Russian Journal of Organic Chemistry, Vol. 37, No. 7, 2001, pp. 901–934. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 7, 2001, pp. 959–986.

REVIEW

Advances in the Chemistry of 4-Azatricyclo[4.3.1.1^{3,8}]undecane (4-Azahomoadamantane) Derivatives

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Received March 27, 2000

Abstract—The review summarizes published data on the synthesis, physical and chemical properties, and biological activity of 4-azatricyclo[4.3.1.1^{3,8}]undecane derivatives and some related tricyclic compounds, tricycloundecane homologs and diadamantane derivatives.

I. INTRODUCTION

Specific chemical properties of adamantane [1, 2] and biological activity of its derivatives [3–5] have stimulated increasing interest in new cage-like heterocyclic systems. In 1964–1965, the first articles have appeared on the antiviral activity of 1-aminoadamantane (**1**) which is also known as Amantadine, Symmetrel, and Midantan [4–6]. Introduction of a nitrogen atom into the lipophilic adamantane molecule should give cage-like heterocyclic compounds with analogous properties. Examples of such structures are 4-azahomoadamantan-5-one (**2**) and its dihydro analog, 4-azahomoadamantane (**3**); the latter is isomeric to amine **1**, and it can readily be obtained by reduction of **2** with lithium aluminum hydride.

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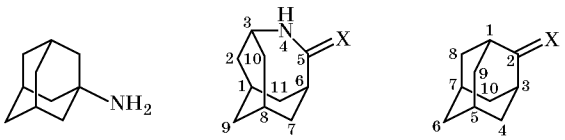
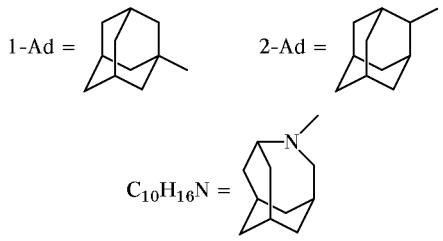


1 **2, 3** **4, 5**

2, **4**, X = O; **3**, X = H_2; **5**, X = NOH.

The following notations will be used in some cases for the sake of brevity:



New heterocyclic compounds **2** and **3** were reported for the first time in 1969 [7], immediately after the synthesis of adamantanone **4** had been published [8]. The antiviral activity of **2**, **3** was weaker than that of **1** [3]; nevertheless, their synthesis gave an impetus to the developments in the chemistry of such heterocyclic compounds. Let us consider methods of synthesis of compound **3** and its derivatives with no regard to their history but in keeping with the mode of formation of the tricyclic azahomoadamantane structure, as well as physical, chemical, and biological properties of these compounds.

II. METHODS OF SYNTHESIS OF 4-AZAHOMOADAMANTANES

Compound **2** can be classed with ω-lactams whose methods of synthesis are known. Polycyclic structure **2** can be built up by the procedures involving intramolecular acylation of the amino group by carboxy or ester groups in positions *3* and *7* of bicyclo[3.3.1]nonane molecule. Also, methods used for preparation of lactams from acyclic compounds [9, 10] can be applied (Scheme 1). The most widely used procedures are based on the Beckmann and Schmidt rearrangements of compounds **4** and **5** [11, 12], which are accompanied by ring expansion. Rearrangements of azido, *N*-chloroamino, and other amino-substituted adamantanes, leading to formation of the molecular skeleton of **3**, should be regarded as a specific class of reactions.

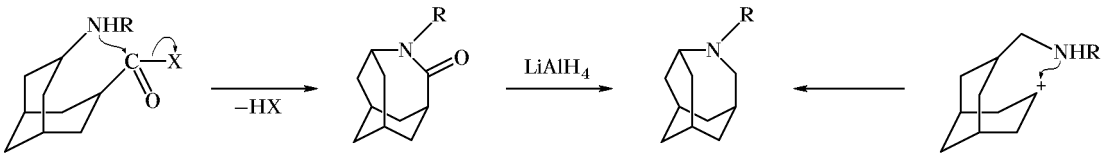
II.1. Synthesis of 4-Azahomoadamantane from Bicyclic Structures

Epoxy derivatives **8a** and **8b** turned out to be convenient starting compounds for intramolecular cyclization into 4-azahomoadamantane derivatives **9a** and **9b** by the action of NaH in dimethoxyethane (DME) or in benzene in the presence of *p*-toluenesulfonic acid [13] (Scheme 2). The *exo* orientation of the hydroxy group in products **9a** and **9b** is determined by the direction of intramolecular attack by the amide nitrogen atom on the epoxy fragment.

Treatment of *exo*-6,7-epoxybicyclo[3.3.1]nonane-*endo*-3-carbonitrile (**8c**) with HBr in acetic acid leads to formation of bromohydrin **10** with *trans* arrangement of the bromine atom and hydroxy group. Reduction of **10** with $LiAlH_4$–$AlCl_3$ results in ring closure with formation of 4-azahomoadamantane derivative **11** [13] (Scheme 3). The reaction of nitrile **8c** with 30% hydrogen peroxide in alkaline medium can be regarded as Ritter reaction [14]. According to [13], peroxy anion **12** is formed as intermediate. Its cyclization to **13** is favored by the molecular geometry and by the possibility for generation of electrophilic center at C^7. Probably, the transformation of **8a** and **8b** into **9a** and **9b** follows an analogous mechanism.

Substituted 4-azahomoadamantanes were obtained by transannular reactions of nitrile **14** which is readily available from ketone **4** [15]. Nitrile **14** can act as both nucleophile and electrophile. Initial protonation of the double bond in **14** generates electrophilic center on C^7, and the latter undergoes intramolecular attack

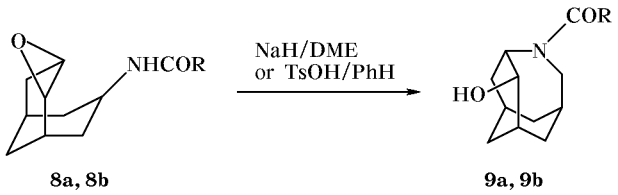
Scheme 1.



6a, 6b **7a, 7b**

R = Et (**a**), Me (**b**).

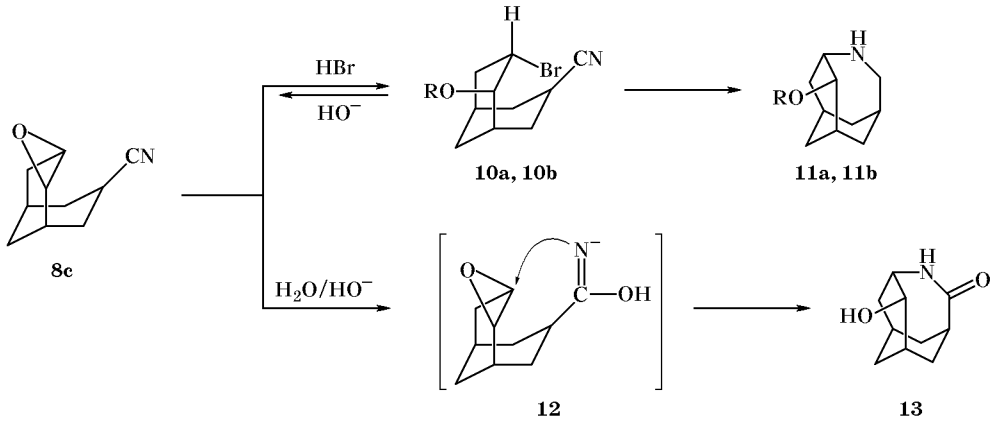
Scheme 2.



8a, 8b **9a, 9b**

R = Me (**a**), OCH_2Ph (**b**).

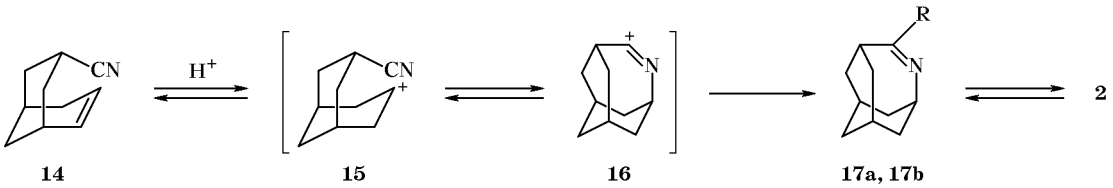
Scheme 3.



8c **10a, 10b** **11a, 11b** **12** **13**

R = H (**a**), 2-tetrahydropyranyl (**b**).

Scheme 4.



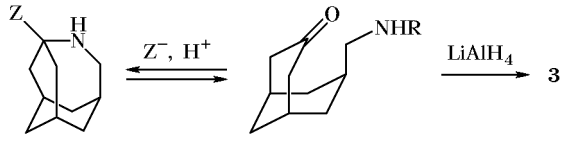
14 **15** **16** **17a, 17b**

R = OH (**a**), Cl (**b**).

by the cyano group to give 4-azahomoadamantane derivative. Korsloot and Keizer [16] studied the Beckmann rearrangement of oxime **5** in HCl and detected nitrile **14** among the products; they proposed a mechanism for transformation of **14** into lactam **2** through intermediate lactim **17a** (Scheme 4).

4-Azatricyclo[4.3.1.1^{3,8}]undecane (**3**) was obtained in quantitative yield by reductive cyclization of amino ketones **18a** and **18b** by the action of $LiAlH_4$ [17, 18] (Scheme 5). Cyclization of aminoketone **18a** in acid medium in the presence of other nucleophiles (anhydrous methanol, benzene, 1,3-dimethoxybenzene) gives 3-substituted 4-azahomoadamantanes **19a**–**19d** [17, 19]. Compound **19b** is formed in the presence of both gaseous HCl and H_2SO_4, whereas compounds **19c** and **19d** can be obtained only in the presence of HCl. Product **19d** was also synthesized by treatment

Scheme 5.



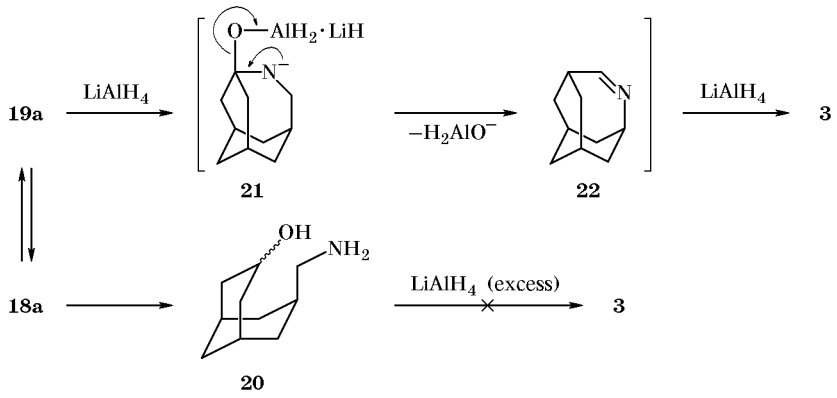
19a–19f **18a, 18b**

18, R = H (**a**), Et (**b**); **19**, Z = HO (**a**), MeO (**b**), PhS (**c**), 2,4-$(MeO)_2C_6H_3$ (**d**), OEt (**e**), CN (**f**).

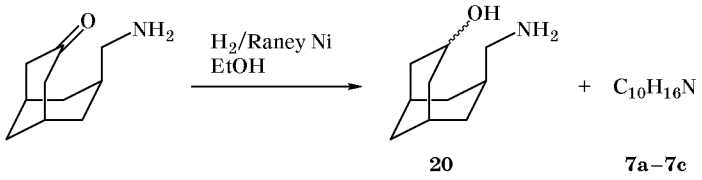
of aminoketone **18a** with aluminum chloride in the presence of dimethoxyethane. The mechanism of formation of 3-substituted 4-azahomoadamantanes **19a**–**19f** from ketone **18a** in the presence of Lewis acids as catalysts is not quite clear. According to [19], bicyclic amino alcohol **20** cannot be intermediate in this process, for it is not converted into **3** on treatment with excess $LiAlH_4$ (Scheme 6). Anion **21** should necessarily be formed to generate intermediate imine **22** containing a double bond in the bridgehead position. The reaction shown in Scheme 6 provides a convenient synthetic route to 3-substituted 4-azahomoadamantanes. The possibility for their formation was studied by theoretical (MMX and AM1) and experimental methods (photoelectron and ^{13}C NMR spectroscopy) [20]. It was found that intramolecular cyclization involving amino and carbonyl groups and resulting in tricyclic structures **19** is possible only when the amino group in ketone **18** occupies the *endo* position.

The reduction of amino ketone **18a** in ethanol in the presence of Raney nickel [21] gives about 40% of *endo*- and *exo*-alcohols **20** (ratio 35 : 65) and up to 50% of *N*-ethyl derivative **7a** which is the product of N-alkylation and reductive cyclization (Scheme 7). The yield of amine **7a** changes insignificantly on raising the temperature to 130°C. Presumably, the process includes cyclization of ketone **18a** to alcohol

Scheme 6.

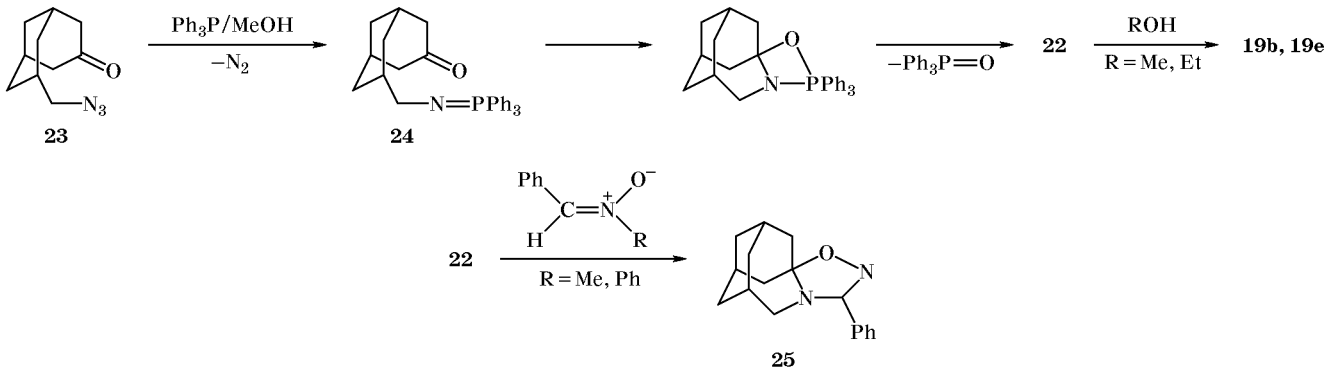


Scheme 7.



R = Et (**a**), Me (**b**), Ac (**c**).

Scheme 8.

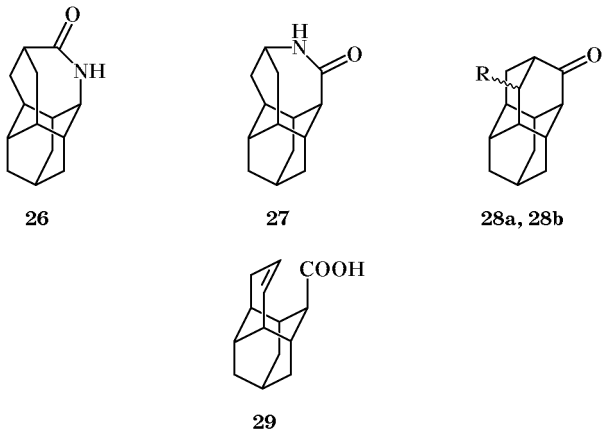


19a, followed by intramolecular dehydration of **19a** to give strained imine **22**. The hydrogenation of **22** and subsequent N-alkylation result in formation of product **7a**. The structure of the latter was established by comparison with its methyl analog **7b** and by independent synthesis, reduction of **7c** with $LiAlH_4$. Strained imine **22** is formed as intermediate in the synthesis of compounds **19b**, **19e** and various heterocyclic compounds from 7-azidomethyl derivative **23** [22]. This procedure for generation from keto azides of imines having a double bond in the bridgehead position is based on the Staudinger reaction followed by the intramolecular aza-Wittig reaction [22].

II.2. Synthesis of 4-Azahomoadamantan-5-one by Beckmann Rearrangement of Adamantan-2-one Oxime

II.2.1. Rearrangement in the presence of mineral acids. Polyphosphoric acid (PPA) is one of widely used catalysts for Beckmann rearrangement. It was reported to catalyze the rearrangement of oxime **5** to lactam **2** at 125°C [7]. Apart from PPA and polyphosphoric ester (PPE) [23–30], various mineral acids were used as catalysts for Beckmann rearrangement. The reaction with HCl in acetonitrile [16] gave 40% of lactam **2** and 35% of nitrile (**14**); the latter was not formed in the presence of PPA. It was shown that treatment of oxime **5** with 96% sulfuric acid leads to fragmentation and formation of nitrile **14** and then of **2** (see above). Conditions were reported (160°C, 4 h, 24.2% HBr) for quantitative preparation of lactam **2** from oxime **5** [31] (cf. [32]). A procedure was developed [33] for preparation of lactam **2** in quantitative yield from equimolar amounts of ketone **4** and hydroxylamine hydrochloride in the presence of trifluoroacetic acid as catalyst, without resorting to preparation of oxime **5**.

8(9)-Azapentacyclo[8.3.1.1^{4,13}.0^{2,7}.0^{6,12}]tetradecan-9(8)-ones **26** and **27** were synthesized from diadamantanone oxime (**28a**) under conditions of acid catalysis [34]. Compounds **26** and **27** were the only products when the Beckmann rearrangement was catalyzed by HNO_2 in various solvents. On passing to sulfuric acid, its mixtures with acetic acid, and trichloroacetic or trifluoroacetic acid, the yield of the lactams was lower; the reaction mixture contained *exo*- and *endo*-hydroxyketones **28b** and diadamantane-3,5-dione. When the reaction was carried out in methanesulfonic acid [35], the products were isomeric lactams **26** and **27** and up to 40% of unsaturated carboxylic acid **29** which was formed by cleavage and hydrolysis of the lactam ring.

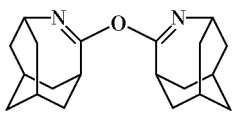


26 **27** **28a, 28b**

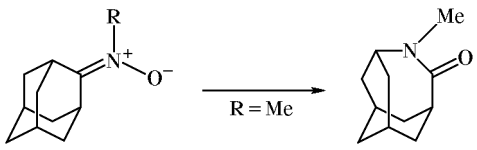
29

R = H (**a**), OH (**b**).

II.2.2. Rearrangement in the presence of Lewis acids. Korsloot and Keizer [16] reported on the synthesis of lactam **2** in 82% yield from oxime **5** in the presence of PCl_5. In this case, the yield was greater than in the presence of PPA (57%). Lactam **2** (as a mixture with the corresponding hydrochloride) was obtained in a good yield by reaction of oxime **5** with a 2–12-fold excess of thionyl chloride [36]. Only 2–5% of nitrile **14** was formed as by-product. The yield of **2** did not change when gaseous HCl and SO_2 were passed through a solution of **5** in ether containing thionyl chloride. This means that neither HCl nor SO_2 are involved in the process. Hydrogen chloride liberated along pathway *a* (Scheme 9) is then consumed for regeneration of the catalyst from lactam precursor. Pathway *b* is analogous to reactions which occur in the absence of acid catalyst. Benzenesulfonyl chloride in pyridine [36] gave rise to only 60% of crude product **2**. Nevertheless, $PhSO_2Cl$ turned out to be a convenient reagent from the preparative viewpoint, and it was frequently used in the synthesis of lactam **2** [37–41]. In the presence of *p*-toluenesulfonyl chloride in DMF, 80% of dimer **30** was obtained. Its structure was proved by spectral methods. Compound **30** was formed as by-product in the synthesis of N-substituted derivatives **6** [28].

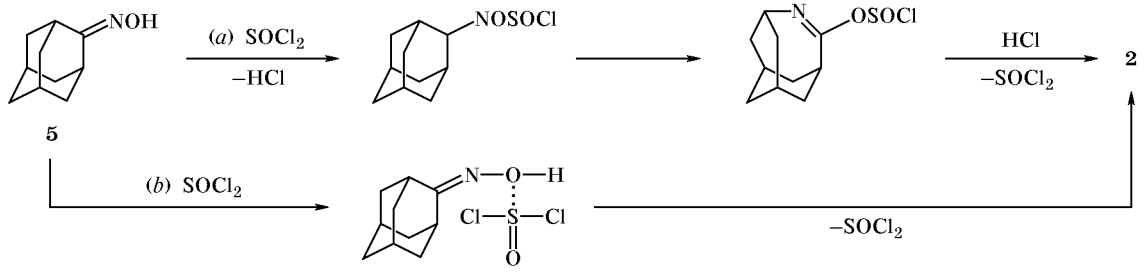


30



31 **6b**

Scheme 9.



p-Toluenesulfonyl chloride was successfully used to catalyze Beckmann rearrangement in the synthesis of *N*-methyl derivative **6b** from *N*-oxide **31**; the latter was obtained by treatment of ketone **4** with excess *N*-methylhydroxylammonium chloride in pyridine or alcohol in the presence of sodium acetate and K_2CO_3 [42]. The rearrangement of **31** into **6b** is accompanied by red coloration of the mixture, and the yield of **6b** is 70% [43]. For comparison, the rearrangement of oxime **5** with sulfuric acid [16], followed by methylation, gave only 25% of lactam **6b**. Lactam **2** was obtained in 64% yield [44] using chlorosulfonyl isocyanate in methylene chloride instead of *p*-toluenesulfonyl chloride in pyridine.

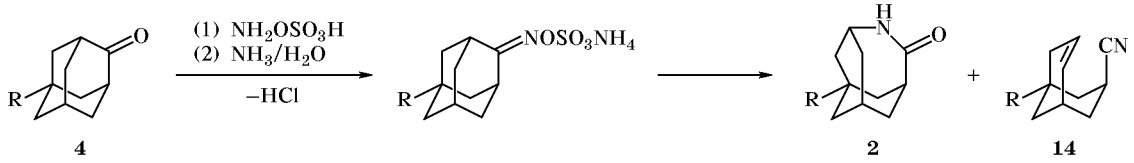
II.2.3. Thermal and photochemical Beckmann type rearrangements. Adamantanone **4** and its 1-bromo derivative readily react with an aqueous solution of hydroxylamine *O*-sulfonic acid; the products are precipitated with aqueous ammonia and are isolated as ammonium salts whose thermal decomposition (150–170°C) yields mixtures of lactams **2** with the corresponding nitriles **14** [45] (Scheme 10).

The same reaction occurs with proto- and homoadamantan-4-ones and diamantanone (**28a**), yielding the corresponding lactams. The presence of substituents in the ketone molecule was shown [45] to slow down the reaction. The available experimental data do not allow us to choose a definite mechanism among those listed below: *a* → *a′* (*a″*), *b* → *b′* (*b″*), or *b* → Ritter reaction.

The rearrangement can also be effected by irradiation. Photolysis of a 0.1% solution of oxime **5** in acetic acid at 20°C gave 89% of lactam **2** [46]. The only by-product was ketone **4**. No fragmentation products were formed, in contrast to the photolysis in methanol or isopropyl alcohol, where fragmentation of **5** was the main process.

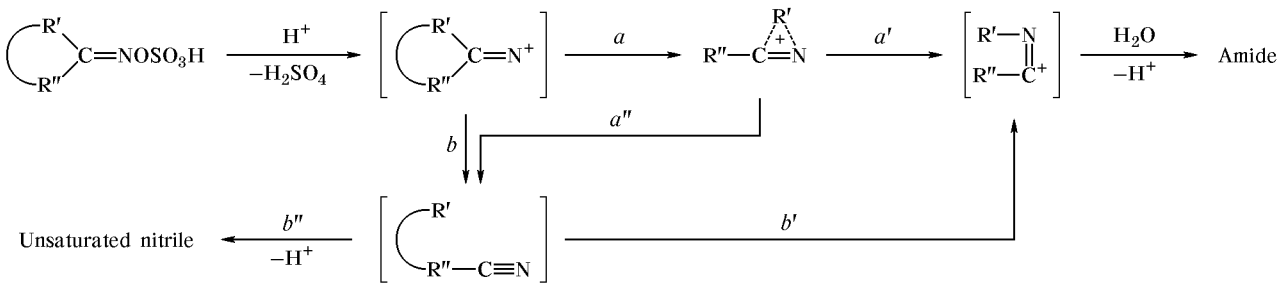
Photochemistry of cyclic ketone oximes was studied in detail in 1972. It was shown that photochemical reaction leading to formation of Beckmann

Scheme 10.

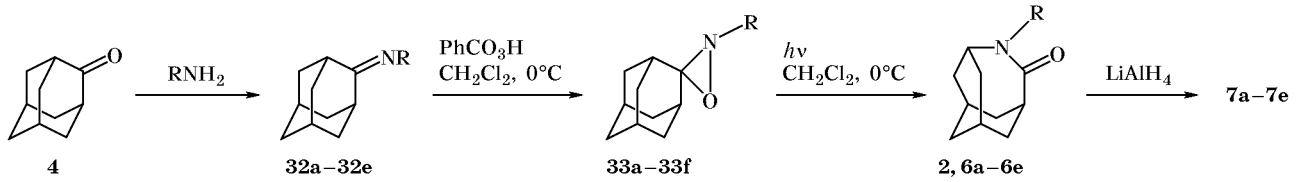


R = H, Br.

Scheme 11.

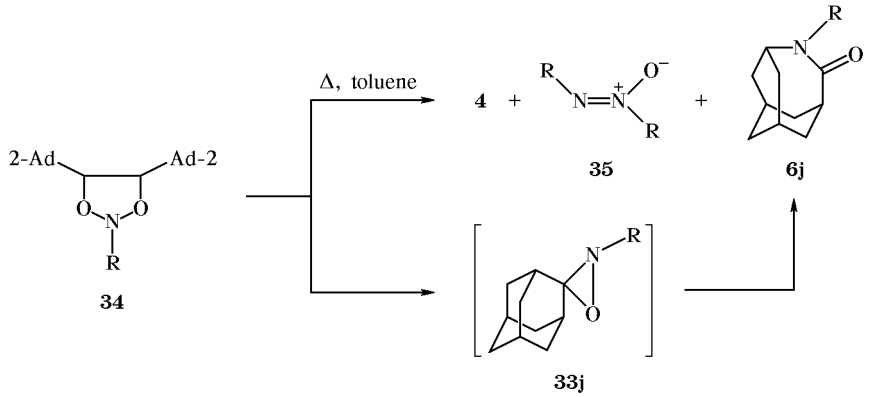


Scheme 12.



R = Et (**a**), Me (**b**), CH_2Ph (**c**), $(CH_2)_2CHPh_2$ (**d**), Ph (**d**); **2**, **33f**, R = H.

Scheme 13.



R = 3,5-Dinitrophenyl.

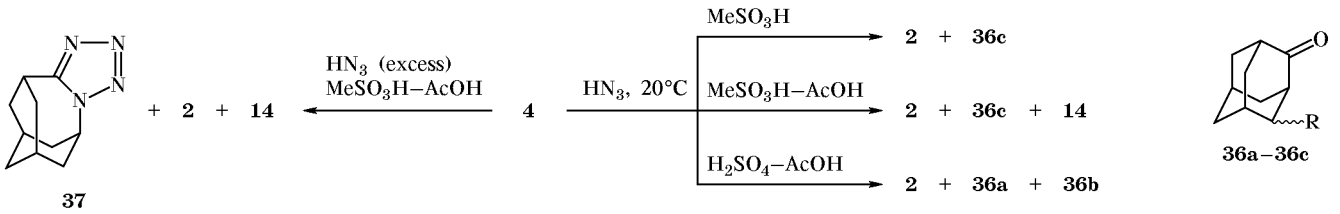
rearrangement products involves intermediate formation of oxaziridines [47]. Ar the same time, Oliveros-Desherces *et al.* [48] found that irradiation of *N*-substituted spirooxaziridines of the adamantane series gives no by-products and that *N*-substituted lactams **6a**–**6e** are thus formed in high yield. The latter are readily reduced to the corresponding amines **7a**–**7e** (Scheme 12). In 1979, Oliveros-Desherces *et al.* [49] proved the assumption that photochemical transformations of oximes into the corresponding amides involves intermediate formation of oxaziridines **33**. Study of the mechanism of photochemical rearrangements of spirooxaziridines showed that the stereoselectivity of the process depends on the solvent, sensitizer nature, and reaction time. Sasaki *et al.* [50] also noted the regioselectivity of the rearrangement of compounds **33b** and **33c** into lactams **6b** and **6c** which were formed in 95 and 85% yield, respectively (under optimal conditions). The oxidation of *N*-adamantylideneaniline (**32e**) with *m*-chloroperoxybenzoic acid was reported [50] to directly afford 35% of lactam **6e**, for intermediate *N*-phenyloxaziridine **33e** is unstable.

Likewise, Beckmann rearrangement products **6g**–**6i** were obtained by thermal isomerization of oxaziridines **33g**–**33i** [R = *cyclo*-C_6H_{11} (**g**), 1-$AdCH_2$ (**h**), 1-Ad (**i**)], which was effected by heating in boiling tetrahydronaphthalene or by heating molten compound **33h** at 230–240°C [51, 52]. Compound **33f** gives rise to lactam **2** when the reaction is carried out in MeOH by shaking the mixture with an equimolar amount of finely powdered $FeSO_4 \cdot 7H_2O$ [53]. Somewhat surprising results were obtained by heating of dioxazolidine **34** in boiling toluene: The product mixture contained ketone **4**, azoxybenzene **35**, and 9% of lactam **6j** [54] (Scheme 13). Presumably, the initially formed oxaziridine **33k** undergoes thermal Beckmann-like rearrangement into lactam **6j**.

II.3. Synthesis of 4-Azahomoadamantan-5-one Derivatives by Schmidt Reaction

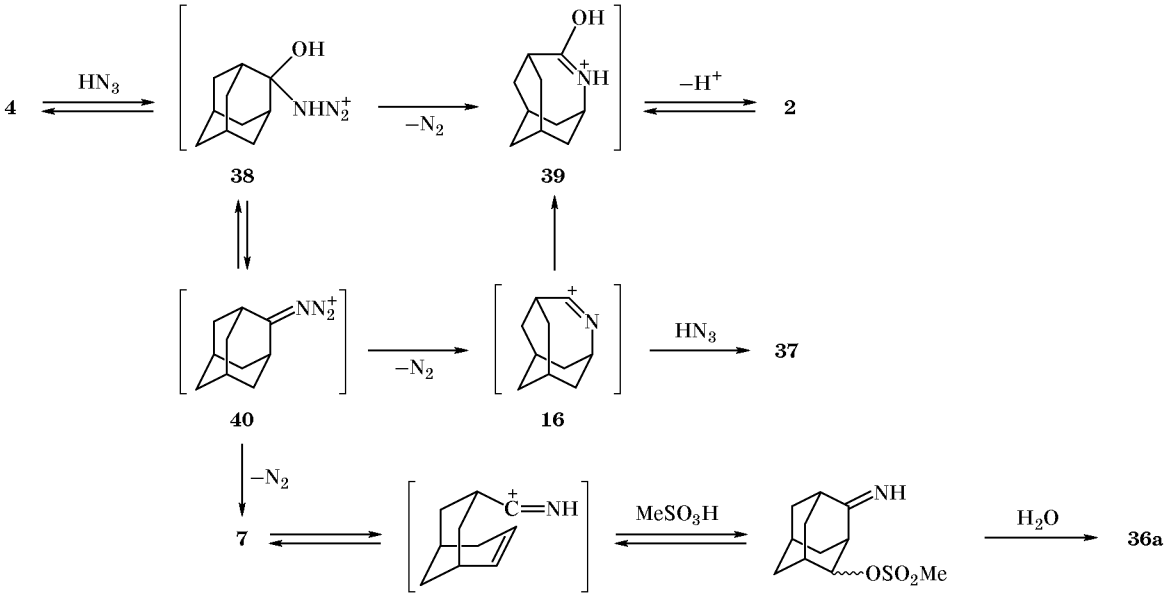
Ketone **4** reacts with hydrazoic acid in AcOH in the presence of *p*-toluenesulfonic acid (Schmidt reaction) [55]. Lactam **2** was thus obtained in 31% yield. The same reaction in methanesulfonic acid gave only 10% of **2**. Later on, Sasaki *et al.* [56] performed a detailed study of the behavior of ketone **4** in the Schmidt reaction under various conditions using equimolar amounts of **4** and HN_3. The results are presented in Scheme 14. Compound **37** was obtained in a poor yield when the reaction was carried out in a mixture

Scheme 14.



R = OH (**a**), OAc (**b**), OSO_2Me (**c**).

Scheme 15.



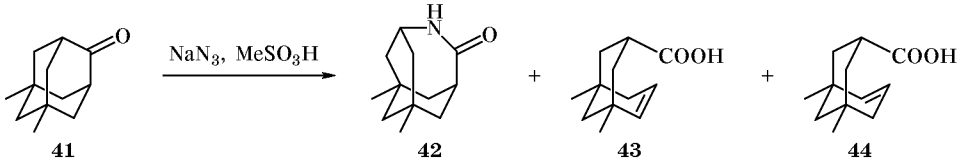
of $MeSO_3H$ with acetic acid or chloroform, but it was not formed in pure methanesulfonic acid. Another route to **37** is based on treatment with sodium azide of cyclic imidoyl chloride **17b** (R = Cl) which was synthesized by reaction of lactam **2** with PCl_5 in chloroform at 0°C. Sasaki *et al.* [56] proposed a mechanism according to which lactam **2** is formed through intermediate ions **38** and **39** (Scheme 15). Depending on the conditions, the yield of **2** ranges from 11% (in $MeSO_3H$) to 60% (in CF_3COOH), but the reaction is always accompanied by formation of other products.

Ketone **41** reacts with sodium azide in $MeSO_3H$ at 0°C to give only 7% of lactam **42** [57], while the major products were isomeric bicyclic acids **43** and **44** (Scheme 16).

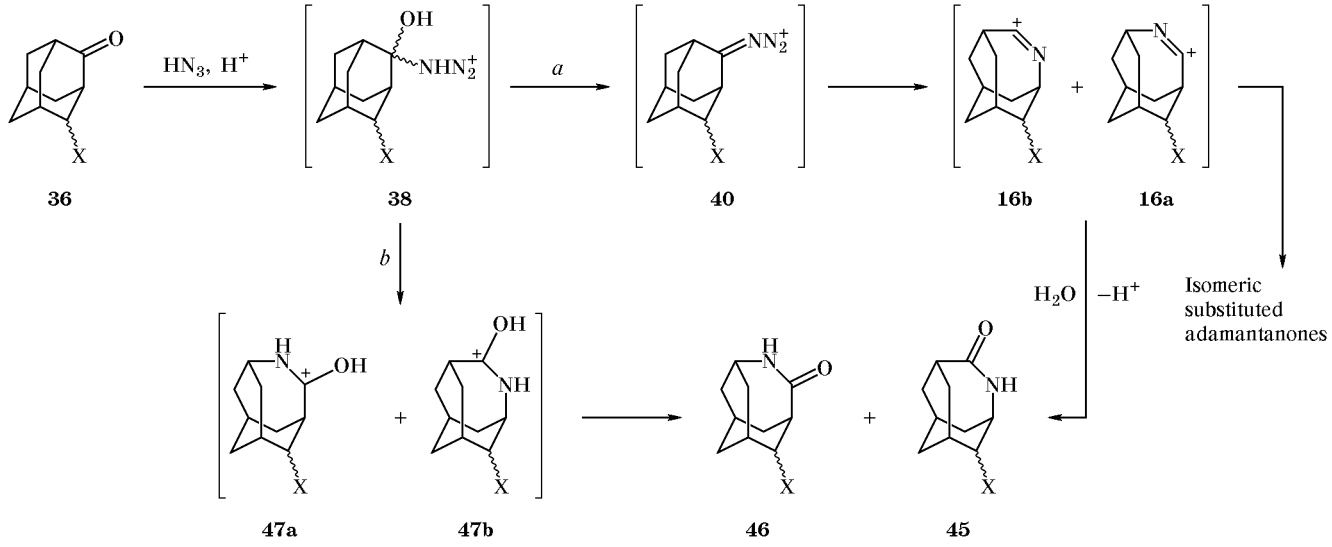
Narayanan and Setescak [25] compared the yields of lactam **2** obtained from oxime **5** via Beckmann rearrangement and by the Schmidt reaction of ketone **4** with NaN_3 at 65–70°C in the presence of PPA. In both cases the yields were 70–80%. Black and Gill [29] obtained lactam **2** in PPA in a considerably lower yield (23%); the latter was increased to 50% using trifluoroacetic acid as catalyst at 0°C.

Reactions of 4-substituted adamantan-2-ones **36** with sodium azide in a mixture of methanesulfonic and acetic acids at 20°C led to formation of isomeric 2-substituted 4-azahomoadamantanones **45** and **46**

Scheme 16.



Scheme 17.



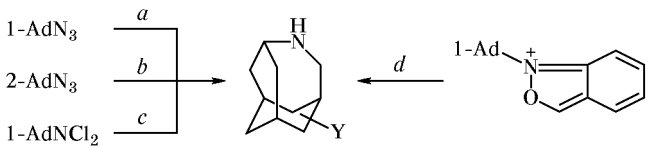
X = Cl, Br, I, CN, OSO_2CH_3.

[58] (Scheme 17). Rearrangement of the initially formed ion **38** can take two pathways: (*a*) through diazoiminium ion **40** to give intermediates **16a** and **16b** and (*b*) with loss of N_2 and formation of two isomeric ions **47a** and **47b**. Both pathways are equally probable, but all these intermediates react differently and hence the amounts of final lactams **45** and **46** are also different. It was found that compounds **45** are formed only from ketones **36** having an axial substituent in position *4*. Ketones **36** in which the 4-substituent is equatorial give rise mainly to lactams **45** and substituted adamantanone. When X = I, the only product is lactam **46**.

The conditions of intramolecular Schmidt reaction of bicyclic azidoketones in the presence of protic or Lewis acids [59] were extended to intermolecular processes [60] involving ketone and alkyl azide; as a result, *N*-substituted lactams were obtained. The reaction of adamantanone **4** with 2 equiv of RN_3 and 2.5 equiv of $TiCl_4$ at 0°C in methylene chloride gave compounds **6c** (R = $PhCH_2$) and **6k** (R = C_6H_{13}) in almost quantitative yield. In the first stage alkyl azide adds to activated ketone to form an intermediate whose further rearrangement along pathway *a* or *b* yields mixtures of isomeric lactams.

II.4. Rearrangements of Adamantanes with Nitrogen-Containing Substituents

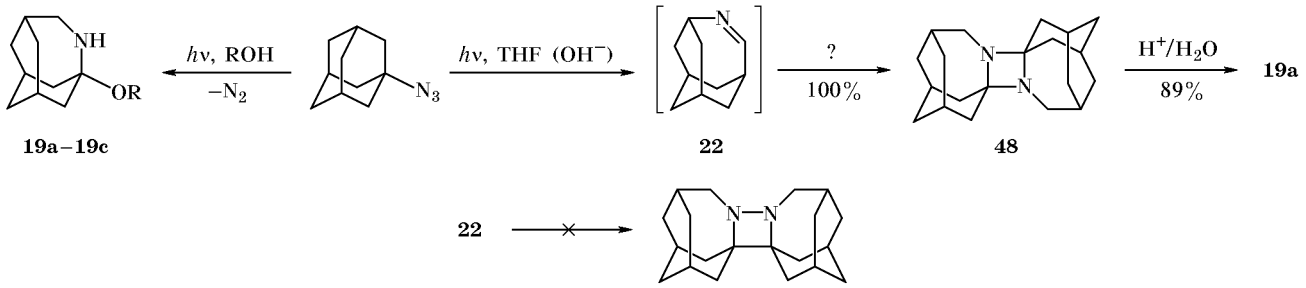
This section describes rearrangements leading to 4-azahomoadamantane derivatives and involving formation of adamantylnitrenium ion as intermediate. Reactions *a–d* shown below are examples of such processes.



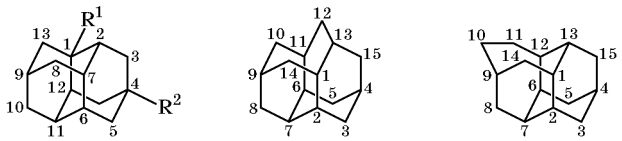
II.4.1. Rearrangements of azidoadamantanes. In 1974, Quast and Ecker [61] reported on a simple procedure for synthesis of 4-azahomoadamantanes by photolysis of 1-azidoadamantane. The latter was obtained by reaction of amine **1** with *p*-toluenesulfonyl azide and subsequent treatment of the product with sodium hydride in THF. The photochemical reaction was carried out in aqueous solvents, lower alcohols, or hydrocarbons (Scheme 18). Photolysis in a hydroxyl-containing medium leads to amines **19a**, **19b**, and **19e**. In a nonalcoholic medium (THF, alkanes, cyclohexane, or cyclohexene) containing sodium hydroxide, dimer **48** is formed; on treatment with 0.1 N $HClO_4$ it is converted into crystalline hydroperchlorate $C_{20}H_{30}N_2 \cdot HClO_4$. Attempts to detect intermediate **22** were unsuccessful.

The above photolytic reactions were used to synthesize isomeric azahomodiadamantane derivatives from 1- and 4-azidodiamantanes **49** and **50** [62]. Isomeric homodiamantane structures, pentacyclo[7.4.1.1^{4,13}.0^{2,7}.0^{6,11}]pentadecane (**51**) and pentacyclo[7.4.1.1^{4,13}.0^{2,7}.0^{6,12}]pentadecane (**52**), were termed 1(2)- and 2(3)-homodiamantanes, respectively [62].

Scheme 18.



The formation of isomeric lactams, 11-aza-2(3)-homodiamantan-10-one or 10-aza-2(3)-homodiamantan-11-one, by the Schmidt reaction [35] or Beckmann rearrangement [45] from 3-diamantanone was reported, but the products either were not characterized or were described as mixtures of regioisomers.

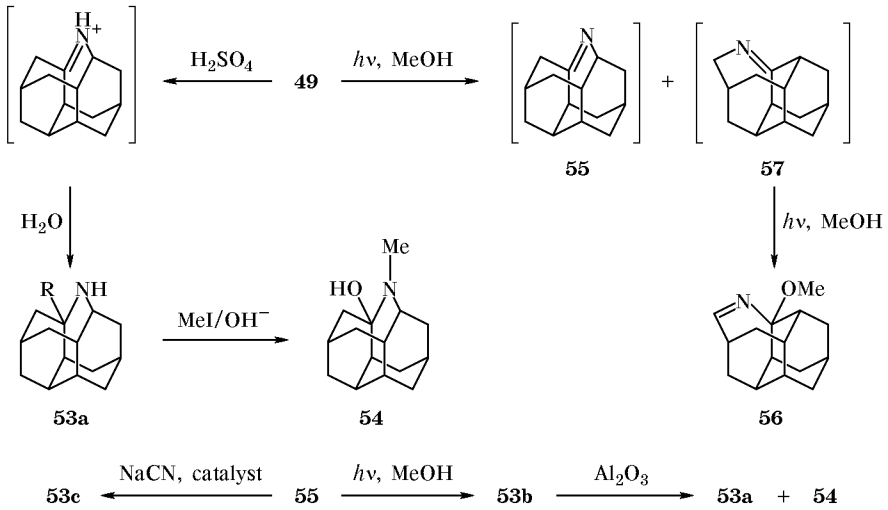


49, 50 **51** **52**

49, $R^1 = N_3$, $R^2 = H$; **50**, $R^1 = H$, $R^2 = N_3$.

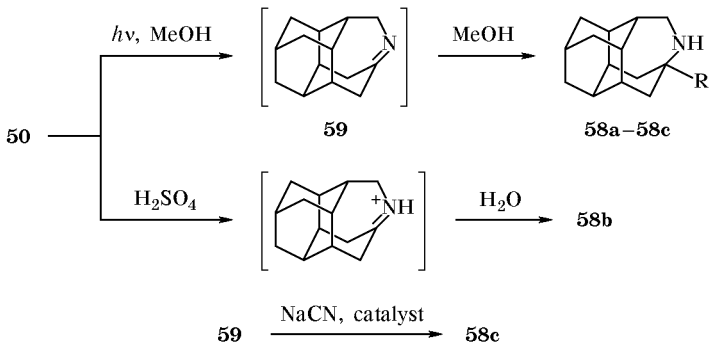
Low regioselectivity is also typical of ring expansion of unsymmetric azides. For example, direct photolysis of compound **49** in methanol gives several products. The major products are 13-azapentacyclo[7.4.1.1^{4,12}.0^{2,7}.0^{6,11}]pentadecan-1-ol (**53a**), which is identical to that obtained by acydolysis of azide **49** with sulfuric acid, and *N*-methyl derivative **54**. Both compounds are formed as a result of hydrolysis and unusual isomerization (O,N-migration of the methyl group) of primary adduct **53b** during chromatographic separation on aluminum oxide. Adduct **53b** is formed from intermediate **55** and MeOH (Scheme 19). Only stable methoxy derivative **56** (9%) can be regarded as a product of direct photolysis of azide **49** in MeOH (through intermediate **57**). Unlike **49**, photolysis of symmetric azide **50** in methanol gives 83% of 9-methoxy-10-azapentacyclo[7.4.1.1^{4,13}.0^{2,7}.0^{6,12}]-pentadecane (**58a**). Treatment of **50** with concentrated sulfuric acid in chloroform leads to formation of hydroxy derivative **58b** [62] (Scheme 20). Intermediates **59** and **55** can be detected by carrying out the photochemical reactions of azides **49** and **50** in the presence of phase-transfer catalyst (NaCN–Adogen 464–H_2O–hexane). In this case, the products are compounds **58c** and **53c**, respectively. Similar conditions were reported in [63] for the synthesis of 3-cyano-4-

Scheme 19.



R = OH (**a**), OMe (**b**), CN (**c**).

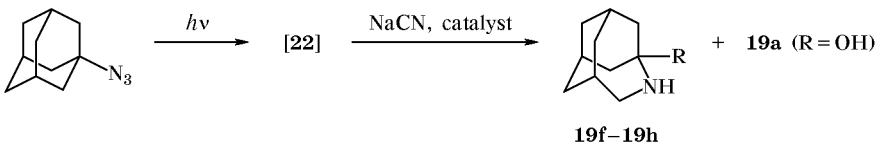
Scheme 20.



R = OMe (**a**), OH (**b**), CN (**c**).

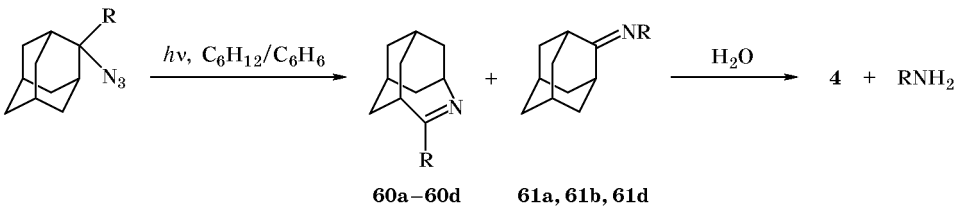
azahomoadamantane (**19f**) as hydrocyanation product of imine **22**. Compound **19f** can readily be converted into acid **19g** (as hydrochloride **19h**). Hydroxy derivative **19a** is formed as by-product (Scheme 21). Adamantane derivatives with an azido group in the bridgehead position and related structures give rise to unstable compounds with a bridgehead C=N bond, and the products are adducts at the C=N bond. By contrast, stable imines are formed from 2-adamantyl azides. The photolysis of 2-adamantyl azides in cyclohexane or benzene [64] results mainly in formation of imines **60a**–**60d** (yield 53–61%) rather than **61a**–**61d** (through migration of H or R to the nitrogen); nevertheless, the fraction of the latter in the products is significant (12–45%). Compounds **61a**, **61b**, and **61d** are unstable. They undergo hydrolysis on exposure to air, yielding adamantanone **4** and the corresponding amine (Scheme 22). Lewis acids catalyze decomposition of adamantyl azides to 4-azahomoadamantane derivatives. Apart from the photochemical reaction [63], nitrile **19f** can also be obtained by catalytic decomposition of 1-adamantyl azide with aluminum chloride in the presence of Me_3SiCN [63] but not in the presence of trimethyl(phenylethynyl)silane [65] (Scheme 23). When the reaction with $AlCl_3$ is carried out in an aromatic substrate, the rearrangement of azide is accompanied by aminoalkylation of the aromatic compound [66]. At an azide–$AlCl_3$–ArH molar ratio of 1 : 10 : 73 more than 90% of 3-aryl-4-azahomoadamantanes **62a**–**62c** is obtained, the *ortho*/*para* ratio being 1 : 1 for **62b** and 1 : 1.8 for **62c**. The reaction is performed at 80°C. At 20°C only 3-hydroxy derivative **19a** is formed (Scheme 24). The acid-catalyzed decomposition of azides involves formation of a complex between the catalyst (Lewis acid) and nitrenium ion; elevated temperature is necessary for the aromatic substitution to occur [67]. The formation of azide–$AlCl_3$ complex and elimination of nitrogen are observed 30 s after addition of the Lewis acid; this means that the rate of formation of this complex is

Scheme 21.



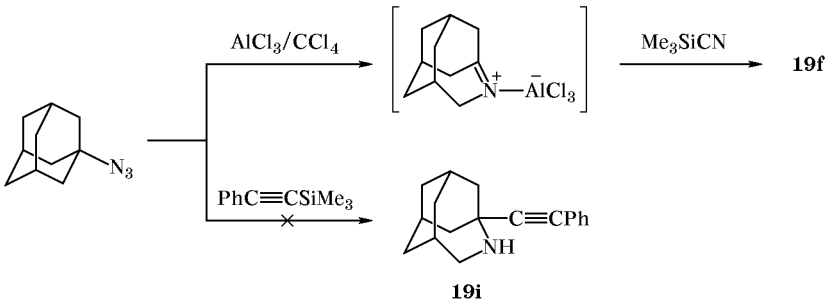
R = CN (**f**), COOH (**g**), COOH·HCl (**h**).

Scheme 22.

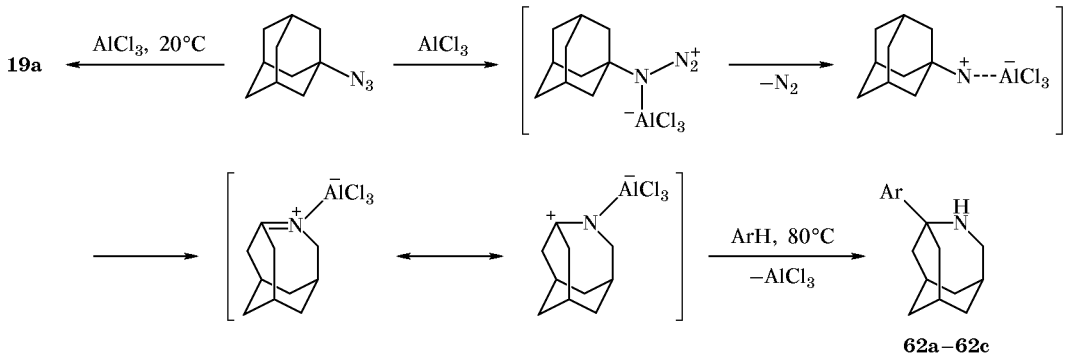


R = H (**a**), Me (**b**), CH_2Ph (**c**), Ph (**d**).

Scheme 23.



Scheme 24.



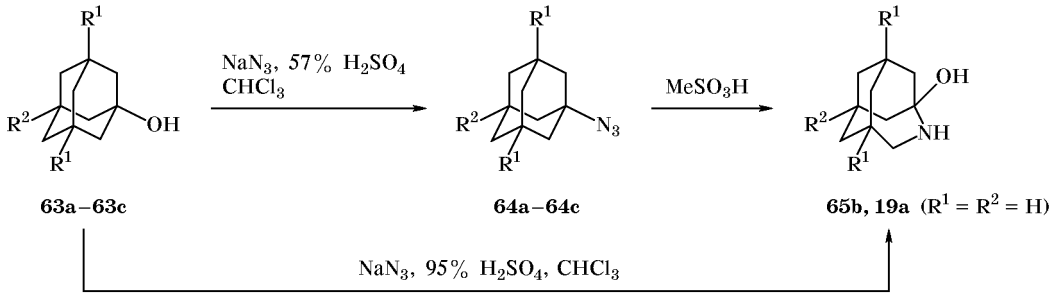
Ar = Ph (**a**), C_6H_4Me (**b**), C_6H_4Cl (**c**).

very high and that the rate-determining stage is decomposition of the complex [67].

In 1977, Sasaki *et al.* [68] proposed a convenient procedure for preparation of 1-azidoadamantanes by treatment of the corresponding alcohols with sodium azide in a 1:1 mixture of 57% H_2SO_4 and chloroform at 0°C. Prior to this publication there was no efficient method for introduction of an azido group into bridgehead positions of polycyclic hydrocarbons. The yields of azides **64a**–**64c** from alcohols **63a**–**63c** were more than 90% (Scheme 25). Azide **64c** was unstable, and it underwent rearrangemt into amine **19a** during the process. Compound **19a** was also formed by treatment of alcohol **63c** with sodium azide in the system 95% sulfuric acid–chloroform.

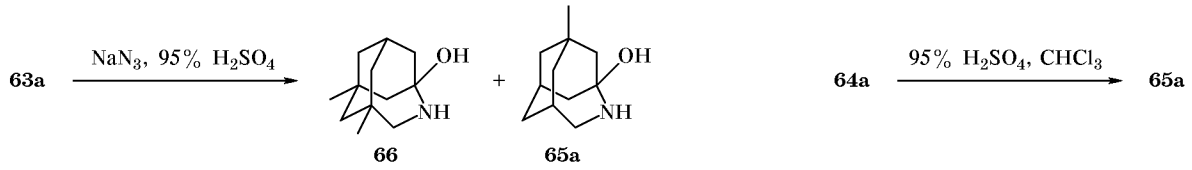
Azides **64a** and **64b** also rearrange into 3-hydroxy derivatives **65a** and **65b** in 95% H_2SO_4; under the same conditions, alcohol **63a** gives rise to a mixture of isomeric lactams **66** and **65a** at a ratio of 2:1 (Scheme 26). Likewise, treatment of 2-hydroxyadamantanes **67a**–**67f** with sodium azide in 57% sulfuric acid or of 2-azidoadamantanes **68b**–**68f** with methane-

Scheme 25.

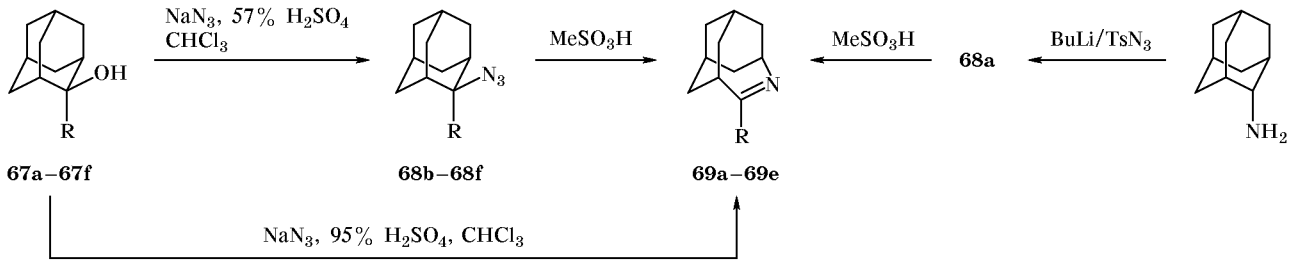


63–**65**, R^1 = Me, R^2 = H (**a**); R^1 = R^2 = Me (**b**); R^1 = R^2 = H (**c**).

Scheme 26.



Scheme 27.

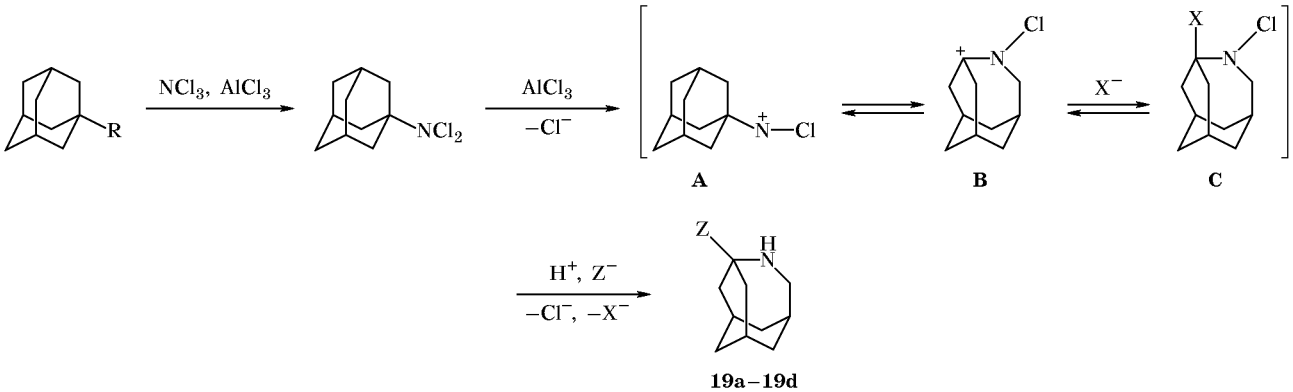


R = H (**a**), Me (**b**), Et (**c**), Bu (**d**), CH_2Ph (**e**), Ph (**f**).

sulfonic acid gave 5-substituted imines **69a**–**69e** [69, 70] (Scheme 27). Azide **68a** cannot be obtained in such a way; it was synthesized by the action of butyllithium and *p*-tolylsulfonyl azide on 2-aminoadamantane (Scheme 27).

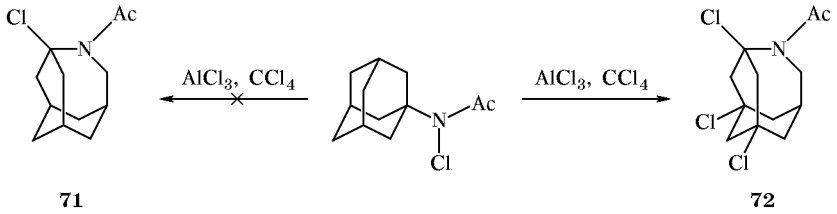
II.4.2. Rearrangements of *N*-substituted aminoadamantanes. *N*,*N*-Dichloro-1-aminoadamantane is formed as intermediate in the synthesis of amine **1** from adamantane and NCl_3 in the presence of $AlCl_3$ [71]. All $AlCl_3$-catalyzed rearrangements of *N*-substituted aminoadamantanes involve nitrenium ion **A**, and $AlCl_3$ catalyzes the nitrenium rearrangement **A** → **B** [72] (Scheme 28). The formation of intermediate **C** becomes obvious when such nucleophile as water, methanol, benzenethiol, or 1,3-dimethoxybenzene participates in the reaction [17]. Analogous rearrangements were revealed for *N*-chloro-*N*-ethyl- [19] and *N*-acetyl-*N*-chloro-1-aminoadamantanes [73, 74]. In contrast to the data of [73], Starewicz *et al*. [74] obtained 1,3,8-trichloro derivative **72** instead of *N*-acetyl-*N*-chloro-4-azahomoadamantane (**71**), when the reaction was carried out in CCl_4 in the presence of $AlCl_3$ (Scheme 29). The rearrangement of *N*-chloro-1-adamantylacetamide into compound **71** was reported [75] to occur under very mild conditions (20°C, exposure to light; Scheme 30). A similar rearrangement was observed in the photochemical decomposition of 1-(1-adamantyl)-3-phenyl-2,1-benzisoxazolium perchlorate (**73**) in acetonitrile [76] (Scheme 31). A colored product was isolated in

Scheme 28.



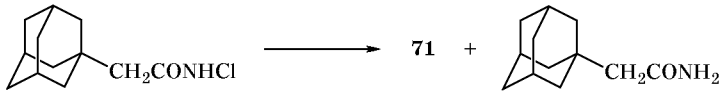
R = H, Br; X = Cl, Br.

Scheme 29.

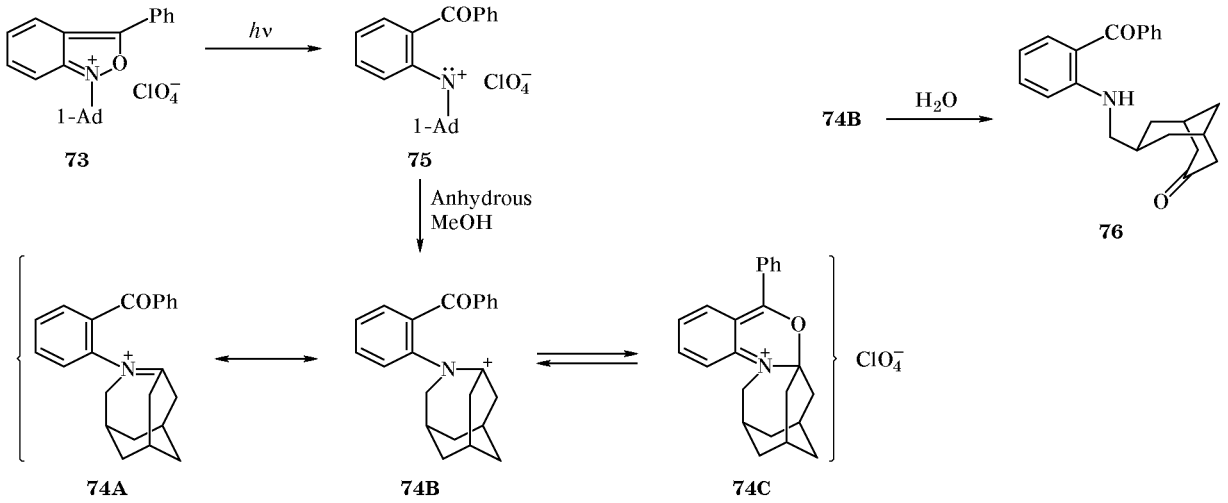


71 **72**

Scheme 30.



Scheme 31.



nearly quantitative yield. Its spectral parameters conformed to perchlorate **74A**, **74B**, or **74C**, which can be formed by ring expansion of arylazonium ion **75** to azahomoadamantane [77] structure. Hydrolysis of perchlorate **74** yields compound **76**. The data of the chemical and spectral studies [76] showed that the isolated crystalline product with mp 225°C has structure **74A** or **74B**.

III. STRUCTURE, SPECTRAL PARAMETERS, AND CHEMICAL PROPERTIES OF 4-AZAHOMOADAMANTANE AND ITS DERIVATIVES

4-Azahomoadamantane (**3**) and its direct precursors, imines **22** and **69a** and their derivatives, as well as lactam **2**, can be used as starting compounds for the synthesis of a number of products exhibiting a wide spectrum of physiological activity and other valuable properties. This section deals with the structure and reactivity of such azahomoadamantane derivatives.

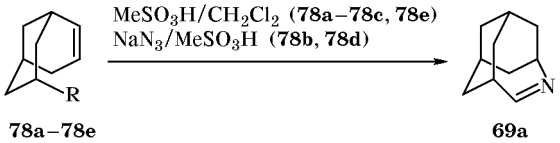
III.I. Dehydro-4-azahomoadamantanes

Anti-Bredt strained imines in which the C=N bond is located in the bridgehead position of polycyclic structures attract increased interest of researchers. These compounds were usually synthesized by photochemical rearrangements of azides derived from norbornane [78], homoadamantane [79], bicyclooctane [80], adamantane [61], and noradamantane [81]. However, the only stable isolated compound was 2-azabicyclo[3.3.1]non-1-ene (**77**) [82]. Highly strained and reactive imine **22** was detected for the first time by IR spectroscopy in the photolysis of 1-azidoadamantane in low-temperature matrices using a high-pressure mercury lamp (200 W) as irradiation source [83]. During the process, absorption bands typical of the azido group (2093 and 2143 cm^{-1}, N_2 matrix) disappeared from the spectrum, and C=N absorption appeared at 1608 and 1600 cm^{-1}; these frequencies are lower by 40–60 cm^{-1} than those

typical of unstrained alkylamines. Attempts to isolate the resulting imine were unsuccessful, and in the mass spectrum only the ion peaks belonging to the corresponding dimer **48** were observed (M^+ 298). The reaction was thoroughly studied by spectral methods, including IR, UV, and Raman spectroscopy and circular dichroism [84, 85], in nitrogen, argon, 3-methylpentane, and polyethylene matrices under irradiation at λ = 250 nm for 2–4 days. Using ^{15}N-labeled imine **22** it was presumed that the molecule is chiral (enantiomers **22A** and **22B**); however, this assumption was not confirmed by spectral data.

77 **22A** **22B**

Unlike highly strained and unstable compound **22**, imine **69a** and its derivatives are stable. Treatment of azide **78a** with a $MeSO_3H$–CH_2Cl_2 mixture (3:1, by volume) at 20°C in 5 h gave 67% of a volatile solid product [86] which was identical to that obtained from enol **78b** by treatment with sodium azide in methanesulfonic acid [69].



78a–78e **69a**

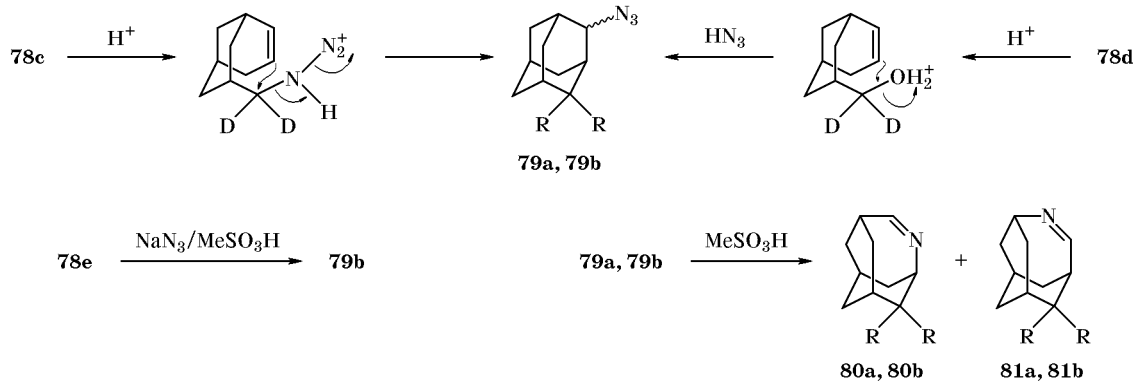
R = CH_2N_3 (**a**), CH_2OH (**b**), CD_2N_3 (**c**), CD_2OH (**d**), CMe_2OH (**e**).

At first glance, the synthesis of imine **69a** from compounds **78a** and **78b** should be regarded as formation of the 4-azahomoadamantane structure from bicyclic derivatives. However, Sasaki *et al.* [86] synthesized deuterated derivatives **78c** and **78d** and found that the scheme of synthesis of imine **69a** includes the stage of formation of azide **79**, followed by ring expansion on treatment with $MeSO_3H$ (Scheme 32). According to the GLC and ^{1}H and ^{13}C NMR data [using $Eu(FOD)_3$ as shift reagent], the product obtained in 90% yield was an equimolar mixture of **80a** and **81a**. The procedure for cyclization of bicyclononene derivatives **78a** and **78b** to 2-azidoadamantane **68a** was applied to the synthesis of 2,2- and 7,7-dimethyl-4-azatricyclo[4.3.1.1^{3,8}]undec-4-enes **80b** and **81b** which were obtained at a ratio of 35:65 by treatment of compound **78e** with sodium azide in methanesulfonic acid. The C=N bond in the above imines can readily be hydrogenated by the action of $NaBH_3CN$ [86, 87] or $NaBH_3OAc$ [70, 88].

Compound **69b** reacts with methyl iodide to give salt **84a** whose treatment with bases leads to formation of 4-methyl-5-methylene-4-azatricyclo[4.3.1.1^{3,8}]-undecane (**85**) [70]; the latter can be converted into perchlorate **84b** by the action of $HClO_4$ (Scheme 33). The condensation of **85** with 1-amino-2-naphthol in DMSO as oxidant activated by $NaHCO_3$ yields 4-methyl-4-azatricyclo[4.3.1.1^{3,8}]undecane-5-spiro-3′-3′*H*-naphtho[2,1-*b*][1,4]oxazine (**86**) [89] which exhibits good photochromic properties.

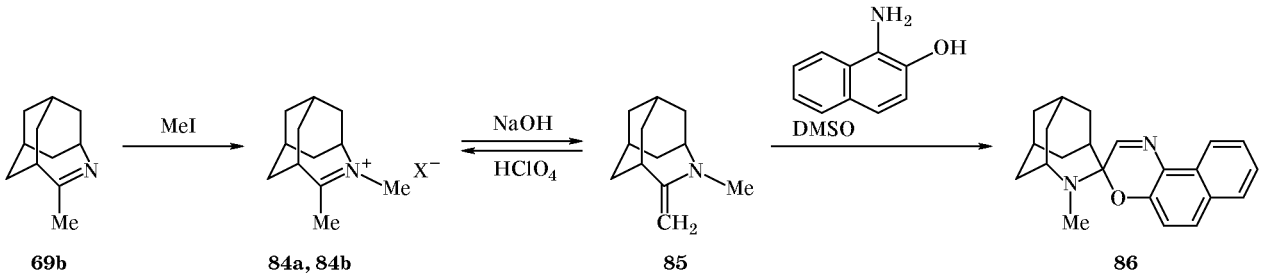
Imine **69b** was treated with acyl chlorides in boiling benzene in the presence of triethylamine (these conditions favor formation of ketenes). As a result, compounds **87a**–**87c** were obtained which were not adducts of ketene and imine **69b** [70]. The oxidation of **69b** with peroxyacetic acid afforded compound **87b** and oxaziridine **88** (Scheme 34). Dichloromethylene generated from $CHCl_3$ and 50% aqueous potassium

Scheme 32.



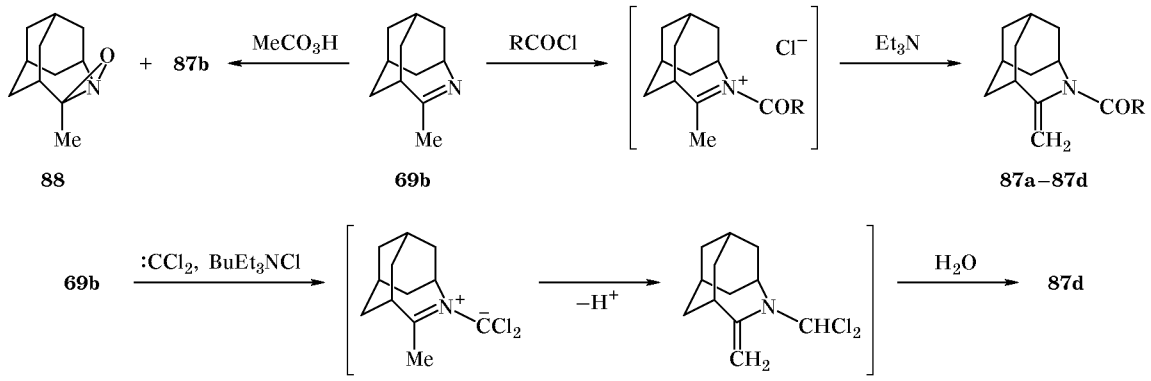
79–**81**, R = D (**a**), CH_3 (**b**).

Scheme 33.



84, X = I (**a**), ClO_4^- (**b**).

Scheme 34.



R = $CHCl_2$ (**a**), CH_3 (**b**), Ph (**c**), H (**d**).

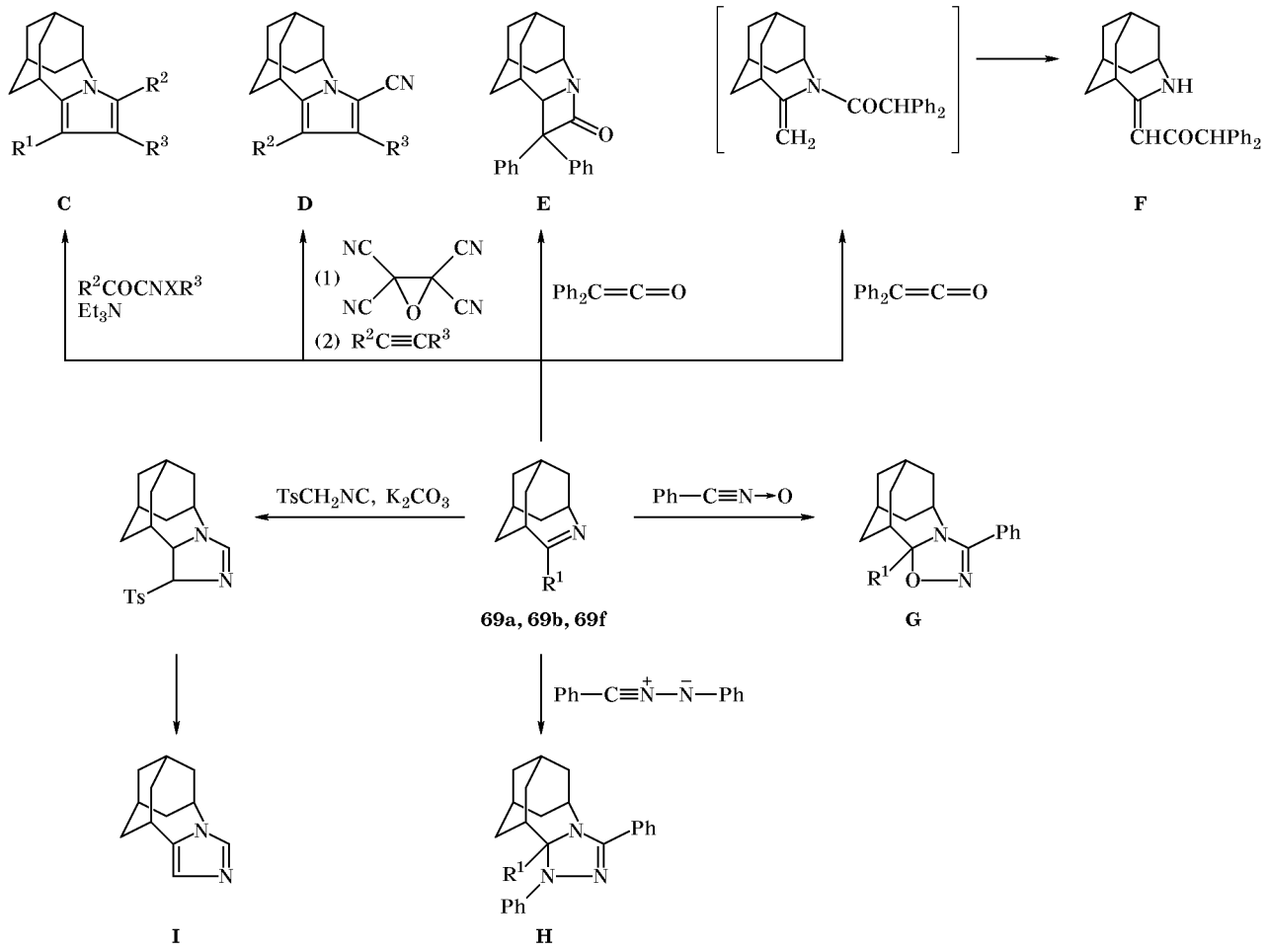
hydroxide in the presence of benzyltriethylammonium chloride as phase-transfer catalyst reacted with imine **69b** to give an oily product whose spectral parameters were consistent with structure **87d**. Probably, it was formed through intermediate [$\overset{+}{N}-\overset{-}{C}$] ylide with subsequent elimination or migration of proton and hydrolysis of the $CHCl_2$ group on the nitrogen atom.

III.1.1. 1,3-Dipolar cycloaddition reactions of 4-azatricyclo[4.3.1.1^{3,8}]undec-4-enes. The high activity of the C=N bond in **69a**–**69c** gives rise to a number of cycloaddition reactions leading to formation of various heterocyclic systems, e.g., **C**–**I** [64] (Scheme 35). Unstable methylide **90** generated by desilylation of iminium salt **89** reacts with dimethyl acetylenedicarboxylate, yielding a mixture of dihydropyrrole **91a** and pyrrole **92a**; in the reaction of **90** with methyl 2-propynoate isomeric pyrroles **92b** and **92c** are formed [90] (Scheme 36).

Various five-membered heterocyclic compounds fused to 4-azahomoadamantane skeleton were synthesized from oxidation products of imines **69**, e.g., epoxy derivative **88** and *N*-oxide **93**. Unlike peroxy acids which give oxaziridine **88** [70], the oxidation with atmospheric oxygen does not involve the C=N bond of **69e**, and the product is imine **69e**. Likewise, the oxidation of **69a** and **69b** with $KMnO_4$ gives no *N*-oxides **93**, but the latter are available via treatment of amines **94** with a mixture of SeO_2 with 30% H_2O_2 [91, 92] (Scheme 37). *N*-Oxides **93a** and **93b** are colorless crystalline substances which are very hygroscopic: they decompose on drying in air.

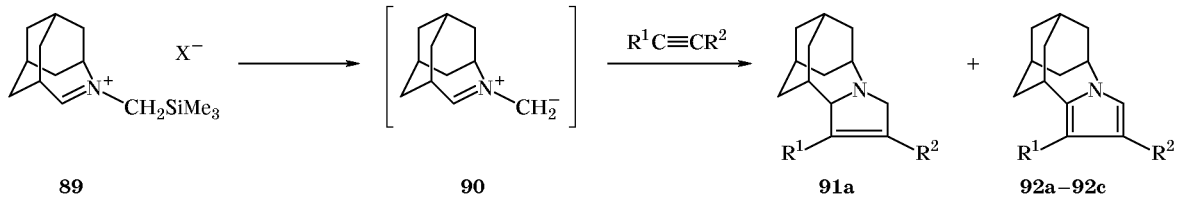
1,3-Dipolar cycloadditions of compounds **93a** and **93b** to alkenes and alkynes in toluene at 20°C were very slow; the products were heterocyclic compounds **95**–**98** [91, 92] (Scheme 38). It was shown in [92, 93] that thermal rearrangement of 3-methyl-2,3-dihydroisoxazoles involves intermediate formation of acylaziridine **97** and that *N*-oxide **93b** is not formed in the reaction of **88** leading to pyrrole **98**. The reaction of **93b** with methyl 2-propynoate was studied in various solvents [92]. In toluene and acetonitrile only cycloaddition product **96a** was obtained in quantitative yield, whereas in methanol, aqueous methanol, or methanol–acetic acid, mixtures of compounds **96a** and **98e** were formed at different ratios (Scheme 39). One-step conversion of the nitrone into pyrrole turned

Scheme 35.



C, R^1 = H, Me, Ph; R^2 = Me; R^3 = H, Me; X = Cl or Br; **D**, R^2 = H, COOMe; R^3 = COOMe.

Scheme 36.

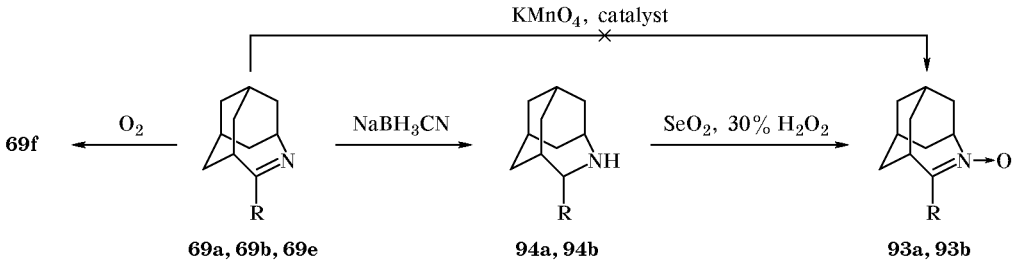


R^1 = R^2 = COOMe (**a**); R^1 = H, R^2 = COOMe (**b**); R^1 = COOMe, R^2 = H (**c**); **89**, X = Cl, Br.

out to be catalyzed by protic solvent. Protonation of **93b** gives intermediate enamine which then reacts with methyl 2-propynoate. Phenylacetylene failed to react with **93b** at 20°C; at 170°C pyrrole **98d** is formed. The reaction of **93a** with phenylacetylene yields adduct **95d** only when the dipolarophile is used as solvent. Oxaziridine **88** reacts with acetylenes, yielding analogous pyrrole derivatives **98**.

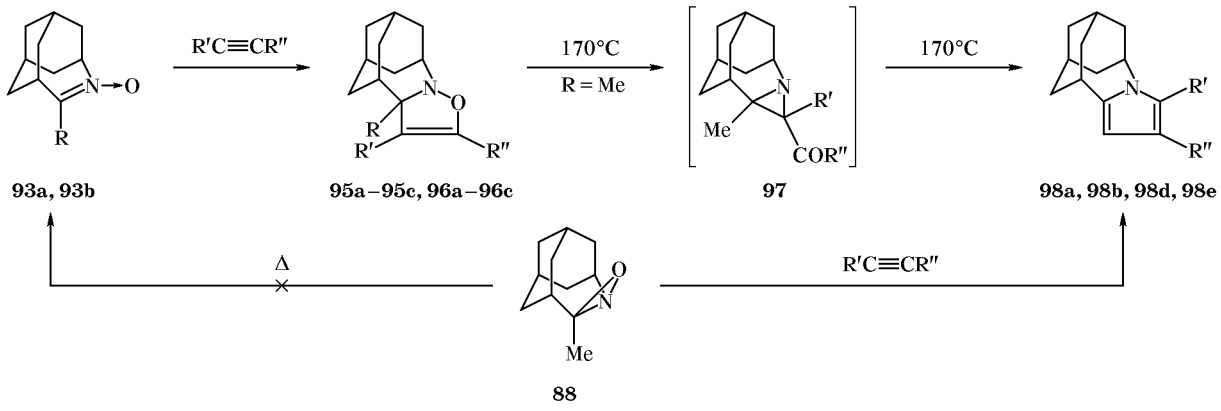
N-Oxide **93a** was brought into 1,3-dipolar cycloadditions with alkenes as dienophiles: methyl acrylate, dimethyl maleate, dimethyl fumarate, acrylonitrile, methyl methacrylate, and methacrylonitrile. These reactions gave a series of new oxazolidine derivatives [94] (Scheme 40). Also, stereochemical aspects of the process were studied and PM3 calculations of the transition states were performed.

Scheme 37.



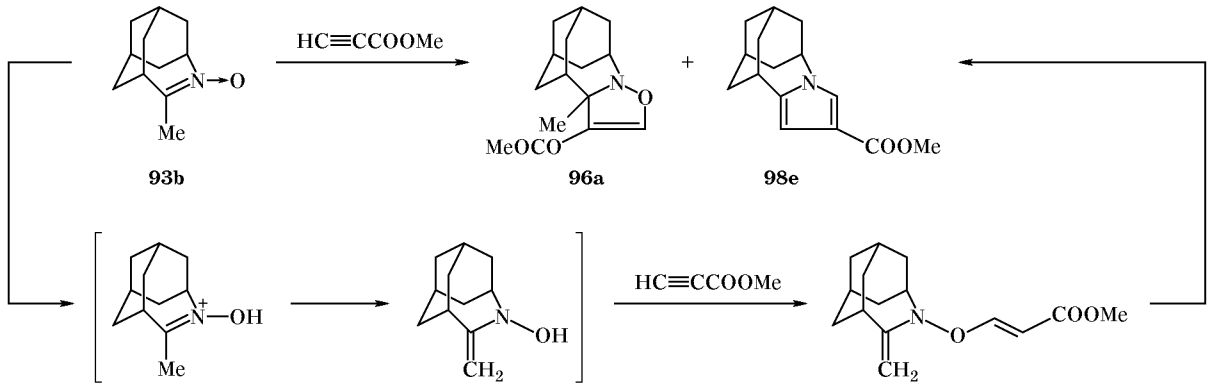
R = H (**a**), Me (**b**), CH_2Ph (**e**), Ph (**f**).

Scheme 38.

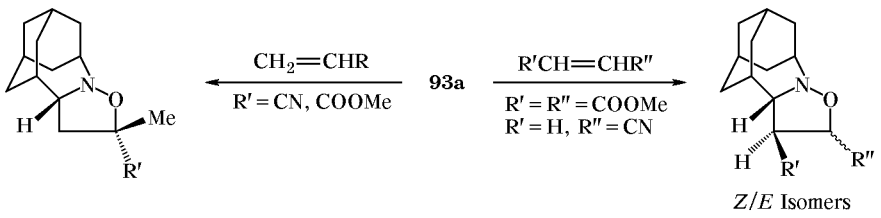


93a, **95a**–**95c**, R = H; **93b**, **96a**–**96c**, R = Me; **95**–**98**, R′ = COOMe, R″ = H (**a**); R′ = R″ = COOMe (**b**); R′ = CN, R″ = H (**c**); R′ = H, R″ = Ph (**d**); R′ = H, R″ = COOMe (**e**).

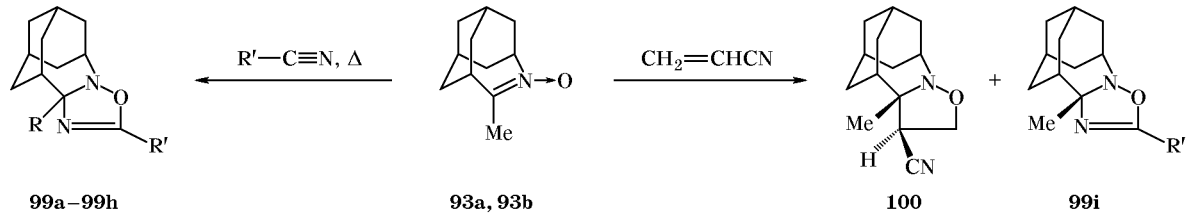
Scheme 39.



Scheme 40.

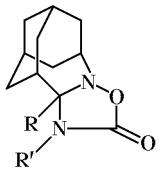


Scheme 41.



R = H (**a**), Me (**b**); R′ = Me (**a**), Ph (**b**), *o*-$MeOC_6H_4$ (**c**), *p*-$MeOC_6H_4$ (**d**), *o*-$NO_2C_6H_4$ (**e**), *m*-$NO_2C_6H_4$ (**f**), *p*-$NO_2C_6H_4$ (**g**), COOMe (**h**), $CH=CH_2$ (**i**).

The cyano group was found to act as dipolarophile in reactions with nitrones. Stable nitrone **93b** reacted with acrylonitrile at 100°C under nitrogen in a closed vessel to give mixtures of cycloadducts at the C=N and C=C bonds at a ratio of 55:45: 2,3-dihydro-1,2,4-oxadiazole **99** and 4-cyanotetrahydroisoxazole **100** [95–97] (Scheme 41). According to [96], the nonactivated C≡N bond in acetonitrile and benzonitrile is sufficiently reactive as heterodipolarophile toward *N*-oxides **93a** and **93b**. The latter readily react with activated nitriles (such as formyl cyanide), yielding the corresponding cycloadducts; this reaction provides a convenient route to 2,3-dihydro-1,2,4-oxadiazoles which are difficult to obtain by other methods. When the reaction is performed under high pressure, it requires a shorter time and a lower temperature [97]. Cycloaddition products **101** were obtained by reactions of **93a** and **93b** with isocyanates and isothiocyanates [98]:

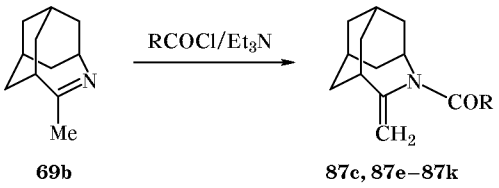


101

X = O, S; R = H, Me; R′ = Me, Ph, Me_3Si, cyclohexyl.

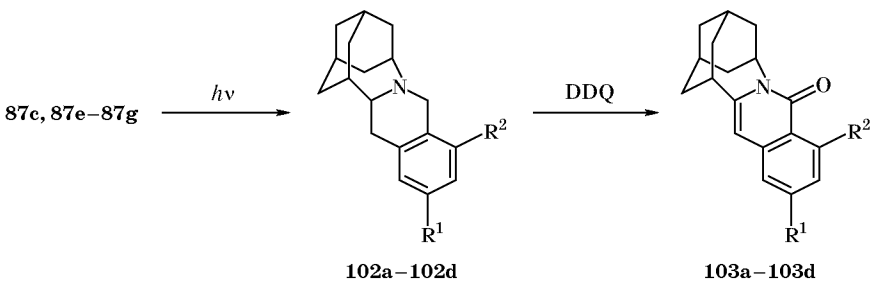
Six-membered heterocycles fused to a 4-azahomoadamantane skeleton were synthesized from 4-aroyl- and 4-acryloyl-5-methylene derivatives **87c** and **87e**–**87k** which can be obtained by acylation of **69b** [99] (Scheme 42). Irradiation of **87c** and **87e**–**87g** in

Scheme 42.



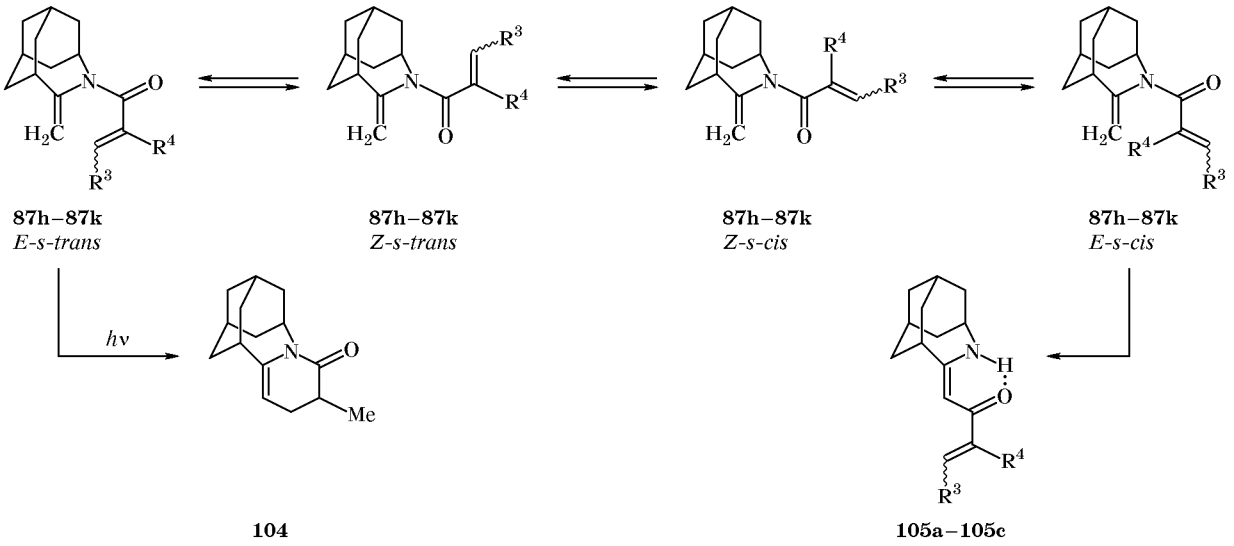
87, R = Ph (**c**), *p*-MeC_6H_4 (**e**), *p*-$MeOC_6H_4$ (**f**), *o*-MeC_6H_4 (**g**), $CH_2=CH$ (**h**), $MeCH=CH$ (**i**), $CH_2=CMe$ (**j**), $PhCH=CH$ (**k**).

Scheme 43.



102, **103**, $R^1 = R^2 = H$ (**a**); $R^1 = Me$, $R^2 = H$ (**b**); $R^1 = OMe$, $R^2 = H$ (**c**); $R^1 = H$, $R^2 = Me$ (**d**).

Scheme 44.



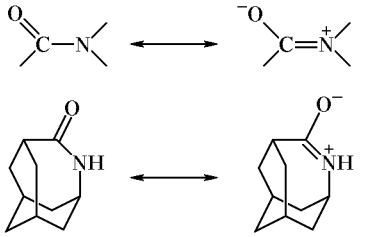
105, $R^3 = R^4 = H$ (**a**); R^3 = Me, R^4 = H (**b**); R^3 = Ph, R^4 = H (**c**).

ether using a low-pressure mercury lamp through a quartz filter under argon gave fused heterocyclic systems **102** in good yields. Compounds **102** are readily converted into hexahydroisoquinolinones **103** by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in boiling benzene. The behavior of *N*-acryloyl derivatives **87h**–**87k** under irradiation differs from that of *N*-aroyl-substituted analogs. Enamide photocyclization product **104** is formed in a poor yield only from methacryloyl derivative **87j** [99]. The other acryloyl derivatives (compounds **87h**, **87i**, and **87k**) are converted into 5-acryloylmethylene derivatives **105a**–**105c** (Scheme 44). Equchi *et al.* [100] examined the photochemical cyclization of **87c**, **87h**, and **87l** (R = 2-furyl) in the presence of oxidants. From *N*-aroyl derivatives, the corresponding isoquinolinones were obtained in good yields. *N*-Acryloyl analog **87h** was converted into amide **104**. Conformational aspects of the photocyclization were discussed in terms of MM2 calculations.

III.2. Azatricyclo[4.3.1.1^{3,8}]undecan-5-one (2)

Lactam **2** is the most interesting representative of azahomoadamantanes, which is widely used in the synthesis of various derivatives.

III.2.1. Structure and physical properties. The ground state of lactam **2** can be given by canonical structures **2A** and **2B**. Insofar as lactam **2** can exhibit both proton-donor (NH) and proton-acceptor properties (C=O), the possibility for lactam–lactim tautomerism was examined [101], and the enthalpy of formation of the lactim tautomer was estimated with full geometry optimization. The results showed that the lactam tautomer is more favorable by about 12.1 kcal/mol.



2A **2B**

Unlike simple amides which show a structural similarity with olefinic bond, the *cis*-amide group in lactam **2** is incorporated into the rigid azahomoadamantane skeleton and is not planar. The molecule of **2** consists of two six-membered and one seven-membered rings. The crystalline structure of lactam **2** was studied by X-ray analysis of a single crystal (prismatic) obtained from acetone solution [102]. The unit cell of lactam **2** in crystal contains molecules in two different conformations. The first of these is characterized by pyramidal structure of the nitrogen atom, and in the second the amide fragment is almost planar. Similar conformers form cyclic dimers through amide hydrogen bonds. No hydrogen bond was found between molecules belonging to different conformational types. The seven-membered lactam ring adopts

an *E-cis* structure, and the NH vibration frequency in the IR spectrum of **2** approaches that typical of acyclic *E-cis* amides (3200–3400 cm^{-1}). The band has a medium intensity. Like all secondary amides, lactam **2** shows in the IR spectrum a strong band belonging to stretching vibrations of the carbonyl group. Its frequency depends on the electron-acceptor power of the substituent on the nitrogen, but in all cases it is observed in the region 1650–1670 cm^{-1} [7, 26, 27, 45, 57, 58].

In the ^1H NMR spectrum of **2** the NH proton signal is located at δ 7 ppm [7], and protons neighboring to the NH and C=O groups give rise to signals at δ 3.3 and 2.7 ppm, respectively. In the spectra of substituted lactam **2** derivatives the NH signal can shift up to 8 ppm [13, 26, 45, 57, 58]. Berger [103] studied the conformational dependence of spin–spin coupling constants. It was found that protonation of the oxygen atom strongly affects the coupling constants: All values of $J(^{15}N, ^{13}C)$ fall down. In order to refine the assignment of signals in the ^1H NMR spectra of lactam **2** and its *N*-substituted analogs (R = Me, cyclohexyl, 1-$AdCH_2$), their behavior in the presence of europium(III), praseodymium(III), and ytterbium(III) tris(dipivalylmethanates) was studied [104–106]. These lanthanide shift reagents (LSR) coordinate at the lactam carbonyl oxygen atom in such a way that the lactam ring is not distorted and the *chair* conformation of the cyclohexane ring is not flattened. Rackham and Chitty [24] examined the interaction between amide substrates and LSRs and determined the absolute binding constant *K* for the complex of **2** with tris(2,2,6,6-tetramethyl-3,5-heptanedionato)-europium(III). It was equal to 210 at 20°C in $CDCl_3$, i.e., almost the same as that found for five-membered lactam, 2-pyrrolidinone (*K* = 211).

III.2.2. Reactivity of 4-azatricyclo[4.3.1.1^{3,8}]-undecan-5-one (2). Studies of the structure of 4-azahomoadamantane and its derivatives by NMR spectroscopy with the use of LSRs [24, 104–107] are possible due to complexing power of lactam **2**. The formation of the complex $CaCl_2 \cdot CaL_6Cl_2$, where L is ligand **2** [108] underlies the procedure for purification of 4-azahomoadamantanone, developed in [109]. According to spectral data, the metal coordinates preferentially to the oxygen rather than nitrogen atom. In the IR spectra of the complexes, the carbonyl frequency is reduced by 10–30 cm^{-1}, as compared to the free amides.

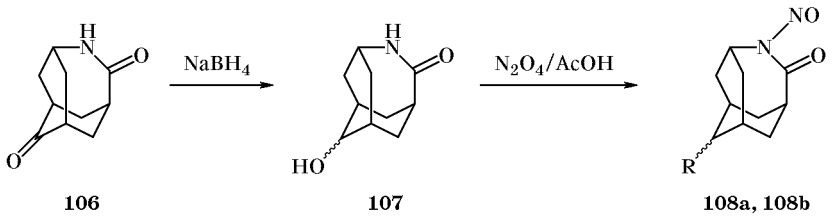
Kondelikova *et al.* [110] failed to obtain chemically stable or heat-resistant polymers by homopolymerization of lactam **2** or copolymerization with ω-caprolactam or 2-pyrrolidone. Probably, in this case the rigid tricyclic structure of **2** is essential.

The carbonyl group in lactam **2** and its derivatives is readily reduced by the action of $LiAlH_4$ in boiling tetrahydrofuran [13, 25, 27, 28, 38, 55], ether [29, 50], dimethoxyetane [27], and related solvents. Treatment of 9-oxo derivative **106** with $NaBH_4$ [111] results in reduction of the 9-oxo group to hydroxy with formation of a mixture of axial and equatorial isomers **107**. The latter react with N_2O_4 in glacial acetic acid at 5°C to give *N*-nitroso derivatives **108a**, the orientation of the hydroxy group being retained (Scheme 45).

N-Nitroso derivatives of 4-azahomoadamantane [111, 112] are unstable compounds which can be identified by spectral methods. *N*-Nitrosolactam **108b** reacts with sodium methoxide with cleavage of the lactam ring and formation of bicyclic product **109** and noradamantane **110b**. Under the same conditions from hydroxy derivative **108a** only noradamantane structure **110a** is formed (Scheme 46). The mechanism of this process was studied in [111]. Compounds **109** and **110** are likely to be formed through intermediate diazonium ions **J** and **K**: unsaturated ester **109** is formed by β-elimination, and structure **110**, by transannular proton elimination.

Hydrolytic cleavage is not typical of unsubstituted lactam **2**. Attempts to effect hydrolysis of diamantane structures **26** and **27** by heating in the presence of an acid or alkali or by nitrosation or nitration [34] were unsuccessful: only the initial compound was recovered from the mixture.

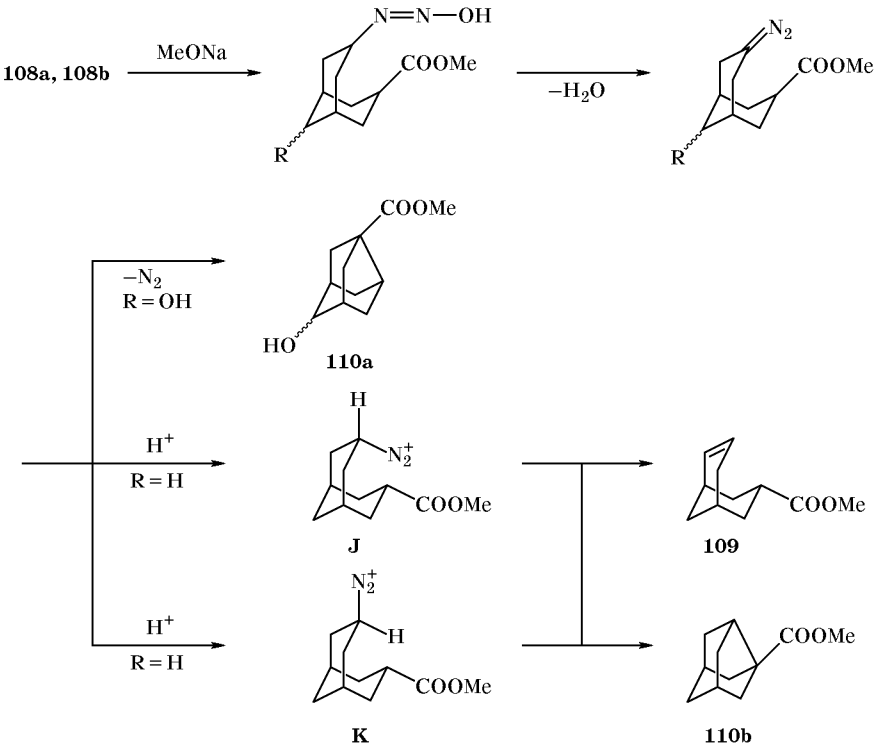
Scheme 45.



106 **107** **108a, 108b**

R = OH (**a**), H (**b**).

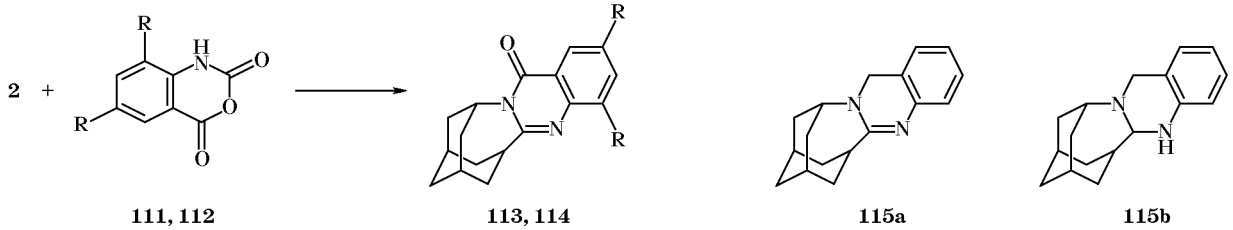
Scheme 46.



Various *N*-substituted derivatives of lactam **2** were synthesized with the goal of studying their biological activity. These compounds are readily available from lactam **2** sodium salt (which is obtained by heating lactam **2** with 50% sodium hydride in dioxane under reflux) and alkyl or acyl halides, as well as by reaction of **2** and isocyanates [28]. Heating of **2** with an aqueous* solution of KCN at 60°C gave carbamoyl derivative **6k** (R = $CONH_2$) [37], and with 2-propynyl bromide in anhydrous methanol, *N*-2-propynyl analog **6l** (R = $CH{\equiv}CCH_2$) was obtained [39, 41]. The following *N*-substituted compounds **6** were synthesized in a similar way [26, 27]: **6b**–**6e**, **6m**–**6z1**, where R = Ac (**m**), COPh (**n**), 2-pyridylcarbonyl (**o**), 4-$MeC_6H_4SO_2CO$ (**p**), 3,4-$Cl_2C_6H_3NHCO$ (**q**), 4-$O_2NC_6H_4NHCO$ (**r**), $Et_2N(CH_2)_3$ (**s**), $PhCH_2CH_2$ (**t**), $Me_2N(CH_2)_n$ (*n* = 2, 3) (**u**), $Me(CH_2)_n$ (*n* = 2, 6) (**v**), R′$C_6H_4CH_2$ (R′ = 4-Br, 3-Me, 4-MeO, 2,4-Cl_2) (**w**), 3-piperidinopropyl or 5-(1-pyrrolidinyl)pentyl (**x**), *cyclo*-$C_5H_9CH_2$ or *cyclo*-$C_6H_{11}CH_2CH_2$ (**y**), R′OCH_2CH_2N⟨⟩$N(CH_2)_3$ (R′ = H, $C_6H_{13}COO$) (**z**), X⟨⟩$N(CH_2)_n$ (*n* = 4, X = S; *n* = 3, X = O) (**z1**).

Simultaneous substitution at the nitrogen atom and condensation at the carbonyl group occurred on fusion

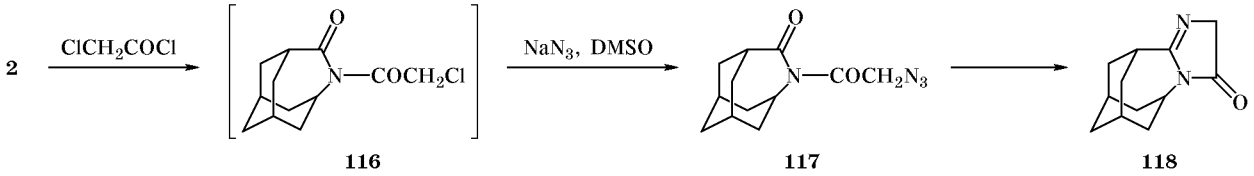
Scheme 47.



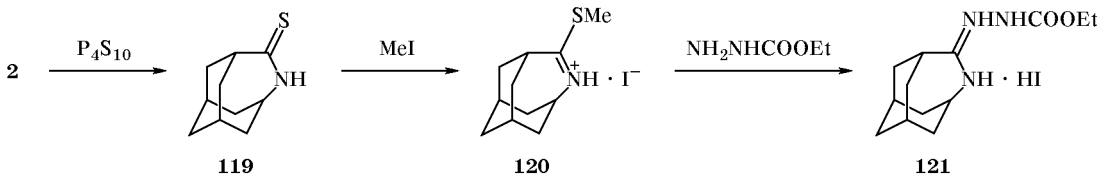
111, **113**, R = H; **112**, **114**, R = Cl.

* The solubility of lactam **2** in water is more than 0.3 M at 25°C [113].

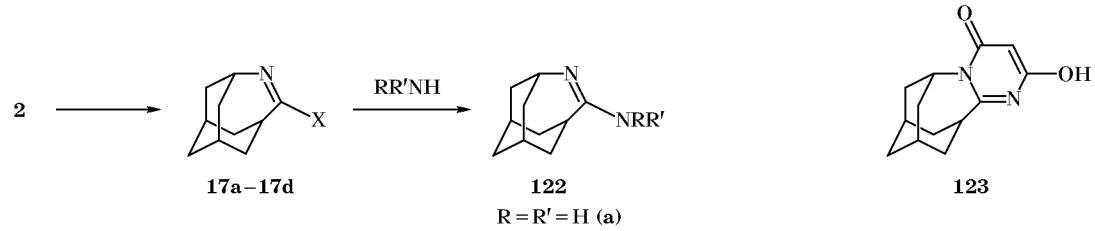
Scheme 48.



Scheme 49.



Scheme 50.



X = OH (**a**), Cl (**b**), OEt (**c**), OMe (**d**).

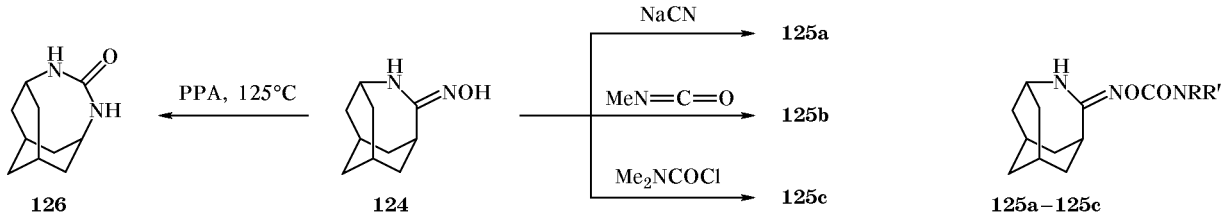
of lactam **2** with anhydrides **111** and **112** at 190°C. The products were quinazolines **113** and **114**, respectively (yield 33 and 20%) [26] (Scheme 47). The reduction of **113** with $LiAlH_4$ in ether yields dihydroquinazoline **115a**, and in THF tetrahydroquinazoline **115b** is formed (60 and 92%, respectively).

Takeuchi *et al*. [114] synthesized heterocyclic structure **118** with an imidazole ring as a model fragment of some alkaloids and drugs. The primary product, chloroacetyl derivative **116**, was not isolated (Scheme 48). The cyclization of azide **117** was effected with the aid of triphenyl- or tributylphosphine in benzene at 20°C. Imidazole derivative **118** was isolated in 91% yield by chromatography on silica gel.

The carbonyl group in lactam **2** was replaced by thiocarbonyl by heating with P_4S_{10} in pyridine. Treatment of thione **119** with CH_3I yields *S*-methyl salt **120** which reacts with $NH_2NHCOOC_2H_5$ on heating in toluene to give cyclic amidrazone **121** [39, 41] (Scheme 49). The reaction of lactam **2** with BF_3–ether complex in CH_2Cl_2 under dry nitrogen [29], as well as heating of **2** with dimethyl sulfate in boiling benzene, gives an unstable colorless crystalline product which shows in the IR spectrum absorption bands at 1680 (C=N) and 1180 cm^{-1} (=C–O); the NMR spectra of the product conform to the assumed structure of lactim **17c** (Scheme 50). Likewise, lactam **2** reacts with $COCl_2$ or dimethyl sulfate, affording lactims **17b** and **17d**, respectively. The latter were then converted into amidines **122** [28] by reaction with various amines RR′NH, where R = H, R′ = H, PhNHNH, 4-$MeOC_6H_4NH$, NH_2CONH, CN, PhNHC(=NH), Ph, $Me_2NCH_2CH_2$, $Et_2NCH_2CH_2$, $Me_2N(CH_2)_3$, 2-morpholinoethyl, $PhNHCH_2CH_2$, $Me(Ph)NCH_2CH_2$, $PhCH_2N(Ph)CH_2CH_2$, $PhOCH_2CH_2$, 2-$MeOC_6H_4$-CH_2CH_2, $MeCONHCH_2CH_2$, 4-$MeOC_6H_4CONH$-CH_2CH_2, α-$C_{10}H_7CH_2CONHCH_2CH_2$; RR′N = 1-pyrrolidinyl, $PhCONHSO_2$. Amidine **122a** reacts with diethyl malonate sodium salt to afford 31% of fused pyrimidinedione **123** [28] (Scheme 50).

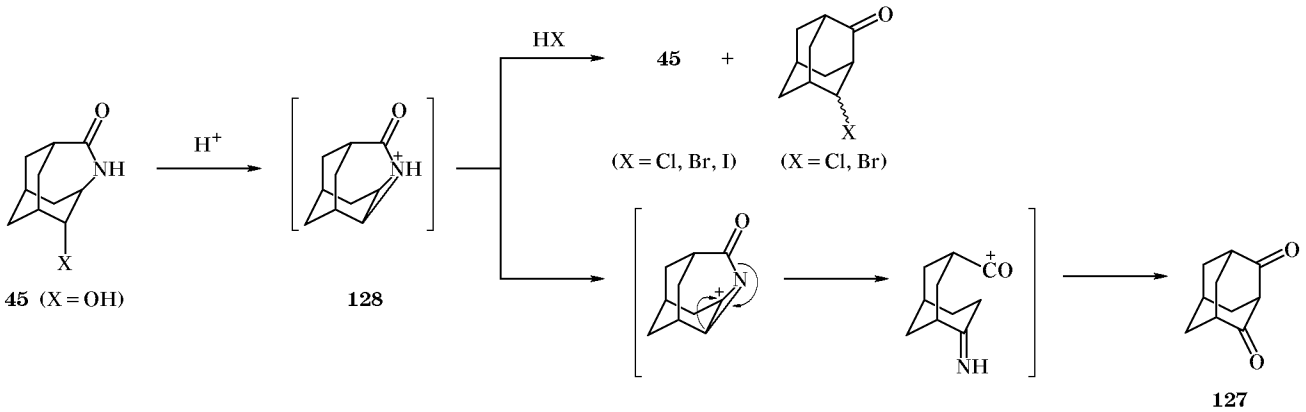
Heating of imidate **17d** with hydroxylamine in boiling methanol gives oxime **124** [115] which reacts at 20°C with sodium cyanide, methyl isocyanate, or dimethylcarbamoyl chloride in the presence of a catalytic amount of triethylamine. The resulting 5-carbamoyloxyimino derivatives **125a**–**125c** exhibit biological activity [116] (Scheme 51). The Beckmann rearrangement of oxime **124** in polyphosphoric acid leads to formation of symmetric urea derivative **126** [115] whose structure was proved by spectral methods.

Scheme 51.



R = R′ = H (**a**); R = H, R′ = Me (**b**); R = R′ = Me (**c**).

Scheme 52.



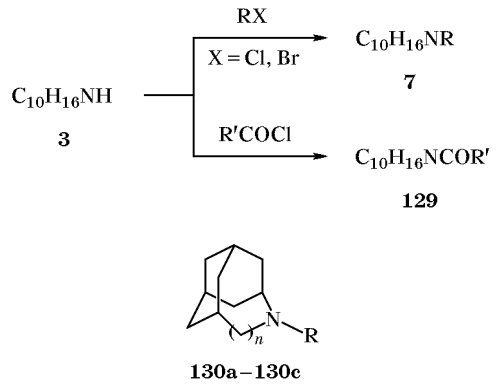
Substitution at the carbon atoms in lactam **2** was studied using *anti*-2-hydroxy-4-azatricyclo[4.3.1.1^{3,8}]-undecan-5-one (**45**) as an example. The hydroxy group is replaced by halogen on heating of **45** for 18 h in boiling concentrated hydrochloric, hydrobromic, or hydroiodic acid (yield 1, 11, and 23%, respectively); also, diketone **127** was obtained [117] (Scheme 52). In the reaction with HCl and HBr, 50 and 22% of the initial compound (**45**, X = OH), respectively, remains unchanged. The formation of the above compounds suggests that the primary product, aziridinium ion **128**, undergoes aziridinium–imine rearrangement. A mechanism for formation of 4-chloro(bromo)adamantanone was also proposed [117].

III.3. 4-Azahomoadamantane (3)

Compound **3** is a typical representative of cage-like secondary amines. The ^{1}H and ^{13}C chemical shifts and coupling constants in the NMR spectra of amine **3** and the corresponding hydrochloride are similar to those of other amines. The mass spectrum of **3** contains the molecular ion peak (*m*/*z* 151) and fragment ion peaks $[M-NH]^+$ (*m*/*z* 136) and $[M-CH_2NH]^+$ (*m*/*z* 122) [55].

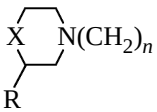
III.3.1. Substitution reactions of 4-azahomoadamantane (3). 4-Azahomoadamantane (**3**) is readily and quantitatively alkylated with alkyl halides [18] and acylated with acyl chlorides in anhydrous ethanol [41] (Scheme 53). The corresponding *N*-acyl derivatives are smoothly formed with acetyl and *p*-nitrobenzoyl chlorides, whereas with bromoacetic anhydride only 10% of the acylation product is formed [118]. By analogy with lactam **2**, the reaction of amine **3** hydrochloride or 4-azatricyclo[5.3.1.1^{3,9}]dodecane (**130a**) hydrochloride with aqueous solution of KCN at 60°C [37, 38] gives 4-carboxamides **130b** and **130c**.

Scheme 53.



130, *n* = 2, R = H (**a**); *n* = 1, R = $CONH_2$ (**b**); *n* = 2, R = $CONH_2$ (**c**).

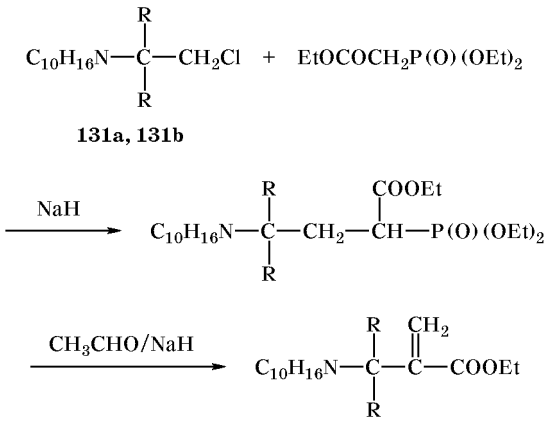
N-Alkyl- and *N*-acyl-4-azahomoadamantanes

Alkyl or acyl	References	Alkyl	References
$CH_2CH_2NHC(=NH)NH_2 \cdot 2HCl$	[28]	Me, Et, *i*-Pr	[18, 27]
$4\text{-}FC_6H_4COCH_2CH_2$	[28]	$CH_2CH_2NH_2 \cdot 2HCl$	[28]
$RNH(CH_2)_n$	[26, 27]		
n = 4, R = Me			
n = 2, R = 1-Ad	[26, 27]		
n = 3, R = H			
$HOCO(CH_2)_n$, *n* = 2, 9	[26, 27]	*n* = 10, R = H, X = NMe	[26, 27]
3-(2-Chlorophenothiazin-10-yl)propyl	[28]	*n* = 3, R = H, X = O	[26, 27]
$3\text{-}CF_3C_6H_4CH{=}CHCO$	[39, 41]	*n* = 2, R = H, X = MeOCH	[27]
$3\text{-}O_2NC_6H_4CO$	[39, 41]	*n* = 2, R = H, X = N–OEt	[27]
$4\text{-}O_2NC_6H_4CO$, MeCO	[41]	*n* = 2, R = CF_3, X = CH_2	[27]
$BrCH_2CO$	[118]	*n* = 4, R = Cl, X = S	[27]
$4\text{-}MeOC_6H_4CH{=}CHCO$	[39, 41]	*n* = 2, R = OMe, X = CH_2	[27]
$4\text{-}O_2NC_6H_4CH{=}CHCO$	[39, 41]	$Me_2NCH_2CH(Me)$	[27]
$4\text{-}MeC_6H_4SO_2NHCO$	[28]	$PhCH{=}CHCH_2$	[39]
		$CH_2{=}CHCH_2CH_2$	[27, 28]

N-Substituted derivatives were successfully obtained by reaction of amine **3** sodium salt with alkyl or acyl halides, as well as by reaction of **3** with isocyanates [28] (see table).

When the substitution occurs in the side chain of 4-azahomoadamantane derivatives, the tricyclic radical as a rule has no effect on the reaction course. Compounds **131a** and **131b** were brought into the Horner–Emmons reaction in order to synthesize unsaturated acid esters with a bulky substituent at the double bond [119] (Scheme 54). The yield of the products attained 60%. Solvolysis of 3- and 4-substituted derivatives **19j**–**19n** in an alcoholic solution of sodium ethoxide provides an example of substitution at the skeletal carbon atoms of **3**. The reaction was shown [120] to follow the S_N1 mechanism with resonance stabilization of the intermediate cation by lone electron pair of the neighboring nitrogen atom (Scheme 55). Ethoxide ion favors elimination of ethanethiol from compounds **19k** and **19l** with subsequent addition of ethanol and formation of ethers **19n** and **19m**. The reaction with **19k** is faster than with **19l**, and the reaction rate is proportional to the concentration of EtONa.

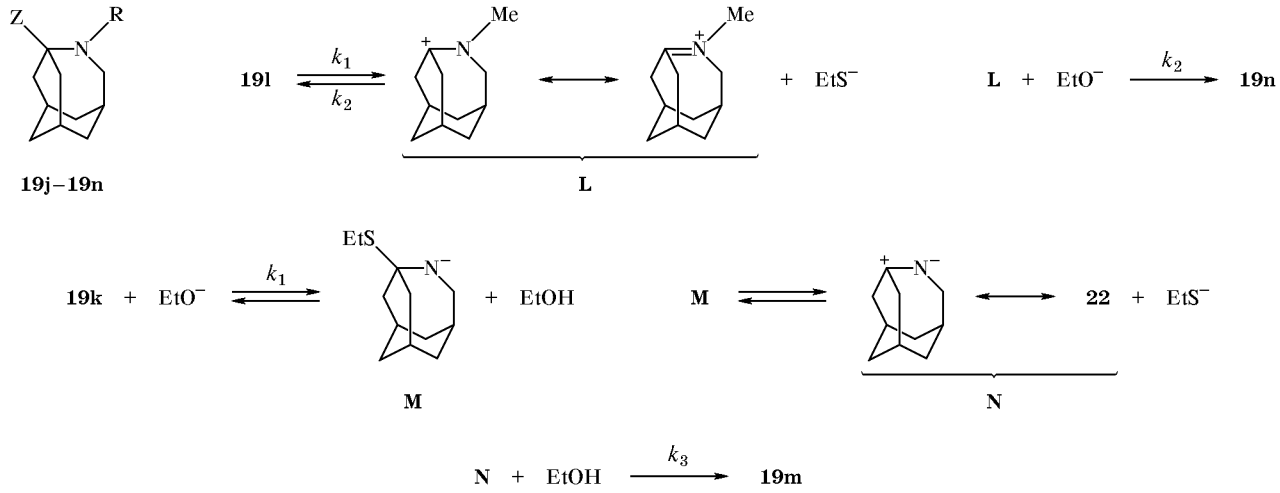
Scheme 54.



R = H (**a**), RR = O (**b**).

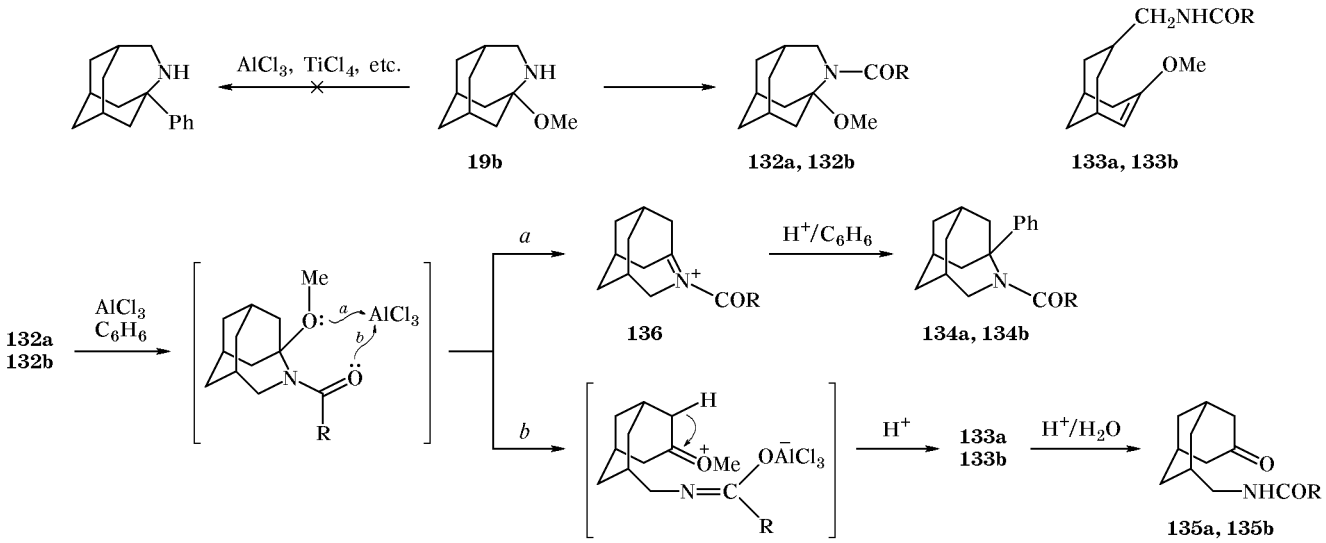
An attempt to replace the methoxy group in **19b** by phenyl [65] via direct treatment with various Lewis acids ($AlCl_3$, $TiCl_4$, or BF_3–ether complex) in benzene resulted in complex formation with the catalyst at the nitrogen atom and decomposition. Such replacement can be effected through *N*-acyliminium ions. The reaction of **19b** with a mixture of NaH with ClCOOMe or Ac_2O in dry ether gave carbamate **132a** and amide **132b** in 49 and 74% yield, respectively (Scheme 56). When the reaction was carried out in THF, a considerable amount of products **133a** and **133b** was formed as a result of ring opening. In the presence of Lewis acids compounds **132a** and **132b** give rise to both substitution (**134a** and **134b**) and ring opening products (**135a** and **135b**). The methoxy group in **132a** can be replaced by phenylethynyl with the aid of $PhC{\equiv}CSiMe_3$ in the presence of $AlCl_3$. Under the same conditions compound **132b** was converted into decomposition product **138** (68%) and benzyl ketone **139** (27%) [65] (Scheme 57).

Scheme 55.



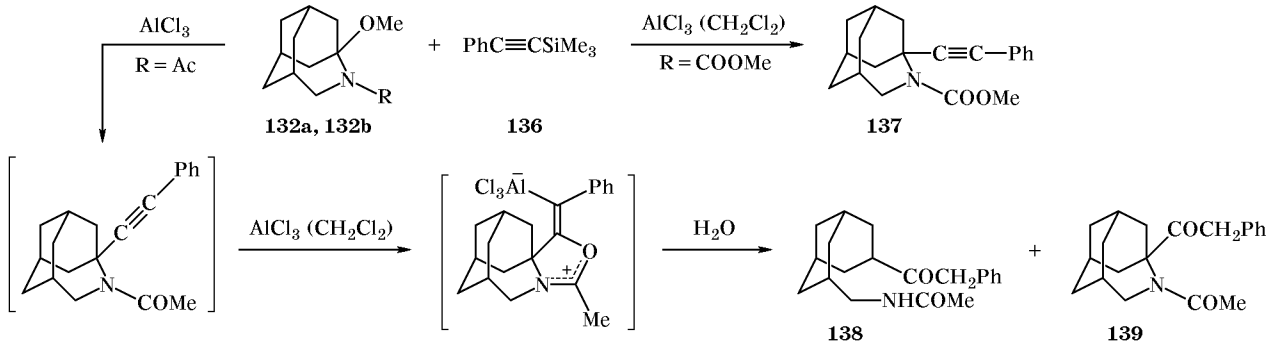
19, R = H, Z = Cl (**j**); R = H, Z = SEt (**k**); R = Me, Z = SEt (**l**); R = H, Z = OEt (**m**); R = Me, Z = OEt (**n**).

Scheme 56.



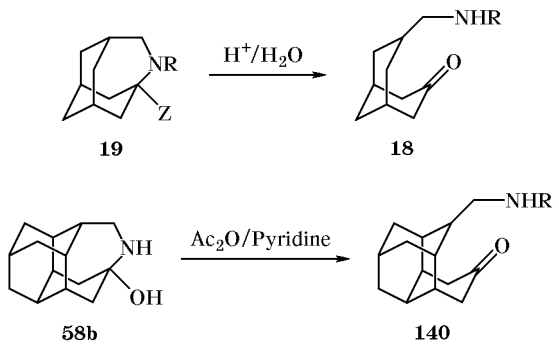
R = OMe (**a**), Me (**b**).

Scheme 57.



III.3.2. Cleavage of the 4-azahomoadamantane skeleton. The formation of bicyclic compounds as by-products in the reactions leading to 4-azahomoadamantane derivatives [58] and in substitution reactions [65] suggests that under certain conditions substituted 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-ones are prone to ring opening. This is especially characteristic of 3-substituted lactams **19** which are converted into bicyclic aminoketone **18a** by the action of dilute acid [17, 21]. In a similar way, by acylation of hydroxylactam **58b** acylaminoketone **140** was obtained [63] (Scheme 58). On the other hand, attempts to open the lactam ring in diamantane isomers **26** and **27** by heating with an acid or alkali, nitrosation, or nitration were unsuccessful [34].

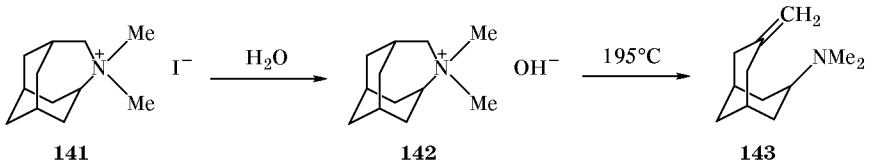
Scheme 58.



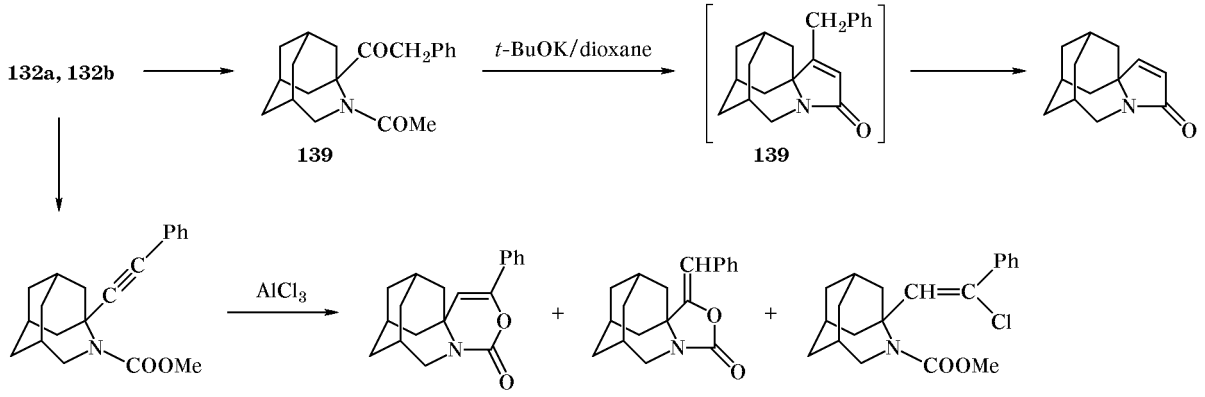
Pyrolysis of quaternary base **142** (which is obtained as a syrup-like substance by treatment with water of doubly methylated product **141**) at 195°C leads to formation of tertiary amine **143** as a result of cleavage of the azahomoadamantane skeleton [18] (Scheme 59). Thus, ring opening reactions are typical of 3- and 4-substituted 4-azahomoadamantanes, in contrast to lactam **2** derivatives among which only *N*-nitroso compounds undergo cleavage of the tricyclic structure [111, 112].

III.3.3. 3,4-Disubstituted 4-azatricyclo[4.3.1.1^{3,8}]-undecanes in the synthesis of fused heterocyclic systems. Replacement of the 3-methoxy group in compounds **19b**, **132a**, and **132b** (through intermediate formation of *N*-acyliminium ion **136**) gave a number of derivatives (e.g., **137** and **139**; see above) which were then used in the syntheses of heterocycles fused to 4-azahomoadamantane skeleton [65]. Analogous intramolecular substitution in compounds **144a**–**144c** which were obtained by reaction of **19b** with aryl isocyanates afforded six-membered heterocyclic systems **145a**–**145c** (Scheme 61) [65]. 3-Cyano derivative **19f** was treated with appropriate isocyanates and isothiocyanates [63] to obtain fused hydantoins, iminohydantoins, and their thio analogs **147a**–**147d** and **148** without isolation of intermediate *N*-substituted products **146a**–**146d** (Scheme 62). The reaction of nitrile **19f** with electron-deficient alkynes and alkenes was proposed as a synthetic route to fused dihydropyrroles **149**–**151** [63] (Scheme 63). Hydrolysis of *N*-acetyl derivative **152** on heating in aqueous acetic acid gives carboxylic acid **154**, whereas nitrile **19f** does not change under these conditions. Probably,

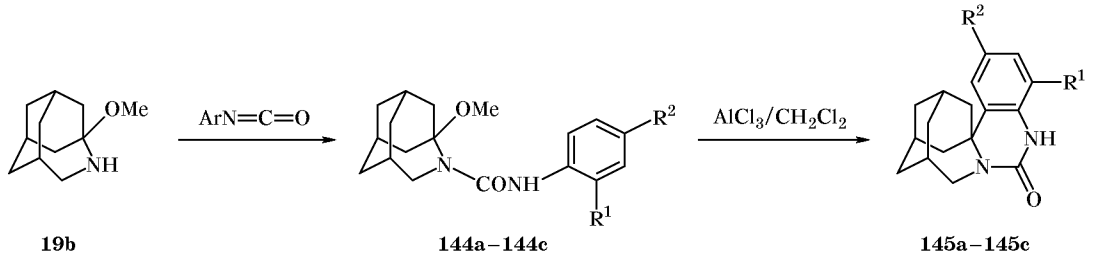
Scheme 59.



Scheme 60.



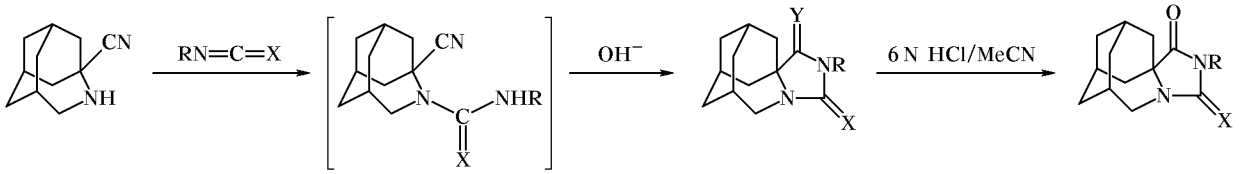
Scheme 61.



19b **144a–144c** **145a–145c**

R^1 = R^2 = H (**a**); R^1 = Cl, R^2 = H (**b**); R^1 = H, R^2 = Cl (**c**).

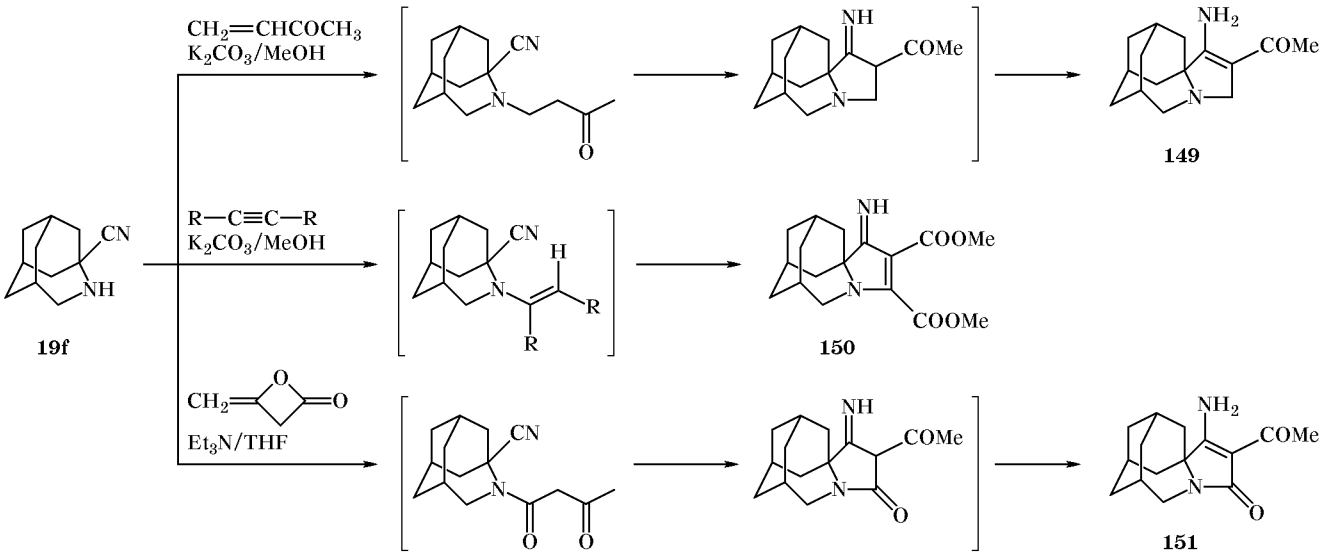
Scheme 62.



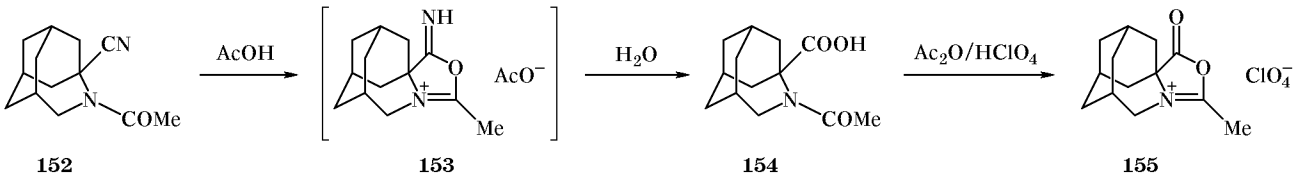
19f **146a–146d** **147a–147d** **148**

146, **147**, R = H, X = O, Y = O (**a**); R = Ph, X = O, Y = NH (**b**); R = Et, X = O, Y = NH (**c**); R = Ph, X = S, Y = NH (**d**); **148**, R = Ph, X = O, S.

Scheme 63.



Scheme 64.



152 **153** **154** **155**

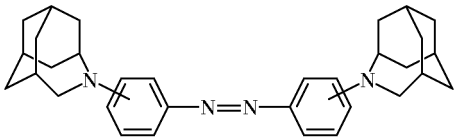
the hydrolysis of **152** involves intermediate formation of oxazolium acetate **153** [63]. Structurally similar perchlorate **155** was isolated in quantitative yield by treatment of **154** with a solution of acetic anhydride in perchloric acid (Scheme 64).

Thus, the presence of certain substituents in positions *3* and *4* of 4-azatricyclo[4.3.1.1^{3,8}]undecane molecule provides the possibility for formation of fused heterocyclic systems which are difficult to obtain by other methods. However, application of this approach is limited because of thermodynamically favorable cleavage of the azahomoadamantane skeleton, leading to bicyclic structures.

IV. PHARMACOLOGICAL APPLICATIONS OF 4-AZAHOMOADAMANTANE DERIVATIVES

Molecules of 4-azahomoadamantane and its derivatives combine a lipophilic adamantane moiety and amine functionality which make them promising from the viewpoint of biological activity. By analogy with physiologically active aminoadamantanes [121–125], studies were carried out in two directions: (1) synthesis of various 4-azahomoadamantane derivatives and testing them for pharmacological activity and (2) introduction of a 4-azahomoadamantane fragment into molecules of already known pharmacologically active compounds.

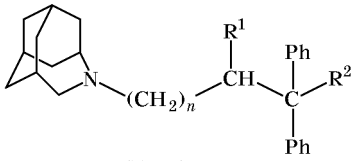
Both unsubstituted (compounds **2** and **3**) [7] and *N*-substituted derivatives (**6a**–**6z1**, **119**–**121**, **125a**–**125c**, **130a**–**130c**; see also *N*-substituted derivatives given in table) showed antiviral [26–28, 40, 41], antiarrhythmic [27], antiinflammatory [27, 28], or cardiovascular activity [26, 28]. Pharmacological screening of some compounds (e.g., **31a**–**31k**, **113a**, **113b**, **114**, **115**, **118**) revealed two kinds of activity: antiviral and antihypertensive. The latter was also found for 5-carbamoyloxyimino derivatives **125a**–**125c** [115]. Azo compounds **156a** and **156b** which were obtained by reduction of **7** (R = *m*- and *p*-$O_2NC_6H_4CO$) with lithium tetrahydridoaluminate showed a moderate activity against herpes viruses [39, 41]:



156a, 156b

156a, *m*,*m′*-isomer; **156b**, *p*,*p′*-isomer.

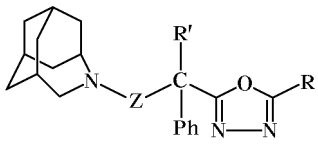
Antiviral, antiarrhythmic, antispasmodic, and other kinds of biological activity were found in oxadiazole derivatives **157** which were synthesized by heating of compound **158** with acetic anhydride in pyridine [126]. Compound **158** was prepared in turn by treatment of a mixture of 4-(2-chloroethyl)-4-azatricyclo-[4.3.1.1^{3,8}]undecane (**131a**) and phenylacetonitrile with sodium hydride, followed by reaction of the resulting nitrile **159** with sodium azide in DMF in the presence of ammonium and lithium chlorides.



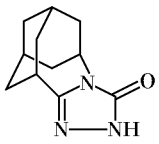
157–159

157, R^2 = 5-R^3-1,3,4-oxadiazol-2-yl; R^1 = H, R^3 = Me, *n* = 1, 2; R^1 = R^3 = H, Me, *n* = 1; **158**, R^1 = H, *n* = 1, R^2 = 4*H*-1,2,4-triazol-3-yl; **159**, R^1 = H, *n* = 1, R^2 = CN.

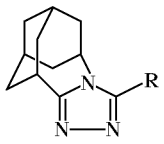
Oxadiazoles **160** [127, 128] and the corresponding hydrochlorides exhibited similar pharmacological properties. Compounds **162** which are available from ketone **161** via known methods showed a strong anti-inflammatory activity [129]:



160



161

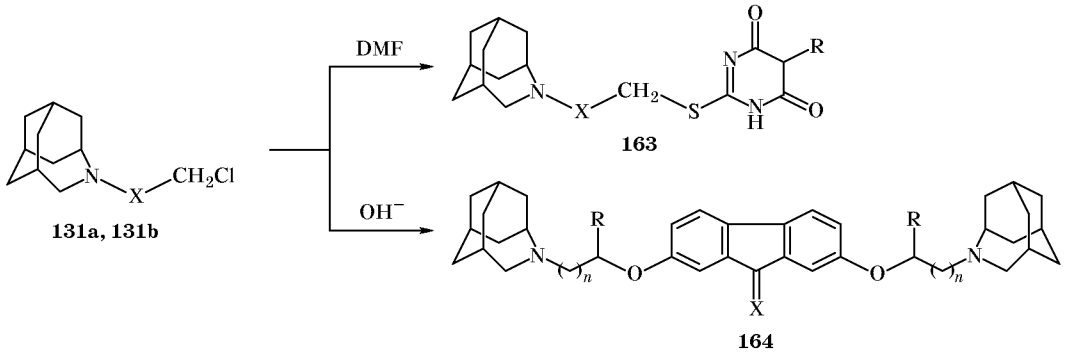


162

160, R = H, Me, R′ = Ph, Z = CH_2CH_2; R = Me, R′ = Ph, Z = CH_2CHMe, $CHMeCH_2$; R = Me, R′ = 2-pyridyl, Z = CH_2CH_2; **162**, R = H, Hlg, C_{1-4}-alkoxy.

Isaev *et al.* [130] developed a procedure for preparation of potential biologically active compounds containing both azahomoadamantane moiety and a known pharmacophoric fragment. *N*-Substituted derivatives **131a** and **131b** were used as alkylating agents toward propyl- and hexyl-substituted thiobarbituric acids. Alkylation of the latter occurred at the reactive thiol group to give compound **163** (Scheme 65). The reaction with 2,7-dihydroxyfluoren-9-one afforded bis-alkylated product **164** (*n* = 1, X = O, R = H); the rate of its formation and yield

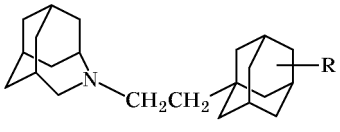
Scheme 65.



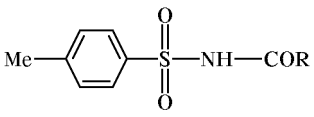
131, X = CH_2 (**a**), CO (**b**); **163**, X = CH_2, CO; R = Pr, C_6H_{11}; **164**, R = H, Me; *n* = 1, 2; C=X = CO, CH_2, CHOH.

can be increased by adding dibenzo-18-crown-6 to the system aqueous alkali–toluene [130]. Compound **164** (R = H, *n* = 1, C=X = CHOH) showed antiviral activity, and ketone **164** (R = H, *n* = 2, X = O) had fungicidal effect at a concentration of 1 mg/ml [131].

The azahomoadamantyl radical was incorporated as substituent in various adamantane derivatives. The resulting structures **165** possess antipsychotic properties [132]. Azahomoadamantyl-substituted oxobenzodiazepinylureas [133] and naphthalenesulfonamides [134] exhibited various kinds of biological activity. The similarity of pharmacological properties of isomeric 1-adamantylamino and 4-azahomoadamant-4-yl radicals is well seen when comparing some hypoglycemic agents, e.g., *N*-arylsulfonyl-*N*-alkylureas which are known to reduce the concentration of sugar in blood. It was presumed that the presence of such a hydrophobic radical as adamantyl should facilitate transport of a number of substances through biological membranes and enhance their interaction with hyidrophobic domains of receptors. In 1967, this assumption was substantiated by indirect data [135]. A great number of various biologically active compounds were modified by introduction of adamantyl radical. In some cases, the modified products showed considerably higher activity. For example, *N*-*p*-tolylsulfonyl-*N*-(1-adamantyl)urea (**166a**) turned out to be 15 times more potent hypoglycemic agent than its *N*-butyl analog **166b** [136]. Amide **166c** also showed hypoglycemic activity in rabbits [137].



165



166a–166c

165, R = OH, OAlk, Alk, Hlg; **166**, R = 1-AdNH (**a**), BuNH (**b**), $C_{10}H_{16}N$ (**c**).

Despite numerous publications on the synthesis and biological activity of various compounds containing adamantyl and related fragments, in most cases their role was not established and molecular aspects of the biological action remained unclear. Experimental results of studies on the molecular mechanisms of antiviral activity of adamantane derivatives were reviewed in [138]. However, up to now there are no reliable data on the mechanism of interaction of cage-like radicals and nitrogen atom therein with cells. Nevertheless, it is generally accepted that any stage of reproduction of viruses may be the scope of action of chemical compounds.

Current studies are aimed at revealing compounds which exhibit a wider spectrum of biological activity against microviruses, as well as those possessing lower toxicity and higher therapeutic index, as compared with 1-aminoadamantane. Reliable data on the mechanism of action of nitrogen-containing cage-like structures on specific cells and organism as a whole could favor purposeful synthesis of biologically active substances.

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