# Heterocyclic [6.7.6] Compounds Synthesis using 2-(4-methylphenoxymethyl)benzoic Acid. Synthesis of 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins

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*New 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins were prepared from the reaction of 2-methyl-11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin with various acid chlorides. The structure of the compounds was confirmed by elemental analyses, IR and NMR experiments. The reaction conditions (temperature, duration) had been also evaluated.*

*Keywords: dibenz[b,e]oxepin, $^{1}$H-NMR, $^{13}$C-NMR, elemental analysis, structure*

Knowing the pharmacological activity potential of the dibenz[b,e]oxepinic heterocycle and of the oximinic group, we combined these two entities in one molecule in order to obtain new compounds with better biological activity profile.

The Friedel-Crafts cyclocondensation of the 4-R substituted 2-phenoxymethylbenzoyl chloride represents a good method to synthesize the 2-R-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one. These ketones are intermediaries for the synthesis of the new 2-R-O-acyl-oximino-dibenz[b,e]oxepins [1- 6].

As part of our program aimed to develop new antimicrobial compounds, we report here the 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins synthesis from 2-methyl-11-hidroximino-6,11-dihidro-dibenz[b,e]oxepin and various acid chlorides.

## Experimental part

2-(4-Methylphenoxymethyl)benzoic acid, 2-(4-methylphenoxymethyl)benzoyl chloride, 2-methyl-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one, 2-methyl-11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin and 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins were prepared by the method previously published [5]. The new compounds were recrystallized from isopropanol.

The reagents and solvents were purchased from common commercial suppliers. 1,2-Dichloroethane was anhydrized over calcium chloride and distillated at normal pressure. Pyridine was stored over potassium hydroxide and distilled.

All melting points were taken in open capillary tubes with an Electrothermal 9100 apparatus and are uncorrected.

The elemental analysis was realized using a Perkin Elmer CHNS/ O Analyser Series II 2400 apparatus.

The NMR spectra were recorded on a Varian Unity Inova 400 instrument with AutoSwichable probe, at room temperature, operating at 400MHz for $^{1}$H and 100MHz for $^{13}$C and an Gemini 300BB instrument, operating at 300 MHz for $^{1}$H and 75 MHz for $^{13}$C. The new oxepins were dissolved in $CDCl_3$ and the chemical shifts were recorded as δ values presented in parts per million (ppm) relative to tetramethylsilane used as internal standard. The coupling constants (*J*) values are reported in Hertz.

The IR spectra were performed with a FT-IR Bruker Vertex 70 apparatus.

## Results and discussions

*The new compounds synthesis (fig.1)*

The synthesis of the new compounds was accomplished in three stages.

In the first stage, the 2-(4-methylphenoxy-methyl) benzoic acid (**1**) was prepared by treating the phtalide (**2**) with potassium *para*-cresolate in xylene under reflux. The resulted potassium 2-(4-methylphenoxy-methyl)benzoate (**3**) shows a good solubility in an 10% aqueous potassium hydroxide solution, allowing its facile separation from xylene. The aforementioned acid was precipitated using a mineral acid solution. The potassium *para*-cresolate was obtained through the reaction of *para*-cresol with potassium hydroxide in xylene, the resulting water being removed by azeotropic distillation.

The 2-methyl-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (**4**) was synthesized in the second stage by a Friedel-Crafts cyclization of the 2-(4-methylphenoxymethyl) benzoic acid chloride (**5**) in dry 1,2-dichloroethane. The aforementioned acid chloride was prepared by refluxing the coresponding acid with excess thionyl chloride in anhydrous 1,2-dichloroethane.

The new compounds, 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins (**6*a-h***), were prepared by acylation of the 2-methyl-11-hydroximino-6,11-dihydro-dibenz[b,e] oxepin (**7**) with various acid chlorides in dry benzene in presence of anhydrous pyridine as a proton fixator. The oxime (**7**) was obtained treating 2-methyl-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one with hydroxylamine hydrochloride in presence of pyridine.

The new compounds are solid, crystalline, white or light yellow, soluble at normal temperature in acetone, benzene, toluene, xylene, chloroform, dichloromethane and

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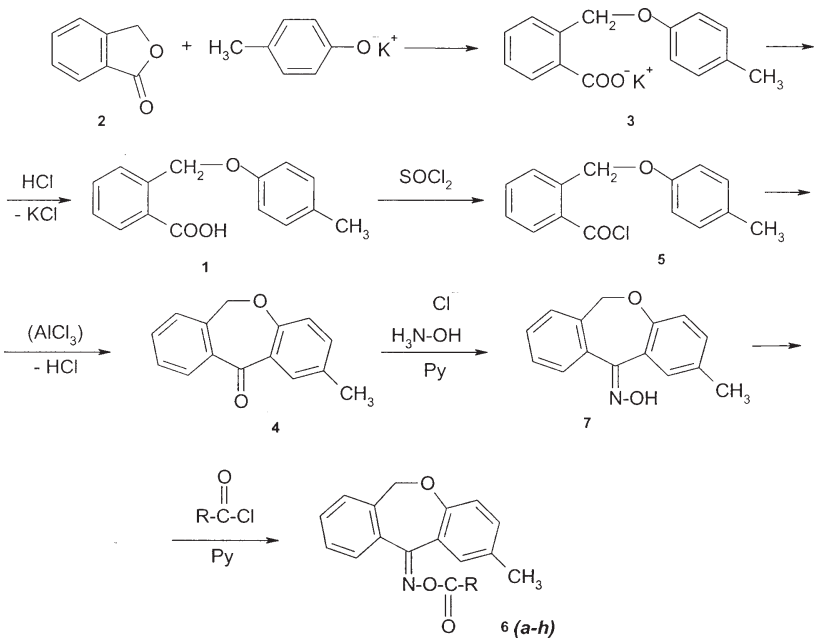


Fig. 1. The new compounds synthesis

R= -$C_6H_4CH_2Br$ (4) (**6a**.), -$C_6H_4F$ (4) (**6b**.), -$C_6H_4Cl$ (3) (**6c**.), -$C_6H_3Cl_2$(3,4) (**6d**.), -$C_6H_4I$ (4) (**6e**.), -$C_6H_4OCH_3$ (3) (**6f**.), -$C_6H_2(OCH_3)_3$(3,4,5) (**6g**.), -$C_6H_4NO_2$ (2) (**6h**.)

dichloroethane and by heating in inferior alcohols, insoluble in water.

The structure, molecular weight, melting point, yield and the elemental analyses of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins are presented in the table 1.

## Spectral data

The structures of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins were established through NMR and IR spectroscopy.

The $^1$H-NMR data are reported in the order: chemical shifts, multiplicity (s, singlet; d, doublet; bd, broad doublet; dd, double doublet; ddd, doublet of double doublets; dt, double triplet; t, triplet; m, multiplet), number of protons, the signals attribution presenting the major ($^M$) and minor ($^m$) signals, produced by the sin/anti isomerism, and the coupling constants. The $^{13}$C-NMR data are reported in the following order: chemical shifts and signal/atom attribution.

In the IR spectra the caracteristic bands of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins are ($cm^{-1}$): $\nu CH_2$ sym: 2837-2859; $\nu CH_2$ asym: 2946- 2987; $\delta CH_2$ sym: 1361-1376; $\delta CH_2$ asym: 1459-1491; νC-O-C sym: 1067-1089; νC-O-C asym: 1204-1226; $\upsilon CH_3$ sym: 2837-2859; $\upsilon CH_3$ asym: ~2966; νC=O: 1747-1754; νC-O 1228-1253; υC=N: 1600-1616;ν=C-H: 3030-3089; νC=C: 1506-1596; νC-F: 1066; νC-Cl: 742-743; νC-Br: 594 and νC-I: < 500

**2-Methyl-O-(4-bromomethylbenzoyl)-11-oximino-6,11-dihydro-dibenz[b,e]oxepin**

**$^1$H-NMR** ($CDCl_3$, δ ppm, *J* Hz): 7.95 (d, 2H, H-14, H-18, 8.3); 7.82 (d, 1H, H-1, 8.4); 7.64 (d, 2H, H-15, H-17, 2.1); 7.34÷ 7.53 (m, 4H, H-7 ÷ H-10); 7.09 (dd, 1H, H-3, 8.3, 2.2); 6.74 (d, 1H, H-4$^M$, 8.4); 6.85 (d, 1H, H-4$^m$, 8.4); 5.15 (s, H-6$^m$); 5.10 (s, H-6$^M$); 4.51 (s, 2H, H-20); 2.25 (s, H-19)

**$^{13}$C-NMR**($CDCl_3$, δ ppm): 164.8(C-12); 163.1(C-11); 155.6(C-4a); 142.7(C-16); 134.7(Cq); 133.6(CH); 133.3(Cq); 130.8(Cq); 130.6(CH); 130.4(CH); 130.2(Cq); 130.1(CH); 129.1(CH); 128.9(CH); 128.5(CH); 128.3(CH); 119.8(CH); 119.4(Cq); 70.81(C-6$^M$) , 70.60(C-6$^m$); 45.1(C-20); 20.15(C-19)

**2-Methyl-O-(4-fluorobenzoyl)-11-oximino-6,11-dihydro-dibenz[b,e]oxepin**

**$^1$H-NMR** ($CDCl_3$, δ ppm, *J* Hz): 7.83 (dd, 2H, H-14, H-18, 6.2, 8.8); 7.62 (bd, 1H, H-1, 1.7); 7.38÷7.50 (m, 6H, H-arom); 7.09 (dd, 1H, H-3, 1.6, 8.5); 7.00 (t, 2H, H-15, H-17, 8.8); 5.09 (s, 2H, H-6); 2.24 (s, 3H, H-19).

**$^{13}$C-NMR** ($CDCl_3$, δ ppm): 165.20 (d, C-16, $J$($^{19}$F-$^{13}$C)=254.2 Hz); 164.33 (C-12); 162.87 (C-11); 155.48 (C-4a); 134.60 (Cq); 133.78 (CH); 133.09 (Cq); 132.39 (d, C-14, C-18, $^3J$($^{19}$F-$^{13}$C)=9.4 Hz); 130.93 (Cq); 130.75(CH); 130.59 (CH); 128.66 (CH); 128.43 (CH); 127.97 (CH); 124.94 (d, C-13, $^4J$($^{19}$F-$^{13}$C)=2.9 Hz); 119.83 (CH); 119.16 (Cq); 115.89 (d, C-15, C-17, $J$($^{19}$F-$^{13}$C)=22.0 Hz); 70.59 (C-6); 20.36 (C-19).

**2-Methyl-O-(3-chlorobenzoyl)-11-oximino-6,11-dihydro-dibenz[b,e]oxepin**

**$^1$H-NMR** ($CDCl_3$, δ ppm, *J* Hz): 8.00 (t, 1H, H-1, 2.2); 7.98 (dt, 1H, H-16, 8.2, 1.2); 7.83 (t, 1H, H-14, 2.2); 7.80 (dt, 1H, 8.4, 1.1); 7.70 (bd, 1H, H-1, 1.9); 7.20÷7.60 (m, 6H, H-arom); 7.19 (dd, 1H, H-3, 2.2, 8.5); 6.80 (d, 1H, H-4, 8.5); 5.22 (s, H-6$^m$); 5.17 (s, H-6$^M$); 2.38 (s, H-19$^m$); 2.32 (s, H-19$^M$).

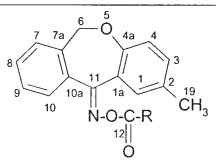
**$^{13}$C-NMR** ($CDCl_3$, δ ppm): 165.00 (C-12); 162.62 (C-11); 134.80 (Cq); 134.39 (Cq); 134.45 (Cq); 133.87 (CH); 133.64 (CH); 133.48 (CH); 130.95 (Cq); 130.72 (CH); 130.48 (CH); 130.31 (Cq); 129.97 (CH); 129.90 (CH); 128.68 (CH); 128.46 (CH); 128.02 (CH); 127.88 (CH); 70.62 (C-6); 20.37 (C-19).

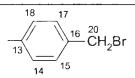
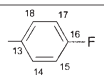
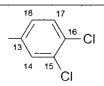
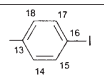
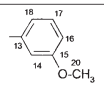
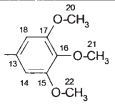
**2-Methyl-O-(3,4-dichlorobenzoyl)-11-oximino-6,11-dihydro-dibenz[b,e]oxepin**

**$^1$H-NMR** ($CDCl_3$, δ ppm, *J* Hz): 7.86 (d, 1H, H-14, 1.9); 7.64 (dd, 1H, H-18, 1.9, 8.2); 7.59 (bd, 1H, H-1, 2.6); 7.42 (m, 6H, H-arom); 7.09 (dd, 1H, H-3, 2.6, 8.4); 6.78 (d, 1H, H-4, 8.4); 5.09 (s, 2H, H-6); 2.24 (s, 3H, H-19).

**$^{13}$C-NMR** ($CDCl_3$, δ ppm): 165.23 (C-12); 161.89 (C-11); 155.57 (C-4a); 138.18 (Cq); 134.36 (Cq); 133.95 (CH); 133.25 (Cq); 133.12 (Cq); 131.72 (CH); 130.98 (Cq); 130.84 (CH); 130.75 (CH); 130.67 (CH); 128.76 (CH); 128.57 (Cq); 128.44 (CH); 127.90 (CH); 119.90 (CH); 118.91(Cq); 70.62 (C-6); 20.36 (C-19).

**Table 1**
DATA ON THE NEW COMPOUNDS



| No. | R | Molecular weight | Melting point ($^0$C) | Yield (%) | C% | | H% | | N% | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | c. | e. | c. | e. | c. | e. |
| 6a. |  | 435.39 | 189.1-190 | 79 | 63.44 | 63.55 | 4.17 | 4.09 | 3.22 | 3.25 |
| 6b. |  | 361.37 | 156–157.2 | 82 | 73.12 | 73.39 | 4.46 | 4.31 | 3.88 | 3.82 |
| 6c. |  | 377.82 | 154.1-156.0 | 74 | 69.94 | 69.78 | 4.27 | 4.29 | 3.71 | 3.71 |
| 6d. |  | 412.27 | 185.4–187.8 | 77 | 64.09 | 64.24 | 3.67 | 3.58 | 3.40 | 3.38 |
| 6e. |  | 469.27 | 156.4-159 | 76 | 56.30 | 56.47 | 3.44 | 3.37 | 2.99 | 3.05 |
| 6f. |  | 373.40 | 192.7-195.9 | 71 | 73.98 | 73.68 | 5.13 | 5.14 | 3.75 | 3.79 |
| 6g. |  | 433.44 | 185.3-187.1 | 82 | 69.27 | 69.49 | 5.35 | 5.41 | 3.23 | 3.21 |
| 6h. |  | 388.37 | 174.5- 177.8 | 65 | 68.03 | 68.21 | 4.15 | 4.14 | 7.21 | 7.27 |

**2-Methyl-O-(4-iodobenzoyl)-11-oximino-6,11-dihydro-dibenz[b,e]oxepin**

**$^1$H-NMR** ($CDCl_3$, δ ppm, *J* Hz): 7.75 (d, 2H, H-14, H-18, 1.7); 7.72 (d, 1H, H-1, 1.5); 7.35- 7.70 (m, H-7 – H-10); 7.08 (d, 2H, H- 15, H- 17, 8.6); 6.84 (dd, 1H, H-3, 8.4, 1.4); 6.73 (dd, 1H, H- 4, 8.4, 1.4); 5.13 (s, 2H, H-6$^m$); 5.08 (s, 2H, H-6$^M$); 2.25 (s, 3H, H-19$^m$); 2.24 (s, 3H, H-19$^M$).

**$^{13}$C-NMR** ($CDCl_3$, δ ppm): 164.7 (C-12); 163.3 (C-11); 155.4 (C-4a); 137.9 (C-15, C-17); 134.4 (Cq); 133.7 (CH); 133.0 (Cq); 131.1 (CH); 130.6 (Cq); 130.5 (CH); 128.6 (CH); 128.3 (CH); 128.1 (CH); 119.6 (CH); 119.0 (Cq); 101.3 (Cq); 70.5 (C-6); 20.46 (C-19$^m$); 20.26 (C-19$^M$).

**2-Methyl-O-(3-methoxybenzoyl)-11-oximino-6,11-dihydro-dibenz[b,e]oxepin**

**$^1$H-NMR** ($CDCl_3$, δ ppm, *J* Hz): 7.63 (d, 1H, H-1, 1.4); 7.58 (m, 2H, H-arom); 7.41 (m, 3H, H-arom); 7.35 (dd, 1H, H-14, 1.7, 2.8); 7.22 (t, 1H, H-17, 8.0); 7.08 (dd, 1H, H-3, 1.6, 8.3); 7.01(ddd, 1H, H-16, 0.8, 2.4, 7.8); 6.70 (d, 1H, H-4, 8.3); 5.10 (s, 2H, H-6); 3.68 (s, 3H, H-20); 2.24 (s, 3H, H-19).

**$^{13}$C-NMR** ($CDCl_3$, δ ppm): 164.19 (C-12); 163.38 (C-11); 159.48 (C-15); 155.24 (C-4a); 134.47 (Cq); 133.50 (CH); 132.87 (Cq); 130.68 (Cq); 130.55 (CH); 130.24 (CH); 129.69 (Cq); 129.42 (CH); 128.39 (CH); 128.13 (CH); 127.89 (CH); 122.02 (CH); 120.09 (CH); 119.57 (CH); 118.99 (Cq); 113.67 (C-4); 70.38 (C-6); 52.25 (C-20); 20.12 (C-19).

**2-Methyl-O-(3,4,5-trimethoxybenzoyl)-11-oximino-6,11-dihydro-dibenz[b,e]oxepin**

**$^1$H-NMR** ($CDCl_3$, δ ppm, *J* Hz): 7.63 (s, 2H, H-14, H-18); 7.55 (d, 1H, H-1, 6.9); 7.19- 7.40 (m, 4H, H-7 – H10); 7.08 (dd, 1H, H-3, 2.3, 8.4); 6.73 (d, 1H, H-4, 8.3); 5.16 (s, 2H, H-6$^m$); 5.09 (s, 2H, H-6$^M$); 2.25 (s, 3H, H-19).

**$^{13}$C-NMR** ($CDCl_3$, δ ppm): 164.1 (C-12); 163.0 (C-11); 155.4 (C-4a); 153.0 (C-15, C-17); 134.8 (Cq); 133.6 (CH); 133.2 (Cq); 130.8 (Cq); 130.6 (CH); 130.4 (CH); 128.6 (CH); 128.0 (CH); 123.3 (Cq); 119.7 (CH); 119.1 (Cq); 107.2 (CH); 70.5 (C-6); 60.9 (C-21), 56.1 (C-20, C-22); 20.23 (C-19).

**2-Methyl-O-(2-nitrobenzoyl)-11-oximino-6,11-dihydro-dibenz[b,e]oxepin**

**$^1$H-NMR** ($CDCl_3$, δ ppm, *J* Hz): 7.93 (dd, 1H, H-15$^m$, 7.7, 1.4); 7.85 (dd, 1H, H-15$^M$, 8.2, 1.4); 7.63 (d, 1H, H-1, 2.0); 7.49÷7.62 (m, 3H, H-16, H-17, H-18); 7.26÷7.33 (m, 4H, H-7, H-8, H-9, H-10); 7.05 (dd, 1H, H-3, 2.3, 8.4); 6.75 (d, 1H, H-4$^m$, 8.4); 6.69 (d, 1H, H-4$^M$, 8.4); 5.08 (s, H-6$^m$); 5.02 (s, H-6$^M$); 2.21 (s, H-19$^M$);2.16 (s, H-19$^m$).

**$^{13}$C-NMR** ($CDCl_3$, δ ppm): 165.3 (C-12); 163.5 (C-11); 155.2 (C-4a); 148.0 (C-14); 134.2 (C-7a); 133.6 (CH); 133.3 (C-10a); 133.2 (CH); 133.1 (CH); 131.6 (CH); 130.7 (Cq); 130.3 (CH); 130.1 (CH); 128.9 (CH); 128.5 (CH); 128.2 (CH); 127.0 (Cq); 123.9 (CH); 119.8 (CH); 119 (Cq); 70.62 (C-6$^M$); 70.46 (C-6$^m$); 20.15 (C-19$^m$); 20.01 (C-19$^M$).

The $^{1}$H-NMR, $^{13}$C-NMR and IR spectral data associated with the elemental analysis confirme the structure of the obtained compounds.

## Conclusions

In this work we synthesized by acylation of the 11-oximino-2-methyl-6,11-dihydro-dibenz[b,e]oxepin with various acid chlorides, eight new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins with potential antimicrobial activity. The structures of the synthesized compounds were confirmed by IR, $^{1}$H-NMR and $^{13}$C-NMR spectral data and elemental analyses. These dibenzoxepins are in course of testing in order to establish their antimicrobial activity.

*Acknowledgements*

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