SYNTHESIS OF SEVERAL NEW PHENYLETHYLAMIDES OF SUBSTITUTED BENZOIC ACIDS

José M. Barbosa Filho, Edvan C. da Silva and Jnanabrata Bhattacharyya
Laboratório de Tecnologia Farmacêutica, Universidade Federal da Paraíba, 58.059 João Pessoa – Paraíba – Brasil.

Synthesis and spectral characteristics of several new p-methoxy-phenylethylamides of substituted benzoic acids which are analogs of some bioactive natural products is described.

Phenylethylamines and *p*-hydroxyphenylethylamines and their derivatives are found extensively distributed in nature. However, amides derived of substituted benzoic acids are relatively rare[1]. Recently, six of these amides have been isolated[2] from the fruits of *Aniba riparia* (Nees) Mez (Lauraceae), two of which, N-benzoyltyramine and its methyl ether, were encountered earlier in Rutaceae[3]. The discovery of the antibiotic activity of the amides isolated from *A. riparia*, led us to synthesize several of the analogs of these amides for studying their spectral characteristics and biological activity.

The compound found to be most active against a group of selected microorganisms is N-[8'-(4'-methoxyphenyl)]-2,6-dihydroxybenzoylamide (I)[2]. Other amides isolated from *A. riparia* were also found to have limited activity against at least one specific fungus of the genus *Cladosporium*. As the active compounds isolated from *A. riparia* are conjugates of O-methyltyramine and substituted benzoic acids, we decided to synthesize several analogs of these keeping the amine moiety constant with variations in the substitution pattern of the benzoic acid moiety.

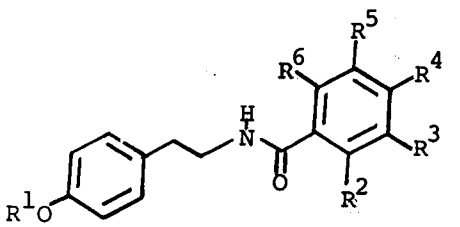
The general method for the synthesis of the compounds I – X involves the preparation of the various substituted benzoylchlorides by the reaction of the corresponding benzoic acids with $SOCl_2$ in the usual way followed by the condensation of the acyl chlorides with O-methyltyramine in the same pot. The yields of the products depended very much on the structures of the starting benzoic acids and were high (64 – 93%) for compounds V – X. The yields of the compounds having free phenolic OH groups (I – IV) were markedly low (2 – 5.5%). The reason for this is the formation of undesired by products due to the side reaction between the OH groups of the starting acids and the acyl chlorides initially formed, thus reducing the yields of the latter.

We believe that because of the similarity of these synthetic amides with those isolated from natural sources, there is a good possibility of encountering one or more of these compounds (I – X) in nature.

EXPERIMENTAL

The General Method for the Preparation of the Amides (I – X):

The benzoic acid (1,0 g) was added to $SOCl_2$ (5 ml) and the mixture was refluxed for 2 hr. The excess reagent was removed *in vacuo*. Benzene was added followed by O-methyltyramine, (2,0 g) and the mixture was refluxed for 30 min. The solvent was then removed *in vacuo*, the residue was triturated with dil. HCl and the acid was removed by filtration. The residue was then washed with water and the solid was collected by filtration. The crude amide was taken up in $CHCl_3$, dried with annydrous Na_2SO_4 and concentrated. The $CHCl_3$ solution was subsequently run through a colunm of silica gel (10.0 g) and eluted with $CHCl_3$. The total $CHCl_3$ elate was evaporated to give a solid which was crystallized several times from ether-benzene.



I	R^1=Me; R^2=R^3=R^5=R^6=H; R^4=OH
II	R^1=Me; R^2=OH; R^3=R^4=R^6=H; R^5=OMe
III	R^1=Me; R^2=OH; R^3=R^5=R^6=H; R^4=OMe
IV	R^1=Me; R^2=R^5=R^6=H; R^3=OCH_3; R^4=OH
V	R^1=Me; R^2=R^5=R^6=H; R^3=R^4=OCH_2O
VI	R^1=Me; R^2=R^4=R^5=R^6=H; R^3=OMe
VII	R^1=Me; R^2=R^5=R^6=H; R^3=R^4=OMe
VIII	R^1=Me; R^2=R^3=R^5=R^6=H; R^4=OMe
IX	R^1=Me; R^2=R^4=R^6=H; R^3=R^5=OMe
X	R^1=Me; R^3=R^4=R^5=OCH_3; R^2=R^6=H

N-[8'-(4'-methoxyphenylethyl)]-4-hydroxybenzoylamide (I)

Mp 170-172° C

UV λ_{max}^{MeOH} nm: 229, 257, 283 (ϵ 14900, 17300, 4050).

IR ν_{max}^{KBr} cm^{-1}: 3420, 3220, 1635, 1605, 1575, 1500.

MS (m/z, rel. int.): M^+ 271 (0.1); 134 (100); 121 (85); 93 (11).

^{1}H NMR (60 MHz, $CDCl_3/CD_3COCD_3$): δ 10.48 (brs, OH); 7.68 (d, J = 8 Hz, H-2, H-6), 7.20 (d, J = 8 Hz, H-2'; H-6'); 6.90 (d, J = 8 Hz, H-3, H-5, H-3', H-5'), 3.80 (s, OMe), 3.70 (brq, 2 H-8'), 2.85 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3/CD_3COCD_3$): δ 167.3 (C-7); 161.3 (C-4); 158.5 (C-4'); 132.3 (C-1'); 130.5 (C-2, C-6); 129.9 (C-2', C-6'); 126.8 (C-1), 115.8 (C-3, C-5), 114.6 (C-3', C-5'); 55.4 (OMe); 42.3 (C-8'), 35.6 (C-7').

N-[8'- (4'-methoxyphenylethyl)] -2-hydroxy-5-methoxy-benzoylamide (II)

Mp 118-120°C

UV λ_{max}^{MeOH} nm: 225, 245, 330 (ε 26180, 11430, 5100).

IR ν_{max}^{KBr} cm^{-1}: 3340, 1615, 1580, 1490.

MS (m/z, rel. int.): M^+ 301 (1); 151 (65); 134 (100).

^{1}H NMR (60 MHz, $CDCl_3$): δ 11.90 (brs, OH); 7.40 – 6.80 (m, Ar-H), 6.53 (brs, N–H); 3.90 (s, Ome); 3.80 (s, OMe); 3.72 (brq, 2 H-8'); 2.95 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3$): δ 169.7 (C-7); 158.7 (C-4'); 155.4 (C-2); 151.8 (C-5); 130.5 (C-1'); 129.8 (C-2', C-6'), 121.0 (C-4), 119.1 (C-3); 114.3 (C-3', C-5'); 110.0 (C-1); 109.8 (C-6); 56.0 (OMe); 55.3 (OMe); 41.0 (C-8'); 34.6 (C-7').

N-[8'- (4'-methoxyphenylethyl)] -2-hydroxy-4-methoxybenzoylamide (III)

Mp 148-150°C

UV λ_{max}^{MeOH} nm: 222, 258, 300 (ε 19560, 10530, 5100).

IR ν_{max}^{KBr} cm^{-1}: 3330, 1620, 1570, 1529, 1480.

MS (m/z, rel. int.): M^+ 301 (5); 151 (69); 134 (100)..

^{1}H NMR (60 MHz, $CDCl_3$): δ 12.5 (brs, OH); 7.30 (d, J = 8 Hz, H-6); 7.18 (d, J = 8 Hz, H-2', H-6'); 6.85 (d, J = 8 Hz, H-3', H-5'); 6.46 (s, H-3); 6.40 (d, J = 8 Hz, H-5); 6.30 (brs, N-H); 3.83 (s, 2 x OMe), 3.75 (brq, 2 H-8'); 2.85 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3$): δ 170.0 (C-7); 164.3 (C-2); 163.9 (C-4); 158.8 (C-4'); 130.7 (C-1'); 129.8 (C-2', C-6'), 126.6 (C-6), 114.4 (C-3', C-5'); 107.6 (C-1); 106.9 (C-5); 101.8 (C-3).

N-[8'- (4'-methoxyphenylethyl)] -3-methoxy-4-hidroxy-benzoylamide (IV)

Mp 118-120°C

UV λ_{max}^{MeOH} nm: 220, 262, 284 (ε 42140, 17450, 9000).

MS (m/z, rel. int.): M^+ 301 (3); 151 (38); 134 (100).).

^{1}H NMR (60 MHz, $CDCl_3$): δ 7.48 (m, H-6); 7.15 (d, 8 Hz, H-2', H-6'); 6.85 (d, 8 Hz, H-3', H-5'); 6.51 (brs, NH); 3.85 (s, OMe); 3.80 (s, OMe); 3.75 (brq, 2 H-8'); 2.82 (t, 2 H-7').

N-[8'-(4'-methoxyphenylethyl)] -4-methoxybenzoylamide (V)

Mp 166-168°C

UV λ_{max}^{MeOH} nm: 228, 254, 284 (ε 11400, 13680, 2300).

IR ν_{max}^{KBr} cm^{-1}: 3300, 1625, 1595, 1535, 1490.

MS (m/z, rel. int.): M^+ 285 (2); 135 (55); 134 (100).

^{1}H NMR (60 MHz, $CDCl_3$): δ 7.72 (d, J = 8 Hz, H-2, H-6); 7.20 (d, J = 8 Hz, H-2', H-6'); 6.92 (d, J = 8 Hz, H-3, H-5); 6.90 (d, J = 8 Hz, H-3', H-5'); 6.25 (brs, NH); 3.83 (s, OMe); 3.80 (s, OMe); 3.70 (brq, 2 H-8'); 2.85 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3$): δ 167.0 (C-7); 162.2 (C-4); 158.4 (C-4'); 131.1 (C-1'); 129.8 (C-2', C-6'); 128.7 (C-2, C-6); 127.1 (C-1); 114.2 (C-3', C-5'); 113.8 (C-3, C-5); 55.3 (OMe); 41.3 (C-8'); 35.0 (C-7').

N-[8'-(4'-methoxyphenylethyl)] -3-methoxybenzoylamide (VI)

Mp 94-96°C

UV λ_{max}^{MeOH} nm: 225, 246, 285 (ε 28500, 9700, 4560).

IR ν_{max}^{KBr} cm^{-1}: 3300, 1630, 1585, 1535, 1515.

MS (m/z, rel. int.): M^+.285 (2); 135 (43); 135 (100); 121 (13).

^{1}H NMR (60 MHz, $CDCl_3$): δ 7.50 – 6.70 (m, Ar-H); 6.50 (brs, NH); 3.80 (s, OMe); 3.70 (brq, 2 H-8'); 2.85 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3$): δ 167.4 (C-7); 159.8 (C-3); 158.3 (C-4'); 136.3 (C-1); 131.0 (C-1'); 129.6 (C-2', C-6'); 129.4 (C-5); 118.8 (C-6); 117.4 (C-4); 114.1 (C-3', C-5'); 112.4 (C-2); 55.2 (OMe); 41.5 (C-8'); 34.8 (C-7').

N-[8'-(4'-methoxyphenylethyl)] -3,4-dimetoxybenzoylamide (VII)

Mp 158-160°C

UV λ_{max}^{MeOH} nm: 218, 261, 286 (ε 24880, 9450, 5000).

IR ν_{max}^{KBr} cm^{-1}: 3280, 1625, 1580, 1545, 1510.

MS (m/z, rel. int.): M^+ 315 (2); 181 (14); 165 (50); 134 (100).

^{1}H NMR (60 MHz, $CDCl_3$): δ 7.48 (m, H-6); 7.25 (s, H-2); 7.18 (d, J = 8 Hz, H-2', H-6'); 6.85 (d, J = 8 Hz, H-3', H-5'); 6.83 (d, J = 8 Hz, H-5); 6.55 (brs, NH); 3.90 (s, OMe); 3.78 (s, OMe); 3.70 (brq, 2 H-8'); 2.85 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3$): δ 167.1 (C-7); 158,4 (C-4'); 151.8 (C-4); 148.8 (C-3); 131.1 (C-1'); 129.8 (C-2', C-6'); 127.6 (C-1); 119.6 (C-6); 114.1 (C-3', C-5'); 110.8 (C-5);

110.6 (C-2); 56.0 (OMe); 55.3 (OMe); 41.5 (C-8'); 34.9 (C-7').

N-[8'-(4'-methoxyphenylethyl)] -3,4-methylenodioxybenzoylamide (VIII)

Mp 153-155°C

UV λ_{max}^{MeOH} nm: 218, 265, 292 (ε 27200, 7470, 5680).

IR ν_{max}^{KBr} cm^{-1}: 3280, 1620, 1595, 1525, 1490.

MS (m/z, rel. int.): M^+ 299 (2); 149 (48); 134 (100); 121 (23).

^1H NMR (60 MHz, $CDCl_3/CF_3COOD$): δ 7.38 (d, J = 8 Hz, H-6); 7.25 (s, H-2); 7.18 (d, J = 8 Hz, H-2', H-6'); 6.86 (d, J = 8 Hz, H-5); 6.80 (d, J = 8 Hz, H-3', H-4'); 6.02 (s, OCH_2O); 3.80 (s, OMe); 3.68 (brq, 2 H-8'); 2.85 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3/CF_3COOD$): δ 170.0 (C-7); 158.1 (C-4'); 151.5 (C-4); 148.3 (C-3); 130.3 (C-1'); 129.7 (C-2', C-6'); 125.4 (C-1); 122.3 (C-6); 114.5 (C-3', C-5'); 108.4 (C-5); 107.3 (C-2); 102.0 (OCH_2O); 55.4 (OMe); 42.1 (C-8'); 34.2 (C-7').

N-[8'-(4'-methoxyphenylethyl)] -3,5-dimethoxybenzoyla-mide (IX)

Mp 99-101°C

UV λ_{max}^{MeOH} nm: 225, 255, 286 (ε 14800, 4400, 1890).

IR ν_{max}^{KBr} cm^{-1}: 3280, 1635, 1598, 1552, 1515.

MS (m/z, rel. int.): M^+ 315 (1); 165 (23); 134 (100); 121 (9).

^1H NMR ($CDCl_3$, 60 MHz): δ 7.20 (d, J = 8 Hz, C-2', C-6'); 7.10 – 6.92 (s, H-2); 6.90 (d, J = 8 Hz, H-3', H-5'); 6.88 (s, H-6); 6.58 (brs, H-4); 6.40 (brs, NH); 3.80 (s, OMe); 3.68 (brq, 2 H-8'); 2.86 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3$): δ 167.5 (C-7); 116.0 (C-3, C-5); 158.1 (C-4'); 137.2 (C-1); 131.1 (C-1'); 129.8 (C-2', C-6'); 114.3 (C-3', C-5'); 105.1 (C-2, C-6); 103.6 (C-4); 55.4 (OMe); 41.5 (C-8'); 34.9 (C-7').

N-[8'-(4'-methoxyphenylethyl)] -3,4,5- trimethoxybenzoylamide (X)

Mp 134-136°C

UV λ_{max}^{MeOH} nm: 215, 264 (ε 66240, 16560).

MS (m/z, rel. int.): M^+ 345 (7); 211 (66); 195 (64); 134 (100); 121 (16).

^1H NMR (60 MHz, $CDCl_3$): δ 7.15 (d, J = 8 Hz, H-2', H-6'); 7.08 (brs, H-2, H-6); 6.80 (d, J = 8 Hz, H-3', H-5'); 3.88, 3.80, 3.72 (s, each, 4 x OMe); 3.60 (brq, 2 H-8'); 2.80 (t, 2 H-7').

^{13}C NMR (20 MHz, $CDCl_3$): δ 167.0 (C-7); 158.0 (C-4'); 152.8 (C-3, C-5); 140.0 (C-4); 130.6 (C-1'); 129.5 (C-2', C-6'); 129.3 (C-1); 113.7 (C-3', C-4'); 104.5 (C-2, C-6); 60.3, 55.9, 55.7 (4 x OMe); 41.3 (C-8'); 34.4 (C-7').

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