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Synthesis of Certain 2-Aminoadamantane Derivatives As Potential Antimicrobial Agents

Hassan M. Eisa, Atif S. Tantawy and Mohamed M. El-Kerdawy
Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt.
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Abstract□N-(2-Adamantyl)-N'-(5-arylhydrazono-6-methyl-4-oxopyrimidin-2-yl) guanidines (IIIa, b), 2-(2-adamantyl-amino)-4-amino-s-triazine (IVa) and its 6-chloromethyl derivative (IVb) were prepared by cyclization of 1-(2-admantyl) biguanide HCl (I) with ethyl 2-arylhydrazono-3-oxobutyrates (II), ethyl formate and ethyl chloroacetate, respectively. Where 1-(2-adamantyl)-3-(4, 5-dioxo-2-imidazolidinylidene) guanidine (V) was used as intermediate for the synthesis of amides (VIIa, b), hydrazide (VIII) and azomethine derivatives (IXa, b) of alkyl 2-(2-adamantyl-amino)-4-amino-s-triazine-6-carboxylates (VI a, b). The antimicrobial testing of the prepared compounds proved that compound IXb was the most active. It showed a marked bacteriostatic effect against *Staphylococcus aureus* and *Bacillus subtilis*.

Keywords□Synthesis, 2-aminoadamantane derivatives, antimicrobial testing.

Interest has been focused on aminoadamantane derivatives which have been demonstrated to posses broad spectrum biological activities[1-3]. Moreover, antiviral and antimicrobial effects have been shown to be associated with many pyrimidine[4, 5] and s-triazine[6, 7] derivatives. These observations prompted us to synthesize some novel 2-amino-adamantane derivatives in which pyrimidine or s-triazine nucleus is incorporated. The preliminary results of antimicrobial testing of the prepared compounds are also reported.

RESULTS AND DISCUSSION

Synthesis

The method of Venkatachala[8] was adopted for the synthesis of 1-(2-adamantyl) biguanide hydrochloride (I) by fusion of 2-adamantylamine hydrochloride and dicyandiamide at 190°C. Treatment of (I) sodium methoxide in methanol followed by cyclization of the liberated 1-(2-adamantyl) biguanide base with ethyl 2-arylhydrazono-3-oxobutyrates[9] (II) afforded N-(2-admantyl)-N'-(5-arylhydrazono-6-methyl-4-oxopyrimidin-2-yl) guanidines (IIIa, b). Reaction of (I) with ethyl formate or ethyl chloracetate in methanolic sodium methoxide solution gave 2-(2-adamantylamino)-4-amino-s-triazine (IVa) and its 6-chloromethyl derivative (IVb), respectively. 1-(2-Adamantyl)-3-(4,5-dioxo-2-imidazolidinylidene)-guanidine (V) was prepared by reacting (I) with diethyl oxalate in anhydrous methanol. Treatment of (V) with the appropriate alcohol or amine afforded 2-(2-admantylamino)-4-amino-s-triazine-6-carboxylic esters (VIa, b) and amides (VIIa, b), respectively. Reaction of (VIa) or (VIb) with hydrazine hydrate yielded the corresponding hydrazide (VIII) from which the azomethine derivatives (IXa , b) were prepared by heating with the respective aldehyde in ethanol.

Antimicrobial testing

The *in-vitro* antimicrobial activity of the prepared compounds were tested using the agar dilution technique[10]. The minimal inhibitory concentrations (MICs) of the prepared compounds are shown in (Table I). Compound (IXb) was the most active against the tested strains of *Staphylococcus aureus* and *Bacillus subtilis*, while (IIIb) was the most active against *Escherichia coli*.

EXPERIMENTAL

Melting points were recorded on an electrothermal melting point apparatus (Fisher-Johns) and are uncorrelated. IR spectra in KBr disc were recorded on a Pye Unicam SP 1000 infrared spectrophotom-

Scheme 1

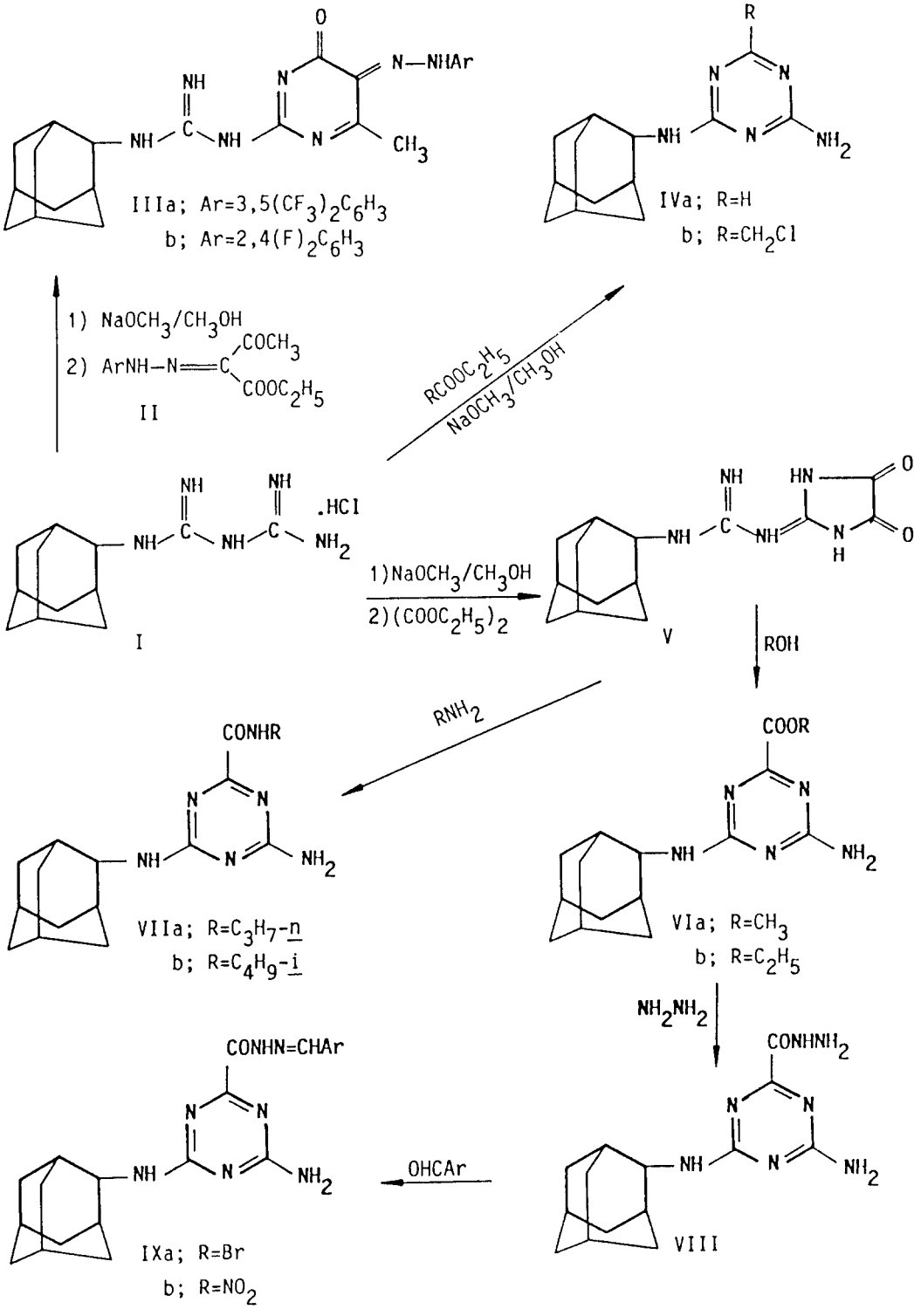
IIIa; Ar=3,5(CF3)2C6H3
b; Ar=2,4(F)2C6H3
IVa; R=H
b; R=CH2Cl
1) NaOCH3/CH3OH
2) ArNH–N=C(COCH3)(COOC2H5)
II
RCOOC2H5
NaOCH3/CH3OH
.HCl
I
1)NaOCH3/CH3OH
2)(COOC2H5)2
V
ROH
RNH2
VIIa; R=C3H7-n
b; R=C4H9-i
VIa; R=CH3
b; R=C2H5
NH2NH2
VIII
OHCAr
IXa; R=Br
b; R=NO2

Table I. Minimal inhibitory concentrations (MICs) of the prepared compounds determined by agar dilution method

Comp. No.	MIC (μg/ml)		
	S.A.	B.S.	E.C.
IIIa	125	250	31.25
IIIb	125	250	15.62
IVa	250	250	31.25
IVb	62.50	125	31.25
VIa	62.50	125	31.25
VIb	62.50	250	31.25
VII	31.25	125	31.25
VIIIa	31.25	250	31.25
VIIIb	62.50	125	62.50
XIa	31.50	31.25	62.50
XIb	15.62	31.25	62.50

S.A., *Staphylococcus aureus;* B.S., *Bacillus subtilis;* E.C., *Escherichia coli.*

eter. ^{1}H-NMR spectra were recorded on an IBM FT-200 NMR spectrometer in DMSO-d_6. UV spectra were taken on Perkin Elmer 550 S spectrometer. Elemental analyses for C, H and N were performed by the microanalytical centre, Cairo University. The analytical results obtained for all compounds were within $\pm$0.4% of the theoretical values.

1-(2-Adamantyl) biguanide-HCl (I)

A mixture of 2-adamantylamine HCl (9.38g, 0.05 mol) and dicyandiamide (4.2g, 0.05 mol) was fused together at 190°C for 20 min. The solid obtained on cooling was crystallized from water to give I as white crystals, m.p. 240-2°C, 85% yield.

N-(2-Adamantyl)-N'-(5-arylhydrazono-6-methyl-4-oxopyrimidin-2-yl) guanidines (IIIa, b)

A solution of sodium methoxide (Na 0.23g, 0.01 mol) in anhydrous methanol (10 m*l*) was added, with stirring and warming, to I (2.7g, 0.01 mol) filteration, the appropriate ethyl 2-arylhydrazono-3-oxobutyrate II (0.02 mol) was added. The reaction mixture was heated under reflux for 5 h. The solid formed on cooling was collected by filteration and crystallized from ethanol. IIIa, was obtained as orange crystals, m.p. 278-9°C, 90% yield. UV λ_{max} at pH 7, 226, 352 nm. IIIb, was obtained as yellowish brown crystals, m.p. 268-9°C, 95% yield. IR ν cm^{-1}, 3100 (NH), 2900-2920 (adamantyl -CH_2 & CH), 1680 (C=O). ^{1}H-NMR δ 0.9-1.4 (m, 15H, adamantyl-H), 2.3 (s, 3H, CH_3), 6.9-7.3 (m, 3H, Ar-H), 7.6-8.3 (m, 4H, 4NH, exchangeable by D_2O).

2-(2-Adamantylamino)-4-amino-s-triazine (IVa) and its 6-chloromethyl derivatrive (IVb)

A solution of sodium methoxide (Na 0.46g, 0.02 mol) in methanol (50 m*l*) was added to I (2.7g, 0.01 mol). The appropriate carboxylic ester (0.01 mol) in methanol (5 m*l*) was added. The reaction mixture was heated under reflux for 2 h. The residue obtained, after distillation of excess alcohol, poured onto water and neutralized with HCl. The solid product, so obtained, was collected by filteration and crystallized from acetic acid to give IVa and from methanol to give IVb. IVa, was obtained as white crystals, m.p. 230-2°C, 70% yield; IR ν cm^{-1}, 3150-3280 (NH), 3400 (NH_2), 2900-2920 (adamantyl-CH_2 & CH). ^{1}H-NMR δ 0.8-1.5 (m, 15H, adamantyl-H), 7.7-8.2 (m, 3H, NH & NH_2, exchangeable by D_2O), 8.3 (s, 1H, triazinyl-H). IVb, was obtained as white crystals, m.p. 185-7°C, 60% yield. ^{1}H-NMR, δ 0.9-1.4 (m, 15H, adamantyl-H), 7.6-8.1 (m, 3H, NH & NH_2, exchangeable by D_2O), 3.5 (s, 2H, CH_2Cl).

1-(2-Adamantyl)-3-(4,5-dioxo-2-imidazolidinylidene) guanidine (V)

A solution of sodium methoxide (Na 1.15g, 0.05 mol) in anhydrous methanol (50 m*l*) was added, with stirring and warming, to I (13.5g, 0.05 mol) in anhydrous methanol (200 m*l*). To the solution, from which precipitated NaCl was removed by filteration, diethyl oxalate (7.3g, 0.05 mol) was added. After warming on a water bath for 0.5 h. The reaction mixture was allowed to stand at room temperature for 2 h. The precipitate that separated on cooling was collected by filteration and crystallized from dimethyl-formamide to give V as yellow crystals, m.p. 220-2°C, 96% yield. IR ν cm^{-1}, 3310 (NH), 2900-2920 (adamantyl-CH_2 & CH), 1700 & 1730 (2 C=O).

Alkyl 2-(2-adamantylamino)-4-amino-s-triazine-6-carboxylates (VIa, b)

A suspension of V (2.9g, 0.01 mol) in anhydrous methanol or ethanol (60 m*l*) was heated under reflux until a clear solution was obtained (about 5 h). The solid separated by cooling was collected, dried and crystallized from ethanol. VIa, was obtained as white crystals, m.p. 197-8°C, 86% yield. ^{1}H-NMR, δ 0.8-1.3 (m, 15H, adamantyl-H), 3.5 (s, 3H, OCH_3), 7.8-8.1 (m, 3H, NH & NH_2, exchangeable by D_2O). UV λ_{max} at pH 7, 229 nm. VIb, was obtained as white crystals, m.p. 215-7°C, 75% yield. IR ν cm^{-1}, 3210-3400 (NH & NH_2), 2900-2920 (adamantyl-CH_2 & CH), 1720 (C=O)

2-(2-Adamantylamino)-4-amino-s-triazine-6-carboxamides (VIIa, b)

A mixture of V (1.45g, 5 mol) and the appropriate amine (15 mol) was heated under reflux in ethanol (20 m*l*) for 3 h. The solid separated on cooling was collected, dried and crystallized from aqueous ethanol. VIIa, was obtained as white crystals, m.p. 183-5°, 62% yield. IR ν cm^{-1}, 3200 (NH), 3400 (NH_2), 2900-2920 (adamantyl-CH_2 & CH), 1660 (C = O). VIIb, was obtained as white crystals, m.p. 168-7°C, 65% yield.

2-(2-Adamantylamino)-4-amino-s-triazine-6-carbohydrazide (VIII)

Hydrazine hydrate (0.5g, 0.01 mol) was added to a suspension of VIa or VIb (0.01 mol) in absolute ethanol (20 m*l*). The reaction mixture was raised to boil and then allowed to set aside for 48 h. The obtained product was filtered, dried and crystallized from ethanol to give VIII as white crystals, m.p. 218-9°C, 90% yield. IR ν cm^{-1}, 3200 & 3250 (NH), 3400 (NH_2), 2900-2920 (admantyl-CH_2 & CH), 1670 (C = O).

Arylmethylene 2-(2-adamantylamino)-4-amino-s-triazine-6-carbohydrazides (IXa, b)

The appropriate aldehyde (5 mol) was added to a suspension of VIII (1.5g, 5 mol) in ethanol (20 m*l*). The reaction mixture was heated for 30 min. On cooling, the separated solid product was filtered and crystallized from acetic acid-water. IXa, was obtained as yellow crystals, m.p. 224-6, 80% yield. IR ν cm^{-1}, 3180 (NH), 3410 (NH_2), 2900-2920 (adamantyl-CH_2 & CH), 1700 (C = O). IXb, was obtained as yellow crystals, m.p. 250-2°C, 85% yield. ^{1}H-NMR, δ 0.8-1.4 (m, 15H, adamantyl-H), 6.1 (s, 1H, N = CH), 6.3 (s 1H, CONHN = , exchangeable by D_2O), 6.9-7.3 (m, 4H, ArH), 7.6-8.1 (m, 3H, NH & NH_2, exchangeable by D_2O).

Agar dilution method

Compartment plates were prepared with serial two fold dilutions of the various compounds. Each cell culture suspension (10 m*l*) was spotted on each compound-containing plates. A control compartment, one having no tested compound, was included for each isolate. All plates was incubated at 37°C for 24 h. The MIC was defined as the lowest concentration of compound which produced no visible growth (Table I).

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