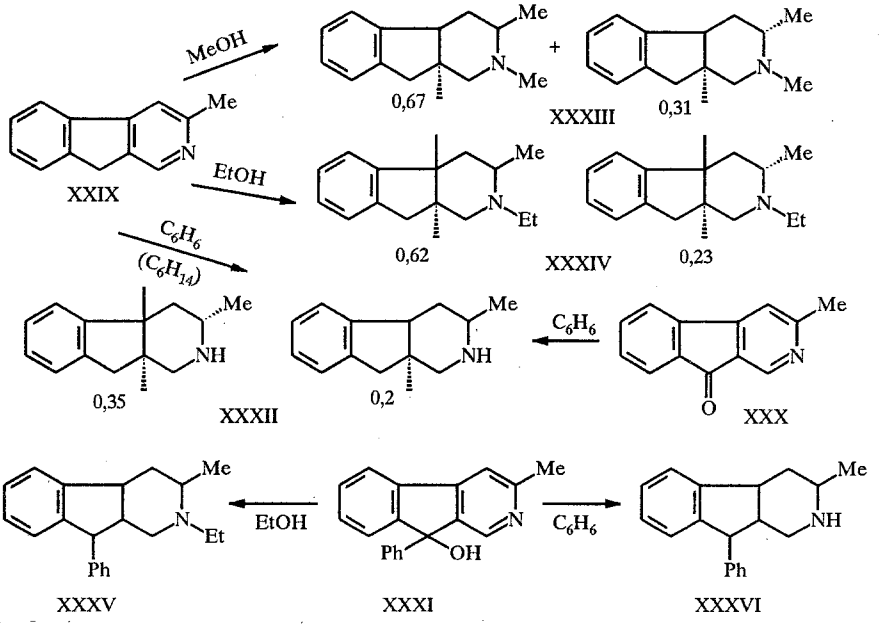
hydrogenated, with preservation of the phenyl groups of the substituents [16], with the yields of perhydroindolizines XXIII and XXVIII reaching 40 and 71%.

During hydrogenation of substituted indolizines XX and XXI, only the indolizine system was hydrogenated, but in each case analogously substituted tetrahydro- and perhydroindolizines were recovered in total yield 15-16%. From compound XX were obtained 5,6,7,8-tetrahydro-6-methyl-2-phenyl-7-(3,4-dimethylphenyl)indolizine (XXVI) and perhydroindolizine XXIV. In the case of compound XXI, tetrahydro derivative XXVII and perhydroindolizine XXV were obtained.

In the indolizine system, the five-membered ring is a pyrrole ring, and the six-membered ring has a pyridylindene structure. Taking that into account, we can assume that the six-membered ring, containing a conjugated diene system, should undergo hydrogenation because complete hydrogenation of the ring results in an aromatic pyrrole system. The obtained experimental data can serve as confirmation of such an assumption.

HYDROGENATION OF INDENO[2,1-c]PYRIDINES

For the case of a tricyclic condensed system of indenopyridines, in which the phenylene fragment is not condensed with the nitrogen-containing ring, a pattern of selectivity of hydrogenation on Re_2S_7 has been determined, namely, only the nitrogen-containing ring is hydrogenated, and the o-phenylene fragment is not affected [17, 18]. Such a direction of the reaction is preserved during hydrogenation of 3-methyl-2-azafluorene (XXIX) and the ketone corresponding to it XXX in benzene (hexane) and also in methanol (ethanol) when hydrogenation is accompanied by N-alkylation.



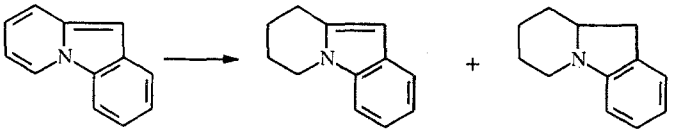
3-Methylindano[2,1-c]piperidine (XXII) was obtained during hydrogenation of compounds XXIX and XXX in neutral solvents, and 2,3-dimethyl- (XXXIII) and 3-methyl-2-ethylindano[2,1-c]piperidines were obtained during hydrogenation of azafluorenone XXIX in alcohols. Similar selectivity was also preserved in the case of hydrogenation of 3-methyl-9-phenyl-2-azafluoren-9-ol (XXXI). 3-Methyl-2-ethyl-9-phenylindano[2,1-c]piperidine (XXXV) was obtained during its hydrogenation in ethanol. Complete reduction of the functional group occurred during hydrogenation of ketone XXX and alcohol XXXI. 3-Methyl-9-phenyl-2-azafluorene (XXXVI) was recovered from the reaction products when hydrogenation of alcohol XXXI was carried out in benzene.

Compounds XXXII-XXXIV were obtained as a mixture of two isomers, which were recovered chromatographically in pure form. They were assigned a structure with trans linkage of piperidine and five-membered rings and different position of the methyl group in the 3 position.

Three pure geometric isomers were recovered from the products of hydrogenation of azafluorenol XXXI, but their structure was not determined.

HYDROGENATION OF BENZO- AND DIBENZOINDOLIZINES

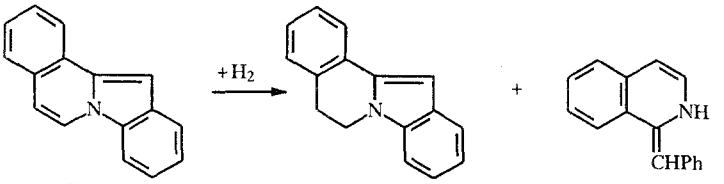
If we take into account the above-presented considerations about the 2(1H)-pyrrolopyrylidene structure of indolizine and also the selective hydrogenation of the nitrogen-containing ring in polycyclic condensed systems on Re_2S_7, we can expect that tetra- and hexahydro derivatives, i.e., products of hydrogenation of nitrogen-containing rings with preservation of the phenylene fragment, are formed during hydrogenation of benzo[b]indolizine (XXXVII). 1,2,3,4-Tetrahydrobenzo[b]indolizine (XXXVIII) and 1,2,3,4,4*a*,5-hexahydroindolizine (XXXIX) were recovered chromatographically from the reaction products [15].



XXXVII XXXVIII 42% XXXIX 24%

Tetrahydro derivative XXXVIII, whose molecule contains an aromatic indole fragment, was probably formed in the first step.

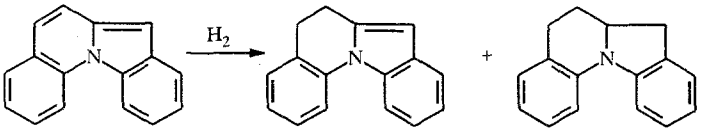
Similar patterns, i.e., hydrogenation of only nitrogen-containing rings and formation of compounds containing aromatic fragments, were determined during hydrogenation of dibenzo[b,g]indolizine (XL) and dibenzo[b,e]indolizine (XLIII) on Re_2S_7. 5,6-Dihydrobenzo[b,g]indolizine (XLI), containing indole and phenylene aromatic fragments, was obtained in 90% yield during hydrogenation of compound X. Here 1-benzylidene-1,2-dihydroisoquinoline (XLII) was recovered in insignificant (3%) yield. It was probably formed as a result of hydrogenolysis of the $N-C_{(3)}$ bond of the indolizine fragment.



XL XLI XLII

5,6-Dihydro- (XLIV) and 5,6,6*a*,7-tetrahydrodibenzo[b,e]indolizines (XLV) were obtained during hydrogenation of dibenzoindolizine XLIII.

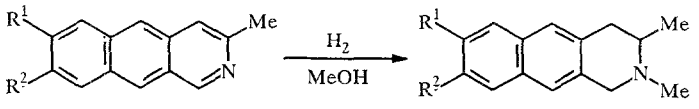
Thus, in this case also, the same selectivity and the same direction of hydrogenation occurred.



XLIII XLIV 40% XLV 16%

HYDROGENATION OF BENZO[g]ISOQUINOLINES

Hydrogenation of methyl-substituted benzo[g]isoquinolines XLVI-XLVIII in methanol ceased in the step of N-methylated tetrahydro derivatives [19]. We can assume that the resulting naphthalene fragment in this condensed system is just as resistant to hydrogenation as the phenylene one.

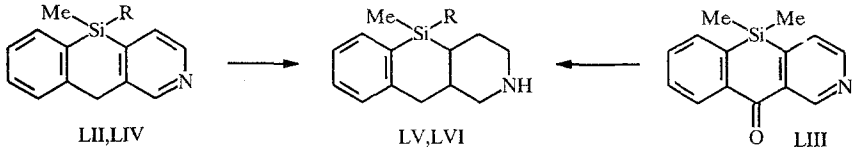


XLVI-XLVIII XLIX, L, LI 20%, 9%, 43%

XLVI, XLVII, XLIX, L R^1 = H; XLVIII, LI R^1 = Me; XLVI, XLIX R^2 = H; XLVII, XLVIII, L, LI R^2 = Me

HYDROGENATION OF 10,10-DIORGANOSILA-9,10-DIHYDRO-2-AZAANTHRACENES

For the case of this heterocyclic system, conclusions about the specific selectivity of Re_2S_7 were also confirmed during hydrogenation of nitrogen-containing heterocyclic compounds of various types. Hydrogenation of 10,10-dimethylsila- (LII) and 10-methyl-10-phenylsila- (LIV) 9,10-dihydro-2-azaanthracenes and silaazaanthrone (LIII) in the presence of Re_2S_7 in benzene was studied [13, 20].



LII,LIV LV,LVI LIII

LII, LV R = Me; LIV, LVI R = Ph

10,10-Dimethyl-1,2,3,4,4*a*,9,9*a*,10-octahydro-10-sila-2-azaanthracene (LV) was obtained from compound LII and also ketone LIII in ~60% yield, and analogous compound LVI was obtained from compound LIV in the same yield. In [20], it was shown that the piperidine fragment of compound LV has a fixed chair conformation and the tetrahydrosilaazanaphthalene fragment has a half-chair conformation, which is usual for cyclohexanes and tetrahydronaphthalenes. These rings are linked trans-diequatorially.

It should be noted that a decisive factor for carrying out all the above-mentioned reactions is the method of preparation of Re_2S_7 [1, 21]. An effective sample of Re_2S_7 was obtained by precipitation with hydrogen sulfide from a hydrochloric acid solution of ammonium perrhenate. The yield of rhenium heptasulfide was ~100%. The thus-obtained sample was characterized by various methods, i.e., chemical, x-ray photoelectron spectroscopy [22, 23], gravimetric, x-ray diffraction, and magnetic Faraday, by differential thermal analysis, and by IR and PMR spectroscopy [1, 21].

From an analysis of the physicochemical data, it is evident that there are acid centers on the catalyst surface. Of interest is the fact that platinum and palladium sulfides do not hydrogenate pyridine, but exhibit activity during hydrogenation of the pyridine ring in arylpyridines. This is possibly related to a change of the basicity of the starting compounds. Probably, Re_2S_7 is better able than platinum and palladium sulfides to bind protons on its surface during reduction, which probably plays an important role in the reduction of pyridine-containing molecules. Results obtained by IR spectroscopy were a confirmation of that: Pyridinium ions and coordinately bonded pyridine were observed on the catalyst surface after hydrogenation of pyridine [1]. Thus, the free electron pair of the nitrogen atom of the pyridine ring can react with the vacant orbital of a proton located on the surface of Re_2S_7 with formation of a pyridinium cation.

From the presented examples, it is evident that rhenium heptasulfide is a specific selective catalyst for hydrogenation of the pyridine ring in arylpyridines and condensed aromatic compounds. Its high efficiency was indicated by the preparation of a series of final substances in yields close to theoretical. Determination of the characteristics of the different directions and degree of hydrogenation of nitrogen-containing aromatic heterocycles in relation to their type and structure is of theoretical interest and deserves further study.

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