

Terephthaldiamides Class Synthesis. III. Synthesis of Some N-monosubstituted Terephthaldiamides

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Introduction: The aim of this experimental paper was the synthesis of some terephthaldiamides, with potential analgesic action.

Material and methods: The reaction consists of acylation of some primary amines, ethanolamine, allylamine, benzylamine, aniline and orthotoluidine, with terephthaloyl chloride. The purified synthesis products were analysed by thin-layer chromatography, mass, IR and UV spectrometry.

Results: The molecular structure of the obtained N-monosubstituted terephthaldiamides was confirmed by spectral analysis.

Conclusions: Five N-monosubstituted terephthaldiamides were synthesized in good yields by condensation of terephthaloyl chloride with primary amines.

Keywords: terephthaldiamides, synthesis, primary amines

Introduction

This research is part of our previous study, regarding the possible analgesic potential of the several terephthalic acid amides. Previous researches have been focused on synthesis of new compounds with analgesic action but without the possibility to induce dependence [1–4].

As a further stage of these studies our aim was the synthesis and structural characterization of some N-monosubstituted terephthaldiamides.

Therefore several terephthalamides have been synthesized by condensing terephthalamides with primary amines. The chemical structures have been elucidated by analytical methods: mass spectrometry (MS), vibration (IR) and electronic (UV) spectrometry.

Material and method

Starting material, terephthaloyl chloride, used in the syn-

thesis of the terephthalamides has been prepared in the laboratory from terephthalic acid and PCl_5 and purified by recrystallization from petroleum ether [5].

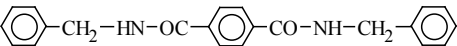
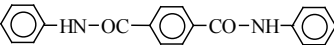
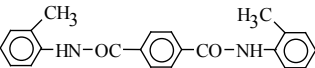
The final products have been obtained by condensation between terephthaloyl chloride and several commercial available primary amines (Merck products, ethanolamine, allylamine, benzylamine, aniline and orthotoluidine). The synthesis method has been developed and described previously [2,3].

All five products (Table I) were synthesized in the same way according to the scheme 1 exemplified for compound 4 N,N'-diphenylterephthalamide:

Used substances: terephthaloyl chloride 4.06 g (0.02 mol), aniline 7.45 g (0.08 mol) and anhydrous benzene 50 ml.

Working technique: Terephthaloyl dichloride (0.02 mol) dissolved in 30 ml anhydrous benzene was added to a

Table I. N-monosubstituted terephthaldiamides

Structural formula	Molecular formula
$\text{OH}-\text{CH}_2-\text{CH}_2-\text{HN}-\text{OC}-\text{C}_6\text{H}_4-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{OH}$ N, N'-Bis(2-hidroxyethyl)terephthaldiamide – Compound 1	$\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_4$
$\text{H}_2\text{C}=\text{CH}-\text{CH}_2-\text{HN}-\text{OC}-\text{C}_6\text{H}_4-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}=\text{CH}_2$ N, N'-Dialylterephthaldiamide – Compound 2	$\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$
 N, N'-Dibenzylterephthaldiamide – Compound 3	$\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$
 N, N'-Diphenylterephthaldiamide – Compound 4	$\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2$
 N, N'-Bis(o-tolyl)terephthaldiamide – Compound 5	$\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$

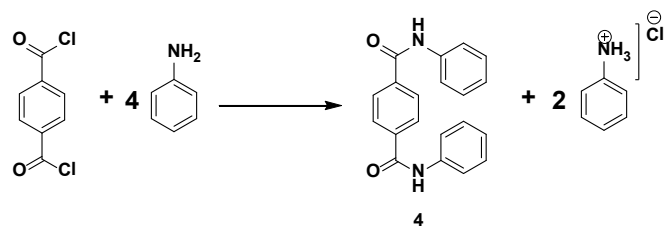


Fig. 1. N, N' – diphenylterephthalamide synthesis

250 ml flask with an ascending condenser equipped with a CaCl_2 tube. Aniline (0.08 mol) was dissolved in dry benzene (20 ml) and then added in small portions to the reaction mixture. The entire mixture was stirred on a ice bath at low temperature. The bath was then removed and the reaction was allowed to reach the room temperature being stirred for another 24 hours.

Crude product diphenylterephthalamide precipitate therefore was separated by filtration, washed well with several portions of water in order to remove amine chlorhydrate and dried when the raw product was obtain almost quantitative (5.96 g, yield: 94.15%).

For thin-layer chromatography (TLC), silica gel 60 F₂₅₄ (Merck) was used as stationery phase, with a fluorescence indicator layer sensitive at $\lambda=254$ nm. The terephthalamides have been dissolved in dimethylsulfoxide and a hexane:dichloromethane:ethanol (5:7:10 volumes) mixture has been used as eluent. The chromatograms have been exposed to iodine vapors for 10 minutes, spots have been marked and R_f -s has been calculated.

Pure compounds melting point has been determined by dry method (with Boetius microscope with heat plate).

Results

All the other amines were synthesized following the same described method for terephthalamide 4, in good yields — 33–95% (Table II).

All compounds were purified by recrystallization from benzene: ethanol (3:1) mixture reaching the pure product in good yields (65–85%). The purity was carried out by TLC methods [6].

N,N'-Bis(2-hydroxyethyl)-terephthaldiamide has been obtained in good yield by recrystallization from water.

The results of TLC analysis are presented in Table II.

N-monosubstituted terephthaldiamides are white crystals compounds, with high solubility in water like

Table II. N-monosubstituted terephthaldiamides R_f values

Terephthaldiamide	R_f
1. N,N'-Diphenylterephthaldiamide	0.74
2. N,N'-Dibenzylterephthaldiamide	0.73
3. N,N'-Diallylterephthaldiamide	0.68
4. N,N'-Bis(o-tolyl)-terephthaldiamide	0.76
5. N,N'-Bis(2-hydroxyethyl)-terephthaldiamide (recrystallized from benzene-ethanol mixture)	0.72
6. N,N'-Bis(2-hydroxyethyl)terephthaldiamide (recrystallized from water)	0.68

N,N'-bis(2-hydroxyethyl)terephthaldiamide or barely soluble in warm water for the other compounds. The solubility in water is an important property in pharmaceutical studies.

Pure compounds melting point was in the range of 218–276 °C (Table III).

The crystals forms have changed at 272–275°C in the case of N,N'-diphenylterephthaldiamide and at 245–247 °C for N,N'-bis(o-tolyl)terephthaldiamide. From 295–300 °C, respectively, 270 °C, the entire crystal is modified. The two amides melt above 340 °C (N,N'-diphenylterephthaldiamide) and between 305–306 °C (N,N'-bis(o-tolyl)terephthaldiamide). After cooling the melted amides rewind to their last form of crystal lattice.

The two terephthaldiamides IR spectra have been recorded after melting and cooling, exhibiting the same structure without significant changes in the structural elements, meaning there is no chemical modification during the melting processes. It can be concluded that the two N-monosubstituted terephthaldiamides present polymorphism.

The molecular structure of the synthesized terephthalamides has been confirmed by MS, IR and UV spectra spectroscopy [7,8,9].

All terephthalamides exhibit an intense absorbance, characteristic to C=O group (amide band I) at 1630–1650 cm^{-1} being in accordance with literature references.

The IR spectra present a characteristic N-H valence vibration absorption band at 3300 cm^{-1} for all synthesized compounds (Table IV).

N,N'-bis(2-hydroxyethyl)terephthaldiamide IR spectrum exhibit at 3380 cm^{-1} an absorption band due to the valence vibration of associative O-H interactions and a C-OH valence vibration band at 1050 cm^{-1} being in agreement with the literature [8,10].

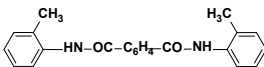
Table III. Molecular formula, molecular weight, yield, melting point and primary amine moieties of the monosubstituted terephthaldiamides

N-monosubstituted terephthaldiamides				
Primary amine	Molecular formula	Molecular weight	Yield %	Melting point (°C)
1. Monoethanolamine	$\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_4$	252.27	33	222–224
2. Allylamine	$\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$	244.29	88	218–219
3. Benzylamine	$\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$	344.41	85	275–276
4. Aniline*	$\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2$	316.36	94	272–275; >340
5. o-Toluidine*	$\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$	344.41	95	245–247; 305–306

Table IV. Terephthaldiamide characteristic vibrations (cm⁻¹)

Terephthaldiamide (TD)	ν_{CO}	γ_{C-H} p' disubstituted aromatic unit	ν_{N-H}	ν_{C-H} (groups – CH ₃ , >CH ₂ , >CH)
1 N,N'-bis(2-hydroxyethyl)TD	1640	830	3300	2970; 2920; 2980; 2850
2 N,N'-diallylTD	1630	850	3300	2920; 2865
3 N,N'-dibenzylTD	1640	870	3300	2945; 2855
4 N,N'-diphenyl	1650	865	3300	–
5 N,N'-bis(o-tolyl)TD	1650	850	3300	2925; 2860

Table V. N-monosubstituted terephthaldiamide maxima absorption

Structural formula	λ_{max} (nm)
1 HO-CH ₂ -CH ₂ -HN-OC-C ₆ H ₄ -CO-NH-CH ₂ -CH ₂ -OH	240.3
2 H ₂ C=CH-CH ₂ -HN-OC-C ₆ H ₄ -CO-NH-CH ₂ -CH=CH ₂	239.2
3 H ₅ C ₆ -H ₂ C-HN-OC-C ₆ H ₄ -CO-NH-CH ₂ -C ₆ H ₅	243.6
4 H ₅ C ₆ -HN-OC-C ₆ H ₄ -CO-NH-C ₆ H ₅	229.2
5 	230.6

Electronic excitation spectra emphasized the existence of amidic substituted benzene nucleus, maximum absorbance in UV appearing in the region of 230–243 nm (Table V) [1,6,8].

The mass spectra exhibit in all cases the molecular ion M⁺, with a good relative abundance, or [M+1]⁺ and [M-1]⁺ due to the presence in molecular structure of ¹³C and ¹⁵N isotopes or from losing of a hydrogen atom from molecular ion (Table VI).

The MS spectra exhibit 2 specific fragments [C₆H₅]⁺ at m/e=77 and [C₆H₅CO]⁺ at m/e=105 due to break of σ -bonds.

Conclusions

Five N-monosubstituted terephthaldiamides have been synthesized in good yields by condensation of terephthaloyl chloride with primary amines.

Several physicochemical constants and the chemical structure of the synthesized compounds have been determined using complex analysis like MS, UV and IR spectrometry.

Table VI. Several ions relative abundance of terephthaldiamide

Terephthaldiamide (TD)	Ions relative abundance (%)				
	[M] ⁺	[M+1] ⁺	[M-1] ⁺	[C ₆ H ₅] ⁺	[C ₆ H ₅ CO] ⁺
N,N'-bis(2-hydroxyethyl)-TD	75.86	27.58	6.03	31.03	9.48
N,N'-diallyl-TD	74.14	19.83	–	81.03	63.79
N,N'-dibenzyl-TD	21.55	–	25.86	14.66	–
N,N'-biphenyl-TD	76.72	20.69	–	35.34	66.38
N,N'-bis(o-tolyl)-TD	27.59	–	72.41	36.21	72.41

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