

SYNTHESIS OF NEW THIOUREAS DERIVED FROM 2-(3,4-DIMETHYL-PHENOXYMETHYL)- AND 2-(2,3-DIMETHYL-PHENOXYMETHYL)-BENZOIC ACID WITH POTENTIAL ANTIMICROBIAL ACTIVITY

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Abstract

This paper presents the continuation of previous research regarding the synthesis of new thioureas derived from 2-(3,4-dimethyl-phenoxyethyl)-benzoic acid and also the new synthesis of thioureas derived from 2-(2,3-dimethyl-phenoxyethyl)-benzoic acid prepared by adding various primary aromatic amines to 2-(3,4-dimethyl-phenoxyethyl)-benzoyl-isothiocyanate respectively to the 2-(2,3-dimethyl-phenoxyethyl)-benzoyl-isothiocyanate. We confirmed the chemical structure and the purity of the original compounds by ¹H-NMR, ¹³C- NMR spectral data, IR spectra and using elemental analysis.

Rezumat

Prezenta lucrare redă sinteza unor noi tioureide ale acidului 2-(3,4-dimetil-fenoximetil)-benzoic și ale acidului 2-(2,3-dimetil-fenoximetil)-benzoic, obținute prin adăugarea diferitelor amine primare aromatice la 2-(3,4-dimetil-fenoximetil)-benzoyl-izotiocianat, respectiv la 2-(2,3-dimetil-fenoximetil)-benzoyl-izotiocianat. Structurile chimice și puritățile compușilor originali au fost confirmate prin analiză spectrală ¹H-RMN, ¹³C-RMN, spectre IR și folosind analiza elementală.

Keywords: Thioureas, 2-(3,4-dimethyl-phenoxyethyl)-benzoic acid, 2-(2,3-dimethyl-phenoxyethyl)-benzoic acid

Introduction

Recently, thiourea derivatives are increasingly investigated compounds for their vast potential therapeutic applications as antimicrobial, antineoplastic, anticonvulsant and analgesic agents. Furthermore, thiourea core may represent an important scaffold for the synthesis of numerous chemical compounds with potential clinical applications [1-7].

One of the most important concern of modern pharmaceutical and medical approach is the concept of antimicrobial multidrug resistance which leads, towards the end of those decade to the urgent need to expand the arsenal of antimicrobial agents.

This paper presents newly pharmaceutical research concerning

compounds of new versatile thiourea derivatives with potential antimicrobial activity. The antimicrobial activity of thiourea derivatives was recently shown in literature [8-10] and the selection of this class for our study was prompted by its unique chemical and biological activities which have lately gained great attention within the scientific chemical and pharmaceutical research.

Materials and Methods

The new thioureas (coded **4** and **8**) were obtained by addition of various primary aromatic amines to isothiocyanates coded **3**, respectively **7**. The isothiocyanates **3** and **7** were obtained from 2-(3,4-dimethyl-phenoxy)methyl)-benzoic acid (**1**) and 2-(2,3-dimethyl-phenoxy)methyl)-benzoic acid (**5**) via acid chlorides **2**, respectively **6**. The general synthesis pathway of the new compounds is depicted in Figure 1 and Figure 2.

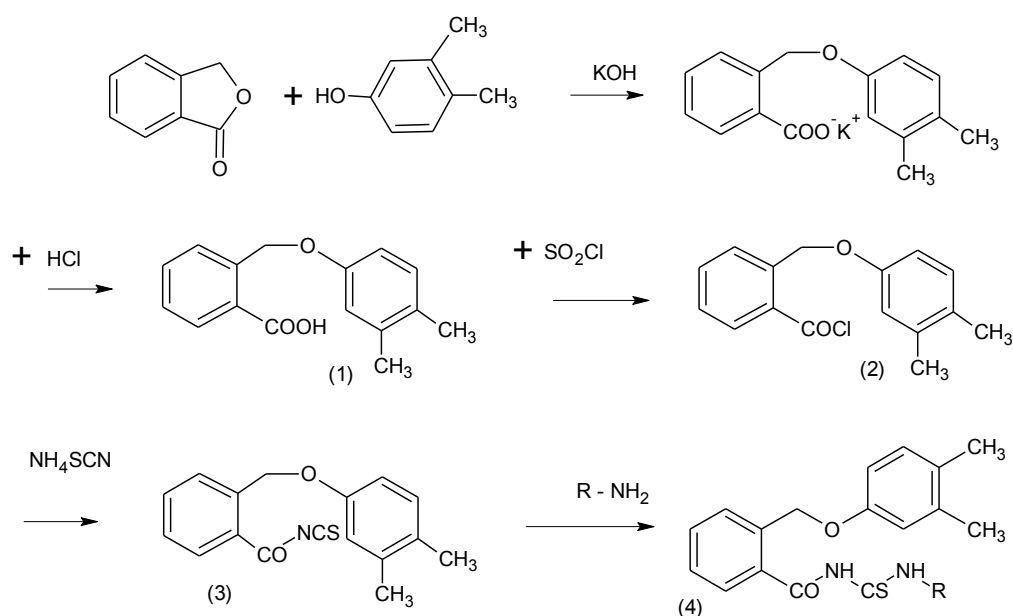
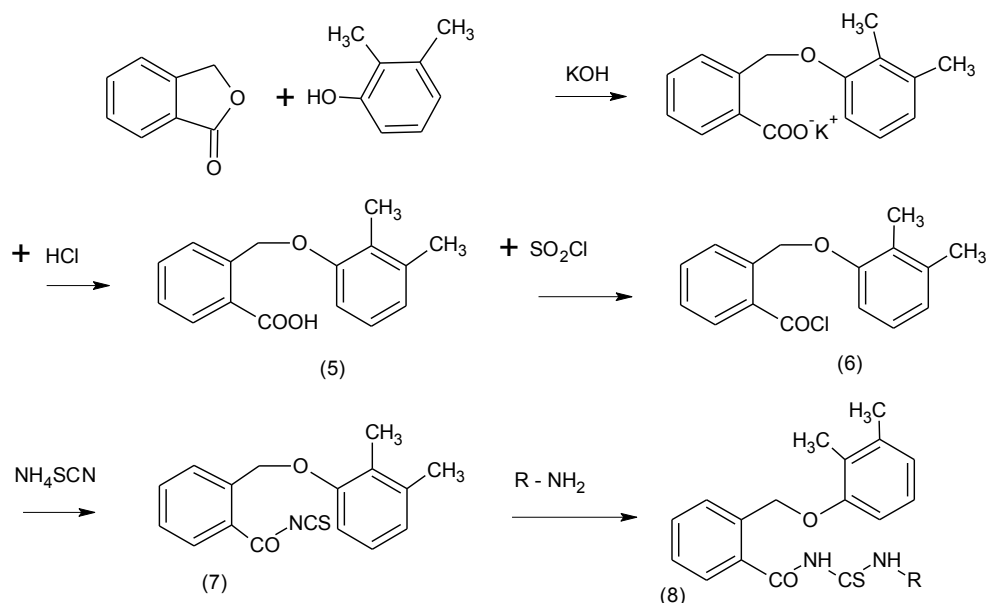


Figure 1.

The synthesis pathway of the thioureas derived from 2-(3,4-dimethyl-phenoxy)methyl)-benzoic acid

**Figure 2**

The synthesis pathway of the thioureas derived from 2-(2,3-dimethylphenoxy)methyl-benzoic acid

Experimental part

Synthesis of thioureas derived from 2-(3,4-dimethyl-phenoxy)methyl-benzoic acid. General procedure.

The synthesis was accomplished according to the previously described procedure starting from phthalide and 3,4-dimethylphenol [14].

Synthesis of thioureas derived from 2-(2,3-dimethyl-phenoxy)methyl-benzoic acid. General procedure.

2-(2,3-dimethyl-phenoxy)methyl-benzoic acid

12.22g (0.1 mol) 2,3-dimethylphenol (C₈H₁₀O) were mixed with 60mL xylene (o,m,p) and subsequently 6.17g (0.11 mol) potassium hydroxide were added. The reaction mixture was refluxed until the water was fully removed; 13.41g (0.1 mol) phthalide were added and the mixture was refluxed for 2.5 hours. After cooling, a fully compact compound was obtained, which was dissolved in 10% potassium hydroxide solution. The solution was diluted with water, the aqueous layer was separated and

afterwards acidulated with 1M hydrochloric acid solution until pH 3, when it could be observed the total precipitation of the 2-(2,3-dimethyl-phenoxyethyl)-benzoic acid. The resulting crude product was recrystallized from toluene. After a second purification using the same solvent there were obtained 35.5g acid with melting temperature 184-185°C.

2-(3,4-dimethyl-phenoxyethyl)-benzoyl chloride

26.5g 2-(2,3-dimethyl-phenoxyethyl)-benzoic acid (0.1 mol), 70mL 1,2-dichloroethane (anhydrous over calcium chloride) and 23.8g (0.2 mol; 14.6 mL) thionyl chloride were placed in a round-bottom flask; the reaction mixture was refluxed for 4 hours. The solvent and the thionyl chloride excess were removed under reduced pressure. After ice cooling, the acid chloride crystallized and could be used in crude status for the next step of the synthesis.

The new thiourea synthesis. General procedure

To a solution of ammonium thiocyanate (0.01 mol) in 15 mL dry acetone it was added a solution of 2-(2,3-dimethyl-phenoxyethyl)-benzoyl chloride (0.01 mol) in 20 mL dry acetone. The reaction mixture was refluxed for 30 minutes. After cooling, 0.01 mol freshly distilled primary aromatic amine in dry acetone (5mL) was added and the mixture was refluxed for one hour. The reaction mixture was poured into water, after cooling, and afterwards separated by filtration.

Results and Discussion

We obtained 13 thioureas derived from 2-(3,4-dimethyl-phenoxyethyl)-benzoic acid (Table I) and 22 thioureas derived from 2-(2,3-dimethyl-phenoxyethyl)-benzoic acid (Table II). The molecular structures of the original thioureas were confirmed by elemental analysis and using IR ¹H-NMR, and ¹³C NMR spectroscopy.

The melting points were recorded with an Electrothermal 9100 apparatus and the presented values were uncorrected.

FT-IR spectra were collected using a JASCO 4200 spectrometer equipped with a Specac Golden Gate attenuated total reflectance (ATR) device, using a resolution of 4 cm⁻¹ and an accumulation of 60 spectra in the 4000-600 cm⁻¹ wavenumbers interval. The ¹H-NMR spectra were obtained at 300 MHz and ¹³C-NMR spectra were recorded at 75.076 MHz using a Varian Gemini 300 BB apparatus in DMSO-d₆ and tetramethylsilane as

internal standard. The ^{13}C -NMR spectra values for thioureas **4** are given in table III. Other results to confirm the structure will be published in subsequent papers.

Table I
Characterization data of the new thioureas (**4**)

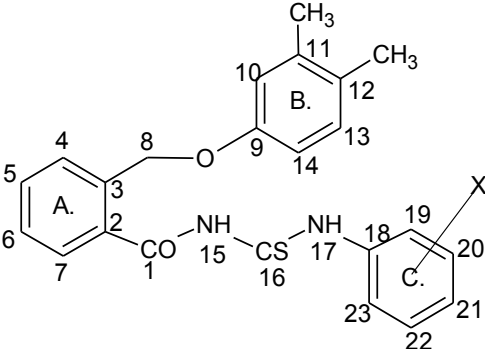
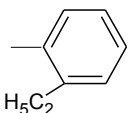
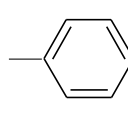
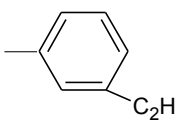
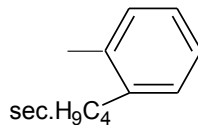
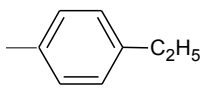
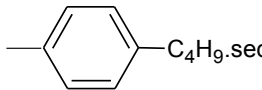
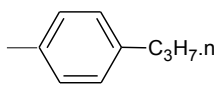
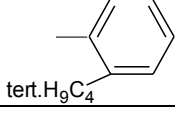
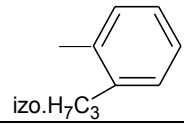
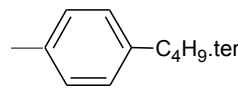
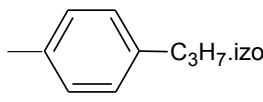
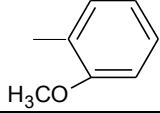
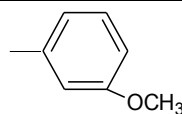
					
Compound	Ar-X	M.p.(°C)	compound	Ar-X	M.p.(°C)
DCA12		125	DCA19		89
DCA13		133-134	DCA20		98
DCA14		167-168	DCA21		114-115
DCA16		229	DCA22		123-124
DCA17		108	DCA23		155
DCA18		131-133	DCA24		123-124
			DCA25		138

Table II
Characterization data of the new thioureas (**8**)

compound	Ar-X	M.p.(°C)	compound	Ar-X	M.p.(°C)
DCB1		132-133	DCB12		109.5
DCB2		98	DCB13		115.5
DCB3		109-110	DCB14		150-152
DCB4		161-162	DCB15		109.5
DCB5		129-130	DCB16		114
DCB6		184-185	DCB17		123-124
DCB7		164-165	DCB18		113-115

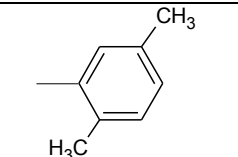
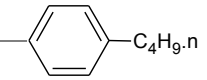
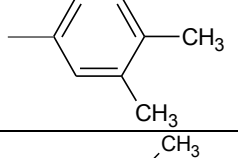
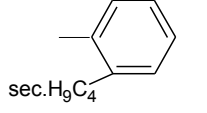
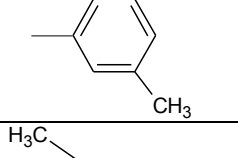
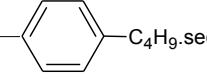
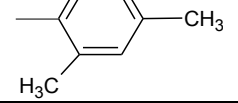
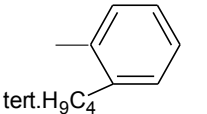
DCB8		159-160	DCB19		79
DCB9		133-134	DCB20		99
DCB10		142-143	DCB21		88
DCB11		178.5	DCB22		66

Table III

¹³C NMR data for the new thioureas (4)

Chemical data for the new thioureas (7)

DCA	X	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
12	19-Et	170.53	133.60	137.25	128.68	130.89	127.81	128.45	67.51	156.37	116.11	135.73	128.61
13	20-Et	170.34	133.41	137.23	128.39	130.88	128.31	128.44	67.51	156.36	116.18	135.83	128.43
14	21-Et	170.25	133.40	137.25	128.41	130.89	128.31	128.31	87.46	156.33	116.20	135.83	128.45
16	21-n.Pr	170.29	133.44	137.21	128.42	130.92	127.71	128.34	67.50	156.38	116.24	138.87	128.43
17	19-izo.Pr	170.37	133.55	137.19	128.63	130.87	127.77	128.42	67.48	156.32	116.02	135.69	128.39
18	21-izo.Pr	170.29	133.43	137.29	128.45	130.93	127.70	128.35	67.49	156.37	116.24	135.88	128.45
19	21-n.Bu	170.19	133.38	137.23	128.32	130.89	127.66	128.38	67.48	156.34	116.21	135.84	128.44
20	19-sec.Bu	170.64	133.63	137.30	128.48	131.00	127.65	128.53	67.54	156.42	116.07	135.96	128.48
21	21-sec.Bu	170.31	133.45	137.28	128.43	130.91	127.71	128.35	67.51	156.38	116.25	135.87	128.47
22	19-tert.Bu	170.80	133.54	137.27	128.93	131.10	127.95	128.59	67.43	156.40	116.22	135.75	128.51
23	21-tert.Bu	170.26	133.45	137.29	128.44	130.92	127.71	128.34	67.48	156.35	116.23	135.30	128.45
24	19-OMe	170.15	133.51	137.15	128.42	130.84	127.71	128.44	67.59	156.28	116.25	135.70	127.71
25	20-OMe	170.25	133.39	137.29	128.43	130.96	127.73	128.50	67.50	16.36	116.05	135.87	128.50

DCA	X	C13	C14	C16	C18	C19	C20	C21	C22	C23	11Me	12Me	
12	19-Et	130.13	111.46	180.32	137.25	138.85	128.45	127.81	127.24	125.99	19.65	18.44	23.91 -CH ₂ -
													14.21 -CH ₃
13	20-Et	130.10	111.51	178.81	137.23	123.32	144.32	125.68	127.68	121.44	19.58	18.39	27.99 -CH ₂ -
													15.38 -CH ₃
14	21-Et	130.10	111.50	178.82	137.25	124.11	127.82	141.85	127.82	124.11	19.59	18.39	27.69 -CH ₂ -
													15.50 -CH ₃
16	21-n.Pr	130.13	111.51	187.76	135.55	123.95	128.42	140.24	128.42	123.95	19.61	18.42	13.61 -CH ₃
													24.02 -CH ₂ -
													36.76 -CH ₂ -
17	19-izo.Pr	130.11	111.51	180.54	135.44	143.58	130.87	125.79	128.63	125.70	19.61	18.38	27.78 $\begin{array}{c} \\ \text{-CH} \\ \end{array}$
													22.84 -CH ₃
18	21-izo.Pr	130.13	111.52	178.82	135.58	124.09	126.39	146.46	126.39	124.09	19.61	18.42	33.05 $\begin{array}{c} \\ \text{-CH} \\ \end{array}$
													23.83 -CH ₃
19	21-n.Bu	130.09	111.47	178.66	135.84	123.88	128.38	140.41	127.66	123.88	19.55	18.36	13.72 -CH ₃
													21.68 -CH ₂ -
													34.31 -CH ₂ -
													33.02 -CH ₂ -
20	19-sec.Bu	130.21	111.58	180.79	135.79	142.53	130.21	126.31	127.90	125.84	19.73	18.50	18.50 -CH ₃
													19.73 $\begin{array}{c} \\ \text{-CH} \\ \end{array}$
													20.83 -CH ₂ -
21	21-sec.Bu	130.12	111.49	178.66	135.61	123.91	126.97	145.20	126.97	123.91	19.59	18.41	18.44 -CH ₃
													19.60 $\begin{array}{c} \\ \text{-CH} \\ \end{array}$
													21.67 -CH ₂ -
22	19-tert.Bu	130.23	111.57	180.87	135.74	145.15	131.11	126.73	130.99	126.31	19.75	18.49	30.43 -CH ₃
													34.77 $\begin{array}{c} \\ \text{-C-} \\ \end{array}$
23	21-tert.Bu	130.13	111.52	178.75	135.87	123.70	125.31	148.67	125.31	123.70	19.60	18.41	31.11 -CH ₃
													34.29 $\begin{array}{c} \\ \text{-C-} \\ \end{array}$
24	19-OMe	130.02	111.57	177.65	135.70	150.44	119.67	126.44	128.44	122.87	19.47	18.34	55.93
25	20-OMe	130.12	111.51	178.53	135.87	109.52	159.30	111.76	129.44	116.24	19.59	18.40	55.23

Conclusions

This paper refers to a method of synthesizing new compounds with antimicrobial activity and low toxicity. The present work is part of the world's concern of obtaining new antimicrobial agents with maximum efficacy and low toxicity, especially strains resistant to current antibiotics. We have synthesized 13 new thioureas derived from 2-(3,4-dimethyl-phenoxy-methyl)-benzoic acid and 22 new thioureas derived from 2-(2,3-dimethyl-phenoxy-methyl)-benzoic acid. The new compounds were characterized by their melting points and spectral analysis. Other results will be published in subsequent papers.

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