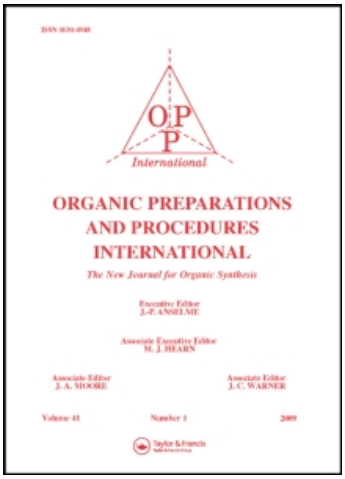


Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

STEROIDAL ADAMANTYLAMIDES AND CARBAMATES. POTENTIAL ANTIVIRAL AGENTS

Josef E. Herz[ab]; Tomasa Corro[a]; Maritza Velarde[a]; Julieta A. Herz[c]
[a] Department of Chemistry, CIEA-IPN, Mexico, DF [b] Department of Biotechnology, Institute for Biomedical Research, UNAM, Mexico, DF [c] Colegio de Ciencias y Humanidades, UNAM, Naucalpan, EM, Mexico

To cite this Article Herz, Josef E. , Corro, Tomasa , Velarde, Maritza and Herz, Julieta A.(1981) 'STEROIDAL ADAMANTYLAMIDES AND CARBAMATES. POTENTIAL ANTIVIRAL AGENTS', Organic Preparations and Procedures International, 13: 5, 383 — 387
To link to this Article: DOI: 10.1080/00304948109356147
URL: http://dx.doi.org/10.1080/00304948109356147

STEROIDAL ADAMANTYLAMIDES AND CARBAMATES. POTENTIAL ANTIVIRAL AGENTS

Submitted by (9/3/80) Josef E. Herz*[a,b], Tomasa Corro[a], Maritza Velarde[a] and Julieta A. Herz[c]

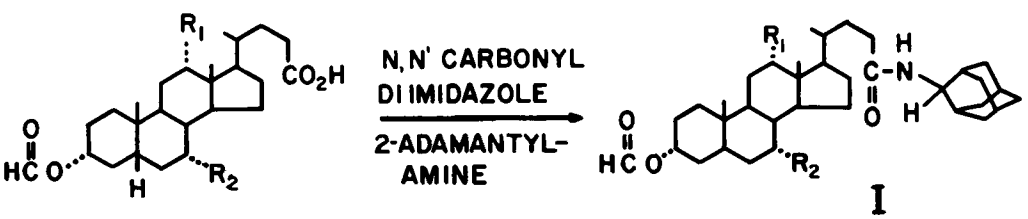
a) Department of Chemistry, CIEA-IPN, Ap. 14-740 Mexico 14, D.F.

b) Department of Biotechnology, Institute for Biomedical Research, UNAM, Ap. 70228 Mexico 20, D.F.

c) Colegio de Ciencias y Humanidades, UNAM, Naucalpan, EM, Mexico

In previous publications[1,2] we reported the preparations and antiviral activities of several steroidal 1-adamantylamides. The promising results obtained induced us to synthesize additional potential antiviral compounds of a similar type. In this publication we describe the preparation of three steroidal N-(2-adamantyl)amides and of the cholesteryl carbamates of 1-amino and 2-aminoadamantane.

A number of methods for the preparation of amides[1] were attempted. Most gave low yields and numerous side-products. The best results were obtained when the imidazolide of the steroidal acid was prepared *in situ* and reacted without isolation with adamantylamine in a suitable solvent such as tetra-



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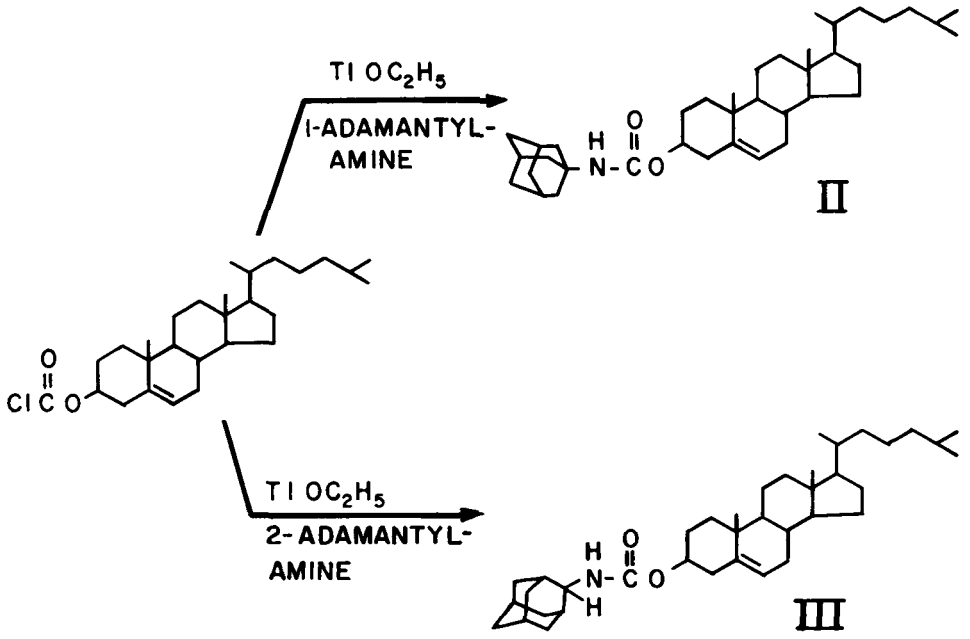
a) $R_1 = R_2 = H$ b) $R_1 = OCHO$, $R_2 = H$ c) $R_1 = R_2 = OCHO$



hydrofuran. To prepare the N-adamantylcarbamates of cholesterol the known cholesteryl chloroformate[3] was treated with the adamantylamine in presence of thallium(I) ethoxide according to a previously described[4] method for the preparation of highly hindered steroidal esters.

EXPERIMENTAL SECTION

N-(2-Adamantyl)amides.- Deoxycholic acid diformate (1.0 g) and N,N'-carbonyl diimidazole (500 mg) were sealed into a dry reaction flask and dry tetrahydrofuran (THF) was added with a syringe. When the formation of CO_2 had ceased, 2-adamantylamine (450 mg) in 10 ml dry THF was added and the mixture heated to reflux for 2 hrs. The mixture was evaporated under vacuum, the residue taken up in ether; the ethereal solution was

washed with water, dried and evaporated. The residue was adsorbed on a silica gel dry column and eluted with benzene-ethyl acetate (60:40).

N-(2-Adamantyl)amide of lithocholic acid formate(Ia), yield 78%, mp. 148-152°, $[\alpha]_D$ + 39° (Chf). IR(CCl_4): 1670 cm^{-1} (amide), 1725 cm^{-1} (formate), 3460 cm^{-1} (amide). NMR($CDCl_3$): δ 4.0 (d, 2'-adamant), 4.8 (m, 3-CH), 5.2 (d, NH), 7.9 (s, HCOO).

Anal. Calcd. for $C_{35}H_{55}NO_3$: C, 78.16; H, 10.31; N, 2.60.
Found: C, 78.31; H, 10.26; N, 2.38.

N-(2-Adamantyl)amide of deoxycholic acid diformate(Ib), yield 73%, mp. 175-177°, $[\alpha]_D$ + 71.5° (Chf). IR(CCl_4): 1660 cm^{-1} (amide), 1720 cm^{-1} (formate), 3460 cm^{-1} (amide). NMR($CDCl_3$): δ 3.8 (d, 2'-adamant), 4.8 (m, NH, 3β CH), 5.2 (s, 12β CH), 8.0 (s), 8.15 (s, HCOO).

Anal. Calcd. for $C_{36}H_{55}NO_5$: C, 74.31; H, 9.53; N, 2.41.
Found: C, 74.27; H, 9.50; N, 2.26.

N-(2-Adamantyl)amide of cholic acid triformate(Ic), yield 67%, mp. 131-133°, $[\alpha]_D$ + 56.75° (Chf). IR(CCl_4): 1660 cm^{-1} (amide), 1715 cm^{-1} (HCOO), 3460 cm^{-1} (amide). NMR($CDCl_3$): δ 3.8 (d, 2'-adamant), 4.8 (b, 3β CH), 5.0 (d, NH), 5.3 (m, 7β, 12β CH), 7.8 (s), 8.0 (s), 8.15 (s, HCOO).

Anal. Calcd. for $C_{37}H_{55}NO_7$: C, 71.02; H, 8.86; N, 2.23.
Found: C, 70.84; H, 8.83; N, 2.22.

Preparation of N-Adamantylcarbamates of Cholesterol.- The adamantylamine (600 mg) was dissolved in about 150 ml dry benzene under nitrogen and with exclusion of moisture. A solution of 1.0 g thallium(I) ethoxide in 10 ml benzene was added. To facilitate the formation of the thallium salt of the amine, the

C_6H_6-C_2H_5OH mixture was concentrated to a small volume (distillation) and replaced by fresh anhydrous benzene. This procedure was repeated 3-4 times. Finally, a solution of 1.8 g cholesteryl chloroformate[3] in 20 ml dry benzene was added dropwise with stirring and heating. A white precipitate formed almost immediately. After 2 hrs of heating at reflux the mixture was cooled to room temperature and filtered through a layer of Celite. The benzene solution was washed with water, dried and evaporated. The product was crystallized from benzene-ethyl acetate (98:2).

N-(1-Adamantyl)carbamate of cholesterol(II), yield 76%, mp. 201-203°, [α] - 106° (Chf), IR(CCl_4): 1735, 3460 cm^{-1} (urethane), NMR($CDCl_3$): δ 4.3 (s, 3α-CH, cholest.), 4.9 (d, NH), 5.25 (m, Δ^5).

Anal. Calcd. for $C_{38}H_{61}NO_2$: C, 80.94; H, 10.90; N, 2.48.
Found: C, 81.01; H, 11.14; N, 2.41.

N-(2-Adamantyl)carbamate of cholesterol(III), yield 81%, mp. 214-217°, $[\alpha]_D$ + 38° (Chf), IR(CCl_4): 1730, 3480 cm^{-1} (urethane), NMR($CDCl_3$): δ 3.8 (d, CH,2'-adamantane), 4.4 (s, 3α-CH, cholest), 4.9 (d, NH), 5.3 (m, Δ^5).

Anal. Calcd. for $C_{38}H_{61}NO_2$: C, 80.94; H, 10.90; N, 2.48.
Found: C, 80.72; H, 10.70; N, 2.28.

Microanalyses were carried out by Butterworth Laboratories, Teddington, ENGLAND.

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