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Synthetic Approach to Preparation of Polycyclic Compounds Possessing Physiological Activity: I. Synthesis of 1,4-Disubstituted Adamantanes with Amino Acid Fragment

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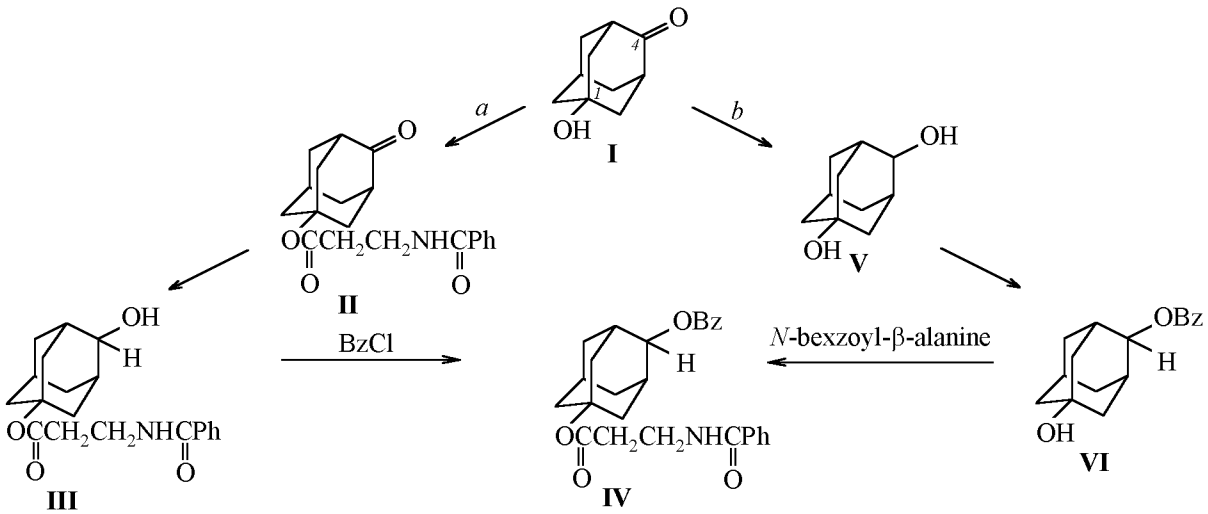
Abstract—In the present publication various synthetic procedures are reported for previously unknown 1,4-disubstituted adamantanes, containing in particular in position 1 an amino acid fragment (*N*-benzoyl-β-alanyloxy group). The procedures developed for modification of functional groups in the adamantane skeleton provide a possibility of synthesis of compounds with potential anticancer activity.

In the last decades syntheses of bioisosteric analogs of the known active substances was extensively used for preparation of new physiologically active compounds. Bioisosteres are obtained by replacing of a group in the parent compound by another fragment with retention of the biological property. Quite a few empirical rules of such replacement exist now. The majority of these rules valid for wide series of compounds with various types of physiological activity consists in replacement of functional groups by fragments similar in size and characteristics (for instance, substitution of carboxy group by sulfo group or tetrazole) [1]. However more complex and uncommon examples of preparation of bioisosteric analogs also exist where the molecular skeleton bearing functional moieties important for interaction with biological targets is substituted by the other structural systems [2]. This type replacements as a rule are substantiated by topological data and are valid for small groups of compounds with a definite type of activity.

We recently showed by computer simulation that taxane skeleton of some anticancer preparations may be substituted by adamantane (or bicyclo[3.3.1]-nonane) fragment. To test whether this substitution is bioisosteric the functional groups that are present in taxane substances and that are important for anticancer activity should be placed in certain positions of the adamantane skeleton. These are primarily benzoyloxy group and amino acid fragment [3] that should be introduced respectively into positions *1* and *4* of the adamantane skeleton. The target of this study was development of synthetic procedures for preparation of such compounds.

As a model amino acid moiety we selected *N*-benzoyl-β-alanine that was prepared by standard

Scheme 1.



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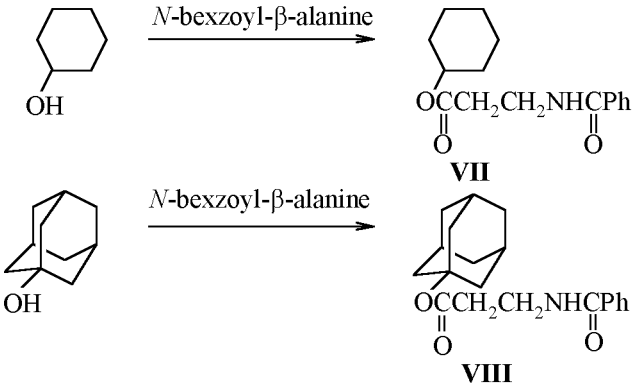
Scheme 2.



procedure from β-alanine and benzoyl chloride. For model adamantane compound was chosen 1-hydroxyadamantan-4-one (**I**) that was prepared by oxidation of adamantanone with 100% nitric acid by procedure we modified [4]. The synthesis of target 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (**IV**) was carried out by two procedures (Scheme 1).

By the first route *a* of 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (**IV**) synthesis the amino acid fragment should be introduced into the molecule of compound **I** by esterification [5] providing ester **II**. Since this reaction was not previously studied on cyclic and cage-like alcohols, we carried out optimization of esterification conditions by examples of two model compounds, cyclohexanol and adamantanol (Scheme 2).

The reaction products, esters **VII** and **VIII**, were obtained in good yield (Table 1) by keeping reagents at room temperature for 12–15 h in THF solution in the presence of dimethylaminopyridine and dicyclohexylcarbodiimide. Under the same conditions from the 1-hydroxyadamantan-4-one was prepared 1-(*N*-benzoyl-β-alanyloxy)adamantan-4-one (**II**). Compounds **II**, **VII**, and **VIII** were synthesized for the first time, and their structure was confirmed by ^{1}H and ^{13}C NMR spectra (Table 2). In the ^{1}H NMR spectra of all esters obtained were observed all proton signals of the amino acid fragment, also those from the side chain and from the aromatic ring. Besides in the spectra of adamantane derivatives were present the signals from protons of the skeleton in 1.65–2.65 ppm region.

1-(*N*-Benzoyl-β-alanyloxy)-4-hydroxyadamantane (**III**) that further was used in preparation of target compound **IV** was obtained by reduction of 1-(*N*-benzoyl-β-alanyloxy)adamantan-4-one (**II**) with sodium borohydride in a mixture of methanol and THF by procedure [6]. The structure of alcohol **III** obtained as a mixture of axial and equatorial isomers was proved by spectral methods (Table 2). In the ^{1}H NMR spectrum of compound **III** alongside the proton signals from the amino acid fragment and protons of the main skeleton were also observed two triplets at 3.74 and 3.92 ppm belonging to the proton attached to the skeleton carbon linked to the hydroxy group in axial and equatorial isomer respectively. (Assignments of signals belonging to each isomer here and hereinafter was performed basing on comparison of ^{1}H and ^{13}C NMR spectra with the known spectra of structurally similar compounds [7–9]). The ratio of equatorial to axial isomers in compound **III** equaled to 1 : 1.

The last stage involved benzoylation of 1-(*N*-benzoyl-β-alanyloxy)-4-hydroxyadamantane (**III**) with benzoyl chloride in pyridine [10]. The final reaction product **IV** was isolated in good yield (Table 1) by column chromatography on silica gel, eluent ethyl acetate–petroleum ether, 1 : 2.5. The structure of 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (**IV**) was confirmed by ^{1}H and ^{13}C NMR spectra (Table 2). The ratio of axial to equatorial isomers in the final product was 1 : 2.

Second synthetic route (b) to 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (**IV**) used the opposite sequence of the substituents introduction. In the first stage 1-hydroxyadamantan-4-one (**I**) was reduced by lithium aluminum hydride into 1,4-dihydroxyadamantane (**V**) along procedure we modified [11]. The reaction of the latter with benzoyl chloride in pyridine furnished 4-benzoyloxy-1-hydroxyadamantane (**VI**) in 31% yield. The variation of reagents ratio that we performed allowed selection of the optimum ratio diol (**V**)–benzoyl chloride for benzoylation of a single hydroxy group (1 : 0.8). Compound **VI** was separated from the reaction mixture by chromatography using as eluent the system ethyl acetate–petroleum ether, 1 : 4. In the ^{1}H NMR spectrum of compound **VI** (Table 2) alongside the signals of aromatic protons and protons of the adamantane skeleton appeared a triplet at 4.84 ppm belonging to the proton attached to the skeleton carbon bearing the benzoyloxy group of the axial isomer. These data unambiguously evidence the prevailing formation in this reaction of the axial isomer in *4* position.

Reaction of compound **VI** with *N*-benzoyl-β-alanine in THF in the presence of dimethylaminopyridine and dicyclohexylcarbodiimide furnished 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane

Table 1. Yields, melting points, and elemental analyses of esters of amino acids with cyclic and cage-like alcohols

Compd. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			*M*
			C	H	N		C	H	N	
II	71	82	70.46	6.76	3.89	$C_{20}H_{23}NO_4$	70.38	6.74	4.11	341
IV	78 (52)[a]									
	71 (21)[b]	89–90	72.85	6.24	3.12	$C_{27}H_{29}NO_5$	72.48	6.49	3.13	447
VII	96	65	70.01	7.62	4.98	$C_{16}H_{21}NO_3$	69.82	7.64	5.09	275
VIII	82	72	73.73	7.77	4.18	$C_{20}H_{25}NO_3$	73.39	7.65	4.28	327

[a] By procedure *a*. [b] By procedure *b*.The yield with respect to the initial compound **I** is given in parentheses.

(**IV**) whose ^{1}H NMR spectrum unlike that of the compound obtained along procedure (a) did not contain a signal at 5.18 ppm belonging to the equatorial isomer (BzOC$\underline{H}_a$); only a triplet in the region 5.06 ppm appeared corresponding to the axial isomer (BzOC$\underline{H}_e$).

Thus depending on the synthetic procedure the samples of 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (**IV**) have different isomeric composition. The prevailing formation of axial isomer A by procedure (b) at the stage of diol **V** benzoylation is apparently caused by steric hindrances from the hydroxy group in position *1* of the adamantane skeleton. The prevalence of equatorial isomer of compound **IV** in the isomer mixture B obtained along procedure (a) as has shown simulation we have carried out may be ascribed to the additional stabilization of this isomer by a hydrogen bond and hydrophobic interactions between benzoyl and amino acid fragments.

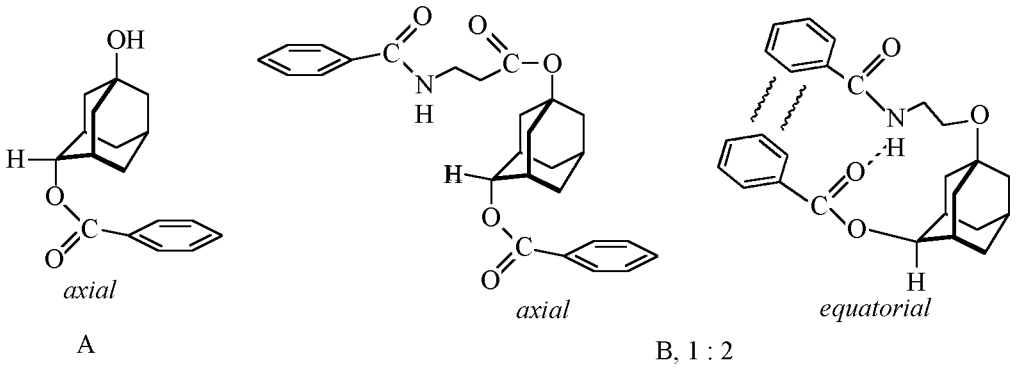
It should be noted in conclusion that in most cases the optimal biological activity is shown by one among the possible isomers of a compound. Therefore the synthesis of cage-like esters with potential anticancer activity will depend on the theoretically calculated activity of each isomer. The latter data may be obtained by including the appropriate ligands into refined computer models of protein molecules that are the targets of the taxane pharmaceuticals in the human body.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on spectrometer VXR-400 (400 MHz) from solutions in $CDCl_3$ with HMDS as internal reference.

The reactions progress was monitored by TLC on Silufol plates, Chromatographic separation was carried out on columns packed with silica gel Merk 60 (220–440 mesh ASTM).

1-Hydroxyadamantan-4-one (I). To 100 ml of 100% HNO_3 cooled to 13–15°C was added at stirring 12 g (80 mmol) of adamantanone. The reaction mixture was maintained at room temperature for 72 h, then it was heated in an open flask on a water bath to 60°C for 2 h. The excess nitric acid was removed by distillation in a vacuum. To the residue



Isomers forming depending on the order of substituents introduction in the course of synthesis of 1-(*N*-benzoyl-β-alanyloxy)-4-benzoyloxyadamantane: A, procedure *b*; B, procedure *a*.

Table 2. ^{1}H and ^{13}C NMR spectra of new 1,4-disubstituted adamantanes

Compd. no.	δ, ppm ($CDCl_3$/HMDS)
II	^{1}H NMR: 1.92–2.65 m (13H, skeleton), 2.58 t (2H, CH_2CO_2), 3.68 m (2H, C<u>H</u>$_2$NH), 6.81 t (1H, NH), 7.39–7.75 m (5H, arom)
III	^{1}H NMR: 1.8–2.4 m (13H, skeleton; 1H, OH), 2.54 t (2H, CH_2CO_2), 3.67 m (2H, C<u>H</u>$_2$NH), 3.74 t (HOC<u>H</u>$_a$), 3.92 t (HOC<u>H</u>$_e$), 6.86 t (1H, NH), 7.4–7.8 m (5H, arom)
IV	^{1}H NMR: 1.8–2.5 m (13H, skeleton), 2.58 t (2H, CH_2CO_2), 3.68 m (2H, CH_2NH), 5.06 t (BzOCH_a), 5.18 t (BzOCH_e), 6.84 t (1H, NH), 7.4–8.1 m (10H, arom); ^{13}C NMR: 29.47–41.04 (8C, skeleton unsubstituted; 1C, CH_2NH; 1C, $O_2C\underline{C}H_2$), 75.04 (1C, OCH_a), 75.53 (1C, OCH_e), 79.65 (1C, C_e^1), 80.00 (1C, C_a^1), 126.86–134.47 (10C, arom); 165.66, 167.20 (1C, $OO\underline{C}CH_2$; 1C, NH<u>C</u>OPh), 171.92 [1C, $PhCO_2$ (*a*)], 172.01 [1C, $PhCO_2$ (*e*)]
VI	^{1}H NMR: 1.16–1.85 m (13H; skeleton; 1H, OH), 4.84 t (1H, BzOC<u>H</u>$_a$), 6.84–8.02 m (5H, arom)
VII	^{1}H NMR: 1.2–1.85 m (10H, $5\times CH_2$), 2.6 t (2H, CH_2CO_2), 3.7 m (2H, C<u>H</u>$_2$NH), 4.76 m (1H, CHO), 7.12 t (1H, NH), 7.25–7.8 m (5H, arom); ^{13}C NMR: 23.30–31.46 (5C, CH_2), 34.2 (1C, CH_2NH), 35.4 (1C, $O_2C\underline{C}H_2$), 73.06 (1C, CHO), 126.86–134.32 (6C, arom), 167.32, 172.00 (1C, $OO\underline{C}CH_2$; 1C, NHCOPh)
VIII	^{1}H NMR: 1.65–2.15 m (15H, skeleton), 2.54 t (2H, CH_2CO_2), 3.7 m (2H, CH_2NH), 6.9 t (1H, NH), 7.4–7.8 m (5H, arom)

was added 40 ml of water and 15 ml of 96% H_2SO_4, the solution was heated on a water bath in an open flask for 1 h, then the mixture was cooled and extracted (2×50 ml) with a mixture petroleum ether (bp 40–60°C)–ethyl ether, 2 : 1. The acidic solution obtained was neutralized with 30% aqueous NaOH and without cooling the solution the reaction product was extracted into chloroform (3×50 ml). The extracts were combined, washed with a saturated NaCl solution, dried with $MgSO_3$, filtered, and evaporated in a vacuum. The residue was dissolved in 15–20 ml of CH_2Cl_2, and to the solution obtained was added petroleum ether (bp 40–60°C) till separation of precipitate finished. The precipitate was filtered off and sublimed in a vacuum at 160–170°C (20 mm Hg). We obtained 9 g (68%) of compound **I** as colorless crystals, mp 318°C (publ. bp 318–320°C [4]).

1-(*N*-Benzoyl-β-alanyloxy)adamantan-4-one (II). To a solution of 1 g (6 mmol) of compound **I** and 0.78 g (4 mmol) of *N*-benzoyl-β-alanine in 30 ml of anhydrous THF was added at stirring in an argon atmosphere 0.9 g (4.4 mmol) of dicyclohexylcarbodiimide and 0.05 g of diethylaminopyridine. The reaction mixture was stirred at room temperature for 12 h. At completion of the reaction 1 drop of acetic acid was added, and the stirring was continued for 15 min more. The precipitate was filtered off, the filtrate was evaporated to dryness, the residual oily fluid was dissolved in 10 ml of ethyl acetate, and this solution was kept at 4°C for 8–12 h. The separated precipitate was filtered off, the filtrate was washed with 0.1 N HCl, then with water, and dried on $MgSO_4$, filtered, and evaporated to dryness. The colorless oily fluid obtained was subjected to chromatography [eluent ethyl acetate–petroleum ether (bp 40–60°C), 1 : 2]. We obtained 0.97 g of compound **II** as colorless crystals.

1-(*N*-Benzoyl-β-alanyloxy)-4-hydroxyadamantane (III). To a mixture of 6 ml of THF and 1.5 ml of MeOH at 0°C was added by portions at stirring 0.15 g (4 mmol) of $NaBH_4$. In 15 min to the mixture obtained was added 0.3 g (0.9 mmol) of compound **II**, and the stirring was continued for 3 h with gradual raising temperature from 0°C to ambient. The reaction mixture was evaporated, 5 ml of water was added, and the reaction product was extracted into hot ethyl acetate. The extract was dried with $MgSO_4$, filtered, and evaporated. We obtained 0.28 g (93%) of compound **III** as colorless viscous fluid.

1-(*N*-Benzoyl-β-alanyloxy)-4-benzoyloxyadamantane (IV). (a) To 0.3 g (0.9 mmol) of compound **III** in 8 ml of pyridine at 0°C was added dropwise while stirring 0.13 g (0.9 mmol) of benzoyl chloride. The reaction mixture was stirred at 0°C for 3 h. Then 1 ml of water was added, and the reaction mixture was evaporated on a rotary evaporator. To the residue 15 ml of water was added, and the reaction product was extracted into chloroform (3×50 ml). The combined extracts were washed with 0.5% HCl,

with water, saturated solution of $NaHCO_3$, and again with water. The solution obtained was dried with $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography [eluent ethyl acetate–petroleum ether (bp 40–60°C), 1 : 2.5]. We isolated 0.31 g of compound **IV** as colorless crystals.

(b) To solution of 0.3 g (1.1 mmol) of compound **VI** and 0.14 g (0.7 mmol) of *N*-benzoyl-β-alanine in 20 ml of THF at stirring under argon atmosphere was added 0.15 g (0.7 mmol) of dicyclohexylcarbodiimide and 0.02 g of diethylaminopyridine. Further procedure is the same as in the synthesis of 1-(*N*-benzoyl-β-alanyloxy)adamantan-4-one (**II**). After the chromatographic purification [eluent ethyl acetate–petroleum ether (bp 40–60°C), 1 : 2.5] we obtained 0.22 g of compound **IV** as colorless crystals.

1,4-Dihydroxyadamantane (V). To 50 ml of ethyl ether at room temperature while stirring was added by portions 1.3 g (34 mmol) of $LiAlH_4$, and to this mixture was added 2.6 g (16 mmol) of compound **I**. The reaction mixture was stirred for 4 h at room temperature, then it was evaporated, 2 ml of water was added, and the mixture was dried in a vacuum. The solid residue was treated with chloroform in a Soxhlet extractor for 4 h. The extract was dried on $MgSO_4$, filtered, and evaporated. We obtained 2.5 g (93%) of compound **V** as colorless crystals, mp 328°C (publ. bp 327–331°C [11]).

4-Benzoyloxy-1-hydroxyadamantane (VI). To 1 g (6 mmol) of compound **V** in 8 ml of pyridine at 0°C while stirring was added dropwise 0.67 g (4.8 mmol) of benzoyl chloride. The reaction mixture was stirred at 0°C for 3 h, then it was evaporated in a rotary evaporator. To the residue 10 ml of water was added, and the mixture was extracted with ethyl acetate (3×20 ml). The combined extracts were washed with 0.5% HCl, water, saturated solution of $NaHCO_3$, and again with water. The solution obtained was dried with $MgSO_4$, filtered, and evaporated. After the chromatographic purification [eluent ethyl acetate–petroleum ether (bp 40–60°C), 1 : 4] we isolated 0.4 g (31%) of compound **VI** as colorless crystals, mp 62°C.

(*N*-Benzoyl-β-alanyloxy)cyclohexane (VII). To a solution of 1.4 g (14 mmol) of cyclohexanol and 1.37 g (7.1 mmol) of *N*-benzoyl-β-alanine in 40 ml of anhydrous THF at stirring under argon atmosphere was added 1.6 g (7.8 mmol) of dicyclohexylcarbodiimide and 0.1 g of diethylaminopyridine. Further procedure was the same as in the synthesis of (*N*-benzoyl-β-alanyloxy)adamantan-4-one (**II**). After chromatographic purification [eluent ethyl acetate–petroleum ether (bp 40–60°C), 1 : 3] we obtained 1.87 g of compound **VII** as colorless crystals.

(*N*-Benzoyl-β-alanyloxy)adamantane (VIII). To a solution of 1 g (6.6 mmol) of adamantanol and 0.84 g (4.4 mmol) of *N*-benzoyl-β-alanine in 20 ml of anhydrous THF at stirring under argon atmosphere was added 1.03 g (4.9 mmol) of dicyclohexylcarbodiimide and 0.05 g of diethylaminopyridine. Further procedure was the same as in the synthesis of (*N*-benzoyl-β-alanyloxy)adamantan-4-one (**II**). After chromatographic purification [eluent ethyl acetate–petroleum ether (bp 40–60°C), 1 : 3] we obtained 1.2 g of compound **VIII** as colorless crystals.

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