HETERYLADAMANTANES: SYNTHETIC INVESTIGATIONS OF RECENT YEARS, BIOLOGICAL ACTIVITY, AND OTHER ASPECTS OF PRACTICAL APPLICATION. (REVIEW)*

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Published data of the last five years on methods for the synthesis of adamantyl-substituted heterocycles were analyzed. Data on the biological activity and other practical applications of heteryladamantanes are reviewed for the first time.

Keywords: heteryladamantanes, biological activity.

The chemistry of adamantane and its derivatives is a comparatively young department of organic chemistry. (About 70 years have elapsed since the discovery of adamantane in petroleum [1].) At the same time a constant growth has been observed in the number of investigations in this region, particularly beginning with the seventies of the twentieth century. This is due not only to the unique structure of the adamantane molecule, resulting in a series of unique features in its physical and chemical characteristics, but also to the prospects for practical application of its derivatives – from heat-resistant polymers, lubricants, plasticizers, jet fuels, and explosives to components of artificial leather (perfluorinated adamantane) and medicines with a wide range of activity. (Currently about 20 effective medicinal products based on adamantane derivatives are being produced.) The introduction of the adamantyl fragment into organic compounds modifies their biological activity, changing and often intensifying it. This is due to change in the stereochemical structure, hydrophobicity, and lipophilicity of the compounds and the more favorable conditions of their transport through biological membranes. Investigators have paid particular attention to heteryladamantanes as shown, in particular, in the reviews [2-13], which include papers on methods for their synthesis and study of their structure and reactivity. Although some of these reviews give fragmentary data on the biological activity of individual derivatives of heteryladamantanes, an analysis of the present state of the problem has not been made.

The present review gives data from the last five years on methods for the synthesis of heteryladamantanes (saturated and aromatic) and classifies and analyzes for the first time data on the biological activity of this promising class of organic compound. The methods of synthesis are grouped on the basis of the size of the heterocyclic fragment, and the biological activity is arranged according to type.

* Dedicated to Academician M. G. Voronkov on his eightieth birthday.

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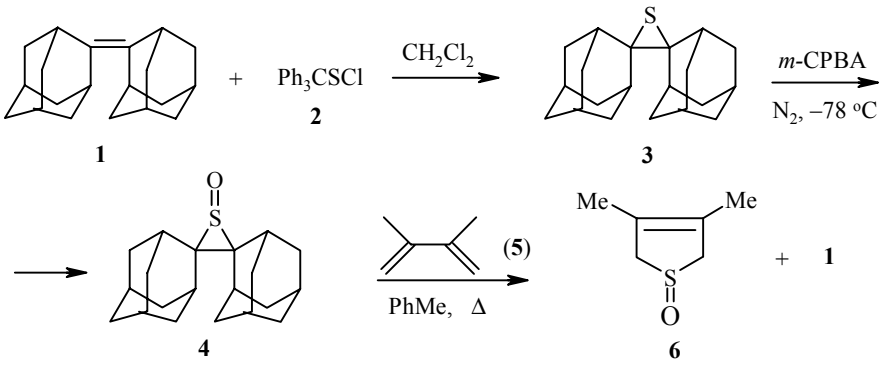
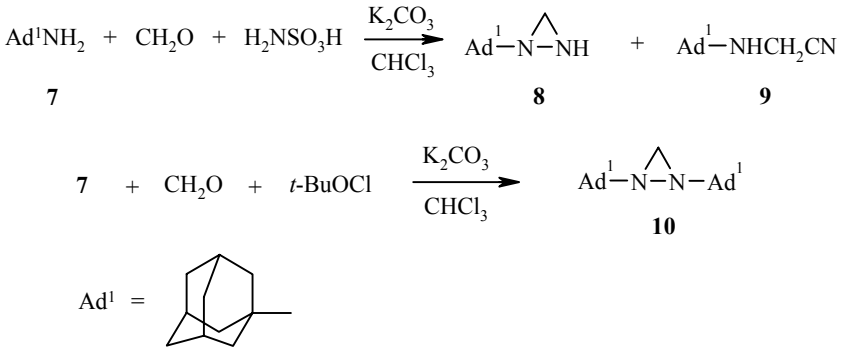
METHODS OF SYNTHESIS OF HETERYLADAMANTANES

Three-membered Heteryladamantanes

Over the last five years several reports have been published on adamantyl-substituted thiiranes and diaziridines. Thus, the reaction of biadamantylidene (**1**) with triphenylmethanesulfenyl chloride (**2**) in an atmosphere of nitrogen gave biadamantylidenethiirane (**3**) with a 93% yield. Treatment of the latter with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at -78°C under nitrogen led to biadamantylidenethiirane 1-oxide. Compound **4** decomposes when heated [14], and with 2,3-dimethyl-1,3-butadiene (**5**) (boiling in toluene, 12 h) it gives a mixture of biadamantylidene (**1**) and 2,5-dihydro-3,4-dimethylthiophene 1-oxide (**6**) [15].



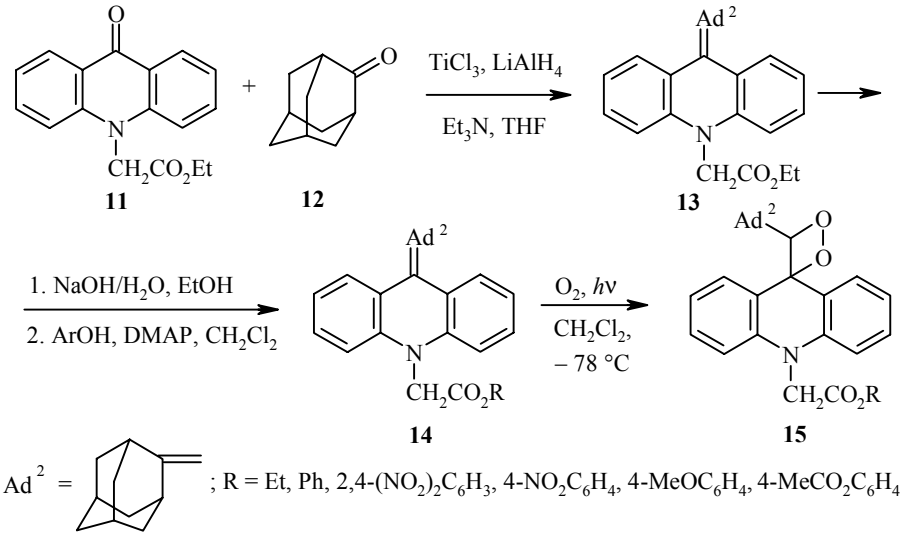
The synthesis of mono- and diadamantyl-substituted diaziridines has been described. Thus, the reaction of 1-aminoadamantane (**7**) with CH_2O in H_2NSO_3H in the presence of potassium carbonate gave the previously unknown 1-(1-adamantyl)diaziridine (**8**) (4%) and (1-adamantyl)aminoacetonitrile (**9**) (13%) [16]. Earlier 1,2-di(1-adamantyl)diaziridine (**10**) had been obtained with a yield of 9.8% by the analogous reaction of the amine **7** with CH_2O and *t*-BuOCl [17].



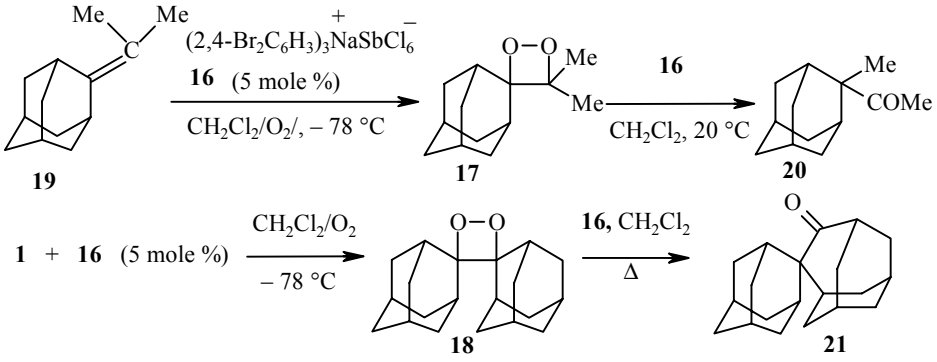
As a result of the photoirradiation of (2-adamantyl)-2,3'-[3H]diaziridine in isooctane at room temperature 2-diazoadamantane and biadamantylidene (**1**) were obtained as the primary products [18].

Four-membered Heteryladamantanes

In the search for new chemiluminescent agents for immunological trials various adamantyl-substituted 1,2-dioxetanes were synthesized [19-26]. Thus, for example, adamantylideneacridine **13** was obtained by the reaction of ethyl acridone-10-acetate (**11**) with 2-adamantanone (**12**) under the conditions of the MacMurray reaction. Its alkaline hydrolysis followed by esterification with phenols led to the esters **14**. The dioxetanes **15** were synthesized with yields of 60-84% by photooxidation of the esters **13**, **14** [27].

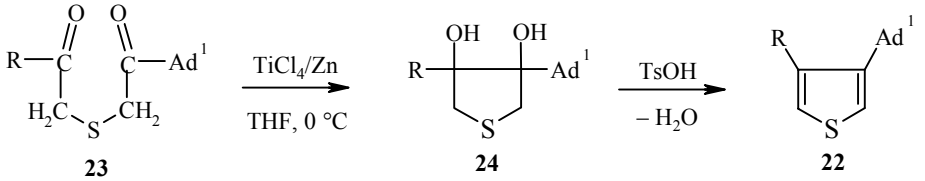


The action of tris(2,4-dibromophenyl)ammonium hexachloroantimonate (**16**) on 4,4-dimethylspiro-(adamantane-2,3'-[1,2]-dioxetane) (**17**) and biadamantylidene-1,2-dioxetane (**18**), obtained from isopropylideneadamantane (**19**) and biadamantylidene (**1**) respectively was studied; 2-methyladamantyl methyl ketone (**20**) (80-85%) was obtained in the first case, and spiro(adamantane-2,4'-homoadamantan-5'-one) (**21**) in the second with other products as impurities [28].

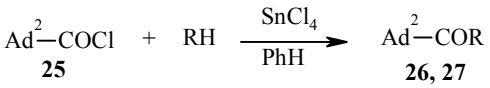


Five-membered and Six-membered Heteryladamantanes

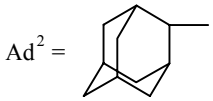
Considerably greater attention has been paid to five-membered adamantyl-substituted heterocycles in the last decade. It is necessary to mention the paper in which sterically overloaded thiophenes – 3,4-di(1-adamantyl)- and 3-(1-adamantyl)-4-*tert*-butylthiophenes **22** – were obtained with satisfactory yields by reductive coupling of 3-thiapentane-1,5-diones **23** followed by acid-catalyzed dehydration of the intermediately formed thiolane-3,4-diols **24** [29].



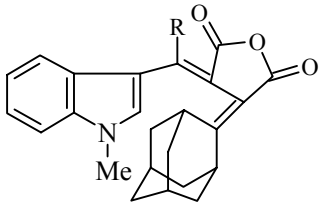
Previously unknown adamantyl thienyl ketones were also synthesized; 2-adamantyl 2-thienyl ketone (**26**) (yield 53%) and 2-adamantyl 2,2'-bithiophen-5-yl ketone (**27**) (yield 85%) were obtained from 2-adamantanoyl chloride (**25**) and thiophene or 2,2'-bithiophene in benzene in the presence of $SnCl_4$ [30].



26 R = 2-thienyl; **27** R = 2,2'-bithiophen-5-yl

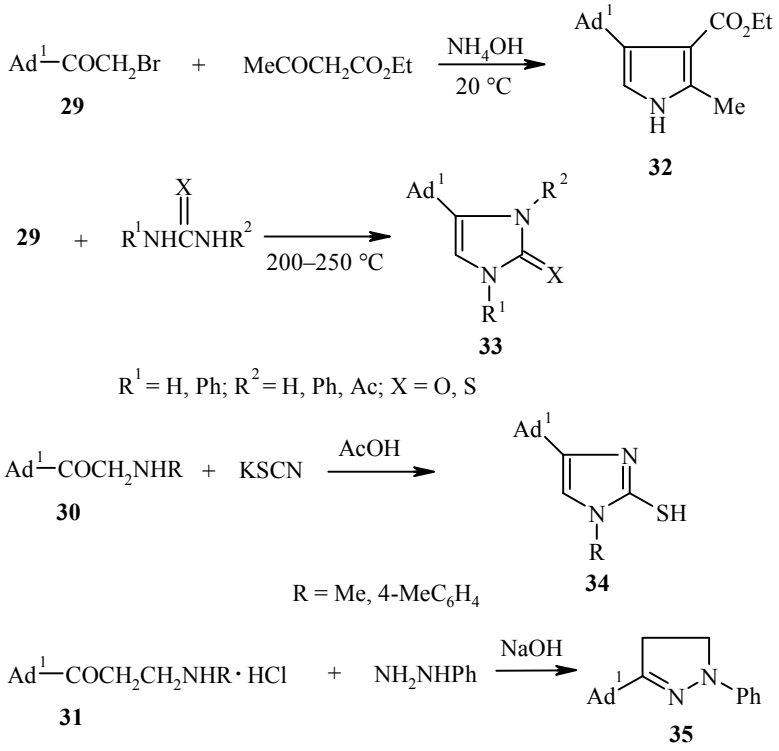


New fulgides of the indole series with an adamantylidene fragment were synthesized. 3-(Adamant-2-ylidene)-2-[1'-(3'-indolylethylidene)]succinic anhydride and 3-(adamant-2-ylidene)-2-(3'-indolylmethylene)-succinic anhydride (**28**) were obtained by the condensation of 1-methyl-3-formyl- and 3-acetyl-1-methylindole with diethyl adamant-2-ylidenesuccinate in the presence of sodium hydride followed by hydrolysis of the esters and treatment of the obtained diacids with acetyl chloride. Their photochemical characteristics were studied [31].

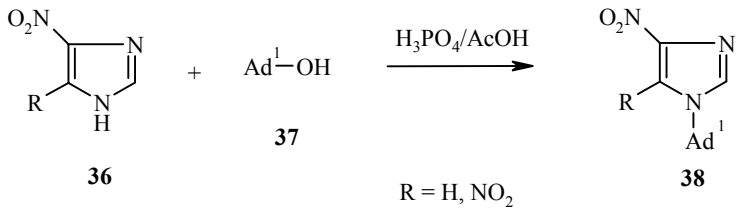


28
R = H, Me

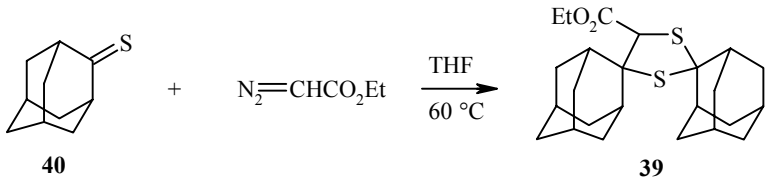
Bromomethyl 1-adamantyl ketone (**29**) and the amino ketones **30**, **31** obtained from it by reaction with amines have been used quite widely as starting compounds in the synthesis of five-membered adamantyl-substituted heterocycles [32-35]. Thus, for example, ethyl 4-(1-adamantyl)-2-methylpyrrole-3-carboxylate (**32**) was obtained with a small yield (7%) from the bromo ketone **29** and acetoacetic ester in water in the presence of ammonia at 20°C [33]. The reaction of the same ketone with ureas or thioureas in ethylene glycol at 200-250°C led to 4-(1-adamantyl)imidazolin-2-ones (or the corresponding thiones) **33** with acceptable yields [32]. The reaction of the amino ketones **30** with potassium thiocyanate in acetic acid gave 4-(1-adamantyl)-2-mercaptoimidazoles **34** with yields of up to 36% [33]. In addition, it was shown that 3-(1-adamantyl)-1-phenylpyrazoline (**35**) is formed from the hydrochlorides of the amino ketones **31** with phenylhydrazine [34].



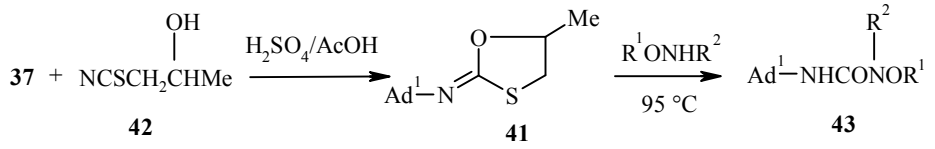
The reactions of nitro-substituted imidazoles **36** with 1-adamantanol (**37**) in sulfuric acid or a mixture of phosphoric and sulfuric acids gave 1-(1-adamantyl)-4-nitroimidazole and 1-(1-adamantyl)-4,5-dinitroimidazole (**38**) [36].



The synthesis of the spiroadamantyl-substituted 1,3-dithiolane-4-carboxylic ester **39** was also realized from ethyl diazoacetate and 2-adamantanethione (**40**) in tetrahydrofuran at 60°C [37].

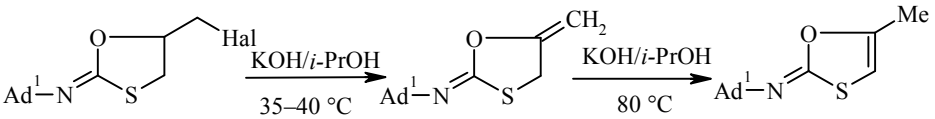


Previously unknown adamantyloxyureas **43** were obtained with yields of 17-93% by the reaction of 2-(1-adamantylimino)-5-methyl-1,3-oxathiolane (**41**), obtained [38] by the reaction of 1-adamantanol (**37**) with 1-thiocyano-2-propanol (**42**) in H_2SO_4/AcOH, with O-substituted derivatives of hydroxylamine and N-methylhydroxylamine at 95°C, accompanied by opening of the oxathiolane ring [39].



R^1 = Me, Et, CH_2Ph; R^2 = H, Me

Dehydrohalogenation of 2-(1-adamantylimino)-5-halogenomethyl-1,3-oxathiolanes **44** was realized by the action of potassium hydroxide in isopropyl alcohol at 35-45°C. It was shown that the initial product was 2-(1-adamantylimino)-5-methylene-1,3-oxathiolane (**45**), which isomerized under the reaction conditions at 80°C to 2-(1-adamantylimino)-5-methyl-1,3-oxathiole (**46**) [40].

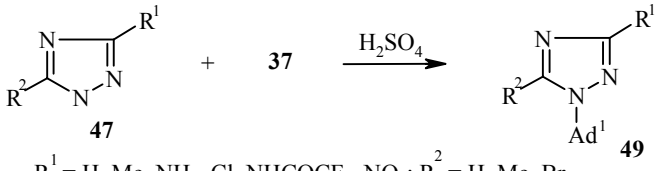


Hal = Cl, Br

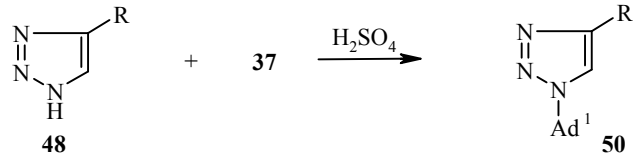
The reaction of 2-(1-adamantylimino)-5-methyl-1,3-oxathiolane with nucleophilic reagents, which takes place with cleavage of the C–S bond of the heterocycle, was studied [41].

A series of adamantyl-substituted pyrazoles [42-44], imidazolidin-4-ones [45], and benzimidazoles [46] were synthesized in order to obtain new biologically active compounds. The vacuum flash photolysis of (1-adamantyl)pyrazoles was also studied [47].

The N-alkylation of 1,2,4-triazoles **47** and tetrazoles **48** by 1-adamantanol (**37**) in sulfuric acid led to the corresponding N-(1-adamantyl)triazoles **49** and tetrazoles **50** [48-51].

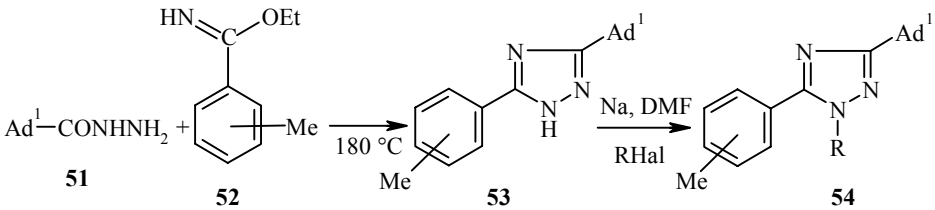


R^1 = H, Me, NH_2, Cl, $NHCOCF_3$, NO_2; R^2 = H, Me, Br



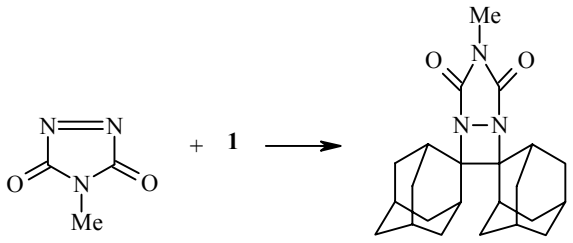
R = H, Me

New adamantyl-substituted 1,2,4-triazoles **53** were obtained with yields of about 80% by the reaction of 1-adamantanecarbohydrazide (**51**) with the imidic esters **52** at 180°C. The products were converted into compounds **54** (yields 70-85%), which are potential antiviral, antibacterial, and antifungal agents [52].



R = 4-MeC_6H_4, $PhCH{=}CHCH_2$

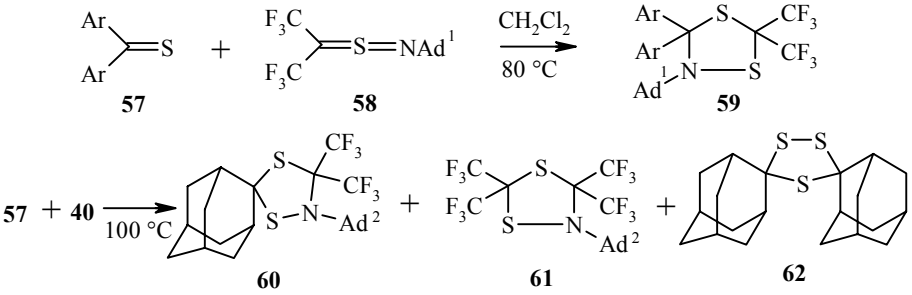
The [2+2] adduct **56** was obtained by the reaction of N-methyltriazolinedione (**55**) with biadamantylidene (**1**) [53].



55 **56**

The thermolysis of 2-adamantyl-substituted 2,5-dihydro-1,3,4-triazoles was studied [54].

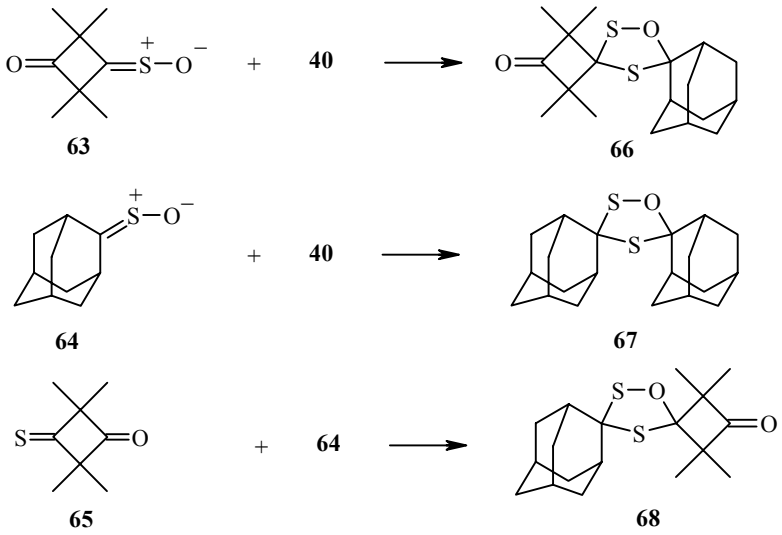
The reaction of the aromatic thiones **57** with N-(1-adamantyl)hexafluorothioacetone S-imide (**58**) in dichloromethane at room temperature gave the products from [3+2]-dipolar cycloaddition – 1,4,2-dithiazolidines **59** – with yields of 49-78% [55]. It was also found that the analogous reaction of **58** with 2-adamantanethione (**40**) does not take place at room temperature, although on heating (100°C) in a sealed tube the previously unknown spiroadamantyl-substituted 1,2,4-dithiazolidine **60** (53%) is formed in a mixture with compounds **61** and **62** [55].



57 **58** **59**

60 **61** **62**

The 1,3-dipolar cycloaddition of alicyclic thione S-oxides with alicyclic thiones was studied. It was shown that heating of the thione S-oxides **63** and **64** with 2-adamantanethione (**40**) or of the thione S-oxide **64** with 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**65**) at 80-100°C in chloroform in a sealed tube is accompanied by the formation of spiro-1,2,4-oxathiolanes **66-68** with yields of 77-85% [56].



63 **66**

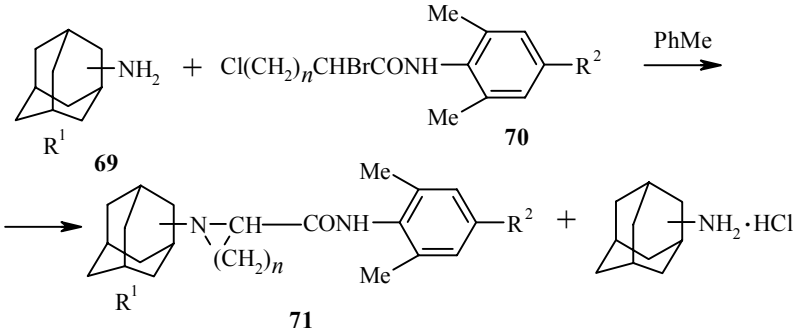
64 **67**

65 **68**

The production of derivatives of 4-(1-adamantyl)-3,5-diphenyl-4,5-dihydro-1,2,4-oxadiazoles, which have antitumor activity, has been described [57]. In addition, the racemates of 4-(1-adamantyl)-5-aryl-3-phenyl-1,2,4-oxadiazolines were resolved on the chiral stationary phase *R*,*R*-DACH-DNB in order the determine the effect of substituents on the enantioselectivity of retention of the 5-aryl-1,2,4-oxadiazolines exhibiting anti-HIV activity [58].

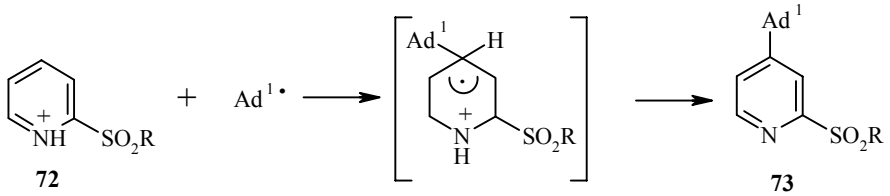
The carbonyl derivatives of adamantane – bromomethyl 1-adamantyl ketone, 3-(1-adamantyl)-1-bromo-2-propanone, N-substituted 2-(1-adamantyl)-1-amino-2-ethanones, and 3-(1-adamantyl)-1-amino-3-propanones – and also the intermediate products in the synthesis of β-aminovinyl ketones, i.e., the sodium salts of 3-(1-adamantyl)-1-hydroxy-1-propen-3-one and 4-(1-adamantyl)-1-hydroxy-1-buten-3-one, were used in the production of various adamantyl-containing five- and six-membered heterocycles (pyrroles, pyrazoles, pyrazolines, isoxazolines, imidazoles, thiazoles, indolizines, pyridines, and pyrimidines) [35, 39].

The reaction of 1- or 2-aminoadamantanes **69** with the mesidide or xylidide of α-bromo-ω-chlorovaleric or α-bromo-ω-chloropropionic acid **70** with boiling in toluene (20-40 h) was used for the synthesis of N-adamantyl derivatives of the arylamides of 2-pyrrolidinecarboxylic and 2-piperidinecarboxylic acids **71** [60].



R^1 = H, OH; R^2 = H, Me; *n* = 3–4

The homolytic adamantylation of protonated 2-alkylsulfonylpyridines **72** was studied. It was shown that the reaction with the 1-adamantyl radical, formed as a result of the oxidative decarboxylation of 1-adamantanecarboxylic acid catalyzed by silver ions, takes place regioselectively with the formation of 4-(1-adamantyl)-2-sulfonylpyridines **73** [61].

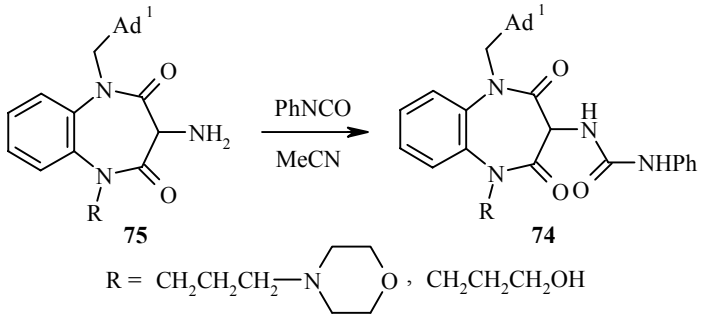


R = Me, *n*-Bu, *t*-Bu

The reaction of 5-nitro-2-chloropyridine with 1-aminoadamantane (**7**) or of 2-amino-5-nitropyridine with 1-chloroadamantane gave 2-(1-adamantylamino)-5-nitropyridine as a component of new organic nonlinear optical materials [62]. The reaction of the amine **7** with 2-chloromethylpyridine was used in the synthesis of N-(1-adamantyl)-N,N-bis(pyridylmethyl)amine – a new tridentate ligand [63].

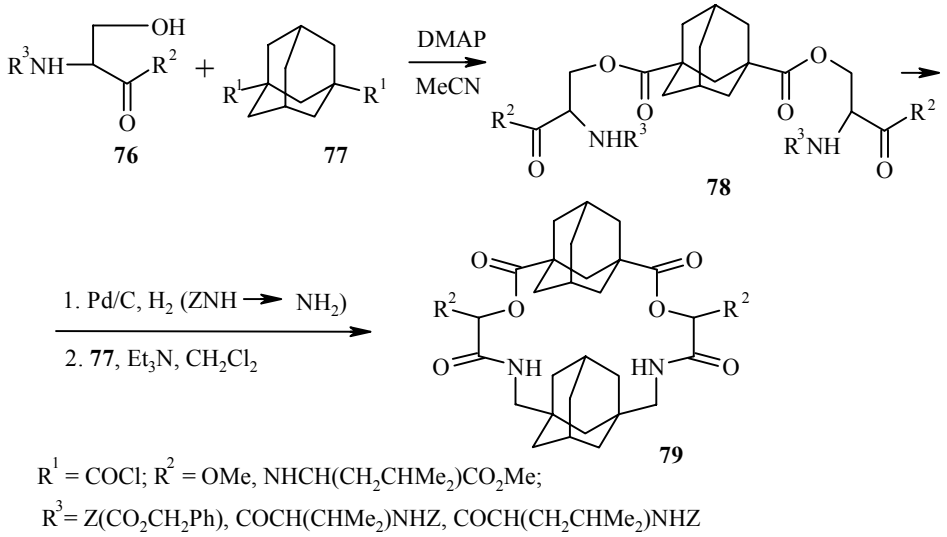
Other Heteryladamantanes

Among other heterocyclic systems with an adamantyl fragment the synthesis of enantiomerically pure N-[1-(1-adamantylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N-phenylureas **74** by the reaction of the racemic amines **75** with phenyl isocyanate in dry acetonitrile as potential antagonists of cholecystokinyne B has been described [64].



75 **74**

The synthesis of a new class of macrocyclic despipeptides with adamantyl fragments, capable of transporting Na, Ca, and Mg ions through membranes, was realized. Thus, for example, the derivatives **78** were obtained by a simple two-stage synthesis including the condensation of N,C-protected hydroxy amino acids or peptides **76** with 1,3-adamantanedicarbonyl dichloride **77**. After removal of the N-protection and repeated reaction with **77** they were converted into the cyclodespipeptides **79** [65].

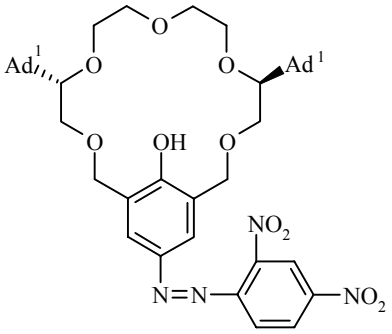


76 **77** **78** **79**

R^1 = COCl; R^2 = OMe, NHCH(CH_2CHMe_2)CO_2Me;

R^3 = Z(CO_2CH_2Ph), COCH($CHMe_2$)NHZ, COCH(CH_2CHMe_2)NHZ

In order to study the temperature dependence of the inversion of enantiomeric selectivity in complex optically active azophenolic crown ethers [(5*S*,13*S*)-5,13-di(1'-adamantyl)-19-(2',4'-dinitrophenylazo)-3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-1(21),17,19-trien-21-ol (**80**) was synthesized in the enantiomerically pure form with a yield of 66% by the reaction of (*S*)-1-(1'-adamantyl)ethane-1,2-diol with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in dry THF in the presence of sodium hydride [66].



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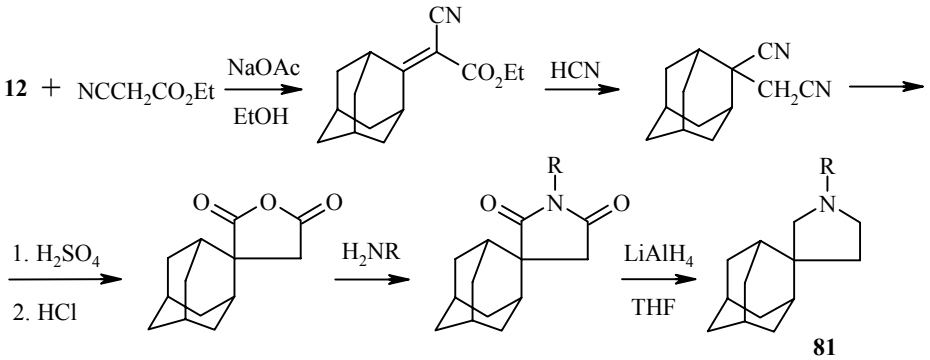
SOME ASPECTS OF THE PRACTICAL APPLICATION OF HETERYLADAMANTANES

As mentioned in the introduction, the range of possible practical applications of adamantane and its derivatives is remarkably wide. In this connection it must be emphasized in particular that a large number of the products exhibiting hypoglycemic, antitumor, immunodepressant, antibacterial and fungistatic, hormonal, analgesic and antipyretic, anti-inflammatory, cholagogic, antiarhythmic, sedative, antimalarial, and anticholesterase activity, stimulation of the central nervous system stimulant, and other characteristics were modified by the introduction of an adamantyl radical. In a number of cases this led to a significant increase in their activity [67].

The discovery in 1964 of antiviral activity in the hydrochlorides of 1-aminoadamantane (trade names, midantan, amantadine, symmetrel) [68, 69] and 1-(1-adamantyl)ethylamine (rimantadine), which has a wider spectrum of antitumor activity, lower toxicity, and a more clearly defined therapeutic effect and is used to the present time [70-72], has greatly accelerated the development of applied investigations in the region of adamantane chemistry, as witnessed by the appearance in the last ten years of more than 400 patents on the antiviral activity of its derivatives. This has prompted a wide search for biologically active and primarily antiviral compounds in heteryladamantanes [8, 73-129]. The most promising among the heteryladamantanes in this respect are the spirocoupled compounds. Thus, (2-adamantyl)spiropyrrolidines **81** with various alkyl, arylalkyl, and other substituents, synthesized according to the scheme presented below, exhibited high activity against Sendai parainfluenza viruses of influenza A and rhinoviruses [73, 74].

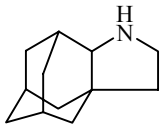


81

The most promising among them is N-methyl-substituted pyrrolidine **81** (R = Me), which is three times more active than amantadine toward viruses of influenza A (Japan, Hongkong) and also exhibits high activity against rhinoviruses (HGR), Koksaki A21, and Sendai parainfluenza viruses, against which amantadine is ineffective [74-76]. It was also shown that although it slightly reduces the magnitude of the effect increase in the

size of the heterocycle to six- and seven-membered, i.e., the transition from adamantylspiropyrrolidines to adamantylspiropiperidine or adamantylspiroazepan does not lead to loss of activity against influenza viruses [77-79].

Pyrrolidines with an annellated adamantane ring system also exhibit high antiviral activity. Thus, adamantano[2,1-*b*]pyrrolidine (**82**), adamantano[1,2-*b*]pyrrolidine (**83**), and their derivatives not only showed high activity against influenza A viruses but also suppressed the replication of hepatic virus MHV and hepatitis virus [80-85].



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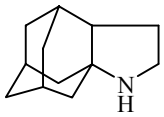


83

Antiviral activity has been detected in a series of other hydrogenated heterocycles containing an adamantyl radical – derivatives of piperidine, piperazine, aziridine [86, 87], isoxazoline [88], and hexahydropyrimidine. The latter are active against influenza virus of the $N2N_zA$/Singapore type [89].

Many heteroaromatic compounds with an adamantyl substituent also possess antiviral activity. Thus, a series of patents have been devoted to derivatives of adamantyl-1,2,3- and adamantyl-1,3,4-thiadiazoles [90-95] (see also [96-98], thiazole [94, 99-101], benzothiazole [102], triazole [103], pyrazole [104], pyrimidine [104-108], quinoline [109, 110], and quinoxaline [111], having activity against various types of viruses. High activity against arboviruses but weak activity against variolovaccines were exhibited by adamantyl and adamantylmethyl esters of nicotinic and isonicotinic acids and their N-oxides [112, 113]. Antiviral activity was also observed in adamantyl-substituted N-methylimidazole [114], 3-amino-1-methyl-1H-pyrazolo[3,4:4',5']-thieno[2,3-*b*]pyridine [115], purine [116], and other heterocyclic systems mentioned, in particular, in patents [117-120] and papers [121-126].

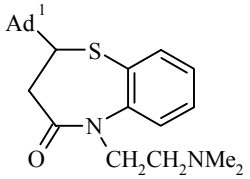
Polymeric compounds, including water-soluble compounds, containing heteryladamantyl fragments and exhibiting antiviral activity have attracted attention [127-129].

Investigations into psychotropic heteryladamantanes have been carried out quite vigorously in two directions with the introduction of an adamantyl radical into known neurotropic products or with the search for new highly active compounds among various N-heterocycles containing an adamantyl substituent.

On the basis of existing data the first direction seems less promising than the second. This is demonstrated in particular by the fact that replacement of the cyclohexyl fragment in the procyclidene molecule by an adamantyl fragment not only did not lead to increase in the activity but even caused loss of the anticholinergic effect [130], while the product from the reaction of isatin and 1-adamantyl methyl ketone had lower anticonvulsive activity than the product from isatin and acetone [131]. Appreciable activity was not detected in the derivatives of adamantanecarboxylic acid [132] and its ester with 3-methyl-1-phenyl-1-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine [133], although the analgesic effect in the adamantyl analog of meperidine is more clearly defined, and its activity is more prolonged [134].

More promising is the synthesis of various adamantyl derivatives of any single heterocyclic system. An example is the synthesis of substituted benzodiazepinones in which the adamantyl fragment is either in the side chain attached to one nitrogen atom [135] or is spirocoupled at position 2 of the heterocyclic system [136, 137] or is even inserted in place of the phenyl fragment in the structure of the familiar antidepressant thiazesim. A product **84** 1.5 times more selective was obtained [138, 139].

We note in this connection papers on the synthesis of the amides and esters of 1-adamantanecarboxylic and adamantane-1-acetic acids in order to create psychotropic agents with prolonged activity [67, 140]. Among them the ester of 1,4-benzodiazepin-2-one **85** has a series of advantages over the familiar product of this class – oxazepam [140-142].



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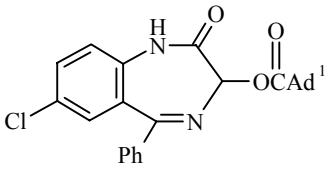


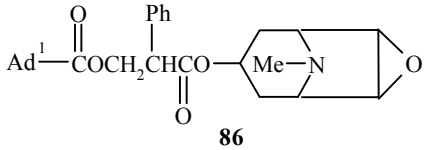
85

In the search for new antidepressants adamantano[2,1-*b*][1,5]benzodiazepine [143] and derivatives of phenothiazine, phenoxazine, and dibenzoxazepine [144-151] and also azabicyclohexanes containing an adamantyl substituent [152, 153] were synthesized, and their properties were studied.

The anti-Parkinson activity and the depressant effect on the central nervous system characteristic of amantadine were also detected in a series of derivatives of heteryladamantanes, 1,2-dimethyladamantano[2,1-*b*]-pyrrolidine [154], adamantano[2,1-*b*]pyrrolidin-5-one [155], adamantano[2,1-*b*]dihydropyridazin-6-ones [156, 157], and 2-bromo-1-methylpiperidinomethyladamantane [158]. ω-N-Piperidinylpropylideneadamantane has high anti-Parkinson activity, and this makes it possible to recommend its use. Its glucouronide is 15 times less toxic than amantadine [159]. It was noticed that the anticonvulsive activity of adamantylaminoalkyl(acyl)piperidinium salts administered by injection is stronger than with phenylbutazone, although the opposite result is obtained if it is administered *per os* [160].

1-(1-Adamantyl)aziridine [161], the hydrochlorides of N-[2-(1-adamantyl)ethyl]- and N-[3-(1-adamantyl)propyl]pyrrolidine, N-[2-(1-adamantyl)ethyl]piperidine [162], N-(1-adamantyl)caprolactam [163], 4,4-diaryl-1-(1-adamantyl)piperidines [164], and many other derivatives of heteryladamantanes (e.g., [165-170]) also affect the central nervous system. Specific activity toward the central nervous system is exhibited by substituted N-(1-adamantyl)- and N-(1-adamantylmethyl)piperazines [171, 172], which in particular prevent catalepsy caused by neuroleptics [173]. In addition, compounds of this series, having a phenylallyl group at the second N atom, have been recommended for use in the case of cerebral trauma [174, 175].

(1-Adamantyl)-4-(3-nitrophenyl)pyrimidin-2-one [176] and the N-adamantylamides of nicotinic and isonicotinic acids [177, 178] have psychostimulant activity. While having low toxicity, the N-adamantylamides of 1-alkyl-2-iminobenzimidazoline-3-acetic acid also exhibit psychostimulant activity, and this shows up in increased physical efficiency and increased motor activity [179]. Together with stimulation of the central nervous system, O-(1-adamantylcarbonyl)scopolamine (**86**) exhibits high anticholinergic and other types of activity [180, 181]. Anticholinergic activity is also exhibited by certain derivatives of (2-adamantyl)spiro-2'-(5'-amino-1',3'-dioxane) [182]. Derivatives of piperazine containing an adamantyl substituent have tranquillizer characteristics [183, 184].



86

Antibacterial characteristics are exhibited by many heterocycles with an adamantyl fragment. Derivatives of imidazole [185], benzimidazole [186], pyrazole [187], isoxazole [106], isoxazoline [188], 4-thiazolidinone [189], 3-isothiazolinone [190], 1,2,4-triazole [191], 1,2,3-thiadiazole [94], piperazine [192], pyridine and quinoline [165] have clearly defined antibacterial characteristics. Antibacterial characteristics were also noticed in a series of adamantoyl derivatives of nucleosides [193]. However, it should be noted that the lack of quantitative estimates of the activity in the individual patents and reports does not make it possible to reach a conclusion about their advantages over known antibacterial products; for the 1- and 2-adamantylamides of

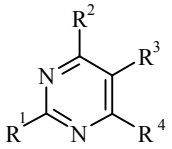
2-oxo-4-phenylpyrrolidine-1-acetic acid [194] and adamantyl-substituted 1,3,4-thiadiazolo[3,2-*a*]pyrimidine-5,7-diones [195] it was noticed that the introduction of an adamantyl substituent in place of alkyl reduces the activity. At the same time, while retaining high activity against staphylococci at a level of 1 μg/ml for adamantylglycine derivatives [196], 0.78 μg/ml for adamantoylated or adamantylacetylated cephalosporins [197], and 0.1 μg/ml for adamantyloxyacetylated penicillins [198] these compounds acquire increased resistance to penicillinase [199-201]. 1H-Tetrazole-5-thiols have been patented as intermediates in the synthesis of cephalosporins and penicillins [202].

A series of patents and reports have been devoted to the analgesic, hypotensive, and anti-inflammatory characteristics of heteryladamantanes. They include derivatives of adamantyl-substituted 1,2,4-triazines [203, 204], 2,4,6-triazines [205], imidazolines [163], morpholines [206], 1,4-dihydro-2-quinazolones [207], caprolactam [163], pyridoindoles [208], azabicyclo[3.1.1]hexanes [209], azabicyclo[3.2.1]octanes [210], and dioxaazabicycles [211].

Antihypertensive activity was detected in the adamantyl derivatives of quinazoline [212-214], pyridazine [215, 216], benzimidazole [217], and pyrazine [218].

The use of heteryladamantanes as immunomodulators is well known. Thus, the adamantoylation of cytarabine increases the duration of the immunodepressant effect to 20 days after injection, although it reduces the magnitude of the effect by a factor of five [219]. It was also reported that the bis[N-(1-adamantyl)]- or bis[N-(2-adamantyl)piperazides of aliphatic dicarboxylic acids in doses of 1/100 LD reduce the production of antibodies by a factor of three [166, 220]. On the other hand N-adamantyl-substituted derivatives of pyrrolidone [221], like 2-aryl-4-adamantoylcarbamoyl-5-hydroxyimidazoles [222] exhibit immunostimulant activity.

Investigations into antitumor activity among various derivatives of heteryladamantanes have developed vigorously. Thus, 2,6-diamino-8-(1-adamantyl)- and 2,6-diamino-8-(1-adamantylmethyl)purines have fairly high activity [223], although they were not singled out among other alkyl-substituted aminopurines [224]. A study was made of the antitumor activity of derivatives of adamantylpyrimidines [225-238], and it was found in particular that derivatives of pyrimidine **87** ($R^1 = R^2 = OH$, $R^3 = Ad^1$, $R^4 = H$) inhibit hepatic folatereductase and exhibit a cytostatic effect on tumor cells [227], while compounds **87** ($R^1 = R^2 = NH_2$, $R^3 = Ad^1$, $R^4 = Alk$) have been recommended as antitumor products [229, 233]. In the case of $R^4 = Et$ the activity is 30 times higher than the activity of methotrexate [229]. Replacement of 1-adamantyl in this compound by alkyl substituents considerably reduces the antitumor activity [230].

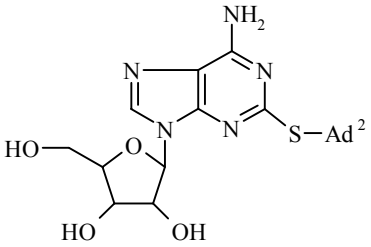


87

R^1, R^2 = OH, NH_2; R^3 = Ad^1, $NHAd^1$; R^4 = Alk, H, OH

Trials carried out among other heteryladamantanes showed that with respect to intracerebral leukemia L-1210 P,P-bis(1-aziridinyl)-N-(1-adamantyl)phosphoramide is removed from the brain more quickly than triethylenephosphoramide [239, 240], while 4-(1-adamantoyloxy)-5-carbamoylimidazole retards the growth of Ehrlich's carcinoma and other malignant tumors [241]. It was also found that among the esters of 3-hydroxypyridines the derivatives of propionic and benzoic acids are active against *Leukemia limfocitica* P-388, whereas the corresponding adamantoate is inactive [242]. The adamantylamide derivative of methotrexate is 2-4 times less active than methotrexate itself against leukemia L-1210 [243]. 2-Adamantyl-substituted thiazoles also exhibited activity against leukemia P-388 [244].

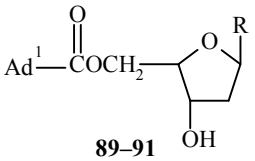
A promising trend in the search for new antitumor products is modification of pharmacologically active nucleosides, during which it is possible to introduce a lipophilic substituent either in the nitrogen heterocycle or in the carbohydrate fragment. The first path was only realized in the case of the reaction of 2-thioadenosine with 2-bromoadamantane in the presence of sodium in DMF, resulting in the formation of S-(2-adamantyl)-2-thioadenosine (**88**) – an inhibitor of the aggregation of thrombocytes [245].



88

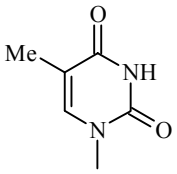
The analogs of nucleosides containing an adamantyl fragment and modified by isothiocyanates were synthesized, but no data on the biological activity of the obtained compounds were given [246].

The second path proved more promising in the search for new antitumor products. Thus, 5'-O-adamantoyl derivatives of deoxyribonucleosides (thymidine **89**, 5-fluoro-2'-deoxyuridine **90**, 2'-deoxyadenosine **91**) and ribonucleosides (adenosine **92**, inosine **93**, 6-thioinosine **94**, and 6-azauridine **95**) were synthesized from nucleosides and 1-adamantanecarbonyl chloride [247, 248]. It was established that the adamantoyl derivatives **90**, **94**, and **95**, like the initial nucleosides, have antitumor and antiviral activity, while compound **94**, unlike the initial 6-thioinosine and its triacetate, inhibits the formation of antibodies and exhibits enhanced immunodepressant activity [247].



89–91

R =



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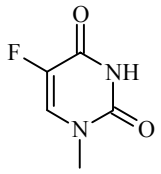

90

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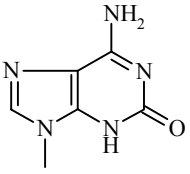

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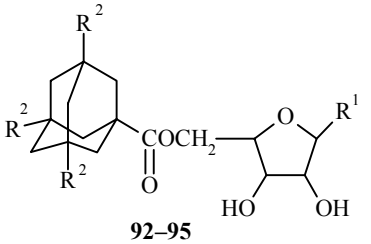
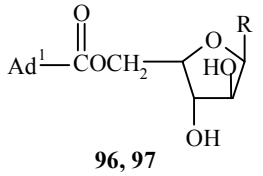


92–95

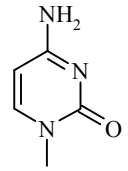
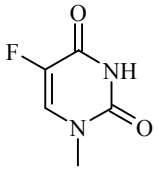
R^1 = adenine **92**, hypoxanthine **93**, 6-mercaptopurine **94**, azauridine **95**; R^2 = H, Me

The adamantoyl fragment was also inserted into the known antileukemia product 1-β-D-arabinofuranosylcytosine [249-252]. The obtained 5'-O-adamantoylarabinofuranosylcytosine (**96**) is a promising therapeutic product [250].

A cytostatic effect was detected in 5'-O-(1-adamantoyl)-β-D-xylofuranosyl-5-fluorouracil (**97**) [253].



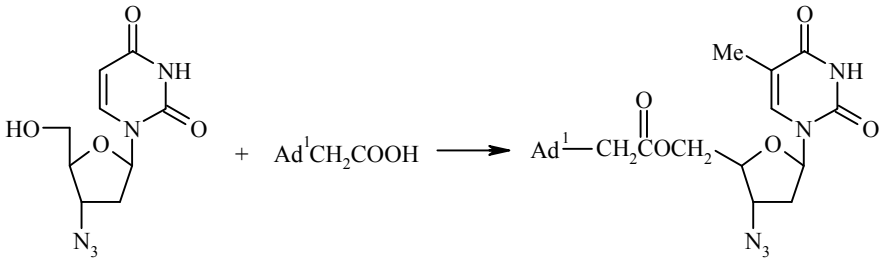
96, 97

R =  ; 

96 **97**

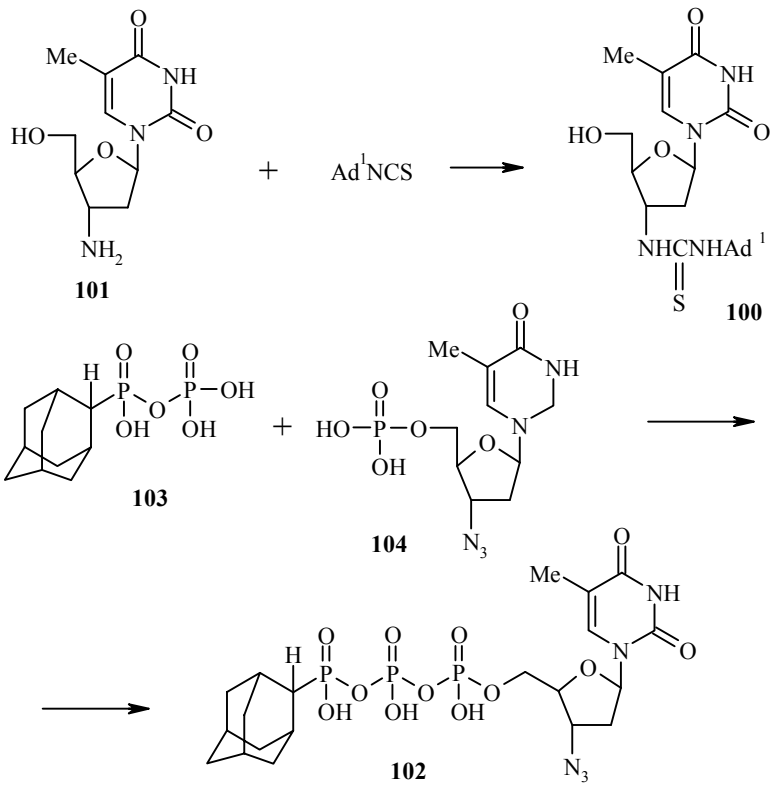
In the search for new antitumor products 1-adamantyl dichlorophosphonate was brought into reaction with thymidine [254], uridine, 5-bromouridine, 5'-fluoro-5'-deoxyuridine [255-257], 6-azauridine [257], adenosine, and 9-β-D-ribofuranosyl-6-methylmercaptopurine [258]. In most cases the formation of complex mixtures of cyclic and acyclic adamantyl phosphonates was observed. The reaction with pyrimidine nucleosides takes place in a similar way [256]. Among the adamantane-substituted phosphorylated nucleosides antitumor activity was found in 5'-O-(1-adamantylalkyl)phosphoryl derivatives of 1-β-D-arabinofuranosylcytosine [259]. A three-component condensation was also realized between inosinedialdehyde, propadienephosphonous acid, and 1-aminomethyladamantane or 2,2'-bis(aminomethyladamantane), leading to the formation of 9-[(1',4'-morpholyl)-3'-hydroxy-N'-(1-adamantylalkyl)-5'-propadienephosphinate-6'-hydroxymethyl-2']hypoxanthines, having antiviral activity against RNA- and DNA-containing infectious and oncogenic viruses [260].

Japanese researchers have developed a method for the synthesis of derivatives of 3'-azido-3'-deoxythymidine (AZT) containing the adamantane fragment at position 5' of the nucleoside [261]. Study of the biological action of the ester **98**, obtained from the azidothydimine **99** and (1-adamantyl)acetic acid, showed that its concentration in the parenchymatous tissue of the brain is 18 times higher than the value obtained in a comparative experiment with AZT. Consequently, the insertion of the adamantane fragment into AZT facilitates the transport of this drug in the tissue of the brain where the AIDS virus enters and attacks the central nervous system [262].



99 **98**

In the search for new anti-AIDS products the 3'-(1-adamantyl)thioureido derivative of thymidine **100** was synthesized by the reaction of 3'-amino-2'-deoxythymidine (**101**) with 1-adamantyl isothiocyanate [263], and azidothymidine 5'-γ-(2-adamantylphosphonyl)-α,β-diphosphate (**102**) was synthesized by the condensation of (2-adamantylphosphonyl)phosphate (**103**) with azidothymidine monophosphate (**104**) [264].



Among other biological characteristics of heteryladamantanes we note the tuberculostatic activity of adamantyl-substituted isoxazolines [89, 188], the antiarhythmic activity of adamantyltetrazoles [265], the antimalarial activity of (1-adamantylamino)quinolines [266], and the sedative activity of derivatives of furotriazines [267]. The esters of pyridinecarboxylic acid N-oxides containing an adamantyl radical are promising for the treatment of hyperlipidemia [268]. The biological activity of adamantyl-substituted heterocycles has been mentioned in a series of other papers (e.g., see [269-277]).

The potential of heteryladamantanes for use in agriculture has been studied to a lesser degree. In this region 4-(1,2,4-oxadiazol-3-yl)phenyl isothiocyanates, including those containing an adamantyl radical, have been patented as antihelminthic agents for animals [278, 279]. Derivatives of imidazole [185], triazine [280], thiazole [189], isothiazole [192], and benzothiazoline [281] containing an adamantyl fragment can be used as fungicides. Adamantyl-substituted 5-oxo-2,5-dihydro-1,2,4-triazines, which have pre- and post-emergence herbicidal activity at rates of 12.5-400 g/hectare, were patented [282]. Trials on the growth-regulating activity of adamantylamino derivatives of 2,4,6-triamino-5-nitropyrimidines showed that in most cases the introduction of the adamantyl radical increases the stimulant properties or reduces the phytotoxicity of the products [283].

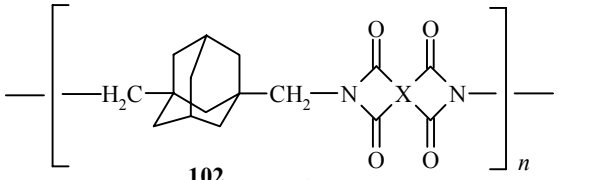
To conclude our examination of the practical uses of heteryladamantanes we mention the ability of derivatives of adamantylidenesuccinic anhydride and adamantylidenesuccinimide to change color under the influence of UV radiation, which makes them promising for holography [284].

Monomers with heteryladamantyl fragments have considerable practical potential for the preparation of heterochain polymers [285-305]. Thus, for example, homo- and copolymerization of 5-(1-adamantyloxy)-2H-pyrrol-2-one with various vinyl monomers leads to polymers in which photochemical transformations occur during UV exposure [295].

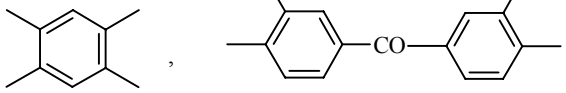
The polymerization of adamantyl-containing epoxides in the presence of triisobutylaluminum and aluminum trisacetoacetate gave polyepoxides, which were proposed as additives for lubricating oils and adhesives [296, 297]. In heat resistance polyepoxides based on adamantane and 1,1-biadamantyl surpass polyepoxides with isopropylidene groups. The softening temperature of adamantane epoxides is 250 and 220°C respectively, while that of the latter is 180°C. Weight loss begins at 390°C in the former and at 34°C in the latter [295-300].

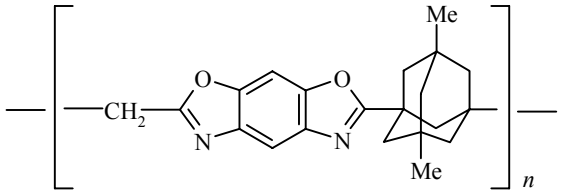
The polyimides **102**, ring–chain polymers with adamantylene groups obtained from the dianhydrides of tetracarboxylic acids and diamines of the adamantane series, are of no lesser practical interest [301, 302]. They have the same thermal stability as aromatic polyimides but unlike the latter are not colored. Their advantages also include resistance to hydrolysis, organic solvents, active chemical reagents, and heat, softening on heating, and the possibility of treatment by pressing or by casting from solution.

The adamantyl-containing polybenzoxazoles **103**, obtained by low-temperature polycondensation of 5,7-dimethyladamantane-1,3-dicarboxylic acid and 3,3'-dihydroxybenzidine, have no lesser valuable characteristics [303]. The polymer **103** is colorless, is soluble in water, and loses only 10 wt.% when heated at 500°C. The production of new soluble adamantyl-containing polyimides and copolyimides, distinguished by enhanced hydrolytic stability, was reported recently [304, 305].



102

X = 



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The vigorous progress in the chemistry of heteryladamantanes, due both to the theoretical interest and particularly to the practical interest in heterocycles containing an adamantyl fragment, is a guarantee of further advances in this region of organic chemistry. At the present time the bibliography devoted to the synthesis of heteryladamantanes and study of their properties, numbers more than 700 titles. Researchers working on the chemistry of heterocyclic compounds and interested in the directed synthesis of biologically active substances containing an adamantane fragment experience certain difficulties due to the lack of papers summarizing the data on the methods of synthesis, the reactivity, and the practical qualities of such compounds. We hope that our previous reviews [11-13] and the present work will be able to fill this gap and will prove useful to a wide circle of organic chemists.

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