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Adamantane derivatives containing heterocyclic substituents in the bridgehead positions. Synthesis and properties

M-G A Shvekhgeimer

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Abstract. Data on the synthesis, transformations, and applications of adamantane derivatives containing heterocyclic substituents in the bridgehead positions are surveyed, described systematically, and analysed. The bibliography includes 202 references.

I. Introduction

Adamantane was discovered in 1933 in a study of petroleum products.[1,2] The adamantane molecule is a rigid structure consisting of three fused six-membered carbon rings and having the shape of almost an ideal sphere. The arrangement of carbon atoms in the adamantane molecule is similar to that in the unit cell of the crystal lattice of diamond. The spatial structure, hydrophobicity, and lipophilicity of adamantane ensure favourable conditions for its transport through biological membranes. The introduction of an adamantyl radical into organic compounds changes and often enhances their biological activities. The influence of the adamantyl radical on the hypoglycemic, antitumour, immunodepressive, antibacterial, fungistatic, hormonal, analgesic, antipyretic, anti-inflammatory, cholagogic, antiarrhythmic, sedative, neuroplenic, antimalarial, and anticholine-esterase activities as well as on the central nervous system stimulating activity of the corresponding medicinal preparations have been noted.[3] Among various compounds of the adamantane series, those containing heterocyclic substituents in their molecules seem to be especially interesting both from the theoretical and practical standpoints.

Despite the great interest of researchers in the chemistry of adamantane derivatives containing heterocyclic substituents and numerous examples of their practical use, no reviews surveying the literature data on the synthesis, transformations, and practical significance of heteryladamantanes have been published; only separate examples of synthesis or biological activity of heteryladamantanes have been reported.[4–11] Among the monographs devoted to adamantane,[12–14] only one paper[13] contains a mention of heteryladamantanes, synthesised before 1975; however, this study also contains virtually no data on the synthesis and properties of adamantane derivatives with heterocyclic substituents.

In our review we survey the published data on the synthesis and properties of adamantane derivatives, the bridgehead positions of which contain heterocyclic radicals either linked directly to the adamantane nucleus or separated from it by a chain of carbon atoms. We consider adamantane derivatives with heterocyclic residues the nucleus of which incorporate nitrogen, oxygen, sulfur, nitrogen and oxygen, or nitrogen and sulfur atoms, as well as residues of other heterocyclic systems.

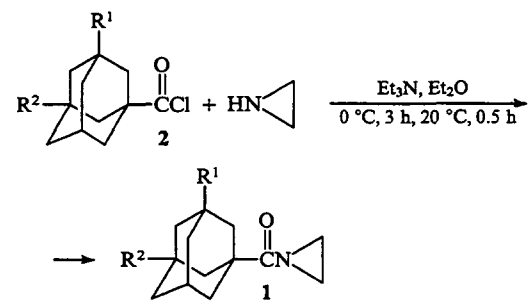
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II. Adamantane derivatives containing heterocyclic nuclei with nitrogen atoms

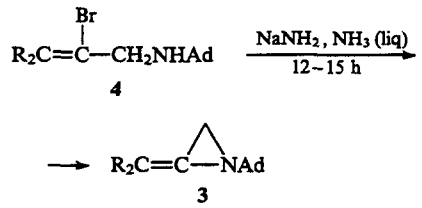
1. Compounds with three-membered heterocycles

Several methods have been proposed for the synthesis of heteryladamantanes containing residues of three-membered nitrogen-containing heterocycles. A series of *N*-adamantoylaziridines **1** were prepared by the reaction of the acid chlorides **2** with aziridine in the presence of triethylamine.[15]



R^1	R^2	R^1	R^2	R^1	R^2
H	H	F	H	Me	Me
Me	H	Cl	H	Me	OH
Ph	H	Br	H	EtO	Et
OH	H	I	H	4-ClC_6H_4	H
MeO	H				

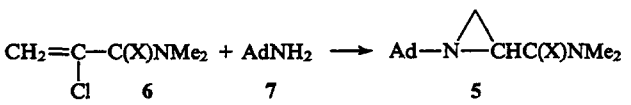
1-(Adamant-1-yl)-2-alkylideneaziridines **3** are formed in a yield of 50% (R = H) or 64% (R = Me) on treatment of the unsaturated bromides **4** with sodium amide in liquid ammonia.[16]



R = H, Me.

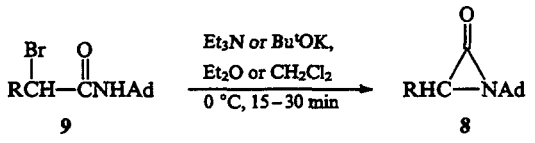
From here on, Ad is adamant-1-yl, $C_{10}H_{15}$.

Substituted aziridines **5** have been synthesised by the interaction of the vinyl chlorides **6** with 1-aminoadamantane **7**.[17]



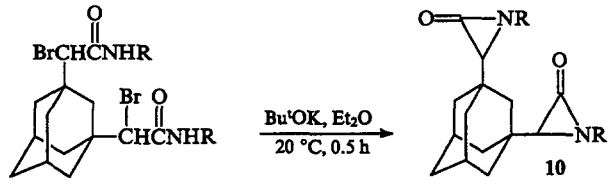
X = H_2, O.

The derivatives of 1-(adamant-1-yl)aziridin-2-one **8** have been obtained by cyclocondensation of *N*-(adamant-1-yl)amides of α-bromocarboxylic acids **9** in 60%–70% yields.[18–20]



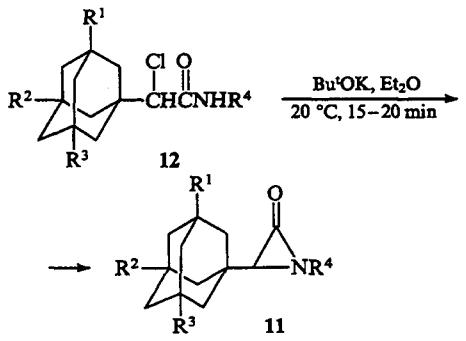
R = Ad (see Ref.18), Bu^t (see Ref.19, 20).

The same method has been used to synthesise compounds **10** containing two aziridinone fragments (yields 60% and 64%).[21]



R = Bu^t, Ad.

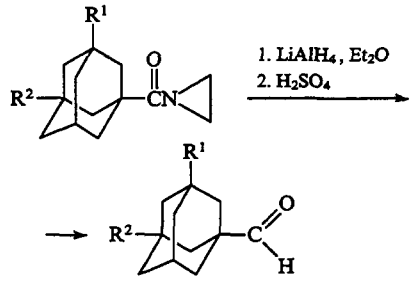
When chloramides **12** are used in this reaction instead of the corresponding bromamides, the aziridinone derivatives **11** are formed equally readily in 60%–70% yields.[22–24]



R^1	R^2	R^3	R^4	Ref.	R^1	R^2	R^3	R^4	Ref.
H	H	H	Bu^t	22	H	H	H	Bu^t	24
Me	Me	Me	Bu^t	22	Me	Me	Me	Bu	24
H	H	H	Bu^t	23	Me	H	H	Bu^t	24
Me	Me	Me	Bu^t	23	Me	Me	H	Bu^t	24
Me	Me	Me	cyclo-C_6H_{11}	23	Me	Me	Me	Bu^t	24
Me	Me	Me	Bu	23	Me	Me	Me	cyclo-C_6H_{11}	24

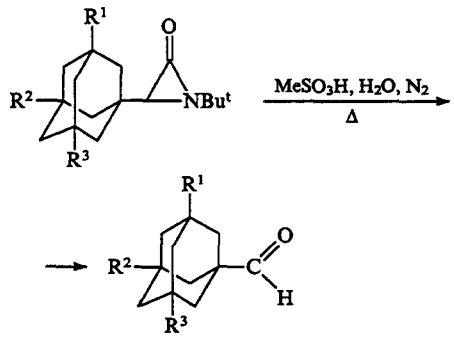
The irradiation of 1-(adamant-1-yl)-4,4-dimethyltriazol-5-one with light from a high-pressure mercury or mercury-xenon lamp in toluene at 15 °C for 4.5 h under a nitrogen atmosphere affords a mixture of products in which 1-(adamant-1-yl)-3,3-dimethylaziridin-2-one was detected by spectral methods.[25]

Treatment of adamantoyl-containing aziridines (reduced preliminarily with lithium tetrahydroaluminate)[15] and adamantyl-containing aziridinones[23,24,26,27] with strong acids (H_2SO_4 or $MeSO_3H$) leads to aldehydes of the adamantane series in more than 90% yields.



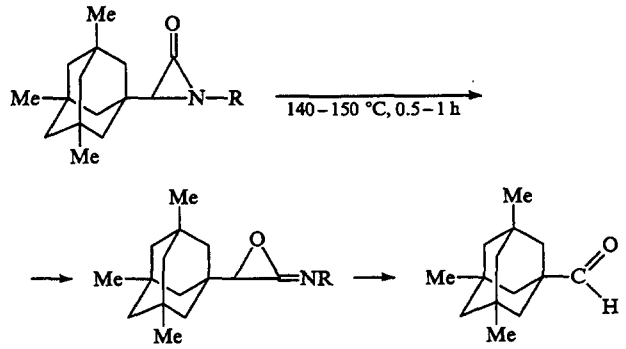
R^2 = H: R^1 = H, Me, Ph, OH, MeO, F, Cl, Br, I, 4-ClC_6H_4;

R^1 = R^2 = Me; R^1 = Me, R^2 = OH; R^1 = EtO, R^2 = Et.



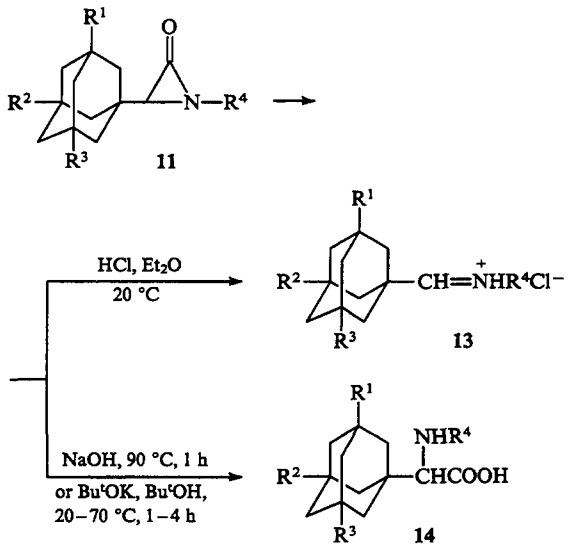
R^1	R^2	R^3	Ref.
H	H	H	24, 26, 27
Me	H	H	24, 26, 27
Me	Me	Me	24, 26, 27
Me	Me	H	24

The transformation of adamantyl-containing aziridinones into aldehydes can also be carried out in the absence of acids, by heating them at 140–150 °C.[23]



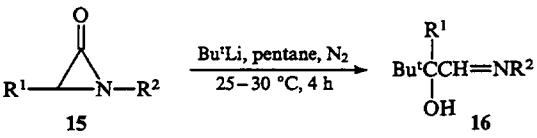
R = Bu, Bu^t, C_5H_{11}.

Treatment of the aziridinone derivatives **11** with HCl in Et_2O gives the salts **13** (yields 95%–96%),[23,24] whereas the reaction of the compounds **11** with sodium hydroxide or potassium *tert*-butoxide affords the amino acids **14** (yields 63%–94%).



11 13 14

Lithium *tert*-butoxide converts compounds **15** into the alcohols **16** in 75%–85% yields.[28]

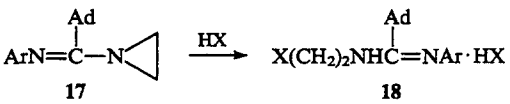


15 16

R^1 = Ad, R^2 = But, Ad;

R^1 = But, R^2 = Ad.

The reaction of azomethines **17** with hydrohalic acids involves the cleavage of the aziridine ring and yields salts **18**.[29]

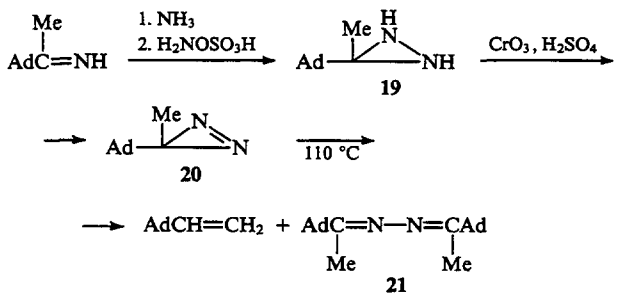


17 18

Ar = Ph, C_6H_4R; X = Cl, Br, I.

1-(Adamant-1-yl)aziridine exhibits antiphlogistic activity and stimulates the central nervous system.[30] 1-(Adamant-1-yl)-3-*tert*-butylaziridin-2-one possesses antiviral activity.[21]

The successive treatment of 1-acetyladamantane imine with ammonia and then with hydroxyaminesulfonic acid resulted in the formation of 3-(adamant-1-yl)diaziridine **19**, which was converted into 3-(adamant-1-yl)diazirine **20** by the action of chromic anhydride in sulfuric acid. The compound **20** is thermally unstable and is converted on heating into a mixture of vinyladamantane and the azine **21** in a ratio of 5.1 : 1.[31]



19 20

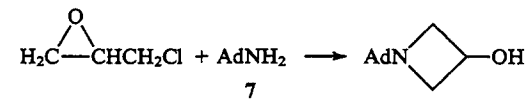
$\longrightarrow$ AdCH=CH$_2$ + AdC(Me)=N–N=C(Me)Ad

21

The transformation of the diazirine **20** into vinyladamantane and the azine **21** involves the intermediate formation of the carbene AdC̈(Me). Diazirines of this type are of interest as initiators of polymerisation or as reagents for introducing a tracer into cell membrane lipids.[31]

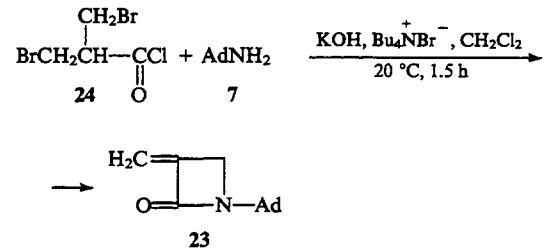
2. Compounds with four-membered heterocycles

In the search for compounds exhibiting an antiarrhythmic activity, the reaction of epichlorohydrin with the amine **7** has been studied. Thus 1-(adamant-1-yl)azetidin-3-ol **22** was obtained in a good yield.[32]



7 22

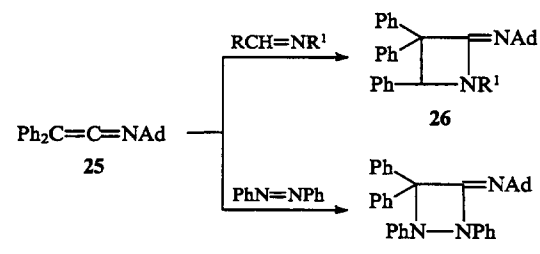
A method for the preparation of 1-(adamant-1-yl)-3-methyleneazetidin-2-one **23** has been developed.[33] The method involves cyclisation of the acid chloride **24** with the amine **7** under the influence of potassium hydroxide under conditions of phase transfer catalysis; the yield of compound **23** is 40%.



24 7 23

The oxygen atom in the compound **23** can be substituted by sulfur by the action of the Lawesson reagent; this reaction affords 1-(adamant-1-yl)-3-methyleneazetidine-2-thione in 46% yield.[33]

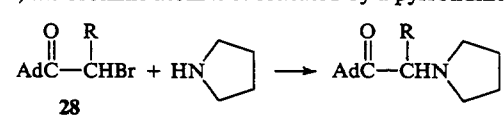
Ketenimine **25** enters into cycloaddition reactions with azomethines or with azobenzene; this results in the formation of the azetidine derivatives **26** or diazetidine derivatives **27**.[34]



25 26 27

3. Compounds with five-membered heterocycles

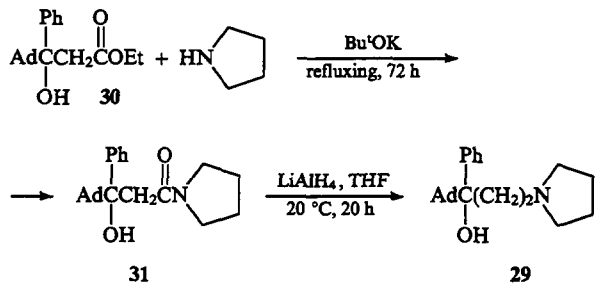
A number of methods have been reported for the introduction of a pyrrolidine ring into adamantyl-containing compounds. For example, in the reaction of the bromoketones **28** with pyrrolidine, the bromine atom is substituted by a pyrrolidine residue.[35]



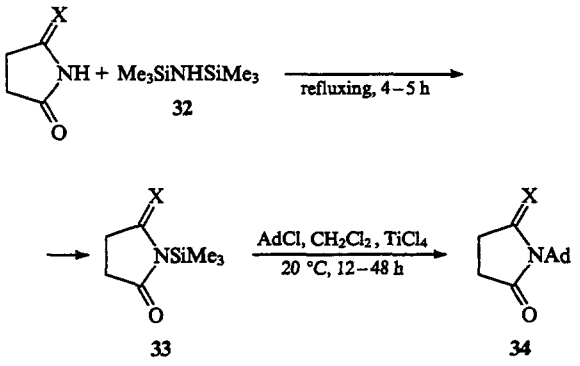
28

R = H, Me.

The alcohol **29**, which causes general depression of the central nervous system, is obtained in 34% yield by refluxing ethyl 3-(adamant-1-yl)-3-hydroxy-3-phenylpropionate **30** in pyrrolidine in the presence of potassium *tert*-butoxide followed by the reduction of the compound **31** thus formed.[36]

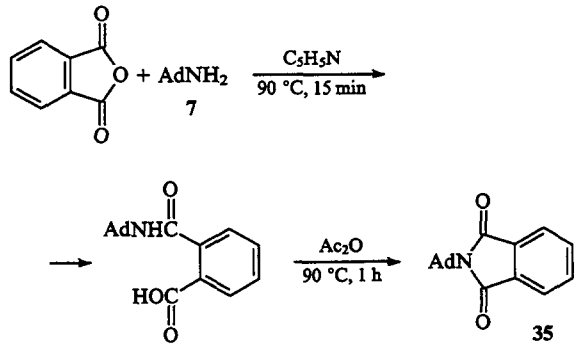


The addition of adamant-1-yl radical to the nitrogen atom of pyrrolidone has been accomplished in two stages: initially, pyrrolidone was refluxed with hexamethyldisilazane **32**, and then the resulting *N*-silylated derivative **33** (X = H_2) was treated with 1-chloroadamantane in the presence of titanium(IV) chloride and chlorotrimethylsilane. The reaction product **34** (X = H_2) was obtained in 54% yield. The *N*-silylated derivative **33** (X = O) and the corresponding adamantylation product **34** (X = O) were obtained in a similar way from pyrrolidine-2,5-dione (yield 33%).[37]



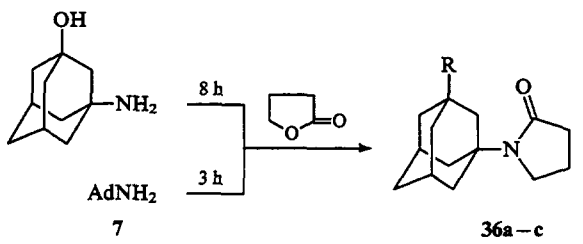
X = H_2, O.

N-(Adamant-1-yl)phthalimide **35** has been obtained in 15% yield by the reaction of the amine **7** with phthalic anhydride with subsequent cyclisation of the resulting *o*-(adamant-1-yl)aminocarbonylbenzoic acid with acetic anhydride.[38]



N-(Adamant-1-yl)maleimide, which possesses antitumour activity and inhibits *Herpes simplex* virus, has been prepared by the reaction of the amine **7** with maleic anhydride followed by cyclisation of the resulting compound AdNHCOCH=CHCOOH with polyphosphoric acid.[39]

Heating of butyrolactone with the amine **7** and with 1-amino-3-hydroxyadamantane at 200–205 °C leads to *N*-substituted derivatives of pyrrolidone **36a** and **36b** in 86.5% and 71.5% yields, respectively.



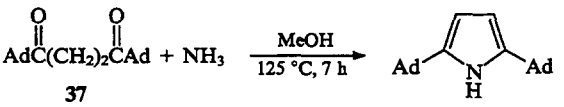
R = H (a), OH (b), COOH (c).

The hydroxy compound **36b** can also be obtained from the adamantyl derivative **36a** by treating it with a mixture of nitric and sulfuric acids (0–5 °C, 2 h, yield 56.3%). The acid **36c** (R = COOH), in its turn, can be synthesised in 69.5% yield from the hydroxy derivative and formic acid in the presence of sulfuric acid (20 °C, 5 h).[40]

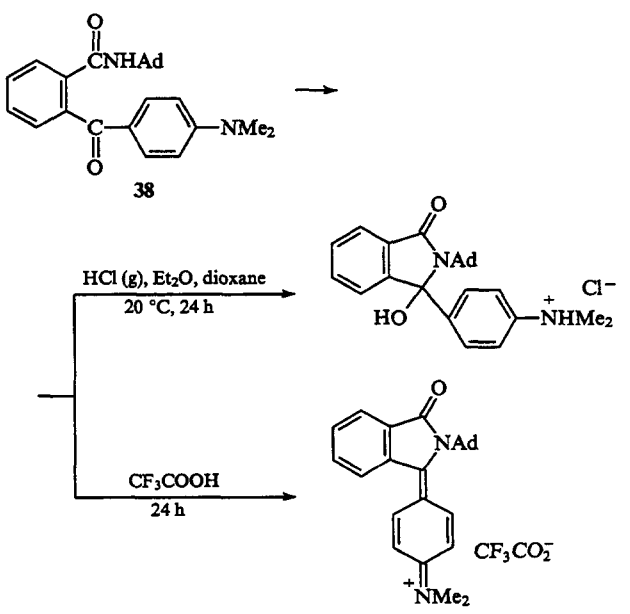
The compounds **36a** and **36b** exhibit an immunostimulating activity, which is higher for **36a**. The introduction of the COOH group exerts no substantial influence on the activity, but decreases markedly the toxicity.[40]

N-(Adamant-1-yl)pyrrolidone and its hydrochloride have been patented as anti-inflammatory agents and also as preparations stimulating the central nervous system and decreasing the cholesterol level.[29] *N*-[2-(Adamant-1-yl)ethyl]pyrrolidine and *N*-[3-(adamant-1-yl)propyl]pyrrolidine hydrochlorides have also been recommended as agents influencing the central nervous system.[41]

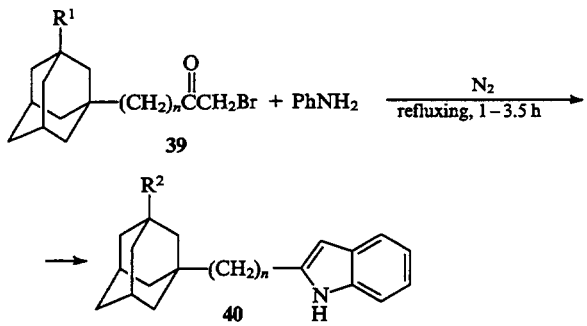
Heating of the diketone **37** with ammonia in a sealed tube affords 2,5-di(adamant-1-yl)pyrrole in a very high yield (95%).[42]



The cyclisation of compound **38** in the presence of hydrogen chloride or trifluoroacetic acid affords two different salt-type products.[43]

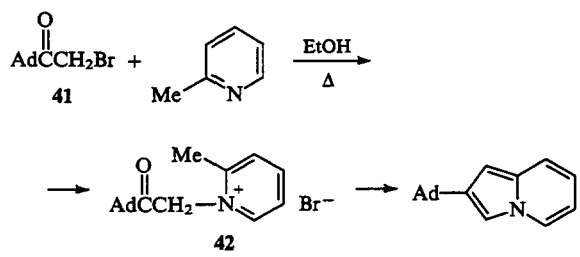


Refluxing of the bromomethyl ketones **39** with aniline leads to their cyclisation into indol derivatives **40** in 48% – 94% yields.[44, 45]

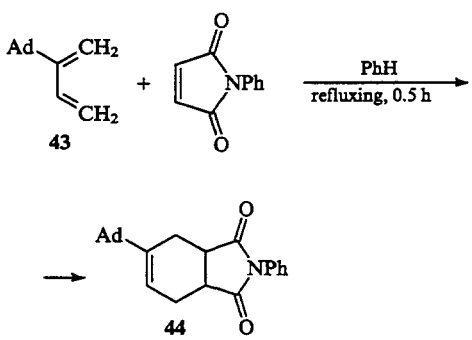


R^1	R^2	n	Ref.
H	H	0	44, 45
H	H	1	44
CH_2Br	CH_2Br	0	44
Cl	NHPh	0	44

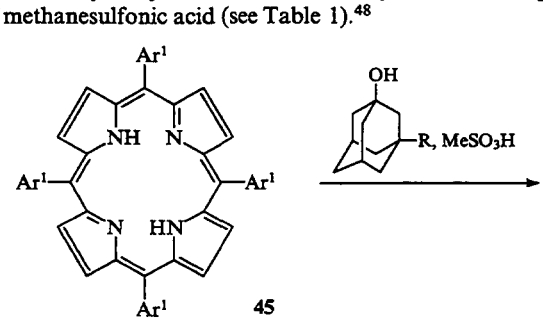
It has been found that the reaction of adamant-1-yl bromomethyl ketone **41** with 2-methylpyridine gives in 50% yield salt **42**, which then cyclises to 2-(adamant-1-yl)indolizine in 58% yield.[46]

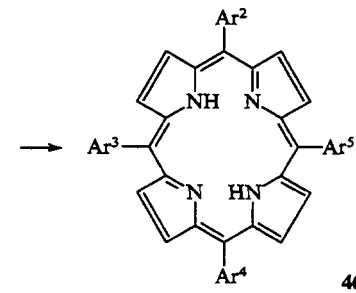


2-(Adamant-1-yl)buta-1,3-diene **43** enters into the Diels–Alder reaction with *N*-phenylmaleimide upon refluxing in benzene to give the corresponding adduct **44** in 63% yield.[47]

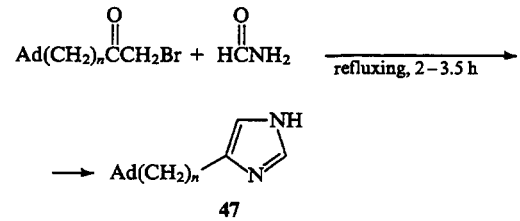


The introduction of an adamantane nucleus into the porphyrin derivatives **45** giving rise to compounds **46** has been accomplished by the action of 3-aminomethyl-1-hydroxyadamantane or 3-hydroxyadamantane-1-carboxylic acid in the presence of methanesulfonic acid (see Table 1).[48]



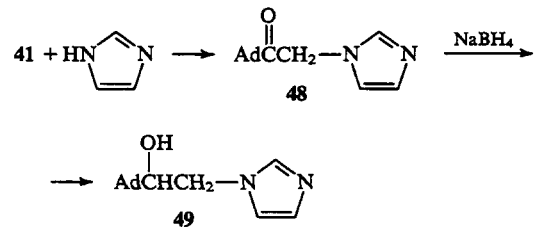


Following refluxing with formamide, the bromoketones $Ad(CH_2)_nCOCH_2Br$ are converted into imidazole derivatives **47** in 43% – 51% yields.[44,45]

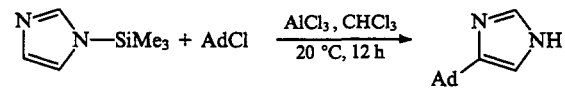


n = 0, 1.

The ketone **48**, which is formed in the reaction of the bromomethyl ketone **41** with imidazole, has been reduced to the corresponding alcohol **49**, the derivatives of which have been recommended as bactericides and fungicides.[49]



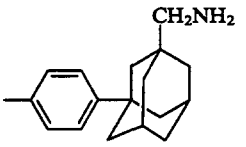
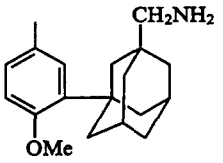
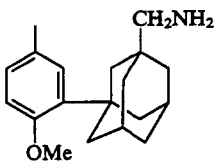
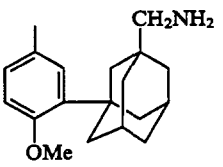
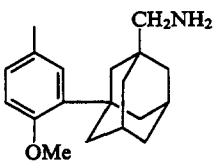
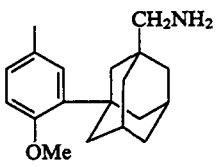
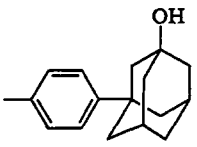
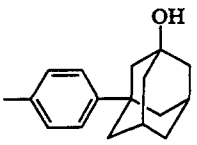
Japanese investigators[50,51] developed a method for the introduction of the adamantyl radical into heterocyclic compounds, which involves the use of organosilicon derivatives of the latter. For example, treatment of *N*-(trimethylsilyl)imidazole with 1-chloroadamantane in the presence of aluminium chloride or titanium(IV) chloride affords 4-(adamant-1-yl)imidazole in 52% yield.[51]

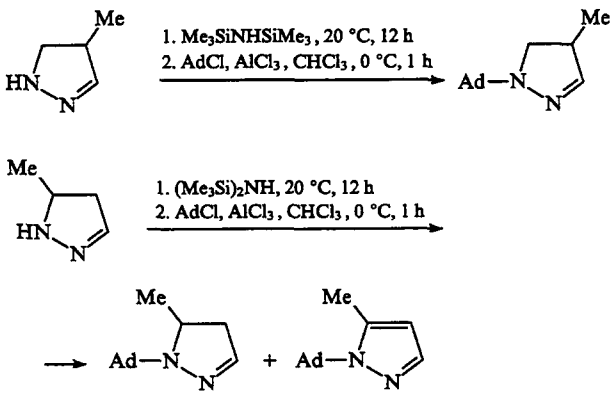


Similarly, in the reaction of 1-(trimethylsilyl)benzimidazole with 1-chloroadamantane, the adamantyl radical adds to the benzene ring rather than to the heterocyclic nucleus; hence, the reaction leads to 5-(adamant-1-yl)benzimidazole (yield 49%).[50]

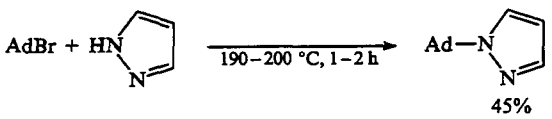
In a more recent study,[37] the *N*-adamantylation of nitrogen-containing heterocycles has been carried out by a one-pot procedure: a heterocyclic compound was initially treated with disilazane, and then 1-chloroadamantane and a Lewis acid were added to the reaction mixture; the process was completed, as a rule, at room temperature. 4-Methylpyrazoline was converted in this way into 1-(adamant-1-yl)-4-methylpyrazoline (yield 60%), while the transformation of 5-methylpyrazoline gave 1-(adamant-1-yl)-5-methylpyrazoline (yield 18%) and the product of its dehydrogenation, 1-(adamant-1-yl)-5-methylpyrazole (yield 37%).[37]

Table 1. Yields of adamantylporphyrins **46**.

Compound	R	Ar^1	Ar^2	Ar^3	Ar^4	Ar^5	Yield (%)
46a	CH_2NH_2	Ph	Ph	Ph	Ph		42
46b	CH_2NH_2	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$MeOC_6H_4$		42
46c	CH_2NH_2	4-$MeOC_6H_4$	4-$MeOC_6H_4$		4-$MeOC_6H_4$		22
46d	CH_2NH_2	4-$MeOC_6H_4$			4-$MeOC_6H_4$	4-$MeOC_6H_4$	22
46e	COOH	Ph	Ph	Ph	Ph		40
46f	COOH	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$MeOC_6H_4$		45



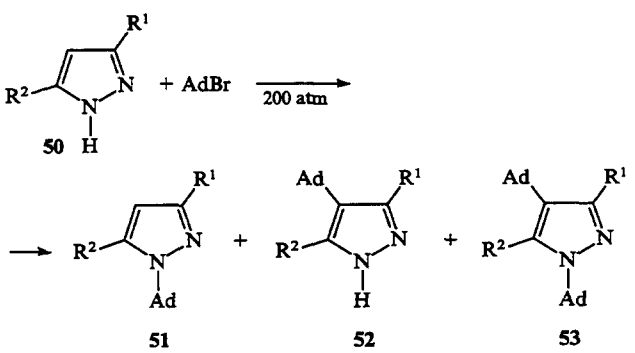
1-(Adamant-1-yl)pyrazole has been obtained by heating pyrazole with 1-bromoadamantane.[52,53]



45%

1-(Adamant-1-yl)imidazole (yield 74%) and 1-(adamant-1-yl)benzimidazole (yield 69%) were synthesised in a similar way from 1-bromoadamantane and imidazole (or benzimidazole).[53]

The reactions of 1-bromoadamantane with pyrazole and its alkyl analogues **50** have been studied in detail. It was found that the interaction of AdBr with pyrazole, 3-methylpyrazole, or 3,5-dimethylpyrazole under a pressure of 200 atm may afford one to three reaction products **51**–**53** depending on the temperature and on the ratio heterocyclic compound : bromide.[54]

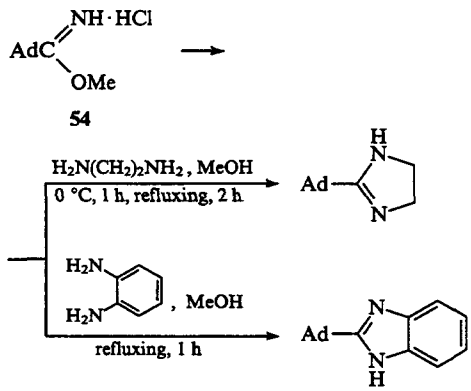


50 **51** **52** **53**

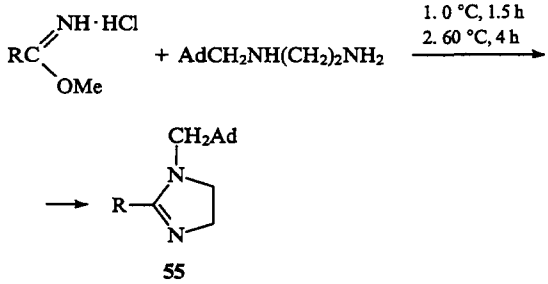
50 : AdBr	T / °C	t / h	Reaction products composition (%)		
			51	52	53
			$R^1 = R^2 = H$		
2 : 1	120	4	100	0	0
2 : 1	230	4	13	86	1
1 : 2	230	1	14	37	49
			$R^1 = Me, R^2 = H$		
1 : 1	230	4	78	25	0
2 : 1	230	4	7	90	3
1 : 2	230	4	9	26	65
			$R^1 = R^2 = Me$		
1 : 1	120	5.5	100	0	0
1 : 1	230	4	0	100	0

In a certain temperature regime, one can obtain only compounds **51**.

The hydrochlorides of iminoesters of carboxylic acids are convenient initial compounds for the synthesis of diverse heterocyclic derivatives. The reaction of methyl adamantane-1-carboximidate hydrochloride **54** with ethylenediamine gives 2-(adamant-1-yl)imidazoline in 92% yield, while the interaction of compound **54** with *o*-phenylenediamine leads to 2-(adamant-1-yl)benzimidazole (yield 71.5%).[55, 56]

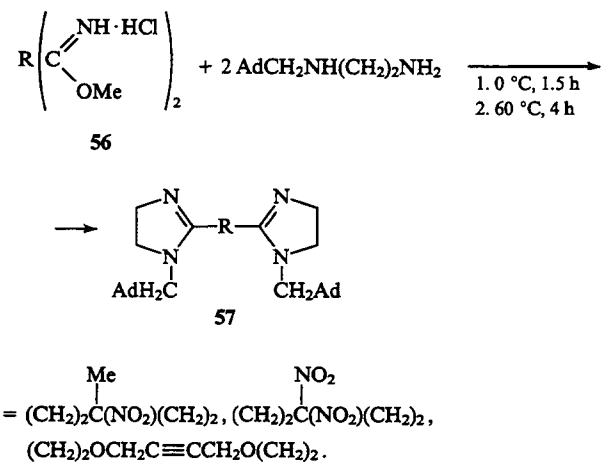


The imidazoline derivatives **55** have been synthesised in 80%–94% yields by cyclocondensation of *N*-(adamant-1-ylmethyl)ethylenediamine with hydrochlorides of various methyl carboximidates.[56]



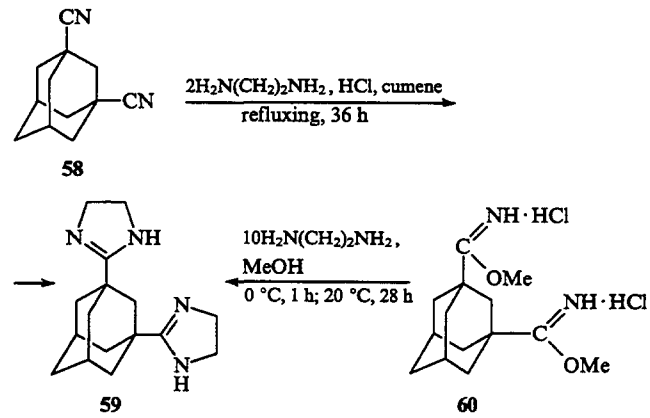
R = Me, Ph, $PhCH_2$, 5-nitrofuryl-2, 2-(benzimidazol-1-yl)ethyl, 3-nitro-3-methylbutyl.

The reaction of hydrochlorides of methyl iminoesters of dicarboxylic acids **56** with two equivalents of *N*-(adamant-1-ylmethyl)ethylenediamine affords compounds **57** containing two *N*-(adamant-1-ylmethyl)imidazoline fragments in 89%–95% yields.[56]

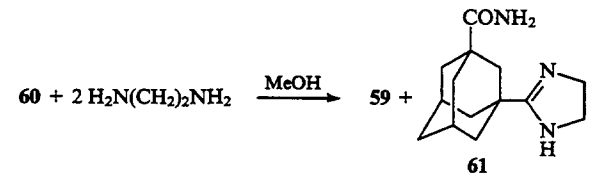


A series of adamantane derivatives containing residues of two identical or different five-membered heterocyclic compounds have been synthesised from 1,3-dicyanoadamantane **58**. Its reaction with ethylenediamine in boiling cumene in the presence of hydrochloric acid gave 1,3-bis(imidazolin-2-yl)adamantane **59** in 86% yield.[56, 57]

The compound **59** is also formed in 83% yield in the reaction of the diiminoester dihydrochloride **60** with a five-fold excess of ethylenediamine in methanol.[56, 57]



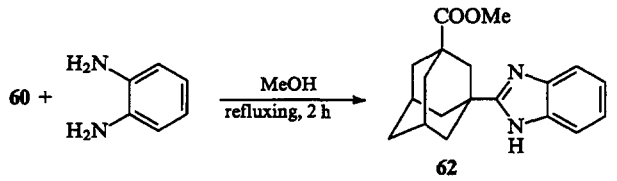
If the reaction of the dihydrochloride **60** involves a stoichiometric amount of ethylenediamine, it leads to the compound **59** and 3-aminocarbonyl-1-(imidazolin-2-yl)adamantane **61**.[56, 57]



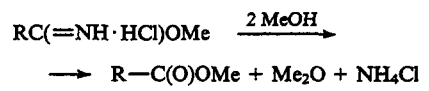
The formation of the amide **61** is accounted for by the fact that one of the iminoester groups undergoes partly the Pinner rearrangement under the reaction conditions

$$R-C(=NH\cdot HCl)OMe \longrightarrow R-C(O)NH_2 + MeCl.$$

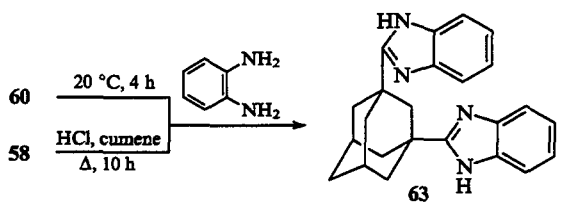
1-(Benzimidazol-2-yl)-3-(methoxycarbonyl)adamantane **62** has been synthesised in 64% yield by the reaction of the dihydrochloride **60** with a stoichiometric amount of *o*-phenylenediamine carried out in boiling methanol.



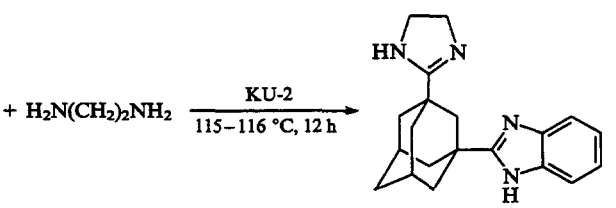
The C(O)OMe group arises *via* the alcoholysis of the iminoester group.[56,57]



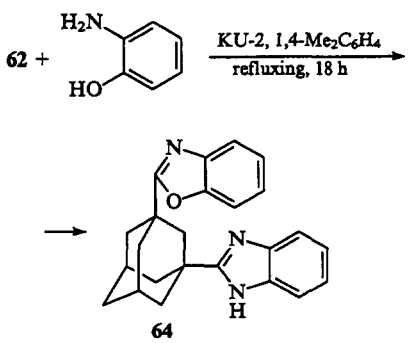
When the dihydrochloride **60** is introduced in the reaction with a fivefold excess of *o*-phenylenediamine at 20 °C, 1,3-bis-(benzimidazol-2-yl)adamantane **63** is obtained in 69% yield. The same compound is formed in 58% yield on refluxing the dinitrile **58** and *o*-phenylenediamine in cumene in the presence of hydrochloric acid.[56,57]



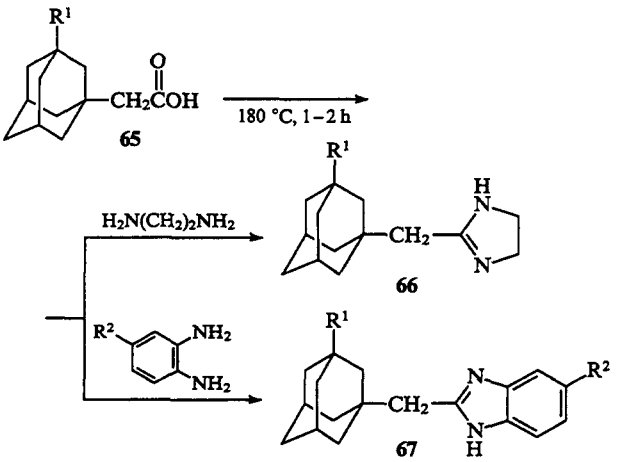
The adamantane derivative containing a benzimidazole residue in the 1-position and an imidazoline fragment in 3-position has been prepared in 71% yield by condensing compound **62** with ethylenediamine in the presence of the KU-2 cation-exchange resin.[56,57]



Refluxing of the compound **62** with *o*-aminophenol in *p*-xylene in the presence of the KU-2 cation-exchange resin with continuous removal of the water liberated affords 1-(benzimidazol-2-yl)-3-(benzoxazol-2-yl)adamantane **64** in 59% yield.[56,57]



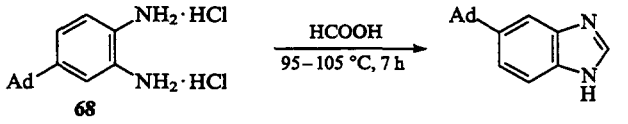
The carboxylic acids of the adamantane series **65** react with ethylenediamine or with *o*-phenylenediamine at a temperature of 180 °C giving the imidazolines **66** (yields 49% and 56%) or benzimidazoles **67** (yields 32%–42%).[58]



66: R^1 = H, OH;
67: R^1 = H; R^2 = H, Me, Cl, Br, OH.

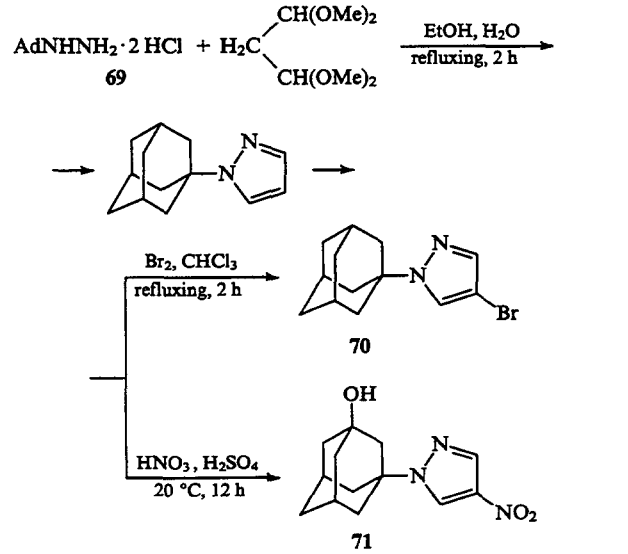
Some of the compounds synthesised were noted to possess antihypertensive and antibacterial activities.[58]

6-(Adamant-1-yl)benzimidazole has been obtained in 98% yield by the cyclocondensation of the bis-hydrochloride **68** with formic acid.[59]

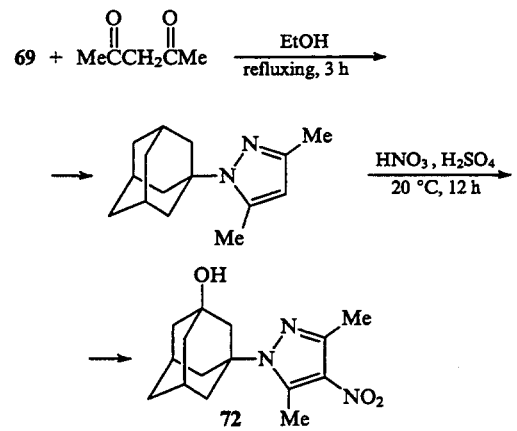


N-(Adamant-1-ylcarbonyl)-*o*-phenylenediamine is converted into 2-(adamant-1-yl)benzimidazole in 96% yield on heating with polyphosphoric acid.[60]

Cyclocondensation of hydrazine or its derivatives with carbonyl compounds is a common method for the synthesis of compounds of the pyrazole series. This method is also used fairly frequently for the synthesis of adamantyl-containing pyrazole derivatives. For example, when *N*-(adamant-1-yl)hydrazine hydrochloride **69** is made to react with the tetramethylacetal of malonaldehyde, 1-(adamant-1-yl)pyrazole is formed in 63% yield; treatment of the latter compound with bromine affords the 4-bromo-derivative **70** (yield 95%). When (adamant-1-yl)pyrazole is treated with a mixture of nitric and sulfuric acids, the nitration of the pyrazole ring and the oxidation of the adamantyl fragment occur simultaneously to give compound **71**, yield 86%.[61]

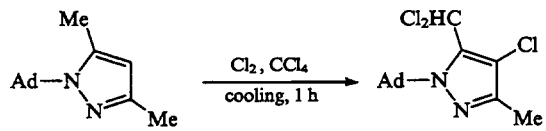


The reaction of pentane-2,4-dione with the dihydrochloride **69** leads to 1-(adamant-1-yl)-3,5-dimethylpyrazole, which is converted into compound **72** in 86% yield on treatment with a mixture of nitric and sulfuric acids.[61]

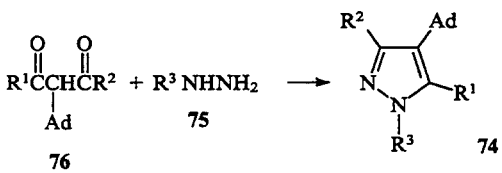


The dihydrochloride **69** reacts with 3-methylpentane-2,4-dione in boiling alcohol (3 h) to give 1-(adamant-1-yl)-3,4,5-trimethylpyrazole (yield 63%).[62]

The chlorination of 1-(adamant-1-yl)-3,5-dimethylpyrazole with chlorine carried out with cooling involves both the pyrazole ring and one of the methyl groups and leads to 1-(adamant-1-yl)-4-chloro-5-dichloromethyl-3-methylpyrazole **73** in 43% yield.[62]

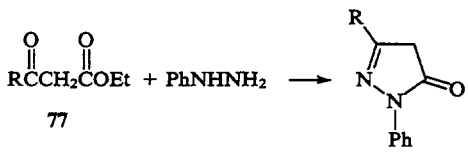


A series of derivatives of 4-(adamant-1-yl)pyrazole **74** have been prepared in 71%–93% yields by the condensation of the hydrazines **75** with the β-diketones **76** carried out in boiling alcohol (1 h), in alcohol at 20 °C (12 h), or without solvent at 130–140 °C (1–1.5 h).[63]



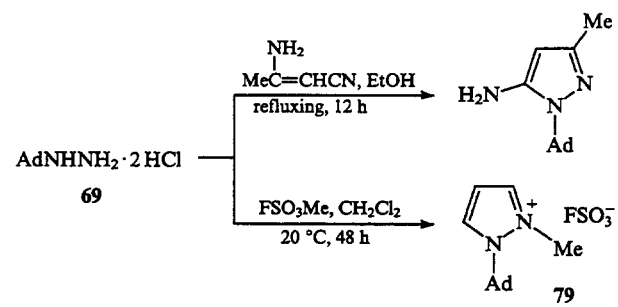
R^1	R^2	R^3	R^1	R^2	R^3
Me	Me	H	Me	Me	Ph
Me	Ph	H	Ph	Ph	Ph
Ph	Ph	H			

In earlier papers,[42,64] the products of the interaction of the β-ketoesters **77** with phenylhydrazine have been identified as the pyrazol-5-one derivatives **78** (yields 67%–80%). The reactions were carried out at 20 °C for 3 h in aqueous acetic acid in the case of the ketoester with R = Ad[42] or without solvent in the case of R = $AdCH_2$.[64]

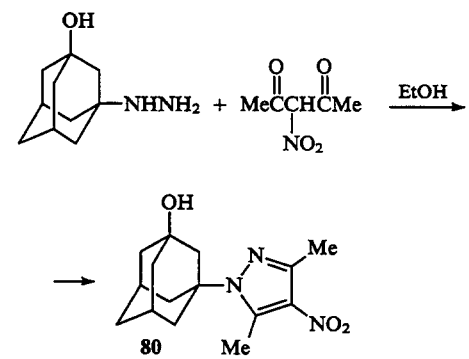


R = Ad, $AdCH_2$.

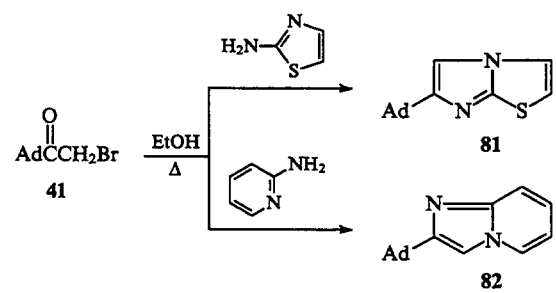
The reaction of the dihydrochloride **69** with β-aminocrotononitrile affords 1-(adamant-1-yl)-5-amino-3-methylpyrazole in 40% yield, whereas the interaction of the compound **69** with methyl fluorosulfonate gives the salt **79** (yield 90%).[61]



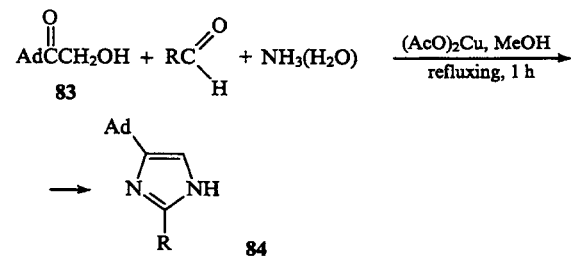
Cyclocondensation of (3-hydroxyadamant-1-yl)hydrazine with 3-nitropentane-2,4-dione leads to compound **80**, which is active against anaerobic bacteria.[65]



The 1-acetyladamantane derivatives, in which one or two hydrogen atoms in the methyl group have been substituted by bromine or by a functional group, have been used as the initial compounds in the syntheses of heteryladamantanes. The bicyclic compounds **81** and **82** were prepared by the condensation of the ketone **41** with 2-aminothiazole and 2-aminopyridine, respectively.[46]

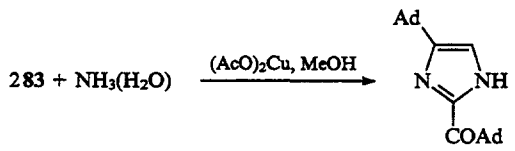


The hydoxy ketone **83** reacts with aldehydes and ammonia in boiling methanol in the presence of copper acetate to give the imidazole derivatives **84**.[66]

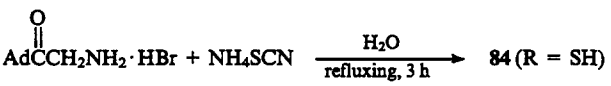


R = H (54%), Pr^i (46%), Ph (54%).

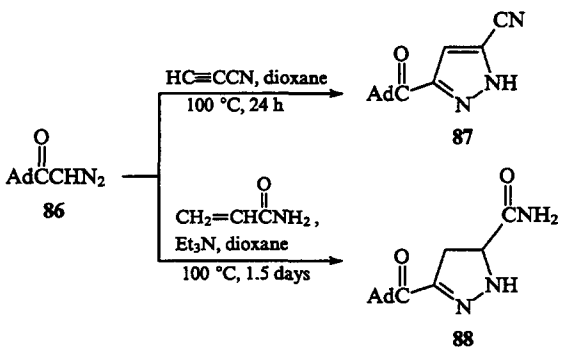
If the hydroxy ketone **83** is made to react with ammonia in the absence of aldehydes, 2-(adamantylcarbonyl)-4-(adamant-1-yl)-imidazole is obtained in 72.5% yield.[66]



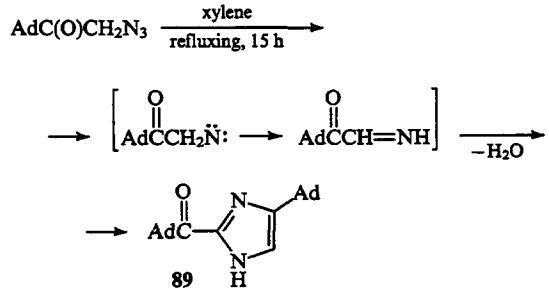
4-(Adamant-1-yl)-2-sulfanylimidazole (**84**, R = SH) has been synthesised in 35% yield by refluxing the hydrobromide **85** with NH_4SCN in water.[66]



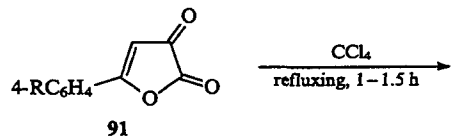
Some investigators have prepared adamantyl-containing pyrazole and pyrazoline derivatives using adamantyl diazomethyl ketones as the initial compounds. The condensation of adamant-1-yl diazomethyl ketone **86** with propiolonitrile or with acrylamide gives 3-adamantylcarbonyl-5-cyanopyrazole **87** (yield 92%) or 3-adamantylcarbonyl-5-aminocarbonylpyrazoline **88** (yield 14%).[60]

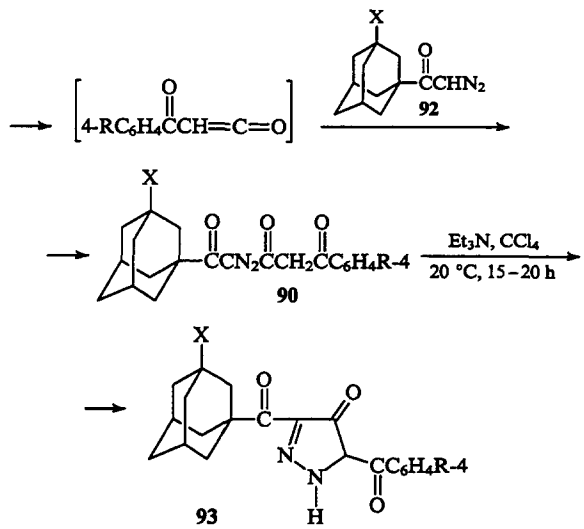


An interesting reaction occurs when adamant-1-yl azidomethyl ketone is heated in xylene; the compound **86** is converted into 2-adamant-1-ylcarbonyl-4-(adamant-1-yl)imidazoline **89** (yield 73%). The authors[67] believe that the process involves the intermediate formation of nitrene, which is converted into imine, and the latter dimerises with intermolecular abstraction of water.



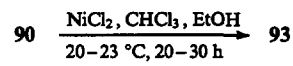
1-(Adamant-1-yl)-5-aryl-2-diazopentane-1,3,5-triones **90**, obtained by heating 5-aryl-2,3-dihydrofuran-2,3-diones **91** with the diazoketones **92** in tetrachloromethane, are converted in the presence of triethylamine into the pyrazolin-4-one derivatives **93** in 63–92% yields.[68]





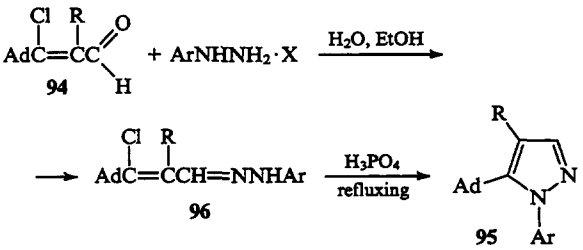
X = H, R = H, Me, OMe, Br, Cl; X = ONO_2; R = H, Br.

The transformation of the derivatives **90** into the corresponding pyrazolin-4-ones **93** can also be carried out with nickel chloride as the catalyst.[69]

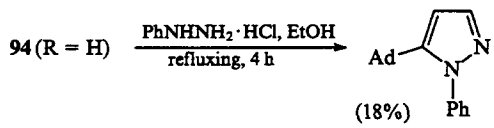


X = H, R = Cl; X = ONO_2, R = H.

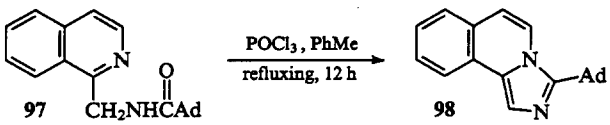
The β-chloroacrolein derivatives $R^1C(Cl)=C(R^2)CHO$ offer considerable synthetic opportunities. These compounds are widely used for the synthesis of various heterocyclic derivatives including heteryladamantanes. For example, the aldehydes **94** have been converted into the pyrazole derivatives **95** by two different procedures.[70,71] One of them[70] involved the reaction of the aldehydes **94** [Ar = 2,4,6-$(NO_2)_3C_6H_2$ and C_5H_5] with phenylhydrazine giving the corresponding hydrazones **96**, which were then converted into the target compounds **95**;[70] whereas according to the other procedure,[71] 5-(adamant-1-yl)-1-phenylpyrazole was obtained without isolation of the intermediate hydrazone **96** (R = H, Ar = Ph).[71]



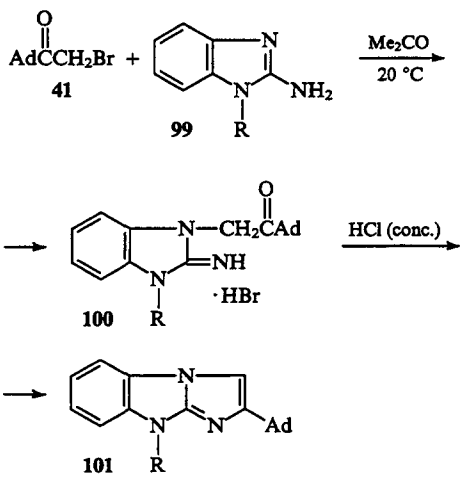
R	Ar	X	t/h		T/°C		Yield (%)	
			95	**96**	**95**	**96**	**95**	**96**
H	Ph	HCl	2	24	160	20	48	73
H	2,4,6-$(O_2N)_3C_6H_2$	–	6	0.25	refluxing (AcOH)	100	41	77
Me	2,4,6-$(O_2N)_3C_6H_2$	–	6	0.2	refluxing (AcOH)	100	54	62



Heating of the isoquinoline derivative **97** with an 18% solution of phosphorus oxychloride in toluene affords 3-(adamant-1-yl)imidazo[5,1-*a*]isoquinoline **98** in 90% yield.[72]

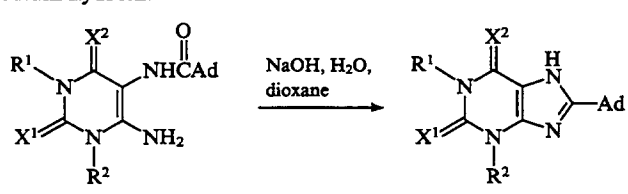


The interaction of the ketone **41** with 2-amino-1-R-benzimidazoles **99** leads to the hydrobromides **100** in quantitative yields; on heating with concentrated hydrochloric acid the latter are converted into the tricyclic compounds **101**, which exhibit immunodepressant properties and are psychotropic inhibitors of cytochrome P-450.[73]



R = Alk, $PhCH_2$, $(CH_2)_2NEt_2$, $(CH_2)_2N(CH_2)_2OCH_2CH_2$.

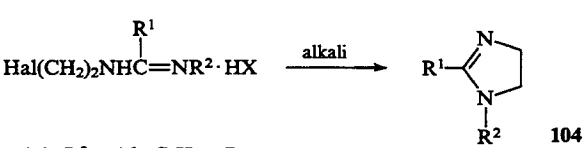
The derivatives of 8-(adamant-1-yl)xanthine or 8-(adamant-1-yl)thioxanthine **102** have been prepared by cyclisation of the amides **103** carried out in dioxane under the action of aqueous sodium hydroxide.[74]



X^1, X^2 = O, S; R^1, R^2 = H, Alk, $CH_2CH{=}CH_2$, $CH_2C{\equiv}CH$.

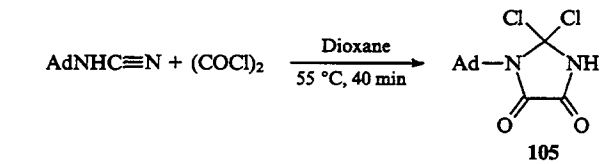
8-(Adamant-1-yl)-1,3-dipropylxanthine, which is an antagonist of adenosine A1, is formed upon heating 6-amino-5-(noradamantanecarbonylamino)-1,3-dipropyluracil with phosphorus oxychloride.[75]

The salts $HalCH_2CH_2NHC(R^1){=}NR^2 \cdot HCl$ cyclise in the presence of alkali to give the imidazoline derivatives **104**.[30]



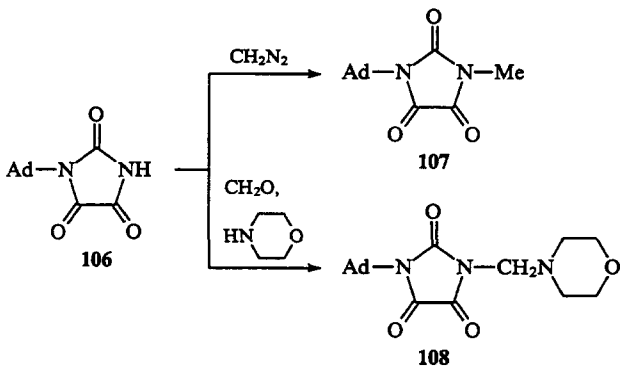
R^1 = Ad; R^2 = Ph, $C_6H_{5-n}R_n$.

1-(Adamant-1yl)-2,2-dichloroimidazolidine-4,5-dione **105**, synthesised from (adamant-1-yl)cyanogen amide and oxalyl chloride, is a promising synthon for the preparation of adamantyl-containing derivatives of imidazolidine-4,5-dione.[76]

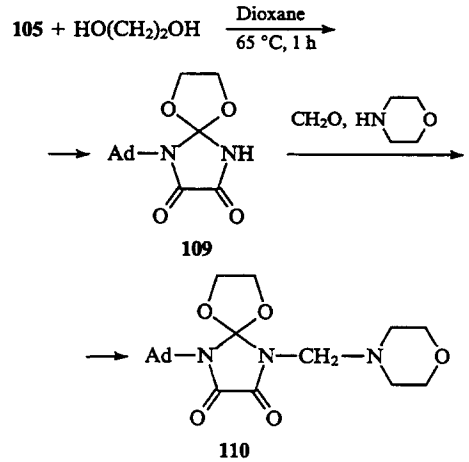


Treatment of the dichloro-derivative **105** with water affords 1-(adamant-1-yl)imidazolidine-2,4,5-trione **106** in 97% yield.[76]

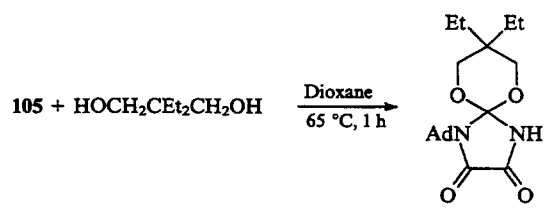
To prepare derivatives of the imidazolidinetrione **106**, namely, compounds **107** and **108** (yields 62% and 92%), the product of the hydrolysis of the dichloride **105** is made to react in situ with diazomethane or with formaldehyde and morpholine.[76]



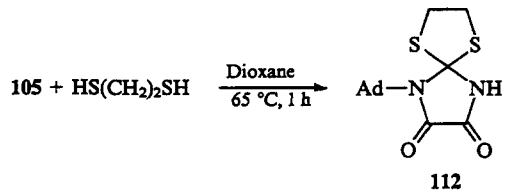
The ketal **109** (yield 48%) is formed in the reaction of adamantylcyanogen amide with oxalyl chloride in the absence of moisture followed by treatment of the resulting dichloride with ethylene glycol; the reaction of the compound **109** with formaldehyde and morpholine leads to the ketal **110** in 77% yield.[76]



Compound **111** is synthesised from the dichloro-derivative **105** and 2,2-diethylpropane-1,3-diol under similar conditions in 11% yield.[76]

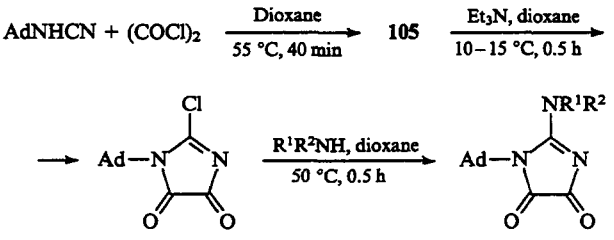


The spiro-compound **112** is prepared in 4% yield by heating the dichloride **105** with ethane-1,2-dithiol in anhydrous dioxane.[76]



112

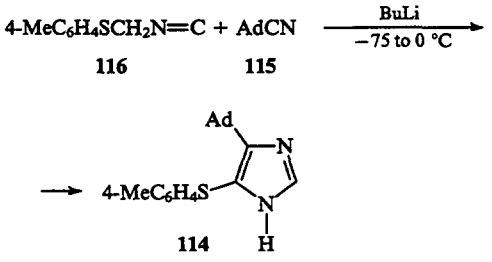
The successive treatment of (adamant-1-yl)cyanogen amide with oxalyl chloride in anhydrous dioxane, with triethylamine, and with secondary amines gives compounds **113** in 65%–90% yields.[76]



113

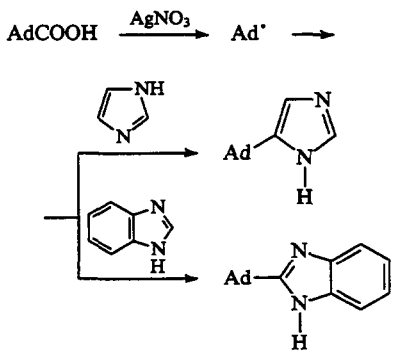
$R^1 = R^2 = (PhCH_2)_2, (Pr^iCH)_2$,
$R^1, R^2 = -O(CH_2CH_2)_2-, -(CH_2)_5-$.

The imidazole derivative **114** is formed in 91% yield in the reaction of the nitrile **115** with the isocyanide **116** at low temperature.[77]



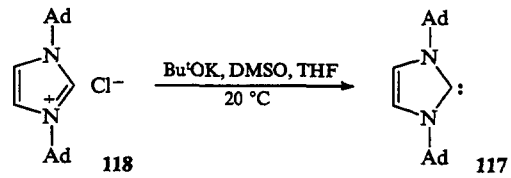
114

The formation of 2-(adamant-1-yl)imidazole or 2-(adamant-1-yl)benzimidazole from adamantane-1-carboxylic acid and imidazole (or benzimidazole) in the presence of silver nitrate is a homolytic reaction. The Ad$^{\bullet}$ radical is generated from adamantane-1-carboxylic acid.[78]



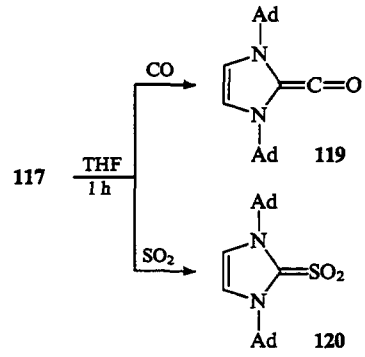
2-(Adamant-1-yl)-1-methylimidazole has been reported[78] to exhibit antiviral activity.

The crystalline carbene **117**, which is stable in the absence of oxygen and moisture, has been synthesised in 96% yield by treating 1,3-di(adamant-1-yl)imidazolium chloride **118** with potassium *tert*-butoxide in dimethyl sulfoxide.[79]



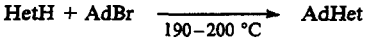
118 **117**

The carbene **117** reacts with carbon monoxide or with sulfur dioxide[80] in THF giving the ketene **119** (yield 34%) or 1,3-di(adamant-1-yl)imidazole-2-thione *S,S*-dioxide **120**.



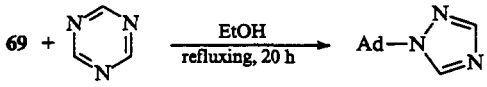
119 **120**

Adamantyl residues have been introduced to the nitrogen atoms in 1,3,4-triazole, 1,2,4-triazole, or benzotriazole by treating these compounds with 1-bromoadamantane with heating.[53]

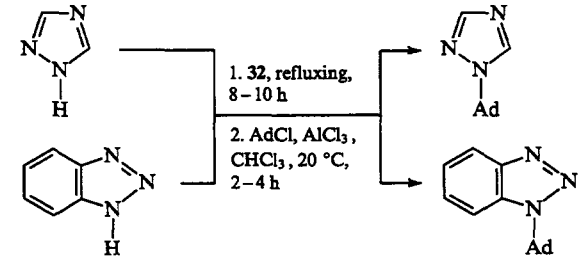


Het = 1,2,4-triazol-1-yl (59%), 1,3,4-triazol-1-yl (3%), benztriazol-1-yl (45%), benztriazol-2-yl (34%).

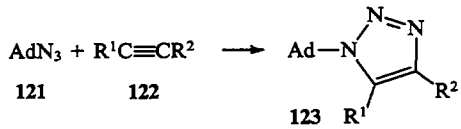
1-(Adamant-1-yl)-1,2,4-triazole is formed in 30% yield on heating *sym*-triazine with the hydrochloride **69** in alcohol.[53]



1-(Adamant-1-yl)-1,2,4-triazole (yield 70%) and 1-(adamant-1-yl)benzotriazole (yield 60%) have been prepared by a two-stage procedure. The first stage consists in the *N*-silylation of the corresponding heterocyclic compounds by refluxing them with disilazane **32**. In the second stage, the products of the *N*-silylation are treated with 1-chloroadamantane in the presence of aluminium chloride at 20 °C.[37]



Japanese scientists[81] have studied systematically the 1,3-dipolar cycloaddition of 1-azidoadamantane **121** to alkynes. The reactions of the azide **121** with alkynes **122** are carried out at 110 °C. The yields of the 1,2,3-triazole derivatives **123** vary from 5% to 84%.[81]

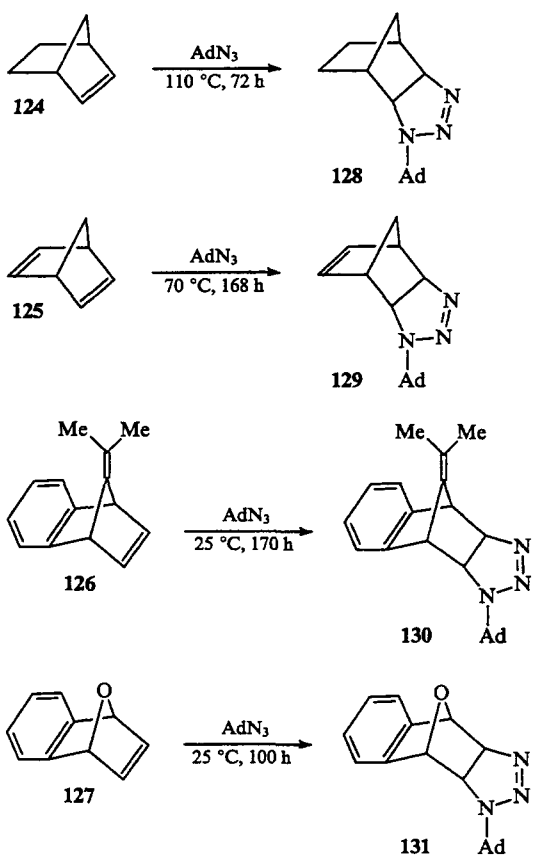


121 **122** **123**

R^1	R^2	Reaction time / h	Yield of **123** (%)
Ph	H	35	21[a]
H	Ad	30	67
H	COOMe	11	84
H	CH_2OH	5	80[b]
H	COOEt	50	77
CH_2OH	CH_2OH	90	32
Ph	Ph	500	17
C(Me)(Et)OH	C(Me)(Et)OH	180	5
COOMe	COOMe	24	77

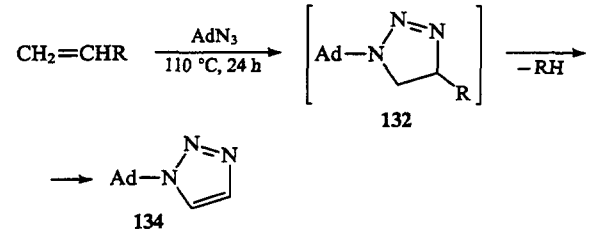
[a] The analogue of **123** with R^1 = H, R^2 = Ph is formed in 60% yield.
[b] The analogue of **123** with R^1 = CH_2OH, R^2 = H is formed in 11%.

The alicyclic alkenes **124**–**127** enter into the 1,3-dipolar cycloaddition with adamantyl azide giving the 1,2,3-triazoline derivatives **128**–**131**, their yields ranging from 40% to 70%.[81]



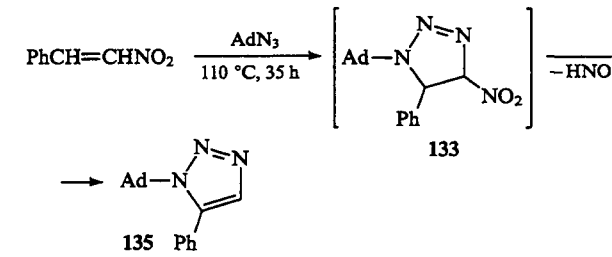
The azide **121** reacts with the ester CH_2 = CHCOOEt at 20 °C and is thus converted into 1-(adamant-1-yl)-4-ethoxycarbonyl-1,2,3-triazoline in 85% yield over a period of 336 h.[81]

The reaction of the azide **121** with alkenes CH_2 = $CHNO_2$, PhCH = $CHNO_2$, and PhSOCH = CH_2 is more complex. In all these cases, the adducts **132** and **133** formed initially eliminate HNO_2 and PhSOH molecules, and the reaction products are the corresponding 1,2,3-triazole derivatives **134** (yields 73% and 88%) and **135** (yield 66%).[81]



132 **134**

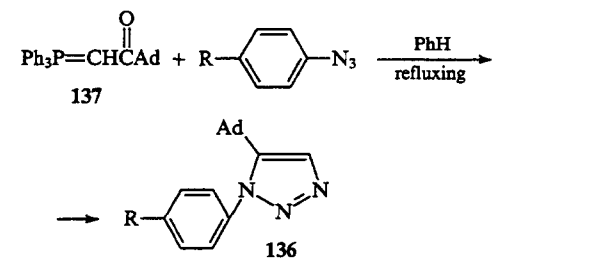
R = NO_2, SOPh.



133 **135**

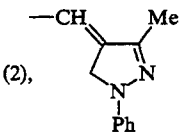
The adduct **131** readily eliminates a C_8H_6O molecule giving rise to 1-(adamant-1-yl)-1,2,3-triazole **134** (yield 71%).[81]

To prepare the derivatives of 1,2,3-triazole **136**, phosphorus ylide **137** has been used as the second component in the reaction with the azides 4-$RC_6H_4N_3$. The yields of the adducts **136** vary from 60% to 99%.[82]



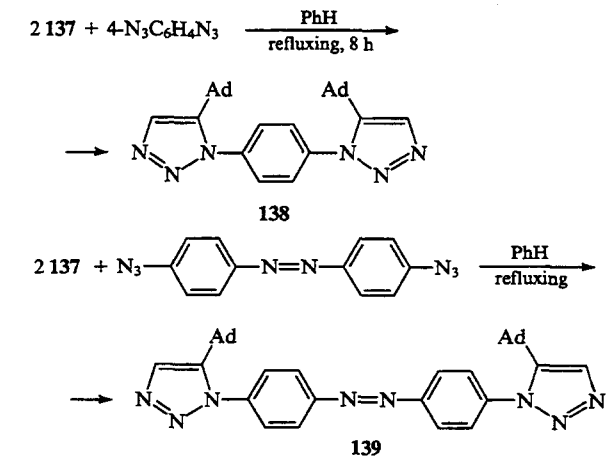
137 **136**

R (reaction time / h) = H (8), F(7), COOMe (3.5), COMe (1.5), CHO (1), NO_2 (0.5), SO_2CF_3 (0.5), N = NPh (5), N = $NC_6N_4NO_2$-4 (2),



(3).

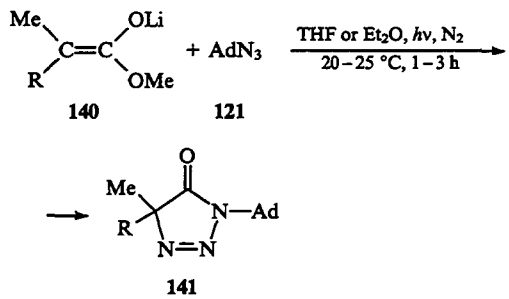
Compounds **138** and **139**, which contain two 1,2,3-triazole nuclei each, are obtained in 98% and 93% yields by the interaction of the ylide **137** with 1,4-bis(azido)benzene or with 4,4′-bis(azido)diphenyldiazene.[82]



138 **139**

The aryl azides containing electron-donating substituents in the *para*-position with respect to the azido group react with the ylide **137** with difficulty or do not react at all.[82]

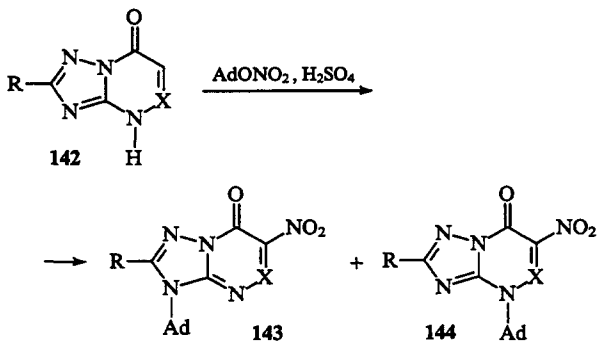
The ester enolates **140** react with the azide **121** on exposure to the radiation from a mercury or mercury-xenon high-pressure lamp to give the 1,2,3-triazol-5-one derivatives **141** in 60%–70% yields.[25,83]



140 **121** **141**

R = Me, Bu^t.

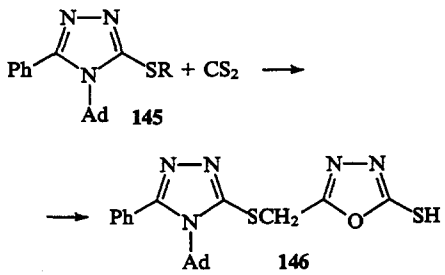
Rusinov et al.[84] accomplished simultaneous introduction of an adamantyl radical and of a nitro-group by treatment of the bicyclic compound **142** with adamant-1-yl nitrate in the presence of concentrated sulfuric acid. The reaction gave a mixture of two compounds **143** and **144** in an overall yield of >70%.[84]



142 **143** **144**

R = H, Me; X = N, CH, CMe, CCF_3.

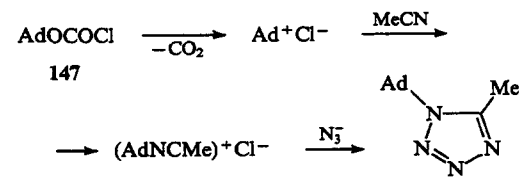
The 1,3,4-triazole derivatives **145**, which contain in the 2-position the residue of thioglycolic acid hydrazide, react with carbon disulfide to give compounds **146**.[85]



145 **146**

R = $CH_2CONHNH_2$.

1-(Adamant-1-yl)-5-methyltetrazole has been obtained in 46% yield by the reaction of the chlorocarbonate **147** with acetonitrile and sodium azide at room temperature over a period of 20 h.[86]



147

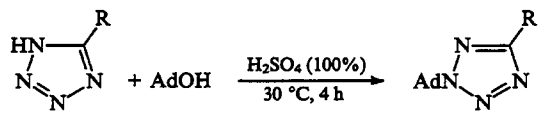
The tetrazoles **148** containing alkyl, alkenyl or aryl substituents in the 5-position have been prepared by the interaction of 1-iodoadamantane with silver hexafluoroantimonate and with the corresponding carbonitriles in the presence of the quaternary ammonium salt $Et_4N^+N_3^-$.[86]

148

R = Me (71%), Et (29%), Pr (64%), Pr^i (43%), Ph (21%), $CH_2=CH$ (20%), $CH=CMe_2$ (14%), $PhCH=CH$ (49%).

When tetrazole is heated with the bromo-derivative of adamantane at 190–200 °C, two compounds are formed, namely, 1-(adamant-1-yl)tetrazole (yield 24%) and 2-(adamant-1-yl)tetrazole (yield 30%).[53]

The direct adamantylation of the tetrazole ring has been carried out by treating 5-methyltetrazole and 5-phenyltetrazole with adamantan-1-ol in the presence of sulfuric acid.[87]

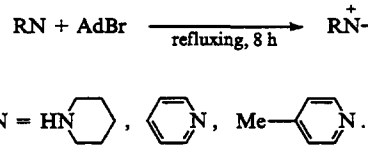


R = Me (57%), Ph (84%).

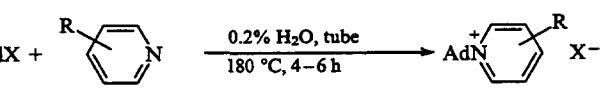
4. Six-membered heterocycles

1-(Adamant-1-yl)-4,4-diarylpiperidines[88] and *N*-[2-(adamant-1-yl)ethyl]piperidine hydrochloride[41] have been patented as stimulants of the central nervous system.

By refluxing AdBr with piperidine, pyridine, or 4-picoline, the corresponding salts have been synthesised; they have been recommended as antiviral agents.[89]



In a study of reactions of pyridine and its derivatives with 1-bromoadamantane and 1-iodoadamantane, it has been shown that the successful formation of the salts **149** requires that a small amount of water be present in the reaction mixture.[90]



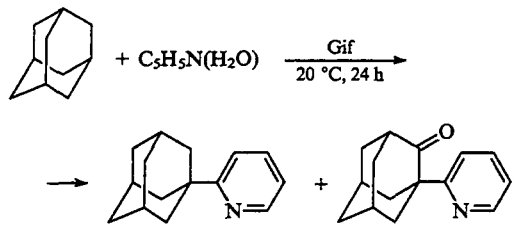
149

X	R	Yield (%)
Br	H	97
I	H	96
Br	3-Me	62
Br	4-Me	80
Br	3-$CONEt_2$	70
Br	4-(pyridyl-4)	98

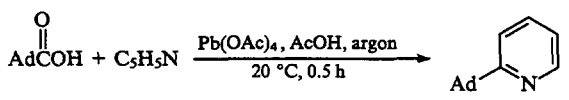
When the reactions are carried out in the absence of water, the salts **149** are formed in low yields. The process should be carried out at 230–250 °C. The corresponding salt with quinoline is not formed.[90] Steric factors play an important role in this reaction: for

example, the salts **149** cannot be obtained from adamant-1-yl halides with 2-picoline, 2,3-lutidine, or 2,4,6-collidine.

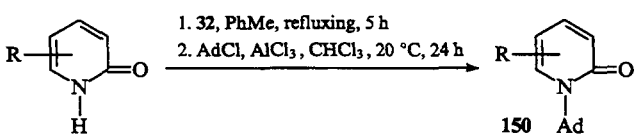
A hydrogen atom in the adamantane molecule can be substituted by a pyridyl radical in the presence of a Gif system ($Fe-O_2-Zn-AcOH-C_5H_5N$). For example, the reaction of adamantane with pyridine in the presence of this system at 20 °C gives rise to two products: 2-(adamant-1-yl)pyridine and 1-(2-pyridyl)adamant-2-one.[91]



The hydrogen atom in the 2-position of pyridine can be substituted by the adamantane residue by a radical mechanism. 2-(Adamant-1-yl)pyridine is formed in 20% yield when a mixture of adamantane-1-carboxylic acid and pyridine is irradiated with a Hanovia lamp (100 W) in the presence of lead(IV) acetate under an argon atmosphere.[91]



A method has been developed for the substitution of the hydrogen atom at the nitrogen atom in the 2-pyridone derivatives by the adamantyl fragment.[37] For this purpose, this hydrogen atom is substituted by the $SiMe_3$ group by treating the initial compounds with disilazane **32**, and then the *N*-silylated products are made to react with chloroadamantane in the presence of aluminium chloride. The electronic nature of the substituents in the heterocyclic nucleus of the initial compound exerts the crucial influence on the yields of the reaction products. In the case where electron-withdrawing substituents (Cl or NO_2) are present in the 5-position, the yields of compounds **150** are 53% or 77%. When the initial compound contains an electron-donating methyl group in the 3-, 4-, or 5-position, the yields of the products **150** are much lower (25%, 30%, and 30%, respectively).[37]

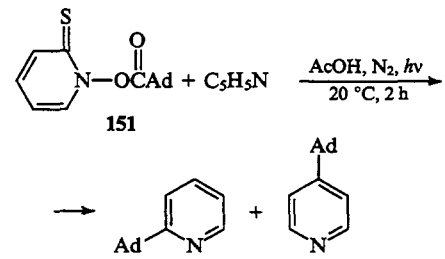


R = 5-Cl, 5-NO_2, 3-Me, 4-Me, 5-Me.

The interaction of 2-quinolone with chloroadamantane under similar conditions leads in 72% yield to (adamant-1-yl)-2-quinolone (the position of the adamantyl substituent has not been mentioned in the paper cited).[37]

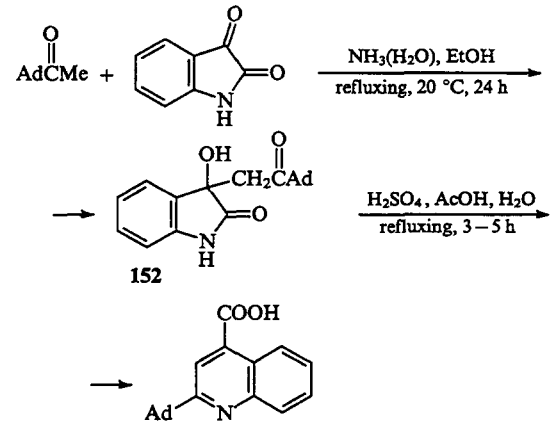
1-(Adamant-1-yl)-2-pyridone has been obtained in 30%–52% yield by the reaction of the chloro-derivative of adamantane with 2-(trimethylsilyloxy)pyridine. The reaction is carried out in the presence of aluminium chloride at 20 °C for 12 h.[50,51]

The reaction of the compound **151** with pyridine in the presence of acetic acid under irradiation with two tungsten lamps (300 W) leads to a complex mixture of products, among which 2-(adamant-1-yl)pyridine (yield 27.5%) and 4-(adamant-1-yl)pyridine (yield 14%) have been identified.[92]



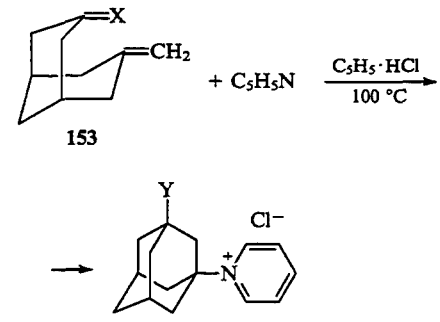
N-(Adamant-1-yl)pyridinium salts are obtained from bromoadamantane and pyridine. If this reaction is carried out in a sealed tube at 230 °C for 30 h, the yield of adamantylpyridinium bromide is 69%,[93] whereas in the reaction carried out at 180 °C for 6 h, the yield reaches 97%.[94] When bromoadamantane reacts with pyridine in the presence of sodium perchlorate in nitromethane at 0 °C for 4 h and then at 20 °C for 14 h, *N*-(adamant-1-yl)pyridinium perchlorate is formed in 54% yield.[95]

Adamant-1-yl methyl ketone condenses with isatin in the presence of ammonia to give the hydroxy diketone **152**, which is converted into 2-(adamant-1-yl)quinoline-4-carboxylic acid in 94% yield in the presence of sulfuric acid. If the reaction is carried out without isolation of the compound **152**, this acid is formed in a yield of only 5%–10%.[96]



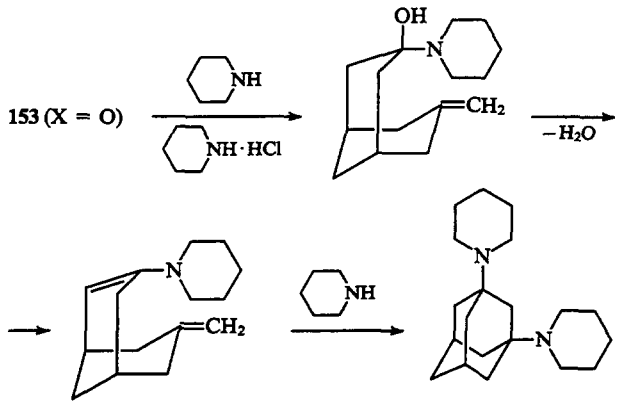
2-(Adamant-1-yl)quinoline has been synthesised in 75% yield by refluxing a mixture of adamant-1-yl methyl ketone with 2-aminobenzaldehyde in an alcoholic solution of potassium hydroxide for 1 h.[96]

In the presence of a weak protic acid, pyridinium chloride, 3,7-dimethylenebicyclo[3.3.1]nonane (**153**, X = CH_2) and 3-methylenebicyclo[3.3.1]nonan-7-one (**153**, X = O) react with pyridine yielding the corresponding pyridinium salts.[97]

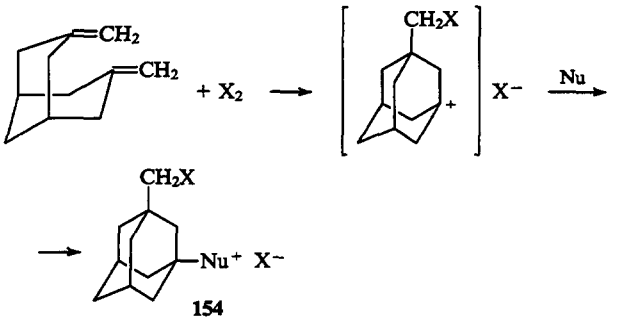


X = CH_2, Y = Me; X = O, Y = OH.

The reaction of the compound **153** (X = O) with piperidine in the presence of piperidine hydrochloride follows a different pathway: piperidine adds to the oxo-group, then a molecule of water is eliminated, and finally, the ring closure occurs.[98]



Salts of heteryladamantanes can be obtained from the precursors of adamantane, namely, compounds **153** (X = CH_2) or 1,3-dehydroadamantane, via conjugated intermolecular haloamination. A number of salts of 1-heteryl-3-halomethyladamantanes **154** have been synthesised by the reaction of the compound **153** (X = CH_2) with pyridine bases or with quinoline.[99]

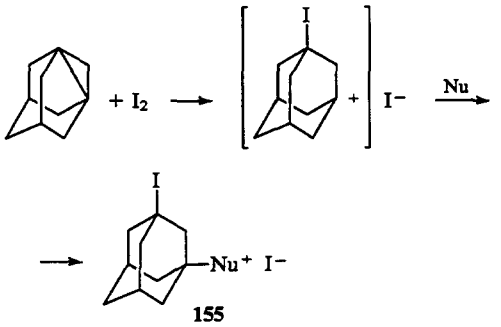


154

X = I: Nu — pyridine, quinoline;
X = Br: Nu — pyridine, 2-picoline, quinoline.

The reactions with bromine were carried out at temperatures from −10 to 0 °C over a period of 10 days, whereas the reactions with iodine were conducted at 20 °C over 10 days. The yields of the salts **154** varied from 44% to 84%.[99]

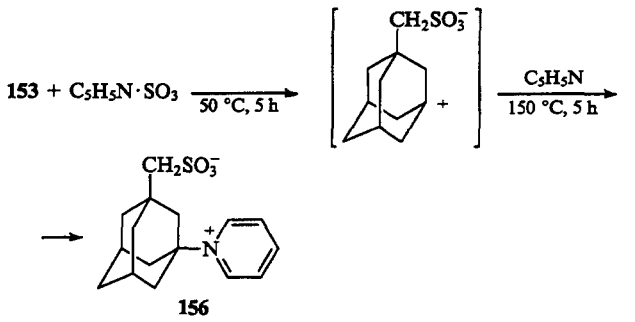
The salts **155** have been prepared in 28%–68% yields by the reactions of 1,3-dehydroadamantane with heterocyclic amines and iodine.[99,100]



155

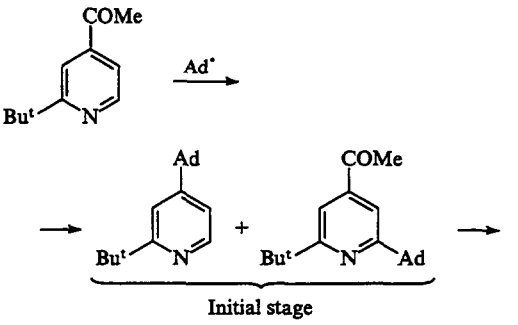
Nu — pyridine, 3-picoline, quinoline, $MeN\overline{CH_2CH_2OCH_2CH_2}$.

The diene **153** (X = CH_2) reacts with pyridine-sulfotrioxide in pyridine giving the salt **156** in 70% yield.[101]

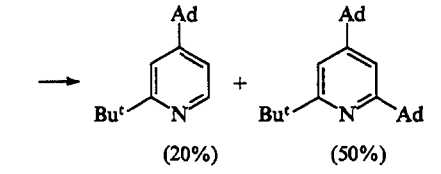


156

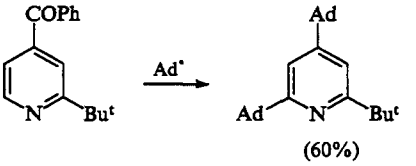
In 1976, a new S_R reaction involving the Ad$^\bullet$ radical was reported.[102] The interaction of adamantane-1-carboxylic acid with ketones of the pyridine series in the presence of ammonium peroxydisulfate and silver nitrate at 80 °C in aqueous ammonia and acetonitrile leads to the generation of adamantyl radical, which substitutes the acyl groups, the hydrogen atoms, or both in pyridine bases.



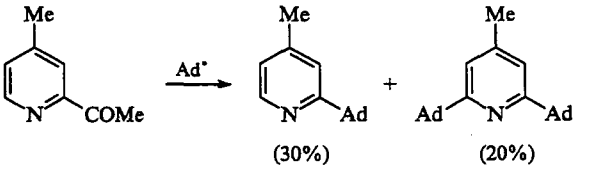
Initial stage



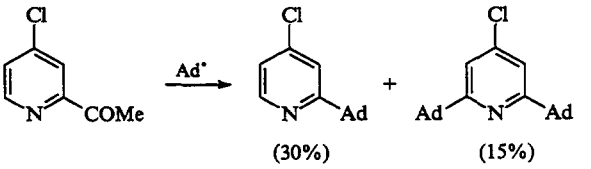
(20%) (50%)



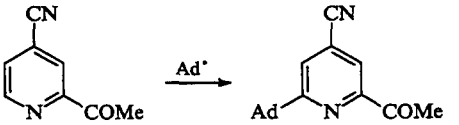
(60%)



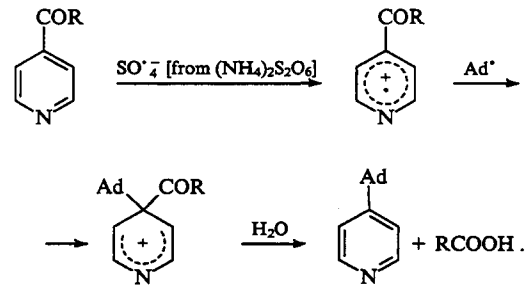
(30%) (20%)



(30%) (15%)



The following scheme of the homolytic *ipso*-substitution has been suggested:[102]



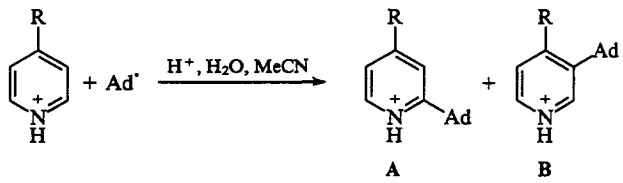
More recently this reaction has been studied [103] in relation to other compounds and a scheme for the formation of the Ad$^{\bullet}$ radical and of the $SO_4^{\bullet-}$ radical-anion has been suggested.

$$S_2O_8^{2-} + Ag^+ \longrightarrow Ag^{2+}SO_4^{2-} + SO_4^{\bullet-}$$

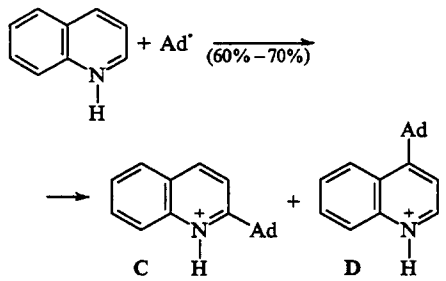
$$SO_4^{\bullet-} + Ag^+ \longrightarrow SO_4^{2-} + Ag^{2+}$$

$$AdCOOH + Ag^{2+} \longrightarrow AdCO_2^{\bullet} + Ag^+ + H^+$$

$$AdCO_2^{\bullet} \longrightarrow Ad^{\bullet} + CO_2$$

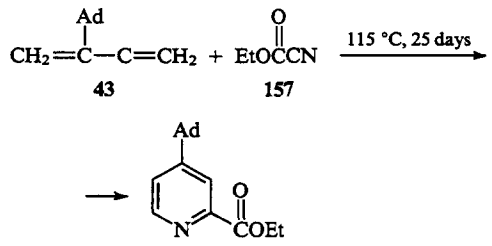


R = CN, COMe; **A** : **B** = 92 : 8.

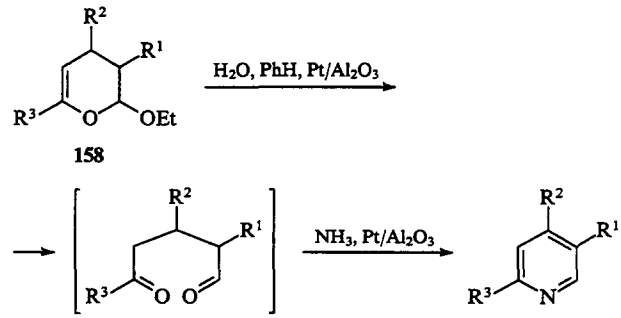


C : **D** = 97 : 3.

4-(Adamant-1-yl)-2-ethoxycarbonylpyridine has been synthesised in 42% yield by cycloaddition of the diene **43** to the nitrile **157**.[47]

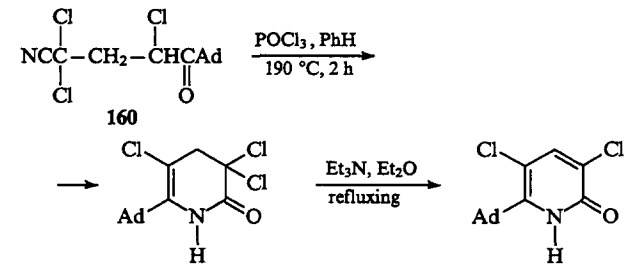


The reaction of the 2,3-dihydropyran derivatives **158** with water in the presence of a platinum catalyst followed by treatment in situ of the resulting 1,5-dicarbonyl compounds with ammonia leads to the pyridine bases **159**, their yields being 32% – 42%.[93]

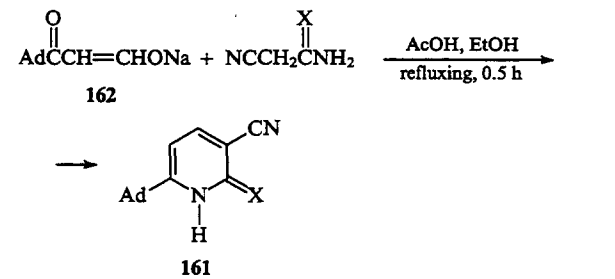


R^1	R^2	R^3
Ad	H	H
$AdCH_2$	H	H
H	$AdCH_2$	H
H	H	Ad

On heating with phosphorus oxychloride in an autoclave the oxonitrile **160** cyclises giving 2-(adamant-1-yl)-3,5,5-trichloro-4,5-dihydro-6-pyridinone in 41% yield; the latter is converted into 6-(adamant-1-yl)-3,5-dichloro-2-pyridone (yield 87%) on treatment with triethylamine.[104]

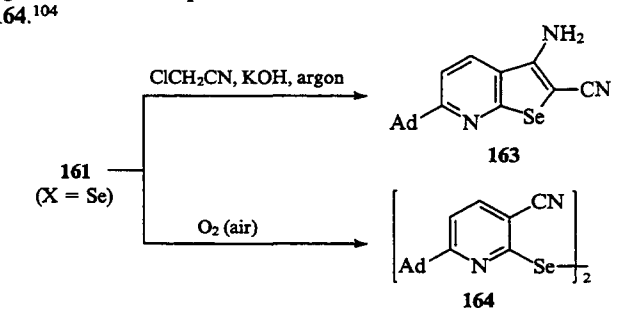


6-(Adamant-1-yl)-3-cyano-2-pyridone (**161**, X = O) and 6-(adamant-1-yl)-3-cyano-2-pyridoselenone (**161**, X = Se) have been synthesised in 33% and 52% yields by refluxing the sodium derivative **162** with compounds $NCCH_2C(X)NH_2$.[105]

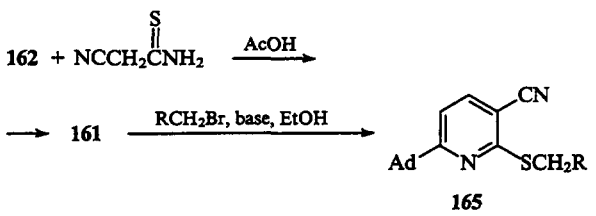


X = O, Se.

The selenone **161** (X = Se) reacts with chloroacetonitrile in the presence of a 10% aqueous solution of potassium hydroxide under an inert atmosphere affording the selenopheno-[2,3-*b*]pyridine derivative **163** (yield 70%), whereas during storage in air the compound **161** is converted into the diselenide **164**.[104]

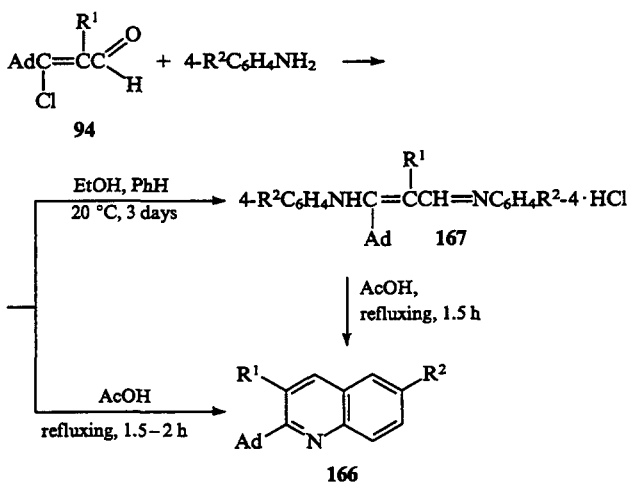


The sulfur-containing analogue **161** (X = S) has been synthesised in 62% yield by the cyclocondensation of the sodium derivative **162** with cyanothioacetamide. The pyridine-2-thione **161** (X = S) thus obtained reacts with the bromo-derivatives RCH_2Br in the presence of bases to give the sulfides **165** (yields 58%–64%).[106]



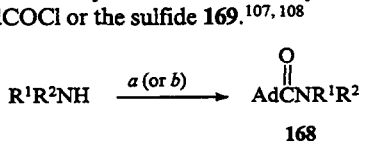
X = S; R = COOMe, COOEt, CN.

The quinoline derivatives **166** are formed in 43%–63% yields in the reaction of the aldehydes **94** with aniline or 4-bromoaniline [70, 71] (in some cases, the intermediate salts **167** can be isolated).



R^1 = H, R^2 = H, Br; R^1 = Me, R^2 = H, Br.

The adamantane-1-carboxamides **168** have been prepared in 72%–92% yields from secondary amines and the acid chloride AdCOCl or the sulfide **169**.[107, 108]



R^1 = Et, R^2 = Et;

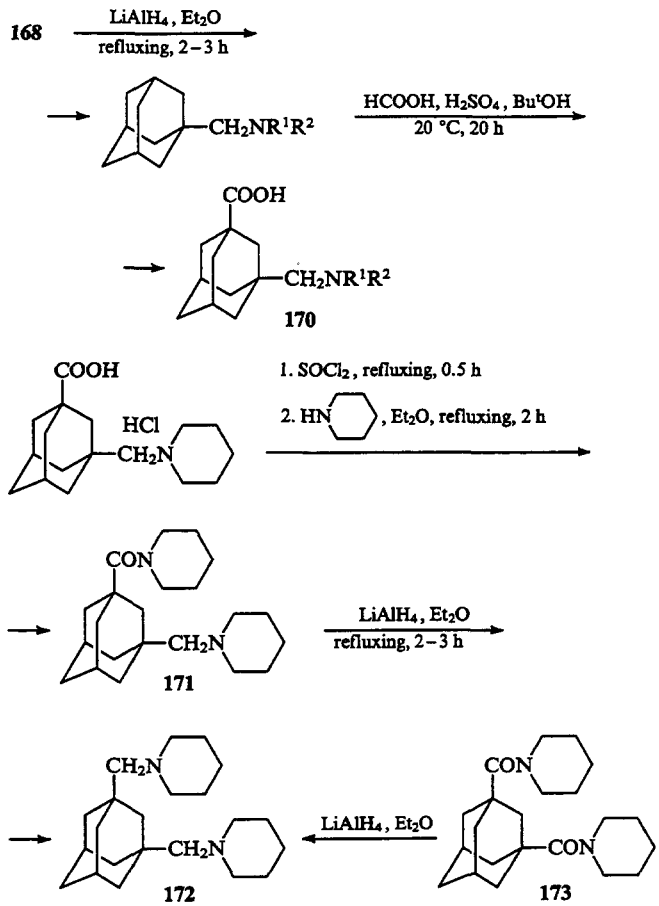
$R^1 + R^2 = -(CH_2)_4-, -(CH_2)_5-, -(CH_2CH_2)_2O-$;

R^3 = Me, H_2N^+ ;

(*a*) AdCOCl, Et_2O (0–20 °C, 1–12 h);

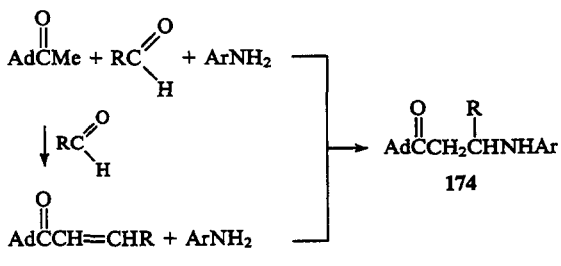
(*b*) $AdCSR^3$ (**169**) (refluxing, 4–6 h).

The amides **168** have been converted into biologically active compounds **170** via several consecutive stages. First, they were reduced with lithium tetrahydroaluminate to amines (yields 94%–97%) and the latter were converted into the carboxylic acids **170**. The hydrochloride of the amino acid **170** [$R^1 + R^2 = -(CH_2)_5-$] was made to react with thionyl chloride and piperidine to give the corresponding amide **171** (yield 91%), which was then reduced with lithium tetrahydroaluminate to the diamine **172**. The latter can also be obtained by the reduction of the diamide **173** (yield 79%).[107]



Hydrochlorides of the acids **170** exhibit analgesic and anti-inflammatory activities.[107]

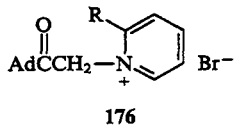
To synthesise the aminoketones **174**, two methods have been suggested, namely, the Mannich reaction of 1-acetyladamantane with aldehydes and arylamines and the addition of arylamines to the α,β-unsaturated ketones **175**, generated from acetyladamantane and aldehydes.[109]



R = pyridyl-3, pyridyl-4, quinolyl-2, quinolyl-6, quinolyl-7;
Ar = Ph, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, naphthyl-2.

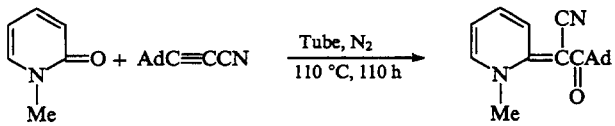
The aminoketones **174** possess a broad spectrum of biological activity: neurotropic, antiviral, antibacterial, fungicidal, psychotropic, and hepatoprotecting activities.[109]

Heating of the ketone **41** with 2-aminopyridine or with 2-picoline in alcohol leads to the corresponding salts **176** (yields 96% and 50%).[46]



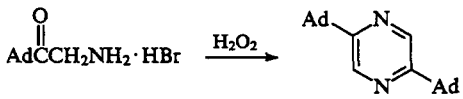
$R = NH_2$, Me.

An unexpected result was obtained when 1-methyl-2-pyridone was heated with 2-(adamant-1-yl)ethyne-1-carbonitrile: compound **177** was found among the reaction products.[110]



177

The hydrobromide **85** is converted into 2,5-di(adamant-1-yl)pyrazine in 30.5% yield on treatment with hydrogen peroxide.[66]



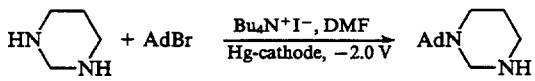
Piperazine derivatives **178** exhibiting an antiviral activity have been prepared by refluxing bromoadamantane with piperazine or with its *N*-monosubstituted derivatives.[89]



178

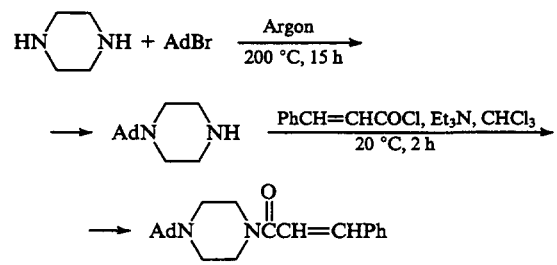
R = H, $HOCH_2CH_2$, Ad, Ph, 3-Cl,4-MeC_6H_3.

Hexahydropyrimidine reacts with AdBr under conditions of phase-transfer catalysis at a mercury cathode in a cell with a double G-5 diaphragm giving the corresponding *N*-adamantyl derivative in 70% yield.[111]



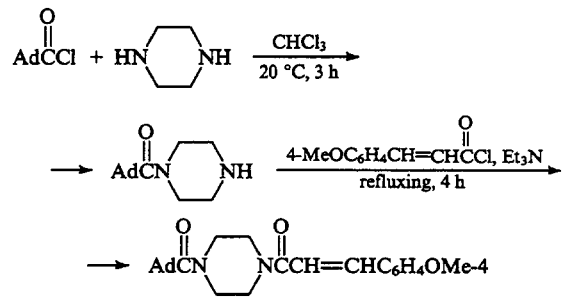
N-(Adamant-1-yl)hexahydropyrimidine and *N*-adamantyl-containing derivatives of other pyrimidines, pyridazines, and pyrazines obtained in a similar way are active against influenza viruses of the H_2N_2A/Singapore type.[111]

N-(Adamant-1-yl)piperazine, synthesised in 85% yield by heating piperazine with bromoadamantane in an autoclave, has been made to react with cinnamoyl chloride in the presence of triethylamine. The compound **179** formed in this reaction (yield 85%) enhances the cerebral circulation.[112]



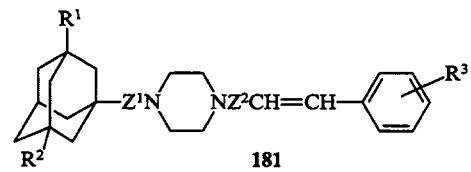
179

It has been reported in a patent[113] that *N*-(adamant-1-ylcarbonyl)piperazine has been synthesised in 40% yield by the acylation of piperazine with the acid chloride AdCOCl. The product of acylation was converted into the *N*,*N*′-diacylpiperazine **180** in 90% yield.[113]



180

Compounds of the general formula **181** have been patented as substances active with respect to the central nervous system.[113]

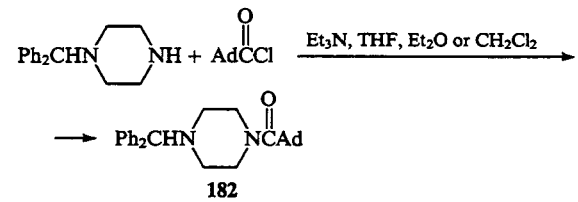


181

R^1 = H, Me, MeO; R^2 = H, Me; R^3 = H, Me, MeO, Cl, F;

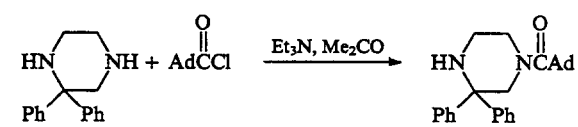
Z^1, Z^2 = CO, CH_2.

The acylation of *N*-(diphenylmethyl)piperazine with the chloride AdCOCl leads to compound **182** exhibiting high antihistamine and antiallergic activities.[114]

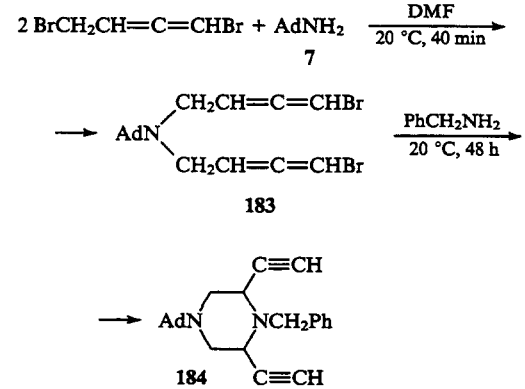


182

1-(Adamant-1-ylcarbonyl)-3,3-diphenylpiperazine has been synthesised from 3,3-diphenylpiperazine and adamantane-1-carboxylic acid chloride in the presence of triethylamine.[115]

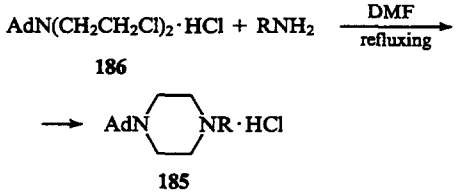


1,4-Dibromobuta-1,2-diene reacts readily with the amine **7** giving the dibromo-derivative **183**, which is converted into the 1,4-disubstituted piperazine **184** on treatment with benzylamine.[116]



184

In 1972, a new method was patented for the synthesis of the *N*-adamantylpiperazines **185**. The method involves cyclisation of the hydrochloride of (adamant-1-yl)bis(2-chloroethyl)amine **186** under the action of primary amines (the yield of compounds **185** ranges from 53% to 70%).[117]



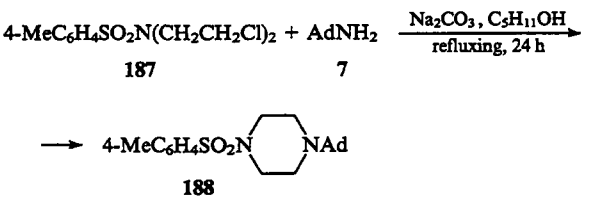
R = cyclo-C_6H_{11}, Pr, Pr^i, Bu, Bu^t, Ph, $PhCH_2$, H.

Later, this method was used to prepare a wider set of 1-(adamant-1-yl)-4-R-piperazines with R = H, Me, Et, Pr, Pr^i, Bu^t, C_5H_{11}, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_8H_{15}, Ad, Ph, $PhCH_2$ and CH_2CH_2OH.

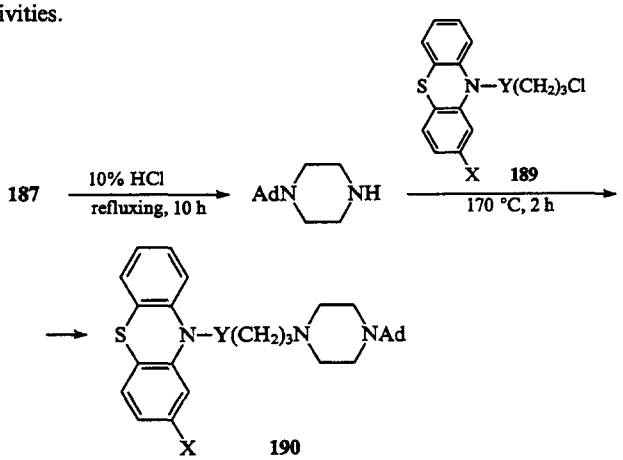
The majority of the hydrochlorides **185** increase the blood pressure. The compounds with R = Et or CH_2CH_2OH have a hypotensive effect, those with R = cyclo-C_6H_{11} slow down cardiac activity, and the compound with R = Bu^t exhibits a vasodilatory activity and an adrenaline-blocking effect.[118]

Compounds like **185** are active with respect to the central nervous system, exhibit analgesic and hypothermal activities, and modify the soporific effects of Hexanal, Medinal and chloral hydrate.[119]

1-(Adamant-1-yl)-4-(tolyl-*p*-sulfonyl)piperazine **188** has been synthesised in 87.5% yield by the condensation of the dichloro-derivative **187** with the amine **7**.[120]

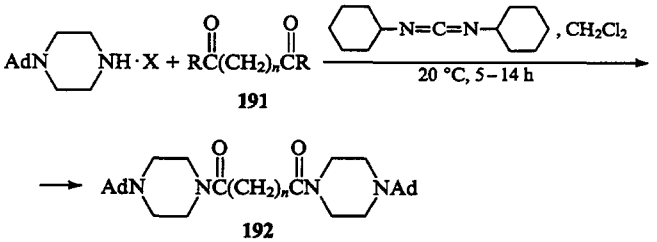


On refluxing in hydrochloric acid compound **188**, is converted into 1-(adamant-1-yl)piperazine (yield 84%), which reacts with the chloro-derivatives **189** to give phenothiazines **190** (yields 49%–50%);[120] the latter exhibit vasodilatory and psychotropic activities.



X = CF_3, Cl; Y = CH_2, CO.

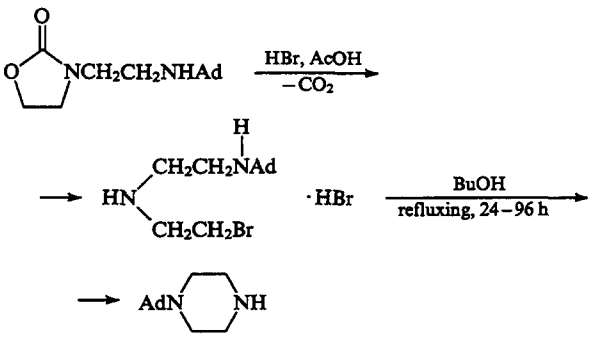
1-(Adamant-1-yl)piperazine and its hydrochloride react with the dicarboxylic acids **191** (in the presence of cyclohexylcarbodiimide) or with the corresponding acyl chlorides giving the diamides **192** (yields 58% and 60%).[121]



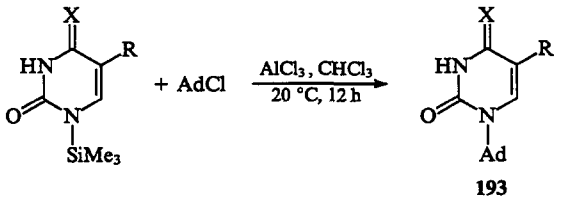
n	R	X
2	OH	–
8	Cl	HCl

The diamide **192** (*n* = 8) possesses an immunodepressive activity.[121]

Treatment of 3-[2-(adamant-1-ylamino)ethyl]oxazolidin-2-one with hydrobromic acid in glacial acetic acid affords a salt, which cyclises to 1-(adamant-1-yl)piperazine on heating in butyl alcohol.[122]

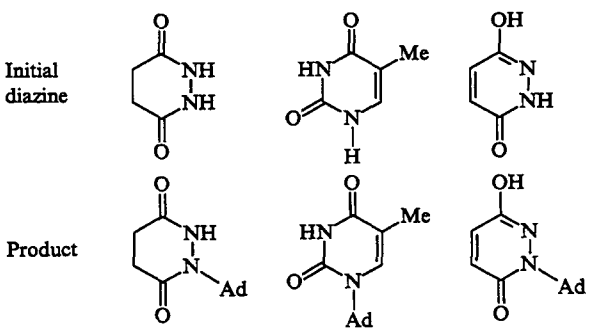


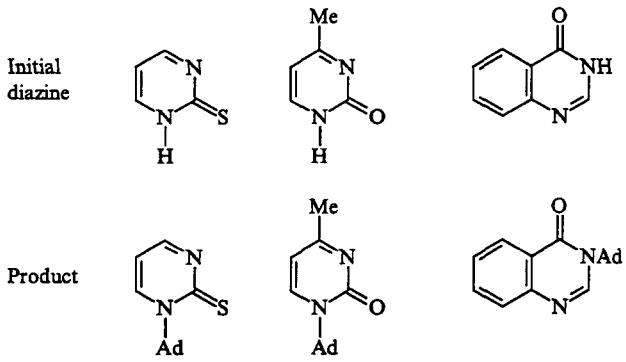
To introduce an adamantyl radical to the nitrogen atom of the cyclic diazines, two procedures have been developed. One of them involves the initial preparation of trimethylsilyl derivatives of diazines, which are then treated with 1-chloroadamantane in the presence of aluminium chloride. Compounds **193** have been synthesised in this way in 38%–53% yields.[50]



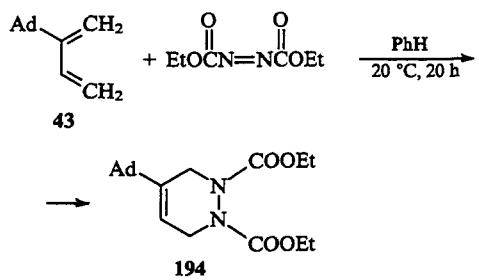
X = O, R = H, F; X = S, R = H.

The second one-pot procedure is used for the synthesis of *N*-adamantyldiazines more frequently. The *N*-trimethylsilyl derivative of diazine is prepared by refluxing the diazine with the disalazane **32**; the obtained compound is introduced directly into the reaction with 1-chloroadamantane in the presence of aluminium chloride (in $CHCl_3$, 20 °C).[37] We present below the examples of *N*-(adamant-1-yl)azines prepared in this way (yields 38%–61%).[37]





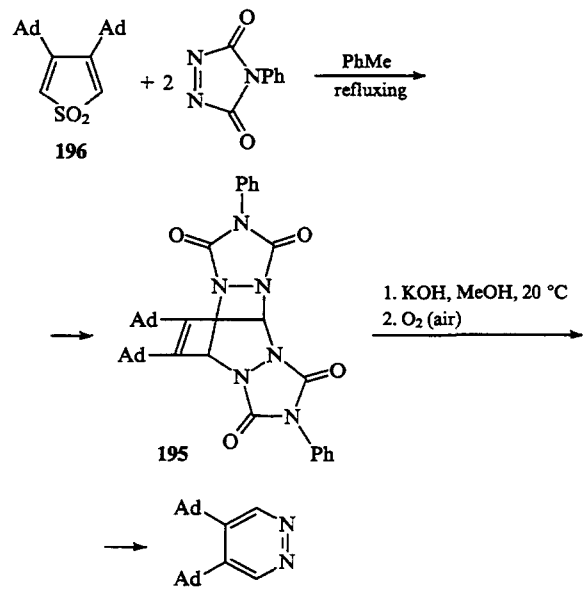
The pyridazine derivative **194** has been obtained in 87% yield by the diene condensation of compound **43** with ethyl diazenedicarboxylate at room temperature.[47]



43

194

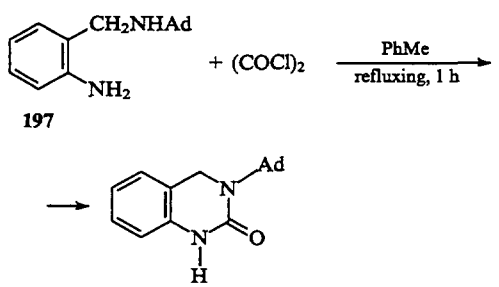
The bis-adduct **195** formed from the cyclic sulfone **196** and an excess of 4-phenyl-1,2,4-triazoline-3,5-dione, is converted into 4,5-di(adamant-1-yl)pyridazine in 56% yield on treatment with potassium hydroxide followed by oxidation in air.[123]



196

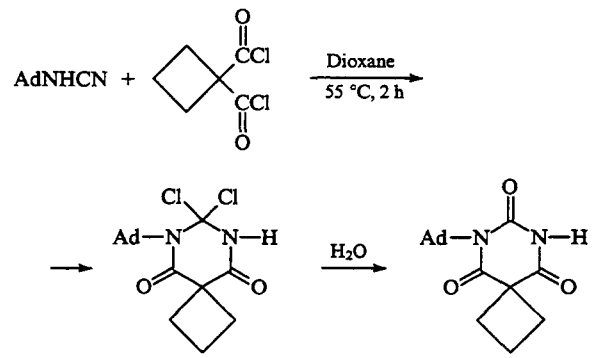
195

When the diamine **197** is refluxed with oxalyl chloride in toluene, 3-(adamant-1-yl)-1,4-dihydro-2-quinazolone is formed, which exhibits anti-inflammatory activity.[124]



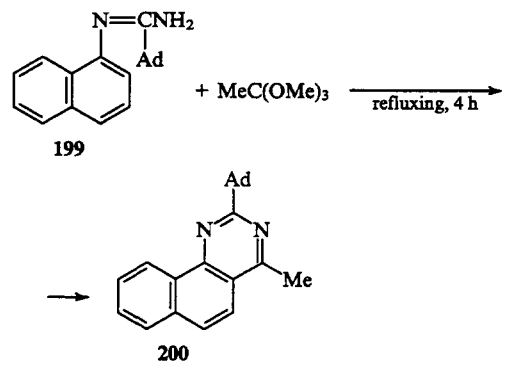
197

The derivative of barbituric acid **198** has been synthesised in 7% yield by the condensation of (adamant-1-yl)cyanogen amide with cyclobutane-1,1-dicarbonyl dichloride in anhydrous dioxane followed by treatment with water.[76]



198

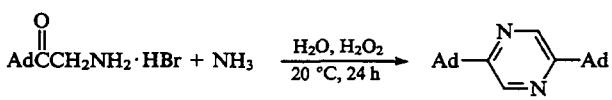
The amidine **199** reacts with the ortho ester $MeC(OMe)_3$ to give the tricyclic compound **200** (yield 60%).[125]



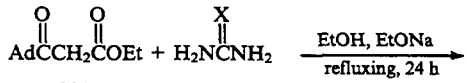
199

200

Treatment of adamant-1-yl aminomethyl ketone hydrobromide with aqueous ammonia in the presence of hydrogen peroxide leads to 2,5-di(adamant-1-yl)pyrimidine in 30.5% yield.[66]



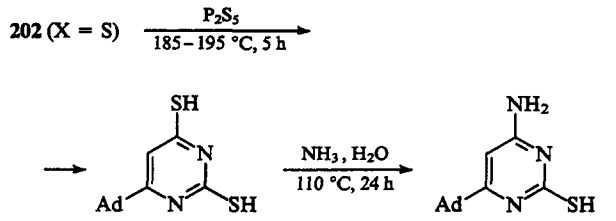
Several other approaches to the synthesis of pyrimidine derivatives containing an adamantane nucleus have been developed. Cyclocondensation of the ester **201** with urea or thiourea in the presence of sodium ethoxide gives rise to 6-(adamant-1-yl)uracil (**202**, X = O) (yield 21.5%) or 6-(adamant-1-yl)thiouracil (**202**, X = S) (yield 60.3%). The latter compound is converted into 6-(adamant-1-yl)-2,4-disulfanylpyrimidine by the action of phosphorus pentasulfide and also into 4-amino-6-(adamant-1-yl)-2-sulfanylpyrimidine (yield 60.5%) by heating with aqueous ammonia.[126]



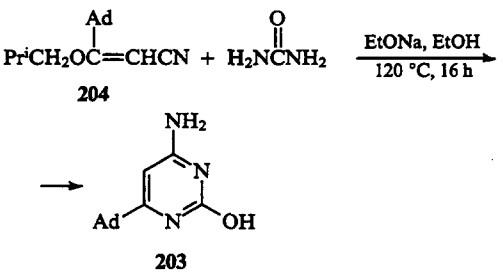
201

202

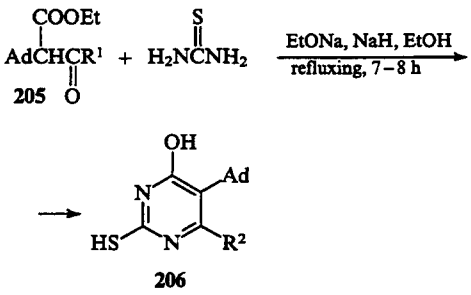
X = O, S.



6-(Adamant-1-yl)cytosine **203** was obtained in 33% yield by the condensation of the nitrile **204** with urea in the presence of sodium ethoxide.[126]

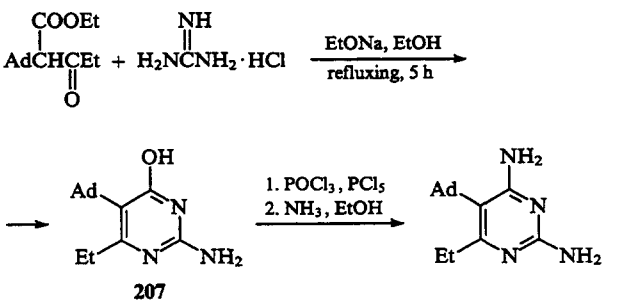


Czech researchers[127] studied the condensation of compounds of the general formula $R^1OOCC(R^2)(Ad)COR^3$ with urea, thiourea, and guanidine. The interaction of compounds **205** with thiourea in the presence of sodium ethoxide and sodium hydride gives the thiouracil derivatives **206** in 27% – 68% yield.



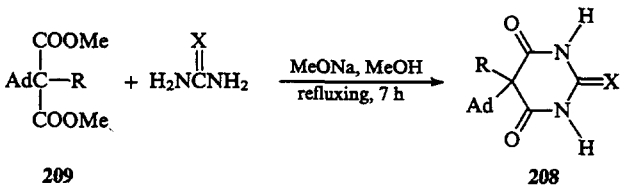
R^1 = H, R^2 = H; R^1 = OEt, R^2 = OH; R^1 = Me, R^2 = Me.

The reaction of the oxoester **205** (R^1 = Et) with guanidine hydrochloride in the presence of sodium ethoxide affords the cytosine derivative **207** (yield 41%), which is converted into 5-(adamant-1-yl)-2,4-diamino-6-ethylpyrimidine by successive treatment with phosphorus oxychloride and phosphorus pentachloride and then with an alcoholic solution of ammonia.



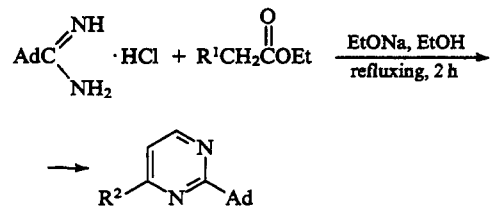
The resulting compound is a 30-fold more effective inhibitor of the growth of mammary carcinoma cells than the compound **206**.[128]

The low-toxicity biologically active compounds **208** have been synthesised in yields of more than 80% by the cyclocondensation of bis-esters **209** with urea or with thiourea in the presence of sodium methoxide.[129]



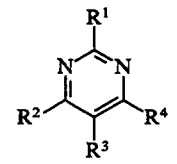
X = O, S; R = H, Me, Et, $CH_2CH=CH_2$.

Adamantane-1-carboximidamide hydrochloride reacts with ethyl malonate or with ethyl cyanoacetate in the presence of sodium ethoxide to give 2-(adamant-1-yl)-6-hydroxypyrimidine and 2-(adamant-1-yl)-6-aminopyrimidine, respectively.[130]



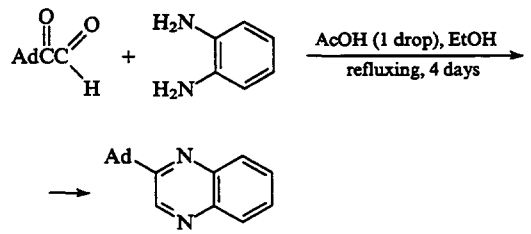
R^1 = COOEt, R^2 = OH; R^1 = CN, R^2 = NH_2.

The pyrimidine derivatives **210** (R^1 = OH, NH_2, R^2 = OH, R^3 = H, R^4 = Ad) inhibit liver folate-reductase and exert a cytostatic effect on tumour cells,[131] whereas the compound **210** (R^1 = R^2 = NH_2, R^3 = Ad, R^4 = Me) has been recommended as an antitumour preparation.[132]

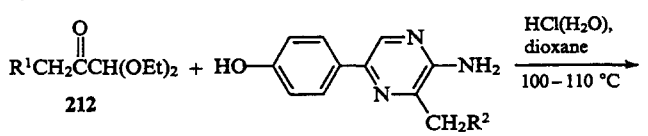


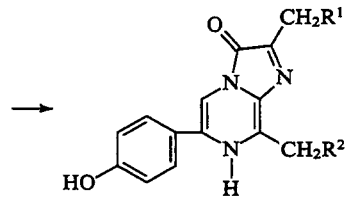
The oxidation of adamant-1-yl aminomethyl ketone hydrobromide with hydrogen peroxide gives 2,5-di(adamant-1-yl)-pyrazine in 30.5% yield.[66]

1,2-Diaminobenzene reacts with (adamant-1-yl)glyoxal on heating in alcohol in the presence of acetic acid affording 2-(adamant-1-yl)quinoxaline in 35% yield.[60]



The imidazopyrazine derivatives **211** have been obtained by the condensation of diethyl acetals **212** with 2-amino-3-benzyl-5-(4-hydroxyphenyl)pyrazine or with 3-(adamant-1-ylmethyl)-2-amino-5-(4-hydroxyphenyl)pyrazine in the presence of dilute hydrochloric acid.[133]

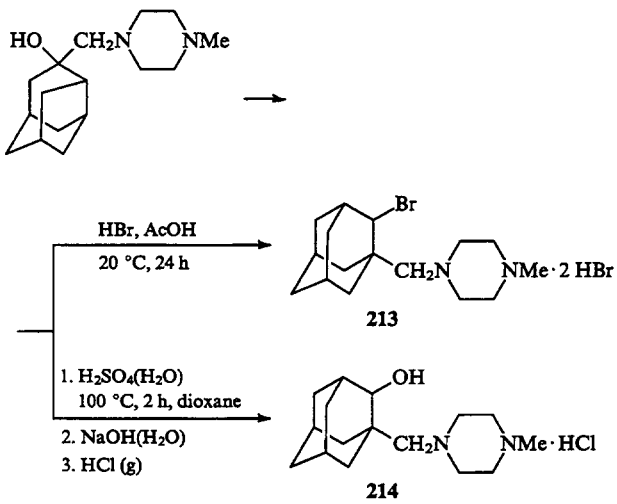




211

R^1	R^2	Yield of 211 (%)
Ad	Ph	44
4-HOC_6H_4	Ad	63

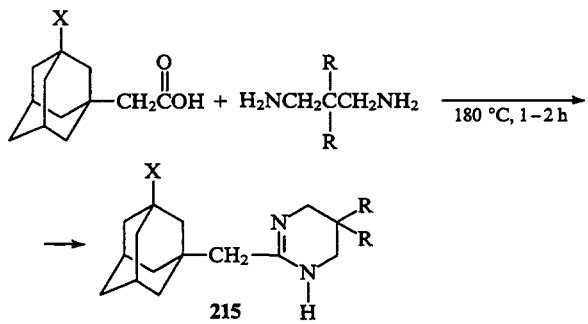
4-(4-Methylpiperazin-1-yl)methylprotoadamantan-4-ol is converted into the salt **213** (yield 40%) on treatment with hydrogen bromide, whereas its reaction with sulfuric acid and hydrogen chloride affords the salt **214** (yield 80%).[134]



213

214

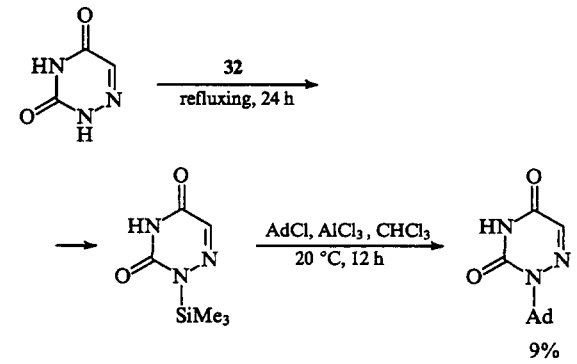
Heating of (adamant-1-yl)acetic acid and (3-hydroxyadamant-1-yl)acetic acid with diamines $H_2NCH_2CR_2CH_2NH_2$ leads to tetrahydropyrimidine derivatives **215** (yields 30% – 59%).[58]



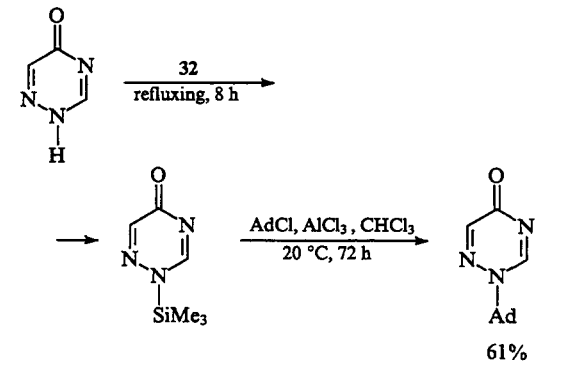
215

X = H, OH; R = H, Me.

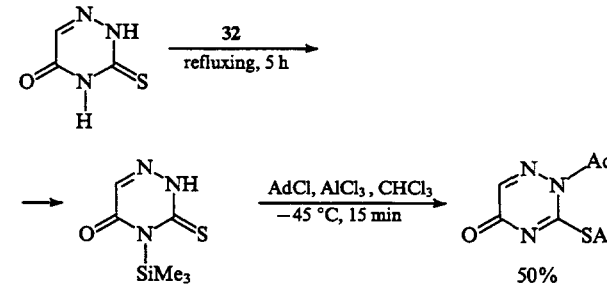
Several methods have been developed for the preparation of 1,2,4-triazine derivatives containing the adamantyl nucleus. Japanese researchers[37] have synthesised these compounds in two stages. The first stage involves the reaction of triazine with disilazane **32** giving the trimethylsilyl derivative, which is then made to react with chloroadamantane in the presence of aluminium chloride.



9%

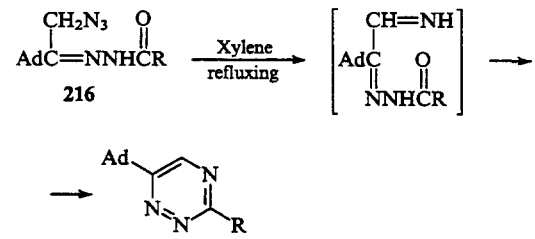


61%



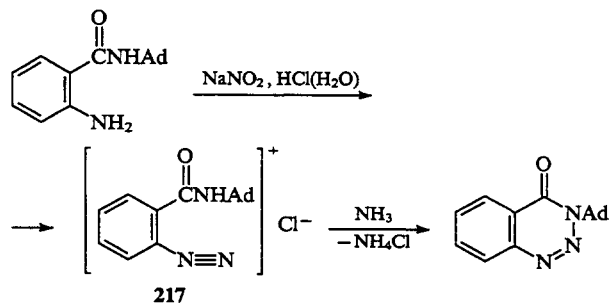
50%

On heating in xylene, the azides **216** cyclise with the elimination of nitrogen giving 3-R-6-(adamant-1-yl)-1,2,4-triazines in 58% – 73% yields.[135]



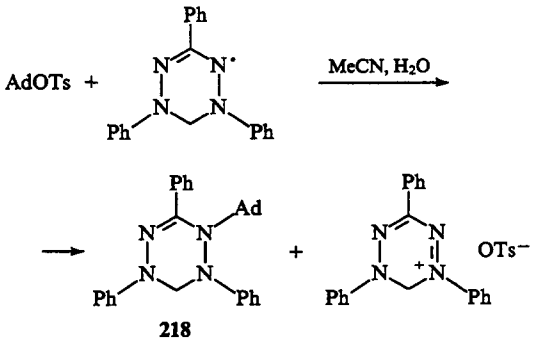
R = Me, Ph, Ad.

The reaction of ammonia with the diazonium salt **217** formed upon diazotisation of the (adamant-1-yl)amide of anthranilic acid gave 3-(adamant-1-yl)-3,4-dihydro-1,2,3-benzotriazin-4-one.[136,137]



217

Only one example[138] of the synthesis of a 1,2,4,5-tetrazine derivative has been reported. 2-(Adamant-1-yl)-1,3,5-triphenyl-1,2,5,6-tetrahydro-1,2,4,5-tetrazine **218** was obtained by the reaction of adamant-1-yl tosylate with 1,3,5-triphenylverdazyl.[138]

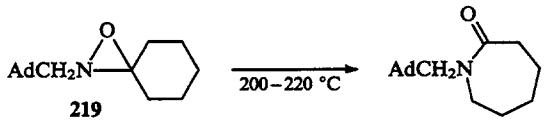


218

5. Compounds with seven-membered heterocycles

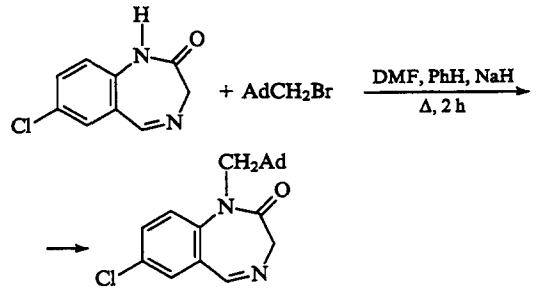
The preparation of *N*-(adamant-1-yl)caprolactam hydrochloride has been described in a patent.[29] The authors noted that this compound exhibits an anti-inflammatory activity, stimulates the central nervous system, reduces the cholesterol level, and decreases appetite.

The oxazaridine derivative **219** isomerises on heating above 200 °C into *N*-(adamant-1-ylmethyl)caprolactam in 70% yield.[139]



219

The reaction of 1-bromomethyladamantane with 7-chloro-1,4-benzodiazepin-2-one in the presence of sodium hydride leads to the *N*-alkylation product **220** in 30% yield.[140]

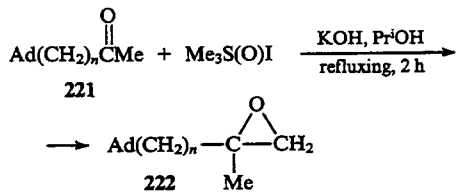


220

III. Adamantane derivatives containing heterocyclic nuclei with oxygen atoms

1. Compounds with three-membered and four-membered heterocycles

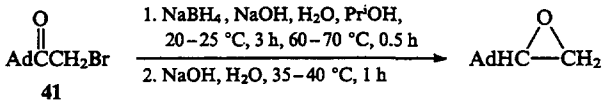
The ketones **221** of the adamantane series enter into the reaction with oxodimethylsulfonium methylide (which is obtained by treating trimethyloxosulfonium iodide with potassium hydroxide), which affords the oxirane derivatives **222** in 88% and 83% yields.[141]



221 **222**

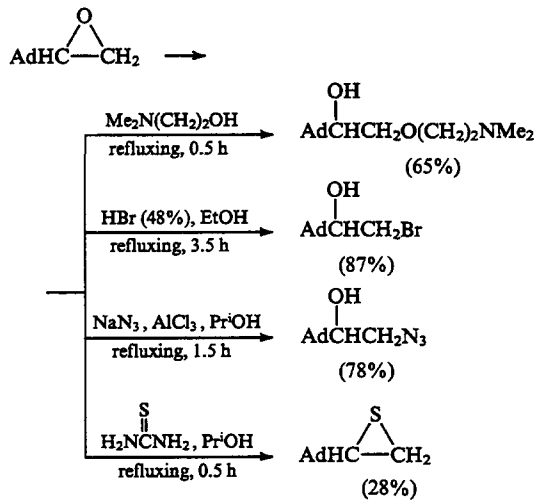
n = 0, 1.

2-(Adamant-1-yl)oxirane has been synthesised in 86% yield in two stages, namely, by the reaction of the ketone **41** with sodium tetrahydroborate in an alkaline medium and the subsequent treatment with aqueous sodium hydroxide.[142]

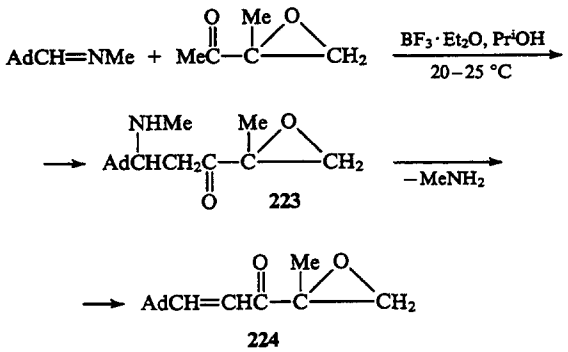


41

The same workers[142] studied the transformations of the obtained oxirane in reactions with nucleophilic and electrophilic reagents.



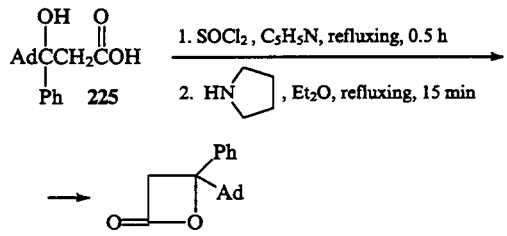
1-Acetyl-1-methyloxirane adds to the imine AdCH=NMe in the presence of boron trifluoride etherate to give unstable aminoketone **223**; the latter eliminates methylamine under the reaction conditions and is thus converted into the unsaturated compound **224**.[143]



223 **224**

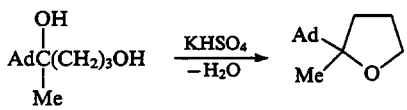
The methods for the synthesis of oxiranes containing an adamantane nucleus have been analysed.[144] These methods include the epoxidation of unsaturated compounds of the adamantane series and transformation of adamantyl-containing ketones. The introduction of an adamantyl fragment into epoxy-polymers was shown to increase their thermal stability and to improve technological characteristics of compositions based on them.

To the best of our knowledge, only one study devoted to the synthesis of adamantane derivatives containing four-membered heterocycles with oxygen atoms has been published.[36] It presents the preparation of 2-(adamant-1-yl)-2-phenyloxetan-4-one from the hydroxy acid **225** under the action of thionyl chloride and pyrrolidine (yield 95%).

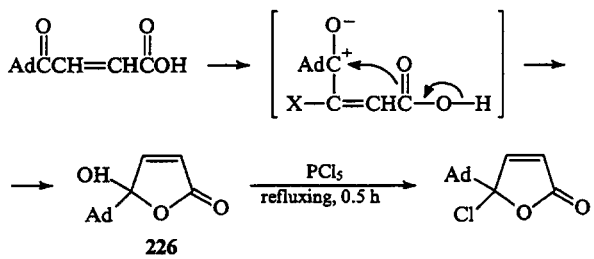


2. Compounds with five-membered heterocycles

4-(Adamant-1-yl)pentane-1,4-diol undergoes intramolecular dehydration in the presence of potassium hydrogen sulfate, which affords 2-(adamant-1-yl)-2-methyltetrahydrofuran.[145]

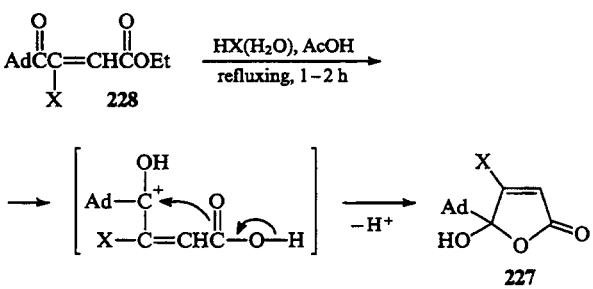


When 3-(adamantoyl)acrylic acid is exposed to sunlight, it cyclises giving compound **226** in 85.5% yield; the hydroxy-group in the latter is substituted by a chlorine atom under the action of phosphorus pentachloride (yield 39.5%).[146]



226

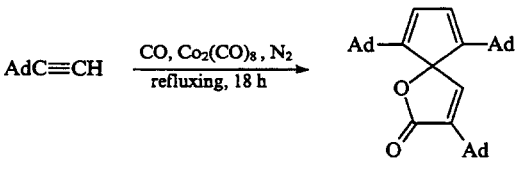
The derivatives of furanone **227** have been synthesised by heating ethyl 2-adamantoyl-2-haloacrylates with hydrohalic acids (yields 84% and 98%).[147]



227

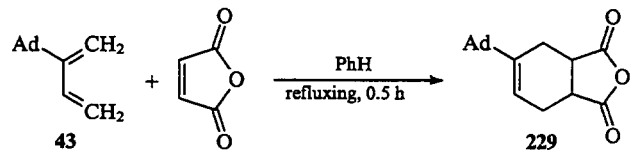
X = Cl, Br.

3,6,9-Tri(adamant-1-yl)-1-oxaspiro[4.4]nona-3,6,8-trien-2-one **228** is formed when 1-ethynyladamantane is heated with cobalt carbonyl in light petroleum in a flow of carbon monoxide.[148]

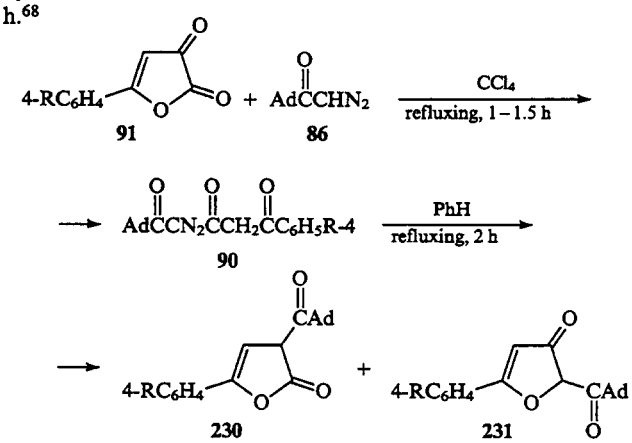


228

The diene **43**, on heating in benzene, enters into diene condensation with maleic anhydride, which leads to the adduct **229** in 70% yield.[47]

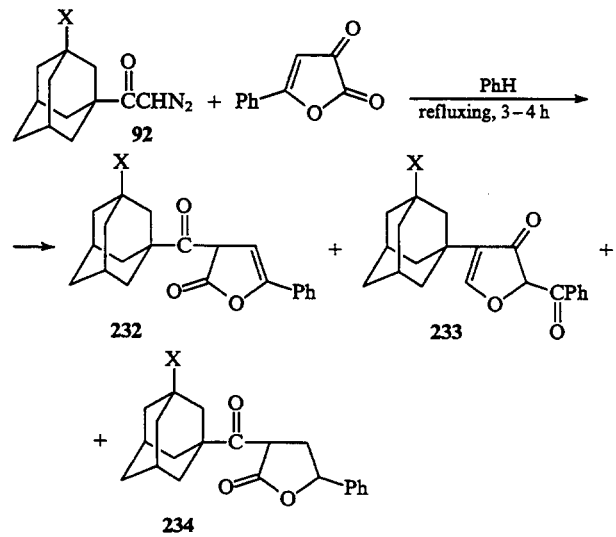


A mixture of adamant-1-ylcarbonyl derivatives of 2,3-dihydrofuran-2-one **230** and 2,3-dihydrofuran-3-one **231** has been synthesised by heating in benzene for 2 h the triketones **90**, which are formed from the diazoketone **86** and dihydrofurandiones **91**. The compounds **230** and **231** can also be obtained without isolation of the triketones **90**, by refluxing a mixture of dihydrofurandiones **91** and the diazoketone **86** in benzene for 3 h.[68]



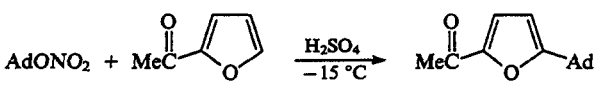
R	Yields (%)	
	230	**231**
H	38	7
Me	71	10
OMe	47	6
Br	14	9

The reaction of 5-phenyl-2,3-dihydrofuran-2,3-dione with the diazoketones **92** has been described in a patent.[149] This reaction yields one, two or three compounds depending on the nature of the substituent X in the diazoketone: for X = Br, three compounds **232–234** are formed, whereas for X = H, two compounds **233** and **234** have been isolated. When X = ONO_2, the reaction yields only compound **232**.

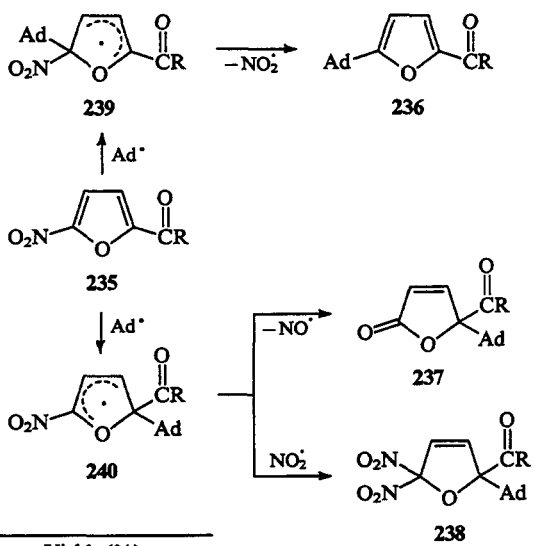


X = H, Br, ONO_2.

The hydrogen atom in the 5-position of 2-acetylfuran is substituted by an adamantyl radical in the reaction with adamant-1-yl nitrate in the presence of sulfuric acid even at −15 °C; the yield of 5-(adamant-1-yl)-2-acetylfuran is 32%.[150]

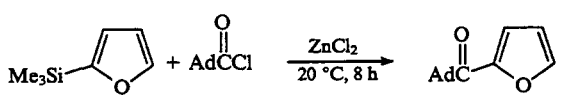


Homolytic *ipso*-substitution in 2-acyl-5-nitrofurans **235** has been studied.[151] The reaction of furan derivatives **235** with the Ad$^{\bullet}$ radical [generated from AdCOOH in the presence of $(NH_4)_2S_2O_8$ and $AgNO_3$ [103]] results in a mixture of three compounds: 2-acyl-5-(adamant-1-yl)furans **236**, 2-acyl-2-(adamant-1-yl)-2,5-dihydrofuran-5-ones **237**, and 2-acyl-2-(adamant-1-yl)-5,5-dinitro-2,5-dihydrofurans **238**. The authors[151] presented the following scheme for these transformations: the reaction of the compounds **235** with the Ad$^{\bullet}$ radical affords pairs of more complex radicals **239** and **240**. The radicals **239** eliminate $NO_2^{\bullet}$ to give compounds **236**. The transformation of the radicals **240** can follow two pathways: it involves either the loss of $NO_2^{\bullet}$ resulting in the formation of the compound **237** or, conversely, the addition of $NO_2^{\bullet}$ leading to the compound **238**.

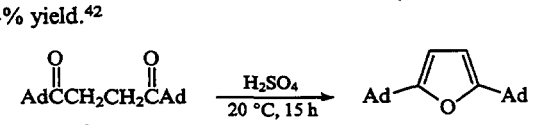


R	Yields (%)		
	236	**237**	**238**
H	35	25	15
OMe	31.5	32	10

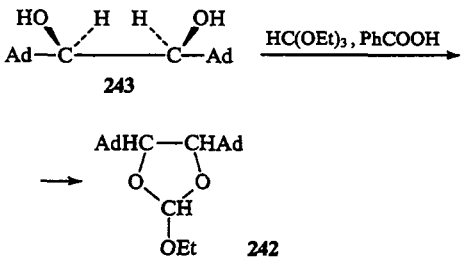
When 2-(trimethylsilyl)furan reacts with the chloride AdCOCl in the presence of zinc chloride, the trimethylsilyl group is substituted by the adamant-1-ylcarbonyl group giving adamant-1-yl 2-furyl ketone in 61% yield.[152]



The cyclocondensation of the diketone **241** in the presence of concentrated sulfuric acid affords 2,5-di(adamant-1-yl)furan in 84% yield.[42]



A mixture of diastereomers of 4,5-di(adamant-1-yl)-2-ethoxy-1,3-dioxolane **242** has been obtained by heating the *meso*-diol **243** with the ortho ester $HC(OEt)_3$ in the presence of benzoic acid.[153]

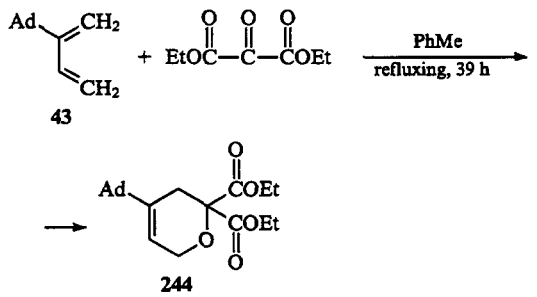


When the dioxolane **242** is heated in benzoic acid at 200 °C, stereoselective *cis*-elimination occurs to give *cis*-1,2-di(adamant-1-yl)ethene in 90% yield.[153]

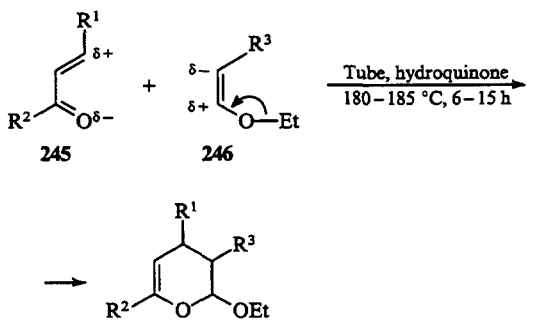


3. Compounds with six-membered heterocycles

The diene **43** in boiling toluene undergoes [4+2]-cycloaddition with the oxo-group of the diethyl ester of mesoxalic acid; the reaction affords the adduct **244** in an almost quantitative yield.[47]

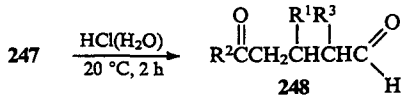


The electron density distribution in the α,β-unsaturated ketones **245** and in the vinyl ethers **246** is favourable for them to enter into [4+2]-cycloaddition. By heating these compounds at 180–185 °C in sealed tubes, the dihydropyran derivatives **247** were synthesised in 50%–88% yields.[154]

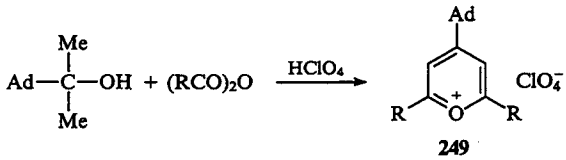


R^1	R^2	R^3
H	H	Ad
H	H	$AdCH_2$
$AdCH_2$	H	H
H	Ad	H

When the dihydropyrans **247** are treated with dilute hydrochloric acid at 20 °C, the heterocyclic ring is cleaved and the 1,5-dicarbonyl compounds **248** are obtained in 84%–92% yields.[154]

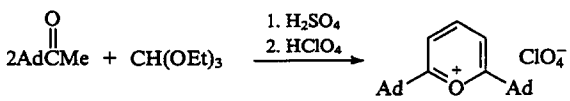


The tertiary alcohol, 2-(adamant-1-yl)propan-2-ol, reacts with perchloric acid and carboxanhydrides to give 2,6-dialkyl-4-(adamant-1-yl)pyrilium perchlorates **249**.[155]

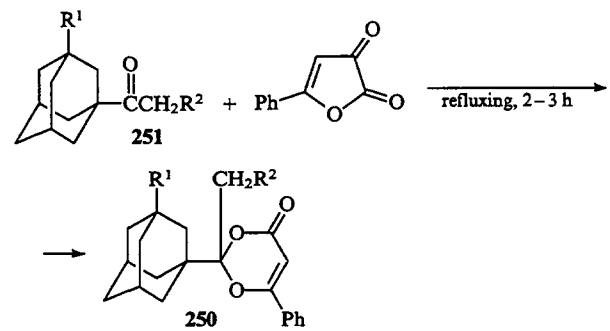


R = Me, Et, Pr.

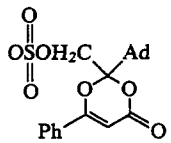
2,6-Di(adamant-1-yl)pyrilium perchlorate is formed in 22% yield in the condensation of 1-acetyladamantane with ethyl orthoformate in the presence of sulfuric acid followed by the treatment of the reaction product with perchloric acid.[155]



A series of adamantyl-containing heterocyclic compounds **250** with two oxygen atoms in the heterocyclic ring have been synthesised by the condensation of the ketones **251** with 5-phenyl-2,3-dihydrofuran-2,3-dione, their yields ranging from 29% to 78%.[156]



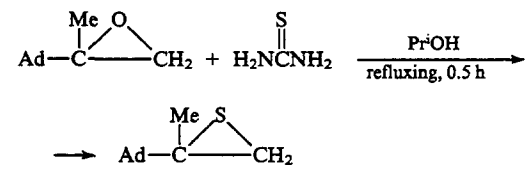
R^1 = Br: R^2 = Br, NO_2; R^1 = NO_2: R^2 = ONO_2;
R^1 = Ph: R^2 = ONO_2; R^1 = ONO_2: R^2 = Br;

R^1 = H: R^2 = H, Cl, Br, ONO_2, 

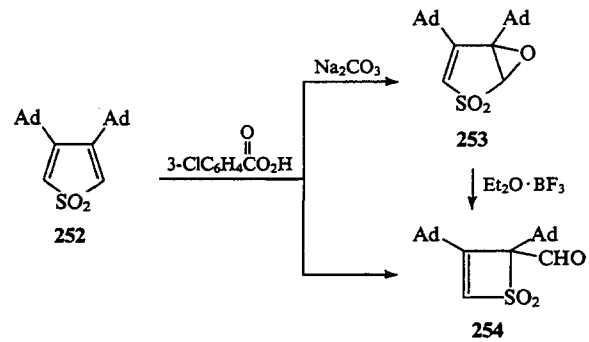
IV. Adamantane derivatives containing heterocyclic nuclei with sulfur atoms

1. Compounds with three-membered and four-membered heterocycles

2-(Adamant-1-yl)-2-methylthiirane is formed in 28% yield on refluxing a mixture of 2-(adamant-1-yl)-2-methyloxirane and thiourea in isopropyl alcohol.[142]

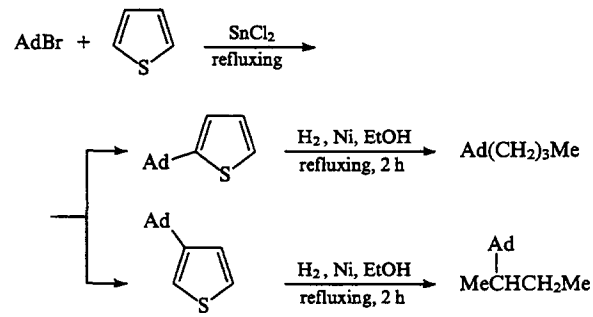


In the only study,[157] which reports synthesis of a compound of the adamantane series containing a four-membered heterocycle with a sulfur atom in the heterocyclic ring, two procedures have been proposed for the transformation of a five-membered ring into a four-membered ring. The cyclic sulfone **252** is converted into the epoxide **253** by reaction with 3-chloroperbenzoic acid in the presence of sodium carbonate; on treatment with boron trifluoride etherate the compound **253** isomerises into the thiete dioxide derivative **254**. Interestingly, the compound **254** is also formed in 78% yield in the reaction of the initial sulfone **252** with 3-chloroperbenzoic acid in the absence of water. This result was explained[157] by the fact that the peracid catalyses the isomerisation of the epoxide **253** formed into the thiete dioxide **254**.

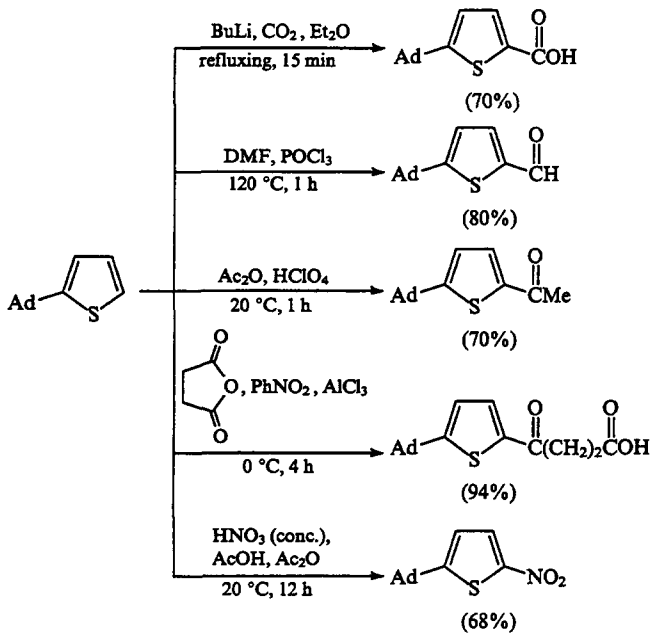


2. Compounds with five-membered heterocycles

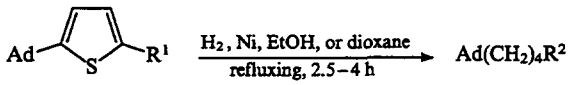
In the presence of tin(II) chloride, thiophene reacts with 1-bromoadamantane to give two adamantylation products, namely, 2-(adamant-1-yl)thiophene (yield 52%) and 3-(adamant-1-yl)thiophene (yield 7%). On treatment with hydrogen over W-7 Raney nickel, the resulting adamantylthiophenes are desulfurised and converted into 1-(adamant-1-yl)butane (yield 80%) and 2-(adamant-1-yl)butane (yield 85%).[158]



Substitution reactions in 2-(adamant-1-yl)thiophene have been studied. A series of thiophene derivatives containing an adamantyl radical in the 2-position and various substituents in the 5-position were thus obtained.[159]

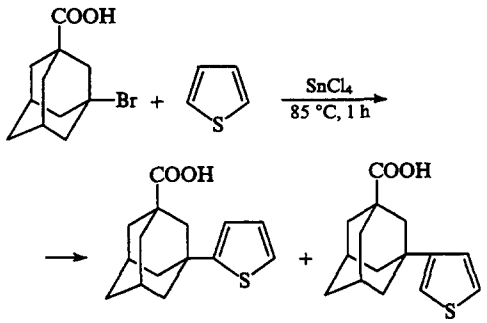


All the above compounds are desulfurised in the presence of the W-7 catalyst in alcohol or in dioxane giving the corresponding adamantane derivatives containing no heterocyclic rings.[159]

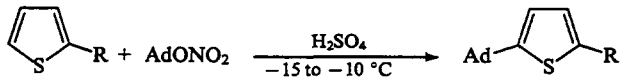


R^1	R^2	Yield (%)
COOH	COOH	66
CHO	CH_2OH	60
COMe	CH(OH)Me	75
$CO(CH_2)_2COOH$	$CH(CH_2)_2CO + CO(CH_2)_2COOH$	75 (total)
NO_2	NH_2	70

Two compounds, 3-(2-thienyl)adamantane-1-carboxylic acid and 3-(3-thienyl)adamantane-1-carboxylic acid have been obtained in a ratio of 2 : 1 in 47% overall yield by the reaction of 3-bromoadamantane-1-carboxylic acid with thiophene in the presence of tin(IV) chloride.[160]



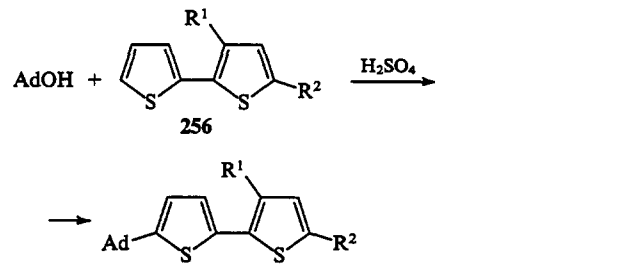
In the presence of concentrated sulfuric acid, adamant-1-yl nitrate reacts with thiophene derivatives containing electron-withdrawing substituents in the 2-position to give compounds **255** (yields 41% and 44%).[150]



255

R = NO_2, COOH.

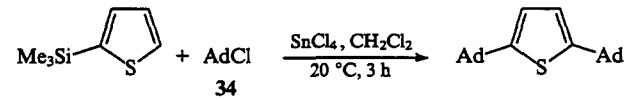
By means of adamantan-1-ol, the adamantyl radical has been introduced into the 2,2′-dithienyl derivatives **256**.[161]



256

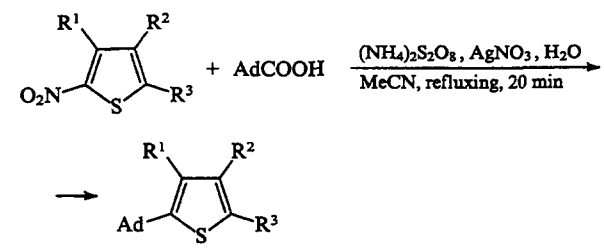
R^1 = H, R^2 = COMe, CHO, COOH; R^1 = NO_2, R^2 = H.

It is of interest that even at 20 °C, 2-(trimethylsilyl)thiophene reacts with chloroadamantane **34** to give 2,5-di(adamant-1-yl)-thiophene (yield 65%).[37]



34

Cogolli et al.[162,163] have studied homolytic *ipso*-substitution in the series of thiophene nitro-derivatives under the action of the Ad˙ radical (generated from AdCOOH[103]). The workers[162] described the interaction of the Ad˙ radical with derivatives of 2-nitrothiophene, containing electron-withdrawing substituents in various positions of the thiophene ring; compounds **257** were thus prepared (yields 43% – 55%).

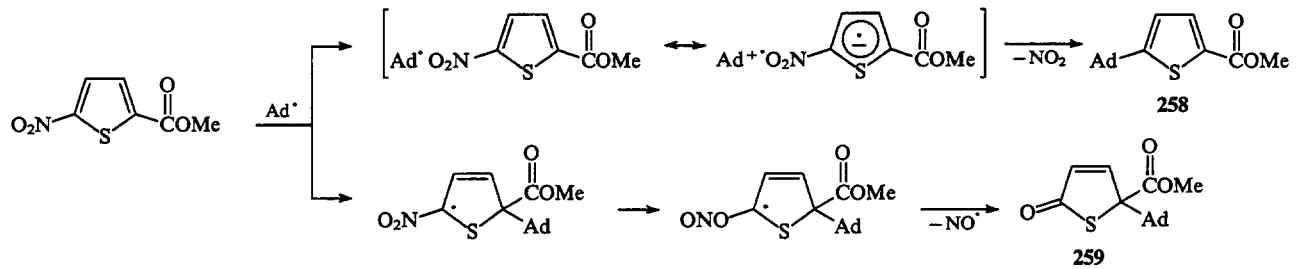


257

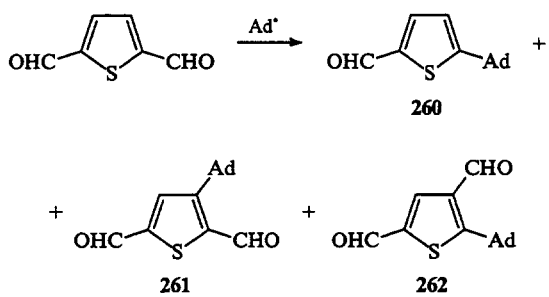
R^1	R^2	R^3
H	H	SO_2Ph
H	H	CHO
H	NO_2	COOMe
NO_2	H	COOMe

The reaction of Ad˙ with 5-methoxycarbonyl-3-nitrothiophene afforded 2-(adamant-1-yl)-5-methoxycarbonyl-3-nitrothiophene in 50% yield,[162] whereas the interaction of this radical with 5-(methoxycarbonyl)-2-nitrothiophene gave two compounds: the normal product of *ipso*-substitution **258** (yield 55%) and the 'unusual' product **259** (yield 8%). A scheme was suggested to explain these results (Scheme 1).[163]

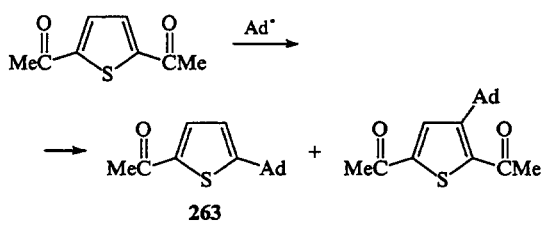
Scheme 1



A more complex picture has been observed in a study of the reactions of the Ad• radical with thiophene derivatives containing formyl, acetyl, or methoxycarbonyl group in various positions of the thiophene ring.[163] For example, three compounds were detected among the products of the reaction of the Ad• radical with 2,5-diformylthiophene, namely, compound **260** (yield 19%), **261** (yield 10%), and **262** (yield 56%), whereas the reaction of 2,4-diformylthiophene with the Ad• radical gave only compound **262** (yield 60%).[163]

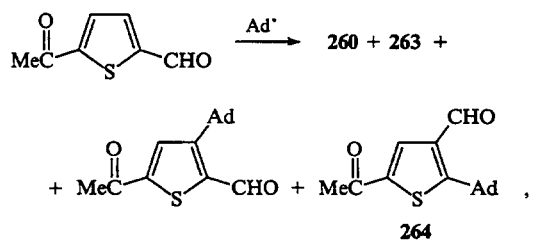


The reaction of 2,5-diacetylthiophene with the Ad• radical leads to two compounds, 2-acetyl-5-(adamant-1-yl)thiophene **263** (yield 33%) and 2,5-diacetyl-3-(adamant-1-yl)thiophene (yield 16%).[163]



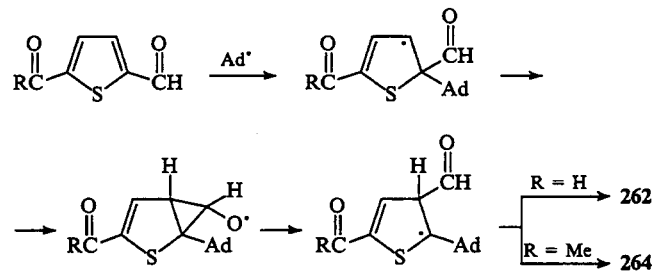
2,5-Di(methoxycarbonyl)thiophene reacts with the Ad• radical to give 3-(adamant-1-yl)-2,5-di(methoxycarbonyl)thiophene (yield 25%).[163]

The interaction of the Ad• radical with 2-acetyl-5-formylthiophene is the most complex: four compounds have been isolated and identified among the reaction products, namely, compound **260** (yield 10%), **263** (yield 17%), 2-acetyl-4-(adamant-1-yl)-5-formylthiophene (yield 11%), and 2-acetyl-5-(adamant-1-yl)-4-formylthiophene **264** (yield 13%),[163]

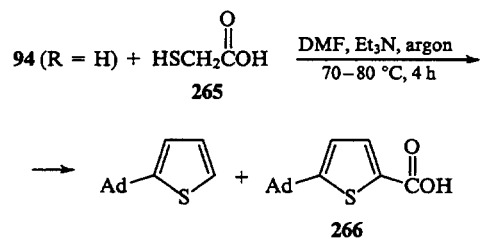


whereas the reaction of 2-acetyl-4-formylthiophene with the Ad• radical gave the compound **264** as the only product (yield 56%).[163]

The formation of the 'unusual' products **262** and **264** in the reactions of the Ad• radical with the derivatives of 2-formylthiophene was explained[163] by assuming a scheme that includes the 1,2-shift of the formyl group.

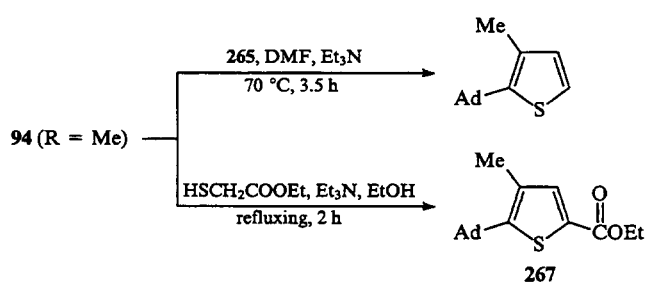


The cyclocondensation of the aldehyde **94** (R = H) with thioglycolic acid **265** carried out in boiling alcohol in the presence of triethylamine over a period of 5 h gives 5-(adamant-1-yl)thiophene-2-carboxylic acid **266** (yield 4.5%) and 2-(adamant-1-yl)thiophene (yield 34%). The latter is obviously formed via decarboxylation of the acid **266** under the reaction conditions.[164] By conducting this reaction in DMF in an argon flow, the yields of the products can be substantially increased: the acid **266** is formed in 24.6% yield and adamantylthiophene is obtained in 53.4% yield.[165]

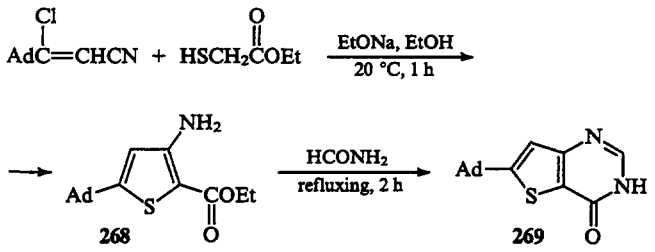


The condensation of the aldehyde **94** (R = H) with thioglycolic acid anilide in DMF in the presence of triethylamine at 60 °C for 3.5 h led to the anilide of the acid **266** (yield 45.5%).[165]

When the aldehyde **94** (R = Me) has been made to react with the acid **265**, only the decarboxylation product, 2-(adamant-1-yl)-3-methylthiophene, has been isolated in 43% yield. Ethyl 5-(adamant-1-yl)-4-methylthiophene-2-carboxylate **267** was synthesised in 71% yield from the aldehyde **94** (R = Me) and ethyl thioglycolate.[71]

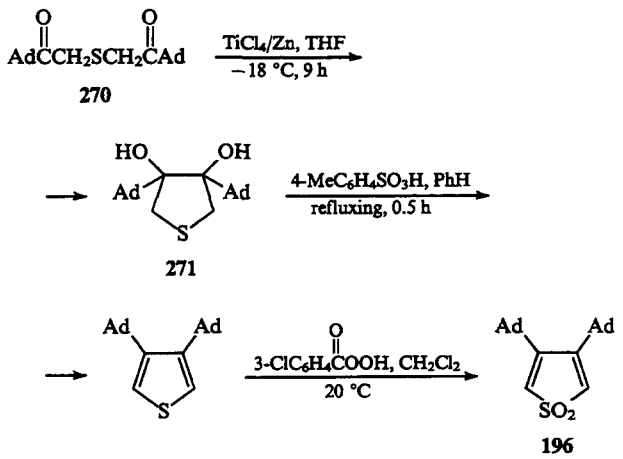


The reaction of 3-(adamant-1-yl)-3-chloroacrylonitrile with ethyl thioglycolate gives the aminoester **268** (yield 40%); heating of the latter with formamide in the presence of sodium ethoxide leads to 6-(adamant-1-yl)thieno[2.3-*e*]pyrimidin-4-one **269** (yield 86.5%).[70]

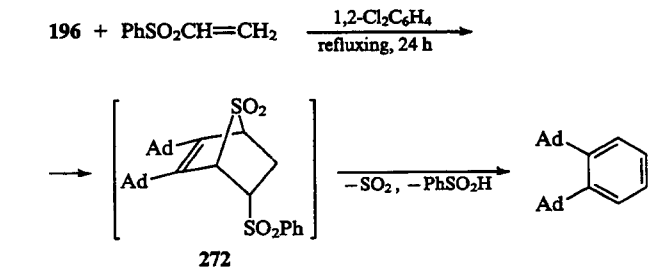


Treatment of 2-(trimethylsilyl)thiophene with AdCOCl in the presence of zinc chloride leads to the substitution of the Me_3Si group by the AdCO group; the reaction affords 2-(adamant-1-ylcarbonyl)thiophene in 82% yield.[152]

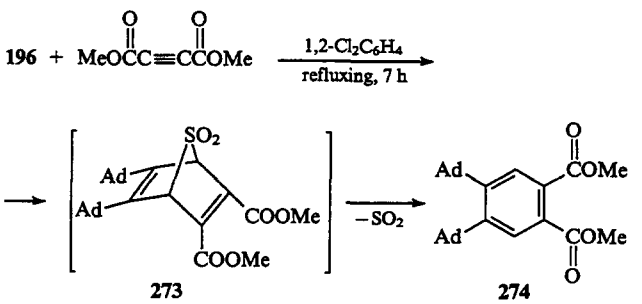
In 1990, an interesting study was published,[123] which was devoted to the synthesis and some transformations of 3,4-di(adamant-1-yl)thiophene 1,1-dioxide **196**. The dioxo sulfide **270** was reduced to the diol **271** (yield 34%), which on heating with toluene-*p*-sulfonic acid is converted to 3,4-di(adamant-1-yl)thiophene (yield 60%). The latter is oxidised with 3-chloroperbenzoic acid to the cyclic sulfone **196** in 75% yield.[123]



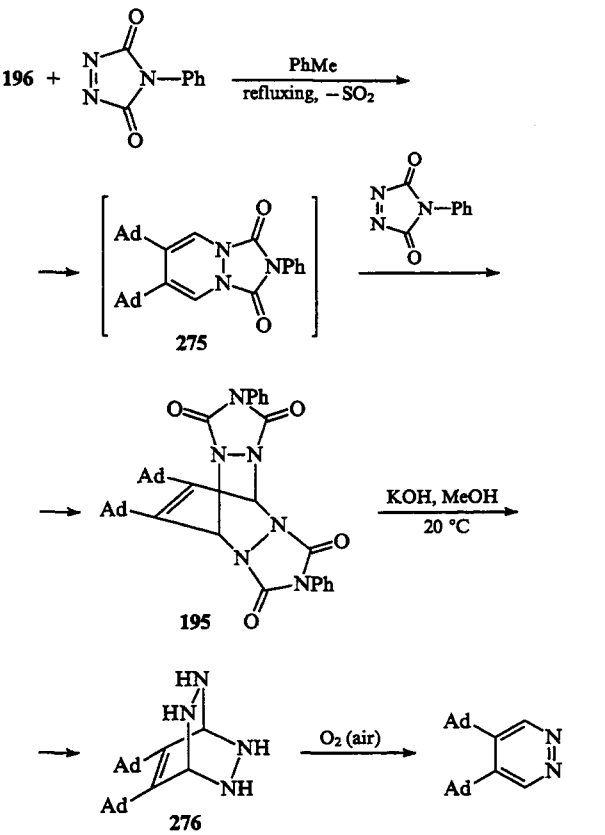
The diene condensation of the sulfone **196** with phenyl vinyl sulfone gives adduct **272**, which decomposes under the reaction conditions into sulfur dioxide, phenylsulfinic acid, and 1,2-di(adamant-1-yl)benzene (yield 92%).[123]



The cycloaddition of the sulfone **196** to the dimethyl ethynedicarboxylate also affords an unstable adduct, compound **273**, which loses sulfur dioxide under the reaction conditions and is converted into dimethyl 4,5-di(adamant-1-yl)phthalate **274** in 90% yield.[123]



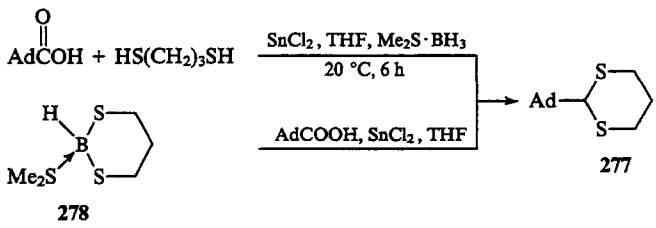
A more complex situation is observed when the sulfone **196** reacts with an excess of 4-phenyl-1,2,4-triazoline-3,5-dione. The adduct **275** of the composition 1 : 1 is formed initially; it reacts further with one more triazolinedione molecule giving the adduct **195** of the composition 1 : 2 (yield 71%). Treatment of the latter with potassium hydroxide in methanol gives the bicyclic compound **276** (yield 82%), which is transformed during storage in air into 4,5-di(adamant-1-yl)pyridazine in 82% yield.[123]



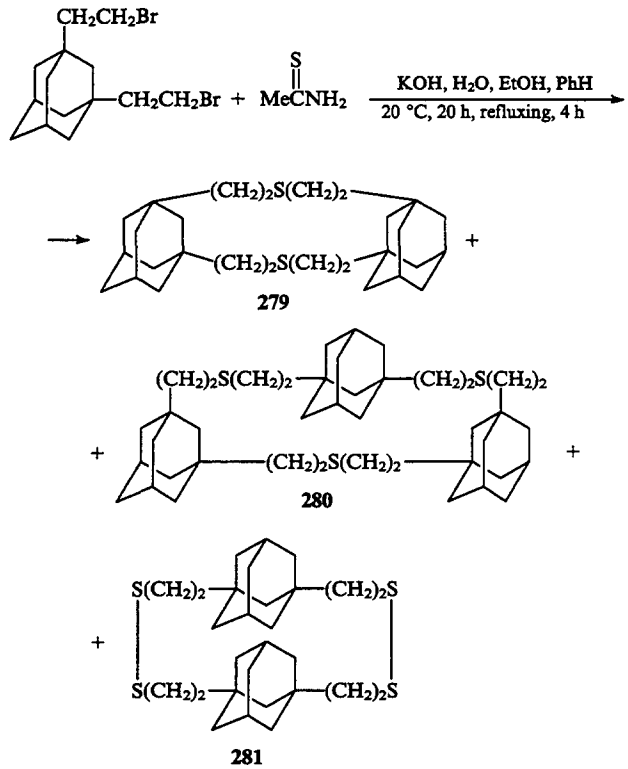
3,4-Di(adamant-1-yl)thiophene in a solution in carbon disulfide in the presence of aluminium chloride is converted into 2,4-di(adamant-1-yl)thiophene in quantitative yield over a period of 6 days at 20 °C.[123]

3. Compounds with six-membered and larger heterocycles

Two methods for the synthesis of 2-(adamant-1-yl)hexahydro-1,3-dithiane **277** have been reported. One of these methods involves cyclocondensation of adamantane-1-carboxylic acid with 1,3-disulfanylpropane in the presence of tin(II) chloride and the complex $Me_2S \cdot BH_3$, and the other method involves the reaction of the same acid with the complex **278** [obtained preliminarily from $HS(CH_2)_3SH$ and $Me_2S \cdot BH_3$] in the presence of tin(II) chloride (yield 80%).[166]



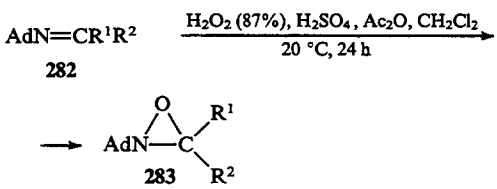
The heterocyclic compounds **279** (yield 34%), **280** (yield 17%), and **281** (yield 3%) containing several adamantane fragments and several sulfur atoms have been synthesised by heating 1,3-bis(2-bromoethyl)adamantane with thioacetamide in the presence of potassium hydroxide.[167]



V. Adamantane derivatives containing heterocyclic nuclei with nitrogen and oxygen atoms

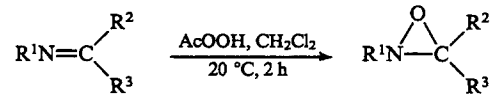
1. Compounds with three-membered heterocycles

Epoxydation of Schiff's bases is a general method for the preparation of oxaziridine derivatives. The Schiff's bases **282** have been converted into the oxaziridines **283** (yield 44%–75%) by treating them with hydrogen peroxide in acetic anhydride in the presence of sulfuric acid.[168]



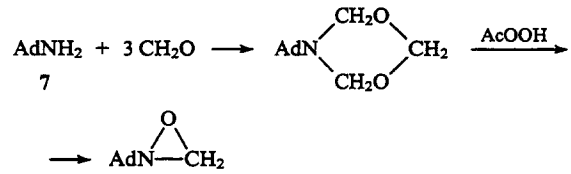
R^1 = H: R^2 = H, Ph; R^1 = cyclo-C_6H_{11}, R^2 = Me; $R^1 + R^2 = -(CH_2)_5-$.

Oxaziridine derivatives have been synthesised by the oxidation of Schiff's bases with peracetic acid; the yields of the oxidation products varied from 47% to 56%.[31,139]

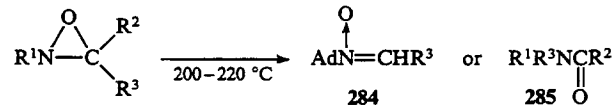


R^1	R^2	R^3
Ad	Ph	H
Ad	Furyl-2	H
$AdCH_2$	Ph	H
$AdCH_2$	$-(CH_2)_5-$	

The oxaziridine containing no substituents at the carbon atom was obtained in 29% yield by the oxidation of the product of condensation of the amine **7** with formaldehyde.[139]

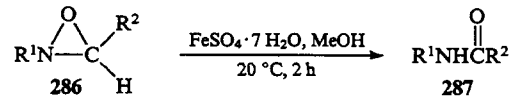


The adamantyloxaziridines **283** are fairly thermally stable compounds. However, at temperatures above 200 °C they isomerise to give the nitrones **284** or amides **285**.[139]



R^1	R^2	R^3	Product	Yield (%)
Ad	H	Ph	**284**	63
Ad	H		**284**	63
Ad	H	H	**285**	91
$AdCH_2$	H	Ph	**285**	53
$AdCH_2$	$-(CH_2)_5-$		**285**	70

The oxaziridines **286** isomerise in the presence of iron(II) sulfate at room temperature to the amides **287** in 70%–76% yields.[139]

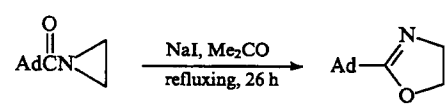


R^1 = Ad, R^2 = Ph, furyl-2; R^1 = $AdCH_2$, R^2 = Ph; R^3 = Alk.

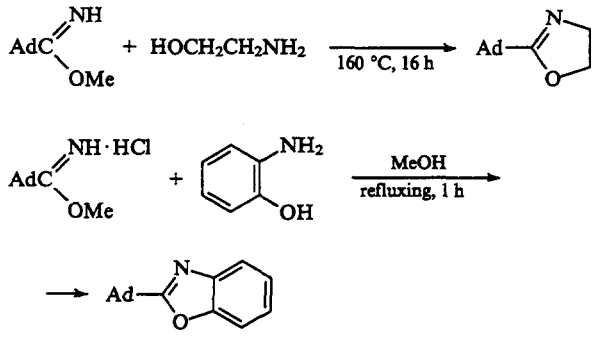
No compounds containing the adamantyl radical linked directly to the oxazetidine ring have been reported in the literature.

2. Compounds with five-membered heterocycles

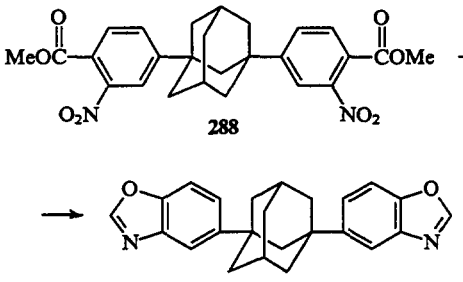
When 1-adamant-1-ylcarbonylaziridine is heated with sodium iodide in acetone, it isomerises to 2-(adamant-1-yl)oxazoline (yield 43%).[60]



2-(Adamant-1yl)oxazoline has been synthesised by the condensation of the methyl iminoester of adamantane-1-carboxylic acid with ethanolamine (yield 93%), whereas the reaction of the hydrochloride of the same iminoester with 2-aminophenol gives 2-(adamant-1-yl)benzoxazole (yield 76%).[55]



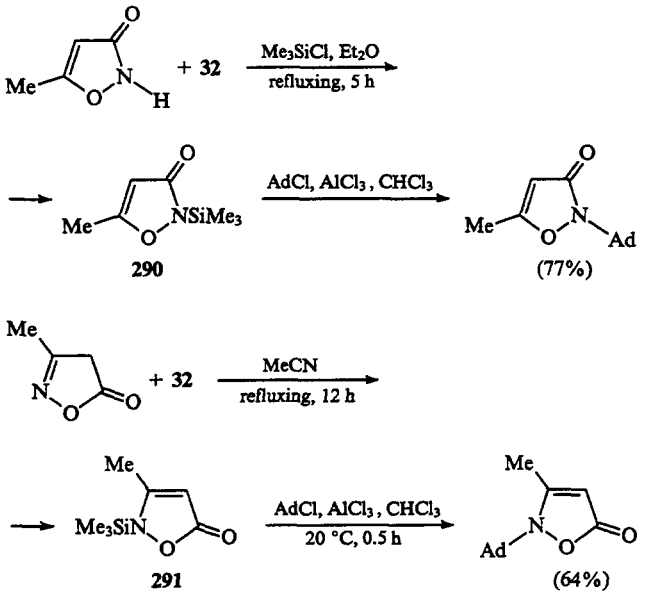
1,3-Di(benzoxazol-5-yl)adamantane **289** has been obtained by the reduction of the adamantane derivative **288** containing the methyl 2-nitrobenzoate residues in the 1- and 3-positions.[169]



288

289

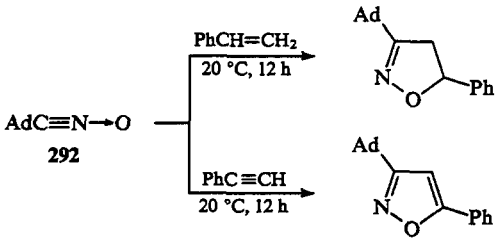
A two-stage procedure proposed for the introduction of adamantyl radical to the nitrogen atoms of 5-methylisoxazolin-3-one or 3-methylisoxazolin-5-one involves *N*-silylation of heterocyclic compounds with disilazane **32** and the subsequent treatment of the resulting silylated products **290** or **291** in situ with 1-chloroadamantane in the presence of aluminium chloride.[37]



290 (77%)

291 (64%)

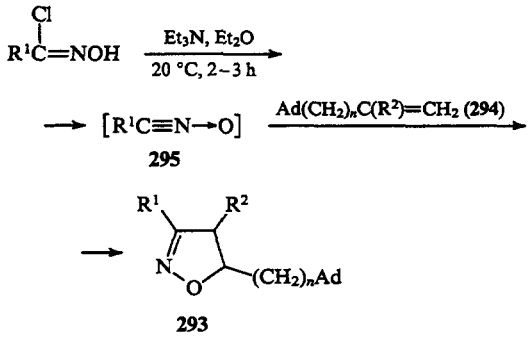
One of the most general methods for the synthesis of isoxazoline and isoxazole derivatives involves the 1,3-dipolar cycloaddition of carbonitrile *N*-oxides to alkenes and alkynes. In 1972, Italian investigators[170] described for the first time the preparation of the *N*-oxide of adamantane-1-carbonitrile **292** and carried out the 1,3-dipolar cycloaddition of the nitrile **292** to styrene and phenylethyne. The corresponding adducts were obtained in 89% and 69% yields.



292

An alternative approach to the synthesis of isoxazolines and isoxazoles containing an adamantyl substituent involves 1,3-dipolar cycloaddition of *N*-oxides of nitriles of aliphatic or aromatic carboxylic acids to unsaturated adamantane derivatives. Carbonitrile *N*-oxides used in situ in these reactions are obtained either by treating hydroxamoyl chlorides with bases or by thermolysis.

The isoxazoline derivatives **293** have been obtained in 63%–98% yields from alkenes **294** of the adamantane series and the aromatic and heterocyclic carboxylic acid nitrile *N*-oxides **295** prepared from the corresponding hydroxamoyl chlorides by treating them with triethylamine.[171,172]

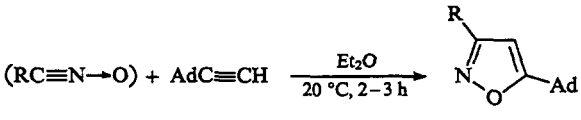


295

293

n = 0, 1; R^1 = Ph, 4-$MeOC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 5-nitrofuryl-2; R^2 = H, Me.

The reaction of 1-ethynyladamantane with nitrile *N*-oxides **295** under similar conditions gives isoxazole derivatives **296** in 68%–95% yields.[171,172]

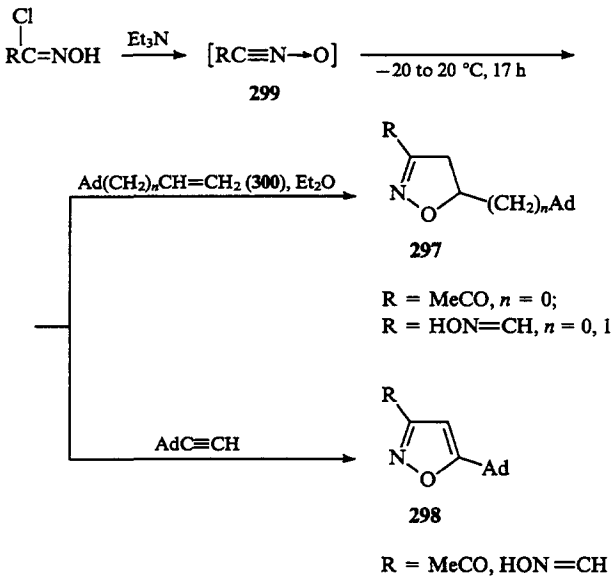


295 **296**

R = Ph, 4-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 5-nitrofuryl-2.

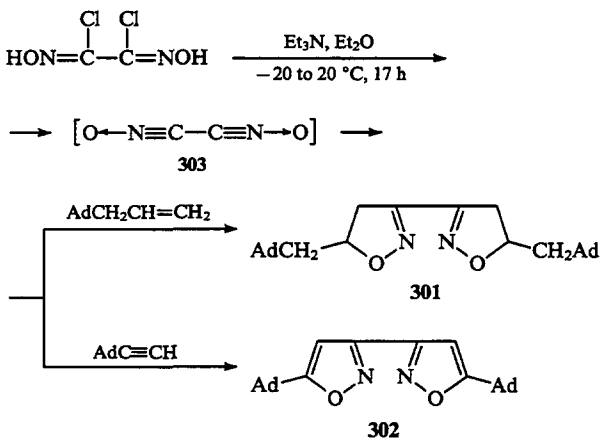
The use of the above procedure permits the preparation of isoxazoline and isoxazole derivatives from unsaturated adamantane derivatives and aliphatic carbonitrile *N*-oxides, their yields ranging from 20 to 40%. The researchers found conditions under which the yields of isoxazolines and isoxazoles increased to 65%.[172]

The isoxazolines **297** and isoxazoles **298** were synthesised in 50–65% yields by the reaction of pyruvonitrile *N*-oxide (**299**, R = MeCO) or hydroxyiminoacetonitrile *N*-oxide (**299**, R = HON=CH) with alkenes **300** or with 1-ethynyladamantane, respectively.[171]

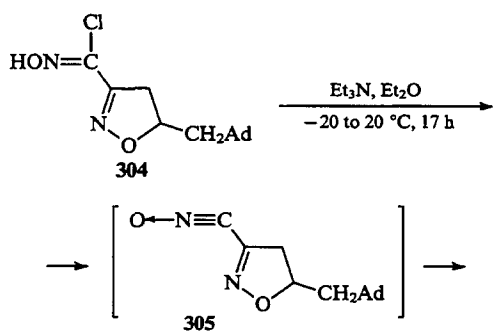


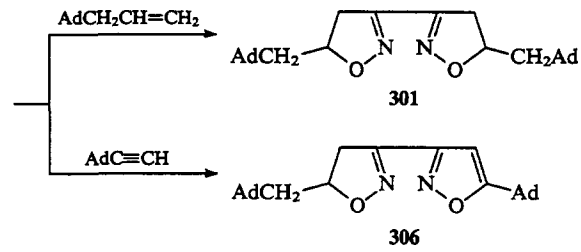
By using aqueous sodium bicarbonate instead of triethylamine in the synthesis of isoxazoline **297** (R = HON=CH, $n = 0$), the yield of the latter can be increased to 92%.[171]

Compounds containing two isoxazoline nuclei **301** or two isoxazole nuclei **302** are formed in the cycloaddition of the bis(*N*-oxide) of oxalic acid dinitrile **303** to 1-allyladamantane or to 1-ethynyladamantane (yields 50 and 42%, respectively).[172]

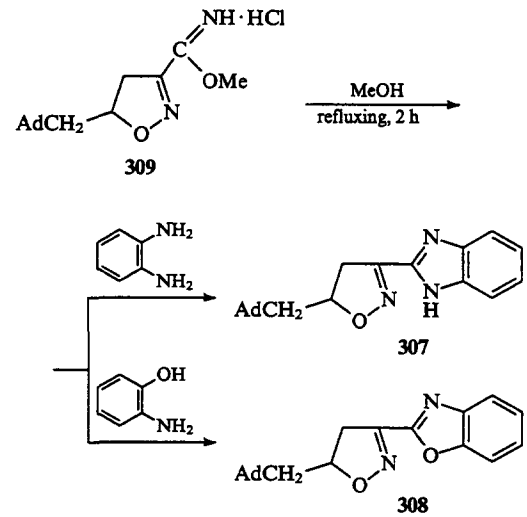


The hydroxamoyl chloride **304** on treatment with triethylamine is converted into the nitrile *N*-oxide **305**, which reacts with 1-allyl and 1-ethynyladamantane to give compounds **301** and **306** (yields 65% and 35%).[172]



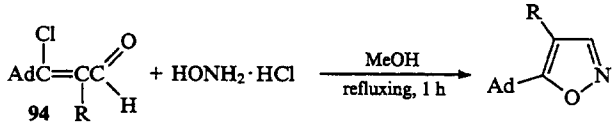


Compound **307** containing isoxazoline and benzimidazole nuclei and compound **308** with imidazoline and benzoxazole nuclei are obtained in 75% and 72% yields by the condensation of the iminoester hydrochloride **309** with *o*-diaminobenzene or *o*-aminophenol.[172]



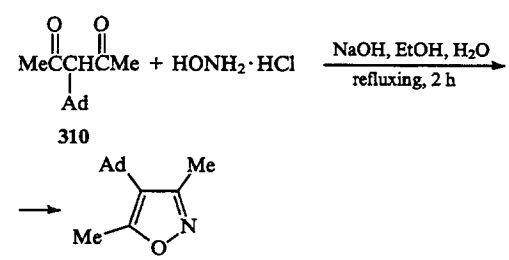
Most of the compounds synthesised from nitrile *N*-oxides and unsaturated adamantane derivatives exhibit a bacteriostatic activity. For example, the adamantyl derivative of isoxazoline **293** with R^1 = 5-nitro-2-furyl, R^2 = Me, and $n = 0$ is active against diphtheria and tuberculosis pathogens, the derivative with R^1 = Ph, R^2 = Me, and $n = 0$ exhibits a high tuberculosostatic activity, and the compound with $R^1 = 3\text{-}O_2NC_6H_4$, R^2 = H, and $n = 0$ possesses a high antiviral activity.[172]

5-(Adamant-1-yl)- and 5-(adamant-1-yl)-4-methylisoxazoles have been synthesised by the reaction of the aldehydes **94** with hydroxylamine hydrochloride in boiling methanol (yield 90%).[165]

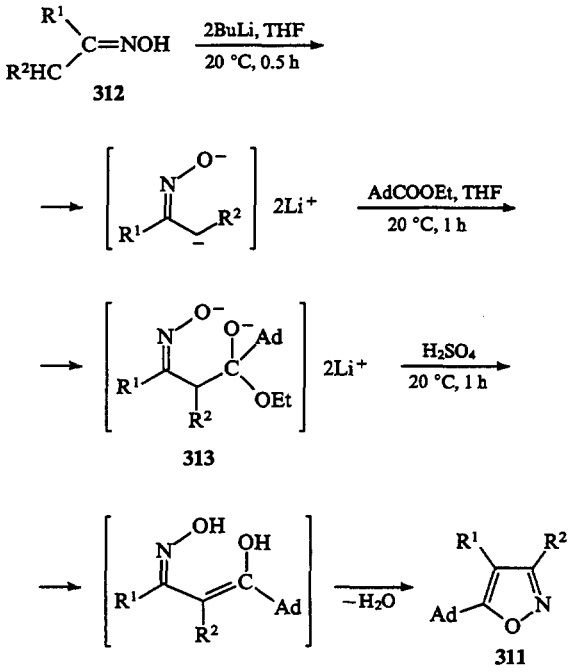


R = H, Me.

Refluxing of 3-(adamant-1-yl)pentane-2,4-dione **310** with hydroxylamine hydrochloride in aqueous alcohol gives rise to 4-(adamant-1-yl)-3,5-dimethylisoxazole (yield 70%).[60]



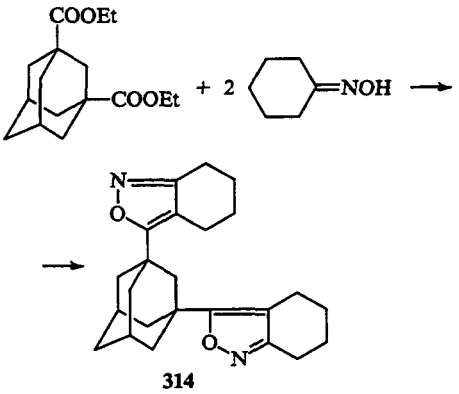
He and Lin proposed [173] an original method for the synthesis of the oxazole derivatives **311**. The oximes of ketones **312** are converted into the corresponding dianions on treatment with butyllithium. The dianions are introduced into the reaction with ethyl adamantane-1-carboxylate. The resulting salts **313** cyclise to the isoxazoles **311** on treatment with sulfuric acid.[173]



312 **313** **311**

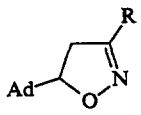
R^1 = Me; R^2 = H; $R^1 + R^2 = -(CH_2)_3-$, $-(CH_2)_4-$.

Compound **314** can be obtained in 64% yield in a similar way from diethyl adamantane-1,3-carboxylate and cyclohexanone oxime.[173]



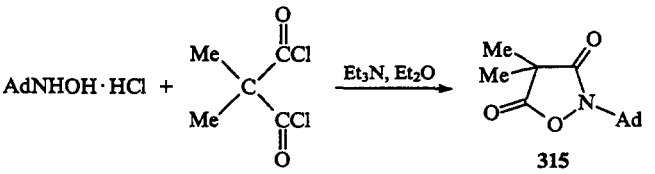
314

Biological activity of the isoxazoline derivatives has been studied.



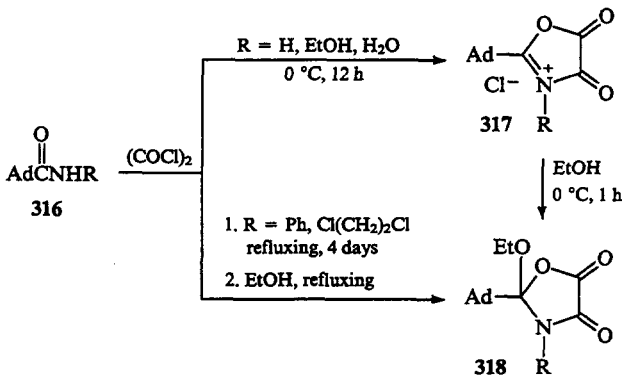
This compound with R = Ph was found to exhibit a tuberculostatic activity, and the compounds with R = 5-nitro-2-furyl and 5-nitro-2-thienyl exhibit an antibacterial activity.[174]

2-(Adamant-1-yl)-4,4-dimethylisoxazolidine-3,5-dione **315** has been obtained in 94% yield by the condensation of *N*-(adamant-1-yl)hydroxylamine hydrochloride with dimethylmalonic acid dichloride.[175]



315

The amide $AdC(O)NH_2$ is converted initially into the salt **317** (yield 72.5%) by treating it with oxalyl chloride; the interaction of this salt with ethanol results in the formation of the ethoxy-derivative **318** (R = H, yield 91%). The anilide AdC(O)NHPh is converted into compound **318** (R = Ph, yield 56%) without isolation of the corresponding salt.[176,177]

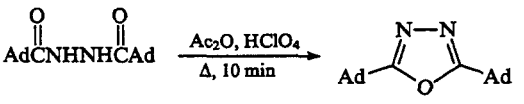


316 **317** **318**

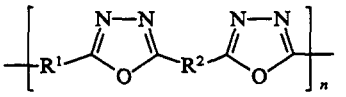
R = H, Ph.

On treatment with ammonia, the compound **318** with R = H is converted into the diamide $AdCONHCOCONH_2$, whereas refluxing of this compound in dichloromethane for 28 h leads to the acyl isocyanate AdCONCO.[176]

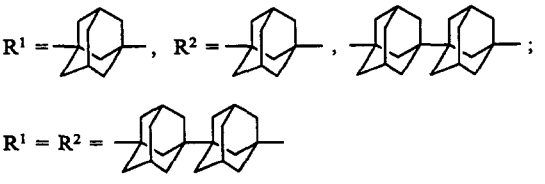
Heating of *N*,*N*′-di(adamant-1-ylcarbonyl)hydrazine in acetic anhydride in the presence of perchloric acid affords 2,5-di(adamant-1-yl)-1,3,4-oxadiazole in 50% yield.[60]



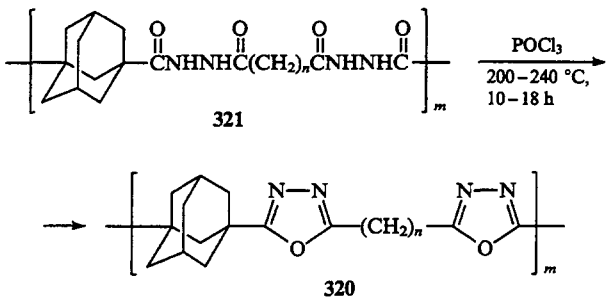
High-molecular-weight thermostable compounds **319** containing adamantyl and 1,3,4-oxadiazole fragments, which are readily moulded at temperatures above the softening point, have been prepared by heating adamantane-1,3-dicarboxylic acid, diadamant-1,1′-yl-3,3′-dicarboxylic acid, or their chlorides with the dihydrazides of the same acids in polyphosphoric acid (with a content of P_2O_5 of 85%–86%) at 140–160 °C for 6 h.[178]



319



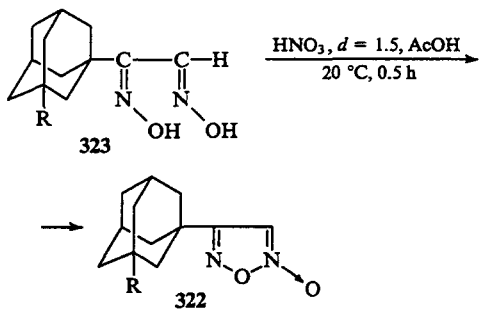
Thermostable polymers are formed in 73–89% yields when *N*,*N*′-diacylpolyhydrazides **321** are heated with phosphorus oxychloride in vacuo.[179]



321 → 320

n = 1–4, 7, 8.

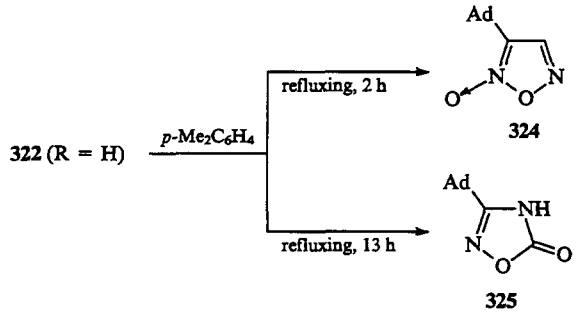
The furoxans **322** containing an adamantyl radical in the 4-position have been prepared by a known method involving the reaction of the *anti*-glyoximes **323** with a fuming nitric acid in glacial acetic acid. The yields of the furoxans **322** in this reaction are 60%–70%.[180]



323 → 322

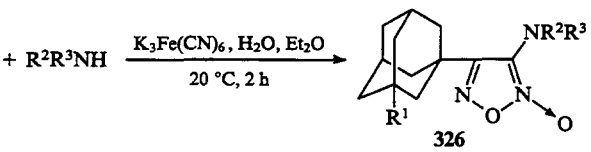
R = H, Me, Cl, 4-MeOC$_6$H$_4$.

On refluxing in *p*-xylene for 2 h the furoxan **322** (R = H) isomerises to the furoxan **324** (yield 22%), whereas on more prolonged refluxing (13 h) the isomerisation leads to 3-(adamant-1-yl)-1,2,4-oxadiazol-5-one **325** (yield 50%).[180]



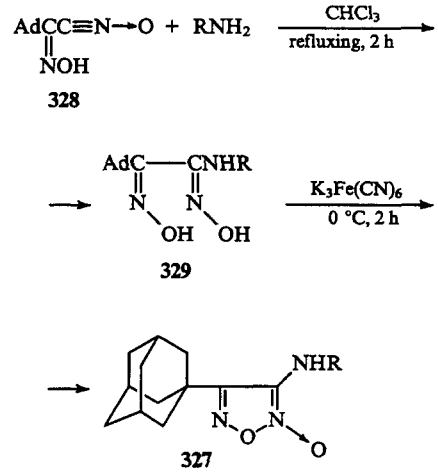
Treatment of the furoxan **322** (R = H) with nitric acid (d = 1.5) at 20 °C for 2 h gives rise to the furoxan **322** (R = ONO$_2$) in 78% yield.[180]

In the presence of K$_3$Fe(CN)$_6$, the glyoximes **323** react with secondary amines giving the furoxans **326** containing residues of the secondary amines in the 5-position (yields 33%–64%).[181]



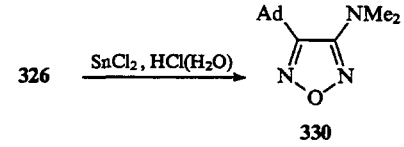
R^1	R^2	R^3	R^1	R^2	R^3
H	Me	Me	OH	Me	Me
Me	Me	Me	H	Et	Et
4-MeC$_6$H$_4$	Me	Me	H	–(CH$_2$)$_5$–	
Cl	Me	Me	H	(CH$_2$CH$_2$)$_2$O	

The furoxans **327** have been obtained by the reaction of the nitrile *N*-oxide **328** with ammonia or methylamine followed by treatment of the resulting glyoximes **329** with potassium hexacyanoferrate(III). The yields of furoxans **327** are 37% (R = H) and 30% (R = Me).[181]



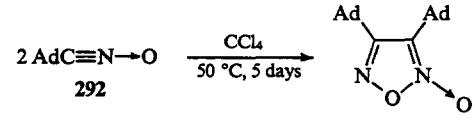
R = H, Me.

The furoxan **326** (R^1 = H, R^2 = R^3 = Me) is reduced by tin(II) chloride in hydrochloric acid to a furazan derivative, 3-(adamant-1-yl)-4-dimethylamino-1,2,5-oxadiazole **330**.[181] The yield of the furazan **330** is 66%.

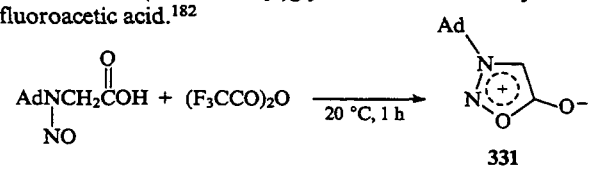


R^1 = H, R^2 = R^3 = Me.

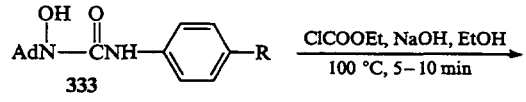
The nitrile *N*-oxide **292** dimerises under mild conditions to give 4,5-di(adamant-1-yl)furoxan (yield 78%).[170]

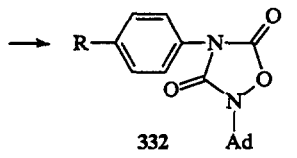


There is only one example of synthesis of a derivative of 1,2,3-oxadiazolidine, namely, 3-(adamant-1-yl)-1,2,3-oxadiazol-5-one **331**. This compound is formed in 80% yield in the reaction in *N*-nitroso-*N*-(adamant-1-yl)glycine with the anhydride of trifluoroacetic acid.[182]



The 1,2,4-oxadiazolidine-3,5-dione derivatives **332** containing an adamantyl radical have been obtained by the condensation of the amides **333** with ethyl chloroformate in the presence of an alcoholic solution of potassium hydroxide (yields 75% and 58%).[183]

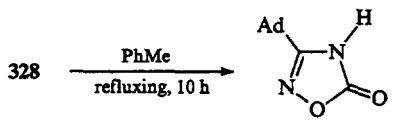




332

R = H, Cl.

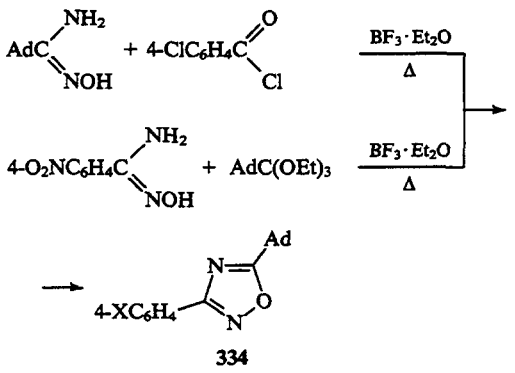
Heating of the nitrile *N*-oxide **328** in toluene affords 3-(adamant-1-yl)-1,2,4-oxadiazol-5-one **325** in 63% yield.[180]



325

It has been found that the formation of the compound **325** involves cleavage of the furoxan ring, the isocyanate rearrangement of the intermediate nitrile *N*-oxide **328**, and its subsequent cyclisation.[180]

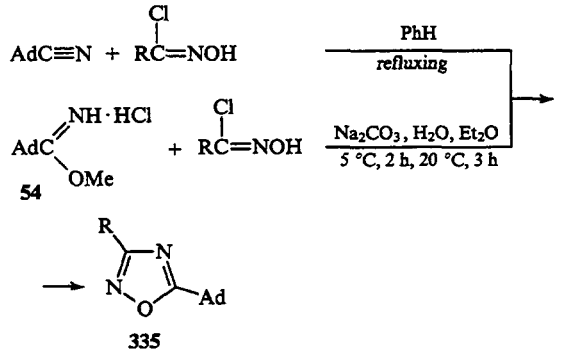
The 1,2,4-oxadiazole derivatives **334** have been synthesised from amidoximes and *p*-chlorobenzoyl chloride[184] or from the orthoester $AdC(OEt)_3$[185] in the presence of boron trifluoride etherate with heating (yield 40%).



334

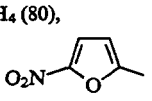
X = Cl, NO_2.

Several procedures have been proposed for the synthesis of adamantyl-containing oxadiazoles. 3-R-5-(Adamant-1-yl)-1,2,4-oxadiazoles **335** have been obtained in 56% – 98% yields from the hydroxamoyl chlorides RC(Cl)=NOH by two procedures: their thermal condensation with 1-cyanoadamantane or their interaction with the methyl iminoester hydrochloride **54** in the presence of sodium carbonate.[56, 186]

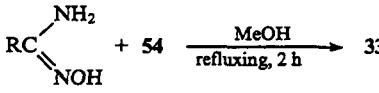


335

R (time of refluxing / h) = Ph (40), 3-$O_2NC_6H_4$ (80),

4-$O_2NC_6H_4$ (110),  (110).

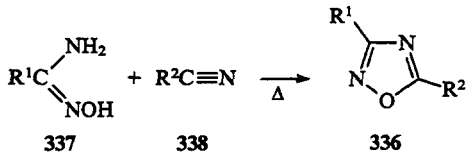
Two alternative methods for the synthesis of the 1,2,4-oxadiazole derivatives **335** and **336** are based on the reaction of the amidoximes **337** with the iminoester hydrochloride **54** (the yields of the target compounds varied from 40% to 88%)[56, 186, 187]



337

R = Me, $PhCH_2$, Ad,

or on the cyclocondensation of amidoximes **337** with carbonitriles **338**.

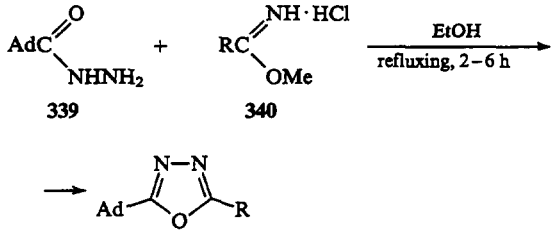


337 338 336

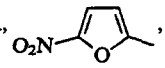
R^1 = Ad: R^2 = CCl_3, 2-ClC_6H_4, Ad;

R^2 = Ad: R^1 = Me, $ClCH_2$, CCl_3, 2-ClC_6H_4.

To prepare 2,5-disubstituted derivatives of 1,3,4-oxadiazole, cyclocondensation of the carboxylic acid hydrazides **339** with iminoester hydrochlorides **340** has been used. The yields of the oxadiazole derivatives were 50% – 70%.[56]

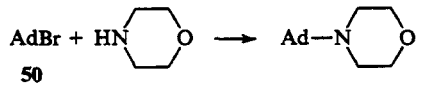


339 340

R = Me, Ph, , Ad.

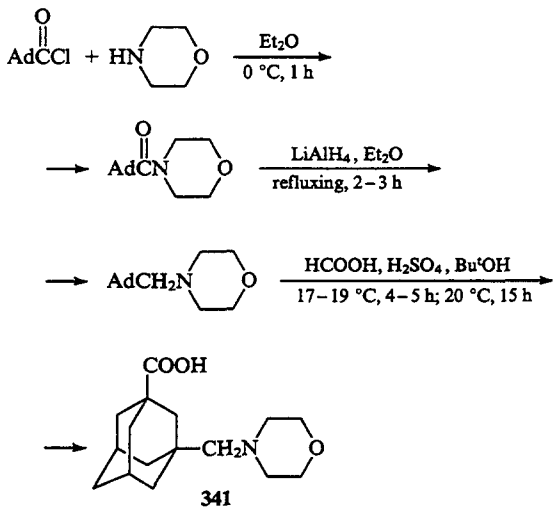
3. Compounds with six-membered heterocycles

Refluxing of a mixture of morpholine and the 1-bromoadamantane for 8 h gives rise to 4-(adamant-1-yl)morpholine, which has been claimed as a compound possessing an antiviral activity.[89]



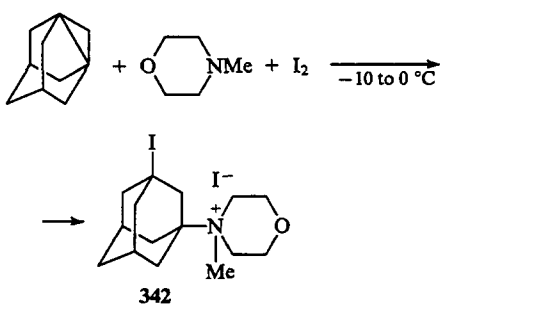
50

A method for preparing 3-(morpholinomethyl)adamantane-1-carboxylic acid **341** has been proposed. The method includes three stages. The reaction of the chloride AdCOCl with morpholine affords the morpholide of this acid (yield 72%), which is then reduced with lithium tetrahydroaluminate to 1-(morpholinomethyl)adamantane (yield 97%). The latter reacts with formic acid in the presence of sulfuric acid to give the compound **341** in 11% yield.[107]

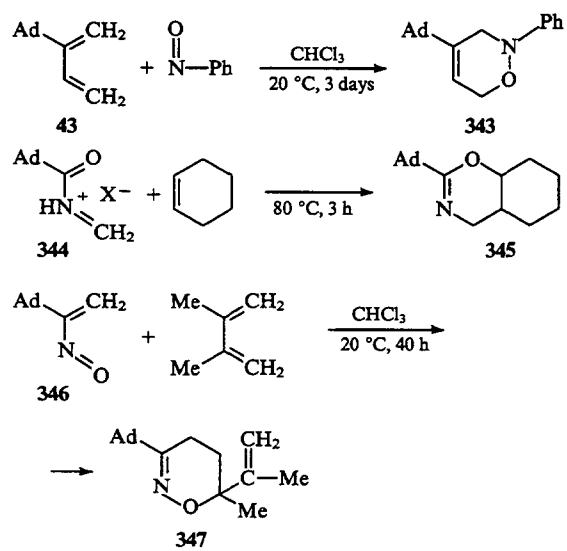


The hydrochloride of the compound **341** exhibits analgesic, anti-inflammatory, antipyretic, and antifibrillar activities.[107]

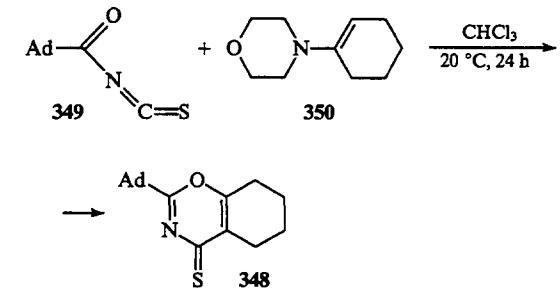
The salt **342** has been obtained in 42% yield from 1,3-dehydroadamantane, 4-methylmorpholine, and iodine by conjugated haloamination.[100]



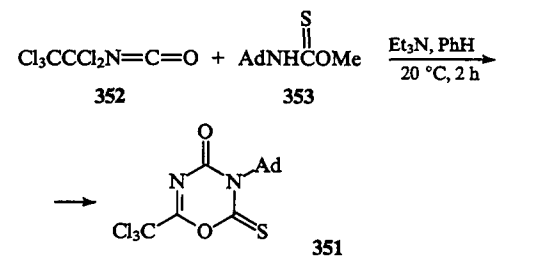
Derivatives of dihydro-1,2- and dihydro-1,3-oxazine have been prepared by diene condensation. 4-(Adamant-1-yl)-2-phenyl-3,6-dihydro-1,2-oxazine **343** has been synthesised in this way from the diene **43** and nitrosobenzene in 51% yield; the adduct **345** was obtained from the diene **344** and cyclohexene in 33% yield; and the interaction of the diene **346** and 2,3-dimethylbuta-1,3-diene gave rise to the adduct **347** (yield 59%).[47]



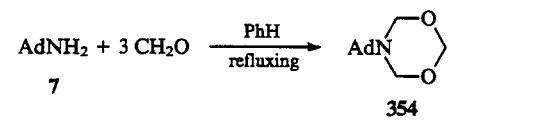
Compound **348** has been synthesised in 50% yield by the diene condensation of adamant-1-ylcarbonyl isothiocyanate **349** with the enamine **350**.[47]



A heteryladamantane, 2-(trichloromethyl)-6-thioxo-5*H*-1,3,5-oxadiazin-4-one **351**, has been obtained in 53% yield by the reaction of perchloroethyl isocyanate **352** with *N*-(adamant-1-yl)-*O*-methylthiourethane **353** in the presence of triethylamine.[188]



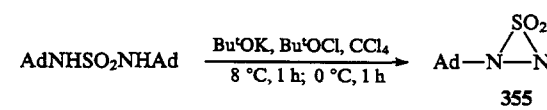
On heating in benzene, $AdNH_2$ condenses with three formaldehyde molecules affording the derivative of 1,3,5-dioxazine **354** (yield 49%).[139]



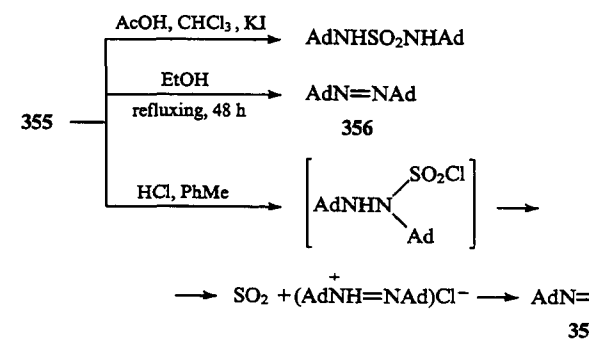
VI. Adamantane derivatives containing heterocyclic nuclei with nitrogen and sulfur atoms

1. Compounds with three-membered and four-membered heterocycles

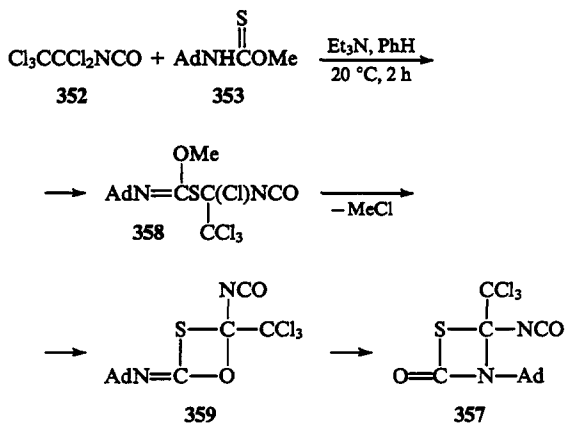
N,*N*'-Bis(adamant-1-yl)sulfonamide is converted into 2,3-di(adamant-1-yl)thiadiaziridine-1,1-dioxide **355** in 92% yield by treating it with potassium *tert*-butoxide and *tert*-butyl hypochlorite in tetrachloromethane.[189]



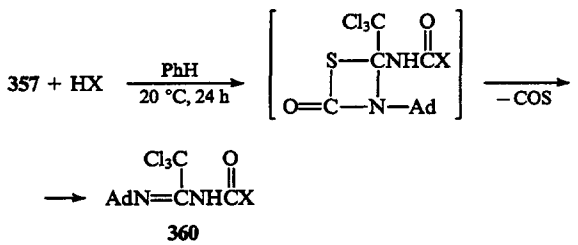
Diadamantyldiazene **356** is formed from the dioxide **355** when it is treated with hydrogen chloride in toluene (yield 100%) or refluxed in ethanol (yield 84%). Treatment of the dioxide **355** with potassium iodide in acetic acid leads to the initial *N*,*N*'-bis(adamant-1-yl)sulfonamide in 72% yield.[189]



When the isocyanate **352** reacts with thiourethane **353**, apart from the 1,3,5-oxadiazine derivative **351** (see above), 3-(adamant-1-yl)-2-isocyanato-2-trichloromethyl-1,3-thiazetidin-4-one **357** is formed in 28% yield. The investigators[188] believe that the formation of the thiazetidine **357** begins with the *S*-alkylation of the thiourethane with isocyanate and involves intermediate formation of unstable compounds **358** and **359**. This course of the reaction is due to the presence of the bulky adamantyl nucleus. In fact, the corresponding *N*-alkyl(aryl)thiourethanes do not give analogues of the compound **357** under these conditions.



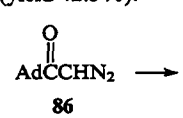
Thiazetidin-4-one **357** reacts with ethanol or with morpholine at 20 °C giving rise to compounds **360** in 65% and 78% yields, respectively.[188]

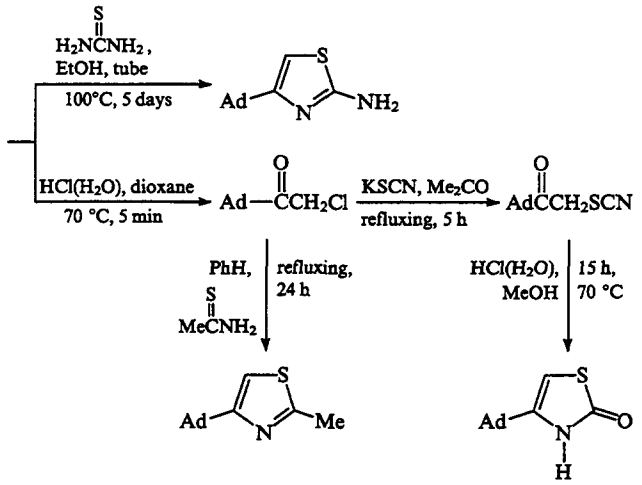


X = OEt, O⟨ ⟩N.

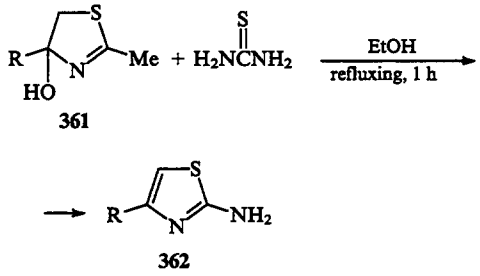
2. Compounds with five-membered heterocycles

Heating the ketone **86** with thiourea in alcohol gives rise to 4-(adamant-1-yl)-2-aminothiazole (yield 20%).[60,190] When the same ketone is treated with concentrated hydrochloric acid, adamant-1-yl chloromethyl ketone is formed (yield 84%); the latter reacts with thioacetamide affording 4-(adamant-1-yl)-2-methylthiazole in 45.5% yield.[60] The reaction of adamant-1-yl chloromethyl ketone with potassium thiocyanate leads to the ketone $AdCOCH_2SCN$, which is converted into 4-(adamant-1-yl)thiazol-2-one on treatment with concentrated hydrochloric acid (yield 42.5%).[60]





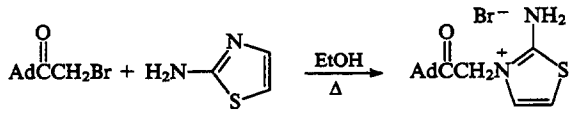
It is of interest that refluxing of the 1,3-thiazoline derivatives **361** with thiourea in alcohol leads to 2-amino-4-R-thiazoles **362** in 85%–98% yields.[191]



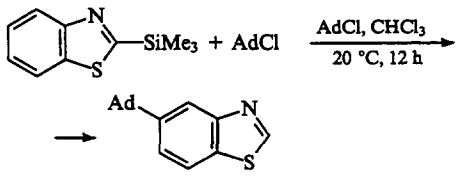
R = Ad, $AdCH_2$, 3-ClAd, 3-BrAd.

5-(Adamant-1-yl)-3-aminothiazole has been synthesised by keeping the aldehyde AdCH(Br)CHO and thiourea at 200 °C for 10 min followed by refluxing in alcohol for 10 min (yield 55%).[191]

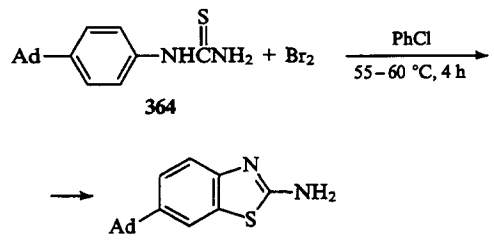
The salt **363** has been obtained in 43% yield by heating 2-aminothiazole with the ketone **41**.[46]



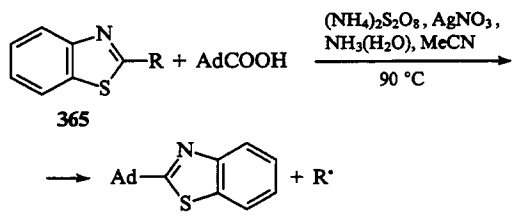
When 2-(trimethylsilyl)benzothiazole reacts with AdCl in the presence of aluminium chloride, the adamantyl radical substitutes the hydrogen atom in the 5-position of the benzene ring, and the Me_3Si group is substituted by the hydrogen atom.[50]



6-(Adamant-1-yl)-2-aminobenzothiazole is formed in the reaction of the thiourea derivative **364** with bromine (yield 40%).[45]

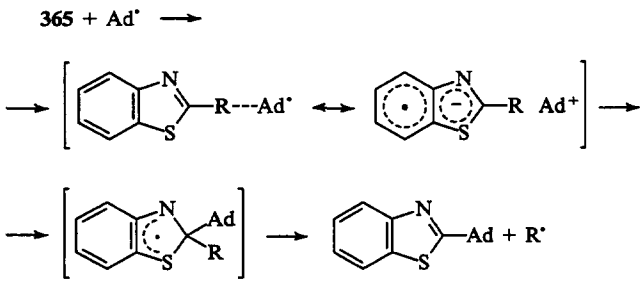


The homolytic *ipso*-substitution in the series of benzothiazole derivatives has been studied fairly comprehensively.[192–194] The benzothiazole derivatives **365** and the acid AdCOOH were treated with ammonium peroxydisulfate and silver nitrate in acetonitrile in the presence of aqueous ammonia at 90 °C for 20 min. The last stage of this reaction is the displacement of the substituent in the 2-position of the benzothiazole nucleus and its substitution by the adamantyl radical.[192–194]

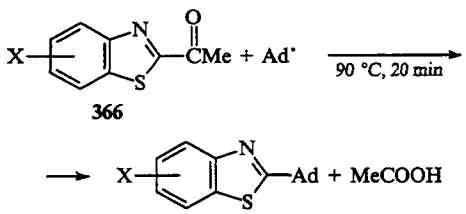


R (yield, %) = $PhSO_2$ (80), PhSO (80), PhCO (55), MeCO (60), CHO (40), MeS (60), MeO (40), Br (70), Cl (50), F (50),[192] CHO (40), MeCO (60), COEt (60), PhCO (55), 4-ClC_6H_4 (56), 4-MeC_6H_4CO (52), 4-$MeOC_6H_4$ (50),[193] NO_2 (100).[194]

A possible scheme for this reaction has been suggested.[192,193]

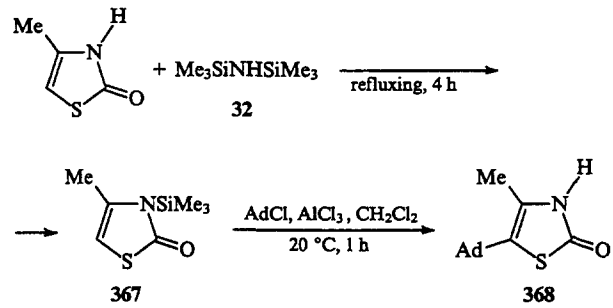


The presence of electron-withdrawing substituents in the 5- or 6-position facilitates this reaction. The relative rates (v) of the substitution of the acetyl radical by the adamantyl radical in the 2-acetylbenzothiazole derivatives **366** have been measured.[193]

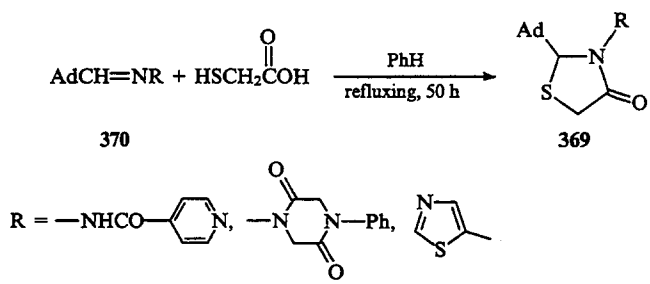


X (v) = 6-CN (10.92), 6-Cl (2.30), 5-Cl (2.18), 5-MeO (1.26), H (1.0), 5-Me (0.86), 6-Me (0.6), 6-MeO (0.46).

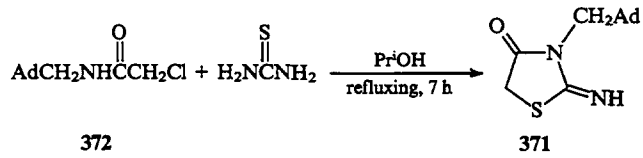
Treatment of compound **367**, obtained by silylation of 4-methyl-3*H*-thiazolin-2-one with disilazane **32**, with 1-chloroadamantane in the presence of $AlCl_3$ has led to 5-(adamant-1-yl)-4-methyl-3*H*-thiazolin-2-one **368**.[37]



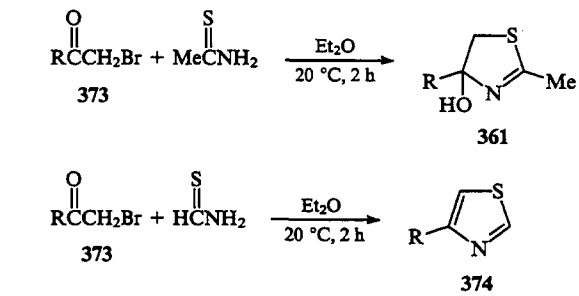
The derivatives of thiazolidin-4-one **369** inhibiting the growth of Gram-positive and Gram-negative bacteria and acting as fungicides have been synthesised by cyclocondensation of the Schiff's bases **370** with thioglycolic acid.[195]

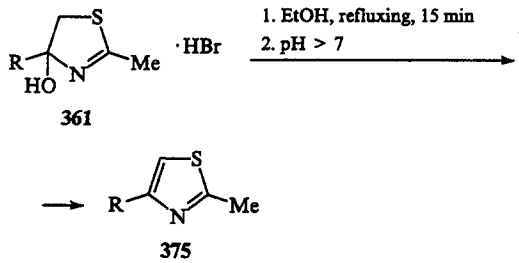


3-(Adamant-1-ylmethyl)-2-iminothiazolidin-4-one **371** is formed on refluxing the chloroacetamide **372** and thiourea in isopropyl alcohol (yield 58%).[196]



The nature of the radical R in the thioamides $RC(S)NH_2$ plays the crucial role in their interaction with the ketones **373**. For example, the reaction of $MeC(S)NH_2$ with the ketones **373** affords the 4-hydroxythiazolines **361**, whereas the interaction of $HC(S)NH_2$ with these ketones leads to the thiazole derivatives **374**. The yields of all the compounds obtained vary from 70% to 97%. Hydroxythiazoline hydrobromides on refluxing in alcohol are converted into the thiazole derivatives **375**.[191]

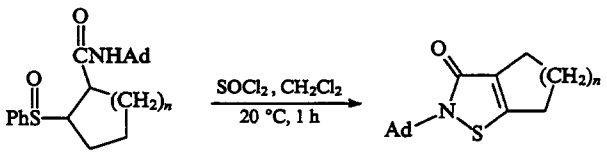




361 → 375

R = Ad, $AdCH_2$, 3-ClAd, 3-$BrCH_2$Ad.

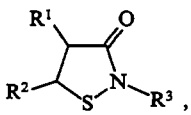
Compounds **376** cyclise on treatment with thionyl chloride giving the isothiazolin-3-one derivatives **377**, which have been recommended as bactericides and fungicides.[197]



376 377

n = 1, 2.

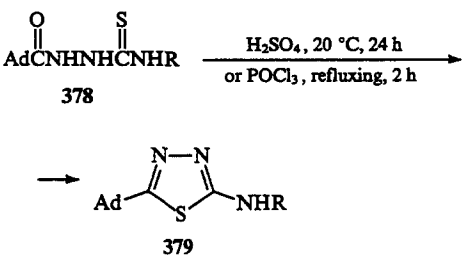
Compounds of the general formula



R^1, R^2 = H, Hal; R^3 = Ad, $AdCH_2$,

were claimed as bactericides and fungicides in the same patent.[197]

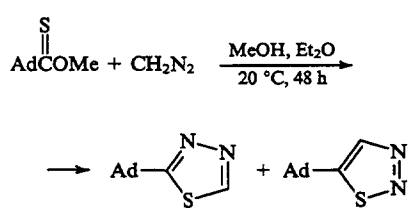
The transformation of adamant-1-ylcarbonylthiosemicarbazide **378** into the 2,5-disubstituted 1,3,4-thiadiazoles **379** has been achieved by means of cyclisation agents such as concentrated sulfuric acid or phosphorus oxychloride.[198] When concentrated sulfuric acid was used for R = Me and Et, the yields of the products **378** were 51% and 55%, whereas with phosphorus oxychloride in the case where R = Me, Et, 4-XC_6H_4 (X = F, Cl, Br), and $PhCH_2$, the yields were 61%–68%.



378 → 379

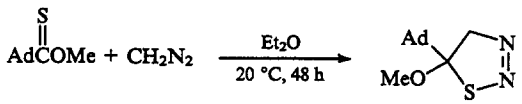
R = H, Me, Et, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, $PhCH_2$.

The interaction of the *O*-methyl adamantane-1-carbothioate with diazomethane in a mixture of ether and methanol in the dark gives rise to two compounds: 1,3,4-thiadiazole **380** and 1,2,3-thiadiazole **381** derivatives (yields 7% and 32%).[108]



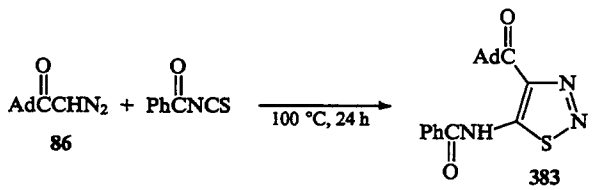
380 381

If this reaction is carried out in the absence of methanol only one compound, 5-(adamant-1-yl)-5-methoxy-1,2,3-thiadiazoline **382** is formed in 22% yield.[108]



382

4-Adamant-1-ylcarbonyl-5-benzoylamino-1,2,3-thiadiazole **383** has been synthesised from the ketone **86** and benzoyl thioisocyanate with heating (yield 50%).[60,199]

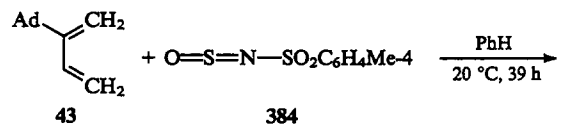


86 383

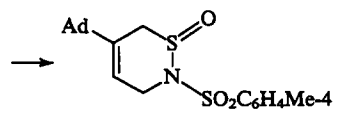
Compound **383** and its 5-aroylamino-analogues possess bactericidal and antiviral activities.[199]

3. Compounds with six-membered heterocycles

The adamantane derivatives containing six-membered heterocyclic nuclei incorporating nitrogen and sulfur atoms can be obtained by diene condensation. Cyclocondensation of *N*-sulfenyltoluene-*p*-sulfonamide **384** with the diene **43** at ambient temperature affords the 1,2-thiazine derivative **385** (yield 89%).[47]

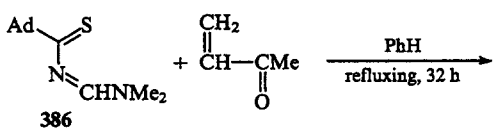


43 384

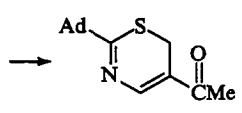


385

N-(Adamant-1-ylthiocarbonyl)-*N'*,*N'*-dimethylformamidine **386** reacts with methyl vinyl ketone on refluxing in benzene giving rise to the 1,3-thiazine derivative **387** (yield 36%).[47]



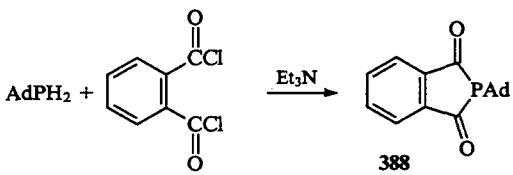
386



387

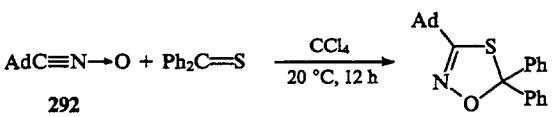
VII. Adamantane derivatives containing other heterocyclic nuclei

The heterocyclic compound **388** containing a five-membered ring with a phosphorus atom has been synthesised by cyclocondensation of (adamant-1-yl)phosphane with phthalic acid chloride in the presence of triethylamine.[200]



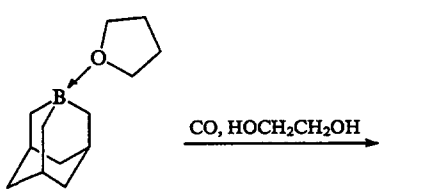
388

At 20 °C, the nitrile *N*-oxide **292** enters into 1,3-dipolar cycloaddition with thiobenzophenone, which affords 3-(adamant-1-yl)-5,5-diphenyl-1,4,2-oxathiazole in 75% yield.[169]

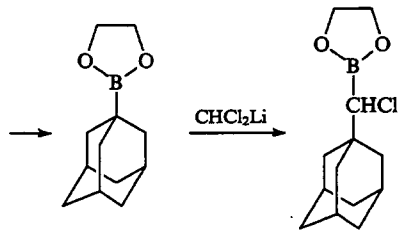


292

The complex of boraadamantane with tetrahydrofuran **389** reacts with carbon monoxide giving (adamant-1-yl)borodioxolane **390**, interaction of which with lithiodichloromethane gives rise to compound **391**.[201]

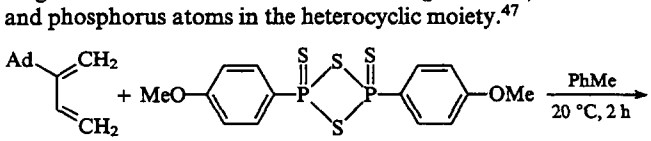


389

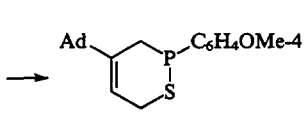


390 391

The Lawesson reagent **392** can act as the dienophile in diene condensation. For example, the reaction of the diene **43** with this reagent at 20 °C affords the adduct **393** (yield 85%) with sulfur and phosphorus atoms in the heterocyclic moiety.[47]

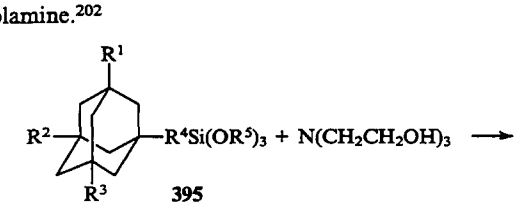


43 392

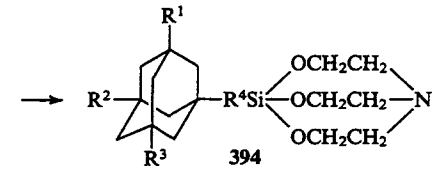


393

Compounds **394** have been synthesised in 50%–80% yields by the condensation of adamantane derivatives **395** with triethanolamine.[202]



395



394

R^1 = H: R^2 = H, Me; R^3 = H, Me, Et;
R^1 = R^2 = R^3 = Me; R^4 = alkylene, arylene, thienylene;
R^5 = alkyl.

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