Canadian Journal of Biomedical Research and Technology

**Can J Biomed Res & Tech**
October 2019 Vol:2, Issue:3


# Synthesis, characterization of Amides of Acetoacetic ACID – I

**Open Access** **Mini Review**

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**Submission:** September 28, 2019
**Published:** October 14, 2019



## 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 huge 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 have a wide range of useful properties, in particular, brightly pronounced biological activity *[1]*. At the same time, it`s to necessary to mentioned, the amides of acetoacetic acid (AAA) are undeservedly little-studied objects. Therefore, the study of them synthesis and chemical behavior (for instance, as alkylation reaction), has of theoretical and practical interest. The synthesized compounds will be the basis for the synthesis of antimicrobial activity drugs.

## The Synthesis of Amids of Acetoacetic ACID ( AAA) Amides

Amids of acetoacetic acid were synthesized by the reaction of diketene with amines *[2]*. Diketene reacts with amines preferably in the presence of an inert diluent such as ethylene dichloride, dioxane and toluene and so forth. The reaction is energetic, exothermic and difficult to control. There is known also, that the synthesis of acetoacetic acid anilide can realized by reacting aniline with acetoacetic acid at 145-160°C *[3]*, as well as similar derivatives of diethylamine and morpholine at 180°C *[1]*. This method is convenient and simple and our attention has focused on it.

The following AAA were synthesized and selected as objects for this study.

$$CH_3COCH_2CONR_2$$

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| $R_2 = (CH_3)_2$ ; | $(C_2H_5)_2$ ; | $(CH_2)_5$ ; | $[(CH_2)_2]_2O$ |

The obtained compounds (1–4) are white crystalline substances, insoluble in water and soluble when heated in organic solvents: dioxane, DMF. We had been reported about the synthesis of AAA previously [4]. In this paper presentc the results of studies to refine the structure of the compounds obtained by 1H NMR spectroscopy, IR, and for the morpholid analogue (n-acetoacetylmorpholine) also by GC / MS (gas chromatography-mass spectrometry) and HPLC / MS (high performance liquid chromatography - mass spectrometry).

It was investigated the synthesis amides of acetoacetic acid (1–4) by the interaction of secondary amines at low temperatures (20-50°C) with acetoacetic ester. It has been shown that this interaction leads to the formation of the corresponding enamines with a quantitative yield *[4]*. The Table 1 shows the data of the 1 H-NMR spectra of the enamines (1e-4e) shows in table 1synthesized at 20°C. The interaction of secondary amines at low temperatures (20-50°C) with acetoacetic ester leads to the formation of the corresponding enamines with a quantitative yield. The table 1 shows the data of the 1 H-NMR spectra of the enamines (1e-4e) synthesized by us at 20°C.

$$CH_3COCH_2COOC_2H_5 + HNR_2 \longrightarrow \underset{\underset{1\,e\,-\,4\,e}{}}{\overset{\overset{NR_2}{|}}{CH_3C=CHCOOC_2H_5}} + H_2O$$

| № | Enamine | =CH | $=CCH_3$ | $OCH_2$ | $CH_3$ | $NR_2$ | |
|---|---|---|---|---|---|---|---|
| 1 | 1e | 4,50 | 2,39 | 4,02 | 1,19 | 2,93 | |
| 2 | 2e | 4,54 | 2,41 | 4,03 | 1,19 | 3,31 | 1,15 |
| 3 | 3e | 4,68 | 2,36 | 4,00 | 1,19 | 3,25 | 1,60 |
| 4 | 4e | 4,73 | 2,34 | 4,01 | 1,19 | 3,20 | 3,70 |

**Table 1**: Chemical shifts of proton signals in the NMR spectra β-dialkylaminocrotonic acid ethyl ester with $CCl_4$

It has been studied the effect of temperature on the reaction using the synthesis of morpholide with acetoacetic ester as an

example *(Table 2)*. It has been shown that 150°C the main product is n-acetoacetylmorpholine above after 2 hours.

| № | The reaction temperature, °C | Reaction products, % | |
|---|---|---|---|
| | | Enamin | Amide |
| 1 | 20 | 98 | The trace |
| 2 | 70 | 80 | 20 |
| 3 | 100 | 60 | 40 |
| 4 | 150 | 10 | 90 |

**Table 2:** The effect of temperature on the interaction of acetoacetic ester withmorpholine (duration of experiments 2 hours).

$$CH_3COCH_2COOC_2H_5 + HNR_2 \rightarrow CH_3COCH_2CONR_2 + C_2H_5OH$$

Acetoacetic acid morpholide(3)&piperidite(4) are precipitated with ether. Amides 1 & 2 are isolated by distillation. The content of the enol form of amide 4 in $CCl_4$ at 35°C reaches 46%, while the content of the enol form of acetoacetic ester under the same conditions is 15%. This fact indicates an increase in the mobility of the hydrogen atom of the methylene group in the acetoacetic acid amide. It should be noted that the determination of the enol form in acetoacetic ether by the classical Meyer method in benzene at 18°C gives a value of 16,2% *[5] (Table 3)*.

| № | Compound | The tautomeric form | $COCH_3$ | $CH_2$ | =CH | $NR_2$ | The content, % |
|---|---|---|---|---|---|---|---|
| 1 | 1 | keton | 2,16 | 3,49 | - | 2,95 | 68 |
| | | enol | 1,88 | - | 5,20 | 2,87 | 32 |
| 2 | 2 | keton | 2,18 | 3,50 | - | 3,26<br>1,09 | 54 |
| | | enol | 1,88 | - | 5,20 | 3,31<br>1,14 | 46 |
| 3 | 3 | keton | 2,18 | 3,56 | - | 3,40<br>1,60 | 64 |
| | | enol | 1,88 | - | 5,18 | 3,40<br>1,60 | 36 |
| 4 | 4 | keton | 2,20 | 3,48 | - | 3,60 | 68 |
| | | enol | 1,92 | - | 5,13 | 3,60 | 32 |
| 5 | Acetoacetic acid | keton | 2,00 | 3,29 | - | 3,98x<br>1,02 | 85 |
| | | enol | 1,76 | - | 4,88 | 3,98x<br>1,025 | 15 |

**Note:** x) for$OC_2H_5$group

**Table 3:** Chemical shifts of proton signals in PMR spectraamides 1–4 at 35°C and acetoacetic ester.

It`s known, that a more polar solvent should favor the formation of a more polar tautomer, since this increases the energy of solvation *[6]*. Meyer found that more polar solvents favor the formation of the keto form of diketone and β-ketoesters *[5]*. Therefore, it was to be expected that for acetoacetic acid amides, an increase in the polarity of the solvent will lead to an increase in the keto form content, and only keto form will be present in solvents such as chloroform or water (Table 4).

| № | Compound | The ratio A:B, % | | | | |
|---|---|---|---|---|---|---|
| | | $H_2O$ | $CHCl_3$ | $CH_3OH$ | $C_6H_6$ | $CCl_4$ |
| 1 | 1 | - | 78:22 | 88:12 | 69:31 | 68:32 |
| 2 | 2 | - | - | 88:12 | 52:48 | 54:46 |
| 3 | 3 | - | - | - | 62:38 | 64:36 |
| 4 | 4 | 100:0 | 100:0 | 95:5 | 70:30 | 68:32 |

**Table 4:** The ratio of tautomeric forms in amides of acetoacetic acid in different solvents.

In the mass spectra 1 and 4, there are quite intense (32% and 100%, respectively) peaks of molecular ions. Considering the small intensities of the ion peaks ( m/e 100 -3% and m/e 114 - 9%, respectively) due to the C-C gap relative to the nitrogen atom in the spectra of amides 1 and 4 (which are, *max* for tertiary aminesas a rule) and the presence of fragments( m/e 140 -28% and m/e 140 - 4%, respectively) and ( m/e 72 - 43% and m/e 86 - 92 %, respectively), it can be assumed that the enol form formed mainly due to carbonyl associated with the amine group.

$$CH_3COCH_2CONRR' \rightleftharpoons CH_3COCH{=}C(OH)NRR'$$

**AB**

In the mass spectra of the compounds, along with the fragment characteristic of the corresponding amides, there are also low-intensity ion peaks with m/e 197 and 157, respectively. Considering that during the amide production reaction, a partial realization of the process leading to the formation of enamines is possible; the above peaks present in the mass spectra of compounds 1 and 4 can be attributed to the molecular peaks of these enamines. The absence of signals of the corresponding enamines in the 1H NMR spectra can be explained by an insignificant concentration of the latter in the reaction products.

The above method for the synthesis of N,N-dialkylamides of acetoacetic acid could not be extended to the synthesis of acetoacetic acid amide (acetoacetamide), as well as to a number of monoalkyl substituted amides of AAA. A synthesis method similar to was developed for these compounds. The

Citation: GH Torosyan. Synthesis, characterization of Amides of Acetoacetic ACID – I 2019;2(3): 3.

yields in this case are not higher; however, the conditions of the experiment and the isolation of the starting reagents without change allow us to hope for the application of this method in laboratory practice.

## Experimental Part

The structure of the obtained compounds is confirmed by 1H NMR spectroscopy, IR and HPLC - MS. 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).

The analysis for morpholideacetoacetic acid (MAA) was carried out using also HPLC/MS grade methanol, acetonitrile and deionized water supplied by Carl Roth, Germany. Formic Acid (98% ACS grade) Carl RothGermany and MAA (500 g/L).The research was carried out using Shimadzu's Nexera X2 High-performance liquid chromatography equipped with CBM-20A controller, two Binary LC-30AD Pumps, connected with DGU-20A5R degasser unit, a SIL-30ACMP auto sampler and column temperature unit CTO-30A (Sciex, Germany). X BridgeC8 1.0 mm x 100 mm dimensions with 3.5 µm particle sizes and 136 Å pore size column was used (Waters, USA). The LC was coupled with Sciex's Triple Quad™ 4500 Mass spectrometry by the Turbo V™ Ion Source (Sciex, USA). Data processing was performed using the software Analyst 1.6.3 (Sciex, Germany).

For the readable part of GC / MS (Gas chromatography / mass spectrometry) it has been used Scallibur 1.4 Core program.

**The synthesis of AAA:** The interaction of secondary amines at 150ºC temperatures with acetoacetic ester leads to the formation of the corresponding amides (1-4) with a high yield [4].

## Conclusion

The developed method was proved to be efficient way for acetoacetic acid amides synthesis. The obtained compounds are characterized by modern methods of physicochemical analysis.

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