Molecular Medicinal Chemistry

IDECEFYN

vol 13 May-August 2007, **26-29** http://www.idecefyn.com.ar ISSN 1666-888X

Total synthesis of *n*-methyl-*n*-formyltyramine, a new β-phenethylamide derivative isolated from *cyathobasis fruticulosa* (bunge) aellen

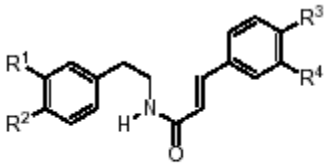
Enrique L. Larghi and Teodoro S. Kaufman*

Instituto de Química Orgánica de Síntesis (IQUIOS, CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531 S2002LRK Rosario, Argentina. E-mail: larghi@iquios.gov.ar

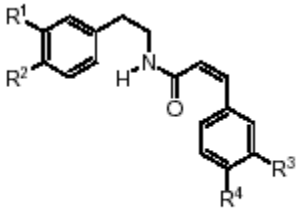
Introduction

The family of β-phenethylamides, exemplified by compounds **1** and **2** (Bohlmann *et al.*, 1984) comprises a large number of substances widely distributed in nature. These substances have been found mostly in the cell wall soluble fractions of higher plants (Martin-Tanguy *et al.*, 1978).

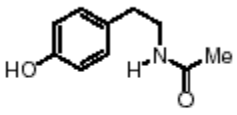
Many β-phenethylamides have been found in different plant species (Suzuki *et al.*, 1981; Adesina *et al.*, 1988; Adesina and Reisch, 1989; Horio *et al.*, 1993; Cutillo *et al.*, 2003; Kim *et al.*, 2005), and *N*-*trans*-feruloyltyramine (**3**) has already been isolated from several plant sources (Yoshihara *et al.*, 1978; Hussain *et al.*, 1982; Fukuda *et al.*, 1983; Achenbach *et al.*, 1991; Gözler *et al.*, 1992; Rahman *et al.*, 1992; Lajide *et al.*, 1995; Claros *et al.*, 2000; Seca *et al.*, 2001). Although there is yet no definitive conclusion about the function of these compounds in plants, a main role in growth and also self-defense processes has been proposed, especially because of its antimicrobial and antiviral effects (Martin-Tanguy, 1985; Martin-Tanguy and Negrel, 1987). Besides, β-phenethylamides such as **4**-**7** have been reported to have diverse and interesting biological activity from DNA strand scission (Ma *et al.*, 2004) to antimutagenic and anticarcinogenic properties (Milić and Milić, 1998). Research groups have noted that these compounds inhibit lipopolysaccharide-induced nitric oxide production in macrophages (Tanaka *et al.*, 1989; Kim *et al.*, 2003), and also inhibit acetylcholinesterase (Kim and Lee, 2003). It is worth to mention that *N*-acetyltyramine (**8**) is an inducible phytoalexine, found in soy seeds (Garcez *et al.*, 2000). On the other hand, Paik *et al.* (2001) have reported the isolation of the unusual compounds **9**-**11** in *Xenorhabdus nematophilus*, a bacterial strain that grows symbiotically with a nematode. These β-phenethylamides have shown cytotoxic activity against five cell lines of human cancer (Paik *et al.*, 2001).



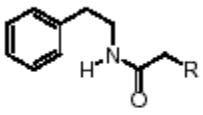
1 R^1= R^2= H, R^3-R^4= OCH_2O
3 R^1= H, R^2= R^3= OH, R^4= OMe
5 R^1= R^4= OMe, R^2= R^3= OH
7 R^1= R^4= H, R^2= R^3= OH



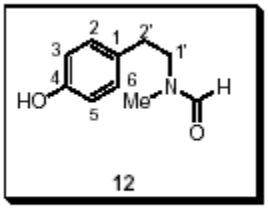
2 R^1=R^2= H, R^3-R^4= OCH_2O
4 R^1= H, R^2=R^4= OH, R^3= OMe
6 R^1=R^3= OMe, R^2=R^4= OH



8



9 R= Ph
10 R= Et
11 R= $CHMe_2$



12

Molecular Medicinal Chemistry
IDECEFYN
vol 13 May-August 2007, **26-29** http://www.idecefyn.com.ar ISSN 1666-888X

Recently, Topçu *et al.* (Bahceevli *et al.*, 2005) isolated *N*-methyl-*N*-formyltyramine (**12**) from the aerial parts and roots of *Cyathobasis fruticulosa* (Bunge) Aellen (Chenopodiaceae), the only species of the genus *Cyathobasis* found in the flora of Turkey, specifically in the region of Central Anatolia.

Taking into account the potential interest in this class of compounds, it was decided to carry out the total synthesis of the β-phenethylamides **12** from commercial 4-hydroxybenzaldehyde (**13**).

Methodology

For carrying out this synthesis usual work procedures of the laboratory of organic synthesis were followed. Reactions were carried out in glass material dried in oven and under nitrogen or argon atmosphere. All compounds led to unique spots when subjected to different TLC conditions.

Spots were visualized under UV light (254 and 365 nm), followed by spraying with appropriate reagents (ethanolic ninhydrin, *p*-anisaldehyde/H_2SO_4/EtOH, Dragendorff).

The final purification of each intermediate was carried out by column chromatography on silica gel 60H, eluting with mixtures of hexane/ethyl acetate under positive pressure using the gradient technique unless stated otherwise.

IR spectra were performed on a Shimadzu IR Prestige 21 spectrophotometer. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra were recorded in an AC200-E Bruker spectrometer (at 200.13 and 50.33 MHz, respectively). HRMS were made by Kent Electronics (UK).

Physical data of *N*-[2'-(4-hydroxyphenyl)ethyl]-*N*-methylformamide **12** (*N*-methyl-*N*-formyltyramine):

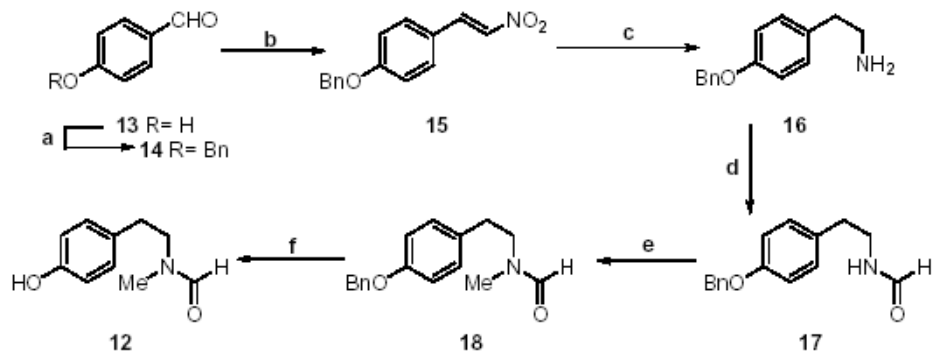
IR (KBr) νmax/cm^{-1}: 3141, 3135, 2945, 2924, 2882, 1657, 1652, 1614, 1595, 1509, 1446, 1394, 1239, 1172, 1072, 816, 768, 655 cm^{-1}; **^{1}H-NMR** (δ) *Z*-form: 2.71-2.80 (m, 2H, ArC*H*$_2$CH$_2$N), 2.86 (s, 3H, NC*H*$_3$), 3.55 (t, *J*= 7.1, 2H, ArCH$_2$C*H*$_2$N), 6.75 (d, *J*= 8.2, 2H, H-3 and H-5), 6.92 (t, *J*= 8.2, 2H, H-2 and H-6), 7.97 (s, 2H, ArOH and NC*H*O); *E*-form: 2.71-2.80 (m, 2H, ArC*H*$_2$CH$_2$N), 2.90 (s, 3H, NC*H*$_3$), 3.42 (t, *J*= 6.5, 2H, ArCH$_2$C*H*$_2$N), 6.72 (d, *J*= 8.0, 2H, H-3 and H-5), 7.03 (t, *J*= 8.0, 2H, H-2 and H-6), 7.66 (s, 1H, NC*H*O), 7.97 (s, 2H, ArOH and NC*H*O); **^{13}C-NMR** (δ) *Z*-form: 32.0 (C-2'), 34.9 (NCH$_3$), 45.9 (C-1'), 115.4 (C-3 and C-5), 129.0 (C-1), 129.5 (C-2 and C-6), 155.2 (C-4), 162.8 (N-*C*HO); *E*-form: 29.9 (C-2'), 33.4 (N*C*H$_3$), 51.7 (C-1'), 115.7 (C-3 and 5), 128.2 (C-1), 129.6 (C-2 and C-6), 155.3 (C-4), 163.2 (-N*C*HO); **HRMS** (IQ): 180.10254 ($M^{+\cdot}$ + 1); $C_{10}H_{14}NO_2$ requires 180.10245.

Results

The synthesis of the amide **12** began with Williamson's etherification of the hydroxyaldehyde **13** and benzyl chloride, giving rise to the ether **14** in almost quantitative yields (Scheme). This ether was subjected to Henry's condensation with nitromethane in the presence of ethylenediammonium diacetate as base (Barton *et al.*, 1982) leading the nitrostyrene **15** in 90% yield. This, in turn, was reduced with $LiAlH_4$ to the corresponding phenethylamine (**16**), which proved to be unstable, thus darkening easily on contact with air. Therefore, to prevent degradation **16** was converted directly, without previous purification, to the formamide **17** by treatment with ethyl formate under reflux. The crude product by chromatography led to the amide **17** in 44% yield for both combined steps (reduction-formamidation). It is interesting to emphasize that in ^{1}H- and ^{13}C-NMR spectra **17** exhibited signals consistent with the presence of two conformers, these being distinguished yet at 70ºC in DMSO-d_6.

Continuing the sequence, the amide **17** was *N*-methylated with methyl iodide in DMF using NaH as base, thus obtaining after purification by column chromatography, 79% of the intermediate **18**. The removal of the benzyl ether of **18** by catalytic hydrogenation in the presence of 10% Pd/C in absolute EtOH, allowed to have the final product **12** in 92% yield.

Molecular Medicinal Chemistry
IDECEFYN
vol 13 May-August 2007, **26-29** http://www.idecefyn.com.ar ISSN 1666-888X



Scheme (*reagents and conditions*): a) BnCl, K_2CO_3, EtOH, reflux (99%); b) $MeNO_2$, $(H_3NCH_2CH_2NH_3)^{++}$. $2AcO^-$, *t*-BuOH, 60ºC, 18 h (90%); c) $LiAlH_4$, THF, reflux, 3 h; d) HCO_2Et, reflux, 8 h (44%, 2 steps); e) 1. NaH, DMF, 65ºC, 10 min; 2. MeI, 45ºC (79%); f) H_2, 1 atm, 10% Pd/C, 4 h (92%).

It was observed that ^{1}H- and ^{13}C-NMR spectra of the synthetic product **12** were in complete agreement with those reported in the literature for the natural compound. In both spectra of **12** and **18** the presence of two conformers was found as indicated for formamide **17**.

Conclusions

The total synthesis of **12** has been carried out in 6 steps from commercial *p*-hydroxybenzaldehyde in a 25% overall yield.

The initial protection of the phenol as benzyl ether allowed adequate handling of reaction intermediates, without loss of efficiency in the synthetic sequence.

Acknowledgements

The authors are grateful to CONICET (PIP 5439) and ANPCyT (Project 06-12532) (Argentina) for financial support, and to Dr. Viviana Nicotra (UNC). E.L.L. thanks CONICET (Argentina) for the post-doctoral fellowship.

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

References

- Adesina S. K., Olatunji O. A., Bergenthal D. and Reisch J. (1988) *trans*-Cinnamoylamides from *Zanthoxylum rubescens* pericarps. *Pharmazie* **43**, 517-518.
- Adesina S. K. and Reisch J. (1989) Amides from *Zanthoxylum rubescens*. *Phytochemistry* **28**, 839-842.
- Achenbach H., Frey D. and Waibel R.(1991) 6a,7-Dehydro-2-hydroxy-4,5-dioxonoraporphine and other alkaloids from *Monocyclanthus vignei*: ^{13}C-nmr studies on 4,5-dioxoaporphines. *J. Nat. Prod.* **54**, 1331-1336.
- Bahceevli A. K., Kurucu S., Kolak U., Topçu G., Adou E. and Kingston D. G. I. (2005) Alkaloids and aromatics of *Cyathobasis fruticulosa* (Bunge) Aellen. *J. Nat. Prod.* **68**, 956-958.
- Barton D. H. R., Motherwell W. B. and Zard S. Z. (1982) A useful synthesis of pyrroles from nitroolefins. *J. Chem.* Soc., *Chem. Commun.* 551-552.
- Bohlmann F., Zdero C., King R. M. and Robinson H. (1984) Phenylethylamide aus *Critoniella acuminata*. *Planta Med.* **50**, 187-188.
- Claros B. M. G., da Silva A. J. R., Vasconcellos M. L. A. A., de Brito A. P. P. and Leitão G. G. (2000) Chemical constituents of two *Mollinedia* species. *Phytochemistry* **55**, 859-862.
- Cutillo F., D'Abrosca B., DellaGreca M., Di Marino C., Golino A., Previtera, L. and Zarrelli A. (2003) Cinnamic acid amides from *Chenopodium album*: effects on seeds germination and plant growth. *Phytochemistry* **64**, 1381-1387.
- Fukuda N., Yonemisu M. and Kimura T. (1983) Studies on the constituents of the stems of *Tinospora tuberculata* Beurnee. I. *N-trans*- and *N-cis*-feruloyl tyramine, and a new phenolic glucoside, tinotuberide. *Chem. Pharm. Bull.* **31**, 156-161.
- Garcez W. S., Martins D., Garcez F. R., Marques M. R., Pereira A. A., Oliveira

Molecular Medicinal Chemistry

IDECEFYN

vol 13 May-August 2007, **26-29** http://www.idecefyn.com.ar ISSN 1666-888X

L.A., Rondon J. N. and Peruca, A. D. (2000) Effect of spores of saprophytic fungi on phytoalexin accumulation in seeds of frog-eye leaf spot and stem canker-resistant and -susceptible soybean (*Glycine max* L.) cultivars. *J. Agric. Food Chem.* **48**, 3662-3665.

- Gözler B., Önür M. A., Bilir S. and Hesse M. (1992) Epimeric isopavine *N*-Oxides from *Roemeria refracta*. *Helv. Chim. Acta* **75**, 260-268.

- Horio T., Yoshida K., Kikuki H., Kawabata J. and Mizutani J. (1993) A phenolic amide from roots of *Chenopodium album*. *Phytochemistry* **33**, 807-808.

- Hussain S. F., Gözler B., Shamma M. and Gözler T. (1982) Feruloyl tyramine from *Hypecoum*. *Phytochemistry* **21**, 2979-2980.

- Kim D. K. and Lee K. (2003) Inhibitory effect of *trans*-*N*-*p*-coumaroyl tyramine from the twigs of *Celtis sinensis* on the acetylcholinesterase. *Arch. Pharm. Res.* **26**, 735-738.

- Kim Y., Han M. S., Lee J. S., Kim J. and Kim Y. C. (2003) Inhibitory phenolic amides on lipopolysaccharide-induced nitric oxide production in RAW 264.7 cells from *Beta vulgaris* var. *cicla* seeds. *Phytother. Res.* **17**, 983-985.

- Kim D. K., Lim J. P., Kim J. W., Park H. W. and Eun J. S. (2005) Antitumor and antiinflammatory constituents from *Celtis sinensis*. *Arch. Pharm. Res.* **28**, 39-43.

- Lajide L., Escoubas P. and Mizutani J. (1995) Termite antifeedant activity in *Xylopia aethiopica*. *Phytochemistry* **40**, 1105-1112.

- Ma J., Jones S. H. and Hecht S. M. (2004) Phenolic acid amides: a new type of DNA strand scission agent from *Piper caninum*. *Bioorg. Med. Chem.* **12**, 3885-3889.

- Martin-Tanguy J., Cabanne F., Perdrizet E. and Martin C. (1978) The distribution of hydroxycinnamic acid amides in flowering plants. *Phytochemistry* **17**, 1927-1928.

- Martin-Tanguy J. (1985) The occurrence and possible function of hydroxycinnamoyl acid amides in plants. *Plant Growth Regul.* **3**, 381-399.

- Martin-Tanguy J. and Negrel J. (1987) *Hydroxycinnamic acid amides, hypersensitivity, flowering and sexual organogenesis in plants*. In: *Plant Molecular Biology*. von Wettstein D. and Chua N. H. (eds.), Plenum, New York; pp 253-263.

- Milić B. L. and Milić N. B. (1998) Protective effects of spice plants on mutagenesis. *Phytother. Res.* **12**, S3-S6.

- Paik S., Park Y. H., Suh S. I., Kim H. S., Lee I. S., Park M. K., Lee C. S. and Park S.H. (2001) Unusual cytotoxic phenethylamides from *Xenorhabdus nematophilus*. *Bull. Korean Chem. Soc.* **22**, 372-374.

- Rahman A. U., Bhatti M. K., Akhtar F. and Choudhary M. I. (1992) Alkaloids of *Fumaria indica*. *Phytochemistry* **31**, 2869-2872.

- Seca A. M. L., Silva A. M. S., Silvestre A. J. D., Cavaleiro J. A. S., Domingues F. M. J. and Pascoal-Neto C. (2001) Lignanamides and other phenolic constituents from the bark of kenaf (*Hibiscus cannabinus*). *Phytochemistry* **58**, 1219-1223.

- Suzuki T., Holden I. and Casida J. E. (1981) Diphenyl ether herbicides remarkably elevate the content in *Spinacia oleracea* of (*E*)-3-(4-hydroxy-3-methoxyphenyl)-*N*-[2-(4-hydroxy-3-methoxyphenyl)ethyl]- 2-propenamide. *J. Agric. Food Chem.* **29**, 992-995.

- Tanaka H., Nakamura T., Ichino K. and Ito K. (1989) A phenolic amide from *Actinodaphne longifolia*. *Phytochemistry* **28**, 2516-2517.

-Yoshihara T., Takamatsu S. and Sakamura S. (1978) Three new phenolic amides from the roots of egg-plant (*Solanum melongena* L.). *Agric. Biol. Chem.* **42**, 623-627.