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SPIRO COMPOUNDS CONTAINING ADAMANTANE AND HETEROCYCLIC FRAGMENTS (REVIEW)

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Data on the synthesis of compounds containing adamantane and heterocyclic fragments with a common carbon atom are reviewed, classified, and analyzed for the first time.

INTRODUCTION

Spiro compounds in which the spiro carbon atom is part of a heterocyclic ring are of potential interest as biologically active substances, components of photochromic systems, and compositions for data recording.

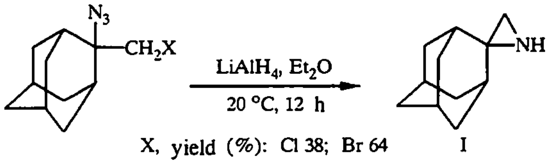
In spite of the large number of publications devoted to the synthesis and investigation of spiro compounds in which the spiro atom is a carbon atom belonging to adamantane and to various heterocyclic systems, there have not so far been any papers reviewing the published data on this subject. Of the large number of reviews devoted to the chemistry of adamantane only three [1-3] mention isolated examples of such compounds.

In the present review we discuss published data on the synthesis of spiro compounds containing adamantane and heterocyclic fragments. The chemical properties of such compounds are only considered in cases where the heterocyclic fragment undergoes a transformation leading to the formation of a different heterocyclic system. If the heterocyclic fragment in the spiro compound consists of several heterocyclic rings, the compound is regarded as a derivative of the heterocyclic system closest to the adamantane fragment.

1. COMPOUNDS CONTAINING THREE-MEMBERED HETEROCYCLES

1.1. Nitrogen-Containing Heterocycles

Spiro[adamantane-2,2′-aziridine] (I) was synthesized by the action of lithium aluminum hydride on 2-azido-2-halogenomethyladamantanes [4]:



X, yield (%): Cl 38; Br 64 I

N-Substituted spiro[adamantane-2,2′-aziridine]-3′-ones (II) are formed as a result of the treatment of the amides (III) with potassium *tert*-butoxide [5]:

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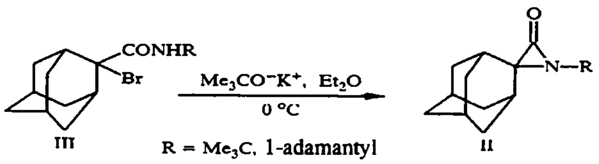
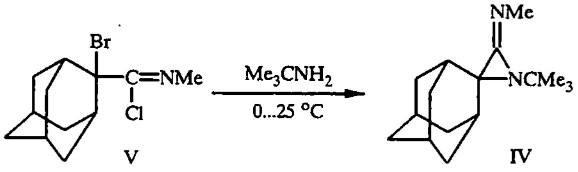
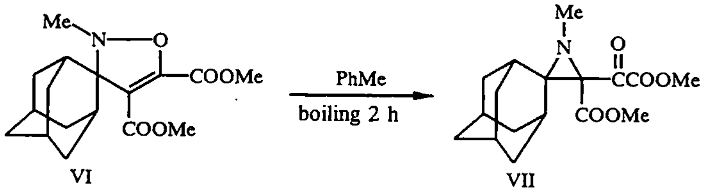


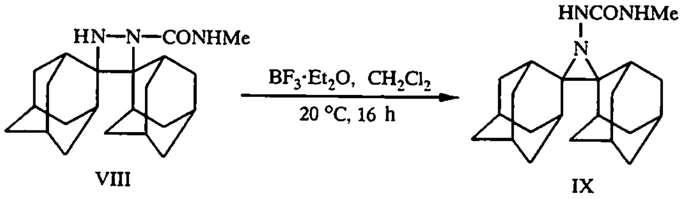
The synthesis of the aziridine derivative (IV) was achieved with an 80% yield by the cyclocondensation of the imidoyl chloride (V) with *tert*-butylamine [6]:



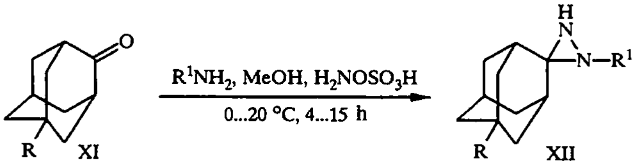
If compound (VI) is boiled in toluene, the isoxazole ring undergoes recyclization to an aziridine ring, and the aziridine derivative (VII) is formed with an 88% yield [7]:



In the presence of boron trifluoride etherate the semicarbazide (VIII) is transformed at normal temperature into compound (IX) with a yield of 37% [8]:

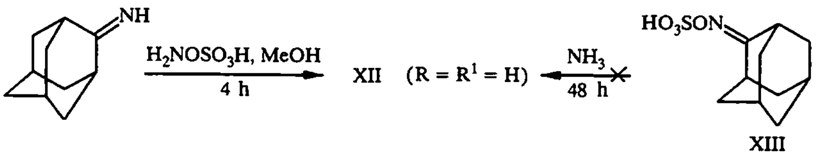


The action of hydroxylamine-O-sulfonic acid (X) and ammonia [9-11] or methylamine [11] on the ketones (XI) leads to the formation of diaziridine derivatives (XII) (yields 62-72%):

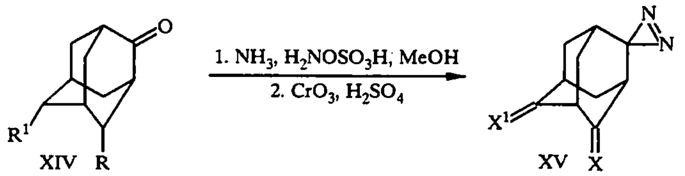


R = H, OH, COOH, COOMe, R^1 = H; R = COOMe, R^1 = Me

While studying the reactions of adamantanone imine with (X) or ammonia with (XIII), the authors in [12] established that the diaziridine derivatives (XII) (R = R^1 = H) are formed only as a result of the first reaction:



During the successive action of ammonia and (X) (−7 to −5°C, 53 h) and then chromic anhydride and sulfuric acid (20°C, 2 h) the hydroxy derivatives of adamantanone (XIV) are converted into the diazirines (XV) [13]:



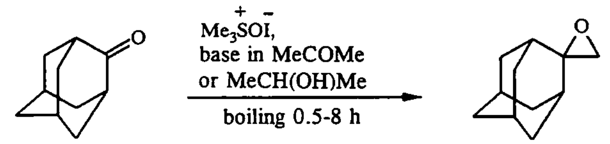
R, R^1, X, X^1, yield (%): OH, H, O, H_2, 18,5; H, OH, H_2, O, 37

Under analogous conditions adamantane-2,4-dione or adamantane-2,6-dione is transformed into bisspiro[adamantane-2,3′,4,3′-diaziridine] (yield 6.5%) or into bisspiro[adamantane-2,3′,6,3′-diazirine] (yield 28.4%) and compound (XV) (X = H_2, X^1 = O) (yield 24.7%) [13].

The diaziridine (XII) (R = R^1 = H) was synthesized with a yield of 48.5% from the adamantanone (XVI) by the action of ammonia and chloramine in methanol [14].

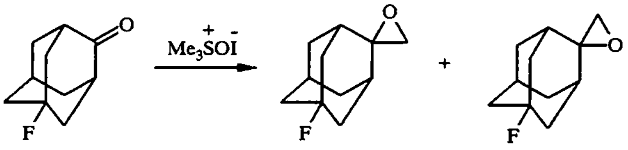
1.2. Oxygen-Containing Heterocycles

The spiro[adamantane-2,2′-oxirane] (XVII) is formed with an 82-96% yield as a result of the reaction of the ketone (XVI) with dimethylsulfoxonium methylide (formed *in situ* by the action of sodium hydroxide [15] or $Me_3CO^-K^+$ [16] on trimethylsulfoxonium iodide) [15-17]:



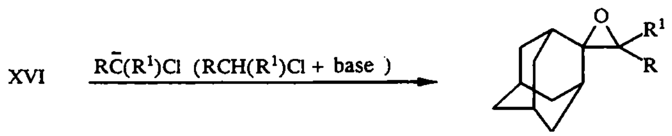
XVI XVII

During the reaction of 5-fluoroadamantanone with trimethylsulfoxonium iodide a 35:65 mixture of the *E* and *Z* isomers of 5-fluorospiro[adamantane-2,2′-oxirane] (XVIII) was obtained [18]:



E-XVIII *Z*-XVIII

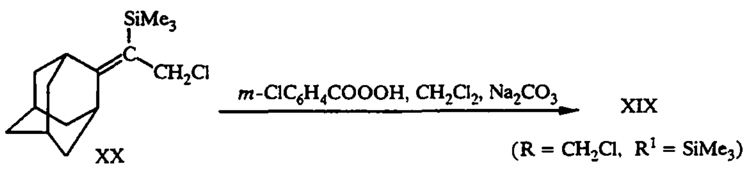
The anions $RC^-(R^1)Cl$, formed from $RCH(R^1)Cl$ by the action of MeCH(Et)Li [19, 20], $(Me_2CH)_2NLi$ [21], or sodium hydroxide [22], react with the ketone (XVI), forming the oxiranes (XIX):



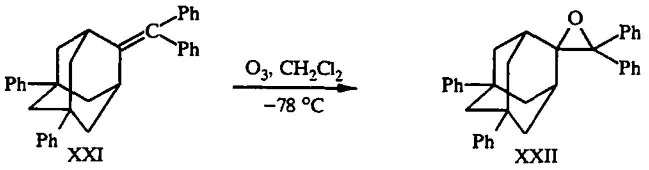
XIX

R,R^1, yield %: Me3Si, Me, 60 [19]; Me3Si, H, 95 [20]; 2-benzothiazolyl , H, 65 [21]; 2-methoxy-1-pyrrolidinyl sulfoxides , H, 47 [22]

The oxirane (XIX) (R = CH_2Cl, R^1 = $SiMe_3$) was obtained with a 70% yield during the oxidation of the adamantane derivative (XX) by *m*-chloroperbenzoic acid [23]:

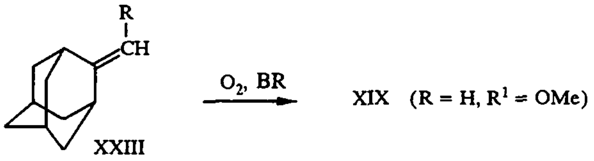


5,7-Diphenyl-2-(diphenylmethylene)adamantane (XXI) is converted by the action of ozone into the oxirane derivative (XXII) (yield 40%) [24]:

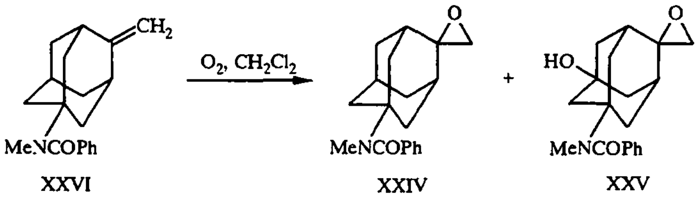


The photooxidation of unsaturated derivatives of adamantane has been used quite often for the production of spiro[adamantaneoxiranes].

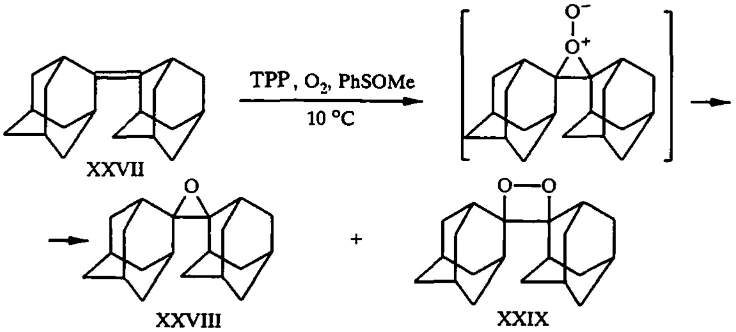
The photooxidation of 2-methoxymethyleneadamantane (XXIII) (R = OMe) in the presence of Bengal rose (BR) as sensitizer gave a 12% yield of the oxirane (XIX) (R = H, R^1 = OMe) [25].



A mixture of two compounds (XXIV, XXV) (yields 5 and 26%) is formed as a result of the oxidation of the alkene (XXVI) in the presence of ATCC 7159 (*Beauveria sulfurescens*) [26]:



The oxidation of adamantylideneadamantane (XXVII) with oxygen in the presence of tetraphenylporphyrin (TPP) with irradiation by a high-pressure sodium lamp (250 W) gives the oxirane (XXVIII) and 1,2-dioxetane (XXIX). The ratio of the compounds depends on the solvent and particularly on whether or not the reaction is conducted in the presence of methyl phenyl sulfoxide [27]:



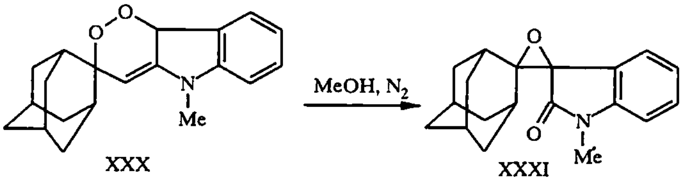
Solvent, yield (%) of (XXVIII) and (XXIX) in the presence or absence of PhSOMe: PhH, 97 and 3 or 6 and 93; CCl_4, 100 and 0 or 13 and 86; CH_2Cl_2, 26 and 75 or 2 and 99

The oxidation of compound (XXVII) by oxygen in the presence of derivatives of TPP in benzene leads to mixtures of (XXVIII) and (XXIX) in various ratios: in the presence of Mn(TPP)Cl 84% of (XXVIII) and 11% of (XXIX); in the presence of Fe(TPP)Cl 72% of (XXVIII) and 26% of (XXIX); in the presence of Mn(TPP)Cl and bicyclo[3.3.1]-nonylidenebicyclo[3.3.1]nonane 88% of (XXVIII) and 12% of (XXIX); without TPP derivatives 6% of (XXVIII) and 94% of (XXIX) [28].

The oxirane (XXVIII) is formed with a 71% yield during the oxidation of compound (XXVI) with oxygen in the presence of $Cr(NO_3)_2$ in DMFA at −78°C for 1 h [29].

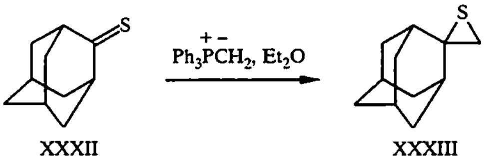
The oxirane derivative (XIX) (R = $OSiMe_3$, R^1 = H) was synthesized with an almost quantitative yield by the reaction of compound (XXIII) (R = $OSiMe_3$) with dimethyloxirane in acetone and dichloromethane at −40°C for 3 h in an atmosphere of nitrogen [30].

Compound (XXX) undergoes recyclization after 3.5 h when dissolved in methanol at −10°C with the formation of the hydroxyindole derivative (XXXI) (yield 62%) [31]:

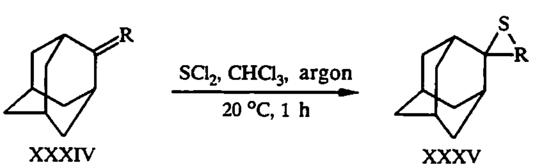


1.3. Sulfur-Containing Heterocycles

The 1,3-dipolar cycloaddition of adamantanethione (XXXII) with the ylide $Ph_3P^+C^-H_2$ (formed *in situ* during the action of butyllithium on Ph_3PCH_2X) leads to spiro[adamantane-2,2′-thiirane] (XXXIII) with a yield of 80% [32]:

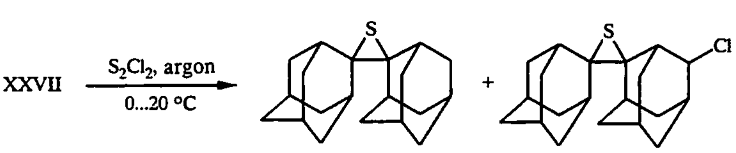


Compound (XXXIV) reacts with sulfur dichloride at 20°C in an atmosphere of argon, and the thiirane derivative (XXXV) is formed with a 43% yield [33]:

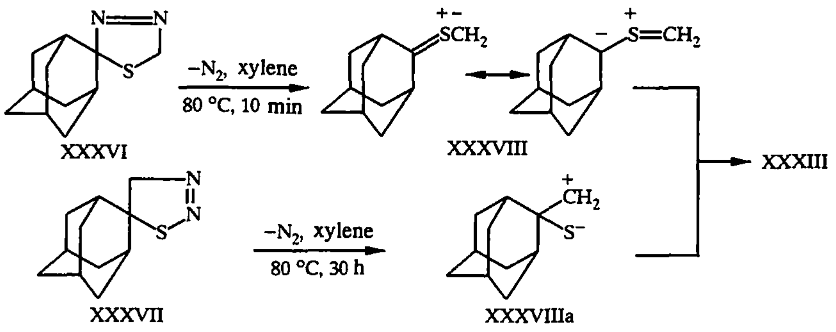


R = 2,3-(methoxycarbonyl)-7-bicyclo[2.2.1]heptylidene

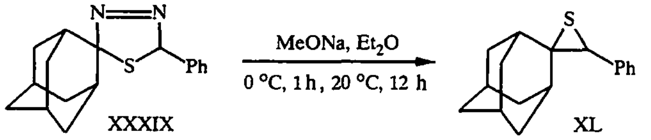
The reaction of compound (XXVII) with sulfur monochloride at 0-20°C in chloroform or methylene chloride results in chlorination of the adamantane ring in addition to insertion of the sulfur at the double bond [34]:



When heated in xylene, the thiazolidine derivatives (XXXVI, XXXVII) lose a nitrogen molecule and give the thiocarbonylylides (XXXVIII) or (XXXVIIIa), which undergo cyclization to the thiirane (XXXIII) (yields 94 and 70% respectively) [35]:

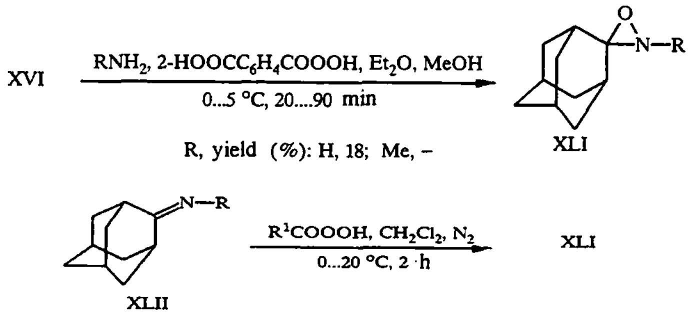


The spiro compound (XXXIX) undergoes recyclization under the influence of sodium methoxide to the thiirane derivative (XL) with a yield of 94%:



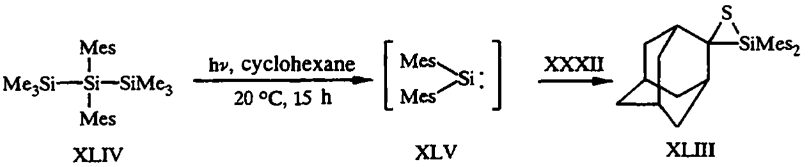
1.4. Heterocycles with Two Different Heteroatoms

The synthesis of the oxaziridine derivatives (XLI) was realized in two ways: by the action of ammonia or methylamine on the ketone (XVI) in the presence of monoperphthalic acid [36] or by the oxidation of the azomethines (XLII) by peracids R^1COOOH [37, 38]:

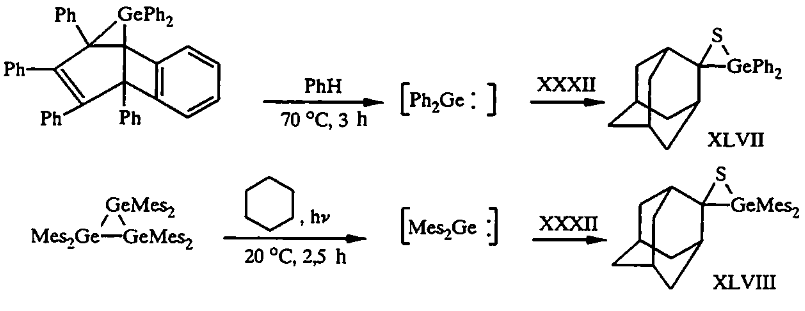


R, R^1, yield, %: Bu, Me, 71; $PhCH_2$, Me, 60; cyclohexyl, Me, 82; 1-adamantylmethyl, Me, 85;
1-adamantylmethyl, Me, 18 [37]; $PhCH_2$, Ph, 95 [38]

The spiro compound (XLIII), which contains a silathiacyclopropane ring, was synthesized with a 29% yield by irradiation of the thioketone (XXXII) and 2,2-dimesityl-1,1,1,3,3,3-hexamethyltrisilane (XLIV) in a quartz tube at 20°C for 15 h. Dimesitylsilylene (XLV) is clearly formed in the reaction [39]:



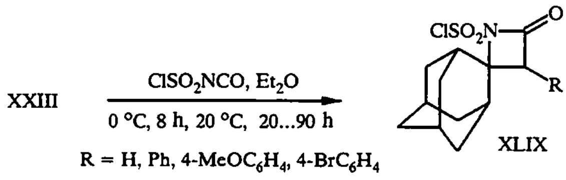
The intermediate formation of diphenylgermylene [40] or dimesitylgermylene [40, 41] was postulated in the reactions of the thioketone (XXXII) with the respective organogermanium compounds. The reaction of the thioketone (XXXII) with compound (XLVI) at 70°C in benzene leads to the germathiirane derivative (XLVII) [40], while the reaction of hexamesitylcyclotrigermane with the thioketone (XXXII) in cyclohexane at 20°C with irradiation by a low-pressure mercury lamp leads to compound (XLVIII) (yield 53%) [40, 41]:



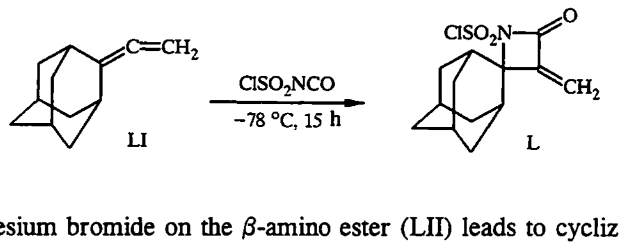
2. COMPOUNDS CONTAINING FOUR-MEMBERED HETEROCYCLES

2.1. Nitrogen-Containing Heterocycles

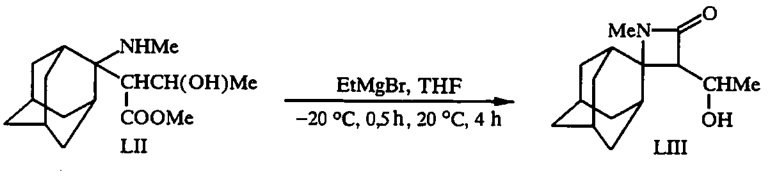
The only described method for the synthesis of spiro[adamantaneazetidines] (XLIX) (yields 51-100%) is 1,3-dipolar cycloaddition of the adamantane derivatives (XXIII) with chlorosulfonyl isocyanate in an inert gas atmosphere [4, 42-44]:



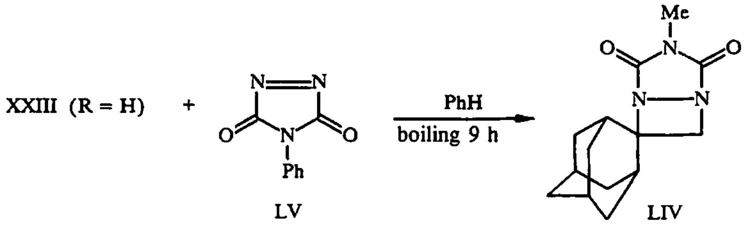
The azetidinone derivative (L) is formed with a yield of 41% as a result of the reaction of the cumulene (LI) chlorosulfonyl isocyanate [45]:



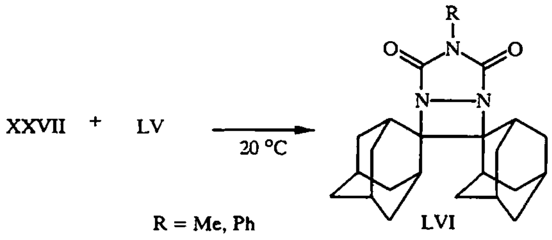
The action of ethylmagnesium bromide on the β-amino ester (LII) leads to cyclization to the spiro compound (LIII) with a yield of 33% [42]:



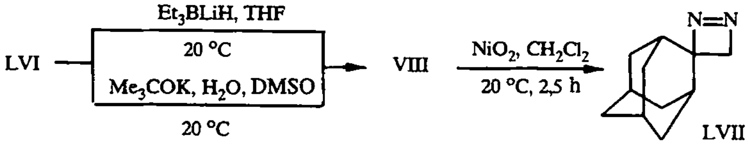
Compound (LIV), which contains a bicyclic heterocyclic ring, was synthesized by the cycloaddition of the olefin (XXIII) (R = H) with the urazole (LV) (R = Ph) [4]:



Adamantylideneadamantane (XXVII) reacts with the urazole derivative (LV) at 20°C, and the adducts (LVI) are formed with high yields [46, 47]:

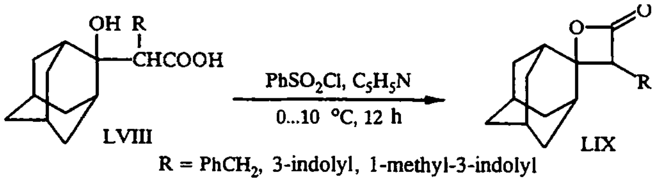


The transformation of the adduct (LVI) into the cyclic semicarbazone (VIII) is realized in two ways, i.e., by the action of Et_3BLiH in THF at 20°C for 4.5 h (yield 87%) or by reaction with $Me_3CO^-K^+$ in water—DMSO at 20°C for 50 min (yield 58%) [8]. When treated with nickel dioxide, the semicarbazide (VIII) is transformed into the diazetine derivative (LVII) [8]:

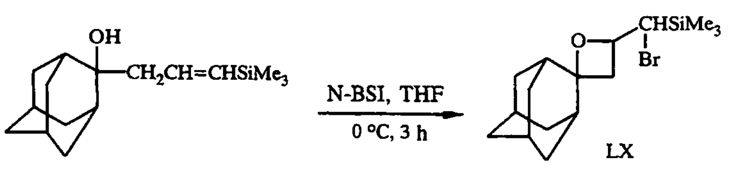


2.2. Oxygen-Containing Heterocycles

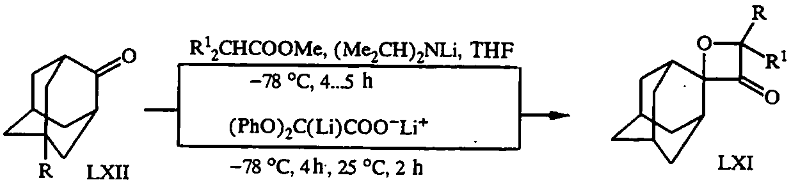
The intramolecular cyclization of β-hydroxy acids (LVIII) by the action of benzenesulfonyl chloride leads to the oxetane derivatives (LIX); the yields are 62-90% [31, 48]:



2-Hydroxy-2-[3-(trimethylsilyl)-2-propenyl]adamantane readily undergoes cyclization when treated with N-bromosuccinimide, forming compound (LX) with yields of 80-92% [49, 50]:

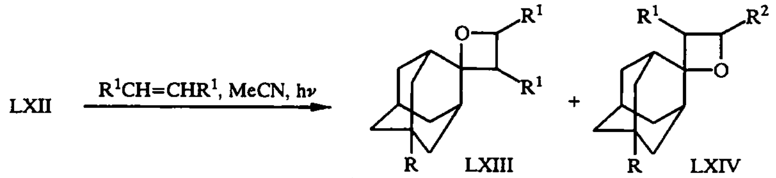


The reactions of the ketones (LXII) with the esters $R_2{}^1CHCOOMe$ in the presence of $(Me_2CH)_2NLi$ or with the dilithium derivatives $(PhO)_2CH(Li)COO^-Li^+$ were investigated for the synthesis of the oxetane derivatives (LXI) [51, 52]:



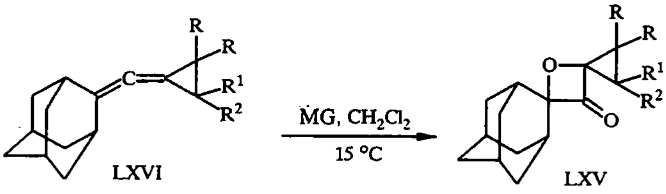
R, R^1, yield, %: H, Me, 85; H, PhO, 40; H, $PhCH_2O$, 3,5; F,Me, -

While studying the photocycloaddition of the ketones (LXII) with fumaronitrile or with *cis*-1,2-diethoxyethylene during irradiation by a 1-kW Xe/Hg lamp for 48 h, the authors of [53, 54] established that the ratio of the products (LXIII, LXIV) was ~60:40; at the same time with low degrees of transformation only compounds (LXIII) were formed:



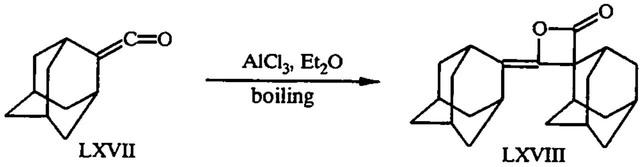
R = F, Cl, Br, OH, Ph, Me_3C; R^1 = CN, OEt

The spiro compounds (LXV) were synthesized with yields of 7-12% by oxidation of the cumulenes (LXVI) by oxygen with irradiation by 1-kW halogen lamps in the presence of "MG" dye as sensitizer [55]:

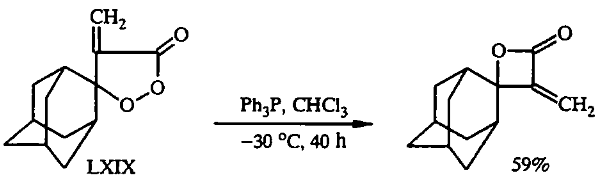


R, R^1, R^2 = Me, Me, H; H, Me, CH=CH_2; H, H, Ph

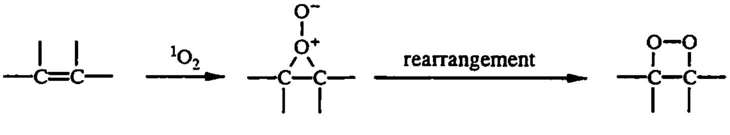
In the presence of aluminum chloride the ketene (LXVII) gives the dimer (LXVIII) with a 50% yield [56]:



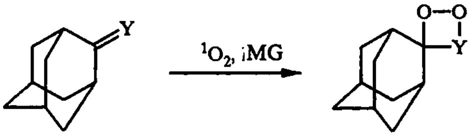
When treated with triphenylphosphine at −15°C in chloroform compound (LXIX) undergoes ring contraction with the loss of an oxygen atom [57]:



The main method for the synthesis of spiroadamantane-1,2-dioxetanes is photooxidation of the unsaturated derivatives of adamantane with a semicyclic double bond usually in the presence of sensitizers. The reagent in these reactions is singlet oxygen.

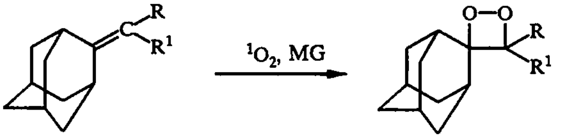


A number of authors have conducted oxidation by singlet oxygen in the presence of the dye MG.



Y, (conditions), yields, %, [references]: camphylidene (500-W lamp, solvents methylene chloride, acetonitrile, methanol, acetone), –, [58]; adamantylidene, [500-W tungsten—iodine lamp, methylene chloride, Corning 3060 filter, 2,4-di(*tert*-butyl)phenol], 66, [59]; adamantylidene, (oxidation by the complex $Ph_3P{\cdot}O_3$), 85, [60]; 10-methyl-9-carbazolylidene, (methylene chloride), 100, [61]; methoxy-(7-acetoxy-2-naphthyl)methylene, (250-W sodium lamp, methylene chloride), 84, [62]; methoxymethylene, (methylene chloride), 100, [63]; 9-xanthylidene, –, 80, [64]

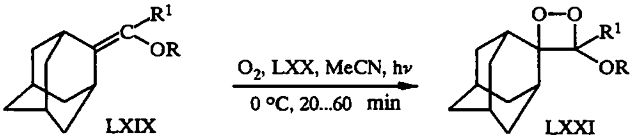
The oxidation of methyleneadamantane and its substituted derivatives in the presence of the dye MG has been investigated.



R, R^1, (conditions), yields, %, [references]: H, H, (here and subsequently 150-W lamp, carbon tetrachloride), –; Ph, Ph, –; CRR^1 = fluorenylidene, 70; Me, Me, –; H, OPh, 25; H, 4-BrC_6H_4O, 25; H, $PhCH_2O$, 23; OPh, OPh, 89; H, N-morpholinyl, –; H, SPh, –; -$\overline{CS(CH_2)_3S}$, -, –, [51]; H, S, Ph, (150-W sodium lamp, deuterochloroform), –, [65]; H, PhO, (here and subsequently 500-W high-pressure sodium lamp, THF), 75; H, 4-ClC_6H_4O, 66; H, 4-MeC_6H_4O, 31; H, 4-$MeOC_6H_4O$, 55, [66]; OMe, 3-OPO_3Na_2-phenyl, –, [67]; OMe, 2-hydroxy-6-naphthyl, (1-kW sodium lamp, methylene chloride), –, [68]; 4-acetoxyphenyl, $-CH_2CH_2R^2$, (1-kW sodium lamp, dioxane-d_8), 95, [69]; 4-hydroxyphenyl, $O(CH_2)_3COO\overline{NC(O)(CH_2)_2C}(O)$, (1-kW sodium lamp, methylene chloride), –, [70]; OMe, 3-OPO_3Na_2-1-naphthyl, (here and subsequently 250-W high-pressure sodium lamp, Amberlist 120-pyridinium sulfate, Na_2PO_4, methylene chloride), 100; MeO, 6-OPO_3Na_2-1-naphthyl, 96; MeO, 6-OPO_3Na_2-2-naphthyl, 57; MeO, 7-OPO_3Na_2-2-naphthyl, 59, [71]

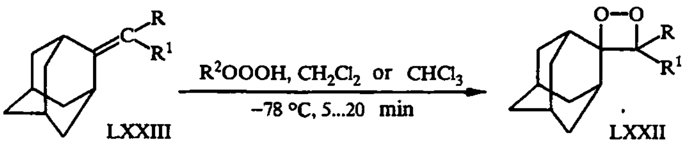
See above for the synthesis of derivatives of 1,2-dioxetanes by the photooxidation of the alkene (XXVI) in the presence of TPP [27, 28].

9,10-Dicyanoanthracene (LXX) was used as sensitizer for the photooxidation of adamantane derivatives (LXIX); the yields of the 1,2-dioxetanes (LXXI) were 92-95%:



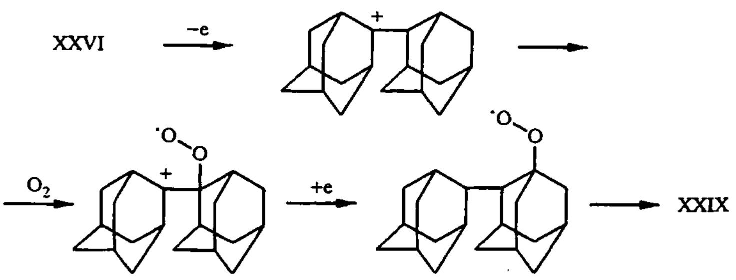
R, R^1 – Me, Ph; Me, 1-naphthyl; Me, 2-naphthyl; $PhCH_2$, Ph; Me, 4-diphenyl

The synthesis of the 1,2-dioxetanes (LXXII) by the oxidation of the alkenes (LXXIII) with the trioxides R^2OOOH at −78°C was reported in two papers [73, 74]:

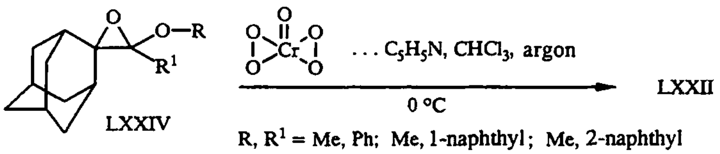


R, R^1, R^2, yield , %: CRR^1-adamantylidene, $Me_2C(OH)$, 24; CRR^1-adamantylidene $Me_2C(OCHMe_2)$, 12; CRR^1-adamantylidene, $MeC(OEt)_2$, 54; CRR^1-adamantylidene, PhCO, 16, [73]; OMe, 3-HOC_6H_4, Et_3Si, 47; OMe, H, Et_3Si, 34; H, Ph, Et_3Si, -, [74]

The authors of [75] carried out the electrochemical oxidation of adamantylideneadamantane (XXVI) to the dioxetane (XXIX) (yield 85%) with oxygen in the presence of tetrabutylammonium perchlorate in methylene chloride at a platinum electrode at a constant potential of 1.6 V. They propose the following mechanism:



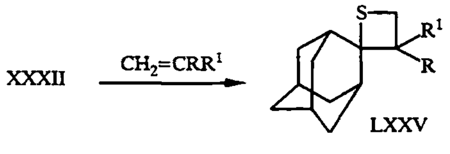
Under the influence of the chromium oxide—peroxide complex with pyridine at 0°C in an inert atmosphere the oxiranes (LXXIV) undergo recyclization and are converted into derivatives of 1,2-dioxetane (LXXII) with yields of more than 80% [76]:



R, R^1 = Me, Ph; Me, 1-naphthyl; Me, 2-naphthyl

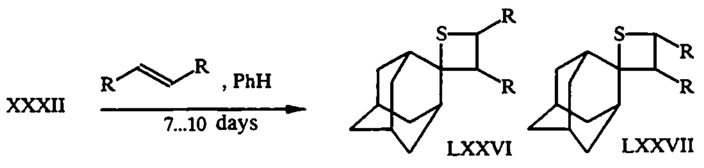
2.3. Sulfur-Containing Heterocycles

The photocycloaddition of the thioketone (XXXII) to the alkenes $RR^1C{=}CH_2$ takes place regioselectively and gives one isomer of each of the thietane derivatives (LXXV) [77, 78]:



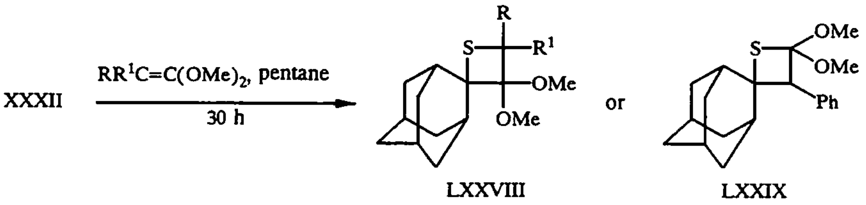
R, R^1, conditions, yield, %, [reference]: H, OEt or CN, tube, cyclohexane, hν (λ 254 nm), 40 min, 50 or 70, [77]; Ph, Ph, here and subsequently 450-W mercury lamp with a Corning 3-72 filter (λ 420 nm), 5-8 days, 8; H, OEt, 72; H, CN, 60; Me, Ph, 31, [78]

The reaction of the thioketone (XXXII) with substituted ethylenes *trans*-RCH=CHR during irradiation by a mercury lamp (λ 420 nm) gives a mixture of stereoisomers (LXXVI, LXXVII) [78]:



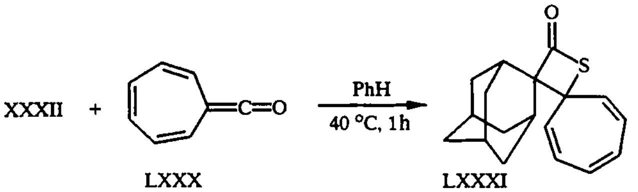
R, ratio LXXVI : LXXVII: CN 1 : 1; Ph 15 : 1

The regioselectivity of the photochemical cycloaddition of the thioketone (XXXII) with the alkenes $RR^1C{=}C(OMe)_2$ during irradiation by a 125-W high-pressure mercury lamp in an inert atmosphere is determined by the nature of the substituents in the olefin: With R and R^1 = H and H, H and Me, or Me and Me the thietanes (LXXVIII) are formed with yields of 42-90%; with R = H and R^1 = Ph the thietane (LXXIX) is formed with a yield of 24% [79]:

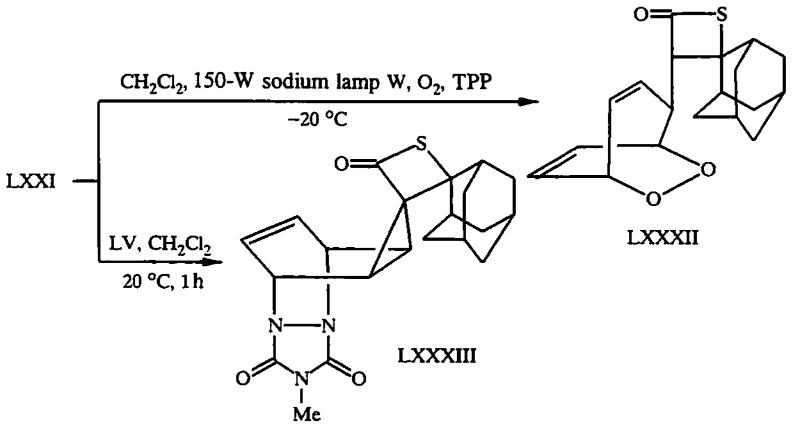


The reaction takes place through the formation of the corresponding biradicals [79].

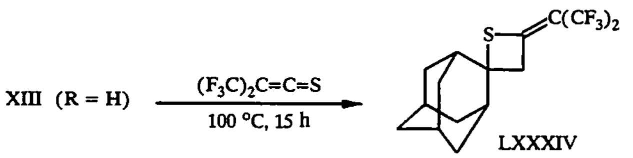
The ketene (LXXX), formed by the action of triethylamine on 2,4,6-cycloheptatrienecarbonyl chloride, reacts with the thioketone (XXXII) at 40°C with the formation of the spiro compound (LXXXI) (yield 69%) [80]:



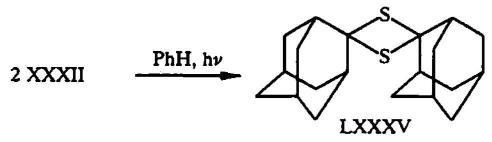
During photochemical oxidation the adduct (LXXXI) gives compound (LXXXII) (yield 72%), while the reaction with urazole (LV) (R = Me) gives the cycloaddition product (LXXXIII) (yield 83%) [80]:



The cyclocondensation of the alkene (XXIII) (R = H) with bis(trifluoromethyl)thioketene was conducted by heating in a tube at 100°C for 15 h; the yield of the adduct (LXXXIV) amounted to 40% [81, 82]:



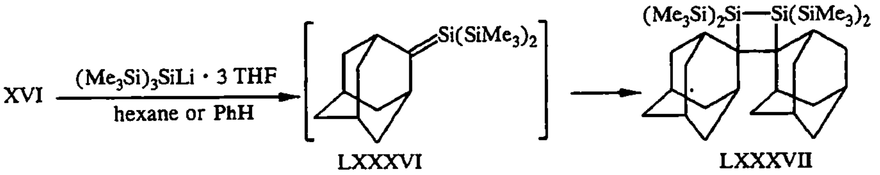
During the irradiation of the thioketone (XXXII) with light of wavelength λ 420 nm in benzene the dimer (LXXXV) is formed with a 72% yield [78]:


2 XXXII

LXXXV

2.4. Silicon-Containing Heterocycle

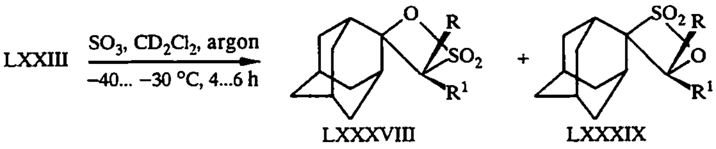
There is a single paper describing the reaction of the ketone (XVI) with the complex $(Me_3Si)_3SiLi \cdot 3THF$. The reaction leads to the silene (LXXXVI), which dimerizes spontaneously to the dispiro compound (LXXXVII) with a yield of 80-90% [83]:


XVI

LXXXVI
LXXXVII

2.5. Heterocycles with Several Different Heteroatoms

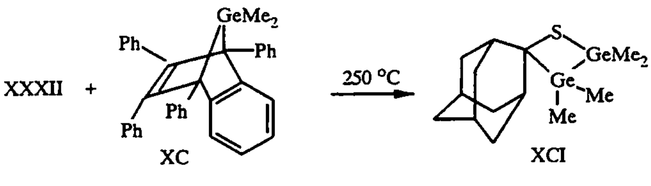
Unsaturated compounds (LXXIII) react regioselectively with SO_3 at low temperature, forming the sultones (LXXXVIII). The exception is the dibromo derivative (LXXIII) (R = R^1 = Br), in the case of which two compounds (LXXXVIII) and (LXXXIX) are formed [84]:


LXXIII

LXXXVIII
LXXXIX

R, R^1, yield %, LXXXVIII: H, H, 46; Me, H, 35; Me, Me, 77; adamantylidene 82;
Br, Br, 50 + 34% LXXXIX

At 250°C the thioketone (XXXII) and the organogermanium compound (XC) form the derivative of digermathietane (XCI) [85]:


XXXII +

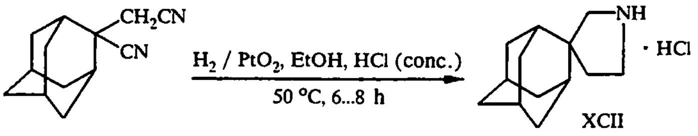
XC
XCI

3. COMPOUNDS CONTAINING FIVE-MEMBERED HETEROCYCLES

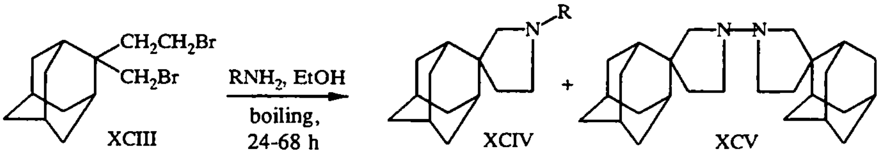
3.1. Nitrogen-Containing Heterocycles

The most widely used method for the synthesis of such spiro compounds involves the formation of the spiro-coupled ring as a result of the reaction of two substituents at position 2 of adamantane.

During hydrogenation over platinum oxide in alcohol and concentrated hydrochloric acid at 50°C 2-cyano-2-cyanomethyladamantane undergoes cyclization to compound (XCII) with a yield of 63% [86]:

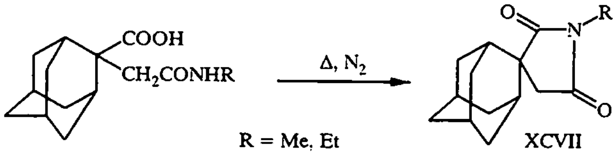


2-Bromomethyl- and 2-(2-bromoethyl)adamantane (XCIII) are converted into a pyrrolidine derivative (XCIV) when treated in alcohol or xylene with primary amines or hydrazine hydrate [in which case 17% of compound (XCV) is also formed] [87]:

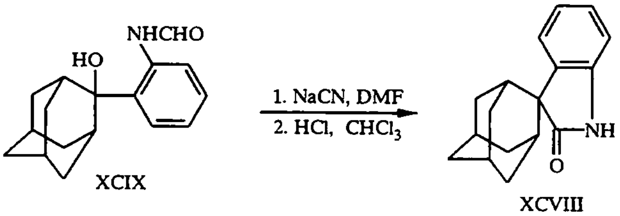


R, yield of XCIV (%): $PhCH_2$, 45; $H_2N(CH_2)_2$, 94; NH_2, 40

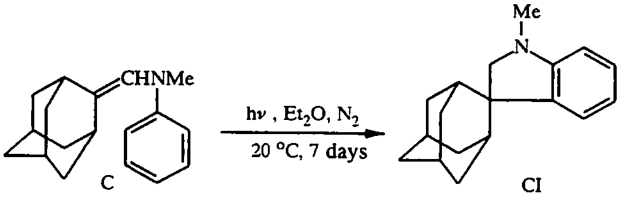
At temperatures 15°C above the melting points the carboxylic acids (XCVI) undergo cyclization to the spiro compounds (XCVII) [88]:



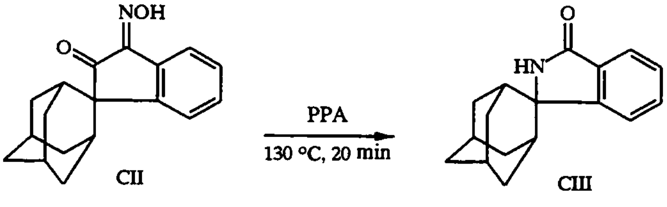
The oxoindole derivative (XCVIII) was synthesized with a 93% yield by the cyclocondensation of compound (XCIX) under the influence of hydrogen chloride at 20°C [89]:



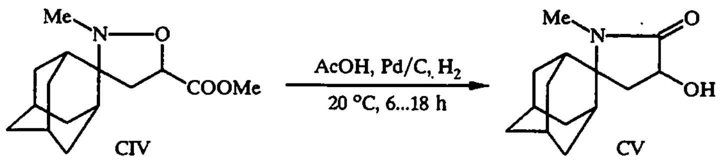
An unusual intramolecular cyclocondensation takes place when the tertiary amine (C) is exposed to a 450-W mercury lamp in an inert atmosphere. The yield of the reaction product (CI) is 34% [90]:



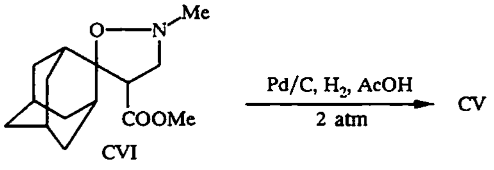
When heated with polyphosphoric acid the oxime (CII) undergoes a Beckmann rearrangement and is transformed into the cyclic amide (CIII) with a yield of 34% [90]:



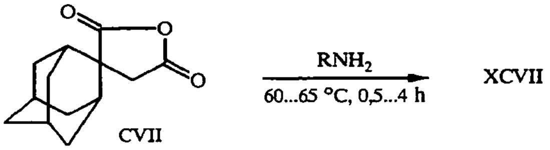
The recyclization of adamantanespiroisoxazolidine (CIV) to the pyrrolidine derivative (CV) was realized under the conditions of hydrogenation over palladium. The yield of compound (CV) was 89% [91]:



Compound (CV) was synthesized by hydrogenation of the isoxazolidine derivative (CVI) over palladium [92]:

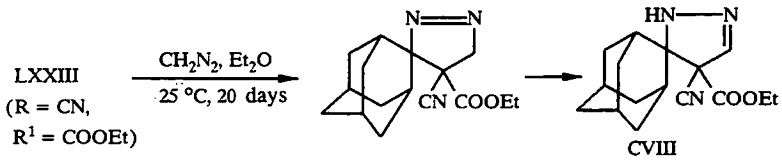


During the reaction of the spiro compounds (CVII) with ammonia [88] or primary amines [86] the oxygen in the five-membered ring is substituted by nitrogen, and compounds (XCVII) are formed with yields of 63-90%:

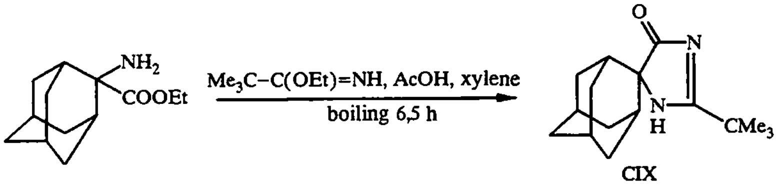


R = H, Me, $CH_2HC{=}CH_2$, cyclohexyl , $PhCH_2$, CH_2CH_2OH

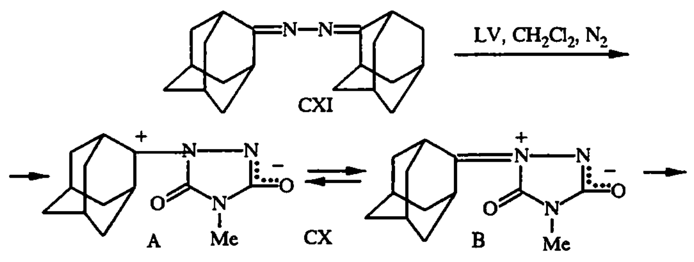
The pyrazoline derivative (CVIII) (yield 34%) was obtained by 1,3-dipolar cycloaddition of the substituted methyleneadamantane (LXXIII) (R = CN, R^1 = COOEt) with diazomethane at 25°C [4]:

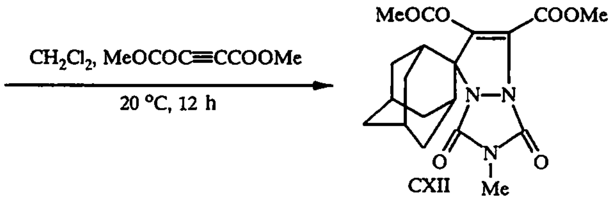


In the presence of acetic acid 2-amino-2-ethoxycarbonyladamantane enters into reaction with the imidic ester $Me_3CC(OEt){=}NH$, and compound (CIX) is formed [93]:



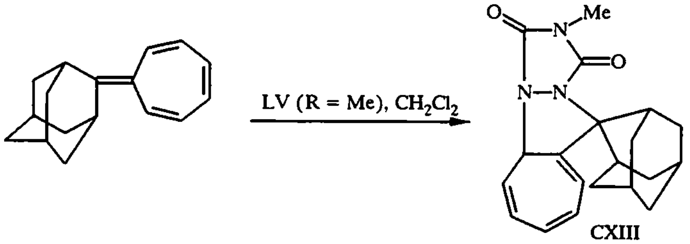
The dipole (CX), formed as a result of an exothermic reaction from the azine (CXI) and the urazole (LV) (R = Me) and existing in form B, enters into reaction *in situ* with dimethyl acetylenedicarboxylate. The reaction product is compound (CXII), the yield of which is 34% [94, 95]:





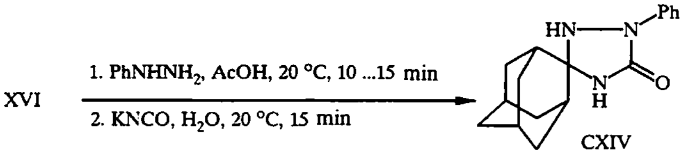
CXII

The product (CXIII) from the [3+2]-cycloaddition of 7-adamantylidene-1,3,5-cyclopentatriene and urazole (LV) (R = Me) is formed with a 50% yield [80]:



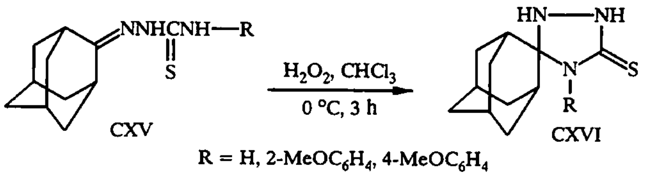
CXIII

A two-stage synthesis of the triazolidine derivative (CXIV) (yield 92%) has been described; the phenylhydrazone of the ketone (XVI) was obtained first, and it was then treated with potassium isocyanate without isolation [96]:

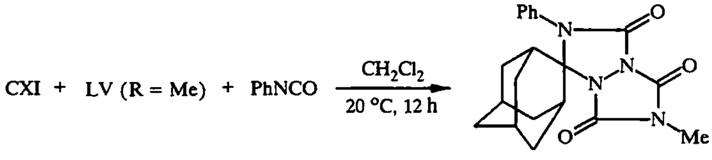


CXIV

Under the influence of hydrogen peroxide at 0°C the thiosemicarbazones (CXV) cyclize with good yields to the spiro compounds (CXVI) [97, 98]:

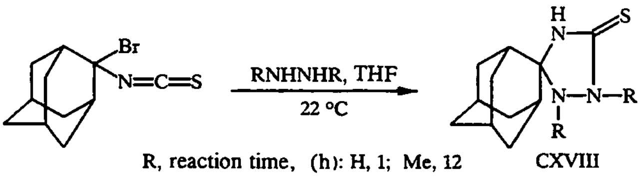


The derivative (CXVII) was synthesized with a 76% yield by a three-component reaction of the azine (CXI), the urazole (LV), and phenyl isocyanate at 20°C [94, 95]:



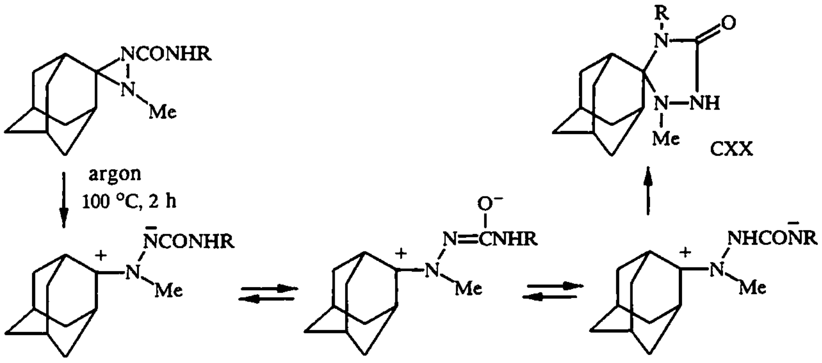
CXVII

The reaction of 2-bromo-2-isothiocyanatoadamantane with hydrazine or N,N'-dimethylhydrazine in the presence of triethylamine was used for the production of the spiro compounds (CXVIII) (yield 76-88%) [99]:



CXVIII

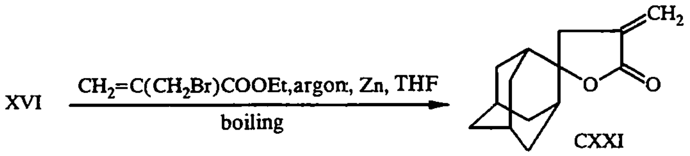
When heated, the diazetidines (CXIX) are transformed into the triazolinone derivatives (CXX)·(yields 50-73%). The authors [11] propose the following recyclization scheme:



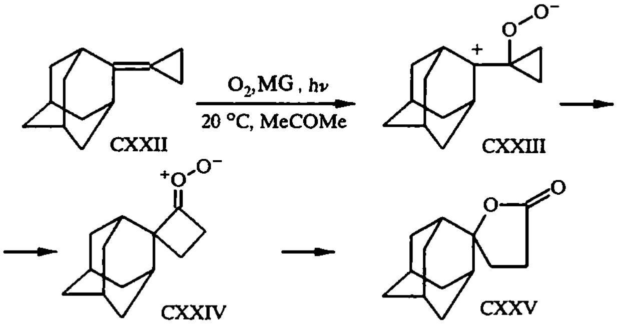
R = Pr, $CHMe_2$, Ph

3.2. Oxygen-Containing Heterocycles

The ketone enters into the Reformatsky reaction with the bromo ester $CH_2{=}C(CH_2Br)COOEt$, forming the adamantane derivative (CXXI) with a yield of 24% [100]:

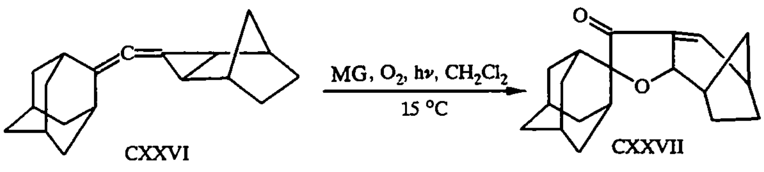


The action of oxygen on the cyclopropane derivative (CXXII) with irradiation by a 400-W lamp (550-770 nm) in the presence of the dye MG leads initially to the formation of the zwitterion (CXXIII). The latter is then converted into the carbonyl oxide (CXXIV), which isomerizes to the final reaction product (CXXV) with a 93% yield [101]:



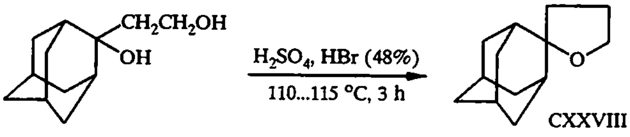
Compound (CXXV) is formed with an 81% yield as a result of the reaction of the alkene (CXXII) with ozone and triphenyl phosphite in acetonitrile at −40°C for 20 min [95].

The oxidation of the cumulene (CXXVI) by oxygen with irradiation by 1-kW halogen lamps in the presence of the dye MG leads to the spiro compound (CXXVII) with a 38% yield [49]:



2-Cyano-2-cyanomethyladamantane undergoes cyclization when heated with concentrated sulfuric acid at 90°C for 5 min, forming compound (CVII) with a yield of 76% [86, 88].

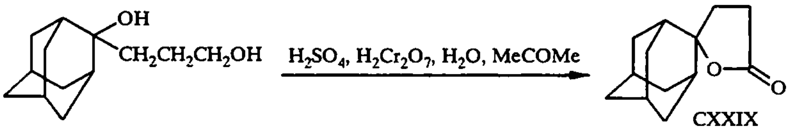
When heated with concentrated sulfuric acid and hydrobromic acid at 110-115°C for 3 h, 2-hydroxy-2-(2-hydroxyethyl)adamantane is transformed with a 93% yield into 3-adamantylidenetetrahydrofuran (CXXVIII) [87]:



CXXVIII

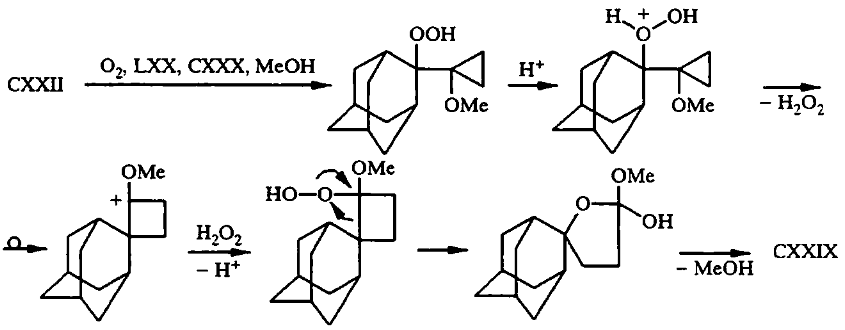
Two approaches to the synthesis of compound (CXXVIII) have been described, i.e., by the action of lead tetraacetate in benzene in the presence of calcium carbonate (yield 29%) or in pyridine (yield 8%) [102].

The treatment of 2-hydroxy-2-(3-hydroxypropyl)adamantane with Jones reagent in acetone gives a 90.5% yield of the spiro compound (CXXIX) [103]:

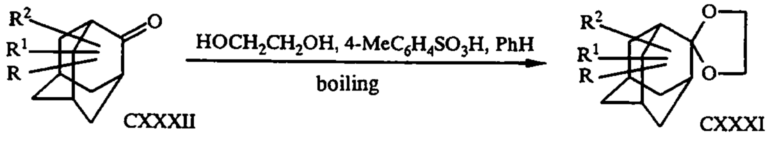


CXXIX

The formation of compound (CXXIX) from cyclopropylideneadamantane (CXXII) and oxygen during irradiation by a 50-W high-pressure mercury lamp in the presence of 9,10-dicyanoanthracene (LXX) and 1,4-diazabicyclo[3.3.0]octane (CXXX) was described by the following scheme [104]:



The most general and the most widely used method for the synthesis of spiroadamantane-1,3-dioxolanes (CXXXI) is the reaction of the keto derivatives of adamantane (CXXXII) with ethylene glycol in the presence of *para*-toluenesulfonic acid:

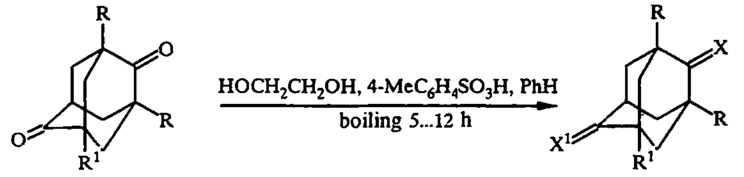


CXXXII

CXXXI

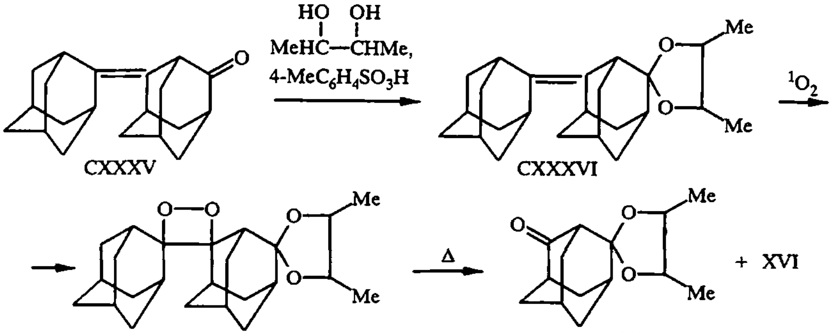
Compounds (CXXXI) were synthesized by this method, R, R^1, R^2, yield, %, [reference]: H, H, 5-Br, 95, [105]; H, 5-OH, 4-COOEt, 6-COOEt, 79, [106]; H, H, 5-COOMe, 93, [107]; H, H, 4-OH, 20, [108]; H, H, 3-OH, 74, [108]; H, H, 3-Cl, 51, [109]; H, H, 5-Br, –, [110]

The fact that the adamantane derivatives (CXXXIII) react with ethylene glycol at one or both keto groups when boiled in benzene in the presence of *p*-toluenesulfonic acid can clearly be explained by steric factors [111, 112]:



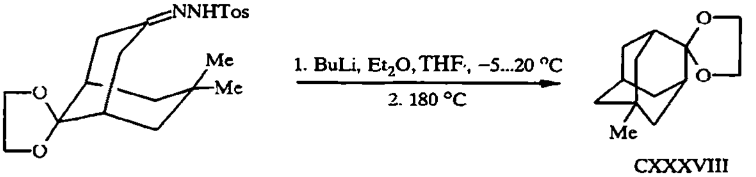
R, R^1, X, X^1, yield, %: H, Br, $-OCH_2CH_2O-$, $-OCH_2CH_2-$, 90;
COOEt, H, O, $-OCH_2CH_2O-$, 79

The spiro compound (CXXXIV) was synthesized from the ketone (CXXXV) by a series of consecutive transformations, i.e., by the reaction of the ketone (CXXXV) with 1,3-dihydroxybutane, oxidation of the obtained compound (CXXXVI), and thermal decomposition of the dioxetane (CXXXVII) [113]:



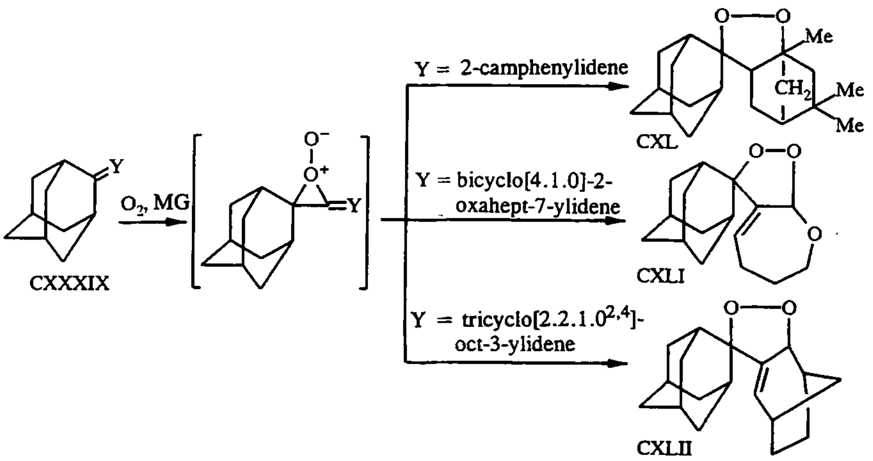
CXXXV CXXXVI CXXXVII CXXXIV

The production of the respective 1,3-dioxolanes from the ketone (XVII) and rutin or quercitrin was described [114]. A completely different path to the synthesis of the dioxolane (CXXXVIII) was described in [115]:



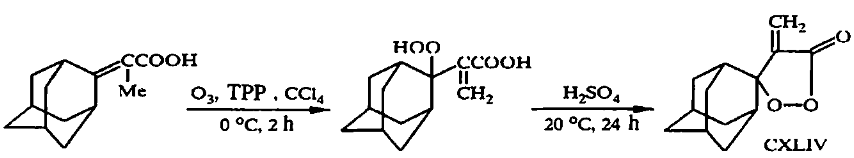
CXXXVIII

Singlet oxygen, formed during irradiation by a 500-W halogen lamp in the presence of the dye MG in methylene chloride, acetonitrile, acetone, methanol, or methanol—water, reacts with the double bond of unsaturated compounds (CXXXIX) with the formation of the corresponding carbonyl oxides, which rearrange to the spiro compounds (CXL) (yield 58%), (CXLI) (yield 75%), or (CXLII) (yield 80%) [116]:



CXXXIX CXL CXLI CXLII

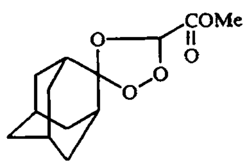
The action of ozone on 2-adamantylidenepropionic acid with irradiation in the presence of TPP gave the hydroperoxide (CXLIII), the treatment of which with sulfuric acid led to the spiro compound (CXLIV) [57]:



CXLIII

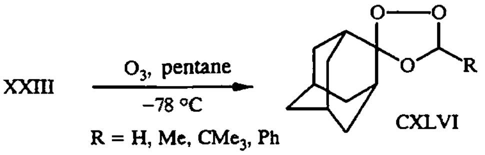
CXLIV

The ozonide (CXLV) is formed with a yield of 32% as a result of the action of ozone on 1-methoxy-1-buten-3-one in the presence of the adamantanethione (XVI) [117]:



CXLV

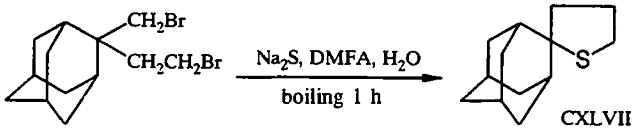
The ozonides (CXLVI) were synthesized with yields of 70-95% by the action of ozone on the alkenes (XXIII) in pentane at −78°C [118]:



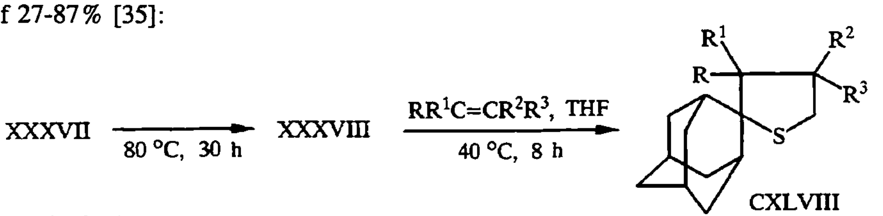
Another method for the synthesis of the ozonide (CXLVI) (R = 4-$O_2NC_6H_4$) is by the action of oxygen on a mixture of the azine (CXI) and 4-nitrobenzaldehyde [94].

3.3. Sulfur-Containing Heterocycles

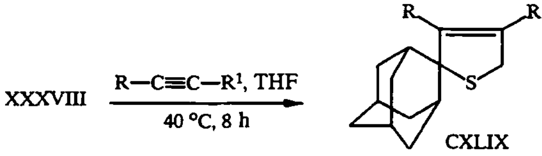
The spiroadamantanethiolane (CXLII) was synthesized with a 95% yield by heating 2-bromomethyl-2-(2-bromoethyl)adamantane with sodium sulfide in aqueous DMFA [87]:



The thiocarbonylylide (XXXVIII), formed when spiroadamantane-1,2,3-thiadiazolidine (XXXVII) is heated, enters into 1,3-dipolar cycloaddition *in situ* with alkenes or alkynes, forming the adducts (CXLVIII) with yields of 82-95% or (CXLIX) with yields of 27-87% [35]:

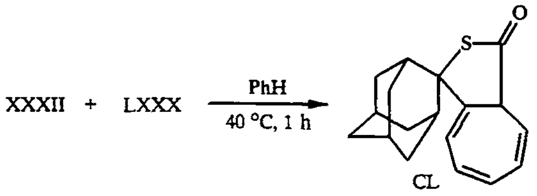


R, R^1, R^2, R^3: H, CN, H, H; H, COOMe, H, H; H, CN, H, CN (trans); H, COOMe, H, COOMe (trans); H, COOMe, H, COOMe (cis); H, -C(O)OC(O)-, H; H, -C(O)N(Ph)C(O)-, H; CN, CN, CN, CN; COOMe, COOMe, COOMe, COOMe; CN, COOMe, CN, COOMe; H, $(CH_2)_6$, H

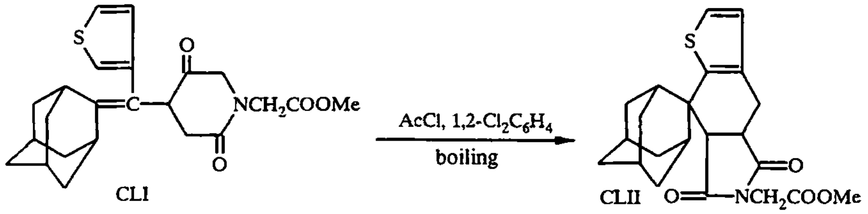


R, R^1 = COOMe, H; H, COOMe; COOMe, COOMe

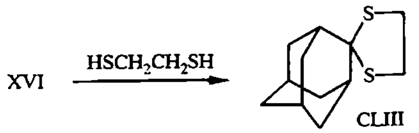
The reaction of the thioketone (XXXII) with the ketene (LXXX) gives the spiro compound (CL) (yield 20%) in addition to the thietane (LXXXI) [80]:



Compound (CLI) undergoes a fairly complex transformation when heated with acetyl chloride in 1,2-dichlorobenzene. The product (CLII) is formed with a yield of 27% [119]:



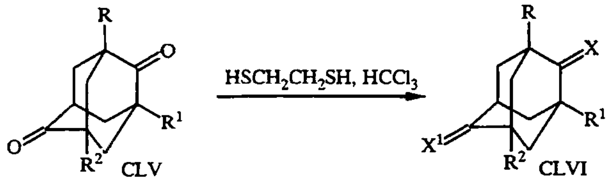
The method most widely used for the synthesis of spiro compounds containing adamantane and 1,3-dithiolane fragments is the reaction of the respective ketones with 1,2-dimercaptoethane. Spiroadamantane-1,3-dithiolane (CLIII) was obtained by this method in [120-124].



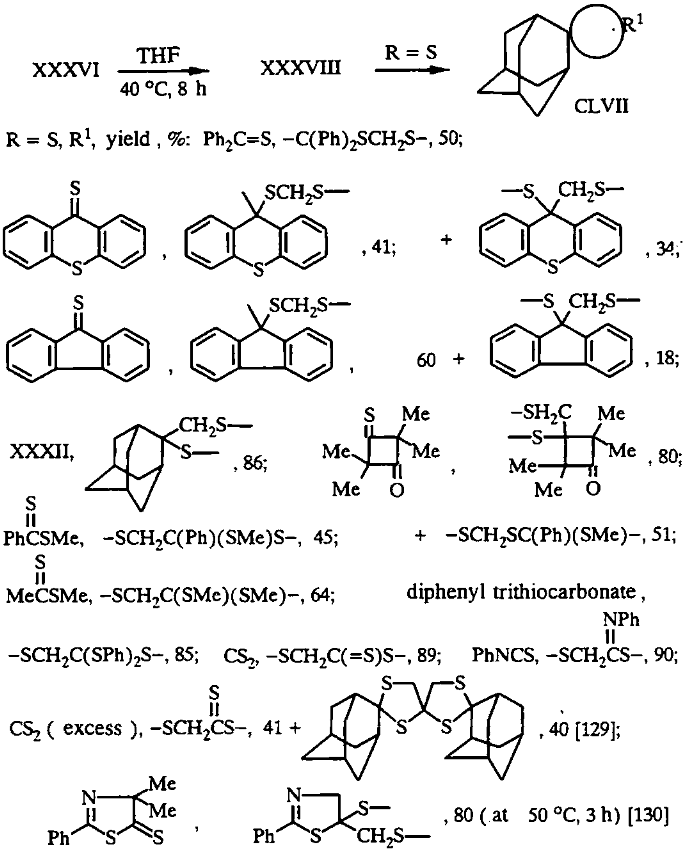
Catalyst, temperature (°C), reaction time, yield of (CLIII) (%), [reference]: 4-$MeC_6H_4SO_3H$, –, –, 92, [120]; montmorillonite KSF (CLIV), boiling in toluene, 93, [121]; $FeCl_3/SiO_2$, 20, in methylene chloride, 1 min, 97, [122]; (CLIV), 20, in methylene chloride, 24 h, 47, [123]; (CLIV), $(Me_3SiO)_2SO_2)/SiO_2$, 20, 2 h in methylene chloride, 92, [124]

The reactions of $HSCH_2CH_2SH$ with the alkene (XXI) (R = OMe) in ether at 20°C in the presence of phosphoric acid [125] or with 2,2-dimethoxyadamantane in methylene chloride at 25°C for 16 h in the presence of Nafilon-H^+ (yield 98%) [126] were used for the production of the dithiolane (CLIII).

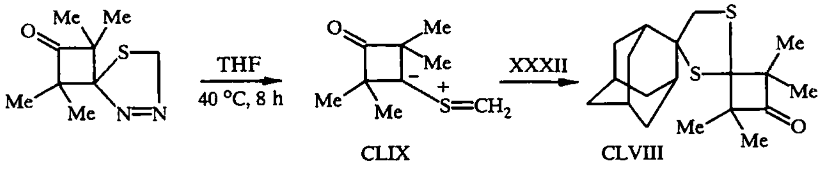
Depending on the structure of the initial ketone and on the reaction conditions, the formation of the dithiolane fragment during the reaction of the 2,6-adamantanedione derivatives (CLV) with 1,2-dimercaptoethane can take place at one or two keto groups with the formation of compounds (CLVI) [112, 127, 128]:



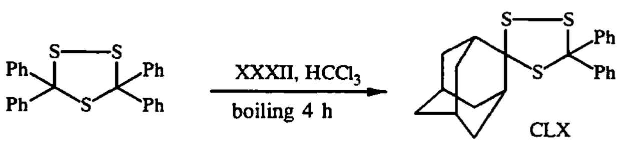
R, R^1, R^2, X, X^1, catalyst, temperature (°C), time (h), [reference]: H, COOEt, COOEt, 0, $-SCH_2CH_2S-$, HCl (d), 20, 8, 81, [112]; COOMe, H, COOMe, ($-SCH_2CH_2S-$, 0 + SCH_2CH_2S-, $-SCH_2CH_2S-$), $BF_3 \cdot Et_2O$, 20, –, –, [127]; H, H, COOEt, $-SCH_2CH_2S-$, $BF_3 \cdot Et_2O$, 0, –, 20, 3.87; H, H, COOH, $-SCH_2CH_2S-$, $-SCH_2CH_2S-$, $BF_3 \cdot Et_2O$, 20, 24, 87, [128] A large number of spiro compounds (CLVII) containing a 1,3-dithiolane fragment were synthesized by the 1,3-dipolar cycloaddition of thiocarbonyl compounds R = S with the thiocarbonylylide (XXXVIII) [formed from the adamantanespirothiodiazoline (XXXVI)] [129, 130]:



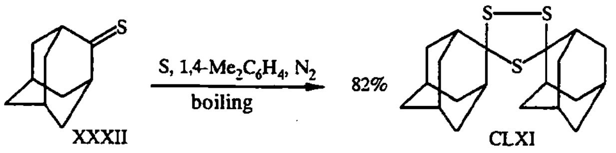
The synthesis of the dithiolane derivative (CLVIII) (yield 88%) also includes the intermediate formation of the thiocarbonylylide (CLIX) [131]:



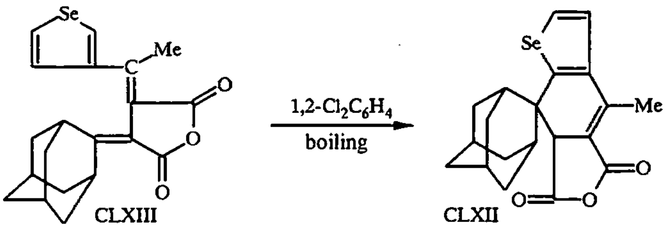
The spiro compound (CLX) was synthesized with a yield of 81% by heating 3,3,5,5-tetraphenyl-1,2,4-trithiolane with the thioketone (XXXII) [132]:



The formation of the 1,2,4-trithiolane (CLXI) is observed when the thioketone (XXXI) is heated with elemental sulfur in xylene under nitrogen [133]:

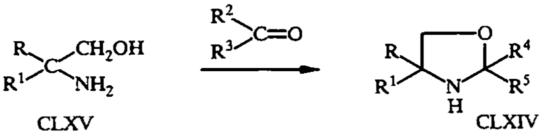


There is only one report [134] on the synthesis of the spiro compound (CLXII) containing the selenophene fragment from the diene (CLXIII):



3.4. Heterocycles with Several Different Heteroatoms

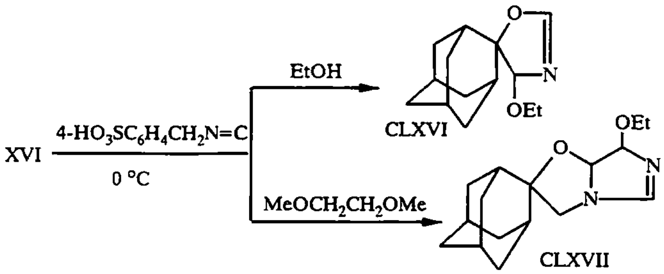
3.4.1. Heterocycles Containing N and O. A series of oxazolidine derivatives (CLXIV) were obtained by the cyclocondensation of the amino alcohols (CLXV) with ketones R^2R^3CO by heating in an autoclave at 70-120°C for 65-160 h; benzene, acetone, and xylene were used as solvents [135]:



R, R^1, R^2R^3CO, R^4, R^5: Me, Me, adamantanone, adamantane residue,.64; adamantane residue, acetone, Me, Me, 45; Me, Me, 5-hydroxy-2-adamantanone, 5-hydroxyadamantane residue, 88; Me, Me, 5-acetoxy-2-adamantanone, 5-acetoxyadamantane residue, 25; adamantane residue, adamantanone, adamantane residue, 42

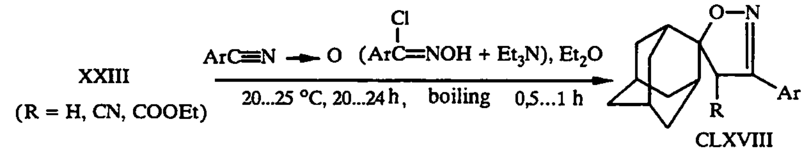
Adamantane derivatives containing two fragments of substituted oxazolidines at positions 2,4 and 2,6 were obtained by the reaction of 2,4-adamantanedione with the amino alcohols (CLXV) (R, R^1 = Me, Me or adamantylidene) [135] or by the reaction of 2,6-adamantanedione with the amino alcohols (CLXV) (R, R^1 = Me, Me or bicyclo[3.3.1]nonanediyl) [136].

Interesting results were obtained in the reaction of $TosCH_2N{=}C$ with the ketone (XVI) in the presence of thallium ethoxide; when the process was carried out in alcohol, compound (CLXVI) was obtained with a 92% yield; in $MeOCH_2CH_2OMe$ as solvent compound (CLXVII) was obtained with a 47% yield [137]:



When the reaction was carried out in a mixture of alcohol and $MeOCH_2CH_2OMe$, only compound (CLXVI) was obtained with a yield of 92% [138].

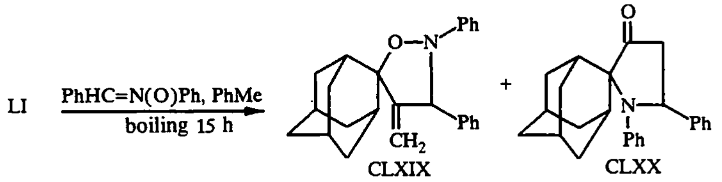
The alkenes (XXIII) enter readily into 1,3-cycloaddition with the N-oxides of nitriles $ArC{\equiv}N{\rightarrow}O$ with the formation of spiroadamantaneisoxazolines (CLXVIII) with yields of 16-51% [4, 139, 140]:



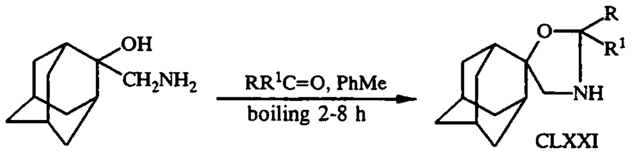
Ar for R = H: Ph [4, 139]; 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-MeC_6H_4, 4-$MeOC_6H_4$ [139]; for R = CN and COOEt, Ar = Ph, 2-$O_2NC_6H_4$ [140]

2′,3′-Diphenylspiro[adamantane-2,5′-isoxazolidine] was obtained with a 35% yield from the alkene (XXIII) (R = H) and the nitrone PhCH=N(O)Ph by boiling in toluene for 24 h [4].

On the other hand, the reaction of the same nitrone with the cumulene (LI) resulted in the formation of two spiro compounds (CLXIX) (yield 16%) and (CLXX) (yield 17%) [45]:

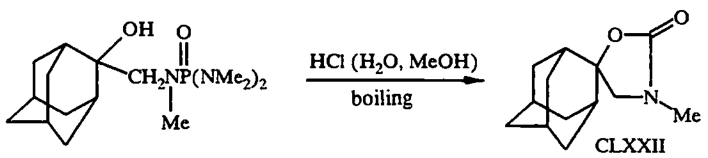


A method was developed for the synthesis of spiroadamantaneoxazolidines (CLXXI) with yields of 20-80% by the cyclocondensation of 2-hydroxy-2-aminomethyladamantane with compounds containing a C=O group [141, 142]:

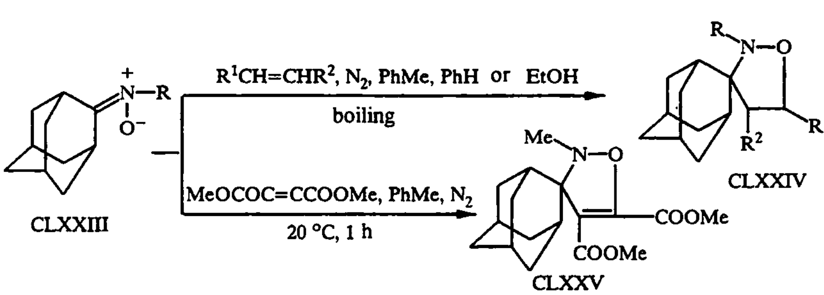


Carbonyl compound, RR^1: $COCl_2$, 0; cyclododecanone, $-(CH_2)_{11}-$; (XVI) (in chloroform, 4 h), adamantylidene; tricyclo[5.2.1.$0^{2,6}$]-8-decanone, tricyclo[5.2.1.$0^{2,6}$]-8-decylidene; 2-norbornanone, 2-norbornylidene [142]

The spiro compound (CLXXII) is formed with a 40% yield when an adamantane derivative containing OH and $CH_2N(Me)P(O)[NMe_2]_2$ at position 2 is boiled in methanol in the presence of 3 N hydrochloric acid [143]:

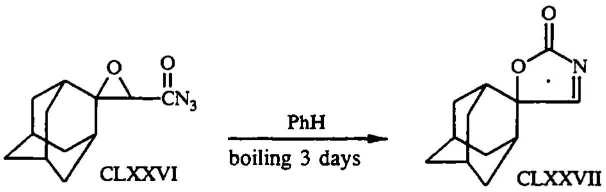


It is possible to observe some interest from researchers in the 1,3-dipolar cycloaddition of nitriles of the adamantane series (CLXXIII) to alkenes [42, 91, 92, 144, 145] or alkynes [7]. Adamantanespirooxazolidines (CLXXIV) (yields 34-67%) or the oxazoline derivative (CLXXV) (yield 81%) were synthesized in this way:

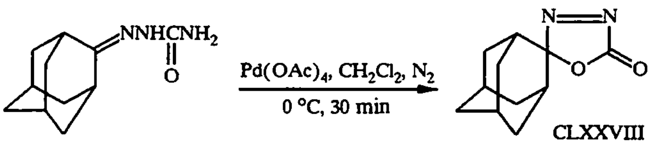


R, R^1, R^2: Me, Me, COOMe [42]; Me, CH_2OH, H; Me, COOMe, H [91]; Me, C_6H_{13}, H [144]; Me, H, COOMe [92]; Me, C_6H_{13}, H; Me, Bu, H; Me, $Me(CH_2)_n$ (n = 5, 7, 9, 13, 15, 17), H; Me, Ph, H; Et, Ph, H [145]

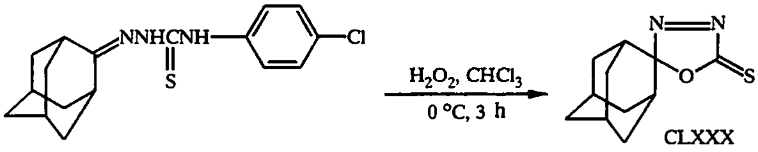
When boiled in benzene the oxirane (CLXXVI) undergoes recyclization to the oxazolinone derivative (CLXXVII) with an 85% yield [146]:



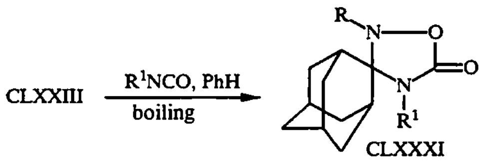
The oxidative cyclization of the ketone semicarbazone (XVI) by the action of lead tetraacetate leads to the spiro compound (CLXXVIII) with a 50% yield [147]:



The treatment of the thiosemicarbazone (CLXXIX) with hydrogen peroxide at 0°C for 3 h unexpectedly gave compound (CLXXX) not containing a chlorophenyl radical [97]:

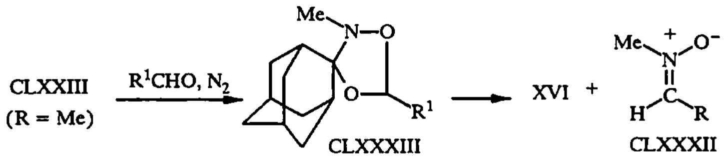


Derivatives of 1,2,4-oxazolidin-5-one were synthesized with yields of 47-91% by boiling a mixture of the nitrones (CLXXIII) and isocyanates in benzene or petroleum ether [148]:



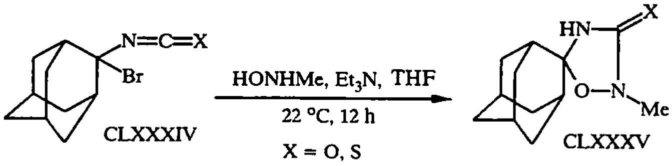
R, R^1: Me, Ph; Me, cyclohexyl; Me, Me; Me, Pr; $PhCH_2$, Ph; $PhCH_2$, Et; $PhCH_2$, Pr; $PhCH_2$, Bu; cyclohexyl, Ph; cyclohexyl, cyclohexyl; cyclohexyl, Me; cyclohexyl, Pr; cyclohexyl, Bu

The reaction of the nitrone (CLXXIII) (R = Me) with aldehydes in boiling toluene for 26 h or in boiling THF for 5.5 h leads to mixtures of the ketone (XVI) and nitrones (CLXXXII). These results indicate that unstable 1,2,4-dioxazolidines (CLXXXIII) are formed initially in this reaction [149]:

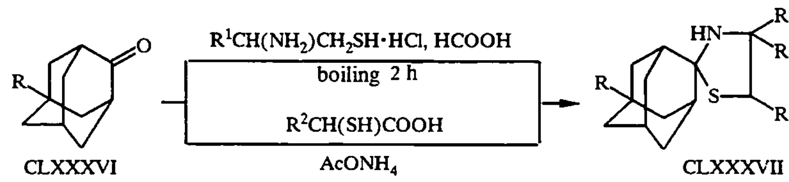


R^1 = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, Pr, CMe_3, C_6H_{13}

2-Bromo-2-isocyanatoadamantane and 2-bromo-2-isothiocyanatoadamantane (CLXXXIV) react readily with N-methylhydroxylamine in the presence of triethylamine and form the respective spiro compounds (CLXXXV) (yields 66-92%) [99, 150]:



3.4.2. Heterocycles Containing N and S. The cyclocondensation of the ketones (CLXXXVI) with amino thioalcohols $HSCH_2CH(R^1)NH_2$ [151] or with acids $R^2CH(SH)COOH$ gives the thiazolidine derivative (CLXXXVII):



For $R^1CH(NH_2)CH_2SH$: R = H, OH, MeO, Br, COOH, $R^1 = R^3 = R^4 = R^5 = H$; $R = R^3 = R^5 = H$, $R^1 = R^4 = COOH$ [151]; for $R^2CH(SH)COOH$: $R = R^2 = R^5 = H$, $R^3R^4 = O$; R = OH, $R^2 = R^5 = H$, $R^3R^4 = O$ [151]; R = H, $R^2 = Me$, $R^3R^4 = O$, $R^5 = Me$

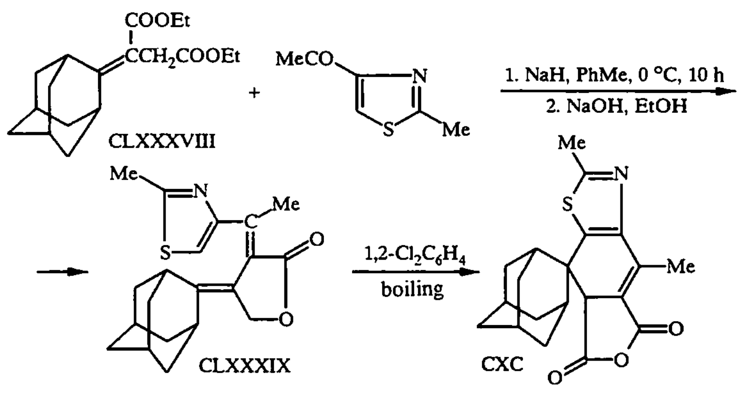
(the reaction can be carried out with H_2NCONH_2 instead of $AcONH_4$) [152]

When the ketone (CLXXXVI) (R = H) and *o*-aminothiophenol are boiled in alcohol for 8 h in an atmosphere of nitrogen, spiro[adamantane-2,2'-benzothiazole] is formed with a 50% yield [153].

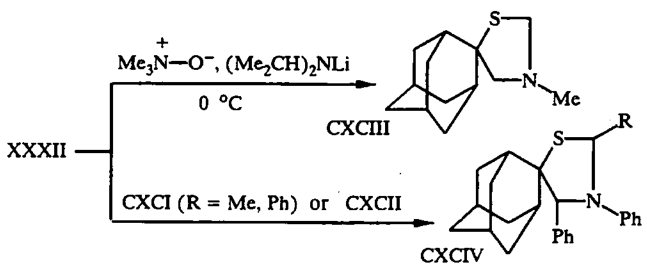
3'-Methyl-4'-phenylspiro[adamantane-2,2'-(1,3-thiazolidine)] was obtained with a yield of 13% by the reaction of the thiocarbonylylide (XXXVIII) with the azomethine PhCH=NMe [35].

The condensation of 2,6-adamantanedione with two equivalents of $HSCH_2CH_2NH_2$ with boiling in alcohol gives dispiro[adamantane-2,2'',6,2'-thiazolidine] with a yield of 56% [151].

In the presence of sodium hydride the adamantylidenesuccinic ester (CLXXXVIII) reacts with 2-methyl-4-acetylthiazole with the formation of the diene (CLXXXIX). The latter undergoes cyclization when heated in 1,2-dichlorobenzene and is converted into compound (CXC) [154]:

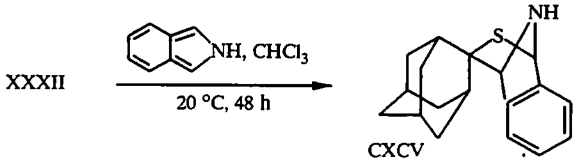


The reactions of the thioketone (XXXII) with triethylamine N-oxide, N-substituted 2,3-diphenylaziridines (CXCI), or 4,4-di(methoxycarbonyl)-1,5-diphenyl-1,2,3-triazoline (CXCII) lead to the thiazolidine derivatives (CXCIII, CXCIV) [155, 156]. [The corresponding azomethine ylides are formed intermediately from the oxide and (CXCI) or (CXCII).]

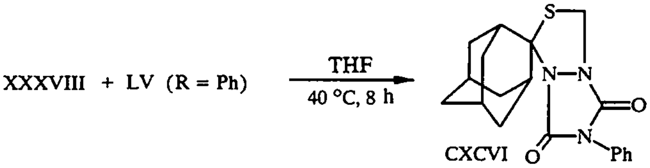


In the reaction of the adamantanethione (XXXII) with the substituted triazoline (CXCII) the spirothiazolidine (CXCIV) (R = H) is formed.

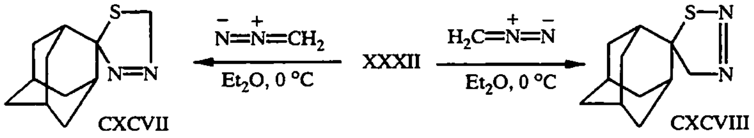
Compound (CXCV) was synthesized with an excellent yield (96%) by the reaction of the thioketone (XXXII) with isoindole [157]:



The spiro compound (CXCVI) is formed with a 55% yield as a result of the reaction of the thiocarbonylylide (XXXVIII) with the urazole (LV) (R = Ph) [35]:



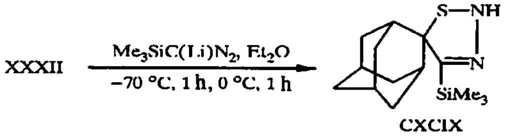
The thioketone (XXXII) reacts with diazomethane with the formation of both possible cycloaddition products (CXCVII, CXCVIII). The ratio of the products depends on the polarity of the employed solvent [35, 36, 158, 159]:



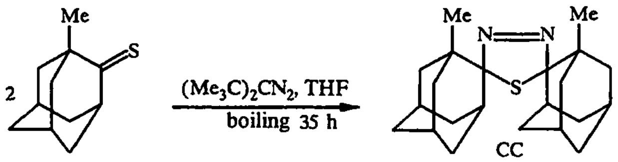
Solvent, ratio CXCVII:CXCVIII: petroleum ether, 87:13; pentane, 91:9; Et_2O, 80:20; MeOH, 26:74; PhH, 76:24; CH_2Cl_2, 58:42; EtOH, 41:59; MeCN, 32:68

However, one isomer, i.e., the derivative (CXCVII) containing the Me radical at position 5, is formed almost exclusively as a result of the reaction of the thioketone (XXXII) with diazoethane in ether [36].

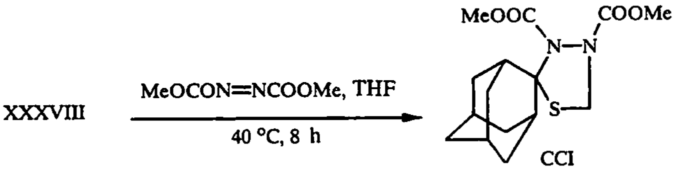
4′-Trimethylsilylspiro[adamantane-2,5′-(1,2,3-thiadiazoline)] (CXCIX) was synthesized by the cycloaddition of lithiotrimethylsilyldiazomethane to the thioketone (XXXII) in ether [160]:



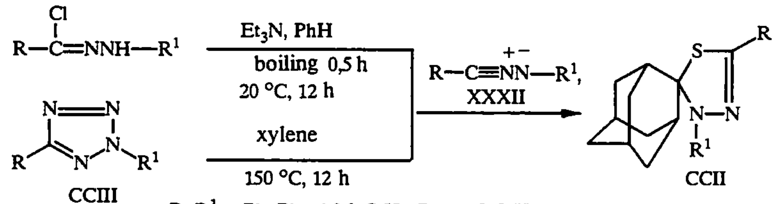
The reaction of 1-methyladamantane-2-thione with bis(*tert*-butyl)diazomethane, leading to the bisspiro compound (CC) (yield 35%), takes place with considerably greater difficulty [161]:



The thiocarbonylylide (XXXVIII) enters into 1,3-dipolar cycloaddition with the azo compound MeOCON=NCOOMe, resulting in the formation of the 1,3,4-thiadiazolidine derivative (CCI) with a 90% yield [35]:

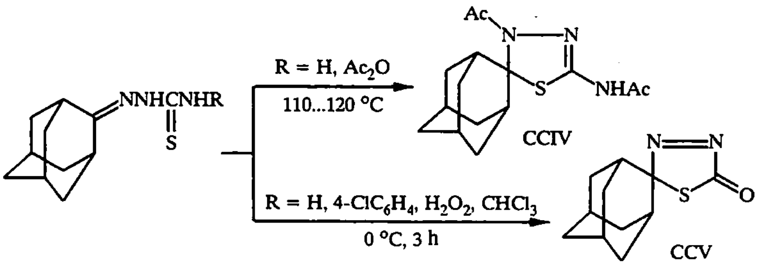


The spiro compounds (CCII) were obtained with 58-94% yields by the 1,3-dipolar cycloaddition of the thioketone (XXXII) with nitrile imines $RC{\equiv}N^{+}N^{-}R^1$ [formed from RC(Cl)=NNHR^1 by the action of triethylamine or from 1,5-disubstituted tetrazoles by boiling in xylene] [36]:



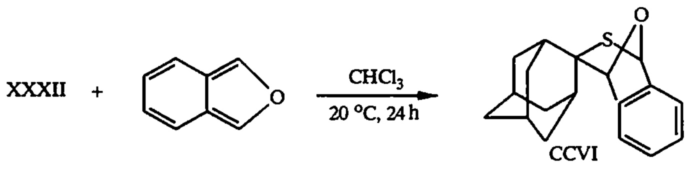
R, R^1 = Ph, Ph; 4-MeC$_6$H$_4$, Ph; 4-ClC$_6$H$_4$, Ph; 4-MeOC$_6$H$_4$, Ph

Various derivatives of 1,3,4-thiadiazoline (CCIV) or (CCV) were obtained starting from the thiosemicarbazones of the ketone (XVI) [97, 98, 162]:

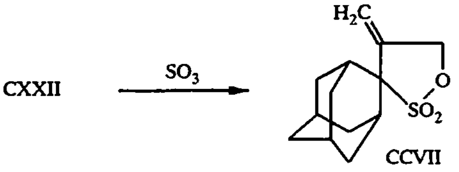


4-(*p*-Tolyl)-1,3,5-dithiazol-2-one is formed with a yield of 60-70% when a mixture of the thioketone (XXXII) and 5-(*p*-tolyl)-1,3,4-oxathiazol-2-one is boiled in xylene [133].

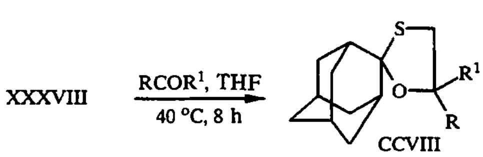
3.4.3. Heterocycles Containing O and S. The diene synthesis reaction of the thioketone (XXXII) with isobenzofuran takes place at normal temperature, and the adduct (CCVI) is formed with a 79% yield [157]:



The synthesis of the sultone (CCVII) from the adamantane derivative (CXXII) and sulfur trioxide was described in [163]:

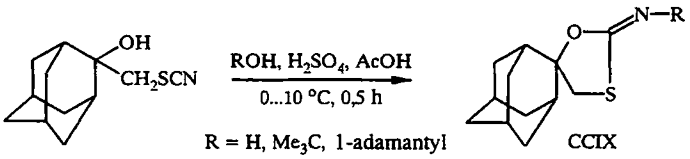


The 1,3-dipolar cycloaddition of the thiocarbonylylide (XXXVIII) with carbonyl compounds was used for the synthesis of 1,3-oxathiolanes (CCVIII) [35]:

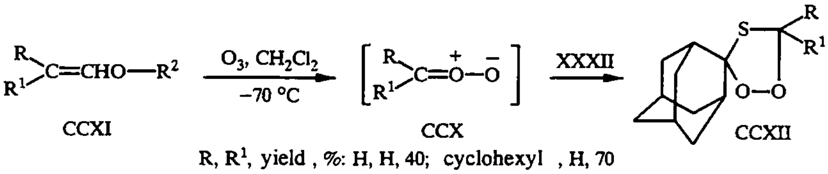


R, R^1 = H, Ph; H, CCl_3; H, COOBu; COOEt, COOEt

A different approach to the production of the spiroadamantylthiolanes (CCIX) with yields of 40-64% [164] made it possible to synthesize compound (CCIX) in the form of a mixture of the *Z* and *E* isomers.

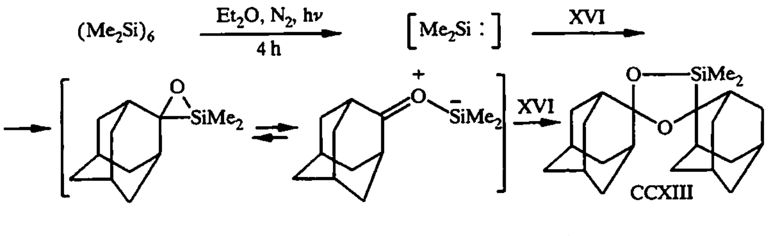


The reaction of the carbonyl O-oxides (CCX) [formed during the action of ozone on vinyl ethers (CCXI)] with the thioketone (XXXII), leading to the 1,2,4-dioxathiolane derivatives (CCXII), was described in [165, 166]:

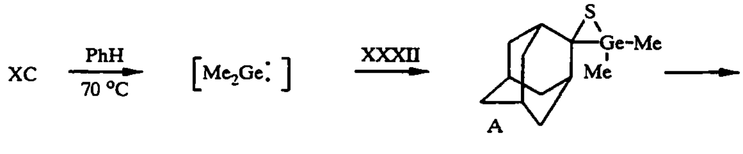


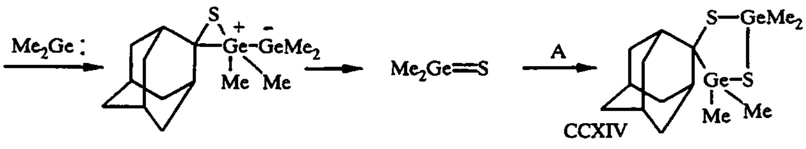
It should be noted that during the ozonization of the vinyl ether (CCXI) ($R = R^1 = H$, $R^2 = Me_2CHCH_2$) in the presence of a mixture of the thioketone (XXXII) and the ketone (XVI) (1:1) the yield of compound (CCXII) ($R = R^1 = H$) is increased to 70% [165].

3.4.4. Heterocycles Containing O and Si or S and Ge. The spiro compound (CCXIII), containing a five-membered heterocycle with a silicon atom and two oxygen atoms, was synthesized by the irradiation of the ketone (XVI) and dodecamethylcyclohexasilane by a low-pressure mercury lamp [167]:



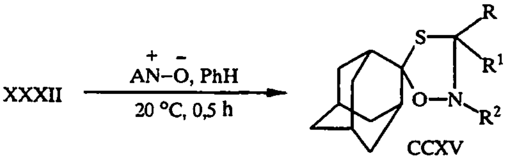
The following scheme was proposed to explain the formation of the digermadithiolane derivative (CCXIV) from the thioketone (XXXII) and compound (XC) [41, 85]:





3.4.5. Heterocycles Containing N, O, and S. Two methods, based on cycloaddition reactions involving the thioketone (XXXII), were developed for the synthesis of spiro[adamantane-2,2′-(1,3,4-thiaoxazolines)].

The production of these compounds was first reported in 1973. The authors of [168] studied the reaction of the thioketones (XXXII) with nitrones $AN^+—O^-$ and established that the spiro compounds (CCXV) were formed with yields of 71-93%:



$\mathrm{A\overset{+}{N}—\overset{-}{O}} = \mathrm{\overset{-}{O}—\overset{+}{N}{=}CH(CH_2)_2CMe_2}$, R = H, $R^1R^2 = -(CH_2)_2CMe_2-$;

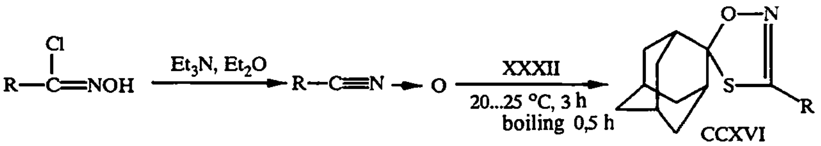
$\mathrm{\overset{-}{O}—\overset{+}{N}{=}CHCMe_2CH_2CMe_2}$, R = H, $R^1R^2 = -CMe_2CH_2CMe_2-$;

$\mathrm{\overset{-}{O}—\overset{+}{N}(Me){=}CHPh}$, R = H, R^1 = Ph, R^2 = Me;

$\mathrm{\overset{-}{O}—\overset{+}{N}(Ph){=}CHPh}$, R = H, $R^1 = R^2$ = Ph;

$\mathrm{\overset{-+}{ON}(Ph){=}CC_6H_4—C_6H_4}$, $RR^1 = C_6H_4\text{-}C_6H_4$, R^2 = Ph

The 5-substituted spiro[adamantane-2,2′-(1,3,5-oxathiazolines)] (CCXVI) were obtained with yields of 75-96% by the 1,3-dipolar cycloaddition of nitrile N-oxides RC≡N→O to the thioketone (XXXII) [36]:



R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, PhCO, 1-adamantyl

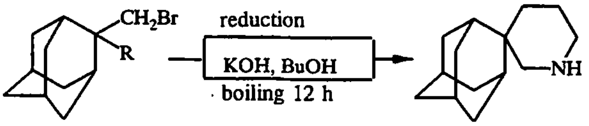
The oxathiazole N-oxide (R = Ph) is formed with an 88% yield as a result of the reaction of adamantane-2-thione N-oxide with PhC≡N→O [169].

4. COMPOUNDS CONTAINING SIX-MEMBERED HETEROCYCLES

4.1. Nitrogen-Containing Heterocycles

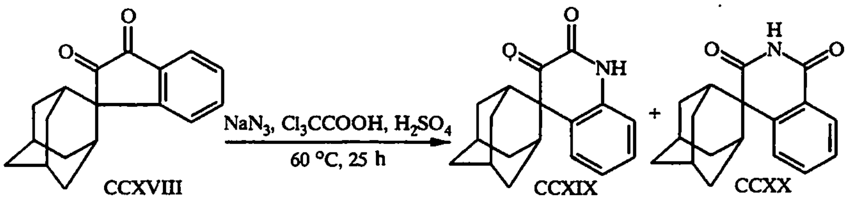
Of the adamantane spiro compounds containing six-membered nitrogen-containing heterocyclic fragments only compounds with one or four nitrogen atoms in the heterocycle have been described.

Spiro[adamantane-2,3′-piperidine] was obtained from compounds (CCXVII) or by reduction (R = CH_2CH_2CN) or by the action of potassium hydroxide (R = $CH_2CH_2CH_2NH_2$) with yields of 68% [87]:

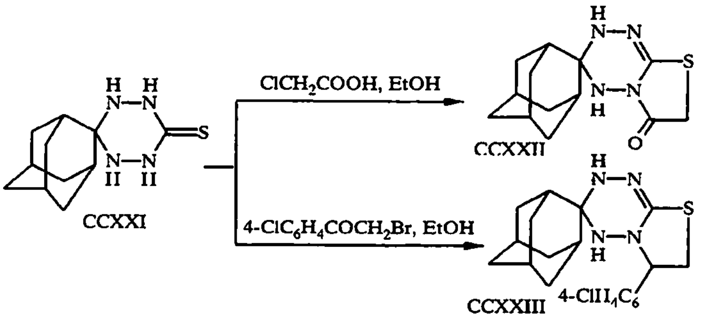


CCXVII

The diketo derivative (CCXVIII) undergoes an unusual recyclization when treated with sodium azide in the presence of trichloroacetic and sulfuric acids. Two compounds [(CCXIX) (yield 14%) and (CCXX) (yield 32%)] are formed as a result of the reaction [90]:

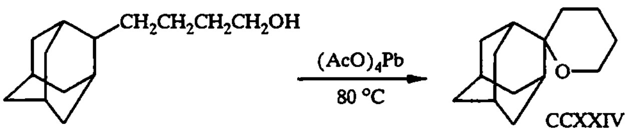


In [171] the cyclocondensation of compound (CCXXI) with chloroacetic acid or with 4-chlorophenacyl bromide was studied, and thiazolo[3,2-*b*]tetrazine derivatives (CCXII) or (CCXXIII) were obtained:

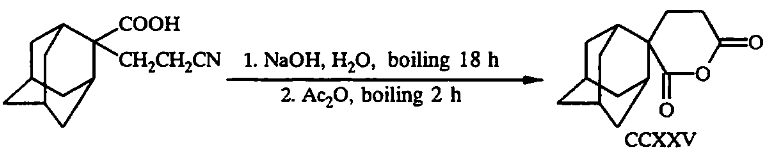


4.2. Oxygen-Containing Heterocycles

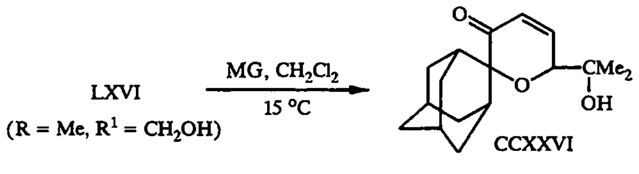
Under the influence of lead tetraacetate at 80°C 2-(4-hydroxybutyl)adamantane undergoes cyclization with a low yield to the pyran derivative (CCXXIV) [102]:



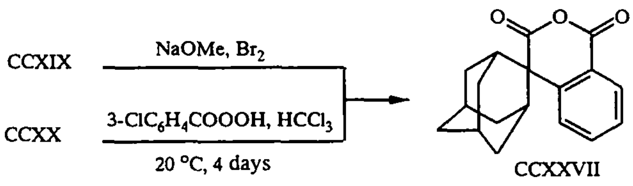
When boiled with 2 N sodium hydroxide and then treated with acetic anhydride 2-(2-cyanoethyl)adamantane-2-carboxylic acid is transformed into the spiro compound (CCXXV) with a yield of 82% [87]:



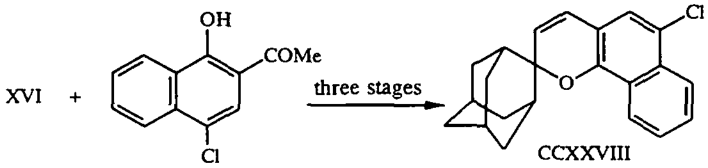
During the irradiation of the cumulene (LXVI) (R = Me, R^1 = CH_2OH) with 1-kW halogen lamps in the presence of the dye MG rearrangement and cyclization occur, leading to compound (CCXXVI) (yield 12%) [55]:



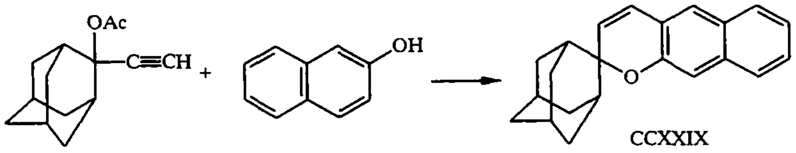
Two methods with different starting compounds [(CCXIX) or (CCXX)] were proposed for the production of the spiro compound (CCXXVII) (yield 64%) [90]:



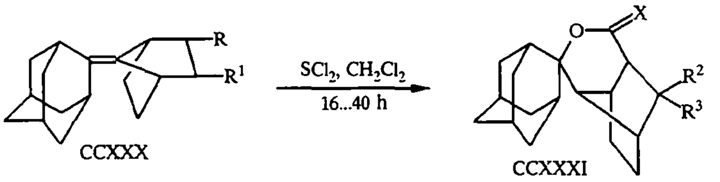
The spiro compound (CCXXVIII) was synthesized in several stages, i.e., by the condensation of the ketone (XVI) with 4-chloro-2-acetyl-1-naphthol with heat in the presence of pyrrolidine, reduction of the reaction product, and heat treatment in the presence of copper sulfate [172]:



The analogous spiro compound (CCXXIX), but with a linear arrangement of the rings in the heterocyclic fragment, is formed as a result of the cyclocondensation of 2-acetoxy-2-ethynyladamantane with 2-naphthol [173]:

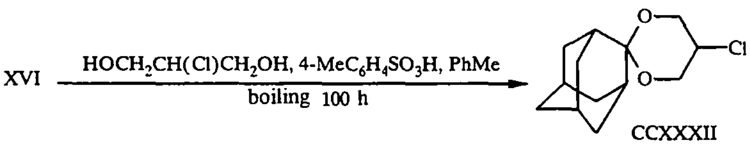


A complex rearrangement of the alkenes (CCXXX) by the action of sulfur dichloride leads to compounds (CCXXXI) [33]:

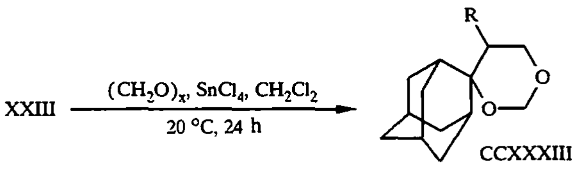


R = R^1 = COOMe, R^2 = H, R^3 = COOMe, X = O, yield 94%;
RR^1 = CH$_2$OCH$_2$, R^2 = H, R^3 = CH$_2$Cl, X = H$_2$, yield 90%

The cyclocondensation of the ketone (XVI) with 2-chloro-1,3-propanediol in the presence of p-toluenesulfonic acid results in the formation of 5′-chlorospiro[adamantane-2,2′-(1,3-dioxane)] (CCXXXII) with an 87% yield [174]:

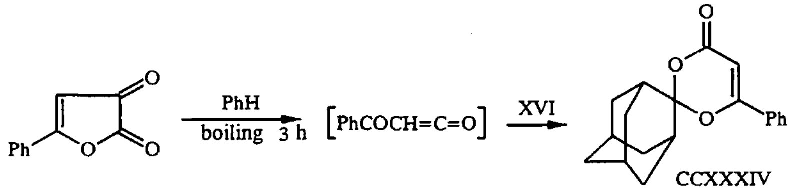


The 1,3-dioxane derivatives (CCXXXIII) were synthesized by the reaction of the alkenes (XXIII) with paraform in the presence of tin tetrachloride [175]:

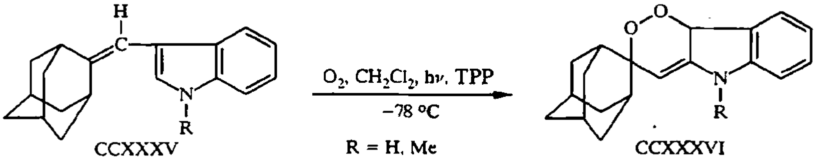


R, yield , %: H, 75; Me, 74; Et, 44; Pr, 62; Me$_2$CH, 30; Ph, 27

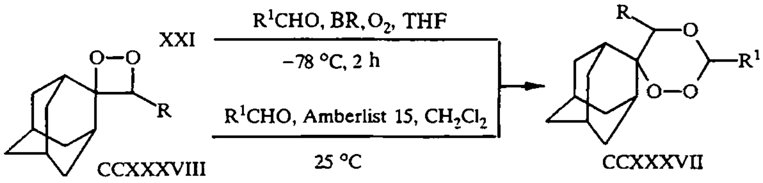
The spiro compound (CCXXXIV), obtained with a yield of 88% when the ketone (XVI) and 2-phenyl-4,5-furandione are heated in benzene, is the product from the cycloaddition of the ketone (XVI) to the intermediately formed ketene PhCOCH═C═O [167]:



The reaction of the indole derivatives (CCXXXV) with oxygen during irradiation by a 400-kW sodium lamp at −78°C in the presence of TPP results in the formation of compound (CCXXXVI) with yields of 73 and 90% respectively [37]:

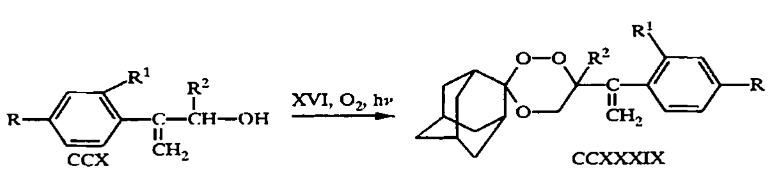


The 1,2,4-trioxanes (CCXXXVII) were synthesized in the form of *cis* and *trans* isomers by the photooxidation of a mixture of the alkenes (XXIII) and aldehydes in the presence of BR as sensitizer or by the reaction of the dioxetanes (CCXXXVIII) with aldehydes in the presence of ion-exchanger Amberlist 15 [66]:



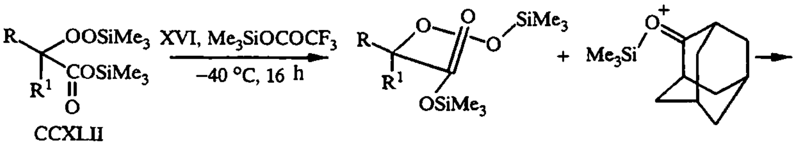
R, R^1, yield, %: OMe, Me, 53; OMe, Et, 45; OMe, CMe$_3$, 22; SMe, Me, 9 [25];
PhO, Me, 47; 4-ClC$_6$H$_4$O, Me, 72; 4-MeC$_6$H$_4$O, Me, 45; 4-MeOC$_6$H$_4$O, Me, 75;
PhO, 4-ClC$_6$H$_4$, 28;
4-ClC$_6$H$_4$O, 4-ClC$_6$H$_4$, 17; PhO, 4-O$_2$NC$_6$H$_4$, 17; PhO, Et, 34 [66]

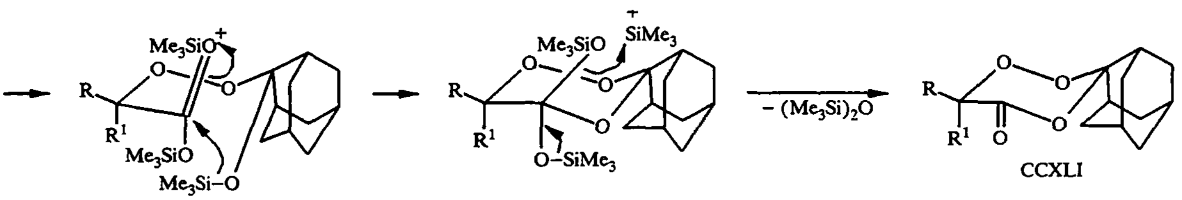
The 1,2,4-trioxanes (CCXXXIX) were obtained by the photooxidation of a mixture of the ketone (XVI) and allyl alcohols (CCXL) in the presence of dyes [177]:



R = H, Me, OMe, F, Cl, R^1 = R^2 = H; R = R^1 = Me, R^2 = H;
R = H, Cl, R^1 = H, R^2 = Me

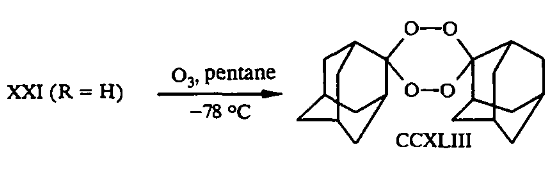
The formation of the spirans (CCXLI) [R = H, R^1 = *t*-Bu; R = H, R^1 = 1-adamantyl; R + R^1 = (CH$_2$)$_5$] from the ketone (XVI) and silylated carboxyperoxides (CCXLII) in the presence of Me$_3$SiOCOCF$_3$ was explained in [178] by the following scheme:





CCXLI

During the ozonization of the methyleneadamantane (XXI) (R = H) the 1,2,4,5-tetroxane derivative (CCXLIII) was isolated with a yield of 20% in addition to the ozonide (CXLVI) described above [118]:

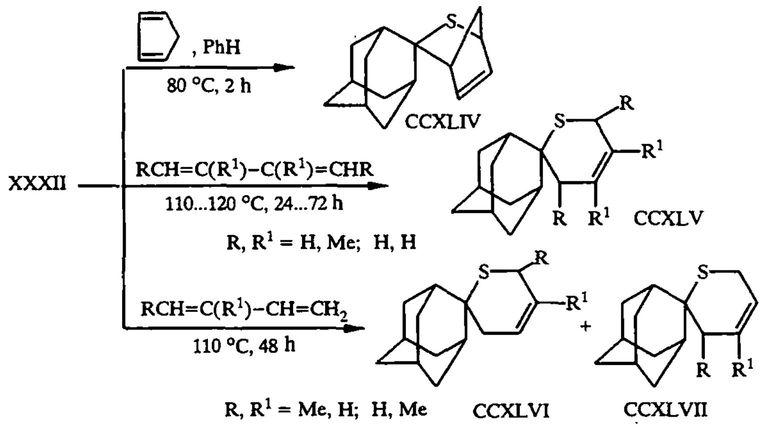


CCXLIII

4.3. Sulfur-Containing Heterocycles

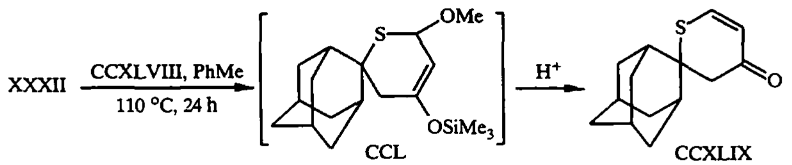
The diene synthesis reaction has often been used for the synthesis of spiro compounds containing adamantane and a six-membered heterocyclic ring with an oxygen atom.

Thus, one adduct each [(CCXLIV) (yield 91%) or (CCXLV) (yield 56-82%)] is formed during the thermal cyclocondensation of the thioketone (XXXII) with cyclopentadiene or with the dienes RCH═C(R^1)—C(R^1)═CHR in toluene or xylene. Two adducts each [(CCXLVI) and (CCXLVII) (yields 80-82% in a 1:1 ratio)] are formed with the dienes RCH═C(R^1)CH═CH$_2$ [157]:



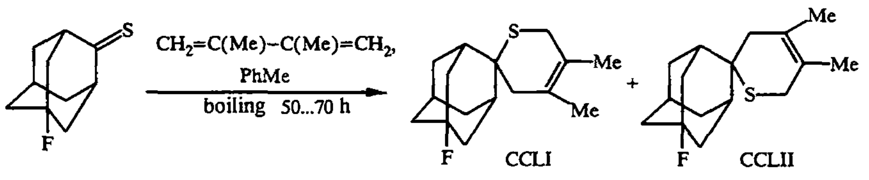
CCXLIV CCXLV CCXLVI CCXLVII

The reaction of the thioketone (XXXII) with the diene MeOCH═CHC(OSiMe$_3$)═CH$_2$ (CCXLVIII) at 110°C followed by treatment of the reaction mixture with acid gave compound (CCXLIX) (yield 64%). This is clearly the product from hydrolysis and dehydration of the initially formed adduct (CCL) [157]:



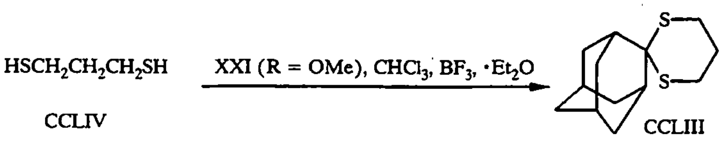
CCL CCXLIX

When 5-fluoro-2-adamantanethione was heated with 2,3-dimethyl-1,3-butadiene in toluene for 50-70 h, a mixture of the isomers (CCLI) and (CCLII) was obtained with an overall yield of 80-83% in a ratio of 2:1 [52, 53]:



CCLI CCLII

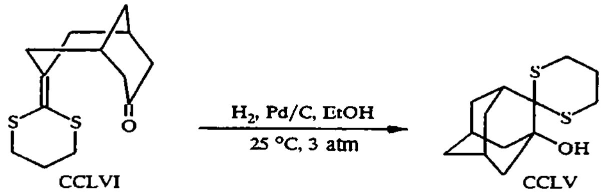
Spiro[adamantane-2,2'-(tetrahydro-1,3-dithiin)] (CCLIII) is formed as a result of the reaction of the alkene (XXI) (R = OMe) with the dithiol (CCLIV) in the presence of boron trifluoride etherate [125]:



CCLIV

CCLIII

An alternative approach was used to obtain the dithiin derivative (CCLV); the framework system was added with the presence of a heterocyclic fragment in the initial compound (CCLVI) [179]:

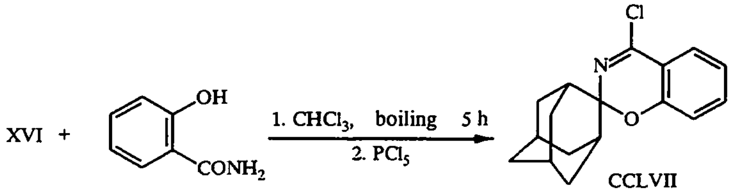


CCLVI

CCLV

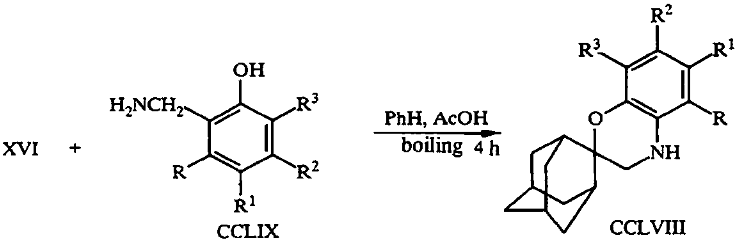
4.4. Heterocycles Containing N and O

The spiro compound (CCLVII) was synthesized by heating the ketone (XVI) with salicylamide in chloroform and treatment of the reaction product with phosphorus pentachloride [180]:



CCLVII

The 1,4-oxazine derivative (CCLVIII) is formed with an 89% yield when the ketone (XVI) and the phenol (CCLIX) are heated in the presence of acetic acid [181]:



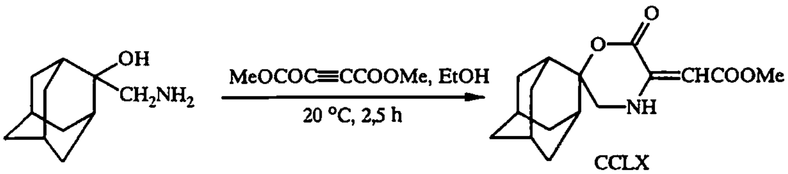
CCLIX

CCLVIII

R, R^1, R^2, R^3 = H, CMe_3, H, I

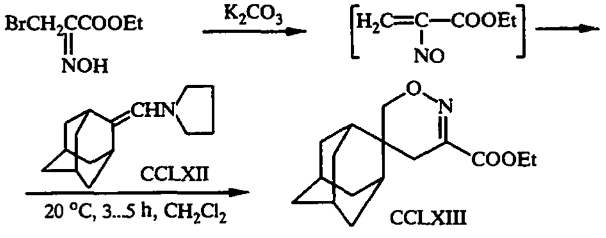
The production of the spiro compound (CCLVIII) (R, R^1, R^2, R^3 = Cl, Cl, H, Cl; H, CMe_3, H, I; MeO, Cl, MeO, Cl) from the ketone (XVI) and the corresponding derivatives of phenol was patented [182].

The 1,4-oxazine derivative (CCLX) (yield 77%) was synthesized by the addition—cyclocondensation of 2-hydroxy-2-aminomethyladamantane with dimethyl acetylenedicarboxylate [183, 184]:



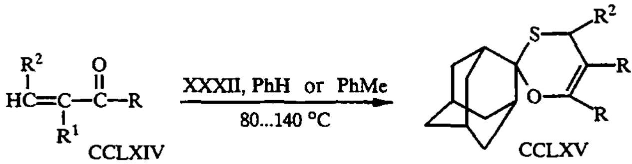
CCLX

The cycloaddition of ethyl 2-nitrosoacrylate, formed from the bromooxime (CCLX) by the action of potassium carbonate, to the alkene (CCLXII) gave compound (CCLXIII) [185]:



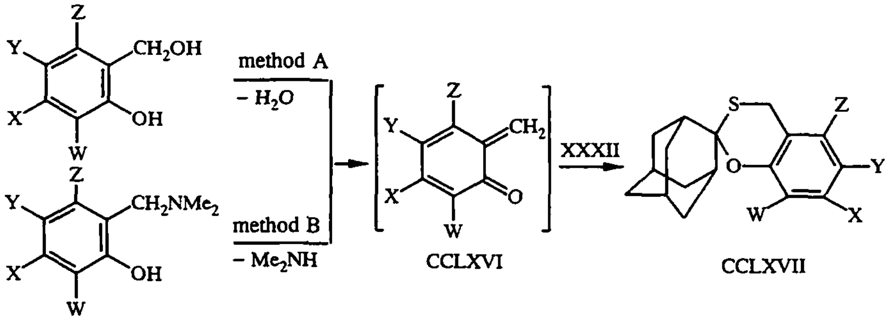
4.5. Heterocycles Containing O and S

The diene synthesis reaction of the thioketone (XXXII) with α,β-unsaturated aldehydes and ketones (CCLXIV) was conducted by heating in tubes in an atmosphere of argon in the presence of hydroquinone. Steric factors have a strong effect on the yields of the reaction products (CCLXV) [186]:



R, R^1, R^2, time (h), yield , %: H, H, H, 4,94; H, Me, H, 12,71; H, H, Me, 14,29;
Me, H, H, 14,82; Me, Me, H, 120,22

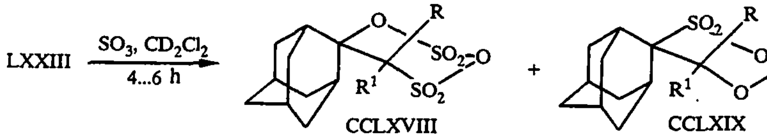
The thioketone (XXXII) enters into the diene synthesis with cyclic vinyl ketones (CCLXVI) (obtained by methods A and B at 140-200°C) with the formation of the spiro compounds (CCLXVII) (yields 40-89%) [187]:



W, X, Y, Z, method, time (h): H, H, H, H, A, 6; H, Me, H, H, A,4; Me, H, H, H, A, 4;
H, H, Cl, H, A, 6; H, H, NO_2, H, A, 20; OMe, H, H, H, A, 30;
Me, H, Me, H,B, 3; H, H, -CH=CH—CH=CH-,B, 5;
-CH=CH—CH=CH-, H, H, A, 20; H, -CH=CH—CH=CH-, H, A, 20;
H, H, -CH=CH—CH=CH-, B, 96

4.6. Heterocycles Containing Two O Atoms and Two S or Si Atoms

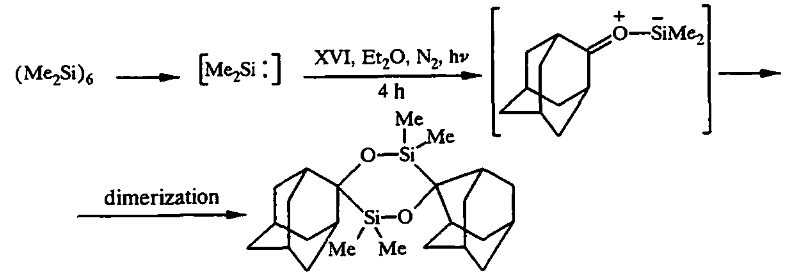
The reaction of the unsaturated compounds (LXXXIII) with sulfur trioxide results in the formation of two types of carbyl sulfates (CCLXVIII) and (CCLXIX) [84]:



CCLXVIII CCLXIX

R, R^1, temperature (°C), yield, %, CCLXVIII and CCLXIX: H, H, 10, 6 and 76; H, H, −60, 10 and –; Me, H, −40, 13 and –; Br, Br, −60, 16 and –

The bisspiro compound (CCLXX), containing two oxygen atoms and two silicon atoms in the heterocyclic fragment, was synthesized with a yield of 18% from the ketone (XVI) and the organosilicon compound $(Me_2Si)_6$ by irradiation with a low-pressure mercury lamp [167]:

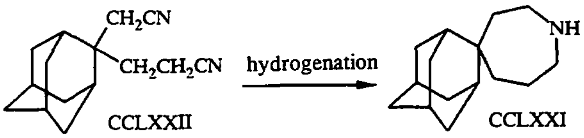


CCLXX

5. COMPOUNDS CONTAINING SEVEN-MEMBERED HETEROCYCLES

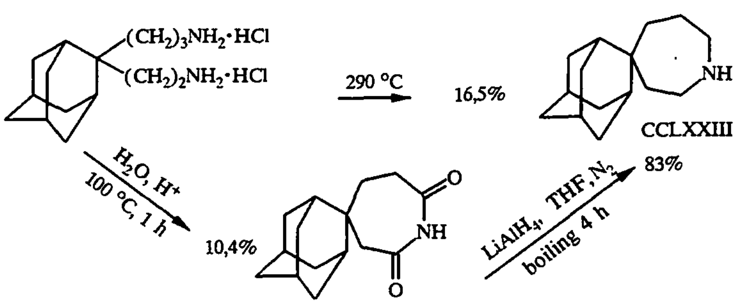
5.1. Nitrogen-Containing Heterocycles

Spiro[adamantane-2,4′-hexahydroazepine] (CCLXXI) is formed during the hydrogenation of the dinitrile (CCLXXII) [170]:



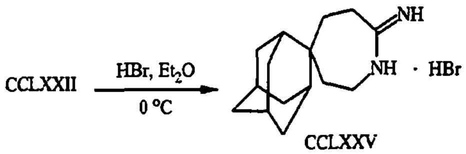
CCLXXII CCLXXI

The authors of [87] developed several methods for the synthesis of azepine derivatives (CCLXXIII, CCLXXIV, CCLXXV):



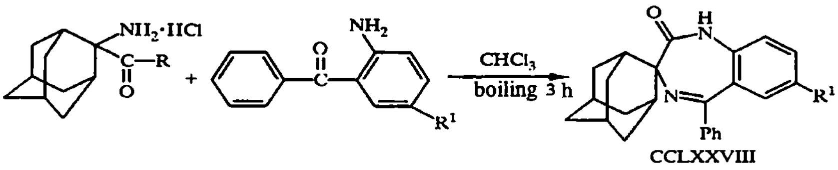
CCLXXIII

CCLXXIV



CCLXXV

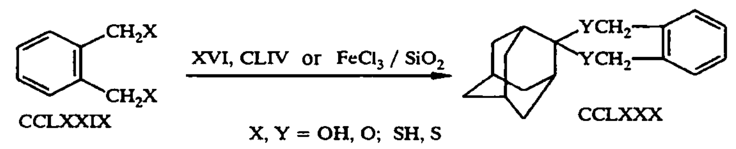
The condensation of the hydrochlorides of 2-amino-2-adamantanecarboxylic acid or its acid chloride (CCLXXVI) with derivatives of benzophenone (CCLXXVII) gives derivatives of spiro(adamantane-2,3'-benzo-1,4-diazepin)-2-ones (CCLXXVIII) [188, 189]:



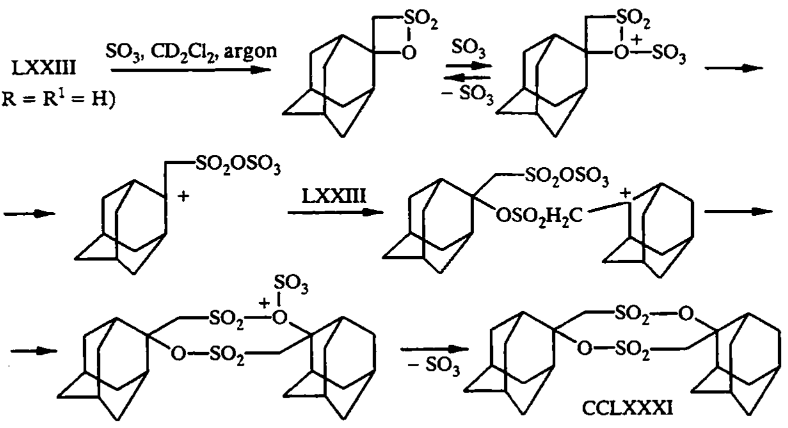
R, R^1: Cl, H; Cl, Me; Cl, Br; OH, H; OH, Me; OH, Cl; OH, Br

5.2. Heterocycles Containing O and S

The cyclocondensation of the ketone (XVI) with bifunctional compounds (CCLXXIX) in the presence of (CLIV) [190, 191] or ferric chloride [192] gave the spiro compounds (CCLXXX):



There is a single report [84] in which the bis-spiro compound (CCLXXXI), containing an eight-membered heterocyclic ring with two oxygen atoms and two sulfur atoms, is described. The authors [84] give the following probable scheme for the formation of this compound:



On the basis of the presented material it is possible to say that two types of adamantane derivatives are mainly used as the starting compounds in the synthesis of spiro compounds containing adamantane and heterocyclic fragments.

On the one hand, in most cases compounds with a semicyclic double bond (adamantanone, adamantanethione, the corresponding alkenes and cumulenes) are used. On the other, suitable compounds include adamantane derivatives containing two functionalized substituents at position 2. At the same time there is only one report on an alternative method for the synthesis of such substances — the addition of a framework ring to heterocyclic compounds not containing an adamantane fragment.

Many routine procedures can be used in the synthesis of spiro compounds containing adamantane and heterocyclic fragments. They include oxidation, reduction, rearrangement, cycloaddition, recyclization, and intramolecular and intermolecular cyclization.

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