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Ketoesters and ketoacids of the adamantane series: synthesis and transformations

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Abstract. Published data on the synthesis and reactivity of ketoesters and ketoacids containing the adamantane nucleus are summarized and generalized. Biological activities of these compounds are discussed. The bibliography includes 105 references.

I. Introduction

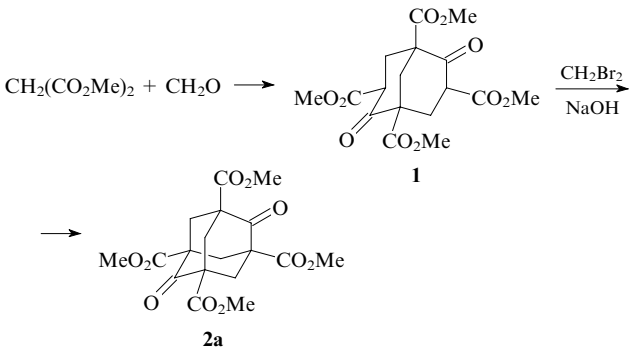
Ketoesters and ketoacids of adamantane series are promising from the viewpoint of their use for the preparation of adamantane derivatives of diverse types. The data on these compounds are encountered only in original papers and are partially covered in general reviews dealing with the adamantane chemistry or the ketoacid chemistry.[1–9]

In developing the history of the adamantane chemistry, its derivatives, such as the adamantanecarboxylic esters containing carbonyl groups in adamantane nucleus, had been known before the hydrocarbon itself was synthesized. In 1922, Meerwein[10] prepared a tetraester of 2,6-dioxobicyclo[3.3.1]nonane-1,3,5,7-tetracarboxylic acid (**1**) from malonic ester and formaldehyde in the presence of pyridine. This product then was used[11] as starting compound in the synthesis of adamantane and its derivatives. An introduction of the methylene bridge in the bicyclononane skeleton of the ester **1** (Bottger,[12] 1937) yielded the compound **2a** having adamantane nucleus (Scheme 1).

Adamantane itself was discovered and isolated by Landa and Machacek[13] from the oil deposit Godonin in Czechoslovakia in 1933.

In the late 1950s, Schleyer and Donaldson[14,15] developed a preparative method for the preparation of adamantane by isomerization of the hydrogenated cyclopentadiene dimer in the presence of aluminium chloride or other Lewis acids. It is this procedure that has been implemented on an industrial scale and so far used all over the world.

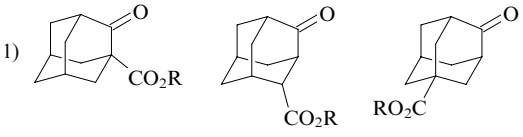
Scheme 1



Present review deals with the synthesis and reactivity of the adamantyl-containing ketoesters and ketoacids. In the review, published data are classified on the basis of the structure of compounds; ketoesters (acids) in which the carbonyl carbon atom is a part of the adamantane nucleus bonded with the ester (carboxy) group and adamantane derivatives in which both these functions are present in a side chain were treated separately.

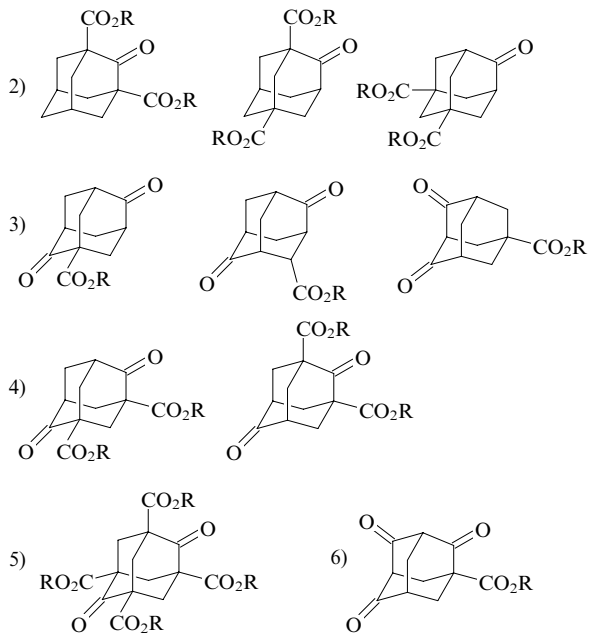
II. Methods for the synthesis of the oxoadamantanecarboxylic acids and their esters

Known to date ketoesters and ketoacids of adamantane series, which will be discussed in this chapter, for convenience could be divided into six classes depending on the number and relative arrangement of carbonyl and ester (carboxy) groups in these molecules.



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R = H, Alk.

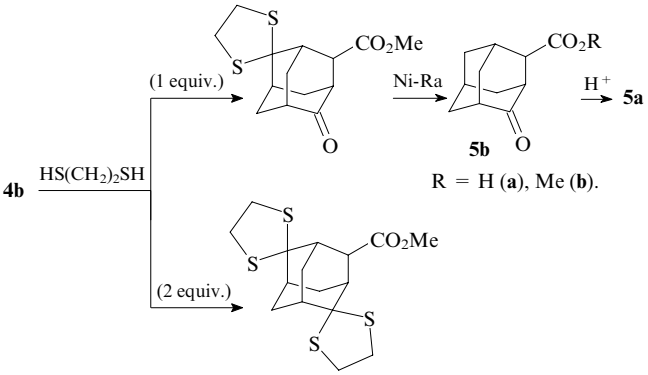
Analysis of the data published in the literature shows that methods for the preparation of the compounds having C=O groups in the adamantane moiety and CO_2R function bonded directly with it could be classified according to the types of starting compounds used. These may be Meerwein's ester (**1**), derivatives of cyclohexanone (as a rule, in enamine form) or of adamantane. In the majority of cases, reaction products are ketoesters (R = Alk) and corresponding ketoacids (R = H), which form as result of their transformations.

1. Synthesis from Meerwein's ester

Based on Meerwein's ester (**1**), oxoadamantanecarboxylic esters **2a** (see Scheme 1),[12] **3a** and **4a**,**b** (see Scheme 2) containing two C=O groups and four, two and one CO_2R functions, respectively, were synthesized.[16–20] Keto groups are converted to methylene bridge by reduction of compounds **2a**, **3a** and **4a** with hydrazine hydrate in the presence of sodium ethoxide to produce adamantane-1,3,5,7-tetra- (Ref. 21, 22), adamantane-1,3-di- (Ref. 16) and adamantane-2-carboxylic esters, respectively.[17]

Ethyl (**4a**) and methyl (**4b**) esters of dioxoadamantanecarboxylic acids containing ester group at secondary carbon atom of adamantane, were synthesized from Meerwein's ester *via* stage of formation of bicyclo[3.3.1]nonanedione.[17–20] Racemic acid **4c** synthesized from ester **4b** was successfully separated into enantiomers by the repeated crystallization of the cinchonidine salt.[19]

Diketoester **4b** was converted to monoketoacid **5a** in three steps; first, selective protection of the sterically less hindered C=O groups was carried out in the presence of boron trifluoride etherate, then dithioketal was desulfurized with Raney nickel (Ni-Ra) and ester **5b** was hydrolyzed under acidic conditions.

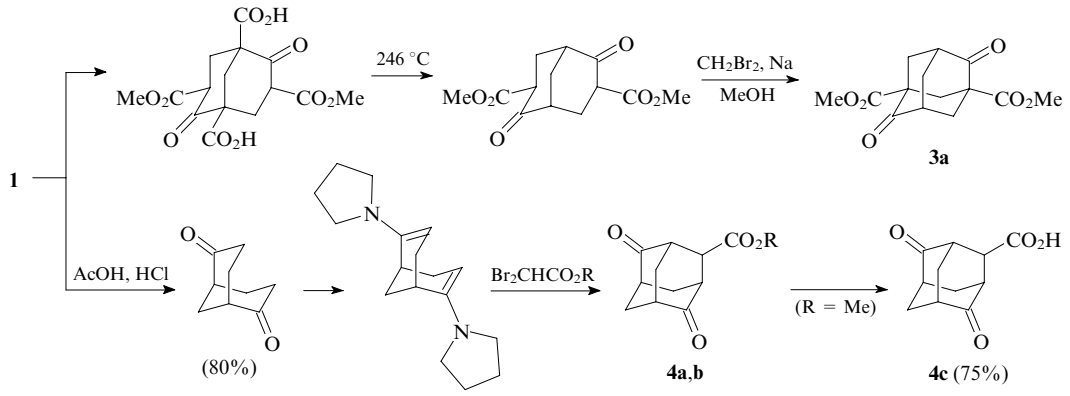


R = H (**a**), Me (**b**).

Some reactions starting from diketoester **4b**, in which the ester function and one keto group are involved, are shown in Scheme 3.[19,23] In these transformations, ketal protection was used to protect the carbonyl groups in adamantane nucleus; mono- and diketals were separated chromatographically.

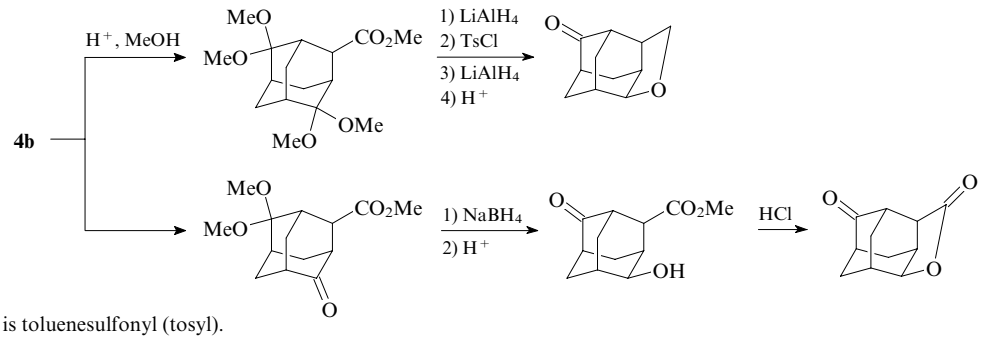
A study of the reduction of diketoester **4b** under various conditions showed[23–25] that if a stoichiometric amount of $NaBH_4$ is used in isopropyl alcohol, the reaction involves only the C=O group relative to which the ester group occurs in equatorial position. This reaction results in mainly (~30%) two possible stereoisomers of hydroxyketoester **6,** which contain hydroxyl group in equatorial (*eq*-**6**) or axial (*ax*-**6**) position. Reduction of the remaining keto groups in compounds **6** with zinc amalgam in HCl with subsequent oxidation of hydroxyl function to give 4-oxoadamantane-2-carboxylic acid with equatorial carboxylic group (*eq*-**5a**) (Scheme 4).

Scheme 2



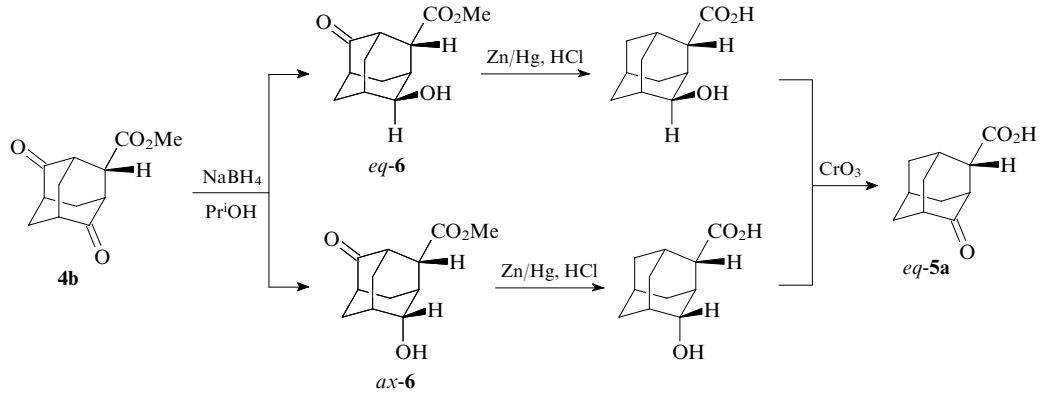
R = Et (**a**, 42%), Me (**b**, 10%).

Scheme 3



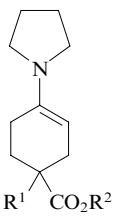
Ts is toluenesulfonyl (tosyl).

Scheme 4

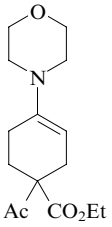


2. Synthesis from cyclohexanone derivatives

Oxoadamantanecarboxylates were synthesized using pyrrolidine (morpholine) enamines (compound **7a–c**, **8**) as precursors, which were introduced in the reaction with derivatives of acrylic,[26–29] methacrylic[29] and crotonic[30] acids.



7a–c

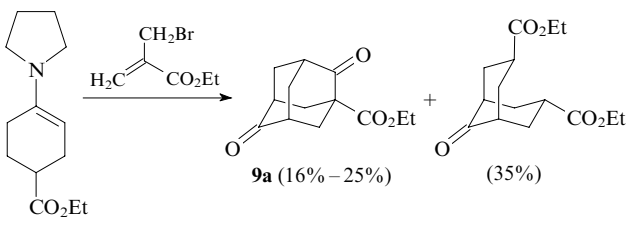


8

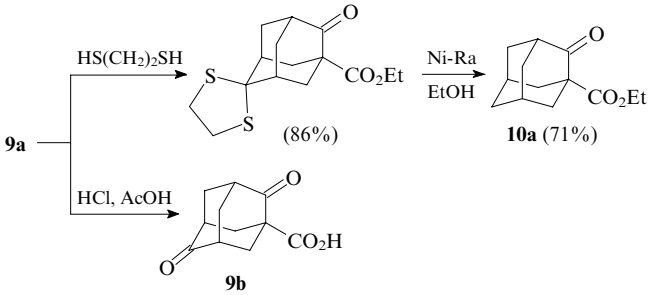
R^2 = Et: R^1 = H (**a**), CO_2Et (**b**);
R^1 = CO_2Me, R^2 = Me (**c**).

Enamine **7a** was prepared from ethyl 4-oxocyclohexanecarboxylate,[31] enamine **7b** was prepared from the corresponding 4-oxocyclohexane-1,1-dicarboxylate.[32]

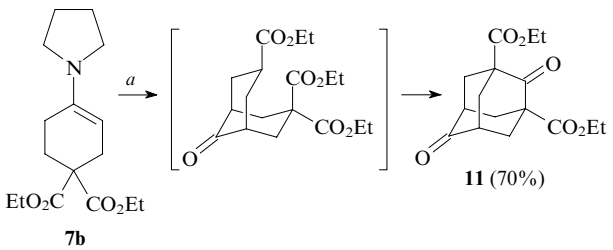
The reaction of 4-pyrrolidinocyclohex-3-enecarboxylate (**7a**) with ethyl 2-bromomethylacrylate gives ester of dioxoadamantanecarboxylic acid **9a** apart from the bicyclic ketone.



Selective reduction of one of C=O groups in compounds **9a** leads to monoketoester **10a** bearing the ethoxycarbonyl group at the tertiary carbon atom of adamantane.[26] Acid hydrolysis of the ester **9a** produces the corresponding acid **9b**.



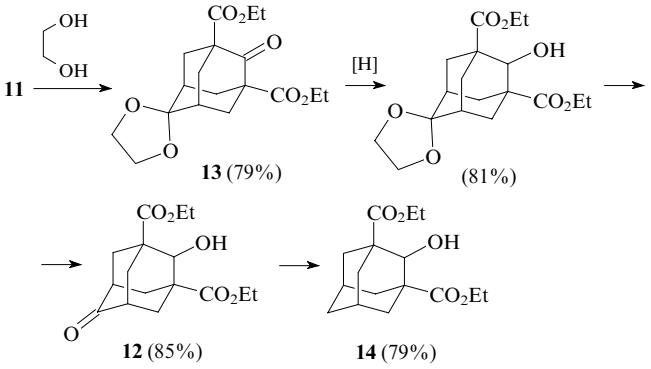
Enamine **7b** reacts with ethyl (2-bromomethyl)acrylate to give diketodiester **11**.[27,28]



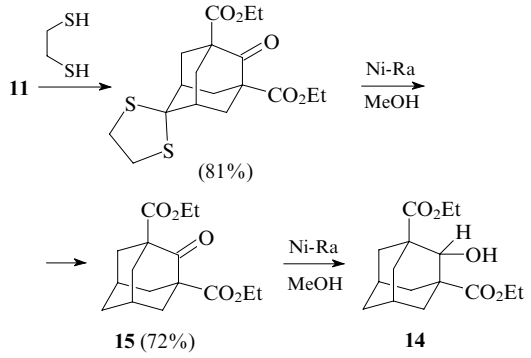
(*a*) $CH_2BrC(=CH_2)CO_2Et$.

Selective ketal protection of one of C=O groups was used to convert diketodiester **11** to monoketodiester **12** having hydroxyl group in α-position to both CO_2Et groups.

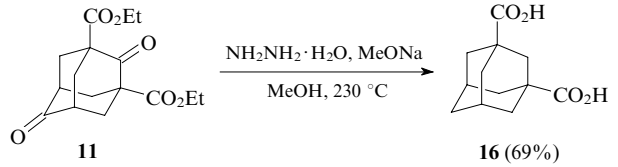
The reaction sequence includes catalytic hydrogenation of monoketal **13** and the subsequent removal of the ketal protection. A Wolff–Kishner reduction of the C=O groups in compounds **12** affords diethyl ester of 2-hydroxyadamantane-1,3-dicarboxylic acid **14**.[27,28]



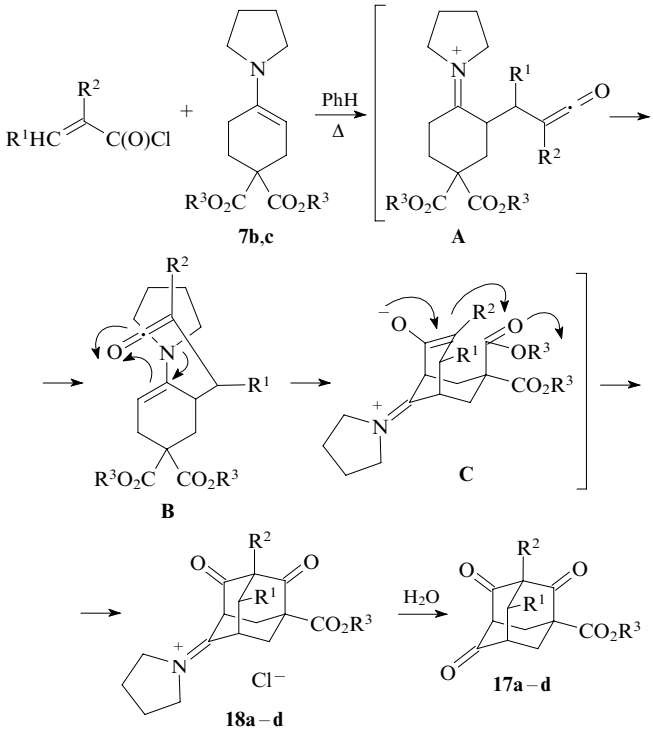
Selective thioketal protection of one of C=O groups of diketoester **11** followed by desulfurization with Raney nickel in methanol leads to monoketodiester **15** containing two CO_2Et groups in the α-position to keto group, and then to hydroxyester **14**.[28]



In the presence of MeONa, hydrazine hydrate in methanol reduces diketoester **11** to adamantane-1,3-dicarboxylic acid **16** (reaction proceeds in autoclave at 230 °C).[28]

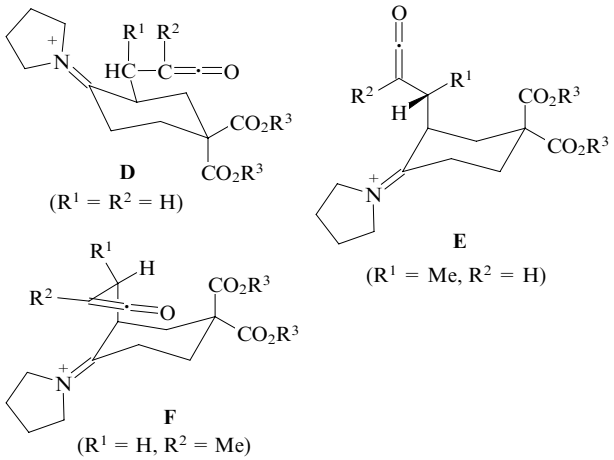


In 1973, the one-step synthesis of esters **17a–d** containing three keto groups in adamantane moiety was reported.[30] The method is based on the reaction of pyrrolidine enamines **7b**,**c** with acid chlorides of crotonic and methacrylic acids. Authors of publication propose a process mechanism including the formation of the intermediate ketene **A** and its enamine form **B**, intramolecular cyclization of which leads to the enolate anion **C**, and then to salts **18a–d**; the latter were prepared in yields of 25%, 2%, 30% and 29%, respectively. Salts **18a–d** were hydrolyzed to form products **17a–d**.



R^1 = H, R^2 = Me: R^3 = Me (**a**), Et (**b**);
R^1 = Me, R^2 = H: R^3 = Me (**c**), Et (**d**).

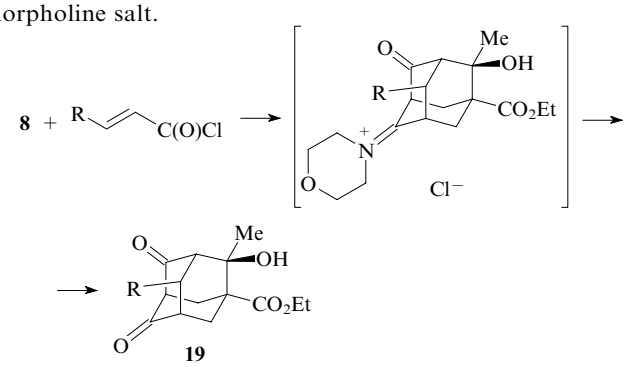
Similar reaction with acrylic acid chloride ($R^1 = R^2 = H$) does not proceed. Perhaps, this is caused by the significant influence of α- or β-alkyl substituent in unsaturated acid chloride on conformation of intermediates **A** and **B**, which play a key role in the cyclization process. Hickmott *et al.*[30] assumed that in case of acryloyl chloride, an intermediate with equatorial orientation of the ketene substituent (structure **D**) is formed, whereas crotonoyl and methacryloyl chlorides give product with axial orientation (structures **E** and **F**):



Conformation **F**, in which methyl group is most distant from the ester function, and ketene functionality is placed straight over the ring, is most favourable for the cyclization to adamantane structure.

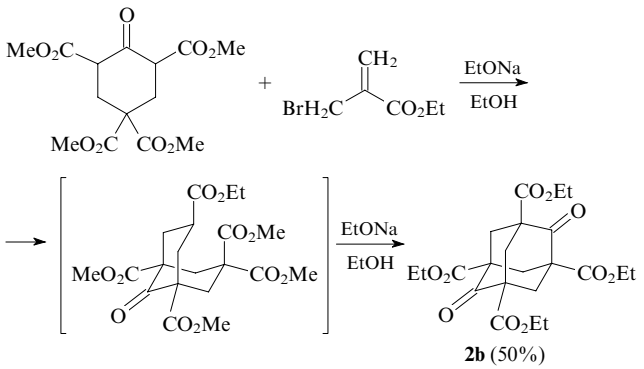
Reaction of morpholinocyclohexenecarboxylate **8** with acid chlorides of acrylic and methacrylic acids produces dioxomonoester **19** containing axial group OH in C(6)-position of the adamantane nucleus.[29] It is obvious that

reaction proceeds *via* the formation of the corresponding morpholine salt.



R = H, Me.

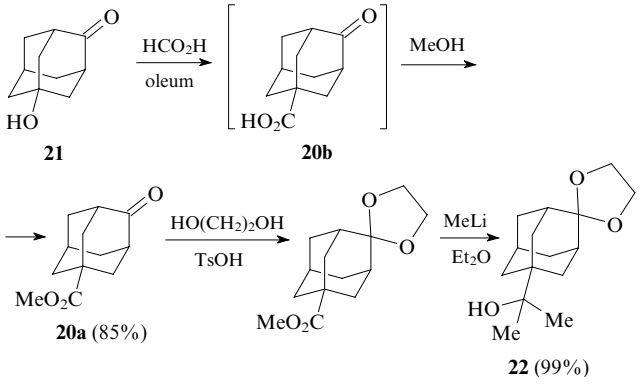
To our knowledge, the only example in which not a corresponding enamine, but the cyclohexanone derivative was used in synthesis of adamantylketoester, is the reaction of ethyl 2-bromomethylacrylate with tetramethyl ester of 4-oxocyclohexane-1,1,3,5-tetracarboxylic acid.[20] The reaction proceeds in dry EtOH in the presence of EtONa and produces tetraethyl ester of 2,6-dioxoadamantane-1,3,5,7-tetracarboxylic acid **2b**.[33]



According to the literature data described in sections II.1 and II.2, both cyclohexanone derivatives (**7**, **8**) and Meerwein's ester (**1**) could be used to prepare adamantylketoesters containing two ketogroups (there were three groups only in one example of compounds **17**) and from one to four groups CO_2R. These compounds could be easily utilized to synthesize other adamantane derivatives.

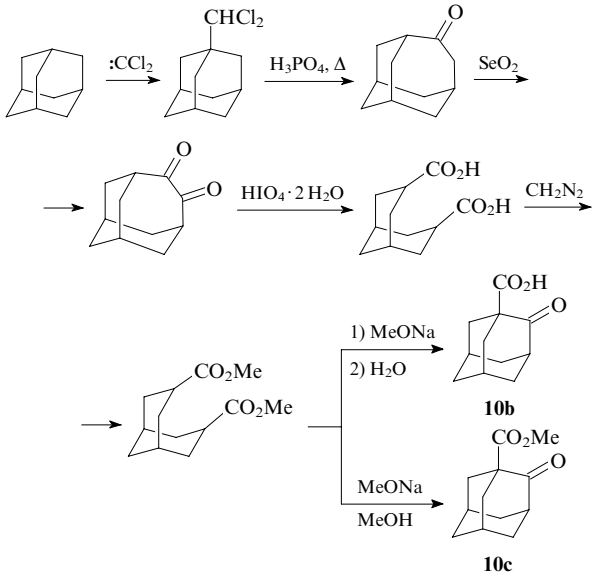
3. Synthesis from the adamantane derivatives

Methyl 2-oxoadamantane-5-carboxylate (**20a**) have been obtained from 5-hydroxy derivative **21**.[34] Carbonylation of the latter with 97% formic acids in 30% oleum at 60 °C

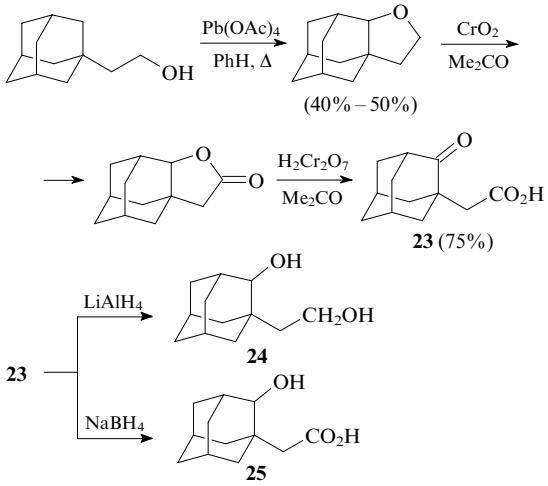


afforded acid **20b**, which was then esterified. Reaction of ketoester **20a** with ethylene glycol in the presence of *p*-toluenesulfonic acid and subsequent treatment of the product with methyllithium afforded the ketal of 5-(2-hydroxy-2-propyl)adamantan-2-one (**22**).

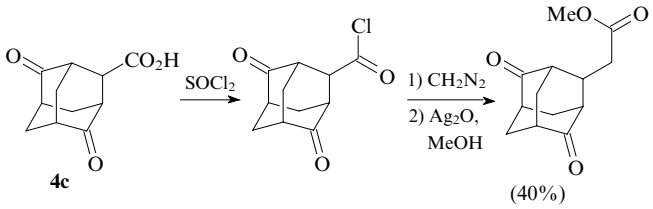
α-Ketoacid of adamantane series (**10b**) and its methyl ester (**10c**) were synthesized from adamantane by six-step synthesis *via* the formation of the corresponding derivatives of homoadamantane and bicyclo[3.3.1]nonane.[35, 36]



In conclusion of this section, two examples of compounds in which C=O group and carboxy group are present in adamantane nucleus being separated by a methylene group will be discussed. Monoketoadamantylcarboxylic acid **23** was synthesized from 2-(1-adamantyl)ethanol.[37] Reduction of ketoacid **23** with lithium aluminium hydride and with sodium borohydride leads to adamantyl-containing diol **24** and to hydroxyacid **25**, relatively.



Adamantane-2-carboxylic acid **4c** containing two C=O groups in adamantane nucleus was used for the preparation of methyl ester of its homologue from the corresponding acid chloride under conditions of Arndt–Eistert–Wolf reaction.[23]



III. Methods for the synthesis of adamantyl-ketoesters (ketoacids)

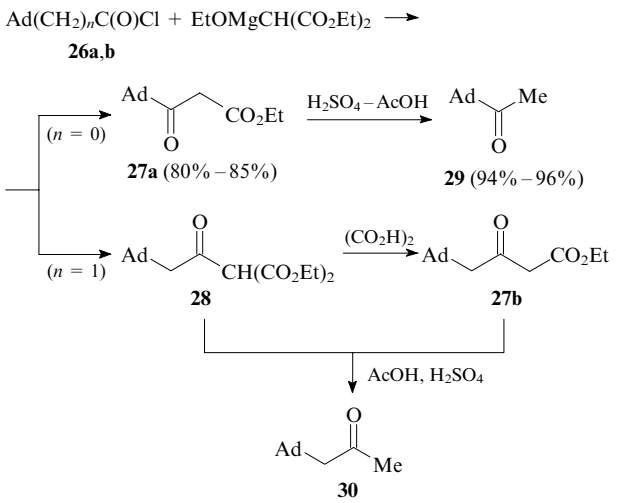
Acylation reaction of acidic compounds having CH-acidity, such as malonic, acetoacetic and cyanoacetic esters, and also their derivatives and analogues, with acid chlorides is widely used in organic chemistry for synthesis of dicarbonyl compounds.

1. Malonic ester, and its analogues, in the synthesis of adamantyl-containing ketones, ketoesters and ketoacids

a. Acylation of diethyl ethoxymagnesiummalonate with adamantane-1-carboxylic acid chlorides

Acylation of diethyl ethoxymagnesiummalonate with acid chloride of adamantane-1-carboxylic acid (**26a**) was first reported in 1960 [38] (Scheme 5). This reaction results in the formation of ethyl ester of β-(1-adamantanoyl)acetic acid (**27a**). Under analogous conditions, 1-adamantylacetic acid chloride (**26b**) gave diethyl 1-adamantylacetylmalonate **28**, heating of which with anhydrous oxalic acid leads to elimination of one ester group and formation of γ-(1-adamantyl)acetoacetic ester (**27b**).[39] Cleavage of ketoesters **27a**,**b** and **28** in mixture of $AcOH-H_2SO_4$ affords adamantyl-containing ketones **29** and **30** (see Scheme 5).

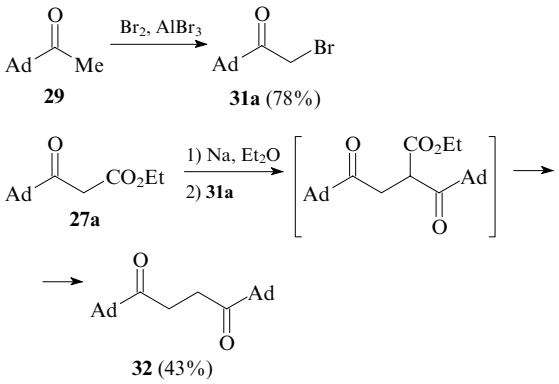
Scheme 5



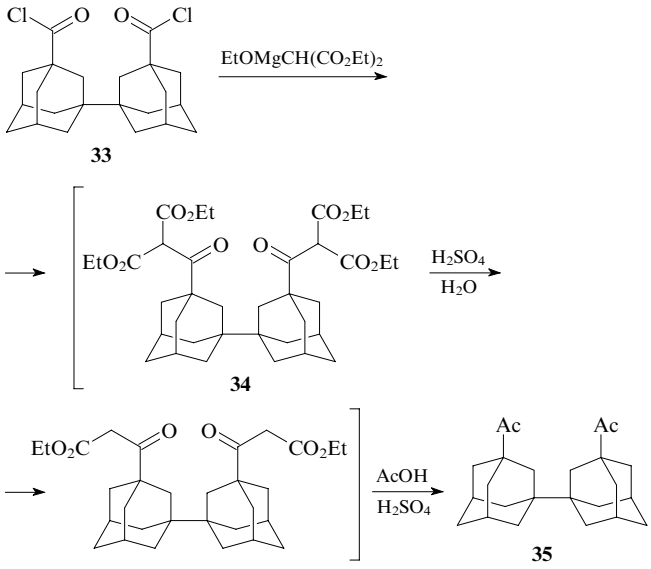
$n = 0$ (**a**), 1 (**b**); Ad is 1-adamantyl.

Formation of adamantylacetylmalonate **28** in reaction of acid chloride **26b** with diethyl malonate was explained [39] by the decrease (as compared with acid chloride **26a**) of electron-donating properties of the adamantyl moiety owing to the presence of the intermediary methylene group.

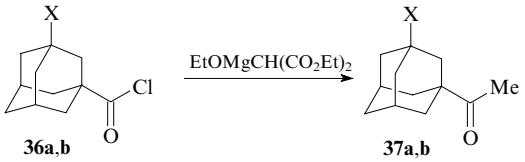
Bromomethyl derivative **31a** was prepared by bromination of 1-acetyladamantane (**29**) in the presence of $AlBr_3$.[38] Reaction of the latter with sodium derivative of ketoester **27a** leads to 1,4-di(1-adamantyl)butane-1,4-dione **32** *via* formation of the corresponding diketoester.



Diethyl ethoxymagnesiummalonate was acylated with 3,3′-di-(chlorocarbonyl)-1,1′-biadamantane (**33**) to give the intermediate acylated malonic ester **34**. Subsequent hydrolysis and decarboxylation of compound **34** give 3,3′-diacetyl-1,1′-biadamantane (**35**) in 70% yield.[40,41]

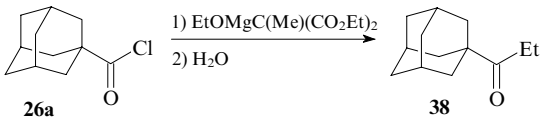


The discussed above method for the synthesis of adamantyl-containing ketones (see Scheme 5) was extended to 3-halogenadamantane-1-carboxylic acid chlorides **36a**,**b**.[42] This synthesis affords ketone **37a**,**b** having halogen atoms in the adamantane nucleus.

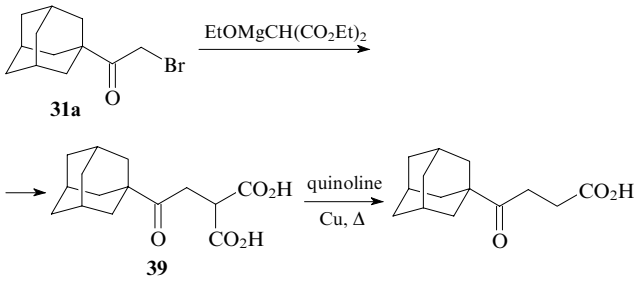


X = Cl (**a**), Br (**b**).

Condensation of acid chloride **26a** with (ethoxymagnesium)methylmalonic ester with subsequent hydrolysis gives 1-propanoyladamantane (**38**).[43]

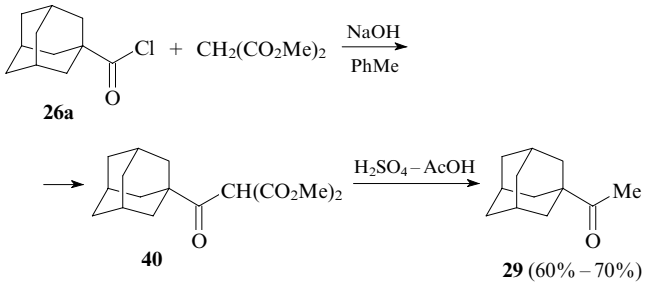


Besides of adamantanecarboxylic acid chlorides, 1-adamantyl bromomethyl ketone (**31a**) was allowed to react with ethoxymagnesiummalonic ester.[44] A condensation gave adamantyl-containing ketodiacid **39**, in which then one carboxylic group was removed by heating with quinoline in the presence of powdered copper.

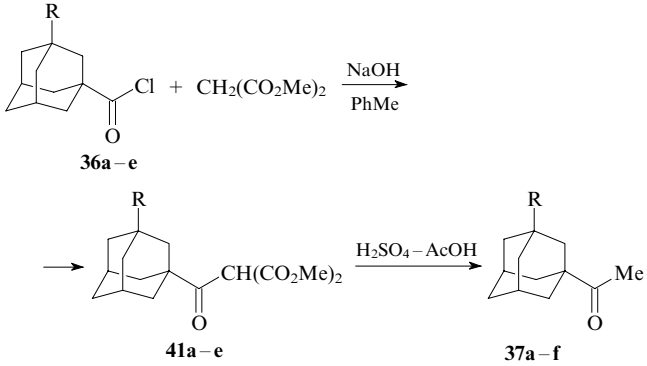


b. Acylation of dimethyl malonate with adamantane-1-carboxylic acid chlorides in the presence of NaOH

The stable malonic ester derivative containing adamantanoyl moiety, compound **40**, was first prepared in 1997.[45] It was formed as a result of reaction of adamantane-1-carboxylic acid chloride (**26a**) with dimethyl malonate in toluene in the presence of NaOH. Acid hydrolysis of methyl ester of adamantanoylmalonic acid (**40**) gives 1-acetyladamantane **29**.

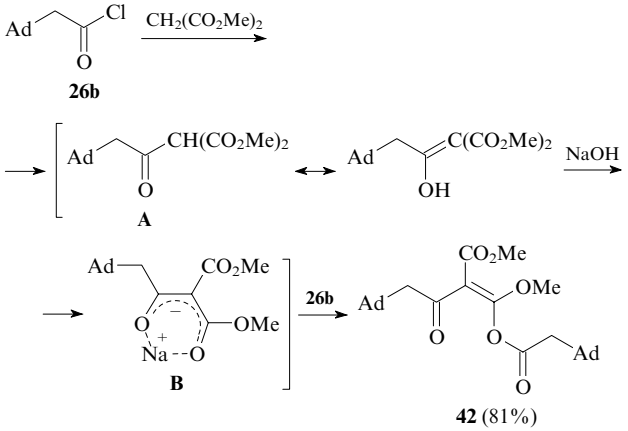


In 1999, this reaction was extended to 3-chloro(bromo)adamantane-1-carboxylic acid chlorides **36a**,**b**,[46] and later to other 3-substituted acid chlorides **36c**–**e**.[47] Pozdnyakov *et al.*[47] proposed this transformation as a general method for the synthesis of adamantyl ketones **37a**–**e**. Intermediate dimethyl (3-R-1-adamantanoyl)malonates **41a**–**e** could be also isolated. In case of halogen-substituted ketoesters **41a**,**b,** hydrolysis causes not only the cleavage of methoxycarbonyl groups, but also full or partial displacement (depending on reaction time) of the halogen atom by hydroxyl group (compound **37f**).

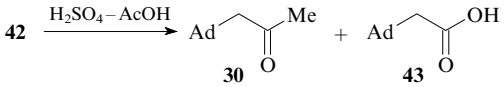


R = Cl (**a**), Br (**b**), Et (**c**), Ph (**d**), NH_2 (**e**), OH (**f**).

It was found recently [48] that reaction of dimethyl malonate with adamantylacetic acid chlorides (**26b**), in the presence of NaOH in toluene gives C,O-acylated methyl [2-(1-adamantylacetyl)-3-(1-adamantylmethylcarbonyloxy)-3-methoxy]prop-2-enoate (**42**).



In opinion of the authors,[48] the first step of the reaction mechanism is C-acylation to give intermediate **A**, which, after enolization, forms the sodium salt **B** being more active than sodium malonic ester. Acylation of salt **B** on the oxygen atom leads to compound **42**. Hydrolysis of the latter in the mixture of $AcOH-H_2SO_4$ affords an equimolar mixture of adamantylacetone (**30**) and 1-adamantylacetic acid (**43**).

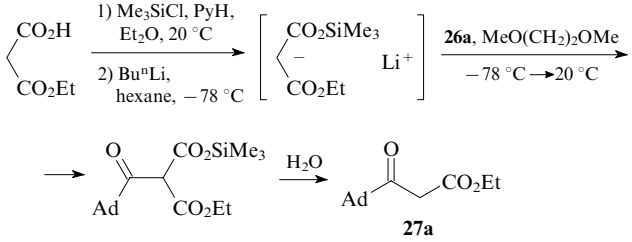


Attempts to prepare products of C,O-acylation with use of acid chlorides of 3-R-adamantane-1-carboxylic and benzoic acids were unsuccessful. Perhaps, this is caused by steric hindrance at the formation of the enol form of C-alkylated intermediate.

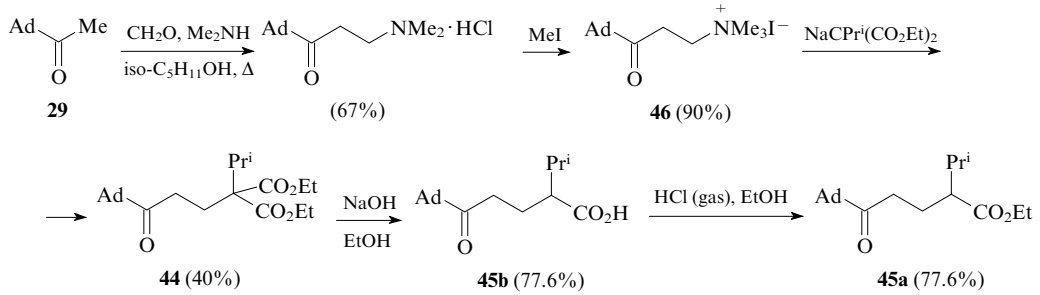
c. Other examples of the use of malonic ester, its homologues and analogues in the synthesis of adamantylketoesters

[2-(1-Adamantanoylethyl)]trimethylammonium iodide **46** prepared from 1-acetyladamantane (**29**) is widely used as precursor in the synthesis of δ-ketodi- (**44**) and δ-ketomonocarboxylic esters (**45a**), and also of δ-ketoacid **45b**.[49] Compound **44** was synthesized by reaction of salt **46** with sodium isopropyl malonic ester. Subsequent transformations lead to the compounds **45a**,**b** (Scheme 6).

Taylor and Turchi [50] proposed a general method for the synthesis of ketoesters $RC(O)CH_2CO_2Et$ (for example,



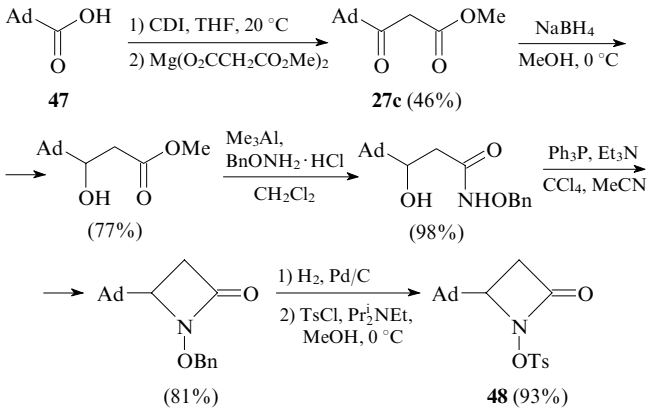
Scheme 6



R = Ad) involving the formation of lithium enolate of ethyl (trimethylsilyl)malonate. The latter could be easily acylated with acid chloride **26a**, then the corresponding intermediate is subjected to hydrolysis and decarboxylation.

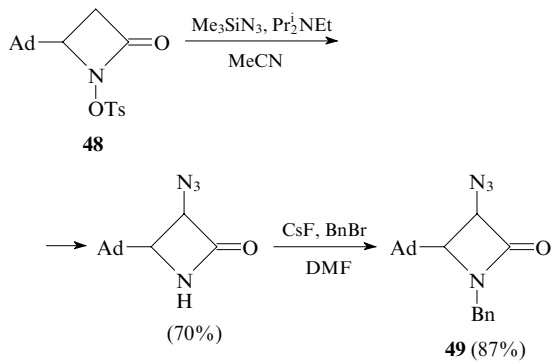
Adamantyl-containing *N*-toluenesulfonyloxy-β-lactam **48** was prepared from adamantane-1-carboxylic acid (**47**) *via* the formation of β-ketoester **27c**.[51] Such derivatives of β-ketoesters are widely used in the enantioselective synthesis of α-amino acids. The reaction sequence used for preparation of β-lactam **48** is shown in Scheme 7.

Scheme 7

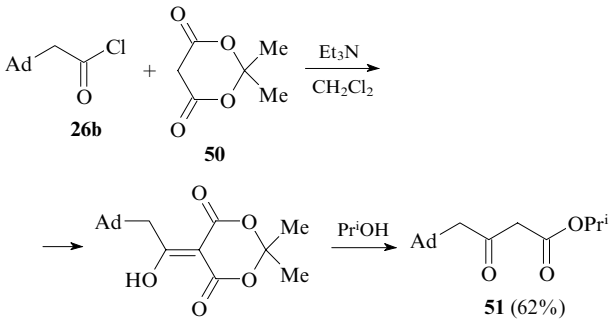


CDI is carbonyldiimidazole.

N-Toluenesulfonyloxy-β-lactam **48** was converted to *N*-benzyl-β-lactam **49** *via* the formation of the corresponding 3-azido derivative.[51]

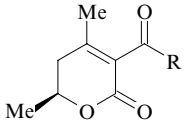


Meldrum's acid (**50**) was also utilized in the synthesis of adamantylketoesters. Thus, reaction of adamantylacetic acid chloride (**26b**) with compound **50** in the presence of triethylamine and subsequent alcoholysis of the acylation product lead to isopropyl 4-(1-adamantyl)-3-oxobutanoate **51**.[52]



Attempt to carry out this reaction in the presence of pyridine was unsuccessful. The authors explained this observation by the fact that pyridine ($pK_{BH^+} = 5.23$) is quaternized with acid halides, as opposed to triethylamine ($pK_{BH^+} = 10.57$), which is not.

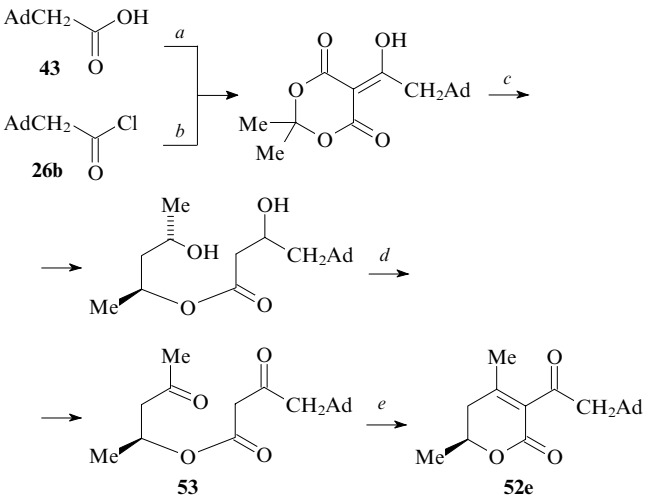
In 2004, Meldrum's acid was used in the synthesis of compound **52e** (R = $AdCH_2$) being adamantyl-containing analogue of natural dictyopyrones **52a**–**d**.[53] A work was made with aim to study pharmacological action of these molecules on growth and morphogenesis of microorganisms *Dictyostelium discoideum*, and also to investigate its activity against human leukemia cells K562. It was established that adamantyl derivative **52e** inhibits growth of *D. discoideum*, but does not affect its morphogenesis, and also inhibits the growth of tumour cells K562.



52a–**e**

R = $(CH_2)_8$–CH=CH–Me (**a**), $(CH_2)_{10}$–CH=CH–Me (**b**), n-$C_{11}H_{23}$ (**c**), Pr^n (**d**), CH_2Ad (**e**).

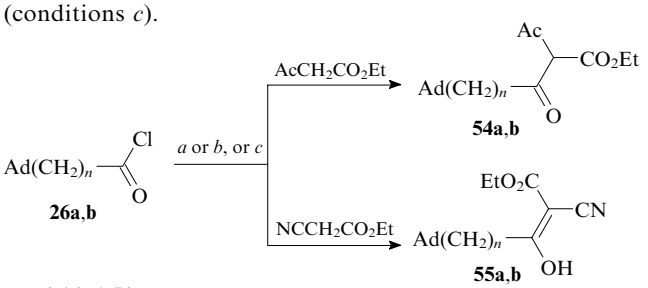
Analogue of dictyopyrone **52e** was synthesized in four steps from adamantylacetic acid (**43**) or its acid chloride **26b** *via* the intermediate formation of the corresponding adamantyl-containing ketoester **53**.



(*a*) **50**, EDCI·HCl, DMAP, CH_2Cl_2, 20 °C; (*b*) DMAP, CH_2Cl_2, 20 °C; (*c*) (2*S*,4*S*)-pentan-2,4-diol, PhMe, 80 °C; (*d*) PCC, CH_2Cl_2; (*e*) EtONa, EtOH, 0 °C; EDCI·HCl is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMAP is 4-dimethylaminopyridine, PCC is pyridinium chlorochromate.

2. Carboxylic acids and esters (ethyl acetate, acetoacetic and cyanoacetic esters) in synthesis of adamantyl-containing ketoesters (acids)

In publication [54] reaction of adamantane-1-carboxylic acid chloride (**26a**,**b**) with acetoacetic (AAE) and cyanoacetic (CAE) esters was studied under various conditions. The authors studied reaction conditions such as the action of Na in diethyl ether (conditions *a*); of NaOH in toluene (conditions *b*) and 40% aqueous solution of NaOH in acetone (conditions *c*).



n = 0 (**a**), 1 (**b**).

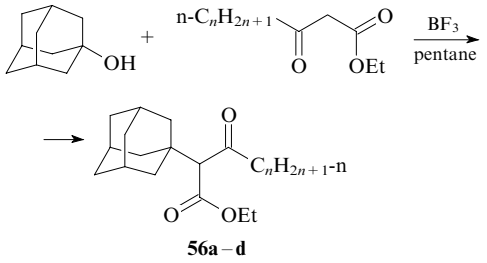
In all cases, reactions with AAE afford predominatly and reactions with CAE afford exclusively C-acylated products, in particular, compounds **54a**,**b** and **55a**,**b**.

The yield of products **54** and **55** depends considerably on the reaction conditions:

Conditions	Yield (%)			
	54a	**54b**	**55a**	**55b**
a	80	85	63	53
b	65	66	69	60
c	–	71	87	86

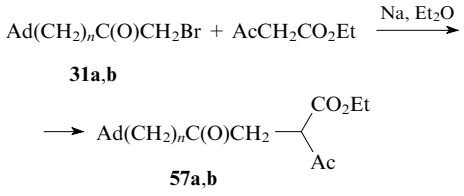
Unexpectedly, acid chloride **26a** did not react with AAE in 40% aqueous solution of NaOH in acetone, whereas acid chloride **26b** under these conditions gave product **54b** in good yield. Authors assumed that the rate of the competing hydrolysis reaction of acid chloride **26a** is higher than the rate of hydrolysis of the compound **26b**.

Reaction of ethyl acetoacetate and its homologues having the structure n-$C_nH_{2n+1}C(O)CH_2CO_2Et$ (n = 1–4) with 1-hydroxyadamantane in pentane in a flow of gaseous BF_3 produces β-ketoesters **56a**–**d**.[55–58]



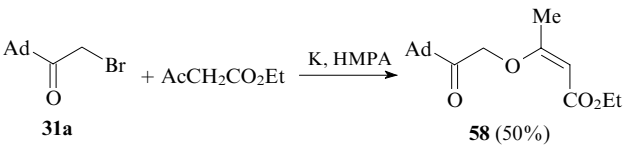
n = 1 (**a**, 44%),[55] 2 (**b**, 34%),[57] 3 (**c**, 22%),[58] 4 (**d**, 34%).[58]

Danilin *et al.*[59] investigated C- and O-alkylation of acetoacetic ester and carboxylic acids with 1-adamantyl bromomethyl ketone (**31a**) and 1-(1-adamantyl)-3-bromopropan-2-one (**31b**). It was established that reaction of bromomethyl ketones **31a**,**b** with AAE in a mixture of anhydrous Et_2O and MeOH in the presence of MeONa, and also in anhydrous Et_2O in the presence of metallic Na, gives the C-alkylated derivatives **57a**,**b**, which are ethyl esters of the corresponding adamantyl-containing diketoacids.



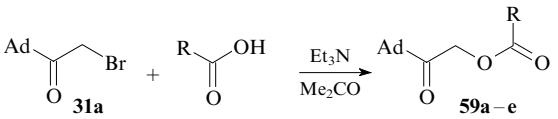
n = 0 (**a**, 90%), 1 (**b**, 73%).

The reaction of bromomethyl ketone **31a** with AAE in hexamethylphosphorotriamide (HMPA) in the presence of metallic potassium proceeds to form the O-alkylated ethyl ester of 3-(1-adamantyl-2-oxoethoxy)but-2-enoic acid (**58**).



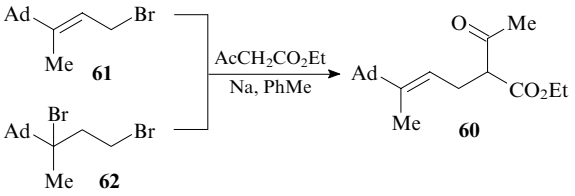
In opinion of authors of publication,[59] metallic potassium reacts with AAE to produce a chelate complex, in which the K^+ ion is coordinated to oxygen atoms of the enolate anion. HMPA efficiently solvates K^+; meanwhile, the enolate anion remains practically unsolvated and therefore, highly nucleophilic.

O-Alkylation occurs in the reaction of bromomethyl ketone **31a** with formic, acetic, furan-2-carboxylic, adamantane-1-carboxylic and 1-adamantylacetic acids.[59] The products of this reaction are compounds **59a**–**e**. The process proceeded in acetone in the presence of 6–9-fold excess of Et_3N taken as a base.

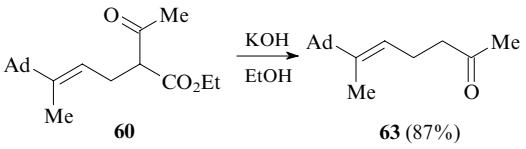


R = H (**a**, 76%), Me (**b**, 98%), 2-Fu (**c**, 63%), Ad (**d**, 65%), $AdCH_2$ (**e**, 35%).

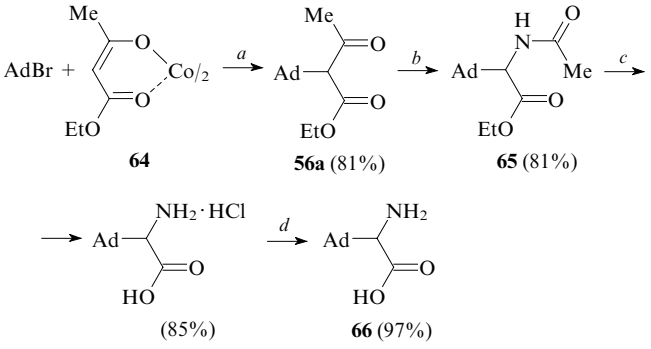
Unsaturated ketoester **60** was synthesized by condensation of bromide **61** with acetoacetic ester in 60% yield.[60] Under similar conditions, AAE reacts with 3-(1-adamantyl)-1,3-dibromobutane (**62**), but the yield of ketoester **60** is lower (40%).[49]



Refluxing of the compound **60** with KOH in ethanol leads to decarboxylation and formation of unsaturated ketone **63**.[60] Based on ketone **63,** some analogues of natural acyclic terpenoids (for example, geraniol and geranic acid) containing adamantane nucleus were synthesized.



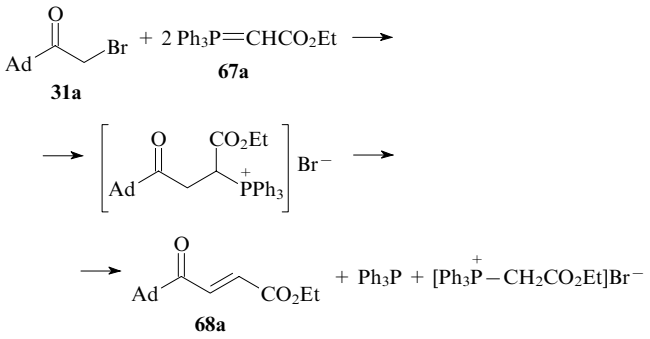
Alkylation of ethyl acetoacetate cobalt complex **64** with 1-bromoadamantane[61,62] led to ketoester **56a**,[63,64] which was converted by the Schmidt rearrangement to amino-derivative **65**. Hydrolysis of the latter produced the racemic form of 1-adamantylglycine **66**.[64]



(*a*) $CoCl_2(PPh_3)_2$, $LaBr_3 \cdot 6H_2O$, $CHCl_3$, 140 °C; (*b*) NaN_3 (3 equiv.), $MeSO_3H$, $MeO(CH_2)_2OMe$, 20 °C; (*c*) 7 M HCl, Δ; (*d*) propylene oxide, EtOH.

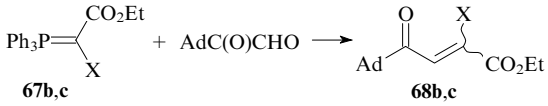
3. Triphenylphosphoranes in synthesis of unsaturated adamantyl-containing ketoesters (ketoacids)

Triphenylphosphoranes **67** are used to synthesize a large diversity of adamantyl-containing unsaturated ketoesters.[65–68] Thus, 1-adamantyl bromomethyl ketone (**31a**) reacts with two equivalents of triphenylphosphorane **67a** to give the compound **68a**.

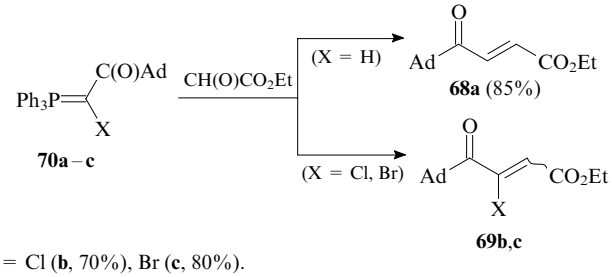


Analogous procedure was used to synthesize α- and β-halogen derivatives **68b**,**c** and **69b**,**c** (X = H **68a** ≡ **69a**) (Scheme 8). Adamantyl motif could be present both in the carbonyl reacting component and in the phosphorane component (compound **70a**–**c**).

Scheme 8



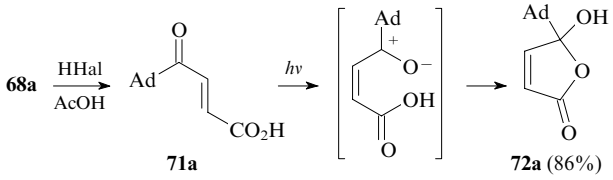
X = Cl (**b**, 80%), Br (**c**, 72%).



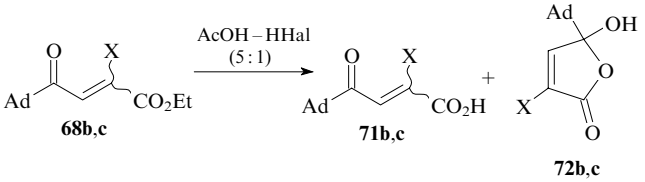
X = Cl (**b**, 70%), Br (**c**, 80%).

If X = H (compound **68a**), synthesized ketoesters **68** have *trans*-configuration between the ester and the adamantylcarbonyl groups. In the cases where halogen atom is present in α-position of phosphorane (compound **67b**,**c**), a mixture of *cis*- and *trans*-isomers are formed.

Ester group of compounds **68a** was hydrolyzed to carboxylic group in acidic medium; *trans*-ketoacid **71a** was formed. After prolonged staying in the light (30 days), it isomerizes to *cis*-form, which undergoes intramolecular cyclization to give hydroxy-γ-lactone **72a**.[65]

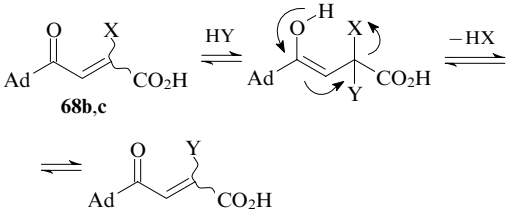


More severe conditions are necessary for acidolisis of the halogen-containing ketoesters **68b**,**c**.[68] The result of acidolisis, which gives a mixture of α-haloketoacids **71b**,**c** and corresponding hydroxy-γ-lactones **72b**,**c**, does not depend on whether the pure *trans*-isomer or mixture of *cis*- and *trans*-isomers of the ester is used. The ratio of products **71** : **72** was 1 : 1.4 for X = Cl and 1 : 1.2 for X = Br.



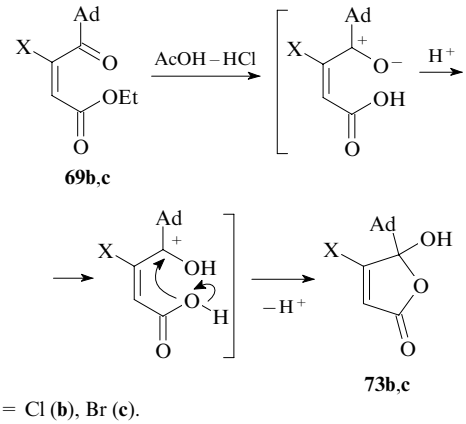
X = Cl (**b**), Br (**c**).

When acidolisis of ketoesters **68b,c** is carried out with hydrohalic acids having halogen atom that is not the same as the halogen atom X present in esters, interchange of the halogen atoms is observed too.[68]



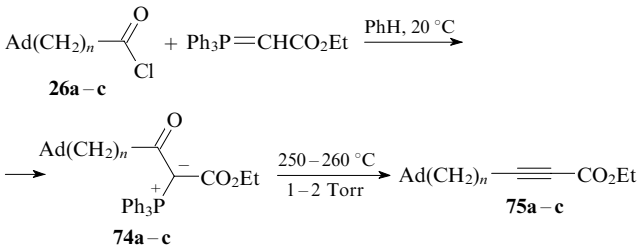
X, Y = Hal; X ≠ Y.

Adamantyl-containing phosphoranes **70b,c** and ethyl ester of glyoxylic acid (see Scheme 8)[67] gave a mixtures of *cis*- and *trans*-isomers of β-chloro- (**69b**) and β-bromoketoesters (**69c**), which contain mainly *trans*-forms (89% – 94%). At refluxing, acidolisis of compounds **69b,c** in a mixture of AcOH – HCl (5 : 1) leads to hydroxy-γ-lactones **73b,c**. Comparing these results with acidolisis of α-haloketoester **68**,[68] one can see that in case of β-halo derivatives **69** lactone is preferentially formed under analogous conditions. This was explained[67] first of all, by different electronic influence of the halogen atom on C=O and CO_2H groups, depending on its relative arrangement.



X = Cl (**b**), Br (**c**).

Reaction of adamantanoylcarboxylic acid chlorides **26a – c** with triphenylphosphonium(ethoxycarbonyl)methylide gave adamantylcarbonyl ylides **74a – c**. These compounds are highly resistant to hydrolysis, but relatively easy undergo thermolysis (250 – 260 °C, 1 – 2 Torr, 25 – 30 min) to give ethyl ester of adamantyl-containing acetylenecarboxylic acids **75a – c**.[69]

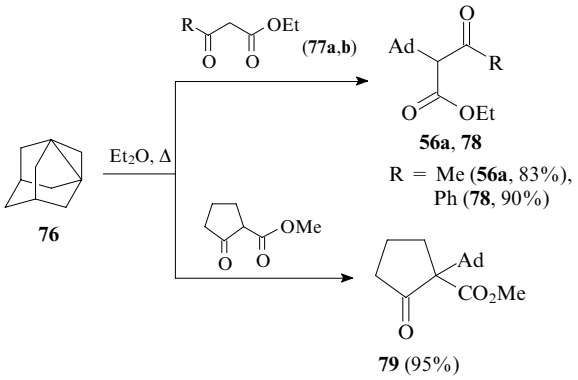


Compound	*n*	Yield (%)	
		74	**75**
a	0	87	88
b	1	82	66
c	2	79	82

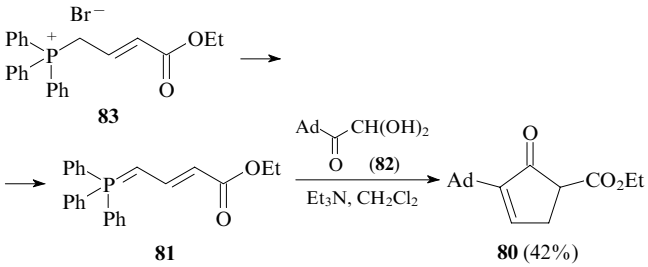
4. Adamantyl-containing ketoesters (acids) having carbo- and heterocyclic motifs in molecules

To date, a variety of adamantyl ketoesters and acids substituted with various carbo- (*e.g.*, cyclopento) and heterocycles (*e.g.*, thiophene, pyrrole, pyrazole, pyrazoline, imidazole and isoxazole) have been reported.

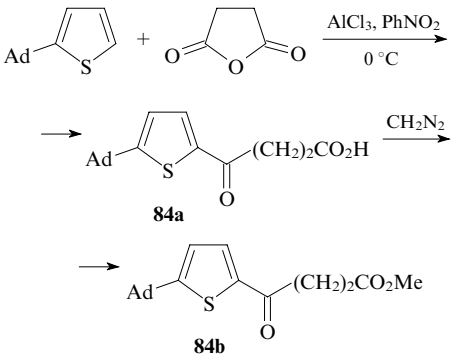
Dehydroadamantane (**76**) was used recently as precursor for the synthesis of adamantyl-containing ketoesters.[70] Besides acetoacetic ester (**77a**) and its phenyl analogue **77b,** methyl 2-oxocyclopentanecarboxylate was introduced in the reaction with compound **76**. The processes were carried out in diethyl ether under anhydrous oxygen-free nitrogen atmosphere. These transformations result in the corresponding ketoesters **56a**, **78** and **79** in high yields.



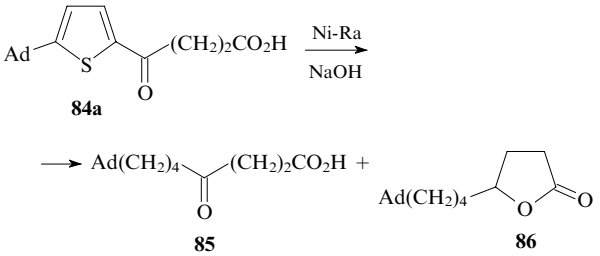
Ethyl 3-(1-adamantyl)-2-oxocyclopent-3-enecarboxylate (**80**), which is adamantyl-containing α-ketoester having five-membered unsaturated carbocycle, was synthesized by [3 + 2]-cyclization of 3-ethoxycarbonylprop-2-enylidene(triphenyl)phosphorane (**81**) with adamantyl derivative of glyoxal monohydrate **82** in the presence of a base.[71] The starting phosphorane **81** was formed *in situ* from triphenylphosphonium bromide **83**.



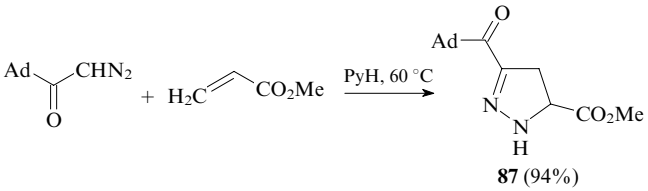
Thiophene-containing ketoacid **84a** was synthesized from 2-(1-adamantyl)thiophene and succinic anhydride in nitrobenzene in the presence of $AlCl_3$.[72, 73] Esterification of acid **84a** with diazomethane leads to methyl ester **84b**.



Desulfurization of thiophene functionality of acid **84a** in the presence of Raney nickel in alkaline medium gives a mixture of adamantylbutyl ketoacid **85** and adamantylbutyldihydrofuran-2-one **86** in total yield of 75%.



The first study of 1,3-dipolar cycloaddition of 1-(1-adamantyl)-2-diazoethanone to methyl acrylate resulting in methyl 3-(1-adamantanoyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate (**87**) was reported.[74]

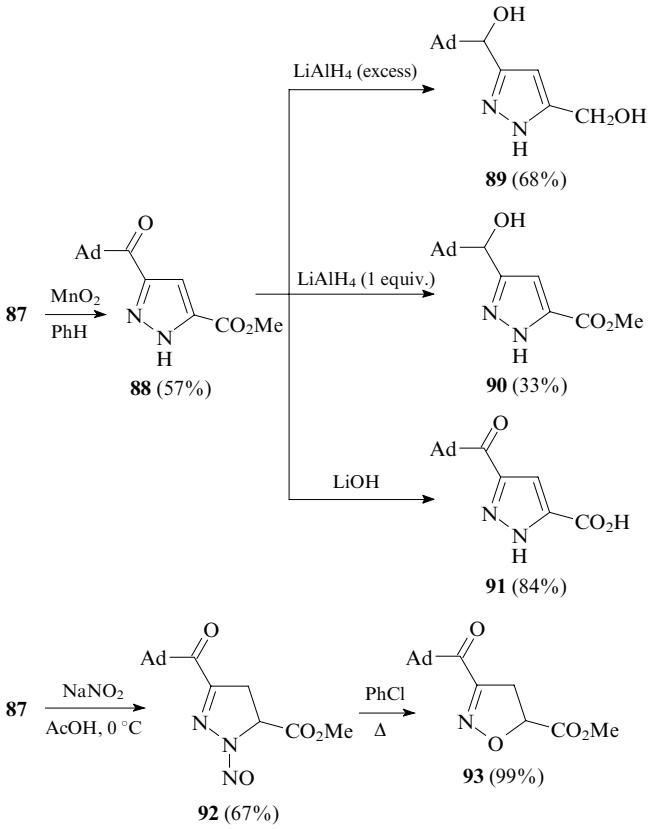


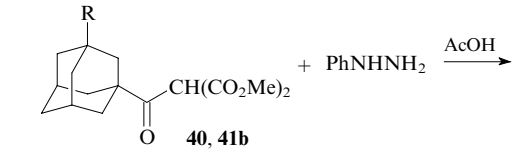
Based on the prepared ester **87**, adamantane derivatives of pyrazole (**88**–**91**), pyrazoline (**92**) and isoxazoline (**93**) were synthesized (Scheme 9).

Among transformations shown in Scheme 9, it should be noted that the synthesis of isoxazoline derivative **93** by refluxing methyl ester of 3-(1-adamantanoyl)-1-nitroso-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid (**92**) in chlorobenzole procceds in quantitative yield.

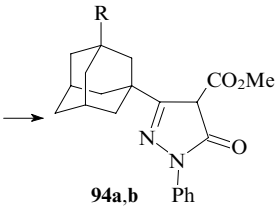
Substituted pyrazolinones (for example, with substituent in adamantane nucleus) **94a**,**b** were synthesized by reaction of the corresponding dimethyl (1-adamantanoyl)malonates **40** and **41b** with phenylhydrazine in acetic acid at room temperature.[47]

Scheme 9





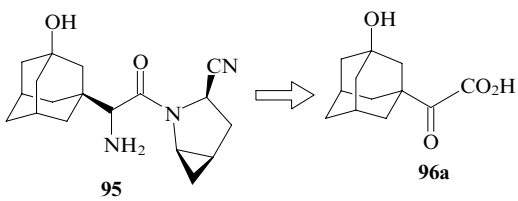
R = H (**40**), Br (**41b**).



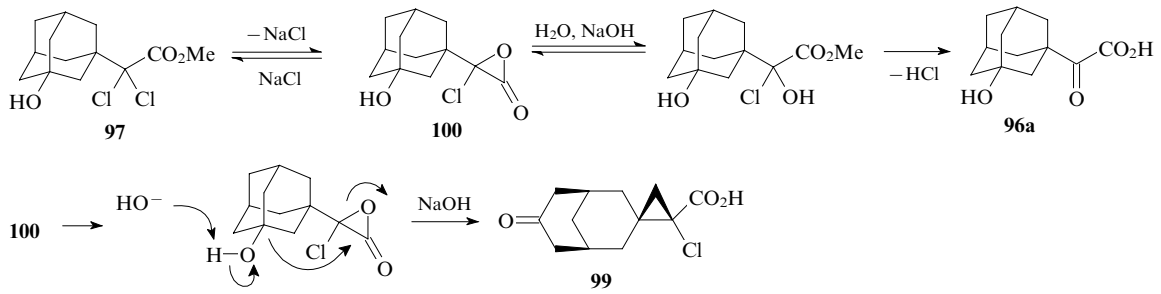
R = H (**a**, 82%), Br (**b**, 51%).

5. Other methods for the preparation of adamantyl-containing ketoesters (acids)

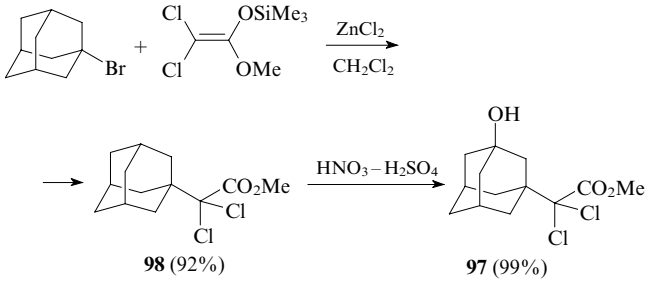
Developing of sufficiently simple, inexpensive and effective methods for the synthesis of saxagliptin (**95**), which is an effective long-acting agent for treatment of type 2 diabetes, has created a need to develop a convenient method for the preparation of the adamantane component, α-ketoacid **96a**.



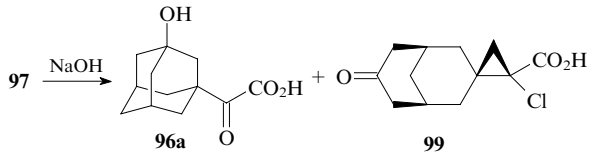
Scheme 10



With this aim, Godfrey *et al.*[75] synthesized adamantanol **97** from 1-bromoadamantane *via* formation of dichloro derivative **98**.

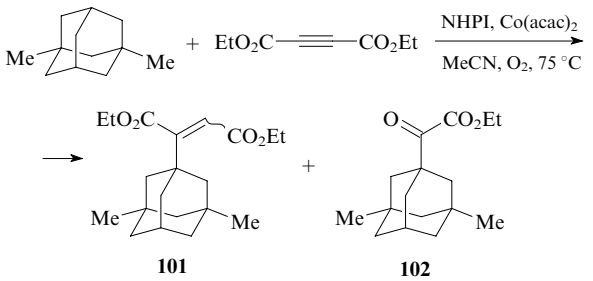


Subsequent hydrolysis of compound **97** was carried out under diverse conditions, such as action of various concentrations of NaOH in aqueous THF or MeOH, action of NaOH, and various reaction temperatures. It was found that the treatment of dichloride **97** with 1.35 equiv. of NaOH in aqueous THF at room temperature gives only the ketoacid **96a**, at the same time, under other conditions, hydrolysis results in unknown 1,4-homofragmentiton and spirocyclic compound **99** is formed as side product.



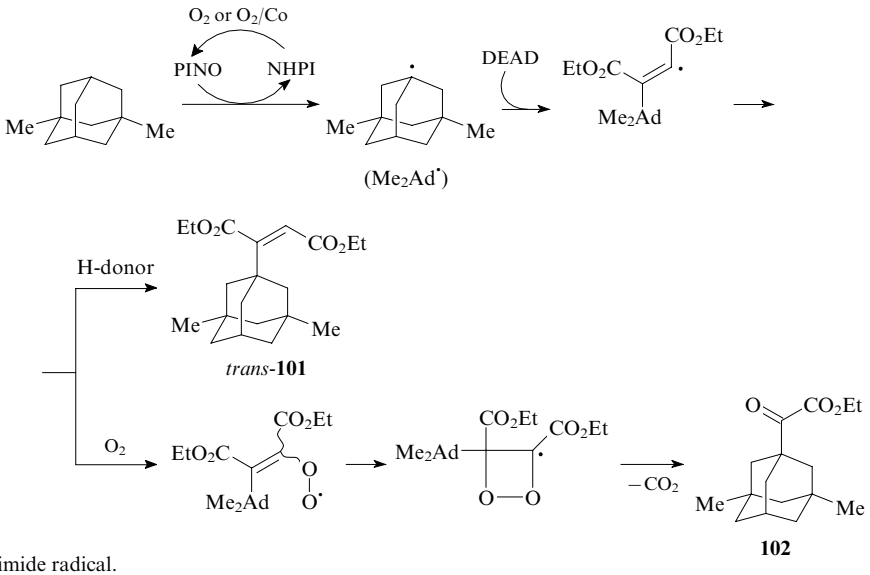
A study of process kinetics permits authors to suggest a reaction mechanism (Scheme 10) including the intermediate formation of α-lactone **100**, which converts both into desired product (**96a**) and into side product (**99**).

In 2006, in a study of radical addition of 1,3-dimethyladamantane to diethyl ester of acetylenedicarboxylic acid (DEAD) in the presence of *N*-hydroxyphthalimide (NHPI) and cobalt acetylacetonate, it was unexpectedly established[76] that α-ketoester **102** is formed along with *cis*- and *trans*-isomers of ester **101**, which are normal reaction products.



The product ration depends on reaction conditions, especially on the concentration of dioxygen in the reaction mixture. When process is carried out under a dioxygen atmosphere, ketoester **102** is formed practically selectively, and its yield reaches 45%. Based on above data, authors of publication[76] proposed a reaction mechanism shown in Scheme 11.

Scheme 11



PINO is *N*-hydroxyphtalimide radical.

IV. Properties of the ketoesters (ketoacids) of the adamantane series

In Sections II and III of present review, main emphasis was made on the methods for the synthesis of ketoesters (acids) of adamantane series, although some reactions of the prepared products were also discussed. Analysis of literature data indicates that properties of these compounds have been studied in three directions including 1) reduction (for example, selectivity of reduction) of C=O and CO_2R groups; 2) decarboxylation reaction and 3) synthesis of various, for example, heterocyclic derivatives of adamantane, starting from these products. The reported results in first two directions were partially considered in Sections II and III, which corresponds to the logic of description of presented data. In this Section, main attention is paid to the perspectives of use of ketoesters and acids of adamantane series in the synthesis of adamantane derivatives of various types.

1. Reactions of oxoadamantanecarboxylic acids and their esters

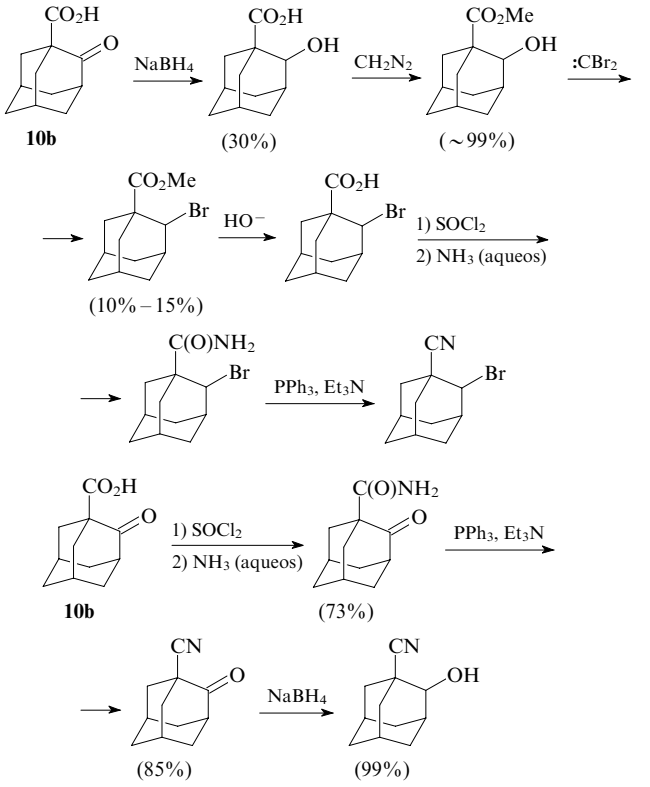
Examples of preparation of various 1,2-disubstituted adamantanes based on monoketoacid **10b** are shown in Scheme 12.[35] Authors synthesized a large number of new derivatives and investigated effect of substituents in obtained compounds on chemical shifts of geminal α-CH-protons by ^{1}H NMR spectroscopy.

2-Substituted adamantane-1-carboxylic acids (Scheme 13) were synthesized with the aim to measure the constants of dissociation.[77] Ketoacid **10b** was also used as the precursor.

Among reactions shown in Scheme 13, two transformations should be noted: 1) treatment of ketoacid **10b** with phosphorus pentachloride taken in less than equimolar amounts affords its anhydride **104** along with the corresponding dichloro-substituted acid **103**; 2) reaction of ketoacid **10b** with hydroxylamine leads to izoxazolin-5-one **106** in high yield, instead of expected oxime **105**.

For twelve 2-substituted adamantane-1-carboxylic acids (for example, compound **10b**) dissociation constants have been measured by potentiometric method in 50% aqueous ethanol. The pK_a values of these acids satisfactorily correlate with inductive constants of substituents (σ_J), which

Scheme 12



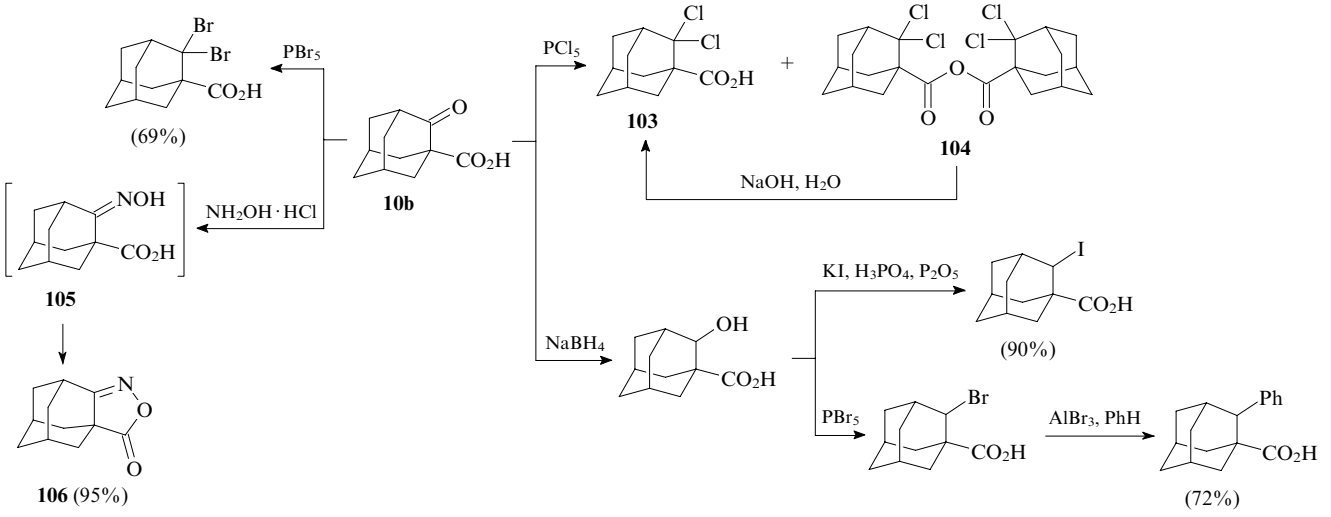
confirms inductive character of their influence. It was established that inductive effect of substituents is transfered to the reaction centre *via* σ-bonds. For the ketoacid **10b,** following pK_a values depending on the concentration of EtOH have been measured at 25 °C:

Concentration EtOH (%)	50	40	30	20	10
pK_a	5.83	5.44	5.11	4.77	4.42

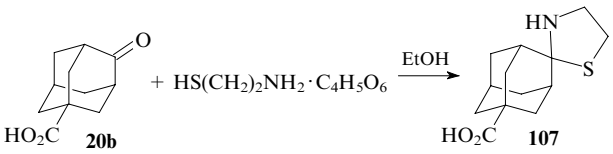
The σ_J value calculated for keto groups is 0.64.[77]

Under conditions of the Leuckart–Wallach reaction, 1-carboxyadamantane-4-spiro(2′-thiazolidine) **107** was synthesized from 4-oxoadamantane-1-carboxylic acid (**20b**) and

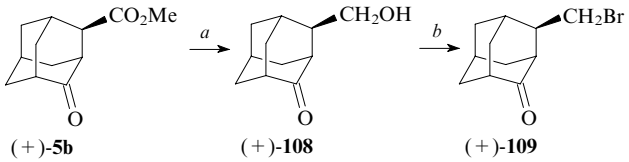
Scheme 13



thioethanolamine hydrogentartrate in ethanol.[78] Performed biological tests show a radioprotective activity of thiazolidine **107** and its antiviral activity against the influenza virus A/Bangkok/1/79 (ED_{50} = 125 μg ml^{-1}).



In publication [19] authors reported three-step transformation of ketoester (+)-**5b** including ketalization (for protection of C=O group), reduction of CO_2Me group to CH_2OH with lithium aluminium hydride and hydrolysis (deprotection). Prepared 2-hydroxymethyladamantane-4-one [(+)-**108**] was converted to bromide (+)-**109**. Based on synthesized 2-R-adamantane-4-ones **108**, **109**, various (for example, spirocyclic) adamantane derivatives were prepared.



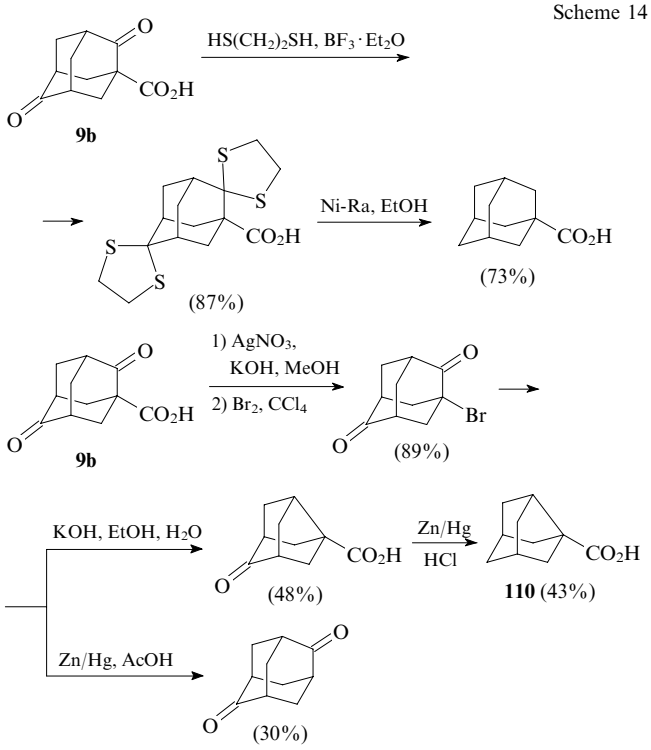
(*a*) 1) $LiAlH_4$, 2) H_2O; (*b*) Br_2, PPh_3, DMF.

Some reactions of dioxoadamantanecarboxylic acid **9b** containing CO_2H group in 1-position are shown in Scheme 14.[26] Among them, transformation of ketoacid **9b** to noradamantane-1-carboxylic acid (**110**) having noradamantane structure should be noted . The latter is formed as the result of bromination of silver salt of starting acid followed by treatment with KOH in mixture of EtOH – H_2O (Favorskii reaction) and reduction by zinc amalgam.

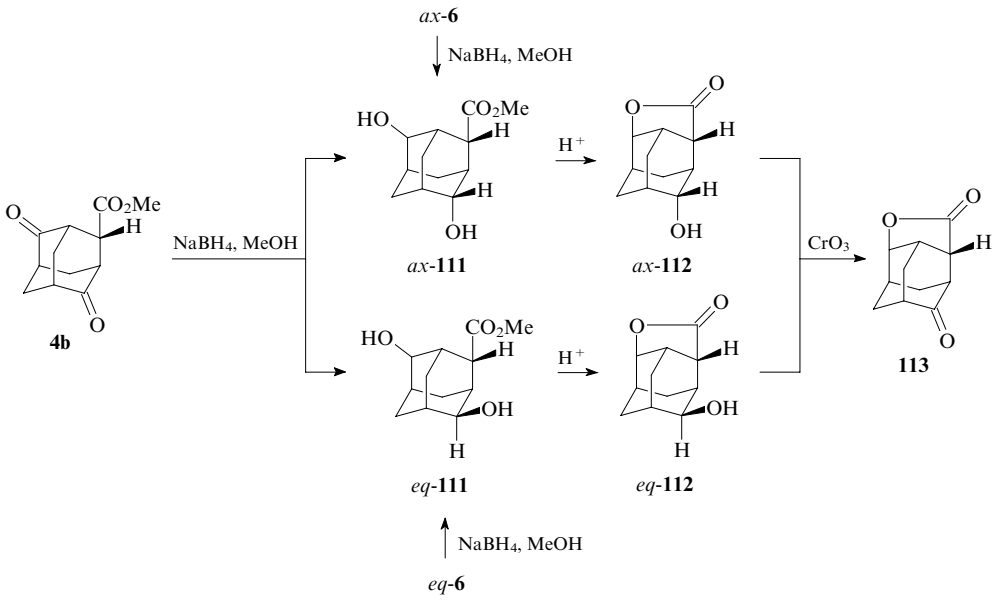
Reduction of hydroxyketoesters **6** with $NaBH_4$ in methanol leads to dihydroxyesters **111**, which could be prepared directly from diketoester **4b**. Both stereoisomers of dihydroxyester (*ax*-**111** and *eq*-**111**) were converted, *via* the formation of the corresponding dihydroxy acid, to hydroxylactone **112** and then oxidized with Jones's reagent [79] to ketolactone **113** (Scheme 15).[24, 25]

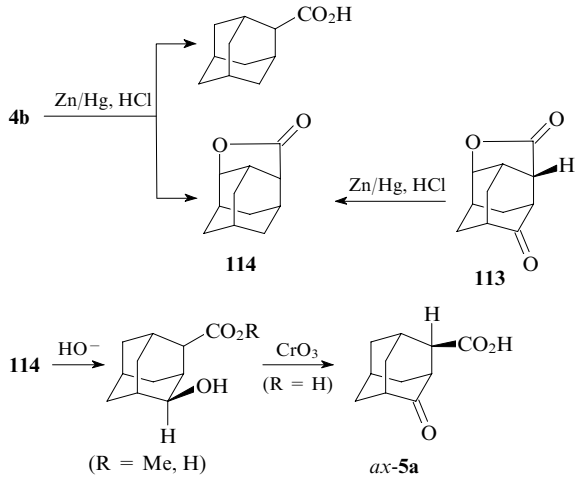
Compound **113** is reduced with zinc amalgam in HCl to adamantane derivative **114**. The latter (in mixture with adamantane-2-carboxylic acid) is also formed from diketoester **4b** under analogous conditions. Ketolactone **114** is successfully utilized to prepare a stereoisomer of 4-oxoadamantane-2-carboxylic acid (*ax*-**5a**).[25]

Scheme 14

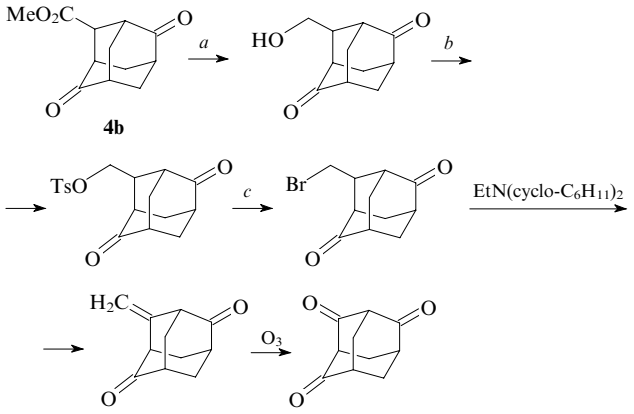


Scheme 15



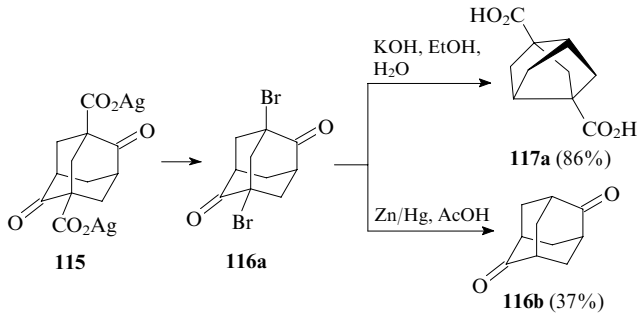


Adamantane-2,4,6-trione synthesized from diketoester **4b** by reaction sequence involving the ester group and corresponding substituent in 2-position.[31]

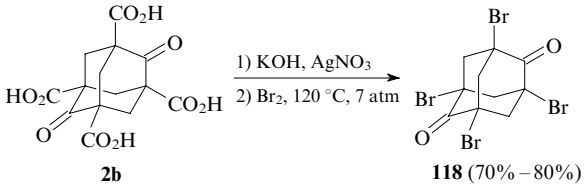


(*a*) 1) H_2SO_4, EtOH; 2) $LiAlH_4$, Et_2O; (*b*) 1) HCl, H_2O; 2) TsOH, Py; (*c*) LiBr, Me_2CO.

In 1964,[80] data relating to transformation of adamantane system into tricyclo[3.3.0.0^{3,7}]octane system were first reported by the examlple of silver salt of 2,6-dioxoadamantane-1,5-dicarboxylic acid **115**. It was found that treatment of compound **115** with bromine produces dibromide **116a**, which slowly rearrange in tricyclo[3.3.0.0^{3,7}]octane-1,3-dicarboxylic acid **117a**. Reduction of dibromodiketone **116a** with zinc amalgam in acetic acid leads to diketone **116b**.

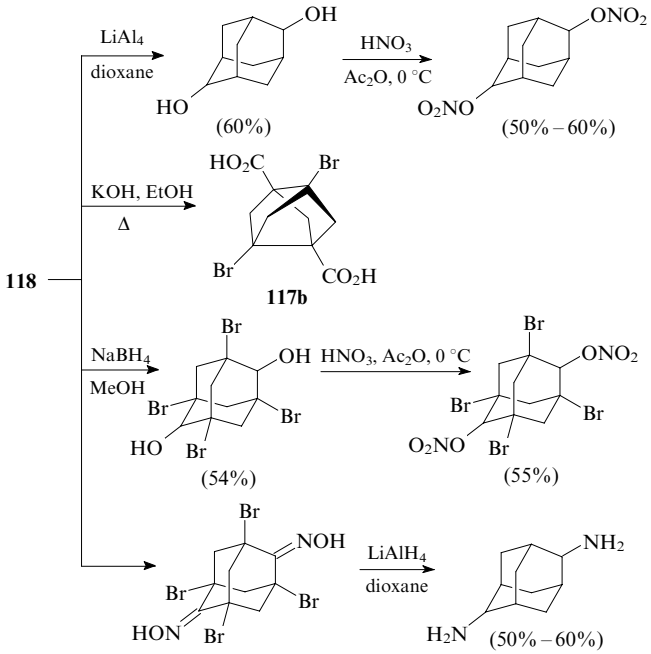


Tetracarboxylic acid **2b** containing two C=O groups in adamantane nucleus was used to synthesize diketo tetrabromide **118**, which was then utilized for the synthesis of various polyfunctional adamantane derivatives (Scheme 16).[81]

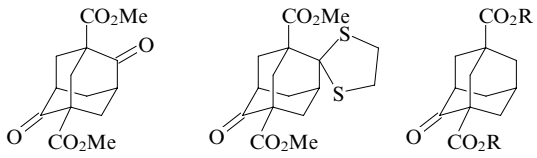


Among the shown reactions, it should be noted that transformation of tetrabromide **118** to dibromide **117b** by hydrolysis under alkaline conditions occurs very easily.

Scheme 16



Influence of the carboxylic and alkoxycarbonyl groups on the optical rotation angle values and circular dichroism spectra (CD) of these compounds were investigated [25, 82, 83] by the example of α- and β-ketoesters and acids of adamantane series which have rigid-system fixed in a chair conformation of the cyclohexane moiety. According to the main postulate of the octant rule, equatorial substituents adjacent with C=O group do not affect considerably Cotton effect in optically active cyclohexanone derivatives.[84] However, exact measurements show [85] that substituents in α-position (for example, methyl groups) could affect the optical rotation, because they are located very closely though not exactly, to the horizontal plane of carbonyl chromophore. This phenomenon was investigated for the adamantanone derivatives, for example optically pure



R = H (**a**), Me (**b**), Bu^n (**c**).

α-substituted adamantanones **119**–**121**, synthesis of which was reported.[82]

In 1967–1968, analogous study was undertaken using β-substituted adamantanones.[25,83]

Enantiomers of racemic acid **121a** are separated by fractional crystallization of didehydroabietylamine salts.[86] Compound (−)-**121a** (molecular ellipticity $[\theta]_{293} = +248 \pm 15$ at concentration 0.144 in 2% aqueous solution of NaOH) and (+)-**121a** ($[\theta]_{293} = 7128 \pm 12$ at concentration 0.101 in 2% aqueous solution of NaOH) were obtained. Acid (−)-**121a** was converted to the corresponding optically active ketodiesters (−)-**121b** or (−)-**121c** by reaction with diazomethane or diazobutane in methanol at 0 °C.

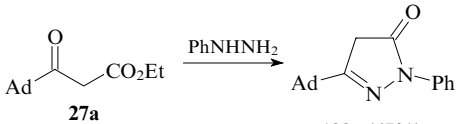
In paper,[82] optical rotatory dispersion and CD spectra of compounds **121a**–**c** were measured. Obtained data, in the opinion of authors, prove that equatorial alkoxycarbonyl or carboxy groups have a little effect on rotation, that is in agreement with the main octant rule.[84]

CD spectra were measured for 39 β-substituted adamantanones in various solvents.[83] It was reported that if axial substituent (for example, CO_2Me groups, in case of compound **5b**), is present in β-position, the observed sign of the Cotton effect is opposite to the sign being required according to the octant rule.

2. Ketoesters (acids) of adamantane series in synthesis of adamantane derivatives having heterocyclic motifs

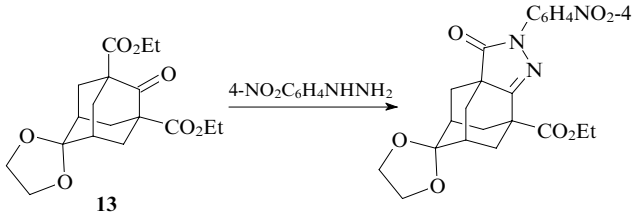
To date, data relating to the synthesis of adamantane derivatives having 4–6-membered heterocyclic moieties with one, two and three (identical and different) heteroatoms, and also heterocycles containing one or more adamantyl substituents have been published in the literature. Practically always, adamantyl-containing ketoesters (acids) bearing C═O and CO_2R groups in the side chain serve as starting compounds.

Adamantylpyrazolone **122a** was first prepared by Stetter[38] in 1960 by reaction of ethyl ester of adamantanoylacetic acid **27a** with phenylhydrazine.



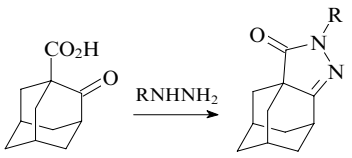
27a **122a** (67%)

In 1967, Stetter and Thomas[27] performed reaction of monoketal **13** with *p*-nitrophenylhydrazine; intramolecular cyclization resulted in formation of the pyrazolinone moiety.



13

Later, analogous transformation was carried out with participation of 2-oxoadamantane-1-carboxylic acid (**10b**).[87]



10b

R = H (75%), Ph (22%).

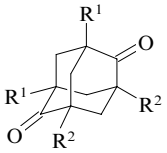
In the synthesis of hydrazones and pyrazolinones of adamantane series, derivatives of adamantane-2,6-dione with two and four groups CO_2H (**3b**, **2c**), their esters

Table 1. Synthesis of the compounds **123**, **124**.

Product	Starting compound	R^1	R^2	R^3	Pathway	Reaction conditions	Yield (%)
123a	**2a**	CO_2Me	CO_2Me	Ph	*a*	$PhNHNH_2$, 20 °C, 24 h	77
123b	**3a**	H	$C(O)NHNH_2$ (see [a])	H	*a*	NH_2NH_2, MeOH, 20 °C, 24 h	22
123c	**3a**	H	CO_2Me	Ph	*a*	$PhNHNH_2$, 20 °C, 24 h	85
123d	**3a**	H	CO_2Me	2,4-$(O_2N)_2C_6H_4$	*a*	2,4-$(O_2N)_2C_6H_4NHNH_2$, 15% H_2SO_4, 20 °C, 24 h	90
124a	**2a**	$C(O)NHNH_2$ (see [a])	–	H	*b*	NH_2NH_2, MeOH, 20 °C, 24 h	60
124b	**2a**	CO_2Me	–	Ph	*b*	$PhNHNH_2$, AcOH, dioxane, H_2O, 20 °C, 24 h	80
124c	**2a**	CO_2Me	–	2,4-$(O_2N)_2C_6H_4$	*b*	2,4-$(O_2N)_2C_6H_4NHNH_2$, 15% H_2SO_4, 20 °C, 24 h	74
124d	**123b**	H	–	H	*c*	KOH, diethylene glycol, 180–200 °C, 6 h	93
	3b	H	–	H	*d*	NH_2NH_2, KOH, diethylene glycol, 120–140°C, 4 h	90
124e	**123c**	H	–	Ph	*c*	KOH, diethylene glycol, 180–200 °C, 6 h	43
124f	**123d**	H	–	2,4-$(O_2N)_2C_6H_4$	*c*	KOH, diethylene glycol, 180–200°C, 6 h	33
124g	**2c** or **2d**	CO_2H	–	Ph	*d*	NH_2NH_2, KOH, diethylene glycol, 120–140 °C, 4 h	73

[a] In the starting compound $R^2 = CO_2H$.

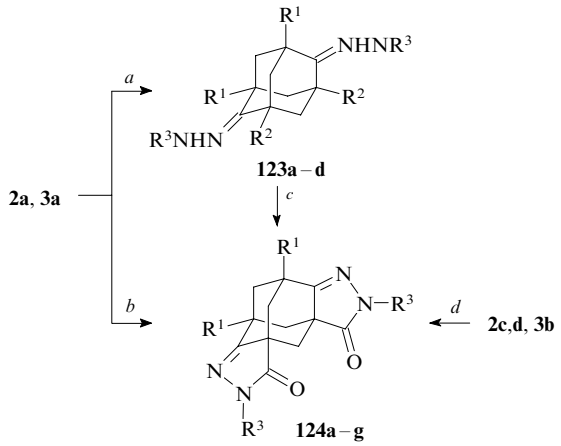
(**3a**, **2a**) and potassium salt of tetracarboxylic acid **2d** were also used.[87]



2a,**c**,**d**, **3a**,**b**

$R^1 = CO_2Me$: $R^2 = H$ (**3a**), CO_2Me (**2a**);
$R^1 = CO_2H$, $R^2 = H$ (**3b**), CO_2H (**2c**);
$R^1 = R^2 = CO_2K$ (**2d**).

The reaction of above compounds with hydrazine, phenyl and 2,4-dinitrophenyl hydrazine gave the corresponding hydrazones **123a**–**d** and products **124a**–**i**; pyrazolinones were formed by intramolecular cyclization (Table 1).



123a–**d** **124a**–**g**

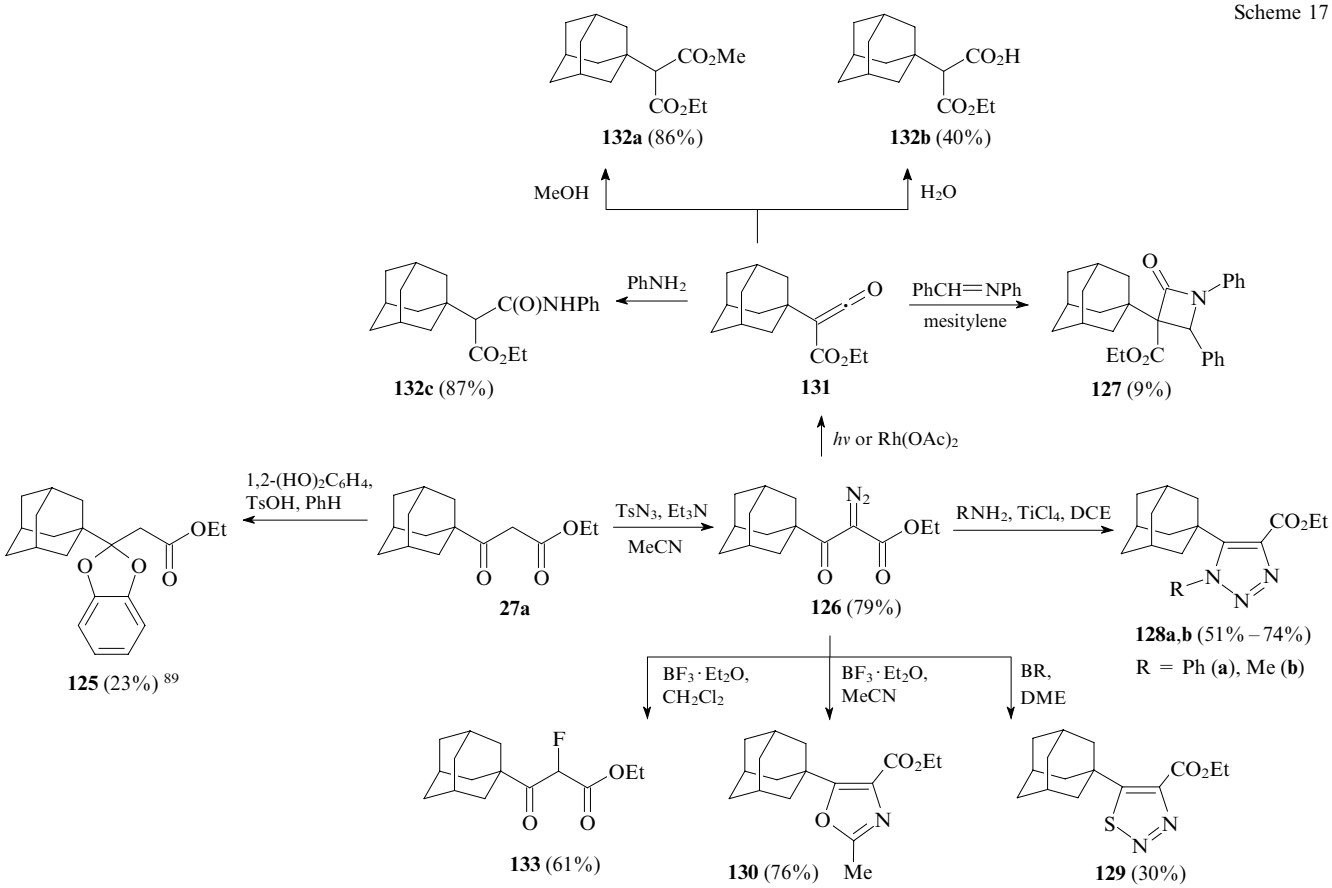
Methods for the preparation of benzo dioxolane **125** and ethyl 3-(1-adamantyl)-2-diazo-3-oxopropanoate (**126**)[88,89] from ketoester **27a** are shown in Scheme 17. Also, possibilities of use of the latter in the synthesis of adamantyl derivatives of diverse types, such as those containing heterocyclic moieties (**127**–**130**), are shown.[88]

As a result of photochemical reaction, diazo derivative **126** is easily converted to stable ketene **131**, which was used to synthesize derivatives of adamantylmalonic acids **132a**–**c**. As [2 + 2]-cycloaddition of ketene **131** with benzylideneaniline in mesitylene affords β-lactam **127**.

Adamantyl-substituted heterocycles could be easily prepared from diazo derivative **126**. Thus, reaction of the latter with aniline or methylamine in dichloroethane in the presence of $TiCl_4$ afforded triazoles **128a**,**b**, with Bello's reagent in dimethoxyethane (DME) thiadiazole **129**, with acetonitrile in the presence of $BF_3 \cdot Et_2O$ oxazole **130**. It is interesting that fluorination of diazo derivative **126** with boron trifluoride etherate proceeds in CH_2Cl_2 to give α-fluoroketoester **133**. Practically all transformations result in moderate or good yields of products.

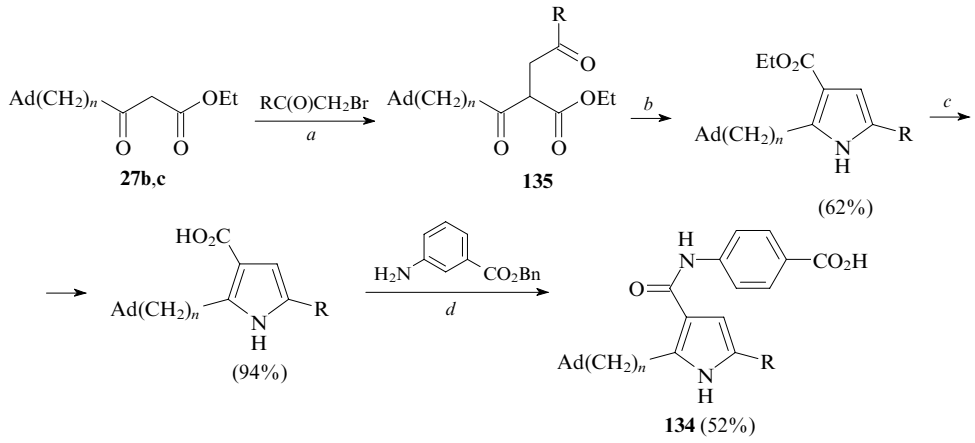
Ethyl esters of adamantyl-containing monoketocarboxylic acids (**27b**,**c**) were used in the synthesis of trisubstituted 2-(1-adamantylalkyl)pyrroles **134** (Scheme 18; yields are shown in parentheses for compounds with R = Ph, $n = 2$).[90,91] At first, alkylation of acids **27b**,**c** with haloketones produced diketocarboxylic esters **135**, then the latter were cyclized to the corresponding pyrrole derivatives.

Scheme 17



BR (reagent Bello) is 2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide; DCE is 1,2-dichloroethane.

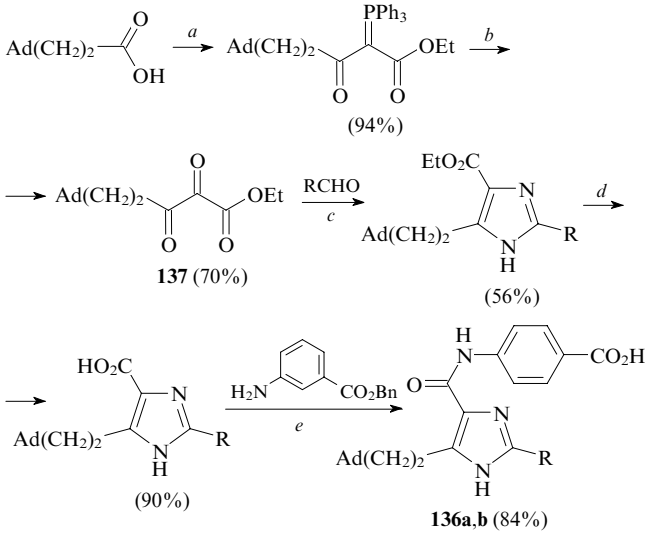
Scheme 18



n = 1 (**b**), 2 (**c**); R = Ph, 2-MeC_6H_4; (*a*) K_2CO_3, NaI, Me_2CO; (*b*) NH_4OAc, AcOH; (*c*) NaOH, EtOH – H_2O; (*d*) 1) $SOCl_2$, DMF, CH_2Cl_2; 2) Pd/C, H_2, THF – MeOH.

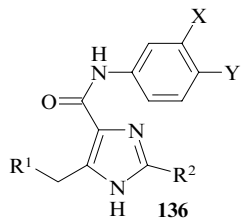
Similar methodology was used for the synthesis of imidazoles **136a**,**b** (Scheme 19, yields are shown for compounds with R = 2-MeC_6H_4). Tricarbonyl compound **137** were prepared from adamantylpropionic acid *via* the formation of the corresponding ketophosphorane.[90]

Scheme 19



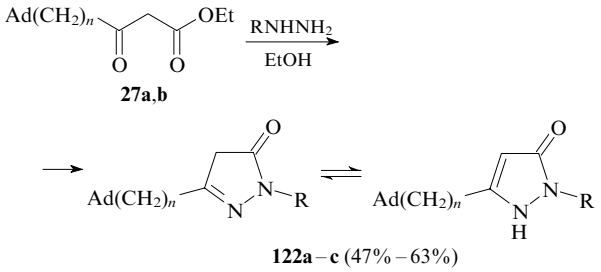
R = Ph (**a**), 2-MeC_6H_4 (**b**);
(*a*) $Ph_3P{=}CHCO_2Et$, DMAP, EDC; (*b*) oxone, THF – H_2O;
(*c*) NH_4OAc, AcOH; (*d*) NaOH, EtOH – H_2O;
(*e*) 1) EDC, HOBt, DMF; 2) Pd/C, H_2, THF – MeOH; oxone is potassium peroxosulfate, HOBt is 1-hydroxybenzotriazole.

Buck *et al.*[90] synthesized over 30 adamantyl-containing imidazoles of general formula **136**, where R^1 is adamantyl-containing moiety (1-adamantyl, 1-adamantylmethyl, 1-adamantyloxy); R^2 is aryl, alkyl, cycloalkyl, bicyclo[2.2.1]octyl; X is carboxy, ester, methyl or methylamine group; Y = H, Me, F, NMe_2, OMe.



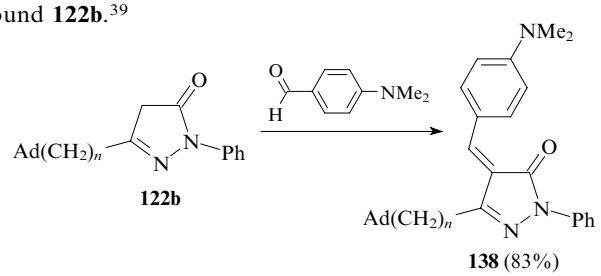
These compounds were tested as orally active antagonists of cholecystokinin-2 (CCK_2).[90]

Reactions of adamantyl-mono- and -diketocarboxylic esters **27a**,**b** and **56a** with hydrazine and phenylhydrazine have been studied in detail.[38, 39, 63, 92] It was established that monoketoesters **27a**,**b** give pyrazolones **122a**–**c** as a result of these reactions.[38, 39, 92]

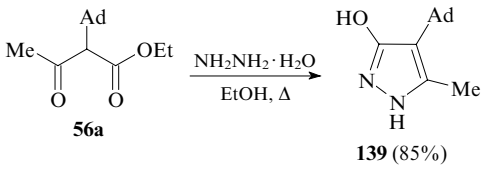


R = Ph: *n* = 0 (**a**), 1 (**b**); R = H, *n* = 0 (**c**).

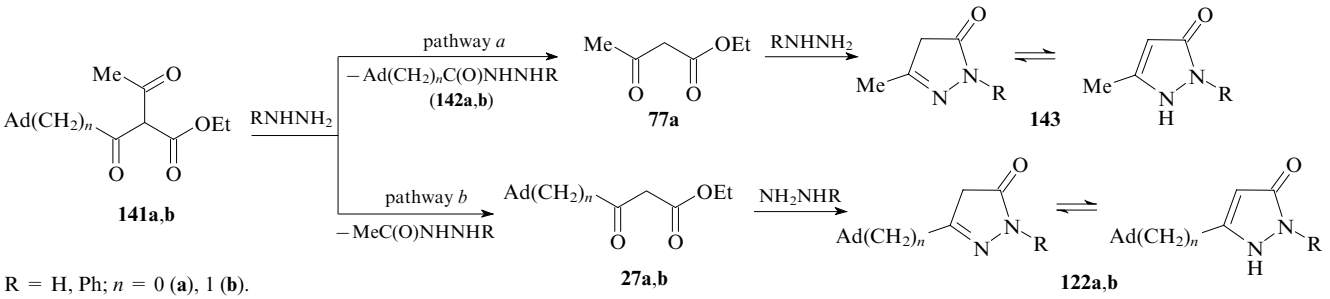
Intra-ionoide dyestuff **138** was prepared based on compound **122b**.[39]



Monoketoester **56a** reacts with hydrazine hydrate in ethanol to give 4-(1-adamantyl)-3(5)-hydroxy-5(3)-methyl-1*H*-pyrazole (**139**) in high yield.[63]

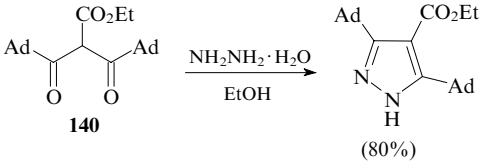


Scheme 20



R = H, Ph; n = 0 (**a**), 1 (**b**).

Both C=O groups participate in the cyclization of diketoester **140** with hydrazine hydrate to produce the only reaction product containing two adamantane moietis.[92]

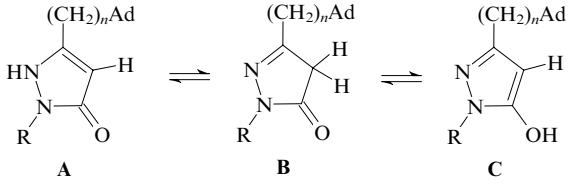


Reaction of both asymmetrical diketoesters **141a**,**b** with hydrazine hydrate and with phenylhydrazine produces mixtures of the corresponding hydrazide **142** and pyrazolinones **122**, **143** (Scheme 20).[92]

In the reaction of diketoester **141a** with hydrazine hydrate, the ratio of the reaction products **142a** : (**143** + **122a**) was 2 : 3, whereas in case of phenylhydrazine only the hydrazide **142a** was isolated in 74% yield. Reaction of diketoester **141b** with hydrazine hydrate or with phenylhydrazine results in pyrazolinones **122b** (R = H, Ph) in yields of 39% and 27%, respectively.

The results were interpreted in the following manner. Quantum chemical calculations of charges on the carbon atoms of carbonyl group of compounds **141a**,**b** show that in case of ketoester **141a** they are equal (0.26), whereas in case of derivative **141b** charges are different (0.27 on carbon atom of acetyl group and 0.22 on carbon atom of adamantyl-containing group). This determines the prefered direction of nucleophile attack.

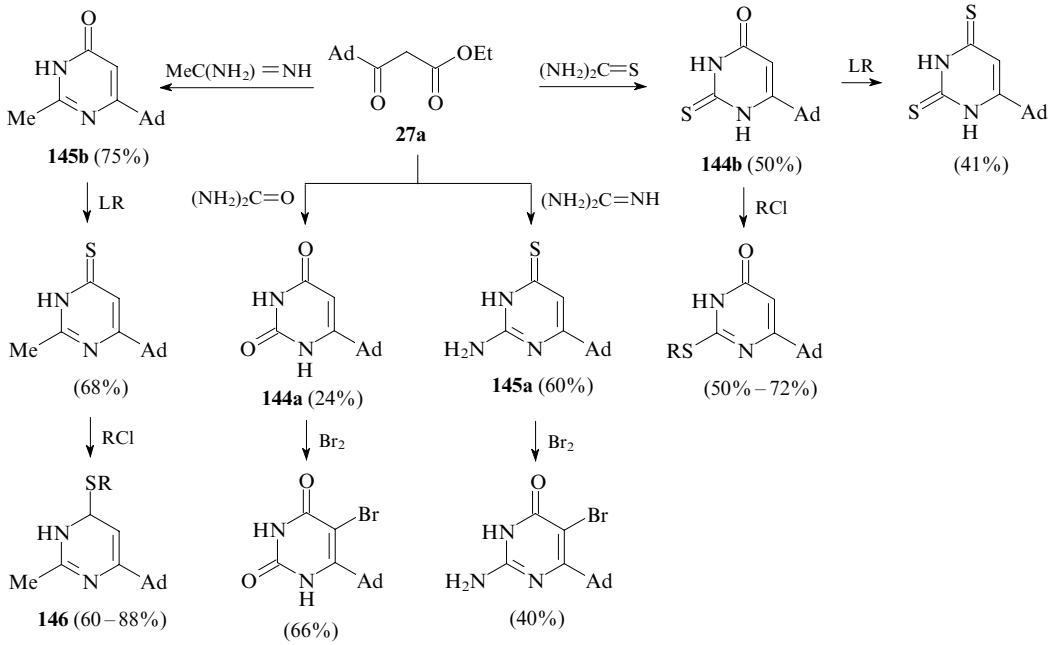
Based on ^{1}H NMR spectroscopy, it was established that out of the three possible tautomeric forms (**A**–**C**), pyrazolones **122** predominately exist as form **A** in solid state and in polar solvents and as form **B** n nonpolar solvents.



Reactions of ethyl ester of adamantyloxopropionic acid **27a** with urea, thiourea, guanidine and acetamidine afford 6-(1-adamantyl)pyrimidines **144a**,**b**, **145a**,**b,** which were then converted to the corresponding bromo-, thio- and thioalkyl derivatives (Scheme 21).[93,94]

In publication,[93] authors studied biological action of all synthesized compounds, such as antibacterial, antifungal and antitumoural activities. Compound **146** (R = $CH_2CH_2NMe_2$), which has also the most powerful

Scheme 21



R = 4-$O_2NC_6H_4CH_2$, 2-$O_2NC_6H_4CH_2$, $Me_2NCH_2CH_2$; LR (Lawesson reagent) is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane 2,4-disulfide).

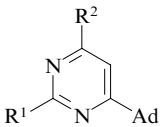
antibacterial action, displays considerable antitumoural activity (especially against leukemia U-937). Results of tests of this compound are shown in Table 2 for a number of tumour cell lines (ID_{80} is concentration that exhibits 80% inhibition of the cell growth).

Table 2. Inhibition of the tumour cell growth by the compound **146** (R = $CH_2CH_2NMe_2$).[93]

Cell lines	ID_{80} /mg ml^{-1} (μmol litre^{-1})	Cell lines	ID_{80} /mg ml^{-1} (μmol litre^{-1})
BALL	17.3 (52.3)	LOK-1	7.0 (21.2)
CEM	17.5 (52.8)	KG-1	18.4 (57.1)
Daudi	20.0 (60.4)	U-937	4.8 (014.5)
HL-60	16.4 (49.5)		

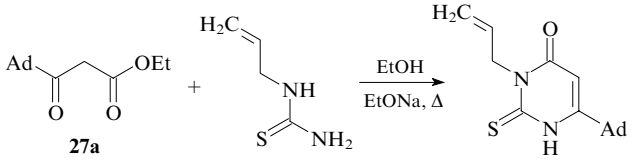
Various adamantyl-containing derivatives **144c**–**k** have been prepared from adamantylthiouracil **144b** by the succession of standard transformations (Table 3).[93]

Primary tests carried out by authors of paper[93] *in vitro* show apparent activity of compounds **144c**,**e**,**g**,**h** against herpes virus Kupka.



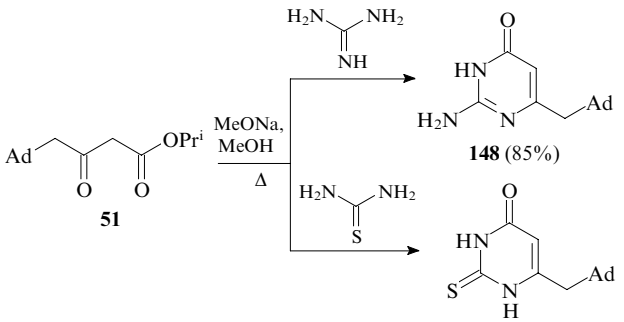
144c–**k**

6-(1-Adamantyl)-3-allyl-2-thiouracil (**147**) was synthesized from ketoester **27a** and allylthiourea.[95–97] Cyclization proceeds by heating of reactants in ethanol in the presence of sodium ethoxide.



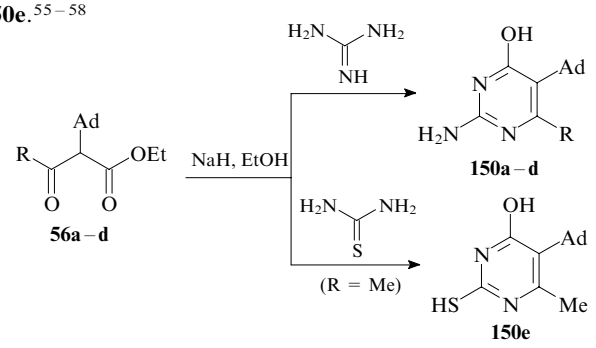
27a **147**

Similar route was used to prepare 6-(1-adamantyl) methyl substituted pyrimidinones **148** and **149** from adamantyloxobutanate **51** and guanidine or thiourea.[52]



51 **148** (85%) **149** (77%)

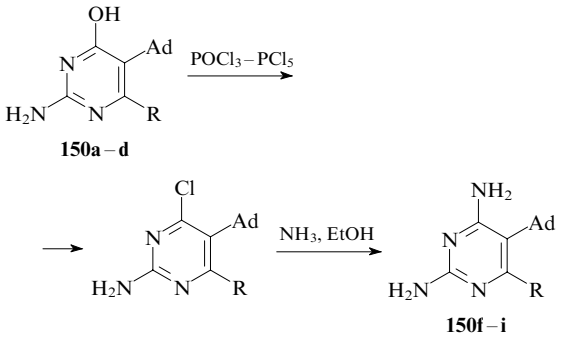
Reaction of β-ketoesters **56a**–**d** with guanidine affords 5-(1-adamantyl)-6-alkyl-2-amino-4-hydroxypyrimidines **150a**–**d**; reaction of ketoester **56a** with thiourea produces 5-(1-adamantyl)-4-hydroxy-6-methyl-2-mercaptopyrimidine **150e**.[55–58]



56a–**d** **150a**–**d** **150e**

R = Me (**a**, 55%),[55] Et (**b**, 41%),[57] Pr^n (**c**), Bu^n (**d**).[58]

4-Hydroxypyrimidines**150a**–**d**, by action of mixture of $POCl_3$–PCl_5, were converted to the corresponding 4-chloropyrimidines, the latter without additional purification were utilized as precursors for diamines **150f**–**i**.



150a–**d** **150f**–**i**

R = Me (**f**, 18%),[57] Et (**g**, 8%),[57] Pr^n (**h**), Bu^n (**i**).[58]

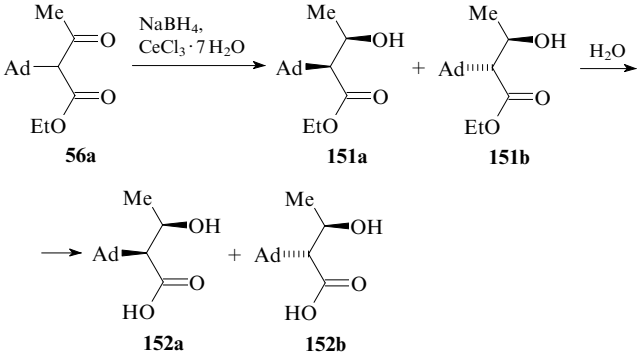
Table 3. Synthesis of the adamantyl-containing uracil analogue **144c**–**k**.[93]

Starting compound	Product	R^1	R^2	Reaction conditions	Yield (%)
144b	**144c**	SCH_2CO_2H	OH	$ClCH_2CO_2Na$, Δ	75
	144d	OH	OH	H_2O_2, 45 °C	70
	144e	SH	SH	P_2S_5, tetralin, 185–195 °C	48
	144f	SMe	OH	MeI, EtOH, NaOH, 60 °C	80
144e	**144g**	SH	NH_2	NH_4OH, autoclave, 110 °C	61
144f	**144h**	NH_2	OH	NH_4OH, autoclave, 160 °C	43
144g	**144i**	SCH_2CO_2H	NH_2	AcONa, NaOH, Δ	85
144i	**144j**	NH_2	NH_2	NH_4OH, autoclave, 160 °C	42.5
	144k	OH	NH_2	conc. HCl, Δ	65

The biological activity of synthesized 5-(1-adamantyl)-pyrimidines are studied in free base form and in form of its ethylsulfonate (ESA) salts.[55–58,98] It ws established that adamantyl-containing hydroxypyrimidine **150a** exhibits moderate inhibitory activity against sarcoma S-180 cells in mice [concentration for 50% inhibition (ID_{50}) is 46–48 μmol litre^{-1}] and higher activity against carcinoma TA3 cells in mice (ID_{50} = 5.0 μmol litre^{-1}).[55] Diamino derivative **150f** exhibits the same high activity against cells TA3 (ID_{50} = 6.0 μmol litre^{-1}).[56,57] The best inhibitory properties were exhibited by ESA-salt of compound **150g** (ID_{50} = 0.002 μmol litre^{-1}), the latter was 4 times more active than methotrexate (ID_{50} = 0.008 μmol litre^{-1}); which is used in complex cancer therapeutics for treatment of leucosis.[58] In addition, it was found that pyrimidine **150g** is stoichiometric inhibitor of enzyme dihydrofolate reductase of cells S-180.[57,58]

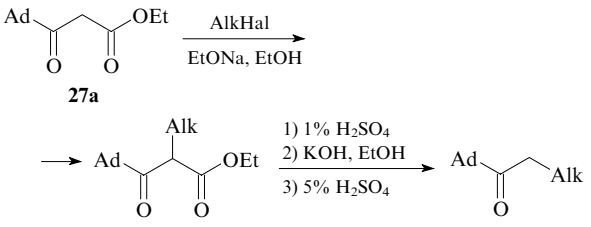
3. Other reactions of adamantylketoesters (ketoacids)

Reduction of ketoester **56a** with sodium borohydride in ethanol in the presence of cerium chloride leads to the mixture of diastereomeric ethyl 2-(1-adamantyl)-3-hydroxybutanoates **151a**,**b** in total yield of 93%; the mixture was separated chromatographically.[99]



The configuration of diastereomers **151a**,**b** was established based on IR-spectroscopy data. In spectrum of compound **151b,** absorption bands were observed at 3619 and 3526 cm^{-1} (OH), and also in area of 1729 cm^{-1} (C=O). In spectrum of compound **151a,** there are broad absorption band at 3526 cm^{-1} (OH) and band at 1709 cm^{-1} (C=O). *syn*-Configuration was assigned to the diastereomer **151a**, and *anti*-configuration was assigned to the compound **151b**. Hydrolysis of *syn*- and *anti*-isomers **151** leads to corresponding acids **152a**,**b**. X-Ray diffraction analysis of crystal of acid **152a** confirmed its *syn*-configuration.

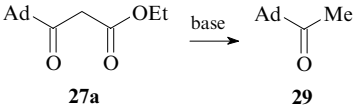
As discussed above, adamantyl-containing ketoesters and acids are widely utilized in the synthesis of adamantylketones. Thus, a large number of 1-adamantylalkyl ketones (average yield of 80%) was prepared by alkylation of ethyl adamantanoylacetate **27a** with the corresponding alkyl halide and subsequent hydrolysis and decarboxylation.[100]



Alk = n-C_nH_{2n+1} (n = 1–6, 8, 10, 12, 14, 16, 18), Pr^i, Bu^i.

Hydrolysis was carried out by action KOH in 95% EtOH at room temperature, the formed potasium salt of alkylated β-ketoacid is easily decarboxylated upon acidification. Such ketones were synthesized with aim to use them as precursors for the preparation of surfactants.

In paper,[101] authors studied selectivity of base-induced decarboxylation of geminal diesters, β-ketoesters and γ-keto-β,γ-unsaturated esters. The bases used were alkaloids such as brucine, tropine, nicotine, reserpine, yohimbine, quinidine. For example, reaction of decarboxylation of ethyl β-(1-adamantyl)-β-oxopropionate (**27a**) to ketone **29** (dry xylene, 144–146 °C, molar ratio base : **27a** = 8 : 1) was studied. The best yields of product **29** were obtained with use of yohimbine, nicotine and brucine hydrochlorides.



Base	Yield (%)
Brucine	49.0
Tropine	2.1
Nicotine	81.0
Reserpine	7.5
Yohimbine hydrochloride	89.7
Quinidine	12.5

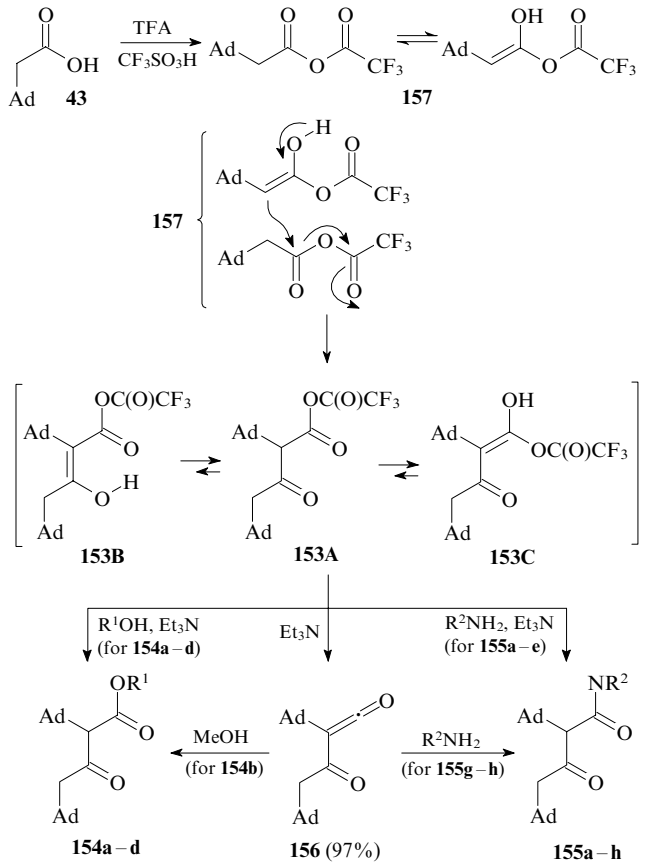
Data reported in publication [101] relating to the ability of above alkaloids to decarboxylate various types of esters with different selectivity permit the authors to hypothesize that one of functions of alkaloids in plants is the catalysis of decarboxylation processes.

4. Self-acylation of 1-adamantylacetic acid in system $(CF_3CO)_2O - CF_3SO_3H$

New original method for the preparation of adamantyl-containing ketoesters and acids was developed by authors of the present review.[102] It bases on self-acylation of 1-adamantylacetic acid (**43**) in trifluoroacetic anhydride (TFA) in the presence of catalytic amounts of trifluoromethanesulfonic acid. Reaction proceeds selectively, quickly (boiling for 2 h) and provides compounds **153**–**156** in high yields. A study of the reaction mechanism by ^{1}H and ^{13}C NMR spectroscopies makes it possible to propose the transformation sequence shown in Scheme 22.

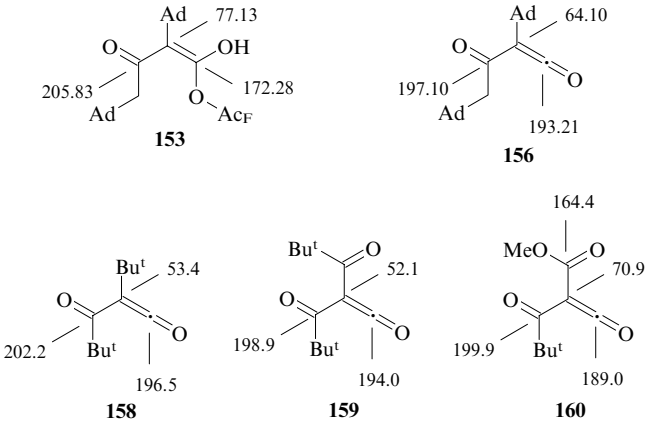
Trifluoroacetic anhydride reacts with starting acid **43** to give the mixed anhydride **157**; CF_3SO_3H alleviates its enolization and allows one to carry out a condensation between tautomeric forms of compound **157**. It leads to the product of self-acylation; compound **153** could exist in three tautomeric forms (**153A**–**153C**). In the absence of CF_3SO_3H, the reaction does not proceed. When some excess of triethylamine is added the solution of compound **153**, 1-adamantylmethylcarbonyl 1-adamantyl ketene (**156**) is formed practically immediately in quantitative yield. Spectroscopic data validate that the form **153C** is present as one of three possible tautomeric forms of the self-acylation product. Formation of enol form of compound **153** is proved by absence of methine proton signal of Ad-CH moiety in its ^{1}H NMR spectrum. Meanwhile, in ^{1}H NMR spectrum of compound **156,** besides signals of adamantane

Scheme 22



R^1 = H (**a**, 97%), Me (**b**, 81%), Et (**c**, 90%), Ph (**d**, 87%);
R^2 = Bn (**a**, 65%), NH_2 (**b**, 98%), NHPh (**c**, 39%), OH (**d**, 52%), $NHC(O)NH_2$ (**e**, 93%), 2-(indol-3-yl)ethyl, (**f**, 59%), 6-methylpyrid-2-yl (**g**, 61%), C_6H_4Me-4 (**h**, 52%).

nuclei protons, only the signal of protons of the methylene group $AdCH_2$ is present. The chemical shifts (δ) of characteristic carbon atoms in C=C–C=O fragment of compound **153** and α-oxoketene **156**, and also in known related *tert*-butyl α-oxoketenes **158**–**160** are given below.[103–105]

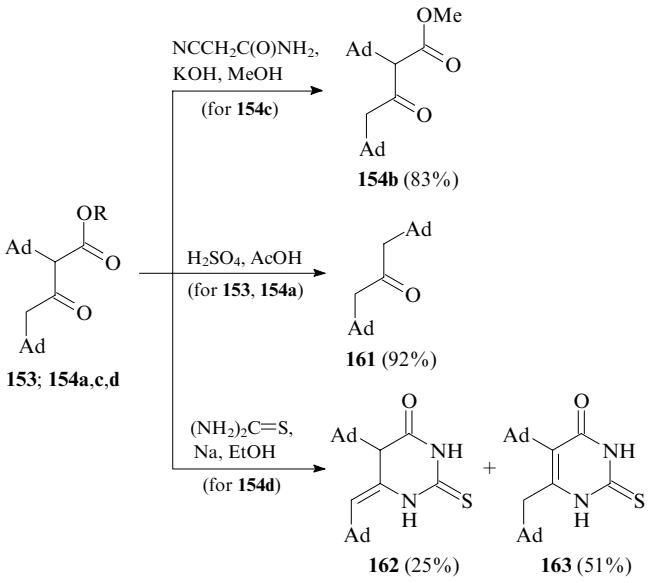


The IR spectrum of compound **156** exhibits a strong absorbation band of C=C=O groups at 2091 cm^{-1} [dipivaloylketene (**159**) at 2131 cm^{-1} (Ref. 104)], this directly proves the formation of ketene functionality.

Product of self-acylation **153** was used by us as acylating agent in some reactions with O- and N-nucleophiles. As result of these transformations, 2,4-di(1-adamantyl)acetoacetic acid **154a** and its derivatives **154b**–**d** ,**155** were prepared in high yields (see Scheme 22).

Some chemical properties of ketoesters **153** and **154c**,**d** and also ketoacid **154a** are shown in Scheme 23.[102] Compounds **153**, **154a** are easily converted by action of sulfuric acid in AcOH to 2,4-di(1-adamantylmethyl) ketone **161**; only the transesterification of ester occurs in reaction of compound **154c** with cyanoacetamide in methanol in the presence of KOH; and cyclization of compound **154d** with thiourea by action of sodium in ethanol leads to the mixture of isomeric adamantyl-containing thiopyrimidinones **162** and **163**.

Scheme 23



R = O_2CCF_3 (**153**), H (**154a**), Et (**154c**), Ph (**154d**).

The above-considered reaction of self-acylation (see Scheme 22) is general and offers broad possibilities for its subsequent use in organic synthesis. Thus, we found [102] that dimeric products of self-acylation are formed from *tert*-butylacetic and isovaleric acids under above conditions with sufficiently high selectivity.

* * *

The discussed published data demonstrate that the use of adamantyl-containing ketocarboxylic acids and esters has perspectives in the organic synthesis, especially in aspect of the synthesis of biologically active compounds from these compounds. In reference to the availability of adamantylketoesters (acids), reactions involving, as precursors, the derivatives of bicyclo[3.3.1]nonane and cyclohexanone, and also acylation reaction with adamantanecarboxylic acid chlorides have been examined in detail. In addition, much attention has been paid in the literature to alkylation of compounds possessing CH-acidity (malonic, acetoacetic, cyanoacetic esters, its analogues and homologues) with bromo- and hydroxy derivatives of adamantane. In our opinion, a promising approach to the synthesis of adamantyl-containing α-ketoacids is the use of trifluoroacetic anhydride–trifluoromethanesulfonic acid system for acylation

of CH-acids. To our knowledge, data relating to the selective preparation of β-ketoacids from carboxylic acids RCH_2CO_2H under acidic conditions have not been reported in the literature.

References

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