New 2-metyl-O-acyloximino-dibenzo[b,e]thiepins
Synthesis and structural characterization

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This paper presents experimental data regarding the synthesis and characterization of new 2-methyl-dibenzo[b,e]thiepine derivatives. The synthesis of the new compounds was performed in several stages. Thus, by reaction of phtalide with potassium p-thiocresolate, we obtained the 2-(4-tolylthiomethyl)benzoic acid. The acid was cyclized with polyphosphoric acid to the 2-methyl-6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one, converted afterwards to the corresponding oxime and subsequently to the 2-methyl-O-acyloximino-dibenzo[b,e]thiepins by acylation with various acid chlorides. The oxidation of 2-methyl-O-acyloximino-dibenzo[b,e]thiepins with hydrogen peroxide afforded the corresponding sulfones. The elemental analysis and the NMR (^1H and ^{13}C) and IR spectroscopy data confirmed the chemical structures and the purity of the compounds.

Keywords: dibenzo[b,e]thiepine, sulfones, NMR spectroscopy

The dibenzo[b,e]thiepine derivatives have been studied intensively due to their diversity of biological effects: antidepressant, antihistaminic, antipsychotic, anxiolytic, hypnotic, antihypertensive, antimicrobial, anti-inflammatory, etc. The most important are *Dosulepine* (Prothiaden®, Dothiepin®), used in the treatment of major depressive disorder and also as adjuvant in the management of pain, and 2-methyl-derivative of dosulepine, m*edosulepine* (Methiaden®), used in the therapy of allergic diseases as antihistaminic drug intended especially for parenteral application. *Dithiadene* is a thieno-benzothiepine tricyclic antihistaminic drug, structurally related to dosulepine. *Tiopinac*, displayed marked anti-inflammatory activity and *amidepine* and *monatepil* (AJ-2615) are used in the treatment of angina and hypertension [1- 4].

As part of our ongoing studies aimed to develop new biologically active compounds [5- 10], in this study we report the synthesis and the characterization of new 2-methyl-O-acyloximino-dibenzo[b,e]thiepins. Moreover, this study was prompted by our previous data which made evident the favorable effects of replacement of S atom by SO_2 group, for the improvement of antimicrobial activity [11, 12].

Experimental part

All starting materials were purchased from commercial suppliers and were used without further purification unless otherwise specified. The melting points were recorded in open capillary tubes on an Electrothermal 9100 apparatus and are uncorrected. The elemental analysis was performed using a Perkin-Elmer CHNS/O Analyser Series II 2400 apparatus.

The NMR spectra were recorded on a Varian Unity-Inova 400 instrument at room temperature, operating at 400 MHz for ^1H and 100 MHz for ^{13}C. The new compounds were dissolved in chloroform-d_1 and the chemical shifts were recorded as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. The coupling constants (J) values are reported in Hertz and the splitting patterns are abbreviated as following: s (singlet), d (doublet), t (triplet), m (multiplet), b (broad). The ^{13}C-NMR data are reported in the following order: chemical shifts and the signal/ atom attribution.

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

Thin layer chromatography (TLC) was performed on silicagel 60F254 Merck plates. For the development chloroform/ethyl acetate (10:1) was used. The visualization was performed using an UV lamp (λ= 254nm) and iodine atmosphere.

The starting compounds *2-(*4-tolylthiomethyl)benzoic acid (**4**), 2-Methyl-6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (**5**) and 11-hydroximino-2-methyl-6,11-dihydro-dibenzo[b,e]thiepine (**6**) were synthesized according to the methods described previously [6, 13].

*The synthesis of 2-(4-tolylthiomethyl)benzoic acid (**4**)*

In a round-bottom flask equipped with a Dean- Stark apparatus, 12.42 g (0.1 mol) p-thiocresol (mol wt 124.21) were dissolved in 60 mL xylene and subsequently 5.61 g (0.1 mol) potassium hydroxide (mol wt 56.11) were added. The reaction mixture was refluxed until 2 mL of water were removed by azeotropic distillation, while potassium p-thiocresolate precipitated; 13.41 g (0.1 mol) phtalide (mol wt 134.14) were added and the mixture was refluxed for 3 h. After cooling, the solidified mixture was dissolved in 10% potassium hydroxide and diluted with 100 mL water. The aqueous phase was separated and acidulated (*p*H 3) with 1M hydrochloric acid solution, when 2-(4-tolylthiomethyl)benzoic acid precipitated. The crude product was filtered and recrystallized from ethanol: water (3:1) (m.p. 134.3- 136.1°C; yield 83%).

*The synthesis of 2-methyl-6,11-dihydrodibenzo [b,e] thiepin-11(6H)-one (**5**)*

140 g polyphosphoric acid (PPA) was heated to 80°C, 25.83 g (0.1 mol) 2-(4-tolylthiomethyl)benzoic acid (mol wt 258.32) were slowly added, under stirring, and afterwards the mixture was heated for 2.5 h to 140- 150°C.

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After partial cooling (80^{0}C) the reaction mixture was poured into an ice-water mixture and stirred. The product was extracted with benzene for three times. The combined organic layers were washed with 5% sodium hydroxide solution and water and afterwards dried over anhydrous calcium chloride. Then, the solvent was removed *in vacuo* and the crude product obtained was recrystallized from ethanol (m.p. 119.3- 120.1^{0}C; yield 74%).

*The synthesis of 11-hydroximino-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (**6**)*

12.01 g (0.05 mol) of 2-methyl-6,11-dihydrodibenzo [b,e]thiepin-11(6H)-one (mol wt 240.31) and 10.5 g (0.15 mol) of hydroxylamine hydrochloride (mol wt 69.49) were boiled under reflux in 100 mL of pyridine for 33 hours. The pyridine was subsequently distilled off *in vacuo*, the residue was triturated with water, suction-filtered, dried and recrystallized from *i*-propanol (m.p. 227.3-228.1^{0}C; yield 82%).

The synthesis of the new 2-methyl-O-acyloximino-dibenzo[b,e]thiepins (7a-d). General procedure

To a solution of 2.55g (10 mmol) 11-hydroximino-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (mol wt 255.33) in anhydrous toluene was added drop wise a solution of 11 mmol appropriated acid chloride in 10 mL anhydrous toluene and 0.79 g (0.8 mL; 10 mmol) dry pyridine (mol wt 79.098; d_4^{25}=0.978). The reaction mixture was refluxed for three hours, afterwards was cooled, the precipitate was filtered and the solvent was removed under reduced pressure. The resulting crude product was recrystallized from an appropriate solvent.

The synthesis of the new sulfones (8a-d). General procedure

To a solution of 10 mmol **7a-d** in glacial acetic acid were added drop wise 2 mL 30% hydrogen peroxide, the mixture was heated for 3 hours and left overnight at room temperature. The reaction mixture was diluted with water and the compound was extracted with chloroform. The organic layer was dried over calcium chloride and the solvent was removed under reduced pressure. The resulting crude product was recrystallized from an appropriate solvent.

Analytical and spectral data for the new compounds, *2-methyl-O-acyl-oximino-dibenzo[b,e]thiepins **(7a-d)*** and their corresponding 5,5-dioxides ***(8a-d)*** are given below.

*11-[O-(4-Ethylbenzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (**7a**)*

$C_{24}H_{21}NO_2S$ (387.49); Colorless crystals, m.p. 128.5-134.1^{0}C (*i*-propanol); yield 77%. R_f= 0.81. Elemental analysis. Calcd. C: 74.39; H: 5.46; N: 3.61; S: 8.27. Found: C: 74.68; H: 5.30; N: 3.48; S: 8.01

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.83(d, H-14^m, H-18^m, 8.5); 7.68(d, H-14^M, H-18^M, 8.5); 7.67(d, H-1, 1.5); 7.56(dd, H-10^m, 1.4, 7.4); 7.47÷7.29(m, H-arom); 7.27÷7.29(m, H-arom); 7.11(dd, H-3, 1.4, 8.2); 7.03(d, H-4, 8.2); 4.62(bs, H-6A); 3.55(bs, H-6B); 2.69(q, H-20^m, 7.4); 2.66(q, H-20^M, 7.4); 2.35(s, H-19^m); 2.34(s, H-19^M); 1.24(t, H-21^m, 7.4); 1.21(t, H-21^M, 7.4).

^{13}C-NMR($CDCl_3$, δ ppm): 166.81(C-11); 163.64(C-12); 150.32(C-16); 135.08(Cq); 134.84(Cq); 133.46(Cq); 133.26(Cq); 128.62(Cq); 125.93(Cq); 132.03(CH^M); 131.58(CH^M); 130.21(CH^M); 129.80(C-14, C-18); 128.02(C-15, C-17); 127.92(CH^M); 127.13(CH^M); 127.08(CH^M); 126.48(CH^M); 131.09(CH^m); 130.75(CH^m); 130.50(CH^m); 129.91(CH^m); 129.22(CH^m); 128.21(CH^m); 128.06(CH^m); 127.74(CH^m); 127.26(CH^m); 33.93(C-6^m); 33.32(C-6^M); 28.97(C-20); 20.80(C-19^m); 20.61(C-19^M); 15.14(C-21).

FT-IR(ATR in solid, ν cm^{-1}): 3036w; 2966w; 2922w; 2871w; 1752vs; 1607m; 1574w; 1451w; 1417w; 1390w; 1324w; 1257vs; 1240vs; 1178m; 1160w; 1080s; 1048s; 1012s; 877m; 859m; 810w; 727m; 656w; 634w. (anexa 84)

*11-[O-(3-Iodobenzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (**7b**)*

$C_{22}H_{16}INO_2S$ (485.33); Colorless crystals, m.p. 146.3-151^{0}C (*i*-propanol); yield 50%. R_f= 0.86. Elemental analysis. Calcd. C: 54.44; H: 3.32; N: 2.89; S: 6.61 Found: C: 54.83; H: 3.20; N: 2.86; S: 6.82

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.17(t, H-14^m, 1.7); 8.05(t, H-14^M, 1.7); 7.94÷7.86(m, H-18^m, H-17^m); 7.84(ddd, H-18^M, 1.2, 2.0, 7.8); 7.73(dt, H-arom, 2.1, 8.2); 7.62(bd, H-1, 1.9); 7.55(dd, H-10^m, 2.3, 8.0); 7.10÷7.50(m, H-arom); 7.04(d, H-4, 8.2); 4.62(bs, H-6); 3.56(bs, H-6); 2.41(s, H-19^m); 2.34(s, H-19^M)

^{13}C-NMR($CDCl_3$, δ ppm): 167.75(C-12); 162.00(C-11); 142.11(C-14); 138.61(CH); 135.22(Cq); 134.93(Cq); 133.51(Cq); 131.99(CH); 131.76(CH); 130.42(CH); 130.14(CH); 129.02(Cq); 128.33(Cq); 128.30(Cq); 128.05(CH); 127.14(CH); 127.09(CH); 126.63(CH); 93.81(C-15); 34.21(C-6^m); 33.40(C-6^M); 20.62(C-19)

FT-IR(ATR in solid, ν cm^{-1}): 3058w; 2962w; 2916w; 1745vs; 1598w; 1561w; 1470w; 1411w; 1226s; 1158w; 1044m; 998s; 912w; 803m; 767w; 726m; 694w; 583w.

*11-[O-(4-Iodobenzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (**7c**)*

$C_{22}H_{16}INO_2S$ (485.33); Colorless crystals, m.p. 218.3-219.8^{0}C (*i*-propanol); yield 75%. R_f= 0.76. Elemental analysis. Calcd. C: 54.44; H: 3.32; N: 2.89; S: 6.61. Found: C: 54.82; H: 3.28; N: 3.05; S: 6.52

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.72(d, H-15, H-17, 8.6); 7.65(d, H-1, 1.4); 7.44(d, H-14, H-18, 8.6); 7.42(m, H-10); 7.36(td, H-8); 7.35(td, H-9, 6.8, 1.4); 7.28(dd, H-7, 1.3, 8.2); 7.10(dd, H-3, 1.4, 8.2); 7.03(d, H-4, 8.2); 4.62(bs, H-6A); 3.56(bs, H-6B); 2.33(s, H-19)

^{13}C-NMR($CDCl_3$, δ ppm): 167.52(C-11); 163.12(C-12); 137.89(C-15, C-17); 135.16(C-4a); 134.92(C-2); 133.42(Cq); 133.25(Cq); 131.98(C-1); 131.73(C-1); 130.96(C-14, C-18); 130.36(C-3); 128.41(Cq); 128.08(Cq); 128.02(C-4); 127.08(C-7); 126.98(C-8 or C-9); 126.59(C-8 or C-9); 101.26(C-16); 33.35(C-6); 20.61(C-19)

FT-IR(ATR in solid, ν cm^{-1}): 3042w; 2913w; 2852w; 1750vs; 1587m; 1474m; 1420w; 1388m; 1246s; 1175m; 1079m; 1051s; 1003m; 909m; 840w; 809m; 764w; 743m; 655w.

*11-[O-(2-Nitrobenzoyl)-oximino]- 2-methyl -6,11-dihydrodibenzo[b,e]thiepine (**7d**)*

$C_{22}H_{16}N_2O_4S$ (404.44); Light yellow crystals, m.p. 166.7-168.4^{0}C (*i*-propanol); yield 87%. Elemental analysis. Calcd. C: 65.34; H: 3.99; N: 6.93; S: 7.93. Found: C: 65.01; H: 4.02; N: 6.71; S: 7.68

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.89(dd, H-15, 1.3, 8.0); 7.72÷7.51(m, 3H, H-16, H-17, H-18); 7.57(bs, H-1); 7.36(td, H-9, 7.6, 1.1); 7.30(dd, H-10, 1.6, 7.6); 7.26(td, H-8, 7.6, 1.6); 7.15(dd, H-7, 1.1, 7.6); 7.09(dd, H-3, 1.9, 8.2); 7.01(d, H-4, 8.2); 4.61(bs, H-6A); 3.57(bs, H-6B); 2.33(s, H-19^M); 2.30(s, H-19^m)

^{13}C-NMR($CDCl_3$, δ ppm): 168.06(C-11^M); 166.87(C-11^m); 163.87(C-11^m); 163.48(C-11^M); 147.84(C-14); 134.84(Cq); 134.68(Cq); 133.47(Cq); 133.30(CH); 132.83(CH); 131.90(CH); 131.80(CH); 131.74(CH); 130.30(CH); 130.20(CH); 128.23(CH); 127.99(CH); 127.39(CH);

126.68(CH); 126.57(Cq); 126.38(C-7); 124.13(C-15^{m}); 124.09(C-15^{M}); 34.09(C-6^{m}); 33.23(C-6^{M}); 20.75(C-19^{m}); 20.57(C-19^{M})

FT-IR(ATR in solid, ν cm^{-1}): 2962w; 2918w; 1768vs; 1608w; 1592w; 1527vs; 1445vs; 1391m; 1235vs; 1102s; 1054s; 1032m; 1011m; 985w; 908m; 862m; 846s; 791m; 764m; 738m; 650w; 590w.

*11-[O-(4-Ethylbenzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepin-5,5-dioxide (**8a**)*

$C_{24}H_{21}NO_4S$ (419.49); Colorless crystals, m.p. 204.3-206.8^{0}C (ethanol abs.); yield 50%. R_f= 0.72. Elemental analysis. Calcd. C: 68.72; H: 5.05; N: 3.34; S: 7.64. Found C: 68.70; H: 5.10; N: 3.32; S: 7.60

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.92(d, 1H, H-2, 8.2); 7.71(d, H-1, 1.5);7.68(d, 2H, H-14, H-18, 8.2); 7.57÷7.47(m, 4H, H-arom); 7.42(m, 1H, H-7); 7.20(d, 2H, H-15, H-17, 8.2); 5.08(bs, H-6A); 4.34(bs, H-6B); 2.67(q, H-20^{m}, 7.6); 2.47(s, H-19); 1.22(t, H-21^{M}, 7.6).

^{13}C-NMR($CDCl_3$, δ ppm): 164.03(C-11); 163.22(C-12); 150.88(C-16); 143.70(Cq); 138.97(Cq); 135.03(Cq); 129.83(Cq); 125.29(Cq); 124.38(Cq); 132.84(C-7); 131.46(CH); 130.87(CH); 130.21(C-1); 129.89(C-14, C-18); 128.90(CH); 128.19(C-15, C-17); 127.81(C-7); 126.17(C-4); 58.55(C-6); 29.00(C-20); 21.37(C-19); 15.09(C-21).

FT-IR(ATR in solid, ν cm^{-1}): 2966w; 2923w; 1744vs; 1607m; 1562w; 1484w; 1457w; 1414w; 1307vs; 1253vs; 1198w; 1180m; 1150s; 1122s; 1081s; 1051s; 1012m; 993m; 927m; 869m; 847w; 820m; 786m; 741w; 713w; 693w; 656w; 633w; 536m; 512m.

*11-[O-(3-Iodobenzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepin-5,5-dioxide (**8b**)*

$C_{22}H_{16}INO_4S$ (517.33); Colorless crystals, m.p. 205.3-207.8^{0}C (ethanol abs); yield 58%. R_f= 0.81. Elemental analysis. Calcd. C: 51.08; H: 3.12; N: 2.71; S: 6.20. Found. C: 50.92; H: 3.18; N: 2.79; S: 6.29

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 8.04(t, 1H, H-14, 1.6); 7.94(d, 1H, H-4, 8.3); 7.87(m, 1H, H-arom); 7.74(dt, 1H, H-16, 7.9, 1.6); 7.70(d, 1H, H-1, 1.2); 7.58÷7.31(m, H-arom); 7.16(t, H-17^{m}, 7.9); 7.12(t, H-17^{M}, 7.9); 5.05(bs, 1H, H-6A); 4.35(bs, 1H, H-6B); 2.54(s, 3H, H-19^{m}); 2.48(s, 3H, H-19^{M}).

^{13}C-NMR($CDCl_3$, δ ppm): 165.00(C-11); 161.60(C-12); 143.77(Cq); 142.54(C-16^{M}); 142.42(C-16^{m}); 139.10(Cq); 138.69(C-14^{M}); 138.57(C-14^{m}); 134.72(Cq); 133.02(CH); 131.96(Cq); 131.61(CH); 131.09(CH); 130.09(CH); 130.16(CH); 129.88(Cq); 128.95(CH); 128.81(CH); 127.75(CH); 126.67(Cq); 126.31(CH); 124.43(Cq); 93.90(C-16); 58.61(C-6); 21.38(C-19).

FT-IR(ATR in solid, ν cm^{-1}): 2968w; 2925w; 1756vs; 1588w; 1565w; 1454w; 1416w; 1306vs; 1263w; 1227vs; 1182w; 1154s; 1123m; 1079m; 1050s; 1016m; 991w; 920m; 882m; 868m; 819w; 782m; 768w; 734m; 691w; 604w; 556w.

*11-[O-(4-Iodobenzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepin-5,5-dioxide (**8c**)*

$C_{22}H_{16}INO_4S$ (517.33); colorless crystals, m.p. 215.9-217.8^{0}C (ethanol abs); yield 64%. R_f= 0.73. Elemental analysis. Calcd. C: 51.08; H: 3.12; N: 2.71; S: 6.20. Found.C: 50.92; H: 3.09; N: 2.78; S: 6.10

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.93(d, 1H, H-4, 8.4); 7.75(d, 2H, H-14, H-18, 8.7); 7.69(d, 1H, H-1, 1.4); 7.54(dd, 1H, H-3, 1.4, 8.4); 7.44(d, 2H, H-15, H-17, 8.7); 7.56÷7.45(m, 3H, H-arom); 7.39(m, 1H, H-7); 5.05(bs, 1H, H-6A); 4.35(bs, 1H, H-6B); 2.47(s, 3H, H-19).

^{13}C-NMR($CDCl_3$, δ ppm): 164.76(C-11); 162.75(C-12); 143.76(Cq); 139.04(Cq); 138.09(C-14, C-18); 134.81(Cq); 132.99(CH); 131.58(CH); 131.02(CH); 130.98(C-15, C-17); 130.14(C-1); 129.62(Cq); 128.90(CH); 127.66(C-7); 127.43(Cq); 126.29(C-4); 124.46(Cq); 101.79(C-16); 58.58(C-6); 21.37(C-19).

FT-IR(ATR in solid, ν cm^{-1}): 3068w; 2969w; 2923w; 1749vs; 1583s; 1477w; 1450w; 1393m; 1304vs; 1244vs; 1196m; 1180m; 1154s; 1125s; 1076m; 1047vs; 1021w; 1002s; 992s; 918m; 878w; 820m; 780m; 740s; 720w; 680w; 657w; 602w; 481m.

*11-[O-(2-Nitrobenzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepin-5,5-dioxide (**8d**)*

$C_{22}H_{16}N_2O_6S$; (436.43); colorless crystals, m.p. 229.1-230.2^{0}C (glacial acetic acid); yield 86.5%. Elemental analysis. Calcd. C: 60.55; H: 3.70; N: 6.42; S: 7.35. Found: C: 60.68; H: 3.74; N: 6.38; S: 7.40

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.91(dd, 1H, H-15, 1.1, 8.3); 7.90(d, 1H, H-4, 8.1); 7.68(dd, 1H, H-3, 1.1, 8.1); 7.72÷7.60(m, H-arom); 7.51÷7.46(m, H-arom); 7.45(td, 1H, H-9, 7.7, 1.4); 7.38(td, 1H, H-8, 7.5, 1.6); 7.25(dd, 1H, H-7, 7.5, 1.4); 5.03(bs, 1H, H-6A); 4.33(bs, 1H, H-6B); 2.47(s, 3H, H-19).

^{13}C-NMR($CDCl_3$, δ ppm): 165.32(C-11); 163.03(C-12); 143.74(Cq); 139.03(Cq); 134.38(Cq); 133.50(CH); 130.00(CH); 132.31(CH); 131.36(CH); 130.89(CH); 130.42(CH); 129.86(CH); 129.48(Cq); 129.24(C-7); 127.40(CH); 126.31(C-4); 125.95(Cq); 124.22(C-15); 124.04(Cq); 104.84(Cq); 58.60(C-6); 21.35(C-19).

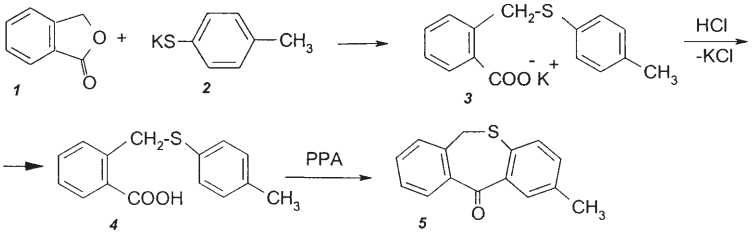
FT-IR(ATR in solid, ν cm^{-1}): 3095w; 3038w; 2963w; 2921w; 1760vs; 1616w; 1590w; 1575w; 1529vs; 1482m; 1452w; 1348s; 1321m; 1303vs; 1259s; 1241vs; 1156m; 1123s; 1107m; 1093m; 1049s; 1012m; 989m; 913m; 871m; 855m; 817m; 789s; 738m; 692m; 484m.

Results and discussions

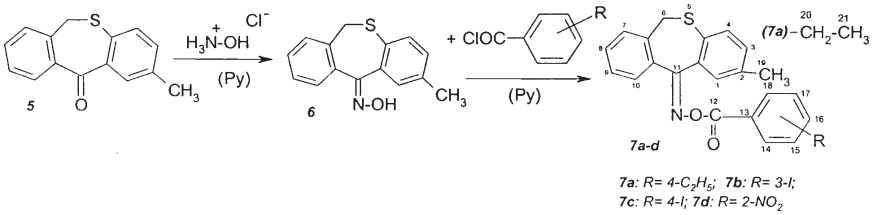
The synthesis of the title compounds was performed in several stages.

The preparation of 2-(4-tolylthiomethyl)benzoic acid (***4***) and 2-methyl-6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (***5***), was accomplished by the synthetic sequences as previously reported [6, 13]. Thus, by reaction of phtalide (***1***) with potassium *p*-thiocresolate (***2***), in xylene under reflux, we obtained the acid (***4***). The resulted potassium salt of 2-(4-tolylthiomethyl)benzoic acid (**3**) has a good solubility in 10% aqueous potassium hydroxide solution, allowing its separation from xylene. The acid (**4**) was precipitated using a mineral acid solution (hydrochloric acid). Potassium *p*-thiocresolate (***2***) was obtained through the reaction of *p*-thiocresol with potassium hydroxide in xylene, the resulting water being removed by azeotropic distillation.

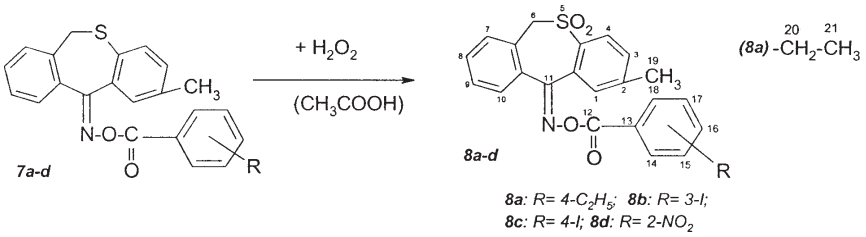
Ketone (***5***) was synthesized by cyclodehydration of acid (***4***) in the presence of polyphosphoric acid (PPA). The reactions are presented in scheme 1.



Scheme 1
Synthesis of 2-(4-tolylthiomethyl)benzoic acid (***4***) and 2-methyl-6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (***5***)



Scheme 2
Synthesis of 2-methyl-O-acyl-oximino-dibenzo[b,e]thiepins (***7***)



Scheme 3
Synthesis of the new 2-methyl-O-acyl-oximino-dibenzo[b,e]thiepin-5,5-dioxides (8)

The ketone (***5***) was converted to the corresponding oxime (***6***) by treatment with hydroxylamine hydrochloride in the presence of pyridine. The new 2-methyl-O-acyloximino-dibenzo[b,e]thiepins (***7***) were prepared by acylation of the 11-hydroximino-2-methyl-6,11-dihydro-dibenzo[b,e]thiepine (***6***) with various acid chlorides, in dry toluene, in the presence of anhydrous pyridine as a proton acceptor. The reactions are presented in scheme 2.

The new sulfones (***8***) were prepared by the oxidation of 2-methyl-O-acyl-oximino-dibenzo[b,e]thiepins (***7***) with 30% hydrogen peroxide in glacial acetic acid at boiling temperature. The reaction is presented in scheme 3. The literature presents [14, 15] the oxidation of the tricycle dibenzo[b,e]thiepine system with hydrogen peroxide (30%) in the presence of acetic acid.

The new compounds are solid, crystallized, white or light yellow. O-acyl-oximino-dibenzo[b,e]thiepins (**7**) and sulfones (**8**) are soluble at room temperature in acetone, chloroform, benzene, toluene, xylene, dichloromethane, by heating in inferior alcohols, insoluble in water. The structures of these compounds were elucidated by FTIR, NMR spectroscopy and elemental analysis (all elemental analyses results were within ±0.4 of the theoretical values). The IR, ^{1}H-NMR and ^{13}C-NMR spectra show all the expected signals.

Owing to the asymmetry induced by sulphur atom in dibenzothiepine nucleus, the oxime (**6**) may have *sin* or *anti* configuration. On this account, a notable difference appears in some compounds (**7a-d**) and (**8a-d**) between the chemical shifting of the protons from the dibenzo rings. Also, the number of the carbon signals is larger than that corresponding to the raw formula, owing to the two different "sin" and "anti" configurations. As to the carbon atoms data, the chemical shifting have been noted by **M** for the major and **m** from the minor compound.

Conclusions

In order to obtain new compounds with antimicrobial activity we have synthesized new dibenzo[b,e]thiepine derivatives, 2-methyl-O-acyloximino-dibenzo[b,e]thiepins **7a-d** and 2-methyl-O-acyloximino-dibenzo[b,e]thiepine-5,5-dioxides **8a-d**. The original dibenzo[b,e]thiepins were prepared by acylation of the 11-hydroximino-2-methyl-6,11-dihydrodibenzo[b,e]thiepine with various acid chlorides, respectively by the oxidation of the compounds **7a-d** to the corresponding 5,5-dioxides.

The new derivatives were characterized by elemental analysis, spectral analysis (^{1}H-NMR, ^{13}C-NMR, IR) and TLC. Preliminary screening for antimicrobial activity exhibited specific antimicrobial properties against different bacterial and fungal strains.

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