Chemistry of Natural Compounds, Vol. 43, No. 6, 2007

ADAMANTANE-CONTAINING 5α-STEROIDS

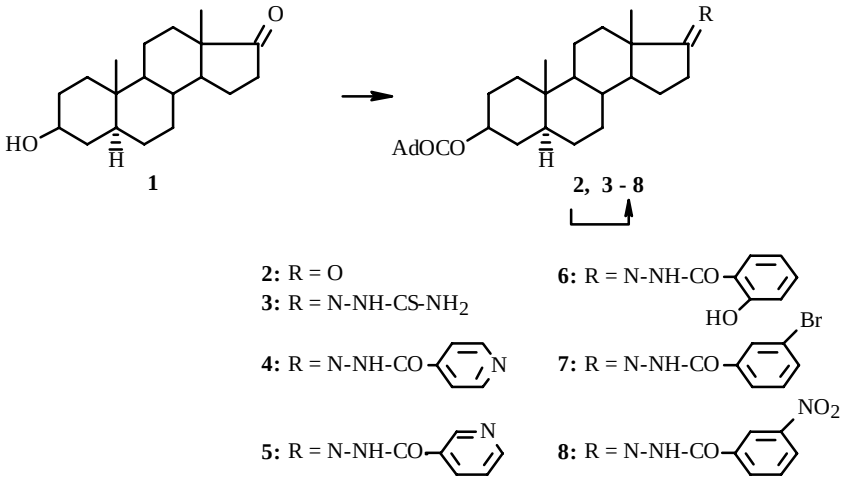
M. I. Sikharulidze,[1] N. Sh. Nadaraia,[1]
M. L. Kakhabrishvili,[1] and M. O. Labartkava[2]

UDC 547.92

Certain derivatives of adamantane-containing carboxylic acids, in particular 17β-(1-adamantoate)-19-nortestosterone or bolmantalate, which has a strong and unique anabolic action and high and prolonged myotropic activity [1, 2], are used in medical practice. It has been demonstrated that adding the adamantane fragment to a steroid molecule decreases the androgenic activity and leads to the appearance of new biological properties [3, 4].

In order to find new biologically active compounds in the 5α-sterol series, epiandrosterone modified with the adamantane moiety was synthesized for the first time.

3β-Substituted epiandrosterone was prepared by reaction of adamantan-1-carboxylic acid chloride with epiandrosterone (**1**), an intermediate in the transformation of tigogenin [5, 6]. The reaction was carried out by refluxing in absolute benzene in the presence of pyridine.



We synthesized **3-8** from modified epiandrosterone **2** by condensation of it with thiosemicarbazide and hydrazides of nicotinic, isonicotinic, salicylic, and *m*-Br- and *m*-NO_2-benzoic acids in ethanol in the presence of CH_3COOH.

The structures of synthesized **3-8** were confirmed by IR and PMR spectroscopy.

The IR spectrum of thiosemicarbazone **3** contained an absorption band for NH_2 stretching vibrations at 1430 cm $^{-1}$ and for C=N and C=S bonds at 1712 and 1345 cm $^{-1}$, respectively.

The IR spectra of hydrazones **4-8** exhibited characteristic absorption bands for NHCO carbonyl at 1720 cm $^{-1}$ and for C=N at 1670-1635 cm $^{-1}$.

The PMR spectrum of **2** gave resonances for C-18 and C-19 angular methyls as singlets with chemical shifts (CS) 0.63 and 0.64 ppm; for H-3, 4.45 ppm. Adding a substituent in the C-17 position of **2** caused a weak-field shift (by 0.23 and 0.32 ppm) of the CS of 18-CH_3 and 19-CH_3 of **3-8**. Protons of the adamantane fragment appeared at 1.7-2.0 ppm as isolated singlets.

PMR spectra in $CDCl_3$ revealed that steroids **4**, **5**, **7**, and **8** exist as mixtures of two conformational isomers because resonances of the NH group on the C=O group formed two singlets (CS of NH protons for *cis*-conformers were 8.26, 9.25, 8.26, and 8.56 ppm, respectively; for *trans*-conformers, 8.16, 9.00, 8.18, and 8.49 ppm, respectively). Also, PMR spectra of **4**, **5**, **7**, and **8** in DMSO-d_6 had resonances for NH protons shifted to weak field as broad singlets with CS in the range 8.7-10.7 ppm.

1) I. Kutateladze Institute of Pharmacochemistry, Tbilisi, 0159, ul. Sarajishvili 36, fax (99532) 52 00 23, e-mail: docmadona@yahoo.com; 2) Sukhumi Filial, Tbilisi State University, Tbilisi, 0128, ul. Jikia, 12. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 624-625, November-December, 2007. Original article submitted May 16, 2007.

0009-3130/07/4306-0753

IR spectra of the compounds in KBr were reecorded on a Thermo Nicolet Avatar-370 spectrometer. PMR spectra in $CDCl_3$ and DMSO-d_6 were measured on a Bruker AM-400 spectrometer (400 MHz). Melting points were measured on a Boetius heated stage.

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using benzene:acetone (4:1). Elemental analyses of all compounds agreed with those calculated. The acid chloride was prepared by refluxing adamantan-1-carboxylic acid with a 3.5-fold excess of thionylchloride [7].

3β-(1-Adamantoate)-epiandrosterone (2). A solution of epiandrosterone (0.5 g, 1.74 mmol) in absolute C_6H_6 (30 mL) and pyridine (0.5 mL) was treated with a solution of adamantan-1-carboxylic acid chloride (2 mmol) in C_6H_6 (10 mL), refluxed for 5 h, cooled to room temperature, diluted with water, and extracted with ether (3 × 20 mL). The extracts were washed with water, Na_2CO_3 solution, and water, and were dried over Na_2SO_4. Solvent was distilled to afford **2** (0.6 g, 74%), mp 216-218°C (MeOH). IR spectrum (ν, cm^{-1}): 1727 (C=O), 2923, 2885 (adamantane C–H), 1627 (ester CO). PMR spectrum (δ, ppm): 0.63 (3H, s, CH_3-18), 0.64 (3H, s, CH_3-19), 4.45 (1H, m, H-3), 2.37 (1H, w.m, H-5), 1.63 (4H, s, CH-Ad), 1.86 (10H, s, CH_2-Ad), 2.00 (1H, s, CH-Ad-1).

3β-(1-Adamantoate)-epiandrosterone Thiosemicarbazone (3). A hot solution of **2** (0.3 g, 0.66 mmol) in ethanol (20 mL) and CH_3COOH (0.5 mL) was treated with thiosemicarbazone (0.073 g, 0.8 mmol), refluxed for 3 h, filtered, and cooled to room temperature. The resulting precipitate was filtered off and washed with water to afford **3** (0.32 g, 91%), mp 281-283°C (MeOH). IR spectrum (ν, cm^{-1}): 1345 (C=S), 1290 (NHCS), 1712 (C=N), 1620 (ester CO), 2910, 2854 (adamantane C–H). PMR spectrum (δ, ppm): 0.86 (3H, s, CH_3-18), 0.87 (3H, s, CH_3-19), 4.65 (1H, m, H-3), 7.17 (2H, br.s, NH_2), 8.2 (1H, br.s, NH), 1.71 (4H, s, CH-Ad), 1.86 (10H, s, CH_2-Ad), 2.00 (1H, s, CH-Ad-1).

3β-(1-Adamantoate)-epiandrosterone Hydrazones (4-8) (general method). A mixture of ketosteroid (**2**, 0.2 g, 0.44 mmol) and the appropriate hydrazide (0.55 mmol) in ethanol (30 mL) and CH_3COOH (0.5 mL) was refluxed for 4 h and cooled to room temperature. The resulting precipitate was filtered, washed with water, and crystallized from ethanol.

3β-(1-Adamantoate)-5α-androstan-17-one Isonicotinoylhydrazone (4). Yield 90%, mp 174-176°C. IR spectrum (ν, cm^{-1}): 1720 (NHC=O), 1670 (C=N), 1625 (ester CO), 2910, 2854 (adamantane C–H). PMR spectrum (δ, ppm, J/Hz): 0.86 (3H, s, CH_3-18), 0.96 (3H, s, CH_3-19), 4.66 (1H, m, H-3), 7.3-7.9 (4H, w.m, J_{ortho} = 7.52, J_{meta} = 1.76, arom. protons), 8.26 (1H, *cis*, NH), 8.16 (1H, *trans*, NH), 1.70 (4H, s, CH-Ad), 1.86 (10H, s, CH_2-Ad), 2.00 (1H, s, CH-Ad-1).

3β-(1-Adamantoate)-5α-androstan-17-one Nicotinoylhydrazone (5). Yield 90%, mp 148-151°C. IR spectrum (ν, cm^{-1}): 1720 (NHC=O), 1658 (C=N), 1625 (ester CO), 2905, 2855 (adamantane C–H). PMR spectrum (δ, ppm): 0.85 (3H, s, CH_3-18), 0.87 (3H, s, CH_3-19), 4.64 (1H, w.m, H-3), 7.4-8.7 (4H, m, arom. protons), 9.25 (1H, *cis*, br.s, NH), 9.00 (1H, *trans*, br.s, NH), 1.71 (4H, s, CH-Ad), 1.86 (10H, s, CH_2-Ad), 2.00 (1H, s, CH-Ad-1).

3β-(1-Adamantoate)-5α-androstan-17-one Salicyloylhydrazone (6). Yield 88%, mp 261-263°C. IR spectrum (ν, cm^{-1}): 3415 (OH), 1720 (NH–CO), 1635 (C=N), 1610 (ester CO), 2910, 2854 (adamantane C–H). PMR spectrum (δ, ppm, J/Hz): 0.87 (3H, s, CH_3-18), 0.96 (3H, s, CH_3-19), 4.66 (1H, m, H-3), 6.84-7.44 (4H, J_{ortho} = 8.96, J_{meta} = 1.8, arom. protons), 7.39 (1H, s, OH), 7.60 (1H, br.s, NH), 1.70 (4H, s, CH-Ad), 1.86 (10H, s, CH_2-Ad), 2.00 (1H, s, CH-Ad-1).

3β-(1-Adamantoate)-5α-androstan-17-one *m*-Br-benzoylhydrazone (7). Yield 80%, mp 251-253°C. IR spectrum (ν, cm^{-1}): 1720 (NH–CO), 1650 (C=N), 1625 (ester CO), 2910, 2854 (adamantane C–H). PMR spectrum (δ, ppm, J/Hz): 0.86 (3H, s, CH_3-18), 0.96 (3H, s, CH_3-19), 4.66 (1H, m, H-3), 7.3-7.9 (4H, w.m, J_{ortho} = 8.96, J_{meta} = 1.8, arom. protons), 8.26 (1H, *cis*, NH), 8.18 (1H, *trans*, NH), 1.7 (4H, s, CH-Ad), 1.86 (10H, s, CH_2-Ad), 2.00 (1H, s, CH-Ad-1).

3β-(1-Adamantoate)-5α-androstan-17-one *m*-nitrobenzoylhydrazone (8). Yield 85%, mp 242-245°C. IR spectrum (ν, cm^{-1}): 1720 (NH–CO), 1650 (C=N), 1625 (ester CO), 2916, 2855 (adamantane C–H). PMR spectrum (δ, ppm, J/Hz): 0.85 (3H, s, CH_3-18), 0.88 (3H, s, CH_3-19), 4.65 (1H, m, H-3), 7.5-8.4 (4H, w.m, J_{ortho} = 8.0, J_{meta} = 2.0, arom. protons), 8.56 (1H, br.s, *syn*, NH), 8.49 (1H, br.s, *anti*, NH), 1.7 (4H, br.s, CH-Ad), 1.86 (10H, br.s, CH_2-Ad), 2.00 (1H, br.s, CH-Ad-1).

ACKNOWLEDGMENT

We thank Candidate of Chemical Sciences D. Zurabishvili for supplying adamantan-1-carboxylic acid.

REFERENCES

1. R. T. Rapala, R. J. Kraay, and K. Gerzon, *J. Med. Chem.*, **8**, 580 (1965).
2. V. Yu. Kovtun and V. M. Plakhotnik, *Khim.-farm. Zh.*, **8**, 931 (1987).
3. R. W. Butcher and E. W. Sutherland, *J. Biol. Chem.*, **237**, 1244 (1962).
4. M. Ridollo, *J. New Drugs*, **6**, 126 (1966).
5. N. I. Men′shova, N. A. Korzinkina, E. P. Kemertelidze, N. Sh. Nadaraya, M. G. Davitishvili, L. I. Lishcheta, and V. S. Grosheva, *Sb. Nauchn. Tr. VNIKhFI*, **10**, 83 (1982).
6. G. R. Pettit, A. K. Gupta, and R. L. Smith, *Can. J. Chem.*, **44**, 17, 2023 (1966).
7. P. D. Klimstra, U.S. Pat. No. 3,483,234 (1969); *Ref. Zh. Khim.*, 2H360P (1971).