
New Hidrazides of the Acrylic Acid Derived from Phenothiazine

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Abstract

*Five new hydrazides **IIa-e** of the acrylic acids of phenothiazine and hydrazide saturated **IV** were obtained by hydrazinolysis of 4-(10H-methyl-phenothiazin-3-yl)-methin-2-phenyloxazol-5(4H)-one **I**. The products were obtained in good yields and their structures were confirmed by ¹H-NMR, ¹³C-NMR, IR spectroscopy and MS.*

Keywords: phenothiazine, oxazolone, hydrazide

Introduction

Phenothiazine derivatives possess a wide spectrum of pharmacological activities and are clinically used as tranquilizers, antiemetics antihistamines, sedatives, antipuritics, etc. [1].

The successful application in chemotherapy of the phenothiazine derivatives has determined the orientation of our research [2-7] in this field towards the synthesis of new potential pharmaceutically active products.

Previous researches on phenothiazine class showed that slight variations in its structure can lead to different biological activities [8-14]. This is why there is a growing interest in finding new phenothiazinic derivatives, which can have new or better pharmaceutical activities.

Recent studies [15-17] present the use of phenothiazine derivatives as citostatics. Calmoduline is a component of cancerous cells and the phenothiazine derivatives inhibit its biochemical activity. Mechanistic studies [1] showed that the inhibition processes are mediated by Ca²⁺ ions, which interact with the free carboxylic groups of the protein, and by the nitrogen atom of the phenothiazine derivative.

The non-proteic amino acids such as the aromatic β-amino acids and heterocyclic amino acids were recently isolated as secondary metabolites from various natural sources [18]. The phenothiazine derivatives are valuable starting materials for the preparation of heterocyclic amino acids.

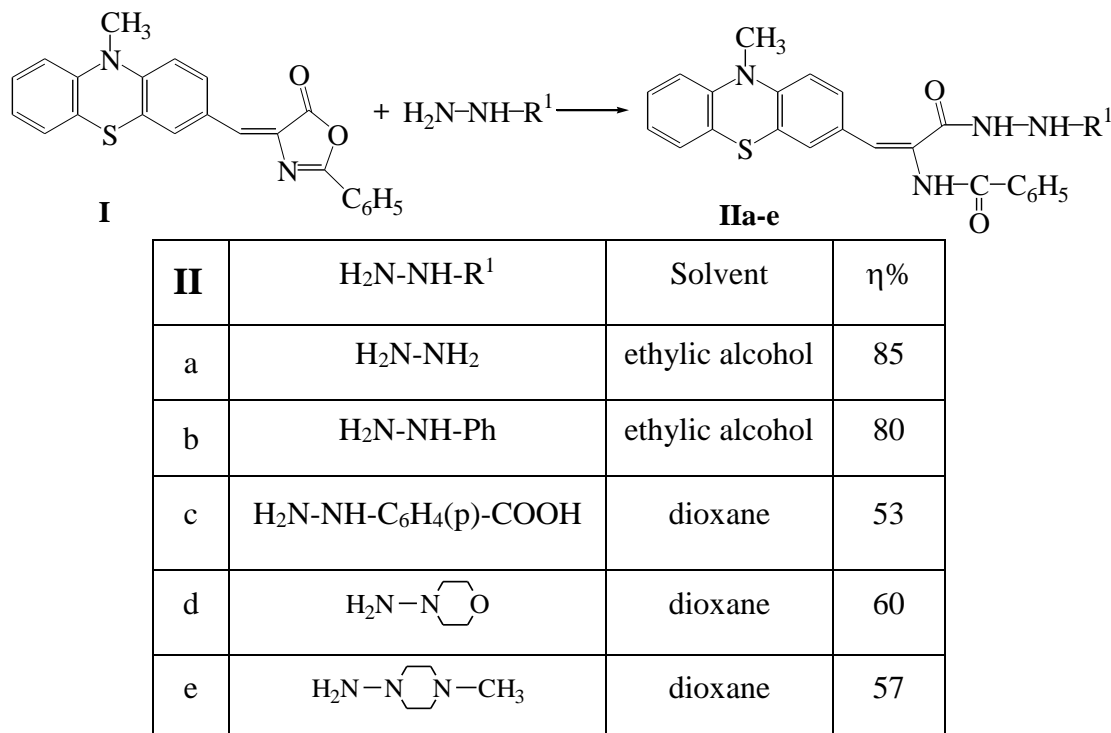
We report here the synthesis of new hydrazides of acrylic acid (**II**) using 4-(10H-methyl-phenothiazin-3-yl)-methin-2-phenyloxazol-5(4H)-one (**I**) as starting material (Scheme 1).

Results and Discussions

Unsaturated azlactones can react with nucleophiles [6, 19-21] such as water, alcohols, thiol, ammonia, amine, amino acids and hydrazine.

4-(10H-methyl-phenothiazin-3-yl)-methin-2-phenyloxazol-5(4H)-one **I** was obtained from phenothiazine according to literature data [6, 22].

The reaction of compound **I** with hydrazines such as: hydrazine hydrate, phenylhydrazine, 4-carboxy-phenylhydrazine, 4-aminomorpholine and 4-methyl-1-amino-piperazine, was the subject of our studies (Scheme 1).



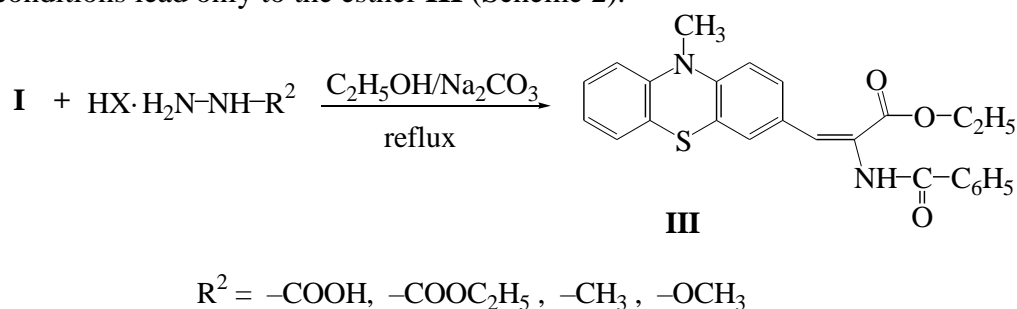
Scheme 1

The reactions occur by addition of the nucleophile to the carbon atom from the carbonyl group (C5), with simultaneous opening of the oxazolone ring.

Generally the reaction takes place with non-stoichiometric amounts of hydrazine derivatives. For phenylhydrazine and 4-carboxy-phenylhydrazine, 4 gram equivalent of the hydrazine were needed. This procedure allowed us to obtain product **II b,c** in 80% and 53% yield respectively.

In the case of 4-aminomorpholine and 4-methyl-1-amino-piperazine, 20 gramme equivalent were necessary for the completion of the reaction. The use of only 2 gramme equivalent led us to low yields and long reaction time.

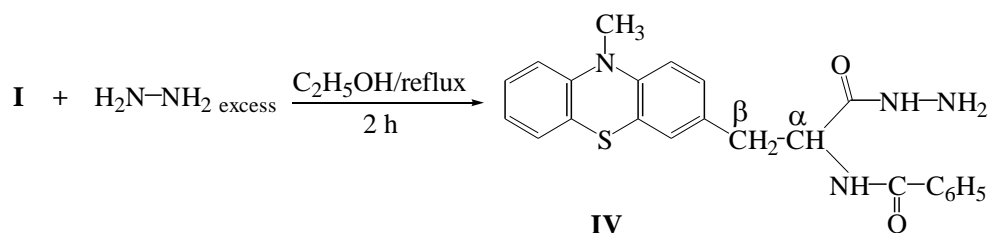
In some cases we have used hydrazine hydrochloride, Na_2CO_3 and ethanol as solvents. These conditions lead only to the ester **III** (Scheme 2).



Scheme 2

To avoid the formation the ester **III**, some reactions were carried out on dioxane with free hydrazines.

In the case of unsubstituted hydrazine we have obtained two products, depending on the reaction conditions. At room temperature, with a high excess of hydrazine hydrate (1:30), the product **IIa** was obtained. At reflux, the excess of hydrazine determines the reduction of the exocyclic double bond and the product **IV** was obtained in 54 % yield (Scheme 3):



Scheme 3

All products were purified by flash chromatography and their structure was established by chemical and spectral analyses (IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, MS).

Structure of compound **IV** was confirmed by $^1\text{H-NMR}$ and mass spectrometry. In the $^1\text{H-NMR}$ there are three aliphatic signals: singlet at 3.24 ppm corresponding to the CH_3 group of the N-phenothiazine, doublet at 2.91 ppm (βCH_2) and quartet at 4.57 ppm corresponding to the αCH . This shows that we have a saturated $\beta\text{C}-\alpha\text{C}$ bond. The mass spectrum also confirmed the proposed structure as the molecular ion M^+ appears at $m/e = 418$ and the fragment resulted from tropylic fragmentation of the heterocycle (Het-CH_2) appears at $m/e = 226$.

For the unsaturated products **IIa**, we have no aliphatic signal except for the CH_3 group of the N-phenothiazine. The proton from the double bond of the acrylic group appears (Het-CH=C-) superposed with the protons of the phenothiazine ring. The hydrogen from NH_2 of the hydrazine group gave a signal at 4.37 ppm in case **IIa** and at 4.32 ppm in case **IV**.

The IR spectra characterize the compounds **IIa-e** and **IV** as hydrazides. The string in the 1790 cm^{-1} region (typical for the carbonyl group of β, γ - unsaturated γ -lactones) disappears, being replaced by broad strings in the $1590\text{-}1680\text{ cm}^{-1}$ region, typical for the amide and hydrazide C=O groups. The vibrations of the N-H bond appear at $3100\text{-}3250\text{ cm}^{-1}$.

Materials and Methods

The melting points were determined with a MEL-TEMP II apparatus and are not corrected. The IR spectra were recorded on a SPECORD 71 spectrometer in KBr pellets. The $^1\text{H-}$ and $^{13}\text{C-NMR}$ spectra were recorded on a BRUCKER AM-300 spectrometer using DMSO-d_6 as solvent. The mass spectra were recorded by a RIBEN-10-10 spectrometer.

α -Benzoylamino- β -(10H-methyl-phenothiazin-3-yl)-acrylhydrazide (**IIa**)

2.5 mL of hydrazine hydrate (98%) were added to a suspension of 4-(10H-methyl-phenothiazin-3-yl)-methin-2-phenyloxazol-5(4H)-one **I**, 0.5 g (1.3 mmol) in 10 mL ethanol. The mixture was stirred at room temperature, for 15 min. when the reaction was completed (follow TLC). The product precipitated from the reaction mixture was filtered and further purified. The pure product was obtained as yellow needles with m.p.= $217\text{-}219^\circ\text{C}$ (lit. $208\text{-}209^\circ\text{C}$ [16]), from ethanol.

Analysis: $C_{23}H_{20}N_4O_2S$ (416); calcd: 66.34 %C, 4.8 % H, 13.46 %N, 7.69 %O, 7.69 %S; found: 64.62 %C, 5.1 %H, 14.01 %N, 7.80 %O, 8.47 %S

1H -NMR (DMSO- d_6), δ , ppm: 3.26 (s, 3H, N-CH₃); 4.37 (s, 2H, NH₂); 6.89-8.01 (m, 12H_{aromatic} and 1H_{olefinic}); 9.44 and 9.77 (s, 1H, NHCO).

^{13}C -NMR (DMSO- d_6), δ , ppm: 35.1 (CH₃); 114.3, 114.7, 121.4, 121.7, 122.7, 126.7, 127.2, 127.4, 127.8, 128.0, 128.1, 128.5, 129.4, 131.5, 133.8, 144.5, 145.3 (CH and C aromatic); 164.3 and 165.7 (2 CONH).

2-Benzoylamino-3-(10H-methyl-phenothiazin-3-yl)-propionhydrazide (IV)

5 mL of hydrazine hydrate (98%) were added to 0.5 g (1.3 mmol) oxazolone **I**, in 20 mL ethanol. The mixture was stirred at reflux for 2h and allowed to cool. After evaporation of the solvent, the solid obtained was collected and crystallized from ethanol. The pure product was obtained as white needles with m.p.= 165-167°C from ethanol.

Analysis: $C_{23}H_{22}N_4O_2S$ (418); calcd: 66.02 %C, 5.26 % H, 13.4 %N, 7.65 %O, 7.66 %S; found: 65.3 %C, 5.7 %H, 12.6 %N, 8.3 %O, 8.1 %S

1H -NMR (DMSO- d_6), δ , ppm: 2.91 (d, 2H, CH₂); 3.24 (s, 3H, N-CH₃); 4.32 (NH₂); 4.57 (q, 1H, CH); 6.81-7.80 (m, 12H_{aromatic}); 8.53 (d, 1H, NHCO); 9.26 (s, 1H, NHCO).

^{13}C -NMR (DMSO- d_6), δ , ppm: 35.0 (CH₃); 36.3 (CH₂); 53.7 (CH); 114.1, 114.4, 121.5, 121.8, 122.2, 126.6, 127.4, 127.6, 128.0, 128.3, 131.2, 132.5, 134.0, 143.5, 145.3 (CH and C aromatic); 166.1 and 170.5 (2 CONH).

Mass spectrum m/z (intensity %) M^+ = 418 (8); 213 (75); 198 (69); 226 (10).

α -Benzoylamino- β -(10H-methyl-phenothiazin-3-yl)-acryl-N-phenylhydrazide (IIb)

1 mL (5.2 mmol) of phenylhydrazine was added to 0.5 g (1.3 mmol) oxazolone **I**, in 20 mL ethanol. The mixture was stirred at reflux for 40 min, when the reaction was completed (follow TLC). The product precipitated from the reaction mixture was filtered and further purified. The pure product was obtained as yellow needles with m.p.= 237-239°C from ethanol.

Analysis: $C_{29}H_{24}N_4O_2S$ (492); calcd: 70.73 %C, 4.87 % H, 11.38 %N, 6.50 %O, 6.50 %S; found: 68.3 %C, 5.7 %H, 11.6 %N, 7.23 %O, 7.17 %S

1H -NMR (DMSO- d_6), δ , ppm: 3.29 (s, 3H, N-CH₃); 6.67-8.05 (m, 17H_{aromatic} and 1H_{olefinic}); 9.97 (s, 1H, NHCO); 10.37 (d, 1H, NHCO).

^{13}C -NMR (DMSO- d_6), δ , ppm: 35.3 (CH₃); 111.6, 113.6, 113.9, 117.4, 120.4, 120.8, 121.8, 125.8, 126.5, 126.6, 126.9, 127.2, 127.3, 127.5, 128.6, 130.6, 132.7, 143.3, 144.3, 148.2 (CH and C aromatic); 163.7 and 164.6 (2 CONH).

α -Benzoylamino- β -(10H-methyl-phenothiazin-3-yl)-acryl-N-(4-carboxyphenyl)-hydrazide (IIc)

1 g (5.2 mmol) of 4-carboxy-phenylhydrazine were added to 0.5 g (1.3 mmol) oxazolone **I**, in 20 mL dioxane. The mixture was stirred at reflux for 20 h, when the reaction was completed (follow TLC). The solvent was distilled off and the residue was chromatographed on alumina with ethyl acetate and hexane (1:1) as eluent. The pure product was obtained as yellow needles with m.p.= 200-203°C.

Analysis: $C_{30}H_{24}N_4O_4S$ (536); calcd: 67.16 %C, 4.47 % H, 10.44 %N, 11.94 %O, 5.97 %S; found: 65.8 %C, 4.7 %H, 12.6 %N, 11.3 %O, 5.6 %S

1H -NMR (DMSO- d_6), δ , ppm: 3.37 (s, 3H, N-CH₃); 6.86-8.83 (m, 16H_{aromatic} and 1H_{olefinic}); 10.14 and 10.23 (2s, 2H, 2NHCO); 12.27 (s, 1H, COOH).

^{13}C -NMR (DMSO- d_6), δ , ppm: 35.2 (CH₃); 111.1, 116.3, 119.8, 122.1, 124.1, 124.3, 127.5, 128.0, 128.4, 130.7, 131.8, 132.2, 133.0, 133.6, 139.0, 139.2, 153.3 (CH and C aromatic); 165.3 and 166.3 (2CONH); 167.3 (COOH).

α -Benzoylamino- β -(10H-methyl-phenothiazin-3-yl)-acryl-N-(morpholin)-amide (II_d).

2 mL (26 mmol) of aminomorpholine were added to 0.5 g (1.3 mmol) oxazolone **I**, in 20 mL dioxane. The mixture was stirred at reflux for 15 min. when the reaction was completed (follow TLC). The solvent was distilled off and the residue was chromatographed on alumina with chloroform and acetone (7:3) as eluent. The pure product was obtained as yellow needles with m.p.= 176-178°C.

Analysis: C₂₇H₂₇N₄O₃S (487); calcd: 66.52 %C, 5.54 % H, 11.5 %N, 9.85 %O, 6.57 %S; found: 65.78 %C, 5.34 %H, 12.01 %N, 9.50 %O, 7.37 %S

¹H-NMR (DMSO-d₆), δ , ppm: 2.83 (t, 2·2H, CH₂-N); 3.28 (s, 3H, N-CH₃); 3.62 (t, 2·2H, CH₂-O); 6.91-8.31 (m, 12H_{aromatic} and 1H_{olefinic}); 9.20 (s, 1H, NHCOPh); 9.86 (s, 1H, NHCO_{morpholine}).

¹³C-NMR (DMSO-d₆), δ , ppm: 35.1 (CH₃); 54.3 (CH₂-N); 66.0 (CH₂-O); 114.3, 114.7, 121.4, 121.7, 122.7, 126.8, 127.2, 127.8, 128.3, 128.5, 129.4, 131.6, 133.6, 144.5, 145.2 (CH and C aromatic); 163.3 and 165.6 (2 CONH).

 α -Benzoylamino- β -(10H-methyl-phenothiazin-3-yl)-acryl-N-(4-methyl-piperazinyl-1)-amide (II_e).

2 mL (26 mmol) of 1-amino-4-methyl-piperazine were added to 0.5 g (1.3 mmol) oxazolone **I**, in 20 mL dioxane. The mixture was stirred at reflux for 20 min. when the reaction was completed (follow TLC). The solvent was distilled off and the residue was chromatographed on alumina with chloroform and acetone (7:3) as eluent. The pure product was obtained as yellow needles with m.p.= 111-113°C.

Analysis: C₂₈H₂₉N₅O₂S (499); calcd: 67.2 %C, 6 % H, 14 %N, 6.4 %O, 6.4 %S; found: 66.3 %C, 5.7 %H, 13.6 %N, 7.3 %O, 7.1 %S

¹H-NMR (DMSO-d₆), δ , ppm: 2.18 (s, CH₃-N_{piperazine}); 2.33 (t, 2·2H, N(CH₂)₂ piperazine); 3.29 (s, 3H, N-CH₃); 3.40 and 3.55 (2t, 2·2H, NH-N(CH₂)₂ piperazine); 6.28-7.98 (m, 12H_{aromatic} and 1H_{olefinic}); 9.80 and 10.19 (s, 2 NHCO).

¹³C-NMR (DMSO-d₆), δ , ppm: 35.1 (CH₃); 45.6 (CH₃-N_{piperazine}); 54.2 ((CH₂)₂N_{piperazine}); 114.4, 114.7, 121.5, 121.8, 122.5, 122.6, 126.6, 127.2, 127.7, 127.8, 128.4, 128.6, 128.8, 131.8, 133.1, 144.6, 144.8 (CH and C aromatic); 165.4 and 167.2 (2 CONH).

Conclusions

The use of 4-(10H-methyl-phenothiazin-3-yl)-methin-2-phenyloxazol-5(4H)-one **I** as starting material we synthesised five new hydrazides of α -benzoylamino- β -(10H-methyl-phenothiazin-3-yl)-acrylic acid **IIa-e** and 2-benzoylamino-3-(10H-methyl-phenothiazin-3-yl)-propionhydrazide **IV**.

New complex components with Fe(III), Cu(II), Cr(III) and Pd(II) were obtained using hydrazide **IIb** as ligand [23].

Hydrazide **IV** was utilized as ligand (L) [24], yielding a new series of Cu(II) complex components with the general formula [CuL(OH₂)₂Cl₂], [Cu₂L(OH₂)₂Cl₄], [Cu₂L₂(OH₂)₂Ac₂]Ac₂ and [Cu₂L(OH₂)₂Ac₄].

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