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Synthetic Approach to the Synthesis of Physiologically Active Compounds: II.* Synthesis of Disubstituted Adamantanes Containing an *N*-Benzoylphenylisoserine Fragment

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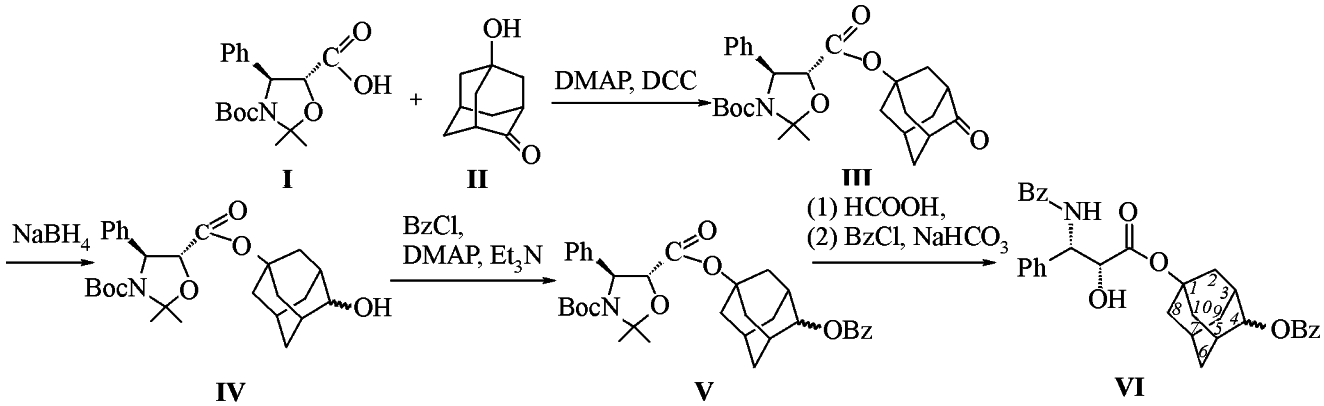
Abstract—A preparation is reported of some previously unknown 1,4-disubstituted adamantane derivatives containing a phenylisoserine fragment.

Within the framework of a program aimed at creation of analogs of taxane antitumor medicines we develop syntheses of derivatives from adamantane and bicyclo[3.3.1]nonane series which in definite skeleton points contain functional groups (benzoyloxy, *N*-benzoylphenylisoserinyl etc.) the most important for bonding to cell targets [1, 2]. In the preceding study we suggested procedures for preparation of 1-(*N*-benzoyl-β-alaninoxy)-4-benzoyloxyadamantane (β*AA*) [1]. The goal of this research was a development of synthesis procedure for 1-(*N*-benzoylphenylisoserinyl)-4-benzoyloxyadamantane (**VI**).

The target compounds was prepared in several stages. As initial compounds served chemantane (**II**) [1] and also acid **I**, a convenient for subsequent esterification N,O-protected form of (2*R*, 3*S*)-*N*-benzoylphenylisoserine [2].

The first stage, esterification, was carried out in dichloromethane at room temperature in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) as catalyst. The reaction product, ester **III**, was obtained in 99% yield, and its structure was confirmed by elemental analysis and the data of ^{1}H and ^{13}C NMR spectra. In the ^{13}C NMR spectrum of ester obtained appear the carbon signals from amino acid fragment and from the skeleton: 28.00–46.93 [8C, skeleton + C($\underline{C}H_3)_2$ + C($\underline{C}H_3)_3$]; 64.16 (1C, CHNH); 79.59 (1C, $\underline{C}^1O_2$C,skeleton); 81.19 (1C, $\underline{C}$HOC); 126.24–128.41 (arom); 154,75; 174.58; 214.86 (carbonyl).

The keto group of ester **III** was reduced under mild conditions with sodium borohydride in a mixture methanol–ethyl ether (1 : 6). In the ^{1}H NMR spectrum of the alcohol (**IV**) obtained are present two triplets in the region 3.74 and 3.92 ppm from skeleton protons at the carbons linked to hydroxy groups in different isomers.



* For communication I see [1].

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We failed to benzoylate the mixture of isomeric alcohols **IV** by a standard procedure [3] with benzoyl chloride in pyridine. However the reaction carried out with triethylamine and dimethylaminopyridine as catalyst [4] gave rise to two isomeric benzoyloxy derivatives **V** in 74% yield. The structure of the synthsized derivative of benzoyloxyadamantane **V** was confirmed by ^{1}H NMR spectra.

The final stage of the synthesis consisted in removing isopropylidene protection in compound **V** by formic acid followed by benzoylation of the nitrogen atom by procedure we had developed earlier [2]. The target product, 1-(*N*-benzoylphenylisoserinyl)-4-benzoyloxyadamantane (**VI,** isomers ratio 1 : 2), was obtained in 83% yield, and its structure was proved by elemental analysis and ^{1}H and ^{13}C APT NMR spectra. In the ^{13}C APT NMR spectrum the signals of C^1 and C^4 from two isomers are observed at 82.36; 81.96 and 74.70; 75.25 ppm. The assignment of the signals to definite isomer may be done basing on similarity to the spectra of 2,4-disubstituted adamantanes [5–7] as we have made in the previous report or by analogy with the spectra of 1,4-disubstituted adamantanes [8, 9]. In the first case the stronger signals at 81.96 and 75.25 should be assigned to the equatorial isomer that should be more stable according to the calculations of the heats of formation (see the experimental data). In the second case the situation should be reversed, and the signals at 81.96 and 75.25 belong to the less stable axial isomer arising in greater amount. It seems that an unambiguous assignment of stereoisomers **VI** can be obtained only from the X-ray diffraction study.

Thus in this study a procedure is developed for synthesis of 1-(*N*-benzoylphenylisoserinyl)-4-benzoyloxyadamantane in an overall yield 60% with respect to compound **I** that makes possible synthesis of a series of potential biologically active compounds.

3-*tert*-Butyl-5-(4-oxoadamantyl)-2,2-dimethyl--phenyl-1,3-oxazolidine-3,5-dicarboxylate (III) was prepared along procedure [2] from 1 g (6 mmol) of chemantane (**I**) and 1.28 g (4 mmol) protected amino acid **II** in anhydrous dichloromethane. The reaction product was purified by chromatography using as eluent ethyl ether–petroleum ether (boiling within 40–70°C), 1 : 2. We obtained 1.85 g of compound **III** as colorless fluid. Yield 99%. ^{1}H NMR spectrum ($CDCl_3$/HMDS), δ, ppm: 1.11 s (9H, *t*-Bu); 1.68 and 1.75 two s [6H, $C(CH_3)_2$]; 1.75–2.64 m (13H, skeleton); 4.35 d (1H, NCHCHO); 4.94 s (1H, NCHCHO); 7.21–7.37 m (5H, arom). Found, %: C 69.31; H 7.02; N 3.11. $C_{27}H_{35}NO_6$. Calculated, %: C 69.08; H 7.46; N 2.99

3-*tert*-Butyl-5-(4-hydroxyadamantyl)-2,2-dimethylphenyl-1,3-oxazolidine-3,5-dicarboxylate (IV) was obtained along procedure [2] from 0.42 g (0.9 mmol) of compound **III** by treating with 0.15 g (4 mmol) of $NaBH_4$ in a mixture of 6 ml of ethyl ether and 1 ml of MeOH at 0°C. We isolated 0.42 g (99%) of compound **IV** as colorless crystals. mp 63–65°C. ^{1}H NMR spectrum ($CDCl_3$/HMDS), δ, ppm: 1.11 s (9H, *t*-Bu); 1.68 and 1.75 two s [6H, $C(CH_3)_2$]; 1.42–2.38 m (14H, skeleton+ OH); 3.74 and 3.92 two t. (1H, CHOH, two isomers – 2 : 1); 4.32 d (1H, NCHCHO); 4.93 s (1H, NCHCHO); 7.23–7.37 m (5H, arom).

5-[4-(Benzoyloxy)adamantyl]-3-*tert*-butyl-2,2-dimethyl-phenyl-1,3-oxazolidine-3,5-dicarboxylate (V). To a solution of 0.078 g (0.64 mmol) of 4-*N*,*N*-dimethylaminopyridine in 40 ml of anhydrous dichloromethane at room temperature was added 1 ml of anhydrous triethylamine, 0.11 g (0.78 mmol) of benzoyl chloride, and at last 0.3 g (0.64 mmol) of ester **IV**. The reaction mixture was stirred for 12 h, then it was diluted with 30–40 ml of ethyl ether, washed with 1 N HCl solution (3 × 25 ml), with saturated solution of $NaHCO_3$ (20 ml) and water (20 ml), dried on $MgSO_4$, and evaporated. The residue was purified by chromatography using as eluent petroleum ether (boiling within 40–70°C)–ethyl acetate, 9 : 1. We obtained 0.27 g (74%) of colorless viscous fluid. ^{1}H NMR spectrum ($CDCl_3$/HMDS), δ, ppm: 1.11 s (9H, *t*-Bu); 1.70 and 1.76 two s [6H, $C(CH_3)_2$]; 1.50–2.52 m (13H, skeleton); 4.36 d (1H, NCHCHO); 4.93 s (1H, NCHCHO); 5.06 and 5.17 two t (1H, CHOBz, two isomers, 2 : 1); 7.26–8.18 m (10H, arom).

1-[1-Hydroxy-2-phenyl-2-(phenylcarboxamido)-ethylcarbonyloxy]-4-benzoyloxyadamantane (VI) was prepared by procedure [2] from 0.4 g of compound **V** in 50 ml of formic acid. The intermediate product was benzoylated with 0.09 ml (0.77 mmol) of benzoyl chloride. The final reaction product was purified by chromatography using as eluent petroleum ether (boiling within 40–70°C)–ethyl acetate, 2.5 : 1. We obtained 0.31 g (83%) of compound **VI** as colorless crystals. mp 94°C. ^{1}H NMR spectrum ($CDCl_3$/HMDS), δ, ppm: 1.52–2.52 m (13H, skeleton); 3.31 s (1H, OH); 4.58 d (1H, CHOH); 5.07 and 5.19 two t (1H, CHOBz, two isomers, 2 : 1); 5.82 m (1H, HNCH); 7.05 d (1H, NH); 7.24–8.15 m (15H,

arom). ^{13}C APT NMR spectrum ($CDCl_3$/HMDS). The chemical shifts for the second isomer are given in brackets. δ, ppm: 29.42 [29.70], 34.80 [33.71] (3C, CH-skeleton); 30.40 [39.23], 35.43 [30.26], 40.46 [40.56] (5C, CH_2-skeleton); 54.60 (1C, CHNH); 73.42 (1C, CHOH); 74.70 [75.25] (1C, CHOBz); 82.36 [81.96] (1C, C^1O_2CCO); 126.80–138.77 (18C, arom, among them 131.50, 134.20 and 138.77 – C_i); 165.60, 166.83 and 171.64 (3C, carbonyl). Found, %: C 73.30; H 6.25; N 2.90. $C_{33}H_{33}NO_6$. Calculated, %: C 73.47; H 6.12; N 2.60. Heat of formation of the axial isomer –164.7 kcal mol^{-1}, of equatorial one –165.1 kcal mol^{-1} (calculation by routine HyperChem Pro 6.0).

^1H and ^{13}C NMR spectra were registered on VXR-400 instrument (operating frequencies 400 and 100 MHz respectively) in $CDCl_3$ with HMDS as reference. The chromatographic separation was carried out on columns charged with silica gel Merck 60 (220-440 mesh ASTM). The study was carried out under financial support of the Russian Foundation for Basic Research (grant no. 02-03-32790).

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