NEW 6,11-DIHYDRODIBENZO[b,e]THIEPINE DERIVATIVES. NOTE VI

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Abstract
The present paper describes the synthesis and characterization of some new 6,11-dihydrodibenzo[b,e]thiepine derivatives. The synthesis was performed in several stages via 11-hydroximino-6,11-dihydrodibenzo[b,e]thiepine, 11-hydroximino-2-methyl-6,11-dihydrodibenzo[b,e]thiepine, respectively. The structures of the newly synthesized compounds were confirmed by elemental analysis and spectroscopic (IR, 1H NMR, 13C-NMR) data.

Keywords: dibenzo[b,e]thiepine, tricyclic derivatives

Introduction
Dibenzo[b,e]thiepine derivatives constitute an important class of therapeutic agents, with a broad spectrum of biological activities [1, 4, 5, 6, 15]. Dosulepine (Prothiaden®, Dothiepin®) is used in the treatment of major depressive disorder and also used as adjuvant in the management of pain. 2-Methyl-derivative of dosulepine, medosulepine (Methiaden®), is 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. Amidepine and monatepil (AJ-2615) are used in the treatment of angina and hypertension.
In previous papers [3, 7-12] we reported the synthesis of some new dibenzo[b,e]thiepine derivatives. The positive results of our preliminary pharmacological investigation (which emphasize antidepressant, psychosedative and analgesic properties [2]) and as part of our ongoing studies in developing new antimicrobial active compounds [13, 14] we present the synthesis and characterization of new 6,11-dihydropibenzo[b,e]thiepine derivatives.

**Materials and methods**

Starting materials were purchased from commercial suppliers and were used without further purification unless otherwise specified.

Melting points (m.p.) were determined in open capillaries on an Electrothermal 9100 apparatus and are uncorrected.

The NMR spectra were recorded on a Varian Gemini 300BB apparatus, at 300 MHz for $^1$H-NMR and 75 MHz for $^{13}$C-NMR and an Unity-Inova 400 operating at 400 MHz in proton and 100 MHz in carbon. Dimethylsulfoxide-d$_6$ and chloroform-d$_1$ were used as solvents. The spectra were recorded at room temperature in usual conditions and sometimes Apt and Cosy sequences are used. The chemical shifts are expressed in $\delta$ parts per million (ppm) values downfield to tetramethylsilane used as internal standard. The coupling constants values are reported in hertz and the splitting patterns are abbreviated as following: s, singlet; d, doublet; t, triplet; m-multiplet; b, broad.

The IR spectra were recorded by ATR technique with an FT-IR Bruker instrument Vertex 70.

Elemental analyses were performed on a Perkin-Elmer CHNS/O Analyser Series II 2400 apparatus.

The synthesis of the new O-acyloxino-dibenzo[b,e]thiepins 6 was accomplished by the synthetic sequences as previously reported [3, 7-12]. Thus, by reaction of phtalide 1 with potassium salt of thiophenol 2a or p-thiocresol 2b, we obtained 2-(phenylthiomethyl)benzoic acid 3a and 2-(4-tolylthiomethyl)benzoic acid 3b, respectively. The synthesis of ketones 4 was carried out by cyclodehydration of acids 3 in the presence of polyphosphoric acid (PPA). Oximes 5 were obtained by the treatment of ketones 4 with hydroxylamine hydrochloride in the presence of pyridine (Py). The oximes were afterwards condensed with various acid chlorides (Fig. 1).
The starting compounds 2-(phenylthiomethyl)benzoic acid (3a) 2-(4-tolylthiomethyl)benzoic acid (3b), 6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (4a), 2-methyl-6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (4b), 11-hydroximino-6,11-dihydrodibenzo[b,e]thiepine (5a) and 11-hydroximino-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (5b) were synthesized according to the methods described previously [3, 7-12].

The acylation of the oximes 5 with various acid chlorides afforded the new O-acyloximino-dibenzo[b,e]thiepins 6.

Synthesis procedures of compounds 3-5, and general procedure for the synthesis of compounds 6

2-(Phenylthiomethyl)benzoic acid (3a); C_{14}H_{12}O_{2}S; 244.30

To a solution of 11g (0.1 mol) thiophenol in 60 mL xylene was added 5.61 g (0.1 mol) potassium hydroxide, and the mixture was refluxed until 2 mL of water were removed; after addition of 13.41 g (0.1 mol) phthalide, the mixture was refluxed for 3h. After cooling, the solidified mixture was dissolved in 10% potassium hydroxide and diluted with 100 mL water. The aqueous phase was separated and it was acidulated (pH= 3) with 1M hydrochloric acid. The precipitate was filtered and further recrystallized from aqueous ethanol.
2-(4-Tolylthiomethyl)benzoic acid (3b); C\textsubscript{15}H\textsubscript{14}O\textsubscript{2}S; 258.32
Similarly to the previous case, 12.42 g (0.1 mol) p-thiocresol and 5.61 g (0.1 mol) phtalide yielded crude product 3b, which was recrystallized from aqueous ethanol.

6,11-Dihydrodibenzo[b,e]thiepin-11(6H)-one (4a); C\textsubscript{14}H\textsubscript{10}OS; 226.29
140 g Polyphosphoric acid was heated to 80\degree C; 24.43 g (0.1 mol) 2-(phenylthiomethyl)benzoic acid (3a) were slowly added, under stirring, and the mixture was heated for 1h to 100-110\degree C. After partial cooling (80\degree C), it was decomposed with ice and water, the product was extracted with dichloromethane, and the extract was washed with water and 5% sodium hydroxide; the solvent was removed under vacuum and the residue was recrystallized from isopropanol.

2-Methyl-6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (4b); C\textsubscript{15}H\textsubscript{12}OS; 240.31
Cyclodehydration of 25.83 g (0.1 mol) 2-(4-tolylthiomethyl)benzoic acid (3b) in the presence of PPA, by heating for 2.5h to 140-150\degree C was carried out similarly to the previous case; the crude product was recrystallized from ethanol.

11-Hydroximino-6,11-dihydrodibenzo[b,e]thiepine (5a); C\textsubscript{14}H\textsubscript{11}NOS; 241.3
A mixture of 11.3 g (0.05 mol) 6,11-dihydrodibenzo[b,e]thiepin-11(6H)-one (4a) and 10.5 g (0.15 mol) hydroxilamine hydrochloride are boiled under reflux in 100 mL of pyridine for 24h. The pyridine was subsequently removed under vacuum; the residue was triturated with water, suction-filtered, dried and recrystallized from isopropanol.

11-Hydroximino-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (5b); C\textsubscript{15}H\textsubscript{13}NOS; 255.33
Similarly to the previous case 12.01 g (0.05 mol) (4b) and 10.5 g (0.15 mol) hydroxilamine hydrochloride yielded crude product 4b which was recrystallized from isopropanol.

**General procedure for the synthesis of compounds 6**

To a solution of 5a or 5b (10 mmol) in 50 mL anhydrous benzene was added 10 mmol of appropriated acid chloride in 50 mL anhydrous benzene; 10 mmol anhydrous pyridine was added and the reaction mixture was heated to reflux for 2h. The reaction mixture was then cooled to room temperature, the precipitate was filtered, and the solvent was removed under reduced pressure. The resulting crude product was recrystallized from an appropriate solvent.
Results and discussion

The starting compounds acids 3a and 3b, ketones 4a and 4b and oximes 5a and 5b were obtained in good yields, according to the literature data [3, 7-12]. The new compounds 6 (Table I) were prepared from intermediates 5 and the appropriate acid chloride according to the General procedure.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R’</th>
<th>Compound</th>
<th>R</th>
<th>R’</th>
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<tbody>
<tr>
<td>6a.1</td>
<td>-H</td>
<td></td>
<td>6b.1</td>
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<tr>
<td>6a.2</td>
<td>-H</td>
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<tr>
<td>6a.3</td>
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<td>6b.3</td>
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</tr>
<tr>
<td>6a.4</td>
<td>-H</td>
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<td>6b.4</td>
<td>-CH₃</td>
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11-[O-(2,5-Dichlorobenzoyl)-oximino]-6,11-dihydrodibenzo[b,e]thiepin (6a.1) C₂₁H₁₃NO₂SCl₂ (414.31); white crystals, m.p. 139.3-141.1 (i-propanol); yield 70.6%. ¹H-NMR (CDCl₃+DMSO (10:1), δ, ppm, J, Hz); 3.51 (bs, 1H, H-6A); 3.60 (bs, 1H, H-6B); 7.05-7.38 (m, 9H); 7.41 (d, 2.2, 1H, H-18); 7.72 (dd, 7.4, 1.7, 1H, H-1). ¹³C-NMR (CDCl₃+DMSO (10:1), δ, ppm); 33.30 (C-6); 124.90 (CH); 126.39 (CH); 126.93 (CH); 127.21 (CH); 128.00 (CH); 128.61 (Cq); 130.36 (CH); 130.55 (CH); 131.12 (CH); 131.37 (CH); 133.27 (Cq); 134.99 (Cq); 137.19 (Cq); 161.62 (C-11); 168.56 (C-12). FT-IR (ATR in solid, ν cm⁻¹): 3520w; 3062w; 2965w; 2924w; 1768vs; 1752s; 1606w; 1579s;
11-[O-(3,4-Dichlorobenzoyl)-oximino]-6,11-dihydrodibenzo[b,e]thiepine (6a.2)  
C_{21}H_{13}NO_2SCl_2 (414.31); white crystals, m.p. 163.2-165.9 \(^0\)C (i-propanol); yield 69.8%.  

\(^1\)H-NMR (CDCl\(_3\), \(\delta\) ppm, J, Hz): 3.52 (bs, 1H, H-6A); 4.62 (bs, 1H, H-6B); 7.10-7.50 (m, 8H); 7.61 (dd, 8.4, 1.9, 1H, H-18); 7.77 (d, 1.9, 1H, H-14); 7.80 (dd, 7.7, 1.7, 1H, H-1); 13C-NMR (CDCl\(_3\), \(\delta\) ppm): 33.34 (C-6); 125.05 (CH); 126.65 (CH); 126.97 (CH); 127.16 (CH); 128.08 (CH); 128.55 (CH); 130.52 (CH); 130.66 (CH); 130.71 (CH); 131.50 (CH); 131.66 (CH); 133.04 (Cq); 133.09 (Cq); 135.14 (Cq); 137.14 (Cq); 138.05 (Cq); 161.63 (C-11); 167.81 (C-12). FT-IR (ATR in solid, \(\nu\) cm\(^{-1}\)): 3478w; 3065w; 2966w; 1751vs; 1585m; 1558w; 1485w; 1465m; 1425m; 1381m; 1327m; 1282m; 1261s; 1218vs; 1167m; 1122w; 1084s; 1065s; 1032m; 982m; 880s; 826w; 786w; 766m; 744m; 729m; 698w; 678m; 636w; 596w. Anal.Calcd.(%) for C_{21}H_{13}NO_2SCl_2: C60.88, H3.16, N3.38, S7.74. Found: C60.61, H3.19, N3.32, S7.69.

11-[O-(2-metoxi-benzoyl)-oximino]-6,11-dihydrodibenzo[b,e]thiepine (6a.3)  
C_{22}H_{17}NO_3S (375.44); white crystals, m.p. 133.2-165.9 \(^0\)C (i-propanol); yield 63.4%.  

\(^1\)H-RMN (CDCl\(_3\), \(\delta\) ppm, J Hz): 3.52 (bs, 1H, H-6A); 4.62 (bs, 1H, H-6B); 6.90-7.60 (m, 10H, H-arom); 7.57 (dd, 1H, H-1, 1.9, 8.0); 7.85 (dd, 1H, H-4, 1.8, 8.3). 13C-RMN (CDCl\(_3\), \(\delta\) ppm): 33.43 (C-6); 55.81 (C-19); 112.06 (CH); 118.54 (Cq); 120.23 (CH); 124.58 (Cq); 125.08 (CH); 126.19 (CH); 127.19 (CH); 127.51 (CH); 128.02 (CH); 129.21 (Cq); 130.22 (CH); 130.55 (CH); 131.98 (CH); 134.04 (CH); 134.36 (Cq); 136.93 (Cq); 159.42 (Cq); 163.88 (Cq); 166.66 (C-12). FT-IR (ATR in solid, \(\nu\) cm\(^{-1}\)): 3066w; 2966w; 1751vs; 1585m; 1558w; 1485w; 1465m; 1381m; 1327m; 1282m; 1261s; 1218vs; 1167m; 1122w; 1084s; 1065s; 1032m; 982m; 880s; 826w; 786w; 766m; 744m; 729m; 698w; 678m; 636w; 596w. Anal.Calcd.(%) for C_{22}H_{17}NO_3S: C70.38, H4.56, N3.73, S8.54. Found: C70.50, H4.49, N3.79, S8.61.

11-[O-(2,5-Dichloro-benzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (6b.1)  
C_{22}H_{15}NO_2SCl_2 (428.34); white crystals, m.p. 164.3-166.8 \(^0\)C (i-propanol); yield 66.5%.  

\(^1\)H-NMR (CDCl\(_3\), \(\delta\) ppm, J, Hz): 2.31 (s, 3H, CH\(_3\)-19); 3.52 (bs, 1H, H-6A); 4.63 (bs, 1H, H-6B); 7.00 (d, 8.1, 1H, H-4); 7.08 (bddd, 8.1, 1.9, 1H, H-3); 7.20-7.48 (m, 7H); 7.62 (bs,1H, H-1). 13C-NMR
11-[O-(3,4-Dichloro-benzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (6b.2). C_{22}H_{15}NO_2SCl_2 (428.34); white crystals, m.p 194.6-196.8 (i-propanol); yield 68.5%. \(^1\)H-NMR (CDCl_3, δ, ppm, J, Hz); 2.31 (s, 3H, CH$_3$-19); 3.52 (bs, 1H, H-6A); 4.61 (bs, 1H, H-6B); 7.01 (d, 8.1, 1H, H-4); 7.09 (dd, 8.1, 2.0, 1H, H-3); 7.23-7.60 (m, 6H); 7.62 (bs, 1H, H-1); 7.77 (d, 1.9, 1H, H-14). \(^{13}\)C-NMR (CDCl_3), δ, ppm); 20.58 (CH$_3$-19); 33.34 (C-6); 126.64 (CH); 126.91 (CH); 127.07 (CH-4); 128.05 (CH-18); 128.54 (CH-17); 128.79 (Cq); 129.65 (Cq); 130.44 (CH); 130.66 (CH); 131.56 (CH-3); 131.79 (CH-14); 131.91 (CH-1); 133.05 (Cq); 133.10 (Cq); 133.51 (Cq); 134.92 (Cq); 135.19 (Cq); 138.04 (Cq); 161.69 (C-11); 167.96 (C-12). FT-IR (ATR in solid, ν cm$^{-1}$): 3089w; 2964w; 2916w; 1751vs; 1589w; 1465w; 1419w; 1381w; 1324m; 1264m; 1233s; 1218vs; 1162w; 1084m; 1058m; 1029m; 1017m; 992w; 919w; 903s; 876w; 837w; 812w; 760w; 746m; 723w; 699w; 570w. Anal.Calcd. (%) for C$_{22}$H$_{15}$NO$_2$SCl$_2$: C 61.69, H 3.53, N 3.27, S 7.49. Found: C 61.45, H 3.54, N 3.20, S 7.39.

11-[O-(2,4-Dichloro-benzoyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (6b.3). C$_{22}$H$_{15}$NO$_2$SCl$_2$ (428.34); white crystals, m.p 165.9-167.0 (i-propanol); yield 70%. \(^1\)H-NMR (CDCl_3, δ, ppm, J, Hz); 2.30 (s, 3H, CH$_3$-19); 3.51 (bs, 1H, H-6A); 4.62 (bs, 1H, H-6B); 7.00 (bd, 7.2, 1H, H-4); 7.07 (bd, 7.2, 1H, H-3); 7.18-7.40 (m, 6H); 7.47 (dd, 8.5, 1.1, 1H, H-17); 7.62 (bs, 1H, H-1). \(^{13}\)C-NMR (CDCl_3), δ, ppm); 20.57 (CH$_3$-19); 33.28 (C-6); 126.38 (CH); 126.95 (CH); 127.02 (CH); 127.19 (CH); 127.99 (CH); 130.33 (CH); 130.99 (CH); 131.73 (CH-3); 131.78 (CH-1); 132.46 (CH-17); 133.34 (Cq); 133.45 (Cq); 134.86 (Cq); 134.95 (Cq); 135.03 (Cq); 135.70 (Cq-4a); 162.18 (C-11); 168.28 (C-12). FT-IR (ATR in solid, ν cm$^{-1}$): 3061w; 2969w; 2924w; 2827w; 1774vs; 1588w; 1573w; 1558w; 1484w; 1464m; 1424w; 1379w; 1324m; 1281m; 1255w; 1216w; 1168w; 1142w; 1093s; 1070w; 1030vs; 978s; 878m; 826m; 789w; 766m; 753m; 730w; 682w; 661w; 638w;

11-[O-(2-Thienylacetyl)-oximino]-2-methyl-6,11-dihydrodibenzo[b,e]thiepine (6b.4). $C_{21}H_{17}NO_2S_2$ (379.49); white crystals, m.p 128.4-129.8°C (i-propanol); yield 79.5%. $^1H$-NMR (CDCl$_3$, $\delta$ ppm, J Hz): 2.30 (s, H-18); 3.53 (bs, H-6B); 3.81 (s, H-13); 4.54 (bs, H-6A); 6.79(dq, H-15, 3.3, 1.0); 6.89 (dd, H-16, 3.3, 5.1); 7.00 (d, H-4, 8.2); 7.07 (dd, H-3, 1.9, 8.2); 7.08 (dd, H-7, 1.4, 7.6); 7.16 (dd, H-17, 1.2, 5.1); 7.25 (td, H-8, 7.6, 1.4); 7.31 (dd, H-10, 1.4, 7.6); 7.38 (td, H-9, 7.6, 1.4); 7.35 (d, H-1, 1.9). $^{13}C$-NMR (CDCl$_3$, $\delta$ ppm): 20.56 (C-18); 33.24 (C-6); 34.26 (C-13); 125.10 (C-17); 126.33 (C-10); 126.85 (C-16); 126.94 (C-7); 127.10 (C-15); 127.26 (C-8); 127.95 (C-4); 128.46 (Cq); 130.16 (C-9); 131.62 (C-3); 131.85 (C-1); 133.03 (Cq); 133.33 (Cq); 133.91 (Cq); 134.78 (Cq); 134.81 (Cq); 167.43 (C-12); 167.50 (C-11). FT-IR(ATR in solid, $\nu$ cm$^{-1}$): 3106w; 3077w; 3042w; 2960w; 2922w; 1772s; 1749vs; 1591m; 1471m; 1394m; 1323s; 1252w; 1202m; 1154m; 1105vs; 1063s; 1036m; 1018m; 920m; 894s; 877m; 810s; 767s; 712s; 695s; 629w. Anal.Calcd.(%) for $C_{21}H_{17}NO_2S_2$: C 66.47, H 4.52, N 3.69, S 16.90. Found: C 66.38, H 4.60, N 3.60, S 17.02.

Conclusions

We have synthesized new 6,11-dihydrodibenzo[b,e]thiepine derivatives as potential new therapeutical agents. All the original compounds were characterized by their main physical properties and their structure was confirmed by spectral analysis ($^1H$-NMR, $^{13}C$-NMR, IR) and elemental analysis. The new compounds will be further investigated for their biological activity.

Acknowledgements

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References

14. Stecoza C. E., Căprioiu M. T., Drăghici C., Chifiriuc M. C., Drăcea N. O., Synthesis, characterization and antimicrobial activity evaluation of some new derivatives of 6,11-dihydrodibenzo[b,e]thiepin 5,5-dioxide, Revista de Chimie (București) 2009, 60(2),137-141

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