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CATALYTIC REDUCTION OF PYRIDINIUM, PYRYLIUM, AND THIOPYRYLIUM SALTS. (REVIEW)

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Published data and the results of the authors' own investigations on the synthesis of six-membered saturated N-, O-, and S-containing heterocycles by catalytic reduction of pyridinium, pyrylium, and thiopyrylium salts are reviewed. The conditions, laws, and special characteristics of the reactions are considered.

Keywords: piperidines, pyridinium salts, pyrylium salts, thiopyrylium salts, tetrahydropyrans, thiacyclohexanes, catalytic reduction.

At the present time the reduction of pyridinium salts and to a lesser degree their O- and S-heteroanalogs have been investigated quite widely. Reduction has been realized by the electrochemical method [1-6] or with metals [3, 4, 7, 8], dihydronicotinamide [9, 10], complex hydrides of metals [3, 7, 8, 11, 12], formic acid [13-15], and sodium dithionite [16] as reducing agents. As a rule the use of the indicated reducing agents leads to the products from partial reduction of the heterocycle, i.e., di- and tetrahydropyridines and dihydropyrans. The fully saturated heterocycles are formed with low yields and are often mixtures of isomers. The development of methods for the synthesis of this type of compound is an urgent task due to their widespread use in medicine, agriculture, and various branches of industry. Six-membered azaheterocycles have a wide range of biological activity [17, 18] and are structural fragments of natural alkaloids [19, 20] and herbicides [21]. Tetrahydropyrans have found use in the synthesis of polymers, perfumes, adhesives, greases, solvents, and intermediates in organic synthesis [22-24]. Saturated cyclic sulfides and their derivatives are used as model compounds during investigation of the composition of sulfur-containing oils, bitumens and coals, antioxidants, photomaterials, stabilizers of polymers, and universal solvents [25].

One of the methods for the synthesis of saturated six-membered N-, O-, and S-containing heterocycles is catalytic reduction of pyridinium, pyrylium, and thiopyrylium salts. The advantages of this method include stereoselectivity, the high product yields, and the use of a cheap reducing agent (molecular oxygen). Despite the significance of this method, there are no papers in the literature summarizing the results of investigations in this region. It is only necessary to mention the reviews [26, 27], in which the activating effect of the acid centers of the catalyst on the hydrogenation of the pyridine ring in arylpyridines and condensed pyridine systems was mentioned. The present review includes material illustrating the potentialities and prospects of the catalytic hydrogenation of pyridinium salts and their O- and S-containing heteroanalogs in the synthesis of saturated heterocycles. The stereochemistry of the latter compounds was described in detail, for example, in [28-35] and is not therefore considered in the present review.

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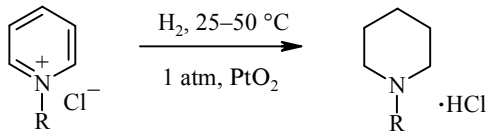
1. Catalytic Reduction of Pyridinium Salts

There are data in the literature on the catalytic reduction of pyridinium salts both under normal conditions and at elevated temperature and hydrogen pressure with various metals (Raney Ni, Pd/C, Ru/C, Rh/C, Ni/Ru) and their oxides (PtO_2, PtO, RuO_2, PdO) as catalysts. The direction of the reaction and its stereochemical effect depend on the number, nature, and character of substituents in the substrate and on the selected conditions.

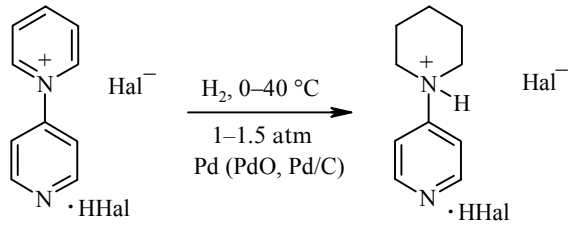
The catalytic reduction of pyridinium salts at platinum black (Adam's catalyst) for the production of N-substituted piperidines was first realized in 1928 [36]:



1a–i **2a–i**

1a, 2a R = H; **1b, 2b** R = C_2H_5; **1c, 2c** R = C_4H_9; **1d, 2d** R = C_6H_5; **1e, 2e** R = $CH_2C_6H_5$; **1f, 2f** R = CH_2COOH; **1g, 2g** R = $CH_2COOC_2H_5$; **1h, 2h** R = $(CH_2)_2OH$; **1i, 2i** R = $(CH_2)_3OH$

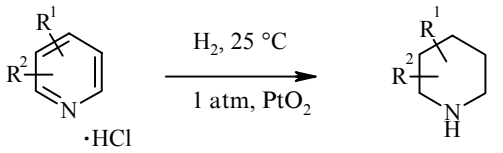
It was shown that increase in temperature from 25 to 50°C reduces the time required to complete the reaction to approximately a third, while the optimum substrate–catalyst ratio is 0.1 mol of the initial salt to 0.15 g of PtO_2. The best solvent is absolute ethanol. Pyridinium salts containing alkyl, aryl, and functionally substituted radicals at the nitrogen atom are reduced more readily than pyridinium hydrochloride. This fact is due to the existence of an equilibrium between the free base and the pyridinium salt in the solution, and here the free base, being adsorbed on the catalyst through the electron pair of the nitrogen atom, leads to deactivation and displaces the equilibrium toward the pyridine base [37, 38]. The results obtained in [39] also indicate that the quaternized pyridinium salts are reduced more readily than the unquaternized salts:



1j,k **2j,k**

1j, 2j Hal = Cl; **1k, 2k** Hal = Br

The papers [40-42] were devoted to study of the hydrogenation of pyridine hydrochlorides and their mixtures by shaking in a hydrogenation flask at room temperature and atmospheric pressure in absolute alcohol:



1a, 3a–6a **2a, 7a–10a**

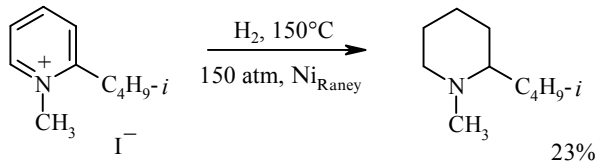
1a, 2a $R^1 = R^2 = H$; **3a, 7a** $R^1 = H$, $R^2 = 2\text{-}CH_3$; **4a, 8a** $R^1 = H$, $R^2 = 3\text{-}CH_3$; **5a, 9a** $R^1 = H$, $R^2 = 4\text{-}CH_3$; **6a, 10a** $R^1 = R^2 = 2\text{-}CH_3$

It was shown that the components in mixtures of the hydrochlorides of pyridine bases (pyridine–α-picoline, pyridine–β-picoline, pyridine–γ-picoline, pyridine–lutidine, α-picoline–lutidine) are reduced in succession; the homolog with the smallest number of substituents is hydrogenated first [41, 42]. For the 2-R-substituted pyridine hydrochlorides the hydrogenation rate (25°C, PtO_2, 1 atm) decreases in the following order [42]:

R=H	>	CH_3	=	$CH_2CH(OH)CH_3$	~	C_2H_5	~	C_3H_7	>	$CH_2C(OH)(CH_3)_2$	>	C_6H_5
1.00		0.57		0.57		0.54		0.52		0.36		0.30

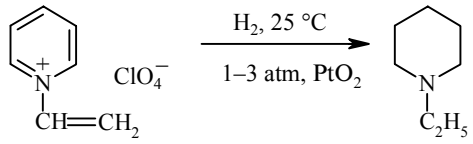
This effect of the substituents at the α-position is due to the steric effect resulting from hindrance of adsorption on the catalyst and, with R = C_6H_5, conjugation between the phenyl substituent and the pyridine ring.

If an isobutyl substituent is introduced at position 2 of the pyridine ring, the saturated product can only be obtained under harsh conditions (150°C, 150 atm, Ni_{Raney}) [43]:



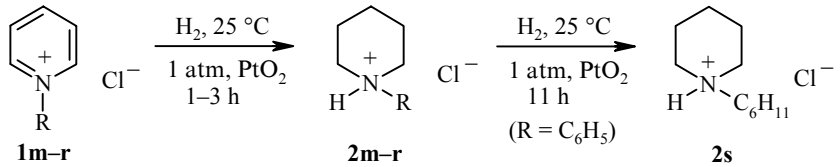
3b **7b**

In the N-vinyl-substituted pyridinium salt **1l** in Parr's apparatus under mild conditions (25°C, 1-3 atm, 90% ethanol) the heteroaromatic cation and the double bond of the substituent are reduced equally readily [44]:



1l **2l**

In the N-aryl-substituted pyridinium chlorides **1m-r** under similar conditions (25°C, atmospheric pressure, methanol, hydrogenation flask) the heterocycle is saturated first, and the benzene ring is then saturated, depending on the amount of catalyst and the duration of hydrogenation [45, 46]:

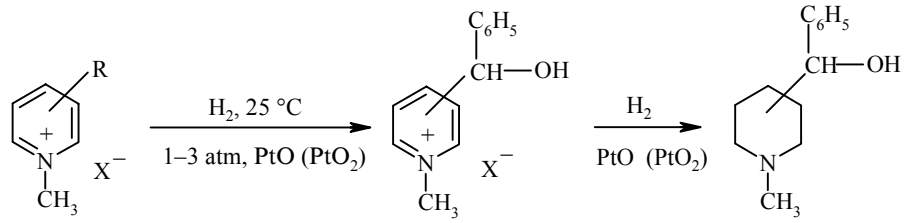


1m–r **2m–r** **2s**

1m, 2m R = C_6H_5; **1n, 2n** R = 4-$CH_3C_6H_4$; **1o, 2o** R = 4-$CH_3OC_6H_4$;
1p, 2p R = 4-$C_2H_5OOCC_6H_4$; **1q** R = 4-$O_2NC_6H_4$; **2q** R = 4-$H_2NC_6H_4$;
1r, 2r R = 4-(4'-C_6H_4)$C_6H_4NH_2$

Hydrogenation of the phenyl substituent is promoted by the strong electron-withdrawing effect of the ammonium group of the heterocycle [45]. Under selected conditions the nitro group of the chloride **1q** is transformed into an amine group [46].

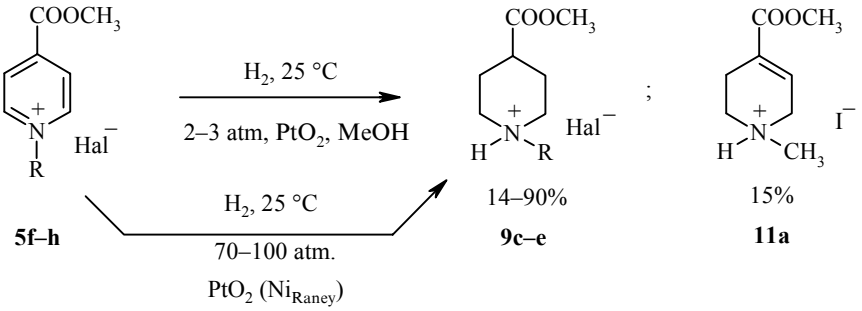
During the catalytic reduction of 1-methylbenzoylpyridinium halides **3c**,**d**, **4b-d**, **5b-d** at platinum oxide at room temperature and 3 atm in ethanol or methanol the carbonyl group is reduced to an alcohol group earlier than the pyridine ring, irrespective of its position, and the obtained salt **5e** can even be isolated [47-49]. Replacement of the solvent by water increases the duration of the reaction leading to the piperidines **7**, **8** from 4 to 24 h [49].



3c,d; 4b–d; 5d–d **5e** **7c, 8b, 9b**

3c, 7c R = 2-COC_6H_5, X = Cl^-; **3d** R = 2-COC_6H_5, X = I^-; **4b, 8b** R = 3-COC_6H_5, X = Cl^-;
4c R = 3-COC_6H_5, X = Br^-; **4d** R = 3-COC_6H_5, X = I^-; **5b, 9b** R = 4-COC_6H_5, X = Cl^-;
5c R = 4-COC_6H_5, X = Br^-; **5d** R = 4-COC_6H_5, X = I^-; **5e** R = 4-$CH(OH)C_6H_5$, X = Br^-

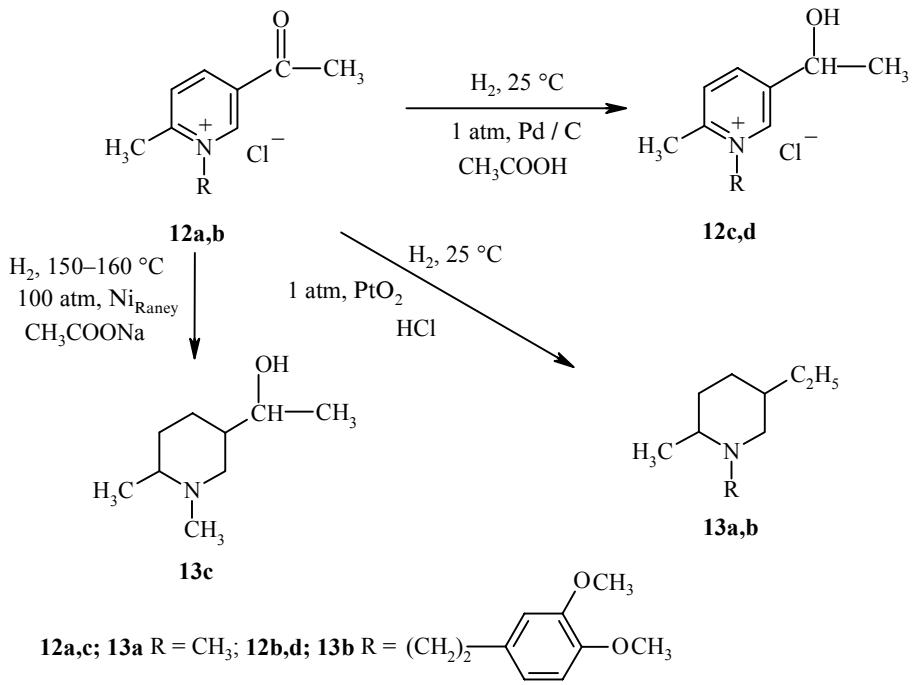
During hydrogenation of the pyridinium salts **5f-h**, containing an ester substituent at position 4, the heterocycle is reduced with the formation of the piperidinium or tetrahydropyridinium cations **9c-e**, **11a** [50-53]:



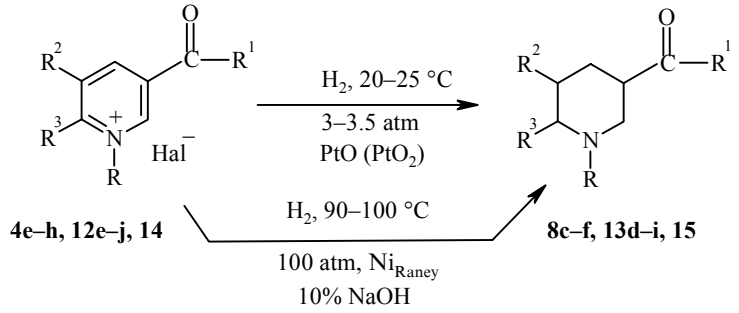
5f–h **9c–e** **11a**

5f, 9c R = CH_3, Hal = Br^-; **5g, 9d** R = CH_3, Hal = I^-; **5h, 9e** R = $CH_2COOC_2H_5$; Hal = Br^-

The data in [54] indicate that under mild conditions (25°C, 1 atm), depending on the catalyst and the acidity of the medium, the 3-acetylpyridinium salts **12a**,**b** are hydrogenated either with retention of the heterocycle (glacial acetic acid, Pd/C) or with exhaustive reduction of the heterocycle and the function to form substituted 3-ethylpiperidines **13a**,**b** (dilute hydrochloric acid, PtO_2). Under harsher conditions (150-160°C, 100 atm, Ni/Ru) in an acetate buffer the carbonyl group is converted into an alcohol group while the pyridine ring is converted into a piperidine ring [54].

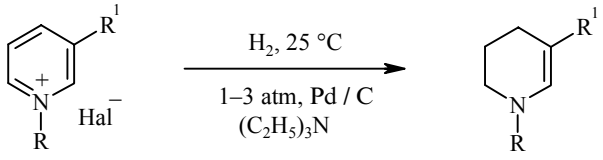


Electron-withdrawing groups (benzoyl, carboxyl, amide) at position 3 of the heterocycle in the salts **4**, **12**, **14** are retained in the products **8**, **13**, **15** during hydrogenation in aqueous solution [47, 50, 55-57]:



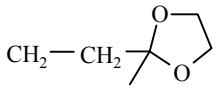
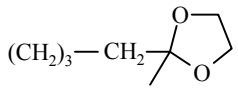
4e, 8c $R^1 = C_6H_5$, Hal = Cl; **4f, 8d** R = CH_3, $R^1 = NH_2$, Hal = Cl; **4g, 8e** R = $CH_2CH_2C_6H_5$; $R^1 = C_6H_5$, Hal = Br; **4h, 8f** R = $CH_2COOC_2H_5$, $R^1 = OC_2H_5$, Hal = Br; **12e, 13d** R = CH_3, $R^1 = N(C_2H_5)_2$, $R^3 = (CH_2)_2C_6H_5$, Hal = I; **12f, 13e** R = CH_3, R^1 = morpholyl, $R^3 = (CH_2)_2C_6H_5$, Hal = Br; **12g, 13f** R = CH_3, $R^1 = N(C_2H_5)_2$, $R^3 = (CH_2)_2C_6H_3(CH_3O)_2$-3,4, Hal = I; **12h, 13g** R = CH_3, R^1 = morpholyl, $R^3 = (CH_2)_2C_6H_3(CH_3O)_2$-3,4, Hal = Br; **12i, 13h** R = CH_3, $R^1 = N(C_2H_5)_2$, $R^3 = (CH_2)_2C_6H_2(CH_3O)_3$-3,4,5, Hal = I; **12j, 13i** R = CH_3, R^1 = morpholyl, $R^3 = (CH_2)_2C_6H_2(CH_3O)_3$-3,4,5, Hal = Br; **14** R = CH_3, $R^1 = O^-$, R^2 = OH; **15** R = CH_3, $R^1 = R^2$ = OH. Where not indicated R = H

During the hydrogenation of N-substituted pyridinium salts containing an electron-withdrawing substituent at position 3 on 10% Pd/C in methanol in the presence of triethylamine the corresponding tetrahydropyridines with a double bond stabilized by conjugation are formed [58-61]:



4i–z **16a–r**

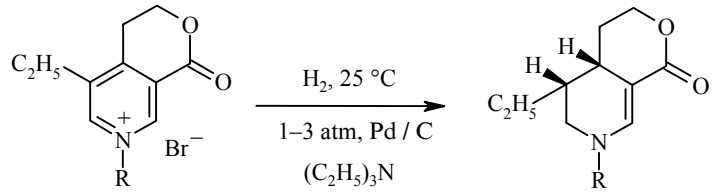
4i, 16a R = H, R^1 = $COOC_4H_9$-*t*; **4j, 16b** R = CH_3, R^1 = $COCH_3$, Hal = I; **4k, 16c** R = CH_3, R^1 = $COOCH_3$; **4l, 16d** R = CH_3, R^1 = $COOC_4H_9$-*t*; **4m, 16e** R = CH_3, R^1 = $CONH_2$, Hal = Cl; **4n, 16f** R = CH_3, R^1 = CH_2COOCH_3; **4o, 16g** R = CH_3, R^1 = CN, Hal = I; **4p, 16h** R = $(CH_2)_2OH$, R^1 = $COCH_3$; **4q, 16i** R = CH_2OCH_3, R^1 = $COCH_3$; **4r, 16j** R = β-(3-indolyl)ethyl, R^1 = $COCH_3$; **4s, 16k** R = β-(3-indolyl)ethyl, R^1 = $COOCH_3$; **4t, 16l** R = β-(3-indolyl)ethyl, R^1 = $COOC_4H_9$-*t*; **4u, 16m** R = β-[3-(2-methylindolyl)]ethyl, R^1 = CHO; **4v, 16n** R = β-[3-(2-methylindolyl)]ethyl, R^1 = $COCH_3$; **4w, 16o** R = β-[3-(2-methylindolyl)]ethyl, R^1 = $COOCH_3$; **4x, 16p** R = β-[3-(2-methylindolyl)]ethyl, R^1 = $COOC_4H_9$-*t*;

4y, 16q R =  , **4z, 16r** R =  , R^1= $COCH_3$

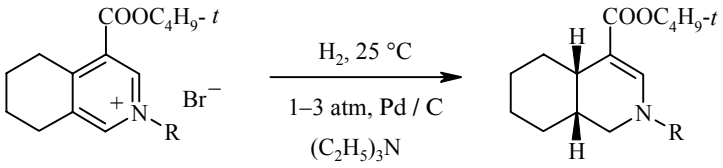
Where not indicated Hal = Br

Such a reaction path may be due to the formation in the basic medium of intermediates of the vinylogous amide type with subsequent reduction of the unconjugated double bond. This reaction was first used in the synthesis of eburnamonine – an alkaloid of the indole series [58, 61].

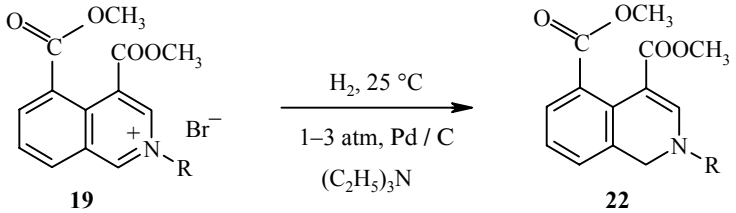
The first stage in the synthesis of alkaloids of the corynantheidine and α-yohimbine series is catalytic reduction of β-acylpyridinium salts **17-19** in a basic medium to compounds **20-22** [59, 61]:



17 **20**



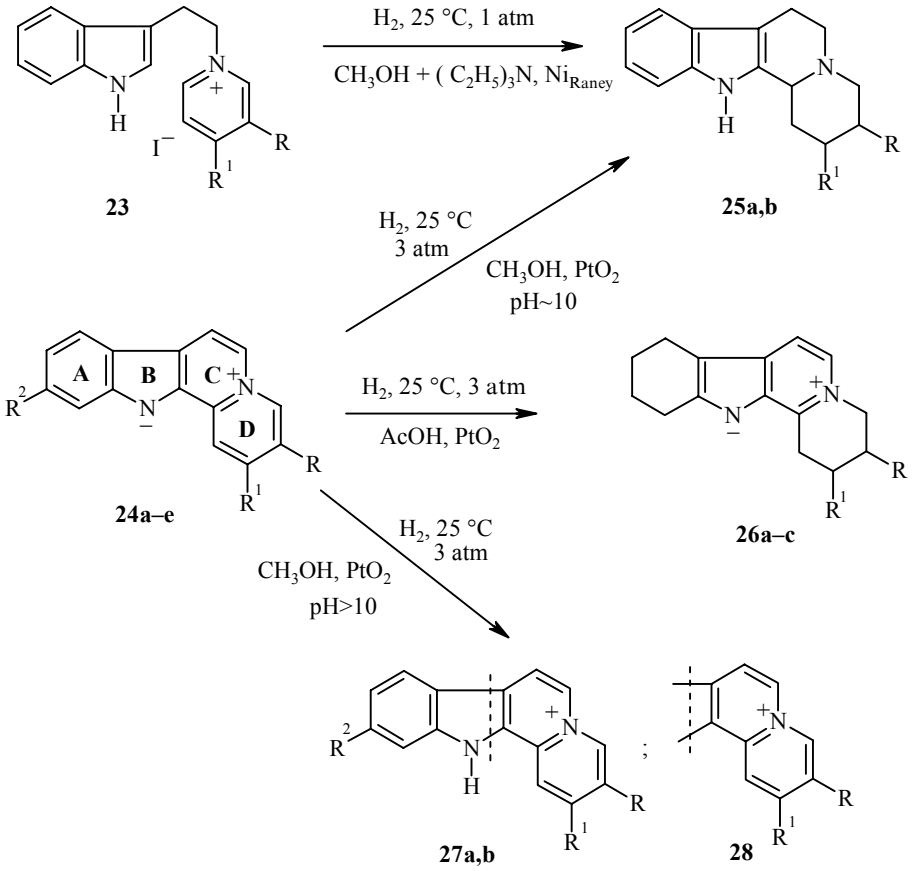
18 **21**



19 **22**

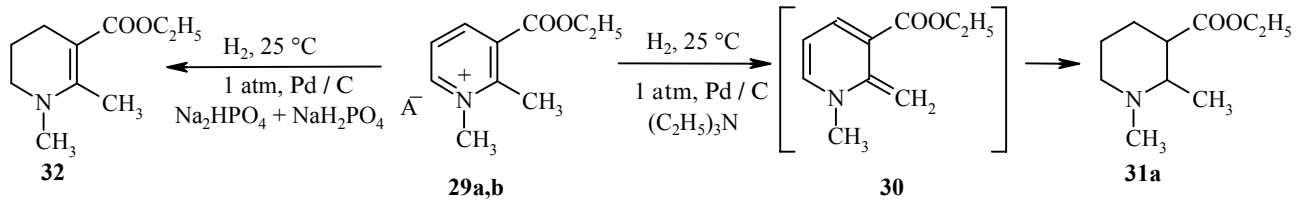
17-22 R = β-(3-indolyl)ethyl

A series of papers have been devoted to the synthesis of compounds **25-28**, containing the indolo[2,3-*a*]-quinolizidine system, from the pyridinium salt **23** and the betaines **24** [62-70]. The behavior of flavopereirin (**24a**) is typical [64, 65]. Over PtO_2 in acetic acid rings A and D are reduced with the formation of the octahydro derivative **26a**; the hydrogenation of sempervirine (**24b**) and serpentine (**24c**) takes place in exactly the same way [64, 66, 67]. However, in the presence of a small amount of alkali rings C and D of flavopereirin are reduced, while ring A is not hydrogenated [64]. Under analogous conditions sempervirine is converted into alloyohimbane (**25b**) [69]. In a strongly alkaline medium ring D of flavopereirin is reduced [64]. Ring D is also reduced during the hydrogenation of alstonilin (**24d**) under analogous conditions [70], whereas the related alstonin (**24e**) is hydrogenated in ring C [68, 70]:

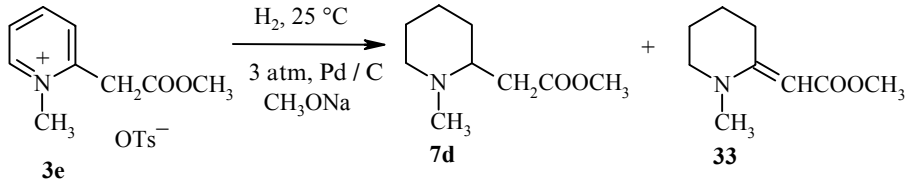


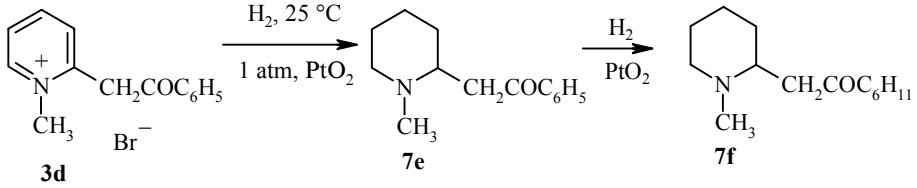
23, 24a, 25a, 26a, 27a R = C_2H_5, $R^1 = R^2 = H$; **24b, 25b, 26b** $R+R^1 = -(CH_2)_4-$, $R^2 = H$;
24c, 26c $R+R^1 = C_4H_5OCOOCH_3$, $R^2 = H$; **24d, 28** $R+R^1 = C_4H_3COOCH_3$, $R^2 = OCH_3$;
24e, 27b $R+R^1 = C_4H_5OCOOCH_3$, $R^2 = H$

The hydrogenation of the 1,2-disubstituted salts **3d**,**e** and 3-ethoxycarbonyl-1,2-dimethylpyridinium salts **29a**,**b** in methanol in the presence of triethylamine or sodium methoxide leads to the formation of the piperidines **7**, **31** and methoxycarbonylmethylenepiperidine **33** [60, 71, 72]; in the presence of a suspension of Na_2HPO_4 and NaH_2PO_4 it gives the tetrahydropyridines **32** [71]:



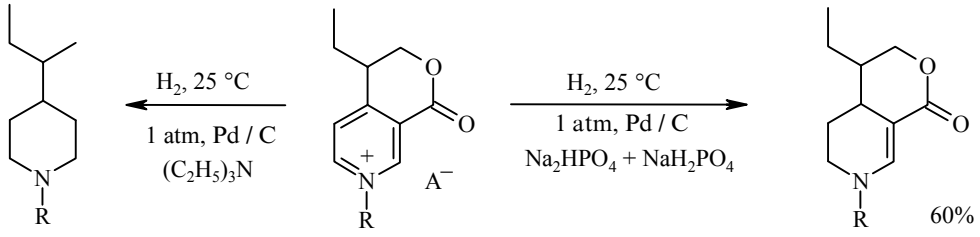
29a A = Cl; **29b** A = OTs



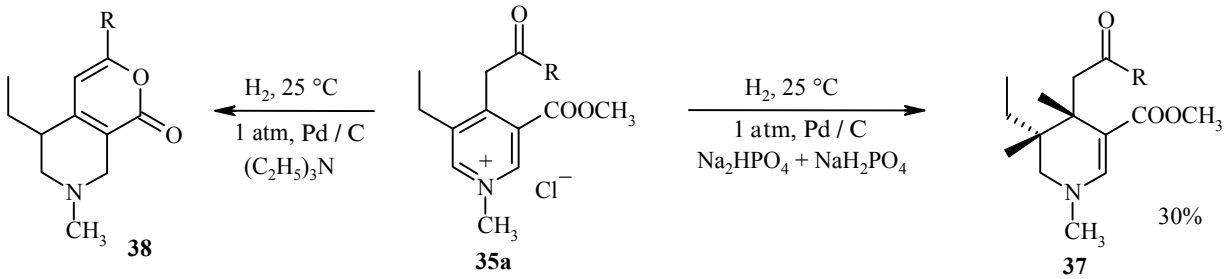


Reduction of the phenyl substituent to cyclohexyl under the selected conditions takes place very slowly and with low yields [72].

By using a phosphate buffer during catalytic reduction of the pyridinium salts **34**, **35** it is possible to obtain the tetrahydropyridines **36**, **37** selectively and avoid the undesirable cleavage of the lactone fragment and heterocyclization of the substituents (in the case of the formation of compound **3b**), which may occur in the presence of triethylamine [71, 73, 74]:



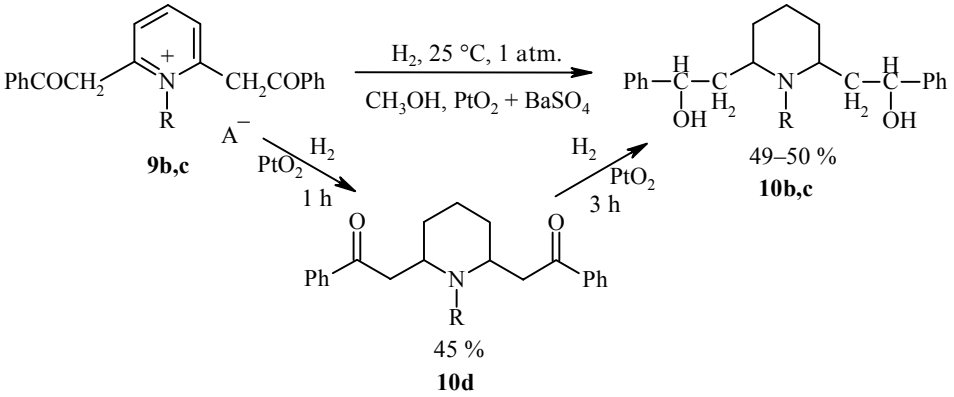
9e; 34a,b; 35 R = tryptophyl; **34a** A = Br^- ; **34b** A = ClO_4^-



36a, 37, 38 R = 2-(1-methylindolyl)

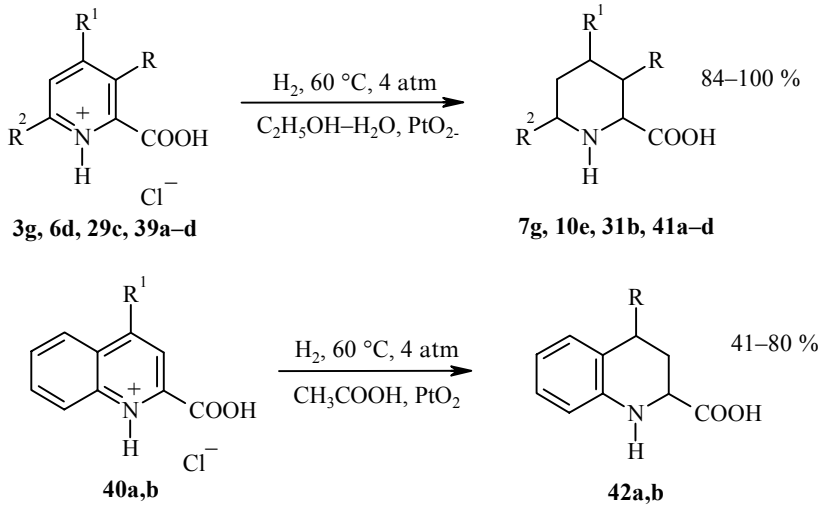
The synthesis of (±)-6-oxosilicin and (±)-$N_{(a)}$-methylervatamine – alkaloids of the indole series – was realized under these conditions [71, 74].

The hydrogenation of 2,6-diphenacylpyridinium salts **9b**,**c** was used in [75] for the production of the natural alkaloids of lobelia – lobelanine, norlobelanine, and lobelanidine:



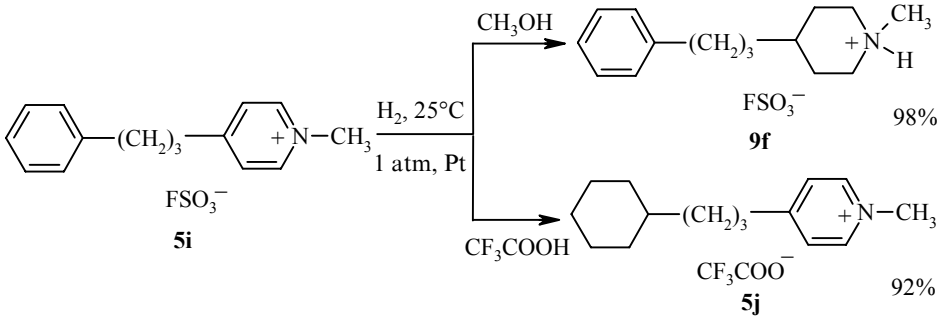
9b, 10b R = H, A = Cl; **9c, 10c,d** R = CH_3, A = OTs

The catalytic reduction of the pyridinium **3g**, **6d**, **29c**, **39a-d** and quinolinium salts was also used in the synthesis of unnatural α-amino acids – inhibitors of protein enzymes [76]. Here racemic mixtures of (*DL-cis*)-substituted homoprolines **7g**, **10e**, **31b**, **41a-d**, **42a**,**b** were obtained with high yields.



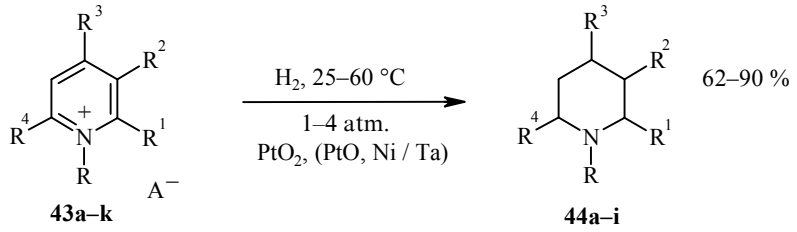
6d, 10e R^2 = CH_3; **29c, 31b** R = CH_3; **39a, 40a** R^1 = CH_3; **39b, 40b** R^1 = C_2H_5;
39c, 40c R^1 = OCH_3, **39d, 40d** R^1 = t-C_4H_9; **41b, 42b** R = CH_3. Where not indicated R = H

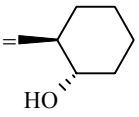
The effect of the nature of the solvent on the direction of hydrogenation of aryl- and alkyl-substituted pyridinium salts was discussed in [77]. The heterocycle is reduced in a neutral medium (methanol), whereas the benzene ring is hydrogenated in trifluoroacetic acid:

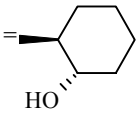
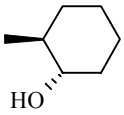


Although the reasons for such selectivity are not entirely clear, it is presumably due to the stabilization of the pyridine ring by the strong solvation and activation of the benzene ring through the formation of σ or π complexes with the trifluoroacetic acid [77].

Under mild conditions (25-60°C, 1-4 atm, at platinum or nickel oxides modified with tantalum in methanol or ethanol) the hydrogenation of alkyl(aryl)-substituted pyridinium salts **43** leads to the corresponding piperidines **44** [47-49, 78-82]:

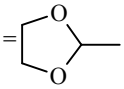


43a, 44a R = C_2H_5, A = Br^-; **43b, 44b** R =  , A = I^- ;

43c R =  , A = ClO_4^-; **43d** R =  , A = OTs^-; **43e, 44c** R = CH_3,

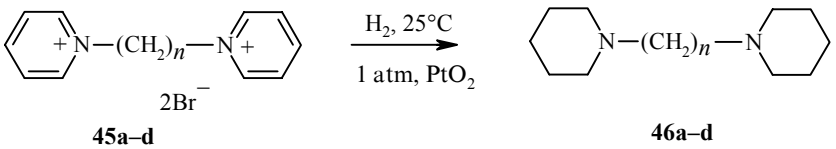
R^1 = 2-$CH_3C_6H_4$, A = I^-; **43f, 44d** R = CH_3, R^1 = $CH(OH)C_6H_4C_6H_5$, A = Cl^-;

43g, 44e R = CH_3, R^1 = $CH_2C_6H_5$, A = Br ; **43h, 44f** R = CH_3, R^1 = $CH(OH)C_6H_5$; A = Br^- ;

43i, 44g R = CH_3, R^1 =  , A = I^-; **43j, 44h** R = CH_3, R^3 = $CH_2C_6H_5$, A = Br^- ;

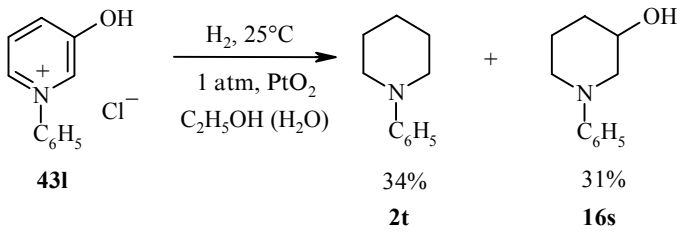
43k, 44i R = R^2 = C_2H_5, R^4 = CH_3, A = Br^-

Exhaustive reduction of the heterocycles takes place during the catalytic reduction of the bispyridinium salts **45a-d** at Adam's catalyst in ethanol with the formation of the bispiperidines **46a-d** [83]:



45a, 46a *n* = 3; **45b, 46b** *n* = 4; **45c, 46c** *n* = 5; **45d, 46d** *n* = 6

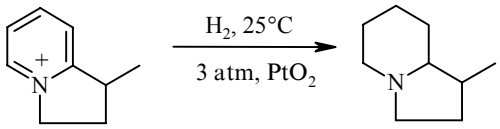
If there is a hydroxyl substituent at position 3 of the pyridine ring hydrogenation takes place both with retention and with elimination of the hydroxyl [84]:



43l **2t** **16s**

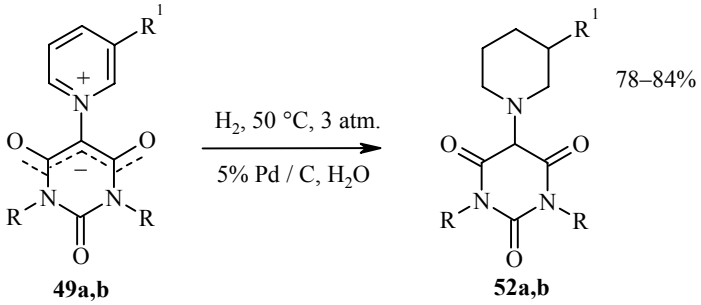
Replacement of the solvent (ethanol by water) does not affect the yields of the reaction products.

The authors of [85] demonstrated the possibility of obtaining indolizidine alkaloids by catalytic reduction of condensed pyridinium salts of the **47** type in a weakly acidic solution in methanol at Adam's catalyst under mild conditions. Here, one diastereomer **48**, the configuration of which was not determined, was obtained with a yield of 52%. The use of Pd/C as catalyst reduces the yield of the product to 20%.



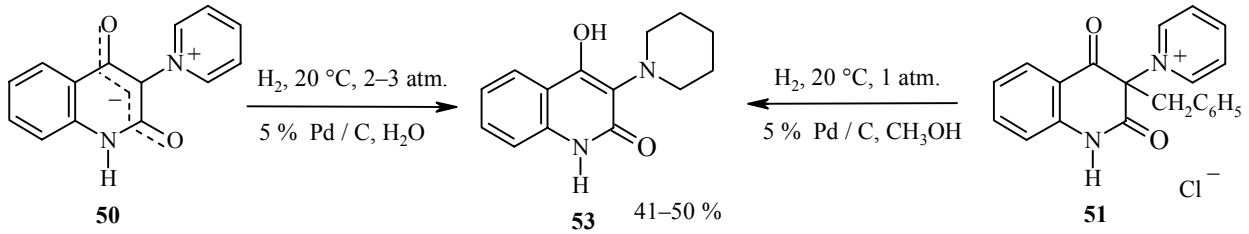
47 **48**

The hydrogenation of the pyridinium ylides **49a**,**b**, **50**, **51** at 5% Pd/C in water or methanol at 20-50°C gives derivatives of barbituric **52a**,**b** and isatoic **53** acids [86, 87]:



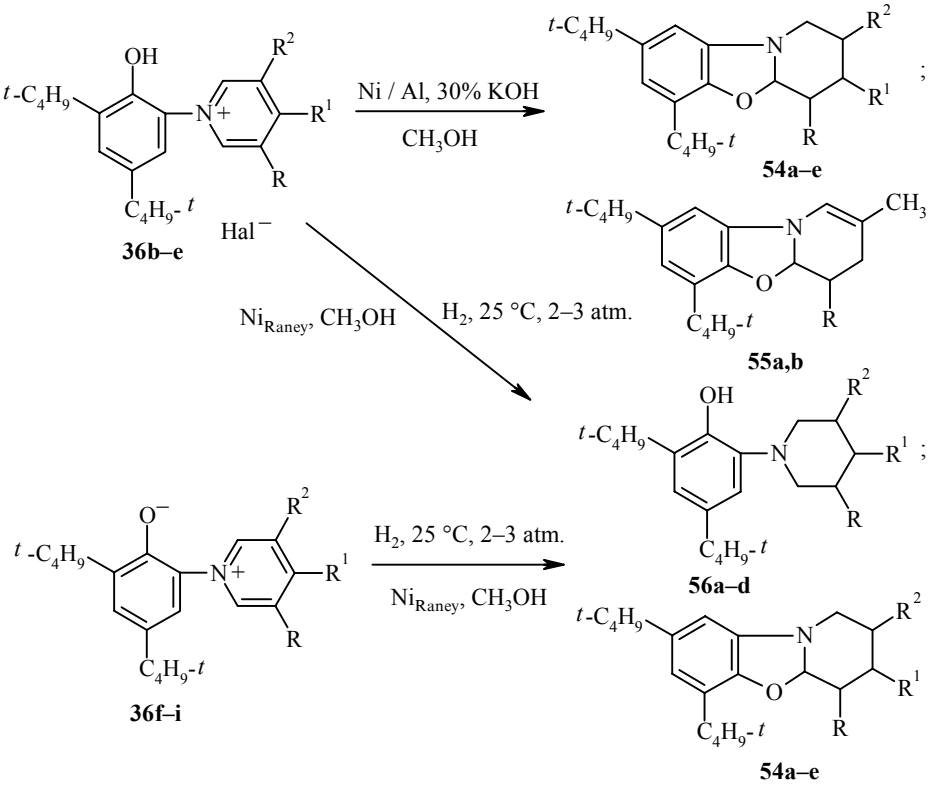
49a,b **52a,b**

49a, 50a R = H, $R^1 = COOC_2H_5$; **49b, 50b** R = CH_3; $R^1 = CONH_2$



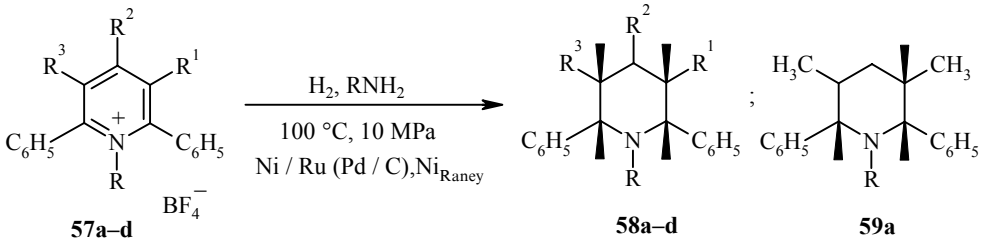
50 **53** **51**

A single example of the reduction of pyridinium salts **36b-e** *in situ* with Raney alloy has been described in the literature [88]. The reaction leads to the formation of the products from intramolecular cyclization, i.e., the benzoxazoles **54**, **55**, whereas the main direction under the conditions of catalytic reduction is the formation of N-hydroxyphenylpiperidines **56** with yields of 94-95%. During hydrogenation at Raney nickel under mild conditions the structurally similar pyridinium ylides **36f-i** form mixtures of benzoxazoles and piperidines [88]:



36b Hal = Br; **36c,g, 54b, 55a, 56b** R = CH_3, Hal = Br; **36d,h, 54c, 55b, 56c** R^1 = CH_3, Hal = Cl; **36e,i, 54d, 56d** R = R^2 = CH_3, Hal = Br; **54e** R^2 = CH_3. Where not indicated R = H

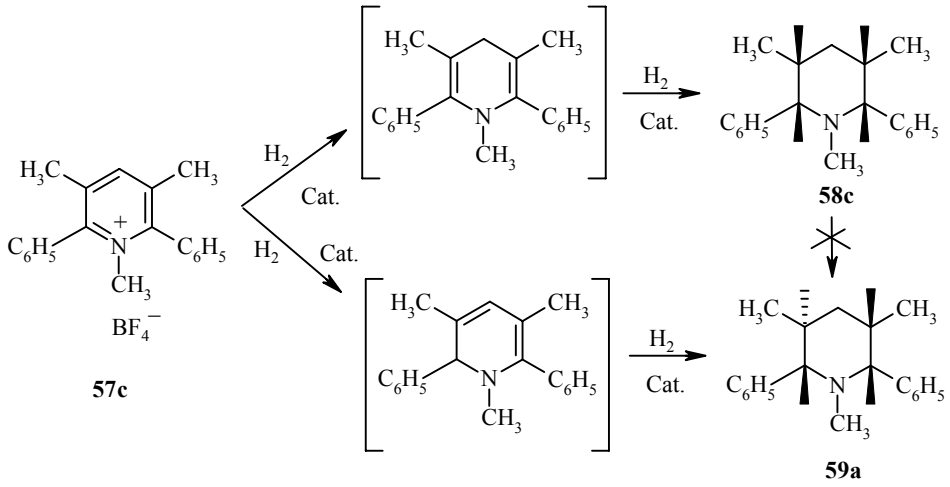
It was established during a study of the catalytic reduction of polysubstituted pyridinium salts [89, 90] that 1-methyl(phenyl)-2,6-diphenyl-3,5-(H, methyl)-4-(H, phenyl)pyridinium tetrafluoroborates **57a-d** undergo selective reduction in the heterocycle under fairly harsh conditions (100°C, ~10 MPa) in methanol solution in the presence of amine, with nickel modified with ruthenium, Raney nickel, or 10% Pd/C as catalyst. The reaction is stereoselective and leads mainly to the formation of the piperidines **58a-d** with high yields (56-96%):



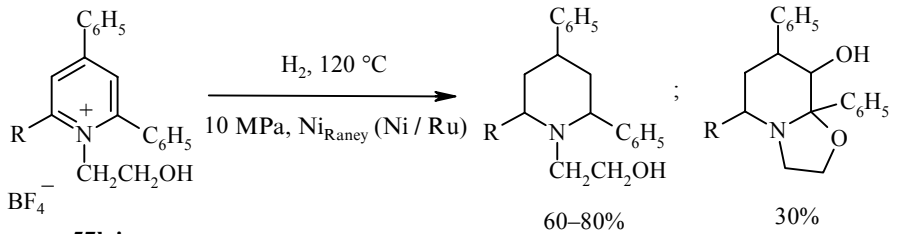
57a, 58a R = CH_3, R^2 = C_6H_5; **57b, 58b** R = R^1 = CH_3, R^2 = C_6H_5; **57c, 58c, 59a** R = R^1 = R^3 = CH_3; **57d, 58d** R = R^2 = C_6H_5. Where not indicated R = H

At lower temperature (50-70°C) the yields of the piperidines are reduced to 55-70%. Replacement of Ni/Ru by Raney nickel or 10% Pd/C does not affect the yield of the obtained piperidines. In the absence of the amine the hydrogenation of α,α'-diaryl-substituted pyridinium salts leads to mixtures of nitrogen-free products from opening of the ring [89].

In the case of 1,2,5-trimethyl-2,6-diphenylpyridinium tetrafluoroborate **57c** a scheme with the formation of stereoisomeric piperidines **58c** and **59a** through 1,4- and 1,2-dihydropyridine intermediates, followed by the *cis*-addition of hydrogen, was proposed [89]:

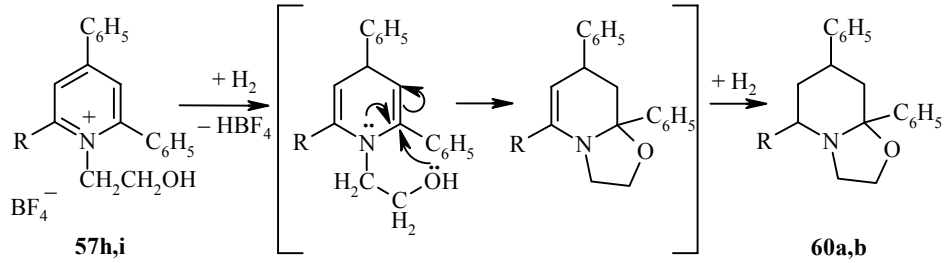


A feature of the hydrogenation of the pyridinium salts **57h**,**i**, containing a 2-hydroxyethyl substituent at the nitrogen atom, is the possible formation, together with the corresponding piperidines **58h**,**i**, of intramolecular cyclization products, i.e., octahydrooxazolopyridines **60a**,**b** [91, 92]:

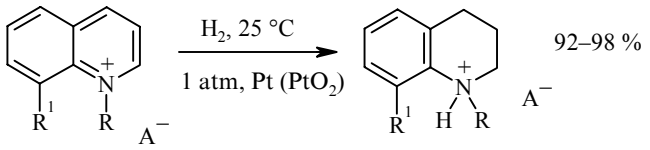


57h, 58h, 60a R = C_2H_5; **57i, 58i, 60b** R = C_6H_5

The formation of the latter can be represented by a scheme involving 1,4-hydrogenation followed by addition of a hydroxyl group at the double bond:

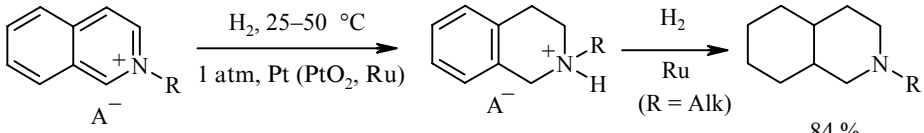


The reduction of quinolinium **61a-j** and isoquinolinium **63a-e** salts in methanol at 25°C and atmospheric pressure at a platinum or platinum black catalyst gives high yields of tetrahydro(iso)quinolines **63**, **64**; at a ruthenium catalyst decahydroisoquinolines **65** are obtained, and the heteroaromatic ring is hydrogenated more readily than the benzene ring under the selected conditions [37, 77, 78, 93]:

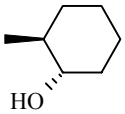


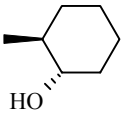
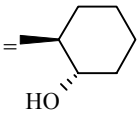
61a–j **63a–d**

61a, 63a R = R^1 = H, A = I; **61b, 63b** R = CH_3, R^1 = H, A = I; **61c, 63c** R = CH_3, R^1 = H, A = CF_3COO; **61d, 63d** R = CH_3, R^1 = H, A = FSO_3; **61e** R = R^1 = CH_3, A = I; **61f** R = R^1 = CH_3, A = CF_3COO; **61g** R = R^1 = CH_3, A = FSO_3; **61h** R = CH_3, R^1 = *t*-C_4H_9, A = I; **61i** R = CH_3, R^1 = *t*-C_4H_9, A = CF_3COO; **61j** R = CH_3, R^1 = *t*-C_4H_9, A = FSO_3



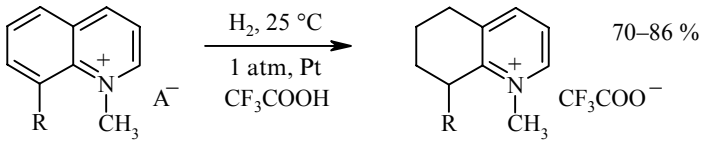
62a–e **64a–e** **65**

62a, 64a, 65 R = CH_3, A = ClO_4; **62b, 64b** R =  , A = ClO_4;

62c, 64c R =  , A = I; **62d, 64d** R =  , A = OTs;

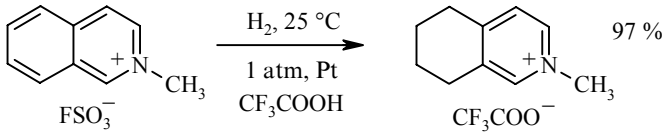
62e, 64e R = CH_3, A = FSO_3

If the solvent is replaced (methanol by trifluoroacetic acid), the benzene ring in the quinolinium and isoquinolinium salts is hydrogenated primarily, as in the previously described example of the reduction of the 4-(3-phenylpropyl)pyridinium salt **5i**, and the 5,6,7,8-tetrahydroquinolinium **66** and 5,6,7,8-tetrahydroisoquinolinium **67** salts are formed [77]:



61b–j **66a–c**

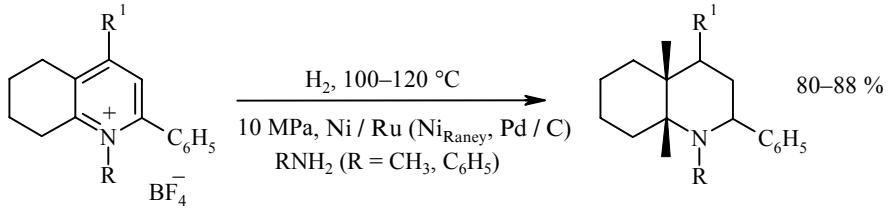
61b, 66a R = CH_3, R^1 = H, A = I; **61c, 66b** R = CH_3, R^1 = H, A = CF_3COO; **61d, 66c** R = CH_3, R^1 = H, A = FSO_3; **61e** R = R^1 = CH_3, A = I; **61f** R = R^1 = CH_3, A = CF_3COO; **61g** R = R^1 = CH_3, A = FSO_3; **61h** R = CH_3, R^1 = *t*-C_4H_9, A = I; **61i** R = CH_3, R^1 = *t*-C_4H_9, A = CF_3COO; **61j** R = CH_3, R^1 = *t*-C_4H_9, A = FSO_3



63e **67**

In [36, 77, 78, 93] the nature of the anion was varied quite widely (I^-, ClO_4^-, OTs^-, FSO_3^-, CF_3COO^-), but the choice of anion had no effect on the hydrogenation process. It can only be mentioned that an anion-exchange reaction is observed during hydrogenation in trifluoroacetic acid [77].

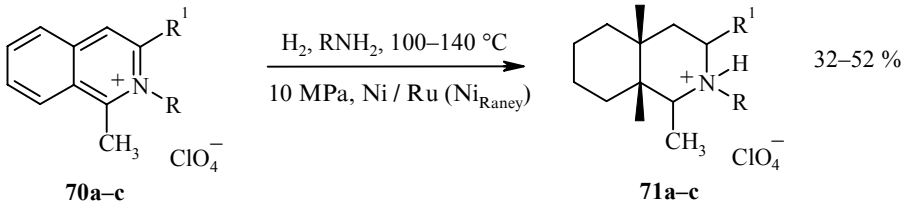
The catalytic reduction of 5,6,7,8-tetrahydroquinolinium tetrafluoroborates **68a-e** leads to high yields of *cis*-decahydroquinolines **69a-e** [89-92]:



68a–e **69a–e**

68a, 69a R = CH_3, R^1 = H; **68b, 69b** R = CH_3, R^1 = C_6H_5; **68c, 69c** R = R^1 = C_6H_5;
68d, 69d R = CH_2CH_2OH, R^1 = C_6H_5; **68e, 69e** R = CH_2CH_2OH, R^1 = 4-$CH_3OC_6H_4$

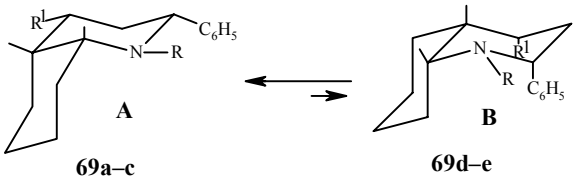
Similarly, during reduction under the same conditions (100°C, 10 MPa) at Ni/Ru the 5,6,7,8-tetrahydroquinolinium perchlorates **70a-c** are converted into the corresponding *cis*-decahydroisoquinolines **71a-c** [90, 94]:



70a–c **71a–c**

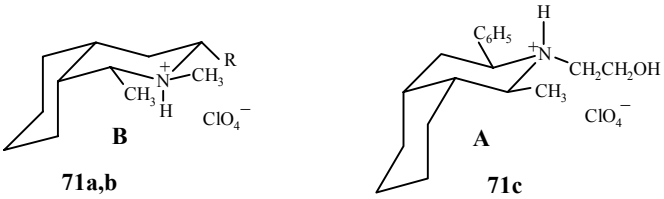
70a, 71a R = R^1 = CH_3; **70b, 71b** R = CH_3, R^1 = C_6H_5; **70c, 71c** R = CH_2CH_2OH, R^1 = C_6H_5

It was determined by ^{13}C NMR spectroscopy that N-methyl(phenyl)-substituted decahydroquinolines **69a-c** are stabilized in conformation **A** [89, 90, 95].

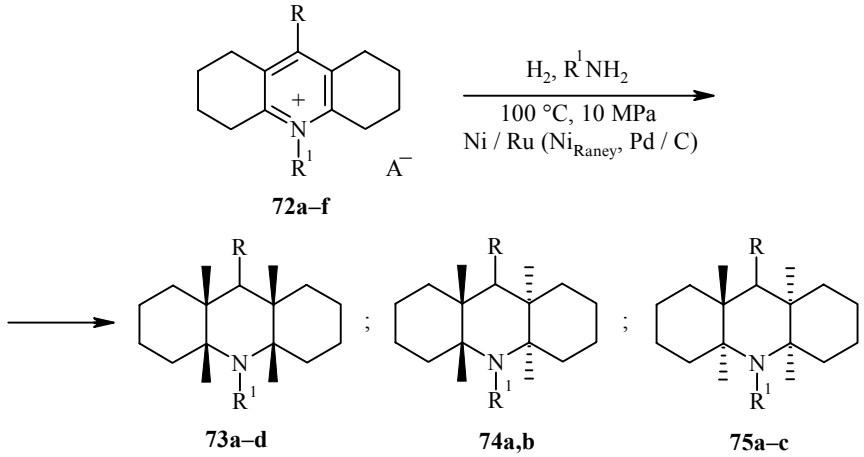


69a–c **69d–e**

It is also noteworthy that in the N-(2-hydroxyethyl)-substituted decahydroquinolines **69d**,**e**, which according to the ^{13}C NMR spectra are the **B** conformers, the phenyl substituent at the $C_{(2)}$ atom is in the axial orientation [91, 92]. The N-methyl-substituted *cis*-decahydroisoquinolines **71a**,**b** are stabilized in conformation **B** [90, 94]. Replacement of the methyl substituent at the nitrogen atom by 2-hydroxyethyl group leads to change in the molecular conformation of the decahydroisoquinoline **71c** [90].

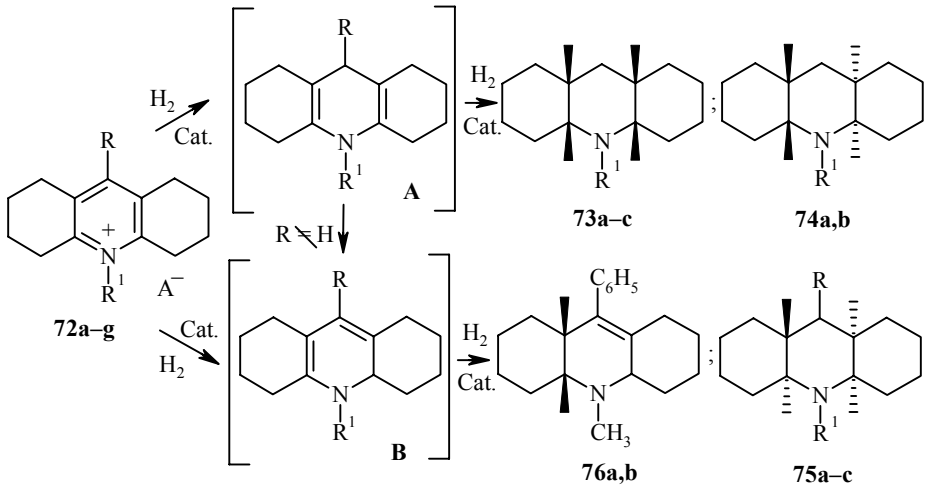


Catalytic reduction of the 10- and 9,10-substituted *sym*-octahydroacridinium salts **72a-f** (100°C, 10 MPa) at nickel modified with ruthenium, Raney nickel, and Pd/C in the presence of the corresponding amine leads to a different stereochemical result, depending on the number and nature of substituting groups [89, 90, 96, 97]. Here, the *cis-syn-cis* (**73a-d**), *cis-anti-cis* (**74a**, **b**), and *trans-anti-cis* (**75a-c**) isomers of perhydroacridines are formed as individual isomers or isomeric mixtures:



72a, **73a** R = H, $R^1 = CH_3$, $A^- = I$; **72b**, **73b, 74a** R = H, $R^1 = C_6H_5$; **72c, 73c, 74b** R = H, $R^1 = C_6H_4CH_3$-4; **72d**, **75a** R = 2-C_4H_3O, $R^1 = C_6H_4CH_3$-4; **72e, 75b** R = $R^1 = C_6H_5$, $A^- = BF_4$; **72f**, **73d, 75c** R = C_6H_5, $R^1 = C_6H_4CH_3$-4. Where not indicated $A^- = ClO_4$

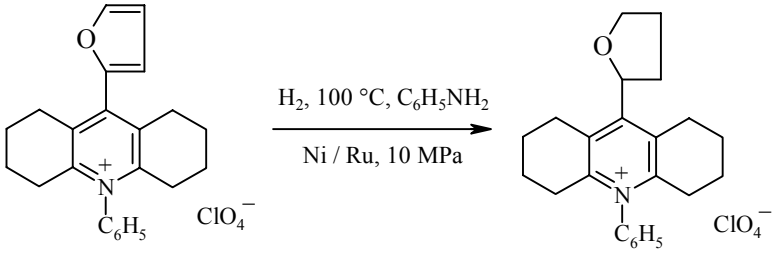
By analogy with the pyridinium salts [89] the scheme for the formation of the hydroacridines with various stereo structures was represented by the authors of [90, 97] through 1,2- and 1,4-dihydropyridine intermediates (**A**, **B**):



72g, **76a** R = C_6H_5, $R^1 = CH_3$, $A^- = BF_4$; **76b** R = C_6H_5, $R^1 = C_6H_4CH_3$-4

According to the scheme, in the case of *sym*-octahydroacridinium salts unsubstituted at position 9 products with the *cis* configuration **73a-c** are formed through intermediates **A** with planar or edge adsorption and the *cis*-addition of hydrogen, which is typical of hydrogenation reactions. The *trans-anti-cis*-perhydroacridines **75a-c** can only arise from 1,2-dihydropyridines of type **B**. The 1,4-dihydropyridine derivatives are probably formed during the initial addition of the hydrogen atom at the unsubstituted γ position of the salt; if, however, this position is occupied, α attack is more favorable. In addition, with the presence of a substituent at position 9 of the substrate it is impossible to rule out isomerization of the dihydropyridine **A** to compound **B**. Evidence for the proposed scheme is provided by the stereoisomeric composition of the reaction products and also by the isolation of products from partial reduction of the intermediates **B**, i.e., the dodecahydroacridines **76a**,**b**, together with the perhydroacridines [90, 97].

An unexpected result was obtained during the hydrogenation of 10-phenyl-9-(2-furyl)-*sym*-octahydroacridinium perchlorate (**72h**) [97]. Under selected conditions selective reduction of the furan ring with retention of the pyridine ring occurs:

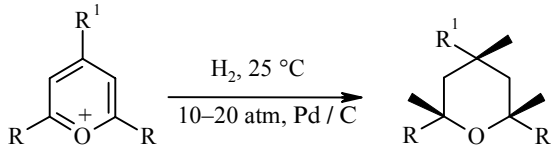


72h **72i**

Thus, the catalytic reduction of pyridinium salts is a potential method for the production of compounds of the piperidine series. By varying the conditions (temperature, pressure, solvent, catalyst) it is possible to achieve the selective reduction of the pyridinium ring or its substituents.

2. Catalytic Reduction of Pyrylium Salts

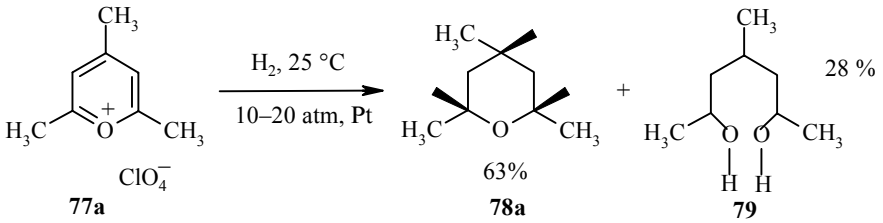
The catalytic reduction of pyrylium salts has been studied very little, and there are only a few isolated papers. One of them [98] reports on results from the hydrogenation of 2,4,6-trialkyl- and 2,4,6-triphenylpyrylium perchlorates. It was shown that hydrogenation can take place both with retention of the ring (the formation of tetrahydropyrans) and with opening of the ring (the formation of hydrocarbons and diols). Under mild conditions (25°C, Pd/C, 10-20 atm) 2,4,6-trialkylpyrylium perchlorates **77a-c** are converted into the corresponding tetrahydropyrans with yields of 78-85% [98]. The reaction is conducted in an autoclave with a magnetic stirrer and with a water–ether mixture as solvent, and the products are isolated by preparative gas-liquid chromatography. On the basis of the data from ^{1}H NMR spectroscopy it was established that the tetrahydropyrans that form have the *cis* configuration:



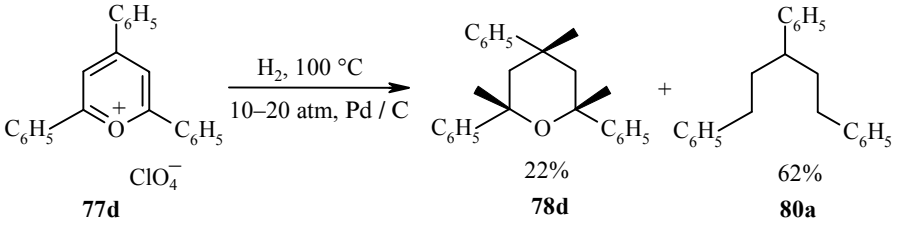
77a–c **78a–c**

77a, 78a R = R^1 = CH_3; **77b, 78b** R = R^1 = CD_3; **77c, 78c** R = $C(CH_3)_3$, R^1 = CH_3

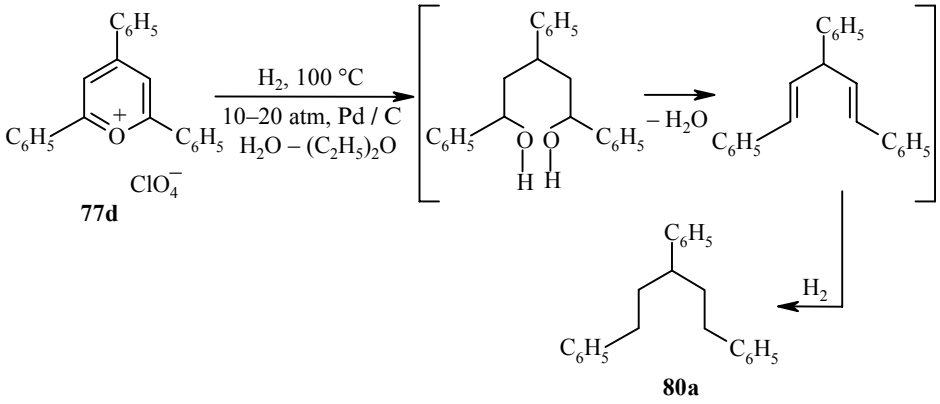
In the case of 2,4,6-trimethylpyrylium perchlorate (**77a**) it was shown that if a platinum catalyst is used instead of Pd/C with other conditions equal the hydrogenation of the heterocycle is complicated by its hydrolytic cleavage with the formation of 1,3,5-trimethyl-1,5-pentanediol (**79**) [98]:



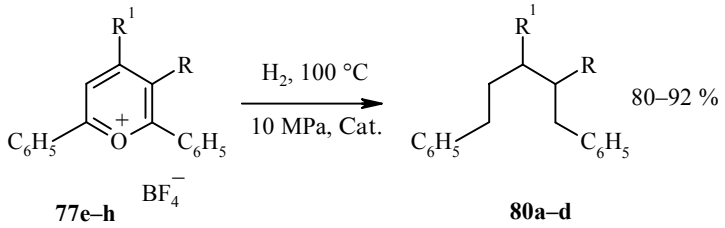
If the alkyl groups in the substrate are replaced by phenyl, hydrogenation only takes place when the temperature is increased to 100°C, and opening of the pyrylium ring becomes the main direction of the reaction. 1,3,5-Triphenylpentane (**80**) (62%) and 2,4,6-triphenyltetrahydropyran (**78d**) (22%) were found in the hydrogenation product:



The authors suggest that the precursor of the hydrocarbon in the water–ether medium is 1,5-pentanediol – the product from hydrolysis of the heterocycle – which is dehydrated at 100°C and is then hydrogenated [98]:



The aliphatic-aromatic hydrocarbons **80a-d** become the only products (yields 80-92%) during the hydrogenation of 2,6-diphenylpyrylium tetrafluoroborates **77d-g** at nickel catalysts or Pd/C at hydrogen pressure 7-12 MPa and temperature 40-100°C. Since ethanol is used as solvent, it can be supposed that their formation results from hydrogenolysis of the pyrylium ring [90, 99].

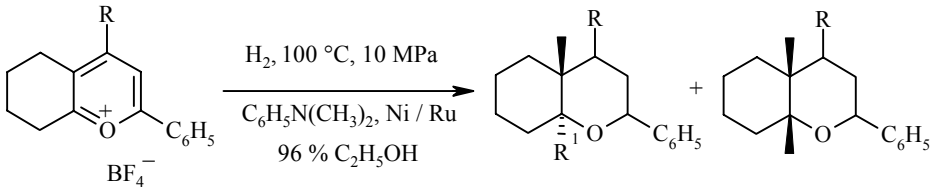


77e–h **80a–d**

77e, 80b R = R^1 = H; **77f, 80c** R = H, R^1 = CH_3; **77g, 80a** R = H, R^1 = C_6H_5;
77h, 80d R = CH_3, R^1 = C_6H_5; Cat. = Ni_{Raney}, Ni/Ru, Pd/C

The effects of temperature, hydrogen pressure, and catalyst on the yield of 1,3,5-triphenylpentane (**80a**) were studied for the case of 2,4,6-triphenylpyrylium tetrafluoroborate (**77g**), and it was established that the best results were obtained at 100°C and 10 MPa with nickel modified by ruthenium as catalyst [90, 99].

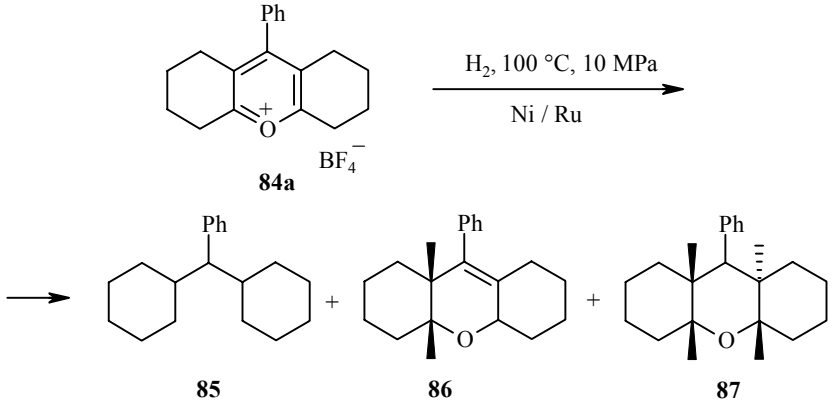
During the catalytic reduction of 5,6,7,8-tetrahydrochromylium salts **81a**,**b** at 100°C with initial hydrogen pressure 10 MPa at Ni/Ru in ethanol a complex mixture of compounds is formed [99]. In the presence of an equimolar amount of N,N-dimethylaniline under the same conditions the octahydrochromenes **82a-d**, **83a**,**b** with *cis*- and *trans*-fusion of the carbo- and heterocycles were isolated [90]:



81a,b **82a–d** **83a,b**

81a, 82a, 83a R = C_6H_5, R^1 = OH; **81b, 82b, 83b** R = $C_6H_4OCH_3$-4, R^1 = OH;
82c R = C_6H_5, R^1 = OC_2H_5; **82d** R = $C_6H_4OCH_3$-4, R^1 = OC_2H_5

During the hydrogenation of 9-phenyl-*sym*-octahydroxanthylium tetrafluoroborate (**84a**) the corresponding hydrocarbon **85** was isolated with a yield of 18 %, while the main products were the hydroxanthenes **86**, **87** with an overall yield of 51% [90, 99].

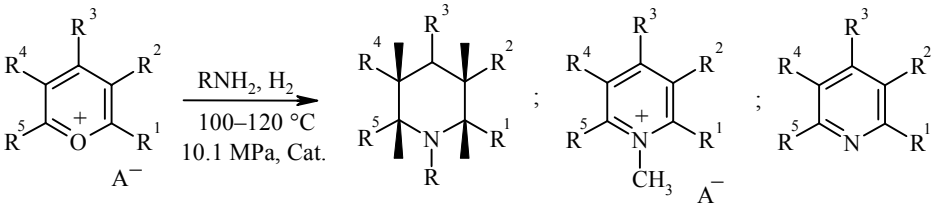


84a **85** **86** **87**

The different behaviors of the polyphenylalkyl-substituted pyrylium salts **77e-h** and the condensed systems **81a**,**b**, **84a** during hydrogenation under identical conditions (100°C, 10 MPa, 96% ethanol, Ni/Ru) can be explained by the lability of the C–O bond in systems in which the hydrogen is bonded to a carbon

atom of the benzylic type, and this agrees with data in [38]. Hydroxanthenes are more resistant to hydrogenolysis, since they do not contain a labile C–O bond, and phenyldicyclohexylmethane **85** is formed with a yield of only 18%.

Among the reactions of pyrylium salts occurring under the conditions of heterogeneous catalysis it is necessary to single out reductive amination. The authors of [92, 95, 100, 101] studied the catalytic hydroamination of the pyrylium salts **77**, **81** and their condensed analogs **84**, **88** at 100-120°C with an initial hydrogen pressure of 10.1 MPa at Raney nickel or nickel promoted with ruthenium in methanol or ethanol. Ammonia, methylamine, aniline, and ethanol were used as aminating agents with the pyrylium salt and amine in a molar ratio of 1:2.

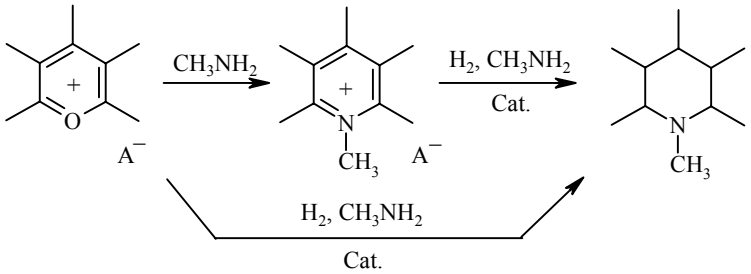


77e–l; 81a,b; 84b; 88a,b — **58a–c, j–p; 59a; 69a,b,d; 73a; 89a,b** — **57a,b; 68b; 72j** — **90a–c**

58l, 90a R = CH_3, $R^1 = R^5 = C_6H_5$; **58j, 77i** R = $R^1 = R^3 = R^5 = CH_3$; **58k** R = C_6H_5, $R^1 = R^3 = R^5 = CH_3$; **58m** R = $R^3 = CH_3$, $R^1 = R^5 = C_6H_5$; **58n, 77k** R = $R^5 = CH_3$, $R^1 = R^3 = C_6H_5$; **58o** R = $(CH_2)_2OH$, $R^1 = R^3 = C_6H_5$, $R^5 = CH_3$; **58p, 77l** R = CH_3, $R^1 = R^3 = C_6H_5$, $R^5 = C_2H_5$; **72j** R = CH_3, $R^1 + R^2 = R^4 + R^5 = -(CH_2)_4-$; **77j** $R^1 = R^5 = C_6H_5$, $R^2 = R^4 = CH_3$; **84b** $R^1 + R^2 = R^4 + R^5 = -(CH_2)_4-$; **88a, 89a** $R^1 = R^3 = C_6H_5$, $R^4 + R^5$ = 2,3-(3,4- dihydronaphtho); **88b, 89b** $R^1 = C_6H_5$, $R^3 = C_6H_3(OCH_3)_2$-3,4, $R^4 + R^5$ = 2,3-(3,4- dihydronaphtho), $A^- = CF_3COO$; **90b** $R^1 = R^3 = R^5 = C_6H_5$; **90c** $R^1 = C_6H_5$, $R^4 + R^5 = -(CH_2)_4-$. Where not indicated R = H, $A^- = BF_4$. Cat. = Ni_{Raney}, Ni/Ru

During hydromethylamination 2,6-diphenylpyrylium tetrafluoroborate **77e**, its methyl and dimethyl homologs **77f**,**j**, and also the 2-alkylpyrylium salts **77i**,**k**,**l**, **81a**,**b**, **84b** are converted with high yields (71-83%) into the respective substituted piperidines **58c**,**j**,**l-n**,**p**, **59a**, **69a**,**b**, **73a** [95, 100, 101]. The introduction of a phenyl substituent at position 4 leads to a decrease in the yield of the piperidine bases **58a**,**b**,**n-p**, **69b**,**d**) to 46-57% and the additional formation of the pyrylium salts **57a**,**b**, **68b** with yields of 26-62%. It is possible to avoid the formation of the latter by increasing the temperature to 120°C [95].

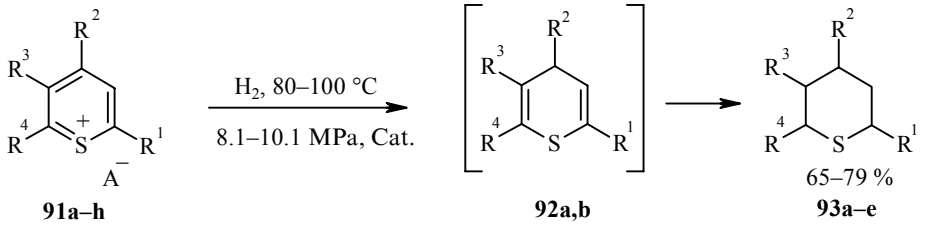
The hydrophenylamination of pyrylium salts only takes place successfully in the absence of aryl substituents at the α position. Under the reaction conditions the pyrylium cations **77e**,**g** undergo recyclization to the pyridine bases **90a**,**b** due to the influence of the ammonia [95]. The scheme for the formation of the piperidine bases from the pyrylium salts under the conditions of "reductive recyclization" includes the formation of pyridinium intermediates and their subsequent reduction [95]:



It was established by ^{13}C NMR spectroscopy that the hydroamination of the pyrylium salts takes place stereoselectively with the formation of the *cis* isomers of the piperidine bases [92, 95, 101].

3. Catalytic Reduction of Thiopyrylium Salts

The reduction of thiopyrylium salts **91a-f** and thiochromylium salts **91g**,**h** in the presence of catalysts based on metals of the platinum group (PtO_2, Pd/C, Rh/C, PdS/C, PdS/Al_2O_3) under various conditions was investigated in [31, 102, 103]. As a result high yields of the substituted thiacyclohexanes and thiadecalins **93a-e** were obtained (65-79%):

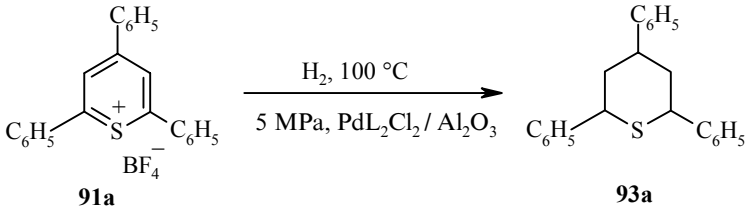


91a–h **92a,b** **93a–e**

91a, 92a, 93a $R^1 = R^2 = R^4 = C_6H_5$; **91b** $R^1 = R^2 = R^4 = C_6H_5$, $A = Cl^-$;
91c $R^1 = R^2 = R^4 = C_6H_5$, $A = CF_3COO^-$; **91d** $R^1 = R^2 = R^4 = C_6H_5$, $A = I^-$;
91e, 93b $R^1 = R^4 = C_6H_5$, $R^2 = CH_3$;
91f, 93c $R^1 = R^4 = C_6H_5$; **91g, 93d** $R^1 = C_6H_5$, $R^3 + R^4 = -(CH_2)_4-$;
91h, 92b, 93e $R^1 = R^2 = C_6H_5$, $R^3 + R^4 = -(CH_2)_4-$.
Where not indicated R = H, $A = BF_4^-$. Cat. = PtO_2, Pd/C, Rh/C, PdS/C, PdS/Al_2O_3

Hydrogenation was conducted in a rotating steel autoclave in ethanol. It was established by ^1H NMR spectroscopy that the thiacyclohexanes had the *cis* configuration [103]. As a result of the investigations [102, 103] conditions were selected for the hydrogenation of thiopyrylium salts and their condensed analogs, making it possible to obtain saturated cyclic sulfides with high yields (temperature 100-110°C, initial hydrogen pressure 10.1 MPa, catalyst 10% Pd/C, substrate to Pd ratio 10:2 by weight). It was established that the anion of the salt had a significant effect on the hydrogenation process; with its variation in the order CF_3COO^-, Cl^-, BF_4^-, I^- the yield of the saturated sulfides under identical reduction conditions decreases, while the amount of catalyst required for complete reduction of the heterocycle increases. The catalytic reduction of the thiopyrylium salts takes place through the formation of 4H-thiopyrans, evidence for which can be found in the isolation of the 2,4,6-triphenylthiopyran **92a** with a 70% yield during the hydrogenation of the respective thiopyrylium salt **91a** under mild conditions (30°C, initial hydrogen pressure 4 MPa) [102, 103].

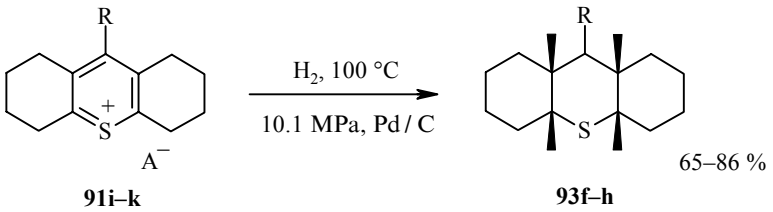
Palladium complexes PdL_2Cl_2 have also been used as catalysts for the hydrogenation of thiopyrylium salts:



91a **93a**

Here the reduction process takes place at a hydrogen pressure of 5 MPa at pH ~6 in dioxane or ethanol, and half the amount of the metal is used in the reduction of the salt to the sulfide. However, successful hydrogenation of the salt to the required thiacyclohexane can only be realized on the condition that the latter is identical to the ligand of the complex [103].

The catalytic reduction of the *sym*-octahydrothioxanthylium salts **91i-k** takes place stereoselectively with the formation of the *cis-syn-cis* isomers of perhydrothioxanthenes **93f-h** with yields of 65-86%:



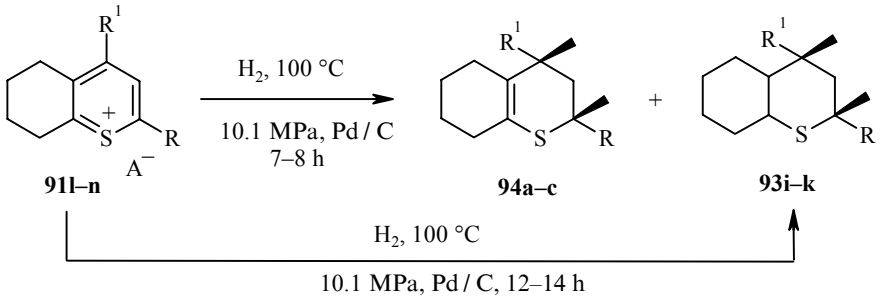
91i–k **93f–h**

91i, 93f R = H, A = BF_4^-; **91j, 93g** R = CH_3, A = BF_4^-; **91k, 93h** R = C_6H_5; A = $SbCl_6^-$

The stereochemistry of the reaction products was determined by ^{13}C NMR spectroscopy [31, 103].

During the hydrogenation of thiopyrylium salts, in contrast to pyrylium salts, the products from opening of the ring are not formed. This is probably explained by the higher stability of the C–S bond compared with the C–O bond in strongly acidic media.

In [30] the stereochemistry of substituted perhydrothiochromans **93i-k** and octahydrothiochromenes **94a-c**, obtained during the catalytic reduction of the 5,6,7,8-tetrahydrothiochromylium salts **91l-n**, was investigated:



91l–n **94a–c** **93i–k**

91l, 93i, 94a R = 4-$CH_3OC_6H_4$, A = BF_4^-; **91m, 93j, 94b** R = 4-$CH_3OC_6H_4$, R^1 = C_6H_5, A = CF_3COO^-; **91n, 93k, 94c** R = R^1 = 4-$CH_3OC_6H_4$, A = CF_3COO^-

Octahydrothiochromenes with the *cis* configuration **94a-c** were isolated with yields of 38-48% 7-8 h after the beginning of the reaction; the hydrogenation product contained a small amount (5-20%) of the corresponding perhydrothiochromans **93i-k**. This fact indicates that the octahydrothiochromenes are intermediates in the hydrogenation of the thiochromylium salts. The decahydrothiochromans **93i-k** also have the *cis* configuration and are formed with yields of 42-56% 12-14 h after the beginning of the reaction. The yields of the products from hydrogenation of the thiochromylium tetrafluoroborates are somewhat higher than for the corresponding trifluoroacetates.

The material presented in the review and the results of the authors' own investigations indicate that positive advances have been made in recent years in the study of the catalytic reduction of heterocyclic onium compounds (pyridinium, pyrylium, and thiopyrylium salts). Above all the broad possibilities of the method in the synthesis of saturated heterocycles of the piperidine, tetrahydropyran, and thiacyclohexane series and their condensed analogs have been revealed; by this method it is possible to obtain the thermodynamically less stable isomers of the *cis* type, and this is particularly important in the stereospecific synthesis of heterocycles with a given structure, including those close to natural heterocycles and those of practical significance. Moreover, by varying the reaction conditions and the nature of the catalyst within wide limits it is possible to realize selective reduction of the heterocycle and the substituting groups and, in the case of pyrylium salts, cleavage of the heterocycle with the formation of aliphatic-aromatic hydrocarbons and 1,5-diols. The data presented in the review demonstrate the prospects of the method and indicate the desirability of further study.

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