

# New Thioureides of the 2-(3,4-dimethylphenyl-oximethyl)-benzoic Acid with Potential Antimicrobial Activity. I.

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*This paper's purpose is to present the synthesis of new thioureides of the 2-(3,4-dimethylphenyl-oximethyl)-benzoic acid, prepared by adding various primary aromatic amines to the 3,4-phenyl-oximethyl-benzoyl-isotiocyanate. We confirmed the chemical structure and the purity of the original compounds by <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR spectra and using elemental analysis.*

**Keywords:** Thioureides, 2-(3,4-dimethyl-phenyl-oximethyl)-benzoic acid, tiourea derivatives

This paper represents further work concerning the thioureides class [1-7] and is based on the antimicrobial activity discovered in several thiourea derivatives series [8-10]. Also many thioureides structures show antiseptic, antiinfective, anthelmintic, diuretic, antidiabetic, tuberculostatic, insecticide, sedative or antidepressant activity, facts that are extensively stated in recent literature [11-13].

## Experimental part

The synthesis is based on the standard condensation from 3,4-fenil-oximetil-benzoil-isotiocyanate(3) and several aromatic amines, using anhydrous acetone as a reaction environment. The isotiocyanate, was prepared from the reaction between the acid chloride(2) and the ammonium tiocyanate; for the next step of the synthesis it was not necessary to be isolated. The chlorination method was used for obtaining the acid chloride(2) using a carboxylic acid and thionyl chloride in excess (1:1,3 molar ratio). These reactions are explained in scheme 1.

## The general synthesis method for the new tioureides of the 2-(3,4-dimethylphenyl-oximethyl)-benzoic acid

12.22g (0.1 moles) of 3,4-dimethyl-phenol (C<sub>8</sub>H<sub>10</sub>O) were mixed with 60mL xylene (ortho, metha, para) and then 6.17g (0.11 moles) potassium hydroxide were added. The reaction mixture is warmed up until the water is fully

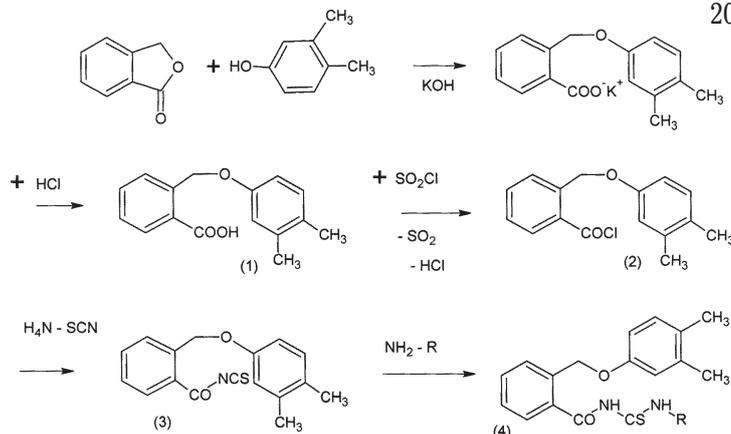
removed. Then, 13.41g (0.1 moles) ftalida were added and the reaction continued for 2.5 h. After cooling, it was obtained a fully compact compound, which was dissolved in KOH 10%, while gently heating the mixture. Then, the solution was diluted with water. The aqueous layer was separated and then acidulated with hydrogen chloride 1M till pH 3, when it can be observed the total precipitation of the 2-(3,4-dimethyl-phenyl-oximethyl)-benzoic acid. The precipitate was separated by filtration and after drying, it was purified using isopropanol and wather (1:1) aprox 1 L. There were obtained 38.5g with melting temperature 150-151°C. After a second recrystallisation resulted 35 g of light yellow needle like crystals, with melting temperature of 151°C.

## 2-(3,4-dimethyl-phenyl-oximethyl)-benzoic choride

26.5g of 2-(3,4-dimethylphenyl-oximethyl)-benzoic acid (0,1 moles) are suspended over 75mL of 1,2-dichlorethane (anhydridized over calcium chloride), 23.8g (0.2 moles; 14.6 mL) thionyl chloride were then added; the reaction mixture was heated to reflux till the sulfur dioxide and the hydrogen chloride emissions ceased (aprox. 4h). The solvent and the thionyl chloride exces were removed under vacuum. After ice cooling the acid chloride cristallized and could be used as such, without purification for the next step of the synthesis.

## New tioureides

The acid chloride (2.75 g; 0.01 moles) was dissolved in 20 mL anhydrous acetone along with 0.001 moles (0.76 g)



Scheme 1

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DCA	X	H-4	H-5	H-6	H-7	H-8	H-10	H-13	H-14	H-15
1	H		7.45-7.63 (7.5)			5.25s	6.79d (2.5)	7.01d (8.2)	6.72dd (8.2,2.5)	11.87 s
2	19-Me		7.45-7.62 (7.5)			5.25s	6.79d (2.8)	7.02d (8.2)	6.72dd (8.2,2.8)	11.90 s
3	20-Me		7.45-7.61 (7.5)			5.24s	6.78d (2.5)	7.01d (8.2)	6.72dd (8.2,2.5)	11.85 s
4	21-Me		7.45-7.63 (7.5)			5.24s	6.78d (2.5)	7.00d (8.0)	6.72dd (8.0,2.5)	11.81 s
5	19-Me 21-Me		7.45-7.61 (7.4)			5.23s	6.78d (2.6)	7.00d (8.1)	6.72dd (8.0,2.6)	11.85 s
6	19-Me 23-Me	7.58dd (1.1,1.7)	7.55tl (7.7,1.5)	7.46 (2.1,7.7)	7.62dl (7.7)	5.24s	6.79d (2.8)	7.01d (8.1)	6.71dd (8.1,2.8)	11.74 s
7	19-Me 20-Me	7.47-7.58 m		7.46td (7.5,2.4)	7.62d (7.5)	5.24s	6.79d (2.6)	7.01d (8.3)	6.72dd (8.3,2.6)	11.86 s
8	19-Me 22-Me	7.47-7.58 m		7.46dd (7.6,2.4)	7.62d (7.4)	5.24s	6.79d (2.5)	7.14d (8.4)	6.72dd (8.4,2.5)	11.88 s
9	20-Me 21-Me	7.47-7.58 m		7.45m (7.3,1.8)	7.60dl (7.3)	5.24s	6.79d (2.5)	7.01d (8.2)	6.72dd (8.2,2.5)	11.81 s
10	20-Me 22-Me	7.46-7.58 m			7.61dl (7.4)	5.23s	6.79d (2.6)	7.00d (8.3)	6.72dd (8.3,2.6)	11.80 s
11	19-Me 21-Me 23-Me	7.58- 7.62				5.25s	6.79d	7.01d	6.71dd	11.68 s

Table 1

DCA	X	H-17	H-19	H-20	H-21	H-22	H-23	11-Me	12-Me		
1	H	12.48 s	7.45 7.67	7.14tl (7.2)	7.26t (7.2)l	7.41tl (7.2)	7.45- 7.65m	2.11s	2.11s		
2	19-Me	12.18 s	-	7.20m	-	7.29m	7.60m	2.14s	2.12s	2.12s	
3	20-Me	12.45 s	7.33sl	-	7.07dl (7.7)	7.29t (7.7)	7.45dd (7.7,2.5)	2.11s	2.11s	2.31s	
4	21-Me	12.41 s	7.21d (8.3)	7.46d (8.3)	-	7.46d (8.3)	7.21d (8.3)	2.11s	2.11s	2.31s	
5	19-Me 21-Me	12.07 s	-	7.07sl	-	7.03dl (7.5)	7.38d (7.5)	2.11s	2.11s	2.28s	2.09s
6	19-Me 23-Me	11.86 s	-	7.10m	7.10m	7.10m	-	2.12s	2.12s	2.16s	2.13s
7	19-Me 20-Me	12.08 s	-	-	7.11d (4.8)	7.22dd (4.9,4.8)	7.11d (4.8)	2.13s	2.12s	2.26s	2.02s
8	19-Me 22-Me	12.12 s	-	7.05d (8.5)	7.98d (8.5)	-	7.31sl	2.13s	2.12s	2.27s	2.09s
9	20-Me 21-Me	12.40 s	7.26d (2.0)	-	-	7.15d (8.0)	7.35dd (8.0,2.0)	2.12s	2.12s	2.21s	2.09s
10	20-Me 22-Me	12.38 s	7.19sl	-	6.90sl	-	7.19sl	2.11s	2.11s	2.27s	2.27s
11	19-Me 21-Me 23-Me	11.48 s	-	7.90s	-	6.90 s	-	2.16s	2.13s	2.24s	2.08 (2s)

ammonium thiocyanate. This mixture was heated to reflux for 30 min.

The next step was the standard condensation from 3,4-fenil-oximetil-benzoil-isotiocyanate and several aromatic amines, using anhydrous acetone as a reaction medium. This mixture is heated to reflux for another hour.

After cooling, the reaction mixture is poured over a mixture of water and ice. The product was isolated by filtration.

#### Analytic tests

We obtained 11 new compounds: thioureides of 2-(3,4-dimethylphenyl-oximethyl)-benzoic acid. The molecular structure of the original thioureides was confirmed by elemental analysis and using IR and NMR spectroscopy. The obtained thioureides will be further investigated for their antimicrobial activity [14,15]

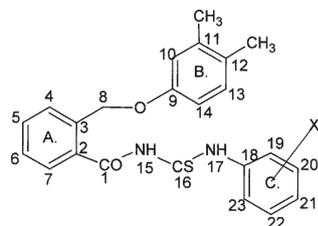
The melting points were recorded with Electrothermal 9100 apparatus and are uncorrected.

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<sup>-1</sup> and an accumulation of 60 spectra in the 4000-600 cm<sup>-1</sup> wavenumbers interval. The <sup>1</sup>H-NMR spectra were obtained at 300 MHz and <sup>13</sup>C-NMR spectra were recorded at 75.076 MHz using a Varian Gemini 300 BB apparatus in DMSO-d<sub>6</sub> and tetramethylsilane as internal standard.

The presence of the amidic -NHCO group is confirmed by the stretching vibration frequency, (C=O) ∈ 1675-1690 cm<sup>-1</sup> and by the stretching vibration, (N-H) in the range of 3160-3250 cm<sup>-1</sup>, overlapping the one of the thioureid group positioned at lower frequency due to the intramolecular hydrogen bond (also confirmed by the <sup>1</sup>H-NMR spectra). The deformation is constant between 1460-1560 cm<sup>-1</sup>, and is revealed as a relatively intense strip. The etheric bond for the semi-aromatic ethers is found through the two symmetric and antisymmetric valence vibrations ranging from 1150-1160 cm<sup>-1</sup> and 1240-1260 cm<sup>-1</sup> respectively. The aromatic rings are characterised by the stretching vibrations in the 3020-3080 cm<sup>-1</sup> range, as well as the deforming ones, found outside of the hydrogen atoms flux in the 690-870 cm<sup>-1</sup> range; They form an area that is hard to discriminate, with an extensive number of strips for the three different substitutions of the three benzene rings. The methyl groups are confirmed by the symmetric vibration strips in the 2840-2860 cm<sup>-1</sup> range and also by the deforming ones in the 1320-1480 cm<sup>-1</sup> range.

#### <sup>1</sup>H-NMR Spectra

The thioureids' spectral parameters are summarized in table 1. The H4-H7 protons within the ortho-substituted A ring show a complex signal in the 7.4-7.7 ppm range, that is generally unresolved. The 1,3,4 trisubstituted ring B displays screened signals for the H10 and H14 protons in



compound	Ar-X	M.p.(°C)	compound	Ar-X(°C)	M.p.(°C)
DCA1		120	DCA6		188-189
DCA2		121-122	DCA7		157-158
DCA3		159-160	DCA8		148-149
DCA4		157.5-158.5	DCA9		131
DCA5		120-121	DCA10		119
DCA11		163-165			

Scheme 2

the range of  $\delta \in 6.71$  to  $6.80$  ppm, with doublet multiplicity with  $J_{10,14}$  ranging between 2.5-2.8 Hz (H-10) and also a doublet of doublets with  $J$  between 8.0 to 8.4 Hz ( $J_{13,14}$  and  $J_{10,14}$ ). Screening is mainly caused by the oxygen atom and partially by the methyl groups. The H19-H23 protons display signals that sometimes overlap with other signals, depending on the nature and position of the X substituents (methyl groups). The H8 methylene group shows a singlet that is constantly noticeable at about 5.25 ppm. Methyl substituents are recognized as a singlet signals through the  $\delta \in 2.10 - 2.20$  ppm. The NH groups, H15 and H17 protons appear at  $\delta \in 11.8$  to  $11.9$  ppm and  $\delta \in 12.0$  to  $12.5$  ppm, respectively.

The distinction is given by the intramolecular hydrogen bond between the 17-th proton and the amidic group, with direct consequences in its deshielding.

#### <sup>13</sup>C-NMR Spectra

The linkage between the three aromatic rings (A-C) appear in the following ranges: C-8 : 67,46-67,57 ppm ; C-1 : 170,06-170,39 ppm ; C-16 : 178,70-180,00 ppm

Ring B shows the most deshield signal for C9 at about 156.5 ppm and the most screened ones are C14 at around 111.5 ppm and C10 at 116.10 to 116.30 ppm, in the ortho position to the oxygen. The quaternary atoms, C11 (135.0 to 136.5 ppm) and C12 (133.5 ppm), appear differentiated by about 2 ppm, and are also influenced by the oxygen

DCA	X	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
1	H	170.33	133.41	137.86	128.34	130.95	127.71	128.45	67.49	156.38	116.23	135.89	128.49
2	19-Me	170.38	133.18	137.26	128.51	130.87	127.77	128.46	67.51	156.36	116.17	136.79	128.52
3	20-Me	170.37	133.43	138.02	128.41	130.91	127.71	128.41	67.52	156.38	116.21	135.84	128.34
4	21-Me	170.29	133.41	137.27	128.32	130.91	127.69	128.47	67.48	156.36	116.22	135.86	128.43
5	19-Me 21-Me	170.35	133.58	137.31	128.48	130.92	127.83	128.58	67.57	156.39	116.22	135.78	128.52
6	19-Me 23-Me	170.06	133.64	137.27	128.58	130.96	127.88	128.83	67.47	156.32	116.20	135.74	128.48
7	19-Me 20-Me	170.36	133.59	137.32	128.58	130.93	127.84	128.53	67.56	156.38	116.23	135.78	128.5
8	19-Me 22-Me	170.38	133.61	137.23	128.40	130.82	127.77	128.51	67.54	156.36	116.13	135.71	128.42
9	20-Me 21-Me	170.32	133.44	137.25	128.44	130.88	127.69	128.33	67.5	156.36	116.20	135.82	128.45
10	20-Me 22-Me	170.39	133.45	137.64	128.38	130.88	127.71	128.38	67.53	156.38	116.19	135.80	128.38
11	19-Me 21-Me 23-Me	170.04	133.53	137.21	128.74	130.88	127.81	128.53	67.40	156.27	116.15	135.69	128.41

Table 2

DCA	X	C13	C14	C16	C18	C19	C20	C21	C22	C23	11Me	12Me	
1	H	130.14	111.5	178.99	137.29	124.16	128.61	126.24	128.61	124.16	19.63	18.43	-
2	19-Me	130.11	111.45	179.83	136.79	133.57	130.35	128.46	126.31	126.01	19.62	18.42	17.41
3	20-Me	130.13	111.49	178.85	135.85	124.51	137.26	128.34	128.41	121.22	19.60	18.42	20.90
4	21-Me	130.12	111.52	178.88	135.30	124.06	129.03	135.58	129.03	124.09	19.63	18.42	20.59
5	19-Me 21-Me	130.16	111.52	179.76	136.25	132.97	130.92	133.65	126.61	126.22	19.68	18.46	20.61 17.38
6	19-Me 23-Me	130.15	111.57	179.99	136.12	135.12	127.88	127.44	127.88	135.12	19.71	18.47	17.76 17.76
7	19-Me 20-Me	130.18	111.53	179.98	133.65	132.32	135.79	125.39	124.63	128.58	19.69	18.46	20.02 13.78
8	19-Me 22-Me	130.16	111.48	179.78	138.13	135.12	130.82	127.63	126.54	126.70	19.61	18.41	20.51 17.02
9	20-Me 21-Me	130.12	111.52	178.76	135.20	125.07	135.47	135.20	129.44	121.50	19.61	18.62	19.53 18.41
10	20-Me 22-Me	130.12	111.48	178.71	138.01	121.64	137.76	127.71	137.76	121.64	19.58	18.40	20.83 19.50
11	19-Me 21-Me 23-Me	130.09	111.51	180.35	137.21	134.67	128.44	134.67	128.44	134.67	19.66	18.42	20.54 17.64 17.64

Table 2

atom. The assignments of the carbon atoms in rings A and C have resulted from bidimensional  $^{13}\text{C}$ -H connection experiments  $^{13}\text{C}$ -H(HETCOR) and from calculations using substituent increments.

The  $^{13}\text{C}$ -NMR spectra are given in table 2.

### References

- MISSIR A.V., CHIRITA I.C., LIMBAN C., Farmacia, XXXIX, no.1-4, 1991, p.61-65
- DESAI, P.H. et al., J Int. Chem. **61**, no. 1, 1989, p. 19
- KAPOOR, K.K. et al., J Indian Chem Soc. **68**, no.2,1991, p.19
- MISSIR A.V., CHIRITA I.C., LIMBAN C., MORUSCIAG L., Farmacia, XL, no.1-4,1992, p.9-13
- MISSIR A.V., CHIRITA I.C., LIMBAN C., Farmacia, XLI, no.1-2, 1993, p.33-36
- MORUSCIAG, L., MISSIR, A.V., ILIE, C., GUTA, R., NANAU-ANDREESCU, D., CAPROIU, M.T., Rev. Chim. (Bucharest), **60**, no.8, 2009, p.805
- LIMBAN, C., MISSIR, A.V., CHIRITA, I.C., NITULESCU, G.M., ILIE, C., CAPROIU, M.T., Rev. Chim. (Bucharest), **60**, no.7, 2009, p.657
- LIMBAN C., GRUMEZESCU A.M., SAVIUC C., VOICU G., CHIFIRIUC C., International Journal of Molecular Sciences, 13, 2012, pag. 12584-12597
- LIMBAN C., GRUMEZESCU A.M., CHIREA M., MATEI L., CHIFIRIUC C., Current Organic Chemistry, 17, no.2, 2013, p. 162-175
- LIMBAN C., MARUNTESCU L., CHIFIRIUC C., Molecules, 16, 2011, p. 7593-7607
- \*\*\* The Merck Index, ed. XIII, Whitehouse Station, New Jersey, 2001
- \*\*\* USAN and the USP dictionary of drug names, Ed. USP, Rockville, 1989
- \*\*\*Pharmazeutische Stoffliste, Ed. ABDATA, Eschborn/Taunus, 1998
- ZECHERU, T; ROTARIU, T; RUSEN, E; MARCULESCU, B; MICULESCU, F; ALEXANDRESCU, L; ANTONIAC, I; STANCU, IC., Journal of materials science-materials in medicine, 21 (10), pp. 2793-2804, 2010.
- STANCU I.C, FILMON R, CINCU C, MARCULESCU B, ZAHARIA C, TOURMEN Y, BASLÉ MF, CHAPPARD D., Biomaterials, 25(2), 205-213, 2004

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