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Synthesis and Antimicrobialactivities of Amides of Decylacetoacetic Acid-II

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Abstract

The results of N,N-dialkylamides of acetoacetic acid (N,N-dialkyl-3-oxo-butanamide)alkylation by decyl chloride in phase transfer catalysis (PTC) condition are presented. Previously it was shown a developed method for the efficient synthesis of acetoacetic acid amides [1]. It was found that only selective mono-C-alkylation of these amides took place in the "liquid - liquid" PTC system with low, medium yields. It was shown also, that in the same medium, but in the absence of PTC, the yield of alkylation product is very low. The resulting compounds are characterized by antimicrobial activity. The synthesized compounds will become the basis for the production of antimicrobial agents.

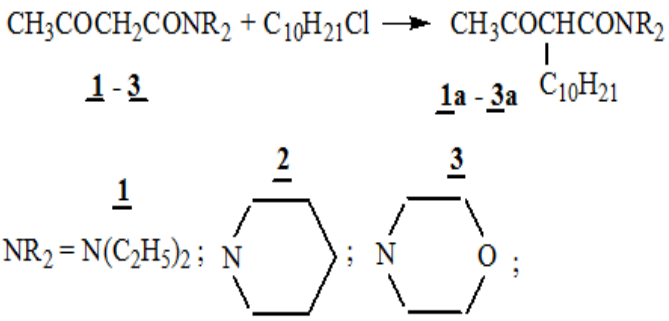
Keywords: amide of acetoaceticacid, alkylation, decyl chloride, phase transfer catalysis, "liquid - liquid" system, super basic medium, antimicrobial activity.

Mini Review

The synthesis of new organic potentially biologically active substances (BAS), the study of their activity and relationships, structure, biological action is an urgent task of pharmaceutical chemistry. Amides of carbonic acid have of importance in a wide variety of industrial and academic fields. They are of particular significance for obtaining pharmaceutical active compounds. As a consequence, there has been a considerable amount of interest in the development to amide synthesis. Amides of acetoacetic acid (AAA) have a wide range of useful properties, in particular, brightly pronounced biological activity [2]. Previously it had been shown the developed method an efficient synthesis of acetoacetic acid amides [1]. It was found also that amides do not possess antimicrobial properties [3]. In the hope that the introduction of long-chain hydrocarbon groups into the AAA structure will give compounds of this class pronounced antimicrobial properties in relation to gram-positive microorganisms [3], studies have been carried out for the synthesis new derivatives of AAA. For this purpose, the alkylation of AAA with decyl chloride previously developed in our group by the method of PTC was studied.

Alkylation of AAA

It had been studied the alkylation of such amides under PTCsystem. The same methods were used for the alkylation of amides as in the case of acetoacetic acid ethyl ester(AAE)[3]. The results of the alkylation of AAA with decyl chloride (DCh) under PTC condition are shown in the (Table 1).



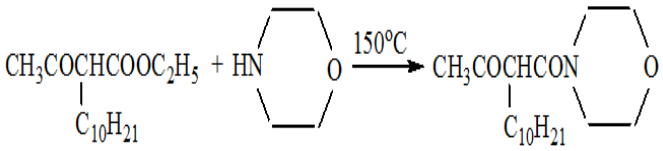
The two-phase catalyst system provides selective α-C-monoalkylation of amides in average yield as from the data obtained it follows. It should be noted that, exceptional C-alkylation as in the case of AAE also takes place here in the same conditions.

Amide	Yield,%	Rf*	B.p. °C/mm
1a	14,0	0,91	185-186/2
2a	20,0	0,88	181-182/2
3a	21,5	0,80	192-193/2

Table 1: Characteristics of of amides of decylacetoacetic acid

The structure and composition of the obtained compounds are confirmed by well-known methods of physicochemical analysis. Structure 3a was also confirmed by counter synthesis by the example of amidation of decylacetic acid ethyl ester with morpholine. It should be noted that the amidation of decyl

acetoacetic ester is difficult and takes place at high temperatures.



The yield of the alkylation reaction, as a typical nucleophilic substitution reaction, depends on the electrophilicity as well as the steric hindrances of the alkyl halides. Here, decyl chloride is weak in electrophilicity and also the most spatially hindered, which leads to the corresponding low yield of the alkylated products–1a-3a. It should be noted that the amide yield does`nt change after 2 hours of stirring, after which only alkaline hydrolysis of the starting and obtained amides takes place.

Antimicrobial Activity of Synthezed Compoundes

It has been known that with a long alkyl chain substituent Quat has highly antimicrobial activity [4]. The introduction of long-chain hydrocarbon into the structure of acetoacetic acid derivatives gives compounds of this class pronounced antimicrobial properties with respect to gram-positive microorganisms. These amides inhibit the growth of cultures of "Staphylococus aureus strain №209 "P" at a concentration of 0.12-0.97mg/ml (Table 2). These compounds can be used in the pharmaceutical industry for the production of new biologically active compounds that selectively suppress the activity of cultures of "Staphylococus aureus.''

Experimental Part

The structure of the obtained compounds is confirmed by PMR spectroscopy, IR and mass spectrometry. 1H NMR spectra were recorded on a Varian MERCURY-300 NMR spectrometer (300 MHz), in DMSO-d6, internal standard - HMDS. IR spectra were recorded on a SPECORD M-80 IR spectrometer. The reaction progress and purity of the compounds were monitored by TLC on SilufolUV-254 plates in a butanol : acetic acid : water system (8:1:1).

Alkylation of Acetoacetic Acid Amides In "Liquid-Liquid" Ptc System

The experiments were carried out at a molar ratio of amide, decyl chloride, alkali and TBAB (tetrabutyl ammonium bromide) 1:1.2:2: 0.1. A mixture of amide, alkyl halide and TBAB was vigorously stirred in a three-necked flask with a reflux condenser and a dropping funnel in a boiling water bath. An aqueous alkali solution was added dropwise over 20 minutes. Heating and stirring continued for another 40 minutes, the reaction mixture was extracted with chloroform, the chloroform extract was dried over magnesium sulfate, chloroform was distilled off, and the residue was distilled in vacuo. The aqueous layer was acidified with hydrochloric acid, distilled off, and the amount of acetic acid was determined by subsequent distillation titration. The yield of amide doesn't change after 2 hours stirred, after that began the alkali hydrolysis of initial & obtained amide. In the IR spectra of 1a-3a there are stretching vibration bands of the carbonyl group at 1640-1650 cm-1, thecarbonyl from CON group at 1720-1730 cm-1. The 1H NMR spectra of N,N-ethyl-3-oxo-2-decyl-butanamidecontain the following signals: CON ($C\underline{H}_2CH_3)_2$ - 4H in 0.51–0.86m ppm, CON ($CH_2C\underline{H}_3)_2$and $CH_2C\underline{H}_3$ (from decyl group)9H at 0.87 and 1.06 ppm, 9 CH_2(from decyl group) 18H in 1,12- 1,14 ppm, $C\underline{H}$-CH_2 1H at 4,25 ppm.In the mass spectra of N,N-ethyl-3-oxo-2-decyl-butanamidethere are quite intense peak of molecular ion, the most common and consistent ions were observed at m/e 197.9.

The Study of Antimicrobial Activity of AAA Derivatives

As indicator microorganisms here used:

a) "Staphylococcus aureus" strain № 209 "P", as the most stable species from the coccal group of bacteria;
b) Escherichia coliseropita 0 III B:4, as the most stable species from gram-negative microorganisms of the family of intestinal bacteria. The antibacterial activity was determined by minimum inhibitory concentration (MIC) values that was represents the minimum concentration of antimicrobial at which there is complete inhibition of the growth of mentioned microorganisms. In the same time was measured the antimicrobial properties of decylacetoacetate ester were studied in vitro by the method of serial dilutions in a liquid nutrient medium (BCH) in relation to the reference strain Staph. aureus №209. It was established that decylacetoacetate ester causes the death of the culture of Staph. aureus strain №209 at a concentration of 31.2 mg/ml and exceeds phenol in activity. The latter inhibits the growth of this Staph. aureus strain at a concentration of 500 mg/ml. Decylacetoacetic acid ethylester can be used also in the pharmaceutical industry to produce new antimicrobial agents.

№/№	Compound	Antimicrobial activity, mg / ml	
		Staph. aureus	Esch. coli
1	N,N-diethyl amid of decylacetoacetic acid(1a)	0.12	x
2	Piperidid of decylacetoacetic acid (2a)	0.97	x
3	Morpholid of decylacetoacetic acid (3a)	0.85	x
4	Decylacetoacetic acid ethyl ester	31.2	x
5	Phenol	500	x

Table 2: Antimicrobial activity of amides decylacetoacetic acid

x) -absence of activity in initial concentration 500mcg/ml

These substances are of significant interest for the preparation of drugs with a narrow spectrum of antimicrobial activity. From the data of the table it follows about the higherantimicrobial activity of the obtained compounds at least with respect to phenol.

Conclusion

The introduction of long-chain hydrocarbon radicals ($C_{10}H_{21}$) into the structure of acetoacetic acid amide gives compounds a pronounced antimicrobial properties.

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