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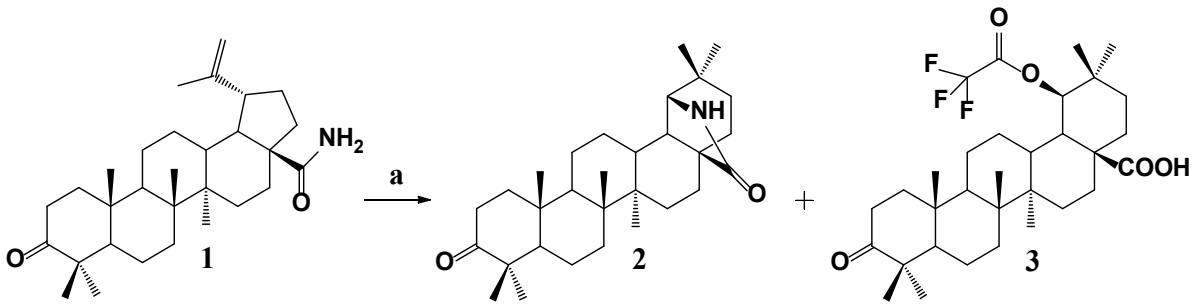
SKELETON REARRANGEMENT OF BETULONIC ACID AMIDE TO OLEANANE AND GERMANICANE TYPES TRITERPENOIDS*

Keywords: Triterpenoids, lupanes, allobetulin, betulin, oleanane, lactames, biological activity.

Natural pentacyclic triterpenoids and their synthetic transformation products exhibit a broad spectrum of biological activity [1–2]. Allobetulin (3β-hydroxy-19β,28-epoxy-18α-oleane) (I) and its derivatives belong to the group of triterpenoids of the germanican family, a very rare class of natural compounds [3]. Allobetulin and related compounds (e. g., 28-oxoallobetulon and 3β-acetoxy-18α-oleanan-28,19β-lactam) can be synthesized from widely occurring natural lupane triterpenoids (e. g., betulin) using the Wagner-Meerwein rearrangement in the presence of acids [4]. Allobetulone derivatives demonstrated anticancer [5], antidiabetic [6] and antiviral activity [7]. Taking into account the interaction of carboxamide of betulonic acid with trifluoroacetic acid (TFA), and considering that lactame product of these reaction based on dimethylsuccinate derivatives have antiretroviral activity [8], in this work we evaluated same reaction based on carboxamide of betulonic acid.

Thus the reaction of carboxamide of betulonic acid **1** with TFA in refluxing chloroform led to a mixture of lactame product **2** (3-oxo-18α-oleanane-28,19β-lactame) and unexpected germanicane type triterpenoid **3** (3-oxo-18β-acetoxy-olenane-28-oic acid). Compound **2** formed based on Wagner-Meerwein rearrangement of 1 under

acidic conditions, on the other hand, formation of product **3** can be explained by the interaction of intermediate product with access of TFA. Structures of compounds 3 confirmed by HSQC and HMBC spectra. It is interesting to note, that reactions of carboxamides of A-lactame or 2-cyano-3,4-seco-4(23)-en-lupanes with TFA under same condition led to formation of same type of products.



Scheme 1. Synthesis of compounds 2 and 3 by the reaction of betulonic amide with trifluoroeacetic acid. Reagent and condition: a. TFA, $CHCl_3$, Δ, 2h

The compounds **1, 2** were evaluated at the University of Queensland (Australia) using five bacterial strains, including Gram-negative *Escherichia coli*, *Klebsiella pneumonia*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* and Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA). The antifungal activity was determined against *Candida albicans* and *Cryptococcus neoformans*. The primary screening of the antimicrobial activity of compounds **1, 2** was carried out in one concentration of 32 mg/ml in tests of the inhibition of cell reproduction. Samples with inhibition value above 80 % were classed as actives. Samples with inhibition values between 50 and 80 % were classed as partial actives. It was found that none of the tested compounds inhibited growth of the pathogenic microorganisms in the studied concentration (Table 1).

Table 1

% Growth inhibition of compound **1, 2** at concentration 32 mg/ml

Comp.	Gram – positive bacteria	Gram – negative bacteria				Fungi	
	Staphylococcus Aureus	*Escherichia coli*	*Klebsiella pneumonia*	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Candida albicans*	*Cryptococcus neoformans var. grubii*
	Strain ATCC43300	Strain ATCC 25922	Strain ATCC 700603	Strain 19606	Strain ATCC 27853	Strain ATCC 90028	Strain H99, ATCC 208821
1	10.58	–6.72	10.6	4.47	16.9	10.93	–8.97
2	–4.52	–6.07	–2.26	10.26	25.36	6.12	–13.08

The screened for *in vitro* α-glucosidase enzyme inhibition of compound **2** did not revealed activity (IC_{50} was < 250 μM) compared with standard drug acarbose (IC_{50} 189.20 μM).

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ANTIVIRAL ACTIVITY OF LUPANE AND OLEANANE A-*SECO*-TRITERPENOIDS*

Keywords: A-*seco*-triterpenoids, oleanane, lupane, antiviral activity, influenza, SARS, X-ray diffraction analysis.