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FIVE-, SIX-, AND SEVEN-MEMBERED LACTIM ETHERS. METHODS OF SYNTHESIS AND CHEMICAL PROPERTIES. (REVIEW)

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Data on methods for the production of 5-7-membered lactim ethers and their chemical transformations published after 1970 are reviewed.

Keywords: lactim ethers, production methods, rearrangements, substitution, recyclization, heterocyclic ring opening.

Lactim ethers (LE) – cyclic imino ethers – have high reactivity and are widely used as starting materials in organic chemistry. Lactim ethers based on five-, six-, and seven-membered nitrogen-containing rings have been used and studied most often. Many interesting compounds having practical application have been obtained from them, and the total synthesis of a series of alkaloids, often of fairly complex structure, has been realized. Some important theoretical aspects of organic chemistry have been resolved during the study of the chemical characteristics of lactim ethers.

In spite of the great interest of many researchers in lactim ethers only one review, published in 1970, of data existing at that time on their production and chemical transformations is known [1]. In the last 40 years a large number of papers on new approaches to the synthesis of lactim ethers and an enormous amount of material on their chemical transformations have been published.

The first part of the present review is devoted to methods for the production of lactim ethers. Some of those examined in [1] are as a rule discussed in general terms with a mention of the most important references.

Data on the chemical properties of lactim ethers are reviewed in the second part of the review. In most sections their reactions with one particular functional group are discussed even if they contain two or more such groups. Since adequate attention was paid earlier [1] to the reactions of lactim ethers with amines and the new material that has appeared is fairly uniform and extensive, these reactions are described in concise form, but almost all the references are retained (see section 2.5).

Reactions of lactim ethers with bifunctional compounds, resulting in cyclization with the formation of new heterocyclic rings, are included in a special section (2.13). Processes accompanied by opening of the lactim ether ring (2.14) and isomerization reactions (2.15) are examined separately. In the concluding section (2.16) individual reactions of lactim ethers with compounds not corresponding the employed classification are described.

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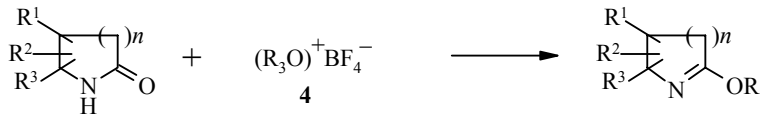
1. METHODS FOR THE SYNTHESIS OF LACTIM ETHERS

γ-Butyrolactam (**1**), δ-valerolactam (**2**), and ε-caprolactam (**3**) and their derivatives are most often used as starting compounds for the production of lactim ethers.

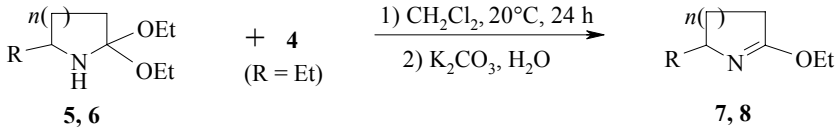
1.1. Reactions of Lactams with Dialkyl Sulfates or Trialkyloxonium Fluoroborates

The heating of lactams with dimethyl sulfate [2-15], or more rarely diethyl sulfate [4, 5, 15-17], is the most widely used method for the synthesis of lactim ethers (Table 1).

The second method in frequency of use for the production of lactim ethers is the treatment of lactams with trialkyloxonium fluoroborates **4** at 20-25°C [3, 4, 16-21] (Table 2).



Treatment of the diethoxy derivatives **5** and **6** with the salt **4** (R = Et) also led to lactim ethers **7** and **8** with yields of 97.0 and 81.5% respectively [22].



5, 6 **7, 8**

5, **7** *n* = 1, R = Pr; **6**, **8** *n* = 2, R = H

TABLE 1. Reactions of Lactams with Dialkyl Sulfates R_2SO_4

n	R	R^1, R^2, R^3 [references]	Reaction conditions *	Yields of LE, %
1	Me	H, H, H [2-6]; H, H, 5-COOMe(Et) [7]; H, H, 5-Me [8, 9]	60-100°C, 4-24 h	30-88
2	Me	H, H, H [6, 10, 11]; H, H, 6-Me [9]; H, H, 6-Et [3]	boiling, 4-24 h and 60°C, 12 h [9]	55-84
	Et	H, H, H [17, 16]		
3	Me	H, H, H [3, 5, 10, 12-14]; H, H, 5-Me [10]; H, H, 5-Bu [10]; H, H, mixture 4- and 6-Me [10]; H, H, mixture 3- and 7-Me [15]; 4,4,6-Me_3 [10]; 4,6,6-Me_3 [10]	80-90°C / heating, 80°C	58-81 86
	Et	H, H, H [15]	—	—

* Solvent PhH [6, 10]; Et_3N, Et_2O [7]; Me_2CO [14].

TABLE 2. Reactions of Lactams with Trialkyloxonium Fluoroborates **4**

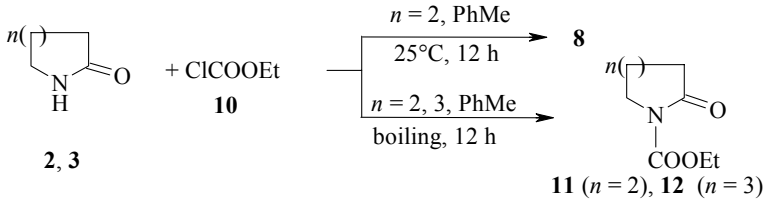
n	R	R^1, R^2, R^3 [references]	Reaction conditions *	Yields of LE,, %
1	Me	H, 4-Me, 5-Et [20]	—	—
	Et	H, H, H [3, 16, 18, 19]; H, H, 3-Me [17, 19]; H, H, 4-Me [19]; H, H, 5-Me [17, 19]; H, H, 4-Ph; H, H, 5-Ph; H, H, 4-(4-MeC_6H_4) [19]; H, H, 3-CH_2Ph [17]; H, 3-COOMe(Et), 4-Ph; H, 3-COOMe, 4-MeC_6H_4; H, 4-Ph, 3-COOMe; H, 4-Ph, 3-Et; H, 4-Ph [19]	20-25°C 6 h [19] 12 h [17], 12-20 h [3, 18], 1 h [16]	45-80 98 [16]
2	Me, Et	H, H, H [4], H, H, H [3, 4]	20°C, 12 h	84-92
3	Me, Et	H, H, H [3, 4]; H, H, H - [21]	20°C, 12 h	80-94

* Solvent CH_2Cl_2 (with $Et_2O{\cdot}HBF_4$) [17], CH_2Cl_2 [3, 16, 18, 19].

1.2. Other Methods for the Synthesis of Lactim Ethers

During treatment of the lactam **3** with methyl fluorosulfonate (**9**) (20°C, 1 h) caprolactim methyl ether was obtained with a yield of 90% [23]. In the case of the lactam **2** (20°C, 1-2 h, CH_2Cl_2) the corresponding lactim ether was obtained with a yield of 78% only when the excess of the ester **9** was removed before the product was isolated. With an excess of the ester **9** the N-methyl derivative of valerolactam is obtained instead of the lactim ether [24].

In [25, 26] it was shown that the conditions have a substantial effect on the reaction between the lactams **2** and **3** and the chlorocarbonic ester (**10**). Thus, as a result of the reaction of the latter with the lactam **2** at 25°C in toluene the lactim ether **8** was obtained with a yield of 7%. From compounds **2**, **3**, and **10** in boiling toluene the corresponding N-ethoxycarbonyllactams **11** and **12** are formed with yields of 55-70% [25].

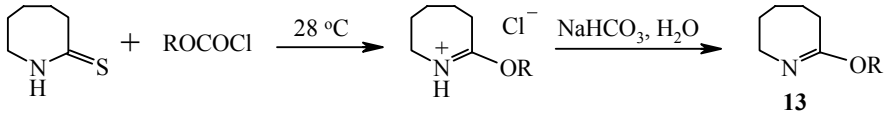


2, **3**

11 (*n* = 2), **12** (*n* = 3)

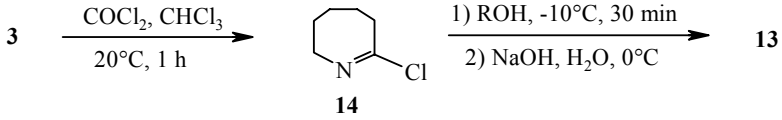
In more recent work [26] it was possible to obtain lactim ethers with good yields (63-65) by reaction of the lactams **2** or **3** with the ester **10** at moderate temperature (40-45°C, 4 h; 25°C, 16 h) without a solvent.

Various lactim ethers **13** were synthesized from thiocaprolactam and chlorocarbonic esters by holding them at 28°C until the release of COS had ceased [27].



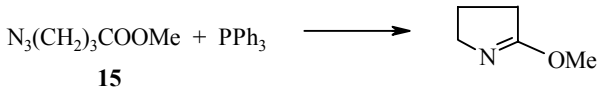
R, (time, min), yield of **13**, %: Et, (20), 83; CH_2CHMe_2, (20), 50; CH_2CMe_3, (45), 40

Lactim ethers of type **13** were also obtained by a two-stage method involving reaction of the caprolactam **3** with phosgene and subsequent treatment of the obtained chlorine derivative **14** with alcohol [28].



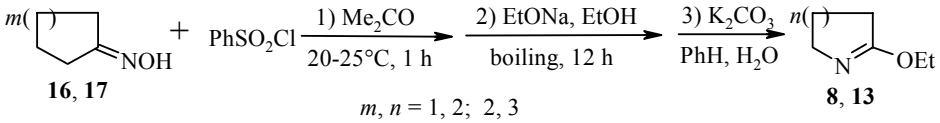
R, yield of **13**, %: Me, 63; *i*-Pr, 61; cyclohexyl, 57; CH_2Ph, 49; Ph, 13; *t*-Bu, 0

With triphenylphosphine methyl 4-azidobutyrate (**15**) undergoes cyclization with the formation of butyrolactim methyl ether [29].



Lactim ethers are formed with high yields (85-95%) when gaseous diazomethane is passed through a solution of the lactams **1-3** in ether at normal temperature in the presence of silica gel and sodium bicarbonate [30, 31].

During reaction with benzenesulfonyl chloride followed by treatment with sodium ethoxide and potassium carbonate the oximes of alicyclic ketones **16** and **17** undergo recyclization and are converted into the ethers of valero- and caprolactims **8** and **13** respectively [26].

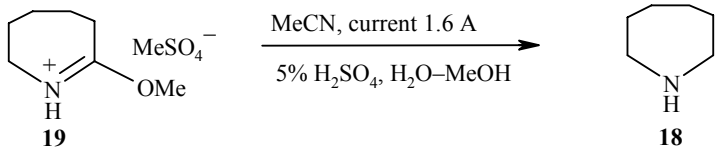


m, *n* = 1, 2; 2, 3

2. CHEMICAL PROPERTIES OF LACTIM ETHERS

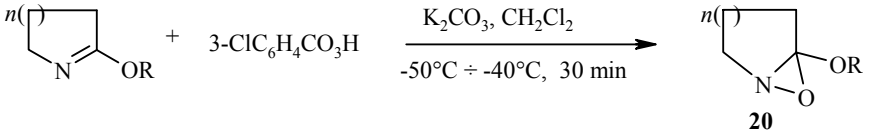
2.1. Reduction

During hydrogenation (120°C, 200 atm, 4 h) over Al_5Co–β-AlCo–Co_2C–Al_2O_3 (86.5:90:3.1:1.4) as catalyst the ethers of butyro- and caprolactim and also the 4,4,6-trimethyl-substituted ether of caprolactim are converted with high yields into the corresponding tetra- and hexamethyleneimines [32]. The hydrogenation of valerolactim methyl ether over nickel catalyst led to pentamethyleneimine with a yield of 76.4% [32]. Hexamethyleneimine (**18**) was obtained with a yield of 82% as a result of cathodic reduction of the salt **19** in an anolyte with 5% of H_2SO_4 in a mixture of water and methanol [33].



2.2. Oxidation

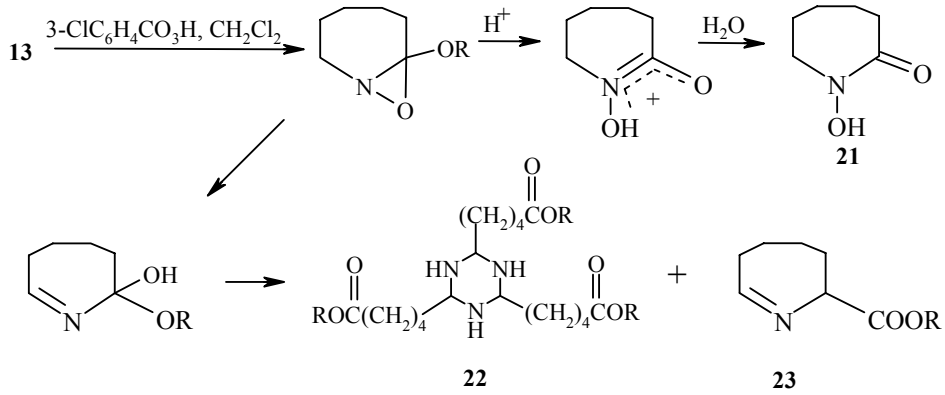
During the oxidation of lactim ethers from lactams **2** and **3** with 3-chloroperbenzoic acid at -50 to -40°C in the presence of K_2CO_3 good yields of the corresponding oxaziridines **20** were obtained [34, 35].



20

n, R, (yield of **20**, %): 1, Me (75); 1, Et (47-66); 3, Me (50)

During oxidation at -60°C and treatment of the reaction mixtures with water small yields of the N-hydroxycaprolactam (**21**) and also the esters **22** in mixture with the monomers **23** that form them were obtained [36, 37].



R, (yield of **21**, yield of **22**, %): Me, (3.0, 1.1); CH_2CH=CHPh (13.0, 13.0)

During oxidation of the lactim ether (R = Me) from the lactam **2** under the same conditions N-hydroxyvalerolactam was isolated with a 10% yield [37].

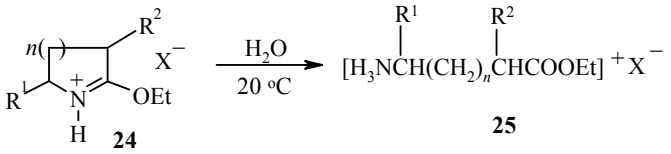
Oxidation of the lactim ether from caprolactam **3** with monoperphthalic acid (K_2CO_3, CH_2Cl_2, Et_2O, -60°C to -10°C, 0.5 h) results in the formation of methyl 6-nitrosocaproate (yield 10%) and methyl 6-iminohexanoate (yield 11%) [37].

3-Acetoxy-2-methoxy-3,4,5,6-tetrahydropyridine was synthesized by the reaction of valerolactim methyl ether with lead tetraacetate in THF in the presence of 4-vinylpyridine polymer (20°C, 2 h, 50°C, 1 h) [38].

2.3. Reactions with Inorganic Reagents

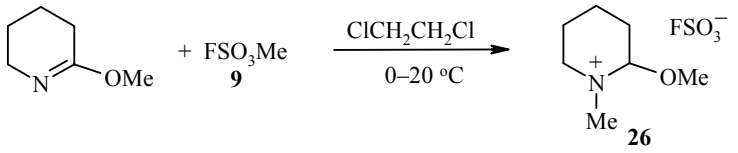
When boiled in water 4-phenylbutyrolactim methyl ether is converted into 4-phenylbutyrolactam [21]. In the same work it was shown that this transformation takes place spontaneously if the lactim ether is held in air for a long time.

The salts of the lactim ether **24**, formed with high yields by the action of gaseous hydrogen chloride (diethyl ether, 25) or hydrofluoroboric acid (methylene chloride, 5°C) on the corresponding lactim ethers, are converted by the action of water at room temperature into the salts of the esters of ω-amino carboxylic acids **25** [16, 17].

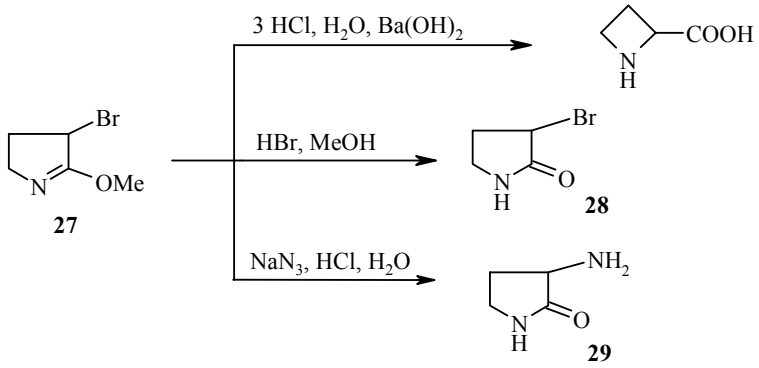


n, R^1, R^2, X, (time, h), yield of **25**, %: 1, H, H, Cl, (10), 88;
2, H, H, BF_4, (72), 90; 3, H, H, Cl, (24), 90; 3, H, H, BF_4, (72), 81; 1, H, Me, Cl, (144), 90;
1, H, CH_2Ph, Cl, (144), 86; 1, H, CH_2Ph, BF_4, (144), 87; 1, Me, H, Cl, (72), 93;
1, Me, H, BF_4, (72), 91

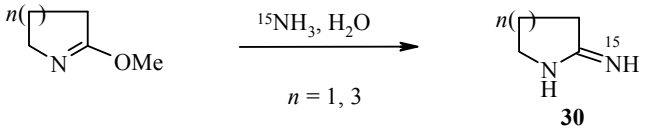
The reaction of valerolactim methyl ether with methyl fluorosulfonate (**9**) gives an 80% yield of the fluorosulfate **26** [24, 39].



The bromine derivative **27**, obtained by the action of N-bromosuccinimide on butyrolactim methyl ether, undergoes recyclization to azetidinecarboxylic acid when treated with hydrochloric acid and barium hydroxide, is converted into 3-bromobutyrolactam **28** in reaction with hydrogen bromide in methanol, and is converted into 3-aminobutyrolactam **29** by the action of sodium azide and hydrochloric acid [40].

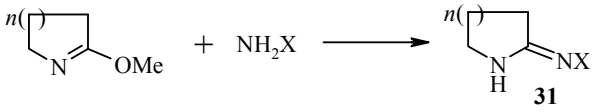


Treatment of butyro- or caprolactim methyl ethers with an aqueous solution of ammonia containing the ^{15}N isotope gave the labeled cyclic amidines **30** [41].



The hydrochlorides of substituted cyclic amidines (derivatives of penta- and tetramethyleneimine) containing the NH·HCl group at position 2 were obtained by the action of ammonium chloride on the methyl ethers of 3- or 7-methylcaprolactim [15], 7-propylcaprolactim [42], and 6-ethyl-4-methylbutyrolactim [20].

Treatment of the respective lactim ethers with hydroxylamines, cyanamides, or thiourea led to derivatives of lactams **1**-**3** of type **31** [14, 43, 44].

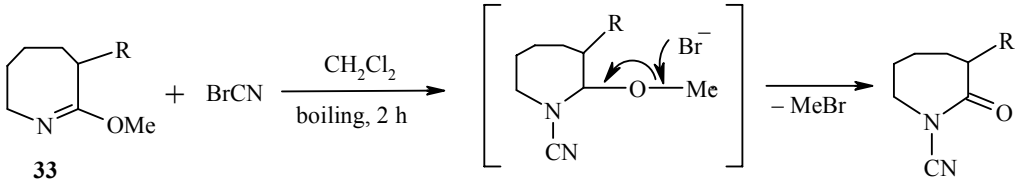


n, X, (conditions), yield of **31**, %: 3, OH (hydrochloride), ($NaHCO_3$, MeOH, boiling, 15 h) 87 [14]; 1, 2, 3, CN (MeOH, 20°C , 2 h), – [43]; 1, 2, 3, $C(=S)NH_2$, (–), 65-72 [44]

Butyrolactim methyl ether condenses with hydrazine hydrochloride at room temperature with substitution of the OMe group by the $NHNH_2$ group and the formation of 2-hydrazino-Δ^1-pyrroline hydroiodide (yield 80%) [45].

The reactions of the lactim ethers from butyro- and caprolactam with hydrazine hydrate gave 2-hydrazinopyrrolidine and 2-hydrazinopiperidine, which were submitted to further transformations without isolation [46].

The derivatives of 1-cyanocaprolactam (**32**) were synthesized by the reaction of the lactim ether **33** with cyanogen bromide [32].

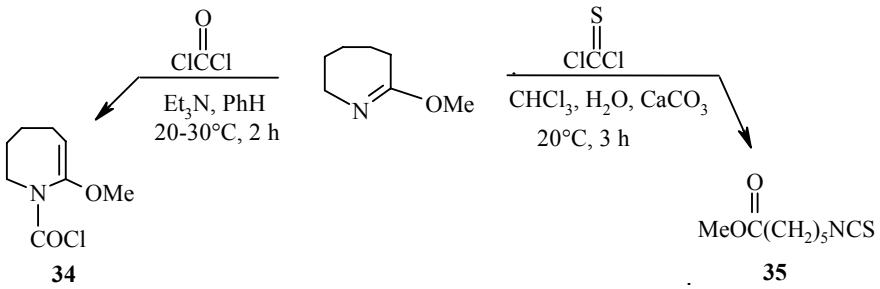


33 **32**

R = Me, Et, Pr

The reaction of caprolactim methyl ether with phosgene in the presence of triethylamine gave a 94% yield of its 1-chlorocarbonyl derivative **34** [47]. It was not possible to obtain a product from the reaction of phosgene with two molecules of the same lactim ether [47].

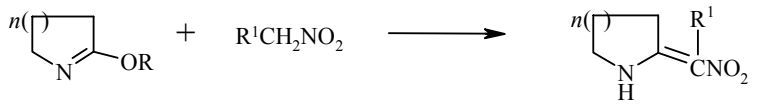
The above-mentioned lactim ether reacts with thiophosgene in a completely different way. In this case the isothiocyanate **35** is formed with a yield of 56% [48].



34 **35**

2.4. Reactions with Compounds Containing Activated CH_2 Groups

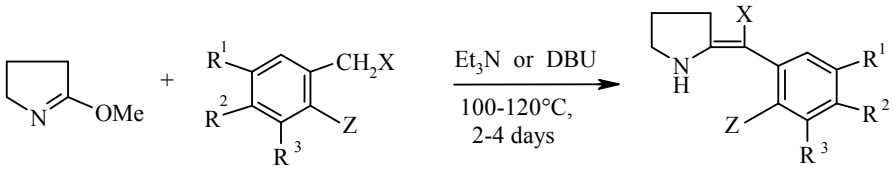
The reactions of lactim ethers with compounds containing CH_2 groups with hydrogen atoms activated by one (X) or two (XX, XY) electron-withdrawing groups lead to derivatives of tetra-, penta-, or hexamethyleneime with the substituent =CHX, $=CX_2$, or =CXY at the α-position to the nitrogen atom of the ring. Thus, heating of valero- or caprolactim ethers with nitromethane [11, 49, 50] or nitroethane [49] without solvents gave the products **36**, which were patented as insecticides [49]. The nitro esters **37** were synthesized from nitroacetic esters and butyrolactim ethyl ether in the form of a mixture (3:2) of the (*E*)- and (*Z*)-isomers.



36 (R^1 = H/Me)
37 (R^1 = $COOR^2$)

n, R, R^1, (conditions): 2, Me, H, (boiling for 3 days) [11]; 2, Me/Et, H/Me (–) [49]; 3, Et, H, (140-145°C, yield 75%) [50]; 1, Et, $COOR^2$ (80°C, 12 h), R^2 = Et, yield 40%, R^2 = (–)-menthyl, yield 30% [51]

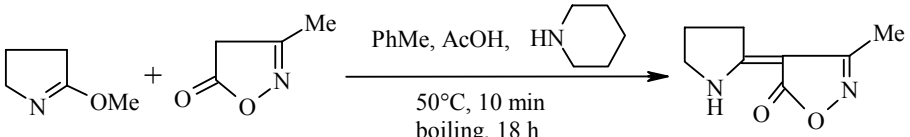
Compounds **39** were formed when butyrolactim methyl ether was heated with derivatives of phenylacetic acid **38** in the presence of triethylamine or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in an inert atmosphere [52, 53].



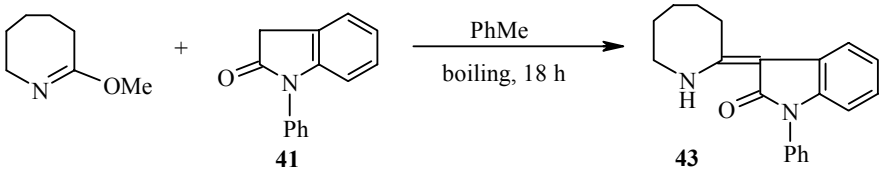
38 **39**

X = CN, R^1, R^2, R^3, Z, (time, days), yield of **39**, %: H, OMe, H, H, (4), 51; OMe, OMe, H, Br, (3), 79; OMe, Me, H, Br, (3), 64; OMe, OMe, Br, H, (2), 75 [52]; H, H, H, H, (4), –, [53]; X = COOMe, R^1+R^2 = OCH_2O, R^3 = Z = H, (4), 10 [52]

When boiled in toluene with the lactim ethers from butyro- or caprolactam compounds **40** or **41**, containing a $–CH_2C(=O)–$ group in the heterocyclic ring, form the crotonic condensation products **42** or **43** with yields of about 50% [54, 55].

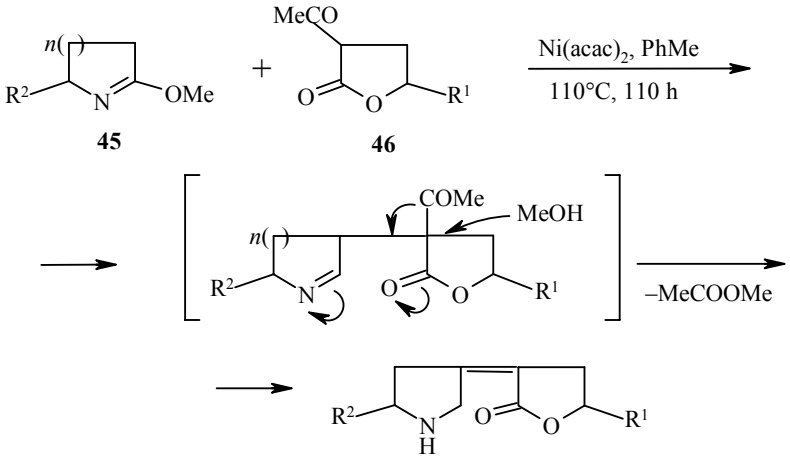


40 **42**



41 **43**

Condensation of the lactim ether **45** with the acetyl derivatives of lactones **46** in the presence of nickel acetylacetonate, which takes place with displacement of the acetyl group, leads to the analogous products **44** [8, 56].

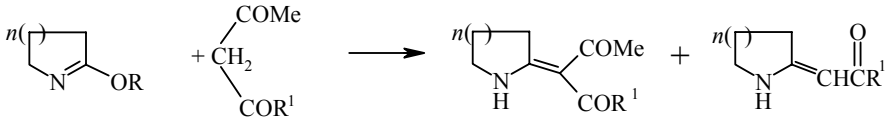


45 **46** **44**

n, R^1, R^2, yield of **44**, %: 1, H, Me, 65 [8, 56]; 1, H, H, 56; 1, Et, H, 53; 1, C_8H_{16}, H, 30; 1, $(CH_2)_2CH{=}CH_2$, H, 40; 1, Ph, H, 14; 1, CH_2Cl, H, 16; 1, H, Me, 65; 1, Et, Me, 40; 1, C_7H_{15}, Me, 19; 2, H, H, 56; 2, Et, H, 33 [56]

The reaction of lactim ethers with compounds in which the CH_2 group is activated by two electron-withdrawing groups was studied in greater detail. Some examples of such reactions have already been given above.

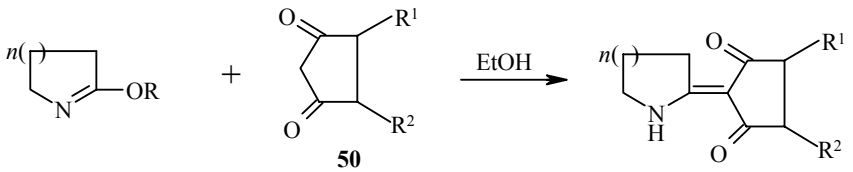
In [22, 57] it was reported that compounds **48** were obtained as a result of reaction of the lactim ethers from butyro- and valerolactam with diketones **47**. More recently, however, the authors of [58] obtained two products **48** and **49** in each case from the ethers of butyro-, valero-, or caprolactim **47** (R^1 = Me).



47 **48** **49**

n, R, R^1, (conditions), yields of **48** and **49**, %: 1, Et, Me, (110°C, 4.5 h), 13, –; 1, Et, Et, (110-120°C, 3.5 h), 18, – [22]; 2, Et, Me, ($Ni(acac)_2$, 100°C, 12 h), 33, – [57]; 1, Et, Me, ($Ni(acac)_2$, 100°C, 12 h), 64, –; 3, Et, Me, ($Ni(acac)_2$, 100°C, 12 h), 36, – [57]; 1, Me, Me, (here and subsequently Et_3N, 100°C, boiling, 2 days), 45, –; 2, Me, Me, 26, 25; 3, Me, Me, 31, 33 [58]

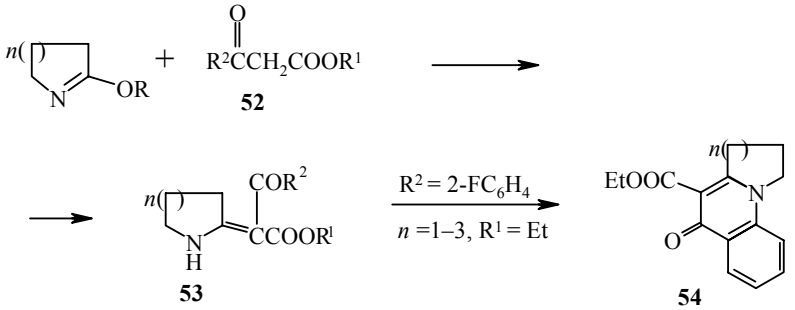
The mono- and bicyclic diketones **50** react with lactim ethers in boiling alcohol with the formation of compounds **51** [22].



50 **51**

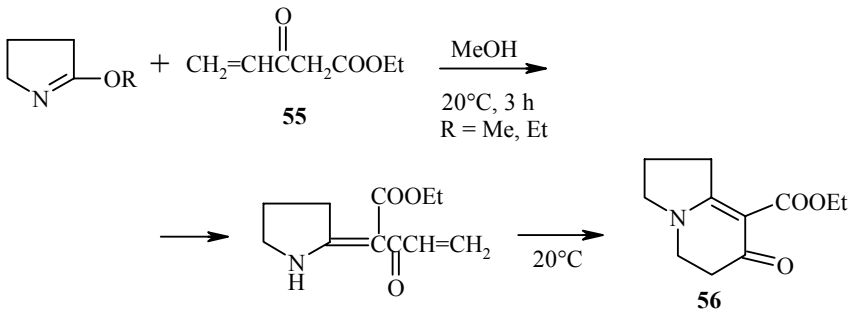
n, R, R^1, R^2, or R^1+R^2, (conditions), yield of **51**, %: 1, Et, H, H, (boiling, 1 h), 43; 2, Et, H, H (boiling, 2 h) 50; 3, Me, H, H, (120-130°C, 2 h), 39; 1, Et, =CH–CH=CH–CH=, (boiling, 5 h), 20

The reactions of lactim ethers with the esters of β-oxo carboxylic acids **52** have been studied for many examples, and the keto esters **53** were synthesized [2, 22, 57, 59-63]. However, with R^2 = 2-FC_6H_4 the reaction products were tricyclic compounds **54** as a result, clearly, of cyclization of the initially formed keto esters **53** [64].

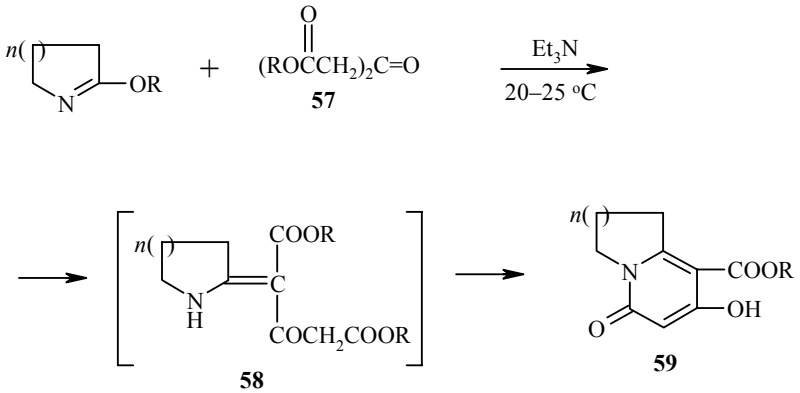


n = 1-3, R, R^1 = Me, Et, R^2, conditions (yield of **53**, %): Me, 85°C, N_2, 72 h (77) [2]; ampule, 100°C, Et_3N, 50 h (47) [59]; ampule 110°C, $PrEt_2N$ (4) [60]; – (90) [61]; 110-120°C, 4 h (16.5) [22]; Me, Pr, *i*-Pr, *t*-Bu, Ph, 100°C, Ni $(acac)_2$, 12 h (28-61) [57]; 2, 4-Cl_2-5-FC_6H_2, 65-80°C, Et_3N, N_2, 48 h (63-80) [62]; 3-chloro-2-quinoxalyl, 20°C, 2.5 days (75) [63]; 2-FC_6H_4, 110-115°C, 3 days, –, yields of product **54** 56-97% [64]

The product from the reaction of butyrolactim methyl and ethyl ethers with the ester of the unsaturated keto acid **55** undergoes cyclization *in situ* even at normal temperature with the formation of the bicyclic compound **56** [65, 66].

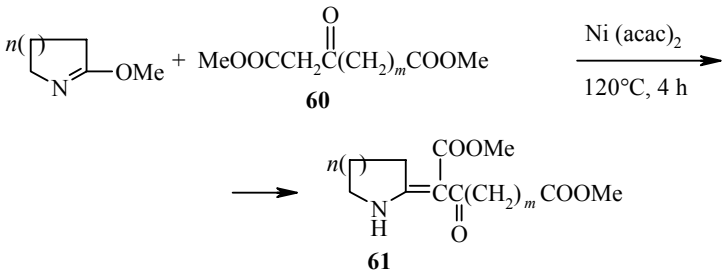


In the case of the diesters of symmetrical oxo dicarboxylic acids **57** it was not possible to obtain the initially formed products **58** even as a result of reaction with the lactim ether from lactams **1** and **2** at normal temperature, since they immediately underwent cyclization to the condensed lactams **59** [67, 68].



n, R, time, days (yield of **59**, %): 1, Me, 2 (66); 3, Me, 2 (55) [67]; 2, Me, 14 (57); 2, Et, 14 (43) [68]

However, the corresponding keto diesters **61** were synthesized with yields of 21-52% from the unsymmetrical ketodiesters **60** and lactim ethers (derivatives of lactams **1**-**3**) by heating in the presence of nickel acetylacetonate [69].

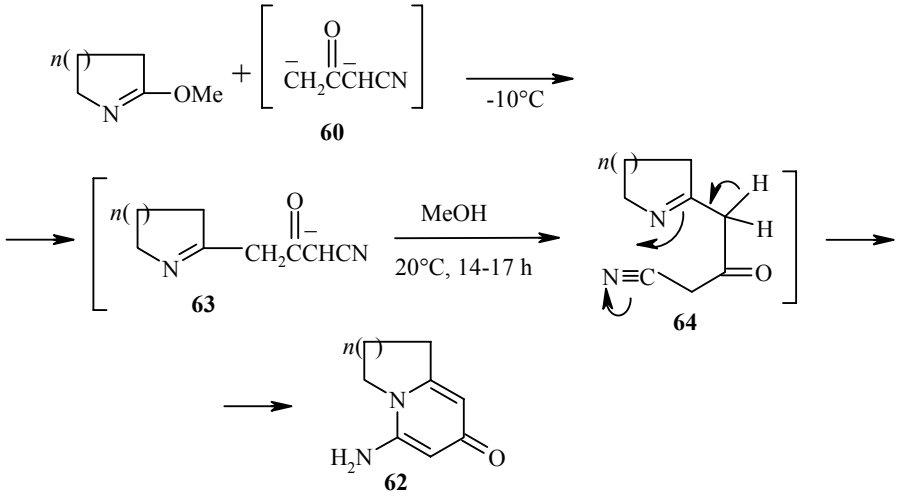


n, *m*, (yield of **61**, %): 1, 2, (52); 2, 2, (41); 1, 3, (47); 3, 2, (21); 2, 3, (34)

When boiled in toluene with the keto nitrile $PhCOCH_2CN$ the lactim ether from butyrolactam (R = Me) forms the corresponding condensation product 2-(benzoylcyanomethylene)tetrahydropyrrole (yield 68%) [70].

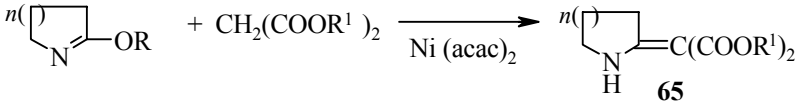
According to the authors of [71], the process leading to the formation of compounds **62** from the lactim ethers and the dianion of $CH_2COCHCN$, produced *in situ* as a result of treatment of 5-methylisoxazole with $(i\text{-Pr})_2NLi$, takes place through the formation of the anion **63**.

The reaction does not go in the absence of methyl alcohol, since during the transformation of the anion **63** into the nitrile **64** proton exchange occurs as an essential stage for the subsequent addition of the nitrogen of the imino group to the CN group [71].



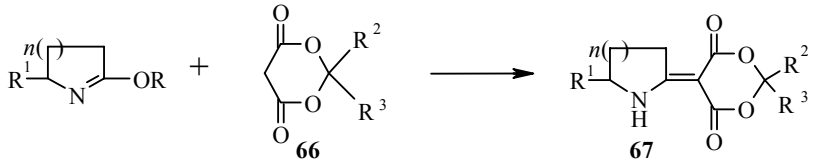
n, (yield of **62**, %): 1 (30), 2 (40), 3 (40)

The reactions of lactim ethers with malonic esters have been studied in a number of papers [57, 72, 73]. As a rule, the yields of the final products **65** were low (17-25%). Only in [73] was it reported that the yield of the diester **65** (*n* = 1, R = Me) amounted to 72%.



n, R, R^1, (conditions): 1, Et, Et, (100°C, 12 h); 2, Et, Et, (–); 3, Et, Et, (–) [57];
1, Me, Me, (boiling, 2 days) [72]; 1, Me, Me, (20°C, 1 h) [73]

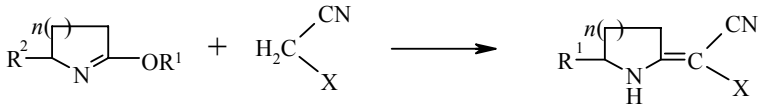
There are a large number of examples of the condensation of lactim ethers with cyclic esters of malonic acid **66**, leading to compounds **67**, under various conditions [7, 9, 22, 58, 74, 75]. However, the obtained results do not make it possible to reach definite conclusions about the dependence of the yields of the products **67** on the structure of the initial compounds and the reaction conditions. The production of compounds **67** [*n* = 1-3, R^1 = H, $Me(CH_2)_{0-14}$, R^2 = R^3 = Me] was filed in a patent [76].



66 **67**

n = 1, 2, 3; R = Me, Et; R^1 и R^2 = H, Me, Pr; R^3 = H, Me, Pr, *i*-Pr. Solvent, catalyst, temperature, °C, time, h (yield of **67**, %):
–, 80-130, 2-6 (20-85) [7, 22], –, 140-150, 2 (9) [22]; EtOH, –, 100, 6 (14) [22]; EtOH, –, boiling, 1 (61) [22];
PhH, AcOH, piperidine (58) [22]; Ph, Et_3N, boiling, 24 (90) [58]; –, $Ni(acac)_2$, (82) [75];
$CHCl_3$, $Ni(acac)_2$, boiling, (75-84) [9]; PhH, Et_3N, boiling, 12 (58-94) [74]

Unsubstituted and also methoxycarbonyl- or ethoxycarbonyl-substituted lactim ethers react readily with derivatives of cyanoacetic acid and malononitrile, forming the corresponding products **68** with moderate (53-70%) or high (75-98%) yields. The reactions with the esters [7, 77, 78] and amide [77, 79] of cyanoacetic acid are usually carried out at 80-120°C for 1-24 h. With R^1 = Me, R^2 = H, and X = COOMe the product **68** was obtained with a yield of 90% after 1 h at only 20°C [73]. Reaction with the amide [80] and substituted amides of cyanoacetic acid and also with the amide of cyanothioacetic acid [81] takes place when the reagents are boiled in DMF (3 h). Malononitrile reacts with the lactim ether at 20°C (1 h) without a solvent [73] or in alcohol [82] and also on boiling (3 h) in DMF [80].



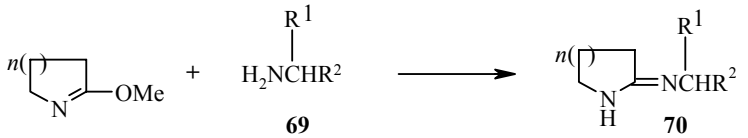
68

n = 1, 2, 3; R^1 = Me, Et; R^2 = H, COOMe, COOEt; X = COOMe, COOEt, $CONH_2$, CONHPh, $CONHCH_2Ph$, $C(=S)NH_2$, CN

2.5. Reactions with Compounds Containing NH_2 or NH Groups

In this section the reactions of lactim ethers with organic compounds containing primary or secondary amino groups occurring at only these groups are examined. The reactions of lactim ethers with aliphatic, acyclic, or aromatic compounds that also contain other functional groups, including cyclization and ring cleavage processes, are examined in other sections. Due to the large number of publications [83-128] in which the reactions of lactim ethers with amines are described and to the enormous number of synthesized compounds, this material is examined in a concise more general form.

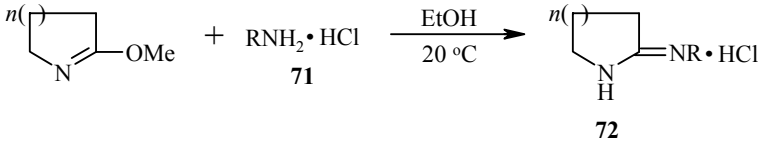
The reaction of lactim ethers with primary amines **69** containing various functional groups (the reactions with R^1 = H and R^2 = Ar were carried out with the amine hydrochlorides), and only products **70** from reaction at the amino group were obtained.



69 **70**

n = 1-3; R^1, R^2, (conditions, yield of **70**, %): R^1 = H, R^2 = $CH(OMe)_2$ [83], CH_2SO_3H [84], PhCO, 4-MeO-4-Cl-, 4-Br-, 4-$O_2NC_6H_4$ [85] (EtOH, 20°C, 24-72 h, 62-83%), $(CH_2)_2SO_3H$ [84] (N_2, DMSO, 110-120°C, 1 h, 82-90%); R^1 = COOH, R^2 = H, *i*-Pr, CH_2Ph [87] (110-120°C, 1-3 h, 5-25%); H, CH_2SH, CMe_2SH, $(CH_2)_2SMe$, $(CH_2)_2CONH_2$ [88] (MeOH, 20-25°C, 4-10 h, 43-93%; MeOH, 50-60°C, 4-9 h, 69-85%, under the latter conditions the reactions with R = CH_2SH 47% and CMe_2SH were realized with 2-ethoxycarbonyl-Δ^1-pyrroline, yields 80-86%); R^1 = $(EtO)_2PO$, R^2 = Ph, 4-Me-, 4-MeO-, 4-ClC_6H_4 [86] (PhH, boiling 11 h, 44-75%; 90-115°C, 17-67%); MeCHSH, MeCHOH [89]

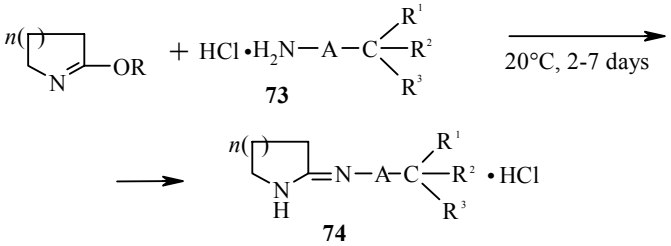
The hydrochlorides **72** were synthesized from lactim ethers and the hydrochlorides of primary amines **71**, mostly of the acyclic series, at 20°C without a solvent [90] or in alcohol [91-95].



71 **72**

n, R: 2, 3, $\overline{CHR^1(CH_2)_mCH}$ (*m* = 1, 3, R^1 = Ph, 4-ClC_6H_4, *cyclo*-C_6H_{11}, 2-thienyl [90]); 2, 3, 1-benzylcyclopentyl [91]; 1-3, 1- and 2-adamantyl, 2-norbornyl [92-94]; 3, 2-phenylcyclopropyl and 2-phenylcyclobutyl, 2-cyclopentylcyclopentyl; 2, 2-cyclohexylcyclopentyl [94]; 2, 3, 2-phenylcyclopentyl; 3, 2-phenylcyclohexyl and 2-phenylcycloheptyl, 2-(4-chlorophenyl)- and 2-cyclohexylcyclopentyl [94, 95]. Reaction time 1-33 days [91-95]. Yields of products **72** 40-80% [94, 95].

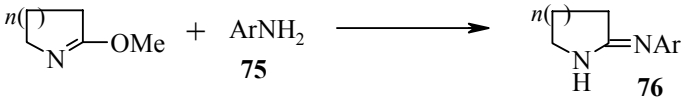
During the condensation of lactim ethers (as a rule at 20°C) with primary amines of the alkyl aromatic series or their hydrochlorides, in which the phenyl or aryl substituents are separated from the amino group by one or several carbon atoms, a large number of products **74** were obtained (yields 25-90%) [94-107]. These reactions were carried out at 20°C (2-26 days) [94-97, 101-107] or with boiling in xylene (10 h) [103], ether (16 h), or methanol [99].



73 **74**

n = 1-3, R = Me, Et; A – single bond, CH_2, CHMe, $(CH_2)_2$; R^1 = H, Me, Pr, Ph, R^2 = H, Me, *cyclo*-C_3H_5, –C_4H_7, –C_5H_9, –C_6H_{11}, –C_7H_{13}, Ph, Ar; R^1+R^2 = $(CH_2)_4$; R^3 = Ph, Ar

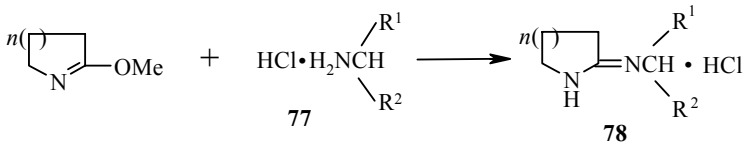
The reaction of lactim ethers with aniline derivatives **75** was carried out by heating in xylene (3 h) [108] or at 140-150°C (10 h) [100], and as a result the cyclic amidines **76** were obtained.



75 **76**

n, Ar, yield of **76**, %: *n* = 3, 4-$CF_3C_6H_4$, – ; 3-$MeOC_6H_4$, – ; 3-ClC_6H_4, –; 2-(*i*-Pr)-3-$CF_3C_6H_3$, –; 3-$CF_3C_6H_4$, – [100]; Ph, 56; 2-ClC_6H_4, 80; 4-$MeOC_6H_4$, 37; 3, 4-$Cl_2C_6H_3$, 40; *n* = 2, Ph, 60; *n* = 1, 4-$MeOC_6H_4$, 60 [108]

The reactions of lactim ethers with primary amines or their hydrochlorides **77**, containing bi- or tricyclic condensed fragments separated from the amino group by a carbon atom or (in one example [97]) by a CH=CH group (here R^2 = *cyclo*-C_3H_5), were reported in the patents [100, 101, 109, 111] and papers [97, 110].

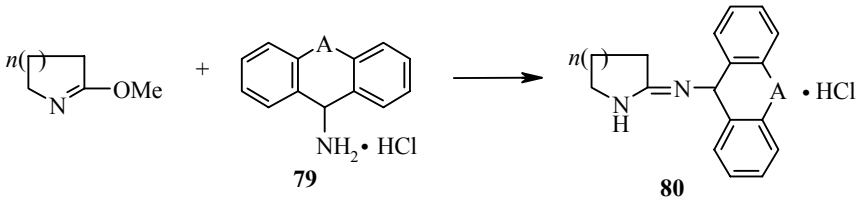


77 **78**

n = 1-3; R^1 = 1-naphthyl-, 2-methyl-, 4-fluoro-, 4-chloro-, 5,6- and 5,8-dimethyl-1-naphthyl, 3-ethyl-5,6,7,8-tetrahydro-2-naphthyl, and 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl, 6-butyl-1,1-dimethylindanyl, 2-fluorenyl, 2-phenanthryl, β-(1-naphthyl)vinyl; R^2 = H, Me, Et, *i*-Pr, *t*-Bu, Ph, 2-MeC_6H_4, *cyclo*-C_3H_5

In most cases the products **78** were obtained with yields of 50-82% [97,110] by keeping the reagents at 20°C for seven days without a solvent [97-111] or in alcohol [95] or by boiling in methanol (3 h) [110] or xylene (10 h) [100].

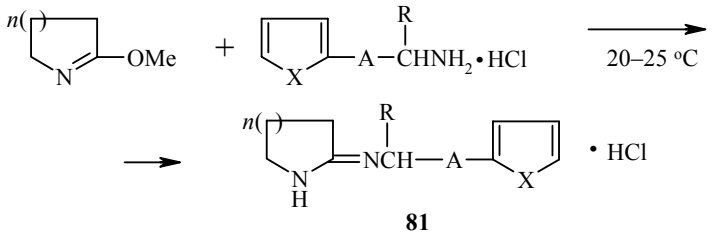
The condensation of lactim ethers with the hydrochlorides of 9-aminofluorene or 5-amino-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene with general formula **79** in boiling methanol or at 20°C for two days leads to the formation of the products **80**, in which the condensed tricyclic fragment is directly attached to the nitrogen atom of the substituent [102].



79 **80**

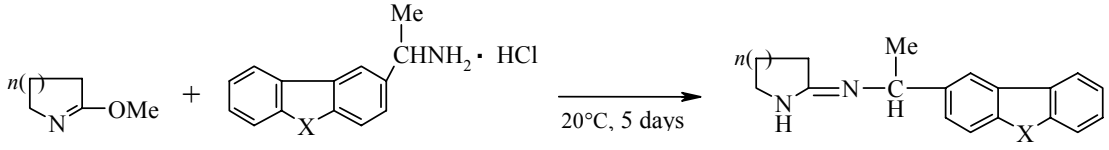
n, A, (yield of **80**, %): 1, bond, (20); 2, bond, (12); 3, bond, (46); 2, CH_2CH_2, (76); 3, CH_2CH_2, (69) [104]

Data on the reaction of lactim ethers with various primary amines or their hydrochlorides containing a heterocycle in the molecule are summarized in the schemes below [97, 111, 114-120].

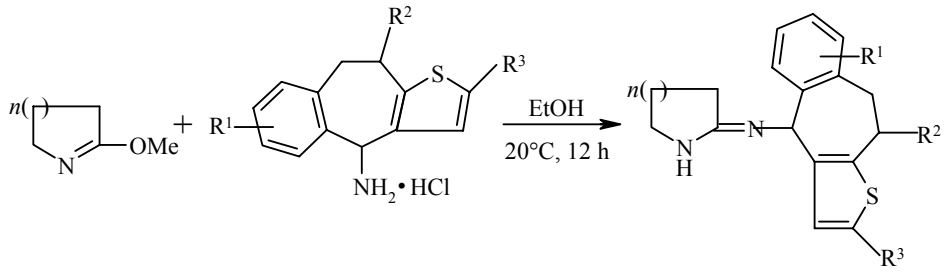


81

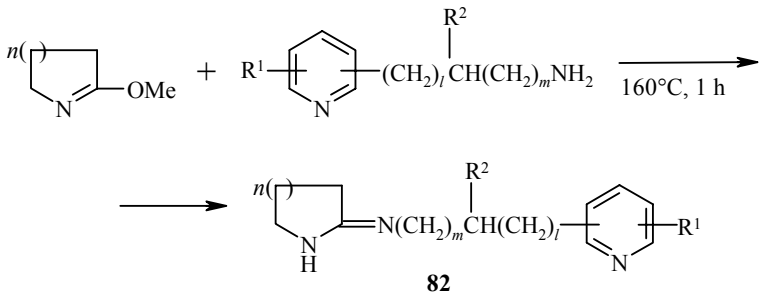
A = 0, X, *n*, R, time, days, (yield of **81**, %): S, 2, *cyclo*-C_3H_5, 12, (72); S, 3, *cyclo*-C_3H_5, 7, (73); S, 4, *cyclo*-C_3H_5, 21, (60); O, 2, Ph, 8, (81); O, 3, Ph, 5, (77); O, 4, Ph, 7, (60); S, 2, Ph, 8, (78); S, 3, Ph, 7, (60); S, 4, Ph, 8, (43).
At A = CH_2, *n* = 3, X = S, R = Et; 5-*tert*-butyl-2-methoxy-Δ^1-pyrroline was also used as lactim ether (8 days, 53%) [97].



n, X: 2, O; 3, O; 3, S [111]

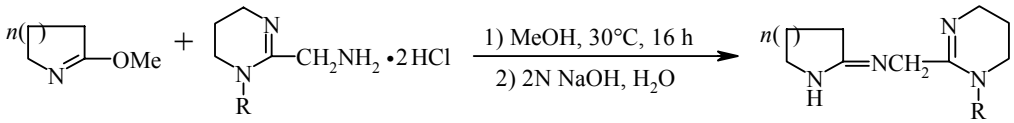


n = 1-3; R^1 = H, 6-Cl, 7-Cl; R^2 = H, Me; R^3 = H, Cl, Me [114, 115]

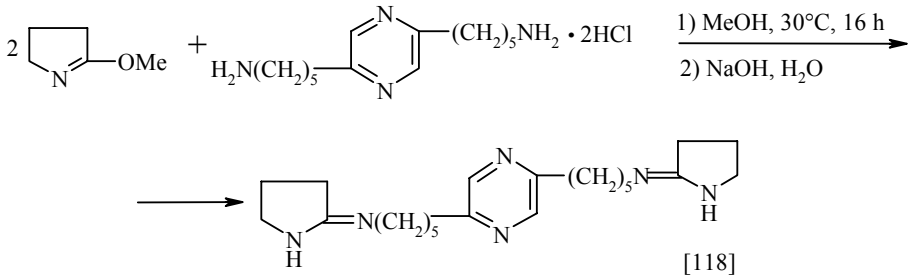


82

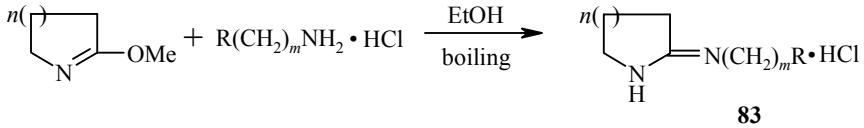
Position of aminoalkyl in pyridine ring, R^1, R^2, *l*, *m*, *n* (yield of **82**, %): 2, H, Ph, 0, 0, 2 (52); 2, 4-Me, Ph, 0, 0, 2 (80); 2, H, Ph, 0, 1, 2 (72); 2, H, Ph, 0, 0, 3 (65); 2, H, Ph, 0, 0, 1 (58); 2, H, Ph, 1, 0, 2 (43); 2, 6-Me, Ph, 0, 0, 1 (54); 4, H, Ph, 0, 0, 1 (63); 3, H, Ph, 0, 0, 1 (77); 4, H, Ph, 0, 0, 2 (48); 3, H, Me, 0, 0, 1 (83) [116]



n, R: 1, Me; 3, H [117]



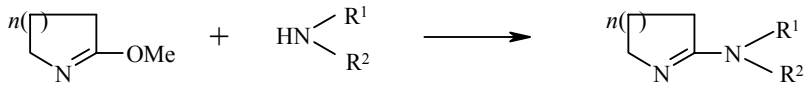
[118]



83

n, *m*, R, time, h (yield of **83**, %): 2 и 3, 2, 6-OH, –SH or $–NMe_2$, 9-purinyl, 11 (74-91); 1-3, 2 и 3, 8-morpholino-, 1-piperidinyl-, 2,3-dimethyl-7-xanthinyl, 2 (50-84) [120]

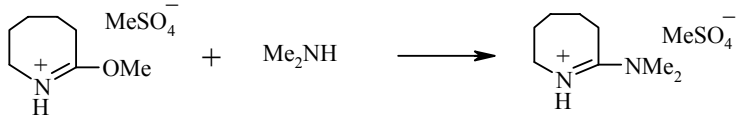
The reaction of lactim ethers with secondary amines was studied for a small number of examples [121-123]. Products of type **84** were synthesized with moderate or high yields by reaction of the reagents at 20°C or by boiling in alcohol.



84

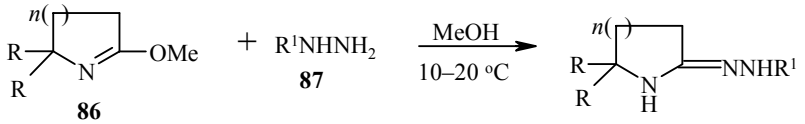
(conditions), *n*, R^1+R^2 or R^1, R^2, yield of **84**, %: (NH_4Br, 20°C, 8 h), 1, CH_2CH_2, 84; 3, CH_2CH_2, 74; 3, CH_2CHMe, 71 [121]; 2, $(CH_2)_4$, 94 (2 days) [122]; (EtOH, boiling for 6-10 h), 1, R^1 subsequently throughout 3-(1,3-dimethyl-7-xanthinyl)-2-hydroxypropyl CH_2CH_2OH, 62; 1, *i*-Pr, 65; 3, Me, 47; 2, CH_2CH_2OH, 42; 3, *i*-Pr, 10 [123]

In [124] the salt **85** was obtained by the reaction of the salt **19** (from caprolactam and dimethyl sulfate) with dimethylamine.



19 **85**

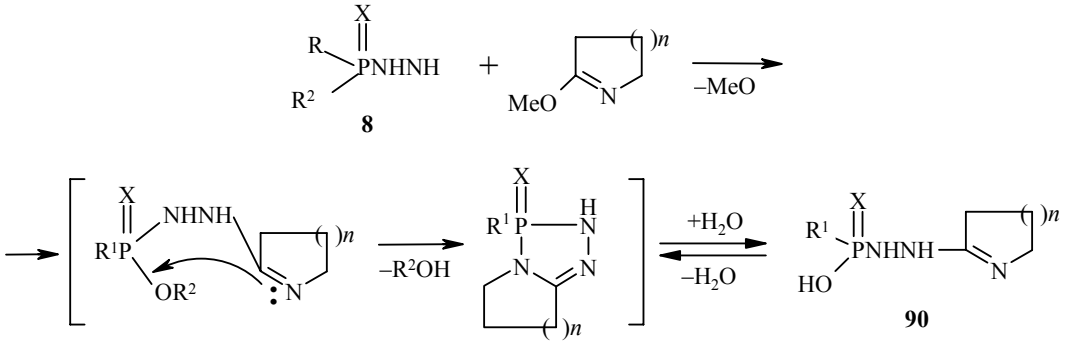
Reactions at an amino group attached to a carbon atom of an alkyl, cycloalkyl, or aryl substituent were examined above. The reactions of lactim ethers with compounds where the amino group is attached to a heteroatom (N, P, O) have also been described. Thus, the lactim ether **86** reacts readily with the aryl(hetaryl)hydrazines **87**, forming the condensation products **88** [125].



86 **87** **88**

n = 1, 3; R = H, Me; R^1 = Ph, Ar, 2-pyridyl, 2-benzothiazolyl

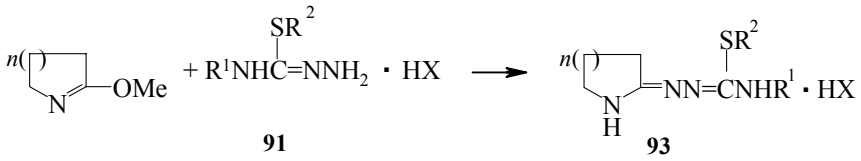
Compounds **90** were synthesized by the reaction of lactim ethers with derivatives of phosphonic or thiophosphonic acids **89** [126].



8 **90**

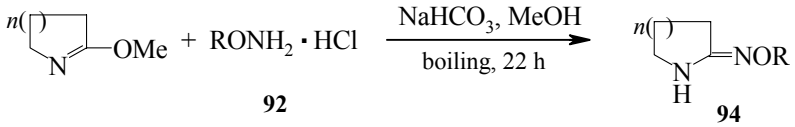
n, X, R^1, R^2, (yield of **90**, %): 1, S, OEt, Et (64); 1, S, Me, H (20); 2, S, OMe, H (44); 2, S, OEt, H (24); 3, S, OEt, H (24); 3, S, Me, H (55); 3, S, OEt, OH (37); 3, O, OPh, OH (10); 3, S, OMe, OH (91)

The products **93** [127] and **94** [126] were obtained from lactim ethers and the salts **91** and **92** respectively.



91 **93**

n = 1, 2, 3; X = I; R^1 = H, Me, Ph; R^2 = Me, Et; X = Br, R^1 = H, Et, R^2 = $CH_2C_6H_4NO_2$-4



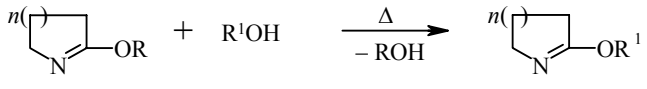
92 **94**

n, R: 1, CH_2Ph; 1, $CH_2C_6H_4F$-2; 1, $CH_2C_6H_4Cl$-4; 1, $CH_2C_6H_3Cl$-2,6; 2, $CH_2C_6H_4Cl$-2; 2, $CH_2C_6H_4Cl$-3; $CH_2C_6H_4Cl_2$-2, 4; 2, $CH_2C_6H_3Cl_2$-2,6

It should be noted in conclusion that many of the compounds synthesized by the reactions of lactim ethers with amines exhibit a wide range of biological activity: They are inhibitors of the coagulation of blood [102, 104-106, 109-112], exhibit hypoglycemic activity [91, 93-95, 104, 108, 109], antiviral activity [92, 93, 103], anti-inflammatory activity [104], antitumor activity [119], and antidiabetic activity [92], and have also been recommended as fungicides [87, 125, 128] or additives that increase the productivity of animals [100].

2.6. Reactions with Alcohols

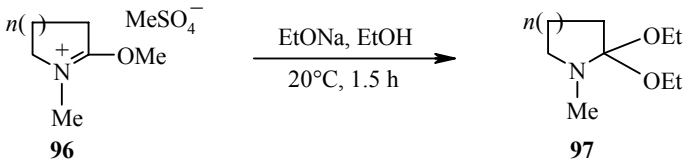
In the reaction of lactim ethers (*n* = 1-3, R = Me, Et) with alcohols transetherification takes place with the formation of the corresponding lactim ether **95** and the release of MeOH or EtOH. The reaction is carried out with heat and usually with distillation of the alcohol. Thus, the lactim ether **95** (*n* = 3, R^1 = CH_2Ph) was obtained with a yield of 82% from caprolactim ether (*n* = 3, R = Me) and benzyl alcohol (5.5 h, benzene, final temperature 120°C) [94]. In the case of butyrolactim ether (*n* = 1, R = Me) and octyl alcohol (5 h, benzene, N_2 atmosphere, final temperature 120°C) the lactim ether (**95**) (*n* = 1, R^1 = C_8H_{17}) was synthesized with a yield of 53.6% [5]. The reaction of the fluorinated alcohol $C_6F_5CH_2CH_2OH$ with lactim ethers was studied in greater detail for various reagent ratios and reaction times [5]. In the case of butyrolactim (*n* = 1, R = Et) and caprolactim (*n* = 3, R = Me) ethers it was shown that the yield of the product (**95**) increases appreciably with increase in the length of the process: from 50% (17 h) to 74% (36 h) in the first case and from 34.7% (6 h) to 98.5% (17 h) in the second.



n = 1–3 **95**

To determine the relative reactivity of the butyrolactim (R = Me, Et) and caprolactim (R = Me) ethers their mixtures were heated with the above-mentioned fluorinated alcohol at 120°C for 5 and 8 h in evacuated tubes, and the ratios of the transetherification products were determined [5]. The results indicate that the transetherification of caprolactim methyl ether is 3-5 times quicker than for butyrolactim methyl and ethyl ethers [5].

The diethoxy derivatives **97** were synthesized with yields of 40-60% as a result of treatment of the salts **96**, formed during the reaction of lactams **1-3** with dimethyl sulfate, with sodium ethoxide in alcohol [6].

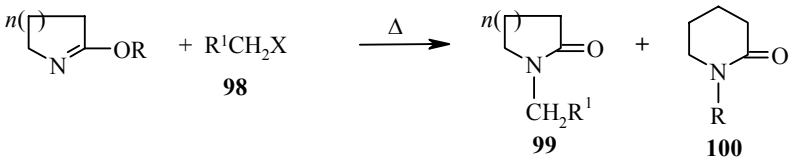


96 **97**

n = 1-3

2.7. Reactions with Halogen Derivatives

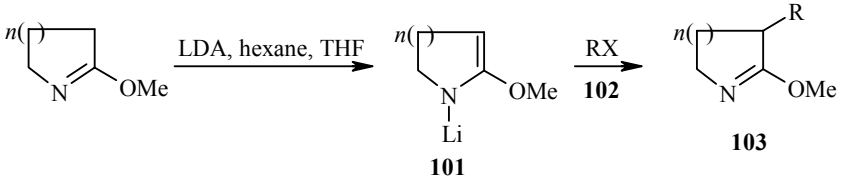
The N-substituted lactams **99** were synthesized by heating the lactim ethers from lactams **1-3** with halogen derivatives **98** in DMF or without a solvent and gave yields of 64% in the case of the chloride (boiling in DMF) [77] and 87-98% in the case of the bromides or iodides (60-100°C, 1-6 h) [3]. The reaction with the iodide $(MeO_2C)_2CH(CH_2)_2I$ was conducted at 110°C in an atmosphere of nitrogen [129]. (The yield of the product **99** was not indicated.) In a number of cases with a longer reaction time an N-R-substituted lactam of type **100** was also isolated in addition to **99**. Thus, compounds **99** and **100** were isolated with yields of 18 and 65% respectively when the lactim ether (*n* = 2, R = Me) was heated with ethyl iodide in DMF (60°C, 48 h). If the length of the process was increased to 240 h, the yield of **99** increased to 52%, while the yield of **100** decreased to 34%. The yields of the products **99** and **100** from benzyl bromide after 10 h under the same conditions were 80 and 12% respectively. In the case of the least reactive β-phenylethyl bromide the yields of compounds **99** and **100** were 27 and 12% (100°C, 28 h).



98 **99** **100**

X = Cl, *n* = 1, R = Me, $R^1 = CH_2Ph$ [77]; X = Br, *n* = 1-3, R = Me, Et, $R^1 = CH_2Ph$, $(CH_2)_2Ph$, $(CH_2)_2C_6H_3(OMe)_2$-3, 4, CH_2COPh, $CH_2COC_6H_3(OMe)_2$-3, 4 [3]; X = I, *n* = 2, R = Me, Et, R^1 = H, Me, $(CH_2)_2CH(COOMe)_2$ [3, 129]

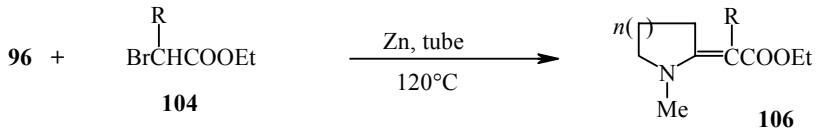
The action of lithium diisopropylamide (LDA) on the lactim ether from valero- or caprolactam leads to isomerization of the double bond in the lactim ether with the formation of compounds **101**. The latter react with the halogen derivatives **102** and are converted into the lactim ether **103** [23, 130].



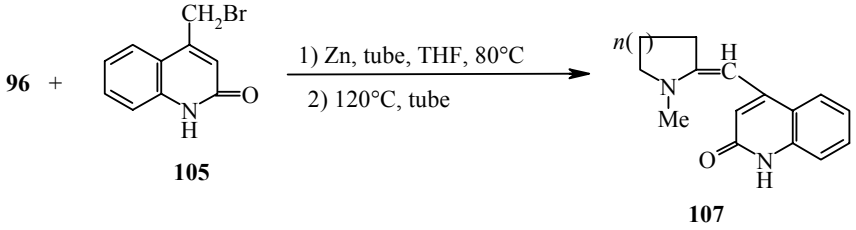
101 **102** **103**

n, R, X, °C, time, h (yield of **103**, %): 3, Me, Br, 0, 3, (68); 3, Et, Br, 0, 3, (65); 3, Pr, Br, 0, 3, (70) [23]; 2, $CH_2CH_2C(Me)=CH_2$, I, 20, 0.33, (60); 2, $CH_2CH_2C(Me)OCH_2CH_2O$, I, 20, 4, (56); 2, $CH_2CH=C(Me)Cl$, Cl, 20, 12, (37) [130]

Compounds **106** or **107** were synthesized with yields of 43-63% from the salts **96** and the bromides **104** or **105** by the Reformatsky reaction by heating in sealed tubes [131].



n, R: 1, H; 1, Me; 1, Et; 2, H; 2, Me

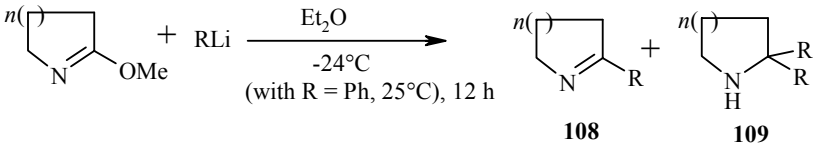


n, yield of **107**, %: 1, 63; 2, 43

1-Trimethylsilylbutyrolactam was obtained with a yield of 19% by the reaction of the lactim ether from butyrolactam (R = Me) with trimethylchlorosilane at 70°C for 40 min [132].

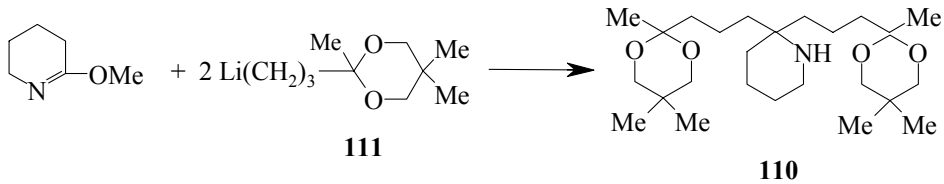
2.8. Reactions with Organometallic Compounds

During study of the reaction of lactim ethers with organolithium compounds it was shown that the yields of the products **108** and **109** depended on the LE:RLi ratio. Thus, if the ratio was 1:1, mixtures of the products were obtained (*n* = 1-3, R = Pr) or only one product **108** was obtained. (With *n* = 2, R = Me the reaction did not occur.) With a ratio of 1:5 compound **108** was only formed with *t*-BuLi. (With *n* = 3 this was the only product, with *n* = 1 or 2 mixtures with compound **109** were obtained.) In other cases compound **109** was obtained with yields of 60-75% [133].



LE: RLi = 1:1; *n* = 1-3; R = Me, Pr, Bu, *t*-Bu, Ph; yields of product **108** 0-85%, **109** 0-33%;
LE: RLi = 1:5; *n* = 1-3; R = Pr, Bu, *t*-Bu, Ph; yields of product **108** 0-68%, **109** 0-75%

The yield of the product **110** from the reaction of valerolactim methyl ether with a twofold excess of 5-lithio-2-pentanone 2',2'-dimethylpropylene ketal (**111**) depends substantially on the procedure used for the process. The highest yield of the α,α-disubstituted pentamethyleneimine **110** (80%) was obtained when the lactim ether was added to the ketal **111** in pentane and the reaction mixture was kept in an argon atmosphere at 0°C for 12 h and then at 20°C for five days [134].



α,α-Diallyltetramethyleneimine was obtained with a 78% yield by treating the lactim ether from butyrolactam (R = Et) with two moles of allylmagnesium bromide (ether, 25°C, 12-20 h). α-Phenyl-substituted tetra-, penta-, and hexamethyleneimines were synthesized from butyro-, valero-, or caprolactim ethers and phenylmagnesium bromine by heating in xylene (120°C, 4 h) [20]. In the same paper, however, it was noted that butyrolactim methyl ether does not react with 3-bromomagnesioindole even under more drastic conditions (130°C, 20 h). The synthesis of 2-substituted Δ^2-pyrrolines by the reaction of the lactim ether from butyrolactam (R = Me) with the Grignard reagent RMgBr (R = Ph, MeC_6H_4-4, $MeOC_6H_4$-4, FC_6H_4-4) was mentioned in [135] (with no indication of the conditions or yields).

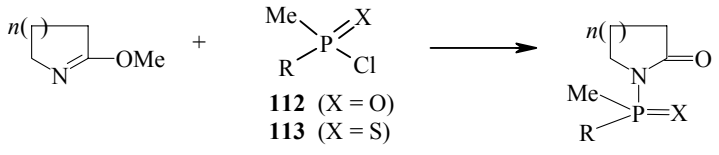
According to [136], caprolactam is formed (yield 78%) when caprolactim methyl ether is heated with methylmagnesium iodide (150°C, 30 min) and the reaction mixture is then treated with water.

2.9. Reactions with the Chlorides of Sulfonic, Phosphonic, and Thiophosphonic Acids

With sulfonic acid chlorides RSO_2Cl (R = Me, Ph, C_6H_4Me-4) in the presence of tetrabutylammonium salts $Bu_4N^+X^-$ (X = Cl, Br, I) in methylene chloride (25°C, 16 h) the lactim ethers from lactams **1-3** give 62-76% yields of butyro-, valero-, and caprolactam derivatives containing the RSO_2 substituent at the nitrogen atom.

Increase in the reaction temperature from 25 to 40°C has practically no effect on the yields of these products [4]. In THF or benzene at 25-80 °C the reagents do not react. When dimethylformamide was used as solvent, the following results were obtained. R, temperature, °C, yield, %: Me, 25, 0; Me, 153, 80; Ph, 25, 0; Ph, 153, 74; C_6H_4Me-4, 25, 0; C_6H_4Me-4, 153, 73 [4].

The lactam derivatives **114** or **115** were synthesized by the reaction of butyro- or caprolactim methyl ethers with phosphonic **112** or thiophosphonic **113** acid chlorides respectively by heating at 100-105°C or boiling in toluene [137].



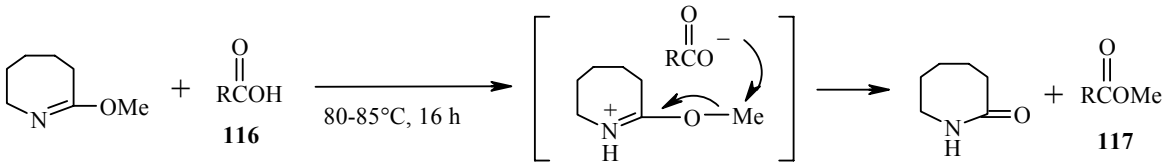
112 (X = O)
113 (X = S)

114 (X = O)
115 (X = S)

n, X, R (yield of **114** or **115**, %): 1, O, NEt_2 (50); 3, O, OPh (64); 3, O, OEt (62); 3, O, NEt_2 (91); 1, S, OPh (–); 3, S, Et (32)

2.10. Reactions with Carboxylic Acids and Their Derivatives

An original method for the esterification of carboxylic acids, proposed in [138], involves heating the carboxylic acids **116** with caprolactim methyl ether under neutral conditions, leading to the formation of the methyl esters of the original acids **117**. In the case of adipic acid the dimethyl ester was obtained with a yield of 72% when a twofold excess of the lactim ether was used.

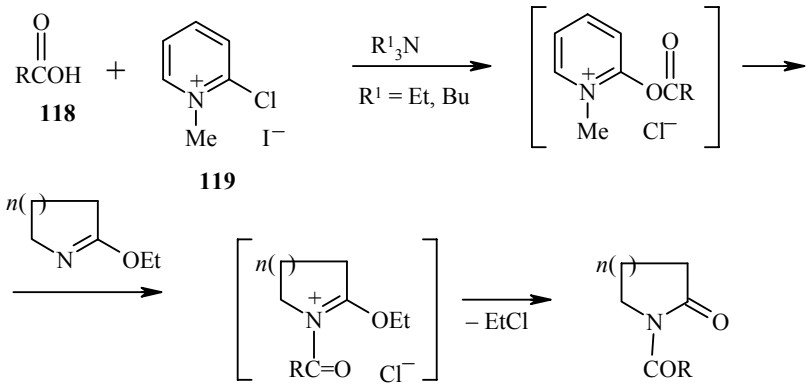


116

117

R, yield of **117**, %: Ph, 91; C_6H_4Me-4, 76; 2-naphthyl, 96; $CH=CMe_2$, 78; C_6H_4OH-4, 80; $CH=CHC_6H_4OMe$-4, 73

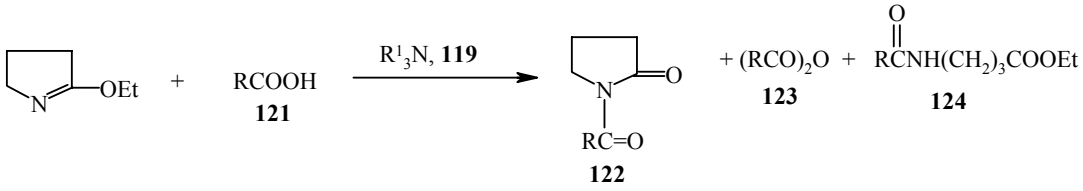
The reaction of butyro- and caprolactim ethers with carboxylic acids **118** in the presence of trialkylamines and 2-chloropyridine methiodide **119** takes place differently. Here the N-acyllactams **120** are formed [139]. The reactions were carried out in $ClCH_2CH_2Cl$ (triethylamine, 50°C, 2 h or 20°C, 15 h) or boiling toluene (tributylamine, 2 h) [139].



120

n, R: 1, $(CH_2)_2COMe$, CH=CHCH=CHMe; 1 и 2, CH_2Ph, $(CH_2)_2Ph$, $(CH_2)_6Me$, $(CH_2)_7CH=CH(CH_2)_7Me$; 2, $(CH_2)_2COOMe$.
Yields of **120** 70-91%

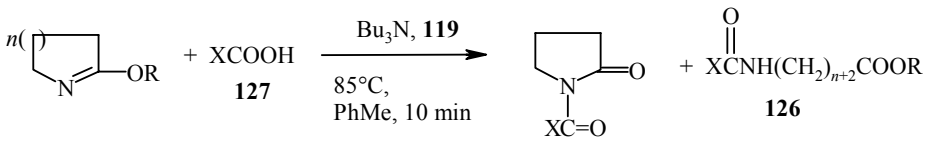
Two methods were also used during study of the reaction of butyrolactim ethyl ether with the acid **121**: 1) Triethylamine in $ClCH_2CH_2Cl$ was added to a mixture of the lactim ether, the salt **119**, and the acid **121**; 2) The acid **121** and R_3N were added to a mixture of the lactim ether and the salt **119**. It was found that the product **122**, the products **122** and **123** (method 1), or the products **122**, **123**, and **124** (method 2) could be isolated from the reaction mixtures depending on the method and conditions [140].



R = CH=CHCH=CHMe; R^1 = Et, Bu

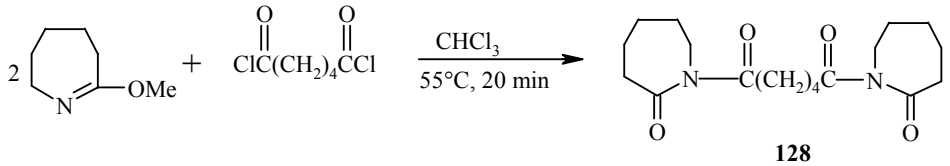
Method, (conditions), yield of **122**, **123**, **124**, %: 1, (0°C, 1 h), –, 93, –; (50°C, 1 h), 11, 70, –;
2, (with Et_3N, $ClCH_2CH_2Cl$, 50°C, 4 h), 59, 8, 17; (MeCN, 50°C, 4 h), 61, 8, 14; (MeCN,
boiling, 4 h), 60, 6, 14; 2, (with Bu_3N, 90°C, 2 h), 63, 7, 18

Mixtures of compounds **125** and **126** were obtained as a result of the condensation of butyro- or valerolactim ethers with the acids **127** in the presence of the salt **119** [140-142].



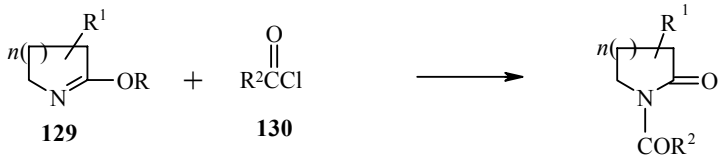
X = CH=CHCH=CHC=CHCHBu; *n*, R, R^1, yield of **125**, **126**, %:
1, Et, Me, 30-37, 10-18; 2, Et, Me, 27, 28; 1, Me, H, 36, 16

The reaction of caprolactim methyl ether with acetyl chloride in the presence of triethylamine gives a 63% yield of 1-acetyl-2-methoxy-4,5,6,7-tetrahydroazepine [47]. The reaction takes place differently in the absence of bases. For example, compound **128** was obtained from the same lactim ether and adipoyl dichloride [143].



128

Various N-acyllactams **131** were synthesized from substituted valero- and caprolactim ethers **129** and acid chlorides **130** [143, 144]. However, attempts to synthesize compounds **131** were not always successful [47, 143].

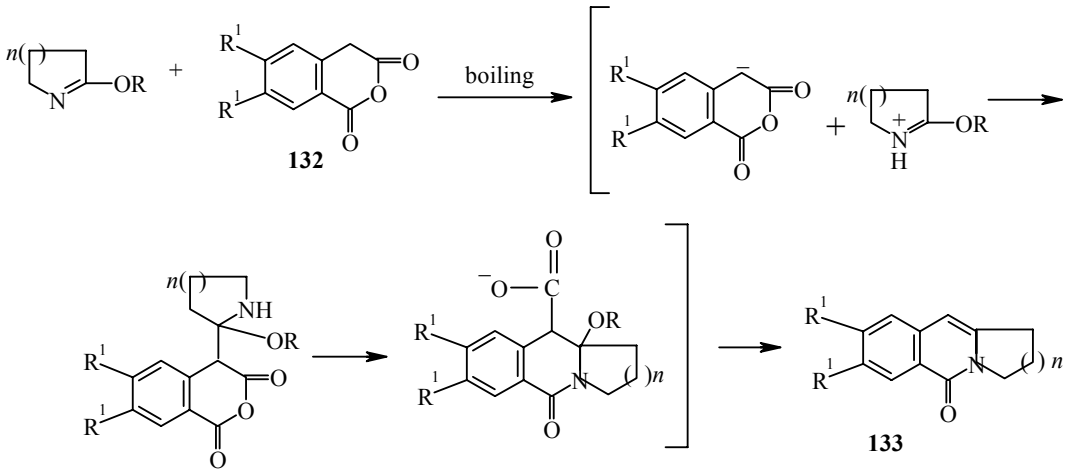


129 **130** **131**

(Conditions), *n*, R, R^1, R^2, yield of **131**, %: ($CHCl_3$, 55°C, 20 min), 2, Me, H, Ph, –; 3, Me, H, Me, 95;
3, Me, H, $(CH_2)_8Me$, – [143]; (DMF, KBr, 60°C, 24 h), 2, Et, H, CH_2 (3-indolyl), 71;
2, Et, 4-CH_2COOEt, CH_2(3-indolyl), 70 (32 h) [144];
(PhMe, boiling, 1 h), 3, Me, H, Me, – [47]

N-Acyl derivatives of caprolactam were also synthesized with yields of 67-75% by boiling caprolactim methyl ether with LiH or NaH in benzene (6 h) followed by the action of 2-furancarbonyl or benzoyl chloride (boiling in benzene for 1-6 h, then holding at 25°C for 19 h) and treatment of the reaction mixture with hydrochloric acid or lithium hydroxide in water [145].

Condensed heterocyclic compounds **132** were synthesized by the reaction of the lactim ethers from lactams **1-3** with homophthalic anhydrides **132**, and the following scheme was proposed to explain their formation [146, 147].

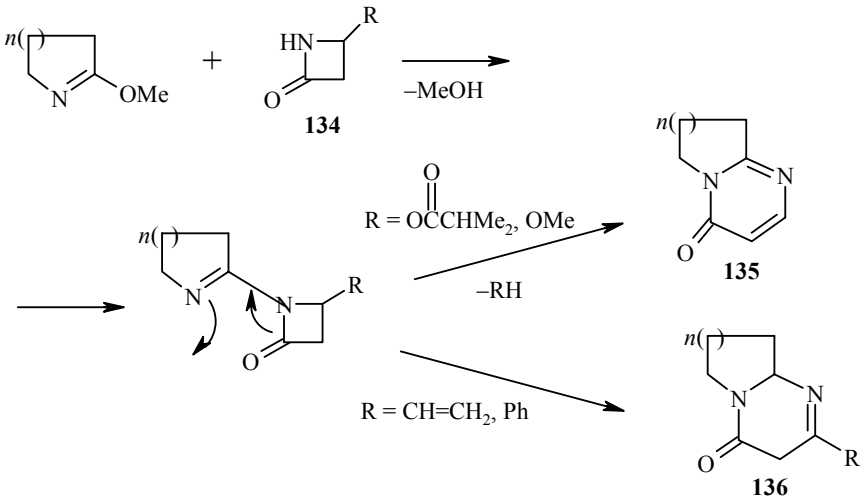


132 **133**

n, R, R^1, (conditions): 1, 2, Me, H/Me, OMe (1 h, at *n* = 1, solvent PhMe;
at *n* = 2 – PhCl [146]); 1-3, Et, H (48 h, PhMe) [147]

Hexamethyleneimines with a $NC(X)C_6H_4R$-4 substituent at position 2 are produced by boiling 4-R-substituted amides (R = Me, OMe) or a thioamide (R = OMe) of benzoic acid with an excess of caprolactim methyl ether (yields 82-87% with X= O, 53% with X = S) [148].

Examples of the reaction of lactim ethers with lactams, in so far as the latter can be regarded as N-substituted cyclic amides, are given below. Thus, the condensation of butyro- or caprolactim ethers with substituted propiolactams **134** leads to the formation of compounds **135** (yields 72-85%) or **136** (yields not indicated), depending on the nature of R in the lactams [149, 150].



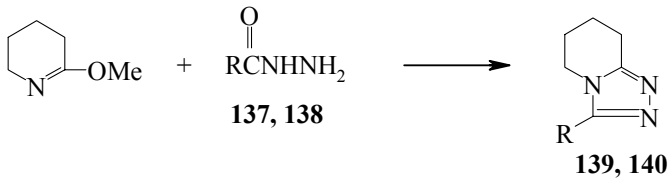
$\overset{O}{\overset{\|}{}}$

n, R, (conditions): 1, $OCCHMe_2$, (120°C, 1 ÷); 3, OMe, (120-130°C, 8 ÷);
1, 3, $CH{=}CH_2$ (not indicated) [149]; 1, Ph, (130°C, 3 ÷; 180-200°C, 2 ÷) [150]

The release of methanol is also observed in the reaction of caprolactim methyl ether with butyrolactam (140-150°C, 6 h), and 2-(2-oxopyrrolidino)hexamethyleneimine is formed with a yield of 34% [151].

R-Butyrolactim methyl [45] and ethyl ethers [R = 4-Ph, 4-C_6H_4Me-4), 5-Me] [152] react readily with hydrazides $R^1CONHNH_2$ (R^1 = 2-furyl, 5-nitro-2-furyl, Ph [45], Me) [152] in methanol (20°C, 18-20 h) with the formation of the corresponding hydrazones (yields 72-93%).

Butyrolactam hydrazone is also formed when butyrolactim methyl ether is heated with benzohydrazide **137** in boiling benzene (yield 60%). At the same time during reaction of the hydrazides **137** [153] and **138** [154, 155] with the valerolactim ether in boiling xylene the analogous products undergo cyclization *in situ* to derivatives of 1,2,4-triazolopyridine **139** (yield 35%) and **140** (yield 73%), respectively.

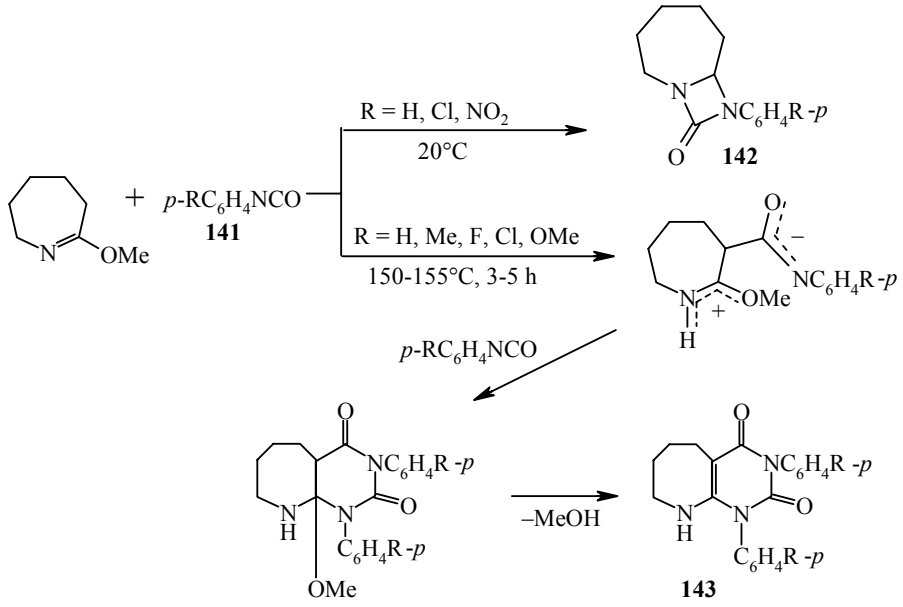


137, 139 R = Ph; **138, 140** R = $(CH_2)_3N(CH_2CH_2)_2NC_6H_4Me$-2

2.11. Reactions with Isocyanates

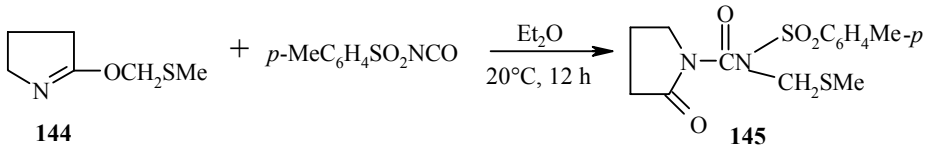
Depending on the temperature regime and the size of the lactim ether ring, the reactions with aryl isocyanates take place in an uncertain manner with the formation of various compounds. Thus, the reaction of isobutyro- and isovalerolactim methyl ethers with isocyanates 4-R-C_6H_4NCO (R = H, Cl, OEt) (20°C, 3-7 days) leads to addition at the NCO group with the formation of lactim ethers containing the substituent $CONHC_6H_4R$-4 at position 3. The yields of such amides (butyrolactam derivatives) amount to 20 (R = OEt) to 43% (R = H), and the yields of the analogous valerolactam derivatives amount to 65-70% [156, 157].

On the other hand the reaction of lactim ethers from caprolactam with isocyanates **141** (R = H, Cl, NO_2) at room temperature results in the formation of bicyclic compounds **142**. If R = H or Cl, the process takes 20 or 10 days, and the yields of the products **142** amount to 45 and 53%, respectively. If R = NO_2 the reactivity of the isocyanate increases sharply, and the yield of the product **142** reaches 87% [158].



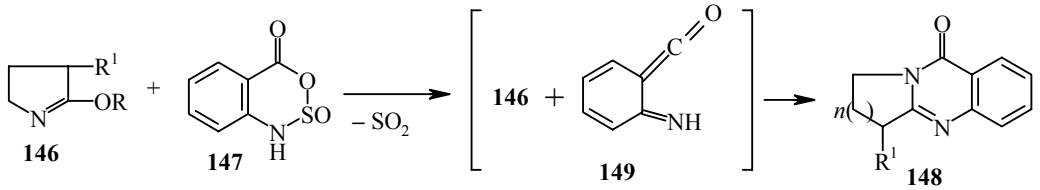
It is interesting that completely different compounds **143** were obtained during the reaction of the same lactim ether with isocyanates **141** (R = H, F, Cl, OMe) at 150-155°C (3-5 h). It is clear that in these cases the isomeric form of the lactim ether with a $C_{(2)}$=$C_{(3)}$ bond takes part in the reaction, and the process involves 1,4-dipolar cycloaddition [159]. The yields of the products **143** were low: 12% (R = OMe) and 38% (R = H).

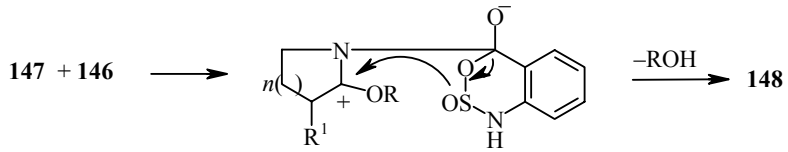
The butyrolactam derivative **145** was obtained by reaction of the lactim ether **144** with tosyl isocyanate [160].



2.12. Reactions with Compounds Containing Cumulated Double Bonds

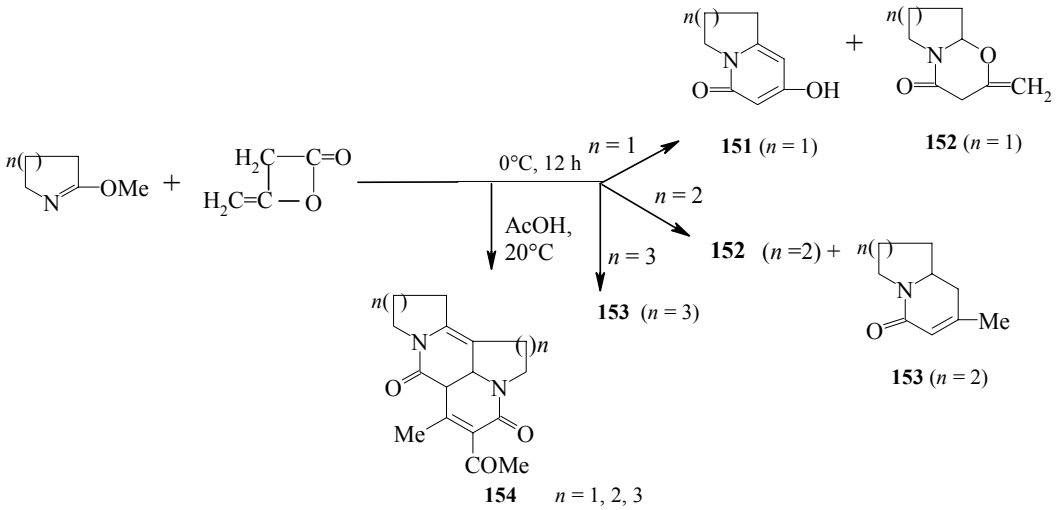
The reaction of the lactim ether **146** with the product **147** from the reaction of anthranilic acid with thionyl chloride *in situ* leads to the quinazolone derivatives **148**. The formation of the latter can be represented as resulting from cycloaddition of the lactim ether to the ketene imine **149**, formed as a result of the elimination of the SO_2 molecule from compound **147**. However, the same quinazolone derivatives **148** were obtained from compound **147**, isolated after the reaction, and the lactim ether **146**. It is therefore more likely that the products **148** are formed through the bipolar ion **150** [161, 162].





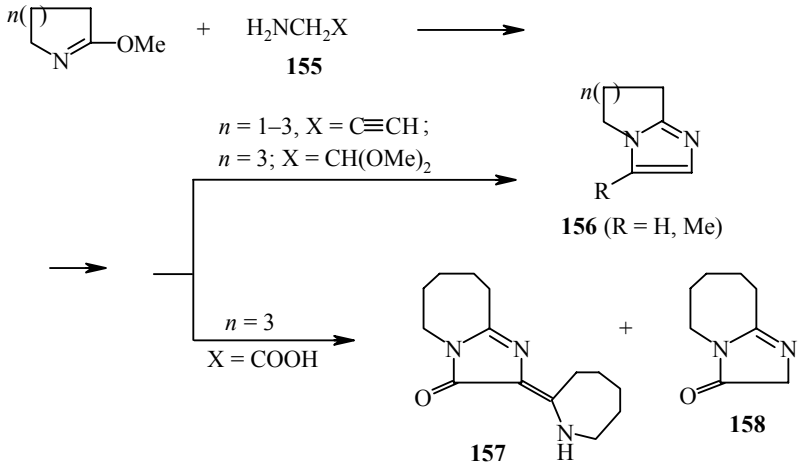
n, R, R^1, time, h (yield of **148**, %): 1, Me, H, 1, (64) [161]; 2, Me, H, 12, (82); 2, Et, OMe, 2, (71) [162]

In [163] it was shown that the composition and structure of the products from reaction of diketene with the lactim ethers from lactams **1-3** at 0°C depend on the size of the ring in the initial lactim ether. Thus, with $n = 1$ two compounds are formed, i.e., the main compound **151** (yield 73%) and a minor compound **152** (yield 11%). With $n = 2$ the product **153** was obtained with a yield of 43%, while the minor compound was also a compound of type **152** (yield 10%). With $n = 3$ only compound **153** was isolated (yield 45%). Tetracyclic compounds **154** were obtained from the same reagents in acetic acid at 20°C ($n = 1$, yield 35%, $n = 2$, yield 66%, $n = 3$, yield 40%) [164]

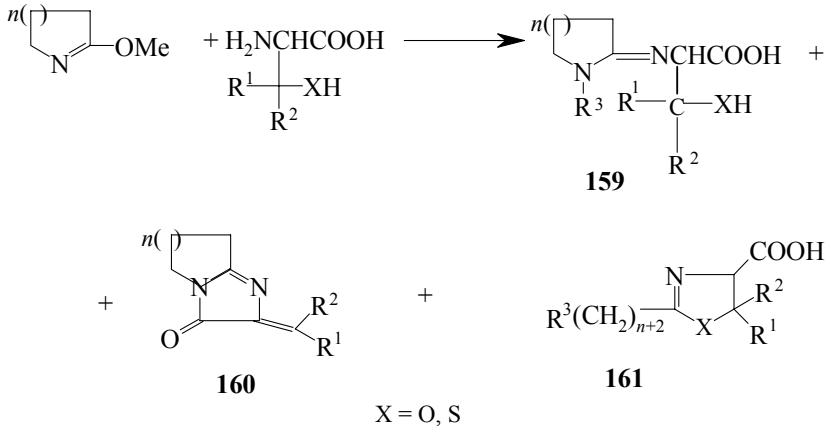


2.13. Reactions with Bifunctional Compounds Involving Cyclization

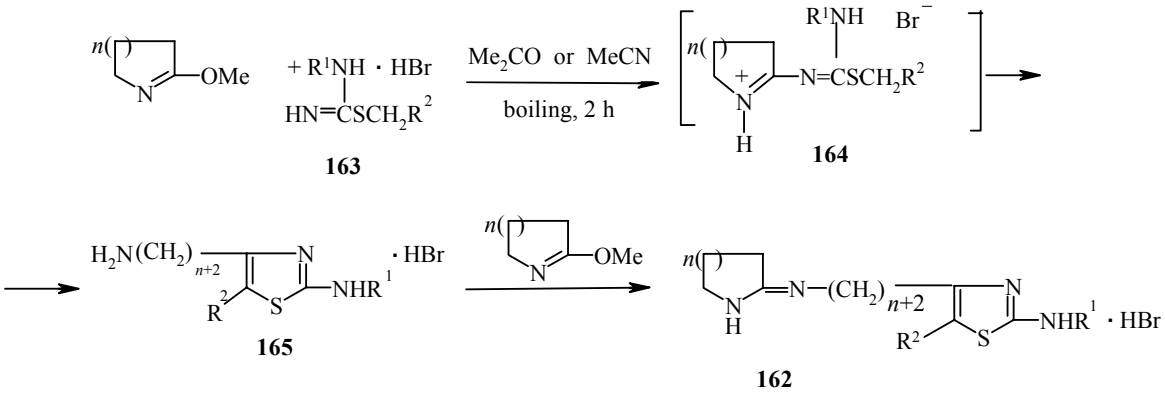
Both functional groups usually take part in the reactions of lactim ethers with bifunctional compounds **155**, and cyclization products are formed. Thus, bicyclic products with the general formula **156** were obtained as a result of the reactions with propargylamine (boiling in toluene, 5 days; R = Me; yields 48-72%) and 2,2-dimethoxyethylamine [boiling with TsOH, 17 h (1), H_2SO_4, 20°C, R = H (2)] [46]. In the case of aminoacetic acid with equimolar amounts of the reagents compounds **157** and **158** were obtained with yields of 25 and 30% respectively, but with a twofold excess of the acid only compound **158** was obtained (yield 90%) [86].



The condensation products **159** (*n* = 1-3, R^1, R^2 = H, Me, R^3 = H) and their further transformation products **160** (*n* = 2, 3, R^1 = H, Me, R^2 = Me) and **161** (*n* = 3, 9, R^1 = R^2 = Me, only for R^3 = NH_2 and X = S in the acid **159** and *n* = 1–3, 9, R^1, R^2 = H, Me, R^3 = –N=C–NH–$(CH_2)_n$) were obtained from α-amino-β-hydroxy and α-amino-β-mercapto acids in reactions with lactim ethers [89].

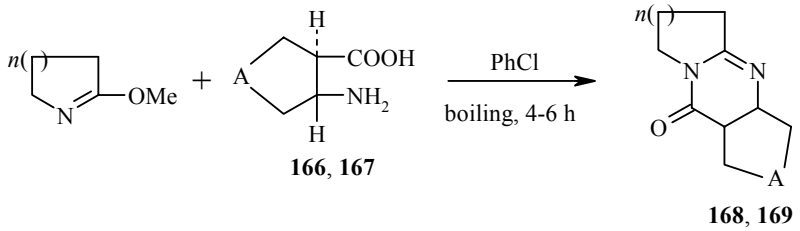


A large number of thiazole derivatives **162** were synthesized by heating the hydrobromides **163** with an excess of the lactim ether in acetone or acetonitrile. It was established that the reaction takes place with the formation of the salts **164** and **165**. Thus, the salt **165** (the product from cyclization of the initially formed salt **164**) was obtained with a 66% yield from equimolar amounts of the lactim ether (*n* = 3, R = Me) and the hydrobromide **163** (R^1 = Et, R^2 = $C_6H_4NO_2$-4, Me_2CO, 0°C, 24 h). Reaction of **165** with an equimolar amount of the same lactim ether led to the salt **162** (yield 81%) [165].



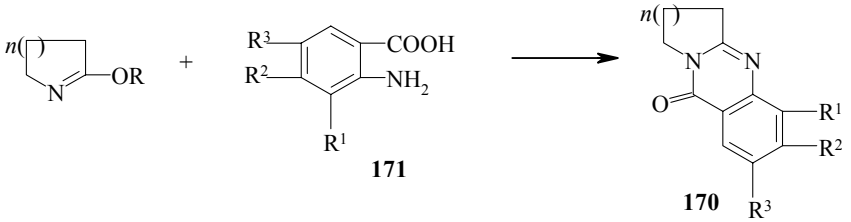
n = 1-3; R^1 = H, Et, *i*-Pr, Ph; R^2 = $C_6H_4NO_2$-4, C_6H_4CN-4. Yields of **165** 31-74%

The reaction of lactim ethers with the *cis* and *trans* isomers of cyclic amino acids **166** and **167** in boiling chlorobenzene gives the corresponding tricyclic products **168** and **169** with yields of 66-68% [166, 167]. For example, the lactim ether (*n* = 3, R = Me) and *cis*-aminocyclohexanecarboxylic acid **166** [A = $(CH_2)_2$] (boiling in alcohol, 15 min) gave 2-(2-hydroxycarbonylamino)-3,4,5,6-tetrahydropyridine (yield 81%), which was converted into the corresponding product **168** by boiling in alcohol (3 h) [166].



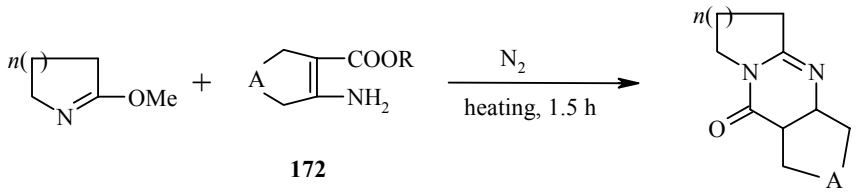
166, **168** A = $(CH_2)_2$; **167**, **169** A = CH=CH; *n* = 1, 2, 3

The pyrroloquinazoline (*n* = 1) or azepinopyrazoline (*n* = 3) derivatives **170** were synthesized by the cyclocondensation of the lactim ethers from lactams **1-3** with anthranilic acid or its substituted derivatives **171** [15, 168-172].



n, R, R^1, R^2, R^3, (conditions), yield of **170**, %: 1-3, Me, H, H, H, (PhH, boiling, 3 h), 64-95 [15];
1-3, Me, COOH (or H), H, H, (DMF, 80-90°C, 3 h), 68-87 [15]; 1-3, Et, H, H, Me (or Cl), H, Me, OMe (or Cl) (PhH, boiling, 5 h), 33-83 [168]; 2, Me, H, H, H, (PhH, boiling, 1 h), 71 [169]; 1, Me, H, NO_2 (or H), H (or NO_2), ($MeOCH_2CH_2OMe$, 80-105°C, 3-4 h), 10 or 30 [170]; 2 or 3, Me, H, H, H, (PhMe, boiling, 1-2 h), 29 or 70 [171]; 3, Me, H, Cl, H, (PhH, azeotropic distillation, 77) [172]

Examples of the reaction of lactim ethers with various heterocyclic amino acids or their esters with general formula **172** are summarized in the scheme below [170, 173-176].



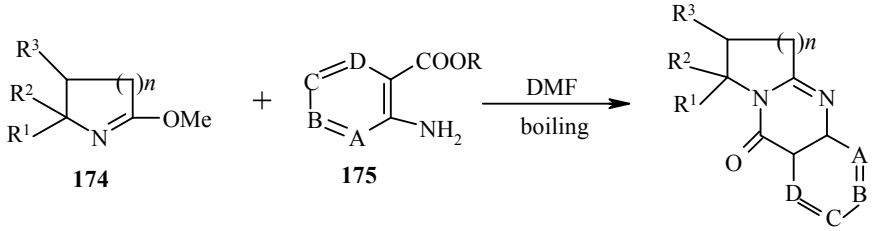
172 **173**

A, *n*, R, conditions, yields of **173**, %: I, 3, H, Et, 110°C (R = H), 160°C (R = Et), 18-24 [173]; II, 1-3, Et, 90-120°C, 14 h, 30-39 [174]; III (*m* = 1–3), 1-3, Et, PPA, PhCl, 140-150°C, 12-24 h, 54-85 [175]; IV, 1-3, Et, 110°C, 1.5 h, 58-66 [176]; V, 1, H, $MeOCH_2CH_2Me$, 80-105°C, 3-4 h, 10 [170].

A = –C(Me)=N–S– (I);  (II); $(CH_2)_m$  (III);

$–(CH_2)_2–$ (IV); –CH=CHCH=CH– (V)

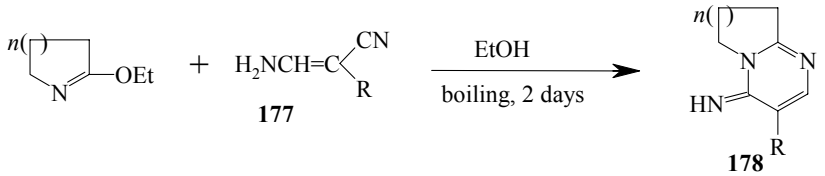
The lactim ethers **174** react when heated with di- and triazines of general formula **175** (A, B, C, or D can be CH or N) and form compounds **176** with yields of 10-52% [177, 178].



174 **175** **176**

n, R, R^1, R^2, R^3, position of N atom (atoms), yield, %: 1, H, H, H, H, A, B, C or D, 10-58; 1, H, Me, H, H, A, B or D, 22-45; 1, H, Me, Me, H, A, B or D, 28-40; 1, H, H, H, Me, A, B, or D, 11–25; 2, H, H, H, H, A, B or D, 12-38; 3, H, H, H, H, A, B or D, 21-47; 2 or 3, H, H, H, H, A, D, 12-17 (throughout DMF, boiling, 10-270 min) [177]; 2, Me, H, H, H, A, D, 41; 3, Me, H, H, H, A, D, 52; 3, Et, H, H, H, A, C, 21 (throughout 120°C, 2 h and 180°C, 24 h) [178]

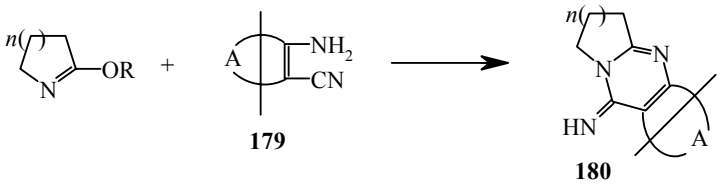
The reaction of lactim ethers with aminonitriles was described in a series of papers [26, 179-182]. Thus, the cyclocondensation of compounds **177** with the lactim ethers from valero- or caprolactams (boiling in alcohol) gave high yields of condensed pyrimidine derivatives **178** [26].



177 **178**

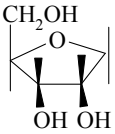
n, R, time, h, (yield of **178**, %): 2, CN, 3, (83); 3, CN, 15, (71); 3, $CONH_2$, 48, (85); 3, COOEt, 16, (88)

The reactions of lactim ethers with heterocyclic aminonitriles **179**, leading to condensed tricyclic compounds **180**, were studied in greater detail [179-182].



179 **180**

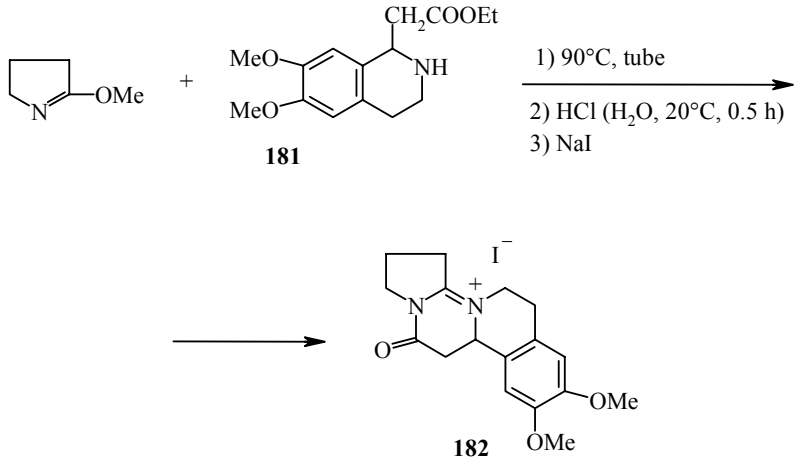
A, *n*, R, conditions, yields of **180**, %: I, 1, Et, boiling in BuOH 2 days, 85 [179]; II, 1-2, Et, boiling in BuOH 1 day, 85-92 [180]; III, 3, Et, 150°C, 124, 93 [181]; IV, 1-3, Me, 140°C, 3 days in PhMe, BuOH (*n* = 1), PrOH (*n* = 2, 3), 8-74 [182]; V, 1 (*m* = 1-3), 2 (*m* = 2), 3 (*m* = 2), 110-150°C in $HOCH_2CH_2OH$, 16-55 [182].

A = –N=CHNH– (I); –N=CHNZ–  (II);

–CH=NCH=N– (III); –CH=CHS– (IV); $–(CH_2)_mCH_2O–$ (V);

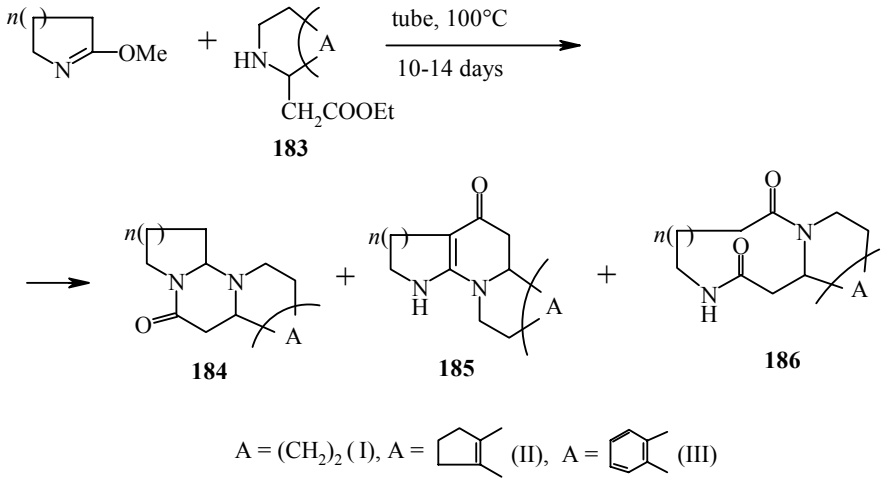
Z = 1-β-D-ribofuranosyl

During the reaction of lactim ethers with cyclic imines containing the CH_2COOEt substituent at the α position to the NH group both functions participate in the reaction, and tri- and tetracyclic products with two nitrogen atoms in the ring are formed. Thus, the salt **182** was obtained from butyrolactim ether and the imine **181** by heating in a tube and then treating the product with hydrochloric acid and sodium iodide [183].



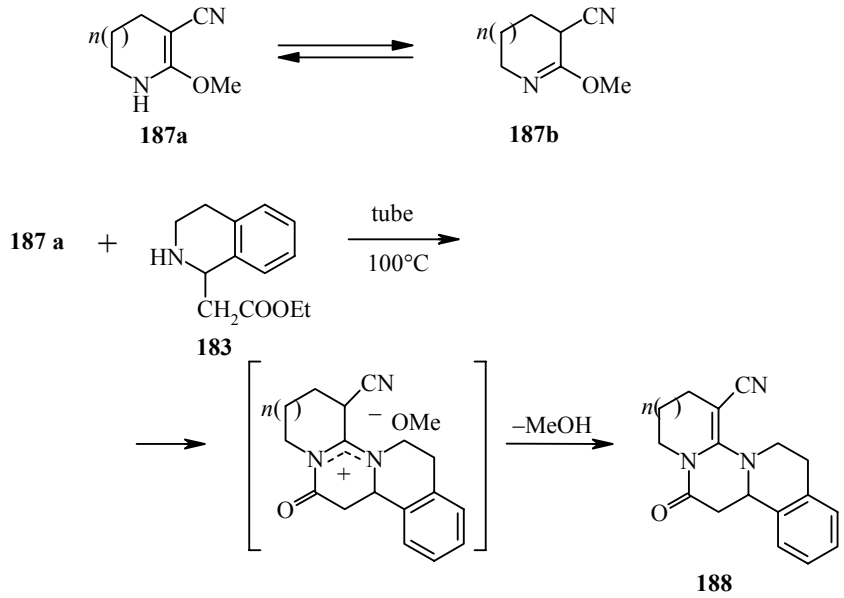
181 **182**

During study of the reactions of lactim ethers with the esters of heterylacetic acids **183** it was found that the structure of the initial compounds determines the composition and structure of the obtained products **184-186** [184-186]. This is determined largely by the tautomeric form in which the lactim ether reacts under the given conditions. It was found by ^1H NMR that butyrolactim methyl ether exists only in the imine form while the valero- and caprolactim ethers exist as equilibrium mixtures of the imine and enamine forms [184]. It was shown the reaction of the ether **183** (A = II) with methoxy- or methylthio-Δ^2-piperideine (the enamine forms of valerolactim ether and its thio analog) gives the product **185** (A = II, *n* = 2) or **186** (A = II, *n* = 2) respectively (yields in both cases 20%) [186].



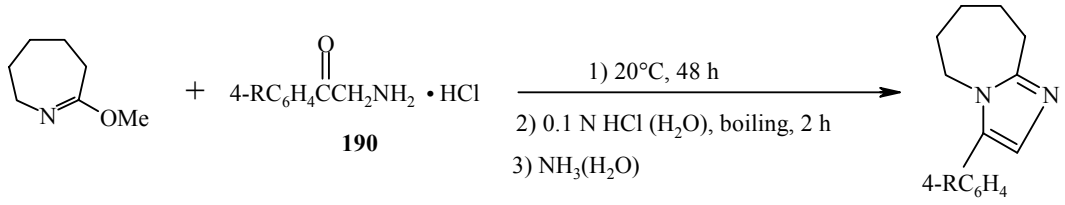
A, *n*, product (yield, %): (I), 1, **184** (26) and **185** (13); (II), 2, 3, **185** (n/d); (III), 1, **184** (n/d) [184, 186]; (I), 2, **185** (54); (I), 3, **185** (26) and **186** (13); (III), 2, **184** (7) and **185** (65); (III), 3, **184** (44), **185** (1) and **186** (13) [185]

The presence of two absorption bands (2180 and 2260 cm^{-1}) in the IR spectra of the lactim ethers **187** indicates that they exist in the two tautomeric forms **187a** and **187b**. In the light of this the formation of two pairs of compounds could be expected in the reactions of these lactim ethers with the aminoesters **183** (A = III). However, under standard conditions only one compound **188** was obtained in each case. Consequently, the lactim ethers **167** react in the tautomeric form **187a** under the investigated conditions [185].



n, (time, days), yield of **188**,%: 1, (12), 32; 2, (7), 26

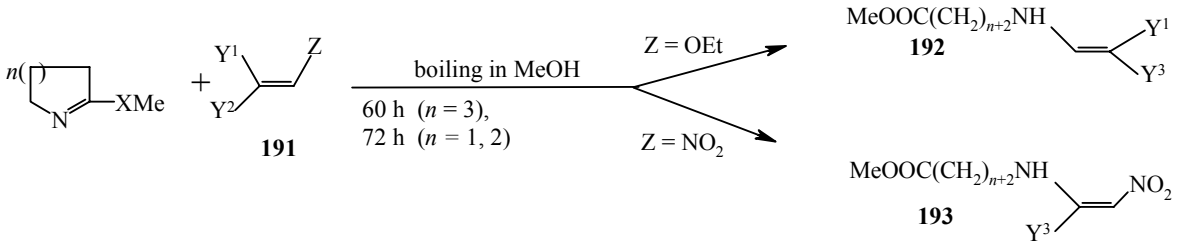
3-Aryl-6,7,8,9-tetrahydro-5H-imidazo[1,2-*a*]azepines **189** were synthesized with yields of 54-74% by condensation of caprolactim methyl ether with the hydrochlorides **190** at room temperature followed by treatment of the reaction mixtures with dilute hydrochloric acid and then with aqueous ammonia to pH 10 [187].



R = H, OMe, Cl, Br

2.14. Reactions with Opening of the Heterocyclic Ring in Lactim Ethers

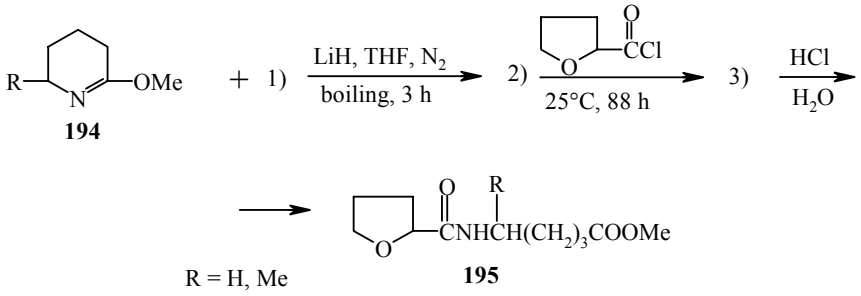
In the reaction of lactim ethers from lactams **1-3** with certain reagents their ring is opened, and the corresponding esters of γ-aminobutyric acid, δ-aminovaleric, or ε-aminocaproic acid substituted in the amino group are formed. Thus, the product from the reaction of butyrolactim methyl ether with 1,4-naphthoquinone (methanol, 50°C, 8 h, 20°C, 65 h) is methyl N-(2-quinolyl)-γ-aminobutyrate (yield 25%) [188]. Examples of the reaction of lactim ethers and their thio analogs with unsaturated compounds **191**, leading to the esters of N-substituted amino acids **192** and **193** (yields 38-60%), are given below [189]. It should be noted that in the case of Y^1 = COMe and Y^2 = COOEt in the initial compound **191** transesterification in the product **192** (Y^3 = COOMe) also takes place during the reaction.



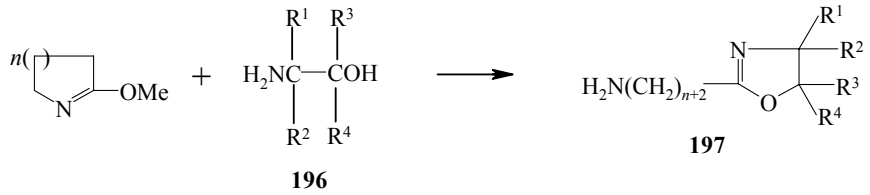
n = 1-3, X = O, S, **186**, **187** Z = OEt, $Y^1 = Y^2 = Y^3$ = COMe; Y^1 = COMe, Y^2 = COOEt, Y^3 = COOEt (*n* = 1), COOMe (*n* = 1, 2); **186**, **188** Z = NO_2, $Y^1 = Y^2$ = SMe, Y^3 = OMe

In the same work the ethyl ester **193** (*n* = 1, Y^3 = SMe) was obtained with a 65% yield from butyrolactim ethyl ether and the nitro-substituted compound **191** ($Y^1 = Y^2$ = SMe) in aqueous dioxane.

In section 2.10 it was shown that N-acyl derivatives are formed as a result of the reaction of lactim ethers with acid chlorides. Prior treatment of the lactim ether with lithium hydride in THF, followed by the action of the acid chloride and treatment with hydrochloric acid, leads mainly to the acylated products from opening of the heterocyclic ring of the lactim ether. The amidoesters **195** were obtained in this way from the lactim ether **194** with yields of 64-73% [145].



There are also examples where opening of the ring of the lactim ether is accompanied by the formation of a new heterocycle. Thus, the oxazoline derivatives **197** were obtained as a result of reaction of the lactim ethers from lactams **1-3** with 2-amino alcohols **196** [190].

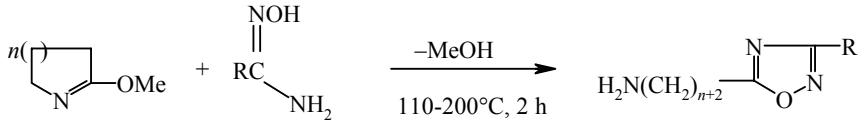


196 **197**

n = 1, 2, 3; R^1 = H, Me, Et; R^2 = H, Me, CH_2OMe; $R^3 = R^4$ = H, Ph

It should be noted that hydroxyethyliminolactams and lactimiminoalkyloxazolones (the products from further reaction of the amino alcohols with the lactim ether) or aminoalkanamides (the products from hydrolysis of the obtained oxazoline derivatives) are formed in these reactions as side products [190].

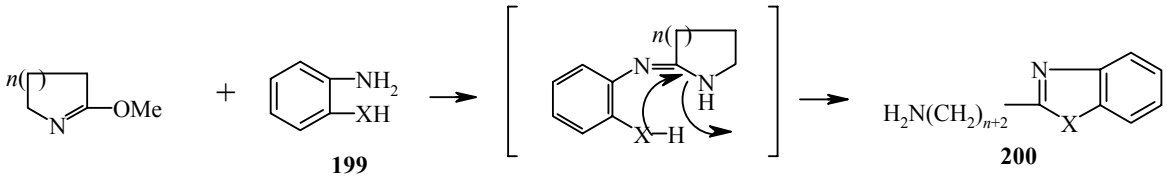
The 1,2,4-oxadiazole derivatives **198**, which are starting compounds in the synthesis of insecticides, were synthesized by heating butyro- or caprolactam methyl ethers with amidoximes with continuous distillation of the released methanol [191, 192].



198

n, R, yield, %: 1, Ph, 65; 3, Ph, 58-88; 1, Et, 68; 3, Et, 42

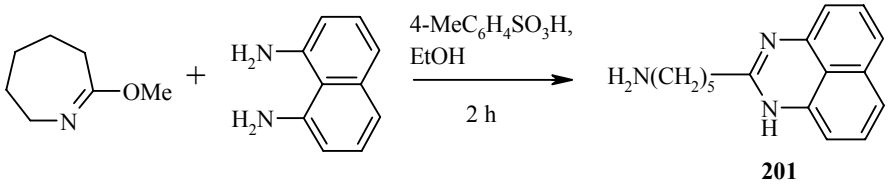
The condensation of the lactim ethers from lactams **1-3** with the aniline derivative **199** begins with attack by the lactim ether at the NH_2 group, followed by opening of the ring in the lactim ether and cyclization, and leads to the benzazoles **200** (yields 60-84%) [193].



199 **200**

n, X, (conditions): 2, NH, (80°C, 6 h, EtOH, HCl); 1, S, (180-200°C, 3 h, TsOH); 3, S, (150-200°C, 2 h, TsOH); 3, O, (80°C, 3 h, EtOH, TsOH)

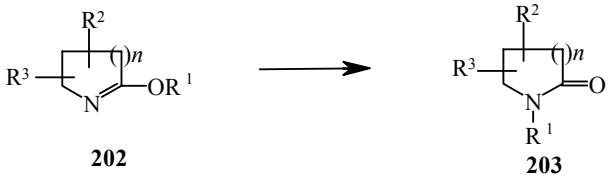
2-(5-Aminopentyl)perimidine **201** is formed with the same yield (28%) as a result of reaction of the lactim ether from caprolactam with 1,8-diaminonaphthalene at 80°C or at 20°C [193].



201

2.15. Rearrangements

It was shown in a series of papers that the lactim ethers **202** can rearrange to the corresponding lactams **203**. Such transformations have been described for unsubstituted lactim ethers (R^1 = Et, *n* = 1-3; heating [194]; 20°C in the presence of $MeSC^-H_2Na^+$ [195]; R^1 = Me, *n* = 2; boiling for 6 h in PhMe with DMSO [12]; R^1 = Me, *n* = 3; 120-140°C, PhH with DMSO [14]) and also for substituted lactim ethers (R^1 = Me, *n* = 3; R^2, R^3, Me at various positions, *t*-Bu, 4,4-Me_2, 6,6-Me_2, boiling for 6 h in DMSO [12]).

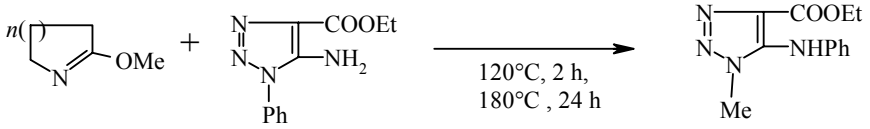


202 **203**

2.16. Other Reactions

The reactions of lactim ethers with types of reagents other than those covered by the classification in sections 2.1-2.14 are considered below.

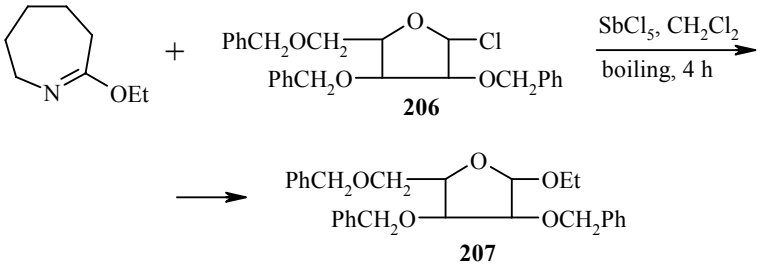
When heated with butyro- or caprolactim methyl ether 4-amino-5-ethoxycarbonyl-3-phenyl-1,2,3-triazole **204** undergoes a Dimroth rearrangement and methylation and is converted into 3-methyl-4-phenylamino-1,2,3-triazole **205** (yields 46 and 75% respectively) [178].



204 **205**

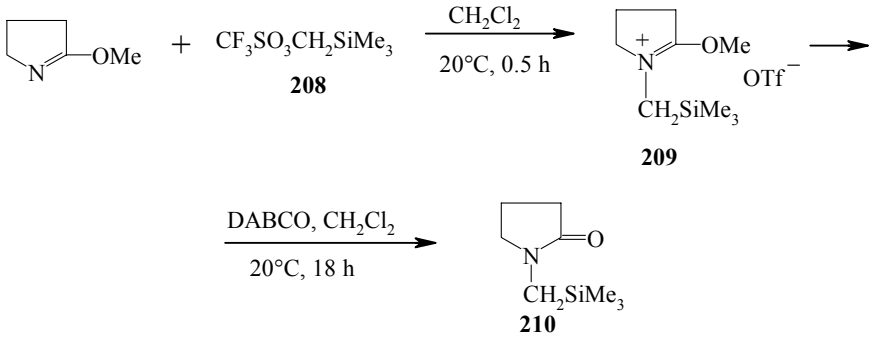
n = 1, 3

It was shown that of butyro-, valero-, and caprolactim ethyl ethers only the latter reacts with the chloride **206** in the presence of $SbCl_5$. The chlorine atom here is substituted by the OEt group, and compound **207** is formed with a yield of 90% [196].

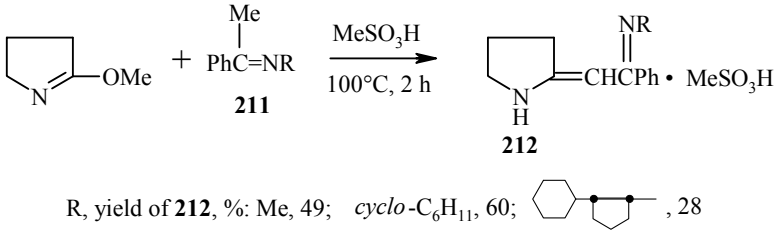


206 **207**

At room temperature butyrolactim methyl ether and the triflate **208** form the salt **209**, which is converted into 1-(trimethylsilylmethyl)butyrolactone **210** when treated with 1,4-diazabicyclo[2.2.2]octane (DABCO) [197].

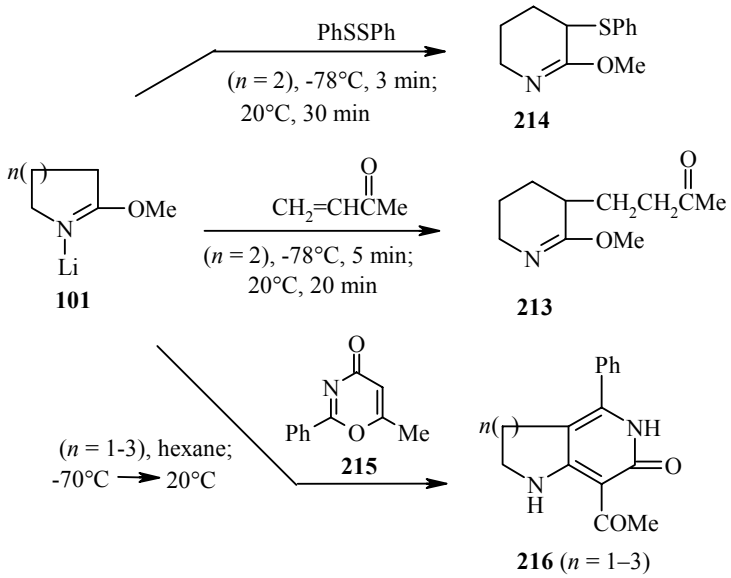


In the presence of methanesulfonic acid the same ether condenses with the imines **211** with the formation of the azadienes **212** [198].

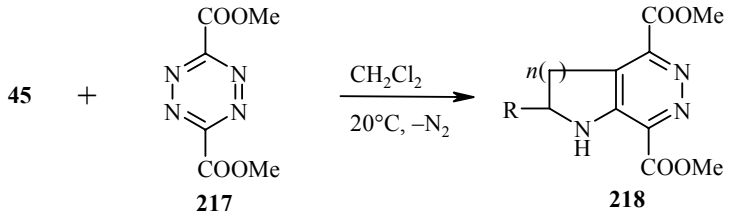


The addition product **213** was obtained with a yield of 31% as a result of reaction of the lithium derivative of the lactim ether **101** (n = 2) with methyl vinyl ketone [130]. The sulfide **214** (yield 66%) was synthesized from the same derivative **101** and diphenyl disulphide under analogous conditions [130].

The reaction of compounds **101** (n = 1, 2, 3) with the substituted 1,3-oxazin-4-one **215** in hexane (the reagents were mixed at -70°C and the mixtures were allowed to heat to room temperature) led to the derivatives **216** of pyrrolopyridine (n = 1), pyridopyridine (n = 2), and azepinopyridine (n = 3) [199].

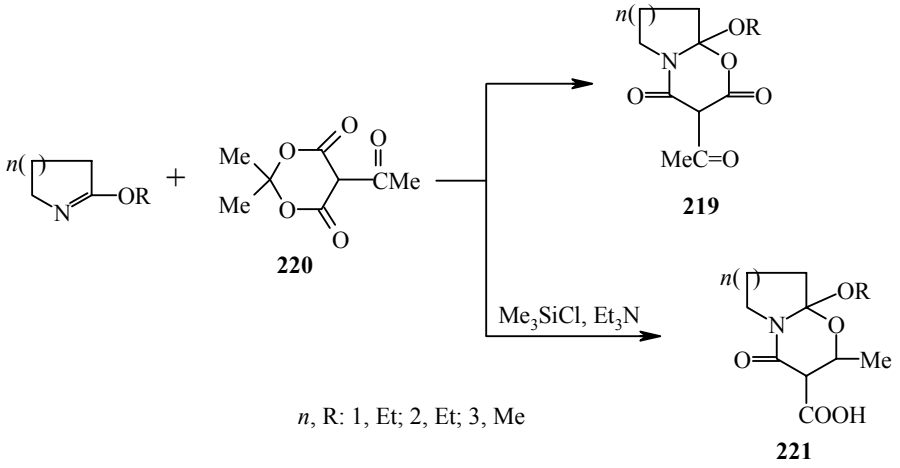


The bicyclic compounds **218** were synthesized by the reaction of the lactim ether **45** with 3,6-di(methoxycarbonyl)-1,2,4,5-tetrazine **217** at normal temperature until the release of N_2 had stopped [200].



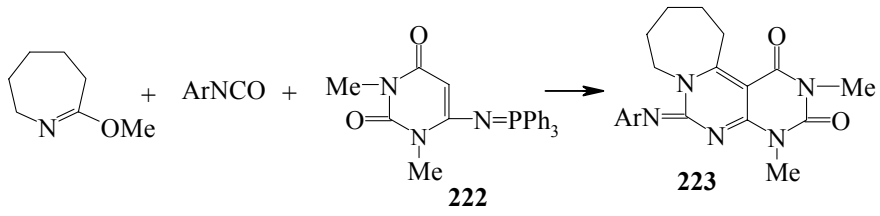
n, R, yield, %: 1, H, 18; 1, Me, 47; 2, H, 28; 3, H, 8

The tricarbonyl compounds **219** are formed with yields of 65-83% during the condensation of the lactim ethers from lactams **1**-**3** with 5-acetyl-2,2-dimethyl-1,3-dioxane-4,6-dione **220**. If these reactions are carried out in the presence of trimethylchlorosilane and triethylamine, the keto acids **221** are obtained [201].



n, R: 1, Et; 2, Et; 3, Me

The tricyclic compounds **223** are formed during the reaction of caprolactim methyl ether with aryl isocyanates and pyrimidine derivatives **222** [202].



Ar = (un)substituted Ph

Analysis of previously published material [1] and the present review provides grounds for concluding that there are a series of simple, accessible, and effective methods for the production of lactim ethers, which are labile compounds that enter readily into various chemical transformations. Various five-, six-, and seven-membered heterocyclic compounds containing nitrogen atoms in the ring and also compounds with several different heteroatoms in the rings have been synthesized from them.

It should be mentioned that researchers have paid significantly less attention to the transformations of lactim ethers leading to acyclic compounds.

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