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Synthesis and biological evaluation of aminomethylidenebisphosphonic derivatives of β-arylethylamines

Waldemar Goldeman [a,*], Anna Nasulewicz-Goldeman [b]

[a] Wrocław University of Technology, Department of Organic Chemistry, Wybrzeże Wyspiańskiego 27, Wrocław 50-370, Poland
[b] Polish Academy of Sciences, Institute of Immunology and Experimental Therapy, Department of Experimental Oncology, Rudolfa Weigla 12, Wrocław 53-114, Poland

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ABSTRACT

Addition of two equivalents of triethyl phosphite to β-arylethylisocyanides to synthesize tetraethyl aminomethylidenebisphosphonates in the presence of a stoichiometric amount of hydrogen chloride is reported. Acid hydrolysis of the tetraethyl esters gave the 2-arylethylaminomethylidenebisphosphonic acids in good yields. Additionally, the obtained bisphosphonates were evaluated for their anti-proliferative effect against MCF-7 human breast cancer cells, J774E mouse macrophages and HL-60 human promyelocytic leukemia cells. β-Phenylphenethylamine derivative showed a selective activity towards J774E cells with IC_{50} values three times lower than *Incadronate* and twice as high as *Zoledronate*.

1. Introduction

2-Arylethylamines represent very attractive building blocks for medicinal and synthetic chemistry. Phenethylamine (2-phenylethylamine) derivatives, in particular, are the most interesting from pharmacological point of view, because they constitute an essential skeleton of many drugs and biologically active compounds.[1] For example, phenethylamine-derived stimulants like β-methylphenethylamine, amphetamine, ephedrine and mescaline, the catecholamine neurotransmitters like adrenaline and dopamine, phenylethanolamine sulfate (*Apophedrin*) used as a topical vasoconstrictor, octopamine used as an α-adrenergic sympathomimetic agent, or the β_2-adrenergic agonists, for example *Salbutamol* and *Salmeterol*, which are used in the treatment of asthma. The 2-aryl(hetaryl)ethylamine core is also an important fragment of some aminoacids like phenylalanine, tryptophane or tyrosine and also some alkaloids, for example codeine or a strong analgesic agent—morphine. Bisphosphonates (BPs) are hydrolytically stabile analogs of inorganic pyrophosphates used in the treatment of diseases connected with calcium metabolism disorders such as Paget's disease,[2,3] osteoporosis[4,5] or tumor-induced hypercalcaemia.[6,7] Bisphosphonates are also used in the therapy of the skeletal related-events in cancer bone metastases.[8,9] In vitro and in vivo studies have revealed direct and indirect antitumor effect of BPs;[10] they inhibit tumor cells proliferation, adhesion and invasion,[11] as well as influence the levels of vascular endothelial growth factor in patients' blood[12] and prevent tumor angiogenesis.[13] BPs manifest activity as antiparasitics,[14,15] herbicides[16] and are used as bone-targeting agents for drugs.[17,18] Nitrogen containing bisphosphonates (N-BPs) inhibit the activity of farnesyl diphosphate (FPP) synthase—a key enzyme in the mevalonate pathway.[19] It has been confirmed that the N-BPs have different mechanism of action and are much more active than the non-nitrogen-containing bisphosphonates (NN-BPs).[20]

Searching the literature we found only few examples of bisphosphonic derivatives of β-arylethylamines (Fig. 1). The first example of such a compound is the simplest derivative of

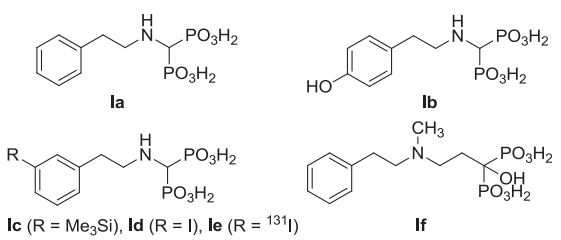

Fig. 1. Bisphosphonic derivatives of phenethylamines described in the literature.

* Corresponding author. Tel.: +48 71 320 2422; fax: +48 320 242771; e-mail address: waldemar.goldeman@pwr.edu.pl (W. Goldeman).

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phenethylamine i.e. 2-phenylethylaminomethylidenebisphosphonic acid (**Ia**), prepared for the first time by Gross et al. in the reaction of appropriate dichloroimine ($PhCH_2CH_2N{=}CCl_2$) with diethyl phosphonate in the presence of sodium.[21] Technetium-99 complexes of the **Ia** were investigated for bone scintigraphy with good skeletal imaging results.[22,23] Bisphosphonate **Ia** and phenethyl analog of *Ibandronate* **If** were investigated for the antibacterial activity.[24] The derivative of tyramine **Ib** was evaluated as potential inhibitor of δ^1-pyrroline-5-carboxylate reductase,[25] or plant glutamine synthetase,[26] as a growth inhibitor of *Entamoeba histolytica* and *Plasmodium falciparum*,[15] and as a herbicide.[16,27] Arstad et al. described the *meta*-substituted derivatives of the phenethylaminomethylidenebisphosphonic acid **Ic**–**e**, and in the case of the radiolabeled bisphosphonate **Ie** a bone affinity and biodistributions were investigated.[28,29]

2. Results and discussion

2.1. Chemistry

With the exception of compounds **Ic**–**e**,[28,29] other aminomethylidenebisphosphonates that is derivatives of phenethylamine **Ia** and tyramine **Ib**, are reported in literature without full characterization data and synthetic details. Gross et al.[20] provide only yield, melting point and elemental analysis of the obtained bisphosphonate **Ia**. The same bisphosphonate was applied in bone scintigraphy, however no information regarding the method of synthesis or the origin of the compound is given in literature.[23] Oldfield et al.[24] reported the synthesis of compound **Ia** in the reaction of phenethylamine with triethyl orthoformate and diethyl phosphonate (so called 'orthoformate' method), but no information about yield, experimental details or spectral data was given in his paper. Similarly, in papers describing the derivative of tyramine **Ib**,[15,16,25–27] no experimental details or spectroscopic data can be found.[30]

Due to the small number of examples of aminomethylidenebisphosphonic derivatives of 2-arylethylamines, the aim of these studies was to prepare a series of these compounds and examine their antiproliferative activity. A number of methods have been reported for the synthesis of aminomethylidenbisphosphonic acids,[31–34] but the reaction of amine, trialkyl orthoformate and dialkyl phosphonate[35] is the most widely used one. Thus, our studies began of the synthesis of phenethylaminomethylidenebisphosphonic acid using orthoformate method. For this purpose, a reaction of phenethylamine, triethyl orthoformate and diethyl phosphonate was performed at 150 °C. The reaction was conducted until ethanol evolution stopped (about 4 h). Then, all volatile components were removed by evaporation in vacuo and the crude reaction mixture was analyzed by ^{31}P NMR spectroscopy. The analysis showed that the reaction mixture contained only about 40% of the main product. Besides the main compound, the unreacted diethyl phosphonate (25%) and four other unidentified phosphonates were present in the mixture (Fig. 2a). Low selectivity of the above reaction, prompted us to search for other more selective methods. Hence, the procedure developed previously in our laboratory was applied. It was discovered that the reaction of isocyanides with trialkyl phosphites in the presence of a stoichiometric amount of hydrogen chloride occurs at mild conditions and proceeds with high selectivity giving the appropriate tetraalkyl aminomethylidenebisphosphonates.[36] In order to compare this procedure with the results obtained for 'orthoformate' method, a reaction of 2-phenylethylisocyanide and triethyl phosphite in the presence of a stoichiometric amount of hydrogen chloride at low temperature (about −15 °C) was performed. ^{31}P NMR Spectroscopic analysis showed that the crude mixture contained the expected product (as its hydrochloride), about 5% of diethyl phosphonate (resulting from dealkylation of the triethyl phosphite) and traces of ethyl phosphonate as the only side products (Fig. 2b).

After a simple work-up procedure, practically pure tetraethyl 2-phenylethylaminomethylidenebisphosphonate was obtained with 84% yield. The obtained tetraethyl ester was hydrolyzed by refluxing 6 M aq hydrochloric acid giving 2-phenylethylaminomethylidenebisphosphonic acid with an 80% yield.

Since the result obtained for the 2-phenylethylisocyanide was promising, we decided to extend the reaction to a range of other 2-arylethylisocyanides. A series of *para*- and β-substituted 2-arylethylisocyanides were investigated under the above conditions. The starting isocyanides were prepared by standard procedure via dehydratation of the required formamides with phosphorous oxychloride in the presence of triethylamine. The starting formamides were obtained by formylation of the commercially available 2-arylethylamines. Amines **1a**–**e** were formylated with formic acid in refluxing toluene. In the case of 4-nitro derivative **1f**, which is sold as hydrochloride, acetic formic anhydride in the presence of triethylamine was used, while 4-*tert*-butoxycarbonyloamino derivative **1g**, was formylated with methylformate—a mild formylating agent (Scheme 1).

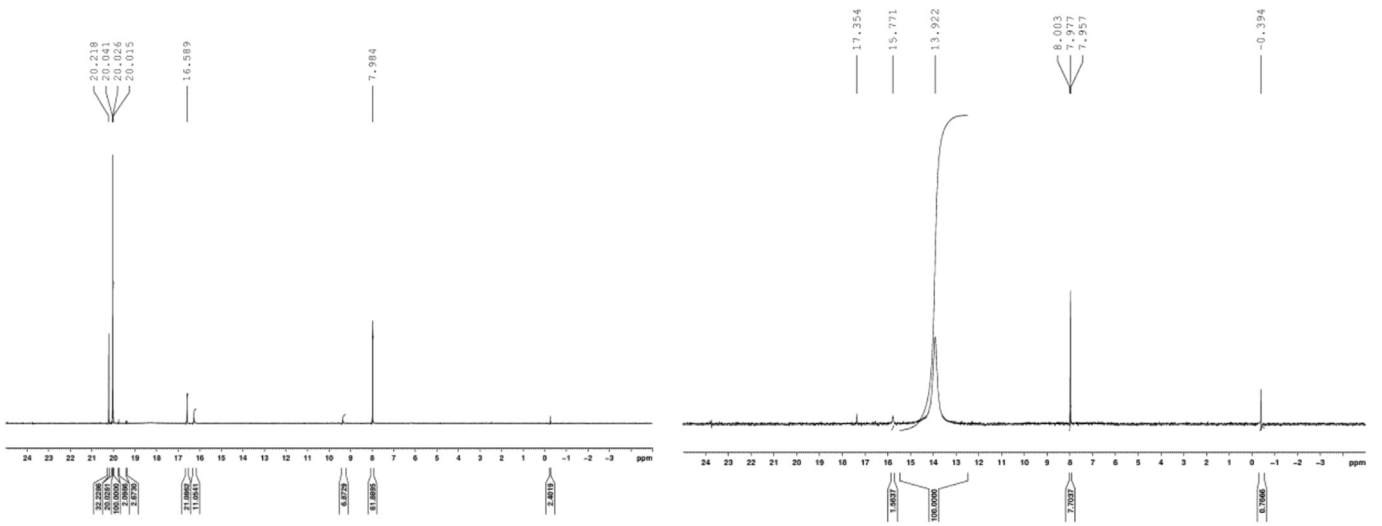

Fig. 2. $^{31}P\{^1H\}$ NMR spectra of the crude reaction mixture after reaction of: a) phenethylamine with triethyl orthoformate and diethyl phosphonate (on the left); b) 2-phenylethylisocyanide with triethyl phosphite in the presence of a stoichiometric amount of hydrogen chloride (on the right).

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