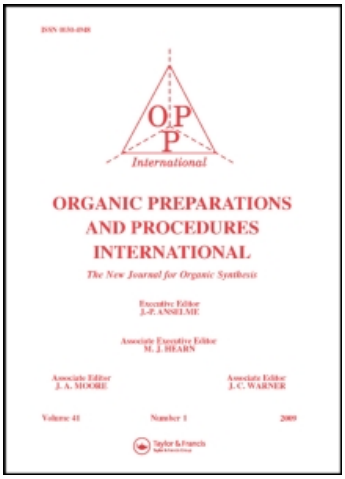

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

HIGHLY EFFICIENT SYNTHESIS OF FATTY ACID DOPAMIDES

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To cite this Article Czarnocki, Z. , Matuszewska, M. P. and Matuszewska, I.(1998) 'HIGHLY EFFICIENT SYNTHESIS OF FATTY ACID DOPAMIDES', Organic Preparations and Procedures International, 30: 6, 699 — 702
To link to this Article: DOI: 10.1080/00304949809355327
URL: http://dx.doi.org/10.1080/00304949809355327

ORGANIC PREPARATIONS AND PROCEDURES INT., 30 (6), 699-719 (1998)

OPPI BRIEFS

HIGHLY EFFICIENT SYNTHESIS OF FATTY ACID DOPAMIDES

Submitted by Z. Czarnocki*, M. P. Matuszewska and I. Matuszewska
(04/01/98)

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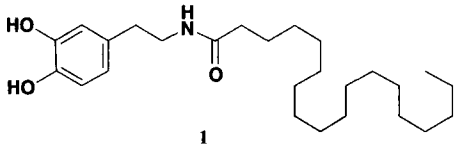
Amides of long-chain polyunsaturated acids and biologically important amines have attracted considerable interest in the last decade, especially in connection with the synthesis of biologically active derivatives.[1] The many methods used for the preparation of these compounds are laborious and give products in poor to medium yields.[1,2] Having been interested in the synthesis of a series of fatty acid dopamides in connection with their possible neurotransmissing properties,[1,2] we investigated with the "mixed anhydride" procedure.[1a] In our hands, however, the method gave a complex mixture of products from which only a trace amounts of the desired amides could be isolated. This fact encouraged us to investigate other possible methodologies for this purpose. We turned our attention to the use of benzotriazol-1-yloxy-*tris*(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) which is widely used in peptide chemistry.[3] A BOP-mediated coupling of protected aminoacids and peptides has proven to be the method of choice for the reactions with unstable or sensitive components. Dopamine and poly-*cis*-unsaturated fatty acids are known to be prone to oxidation or isomerization side-reactions. We thus anticipated that BOP-mediated coupling under very mild conditions would minimize all undesired transformations.

In our procedure, dopamine hydrochloride was mixed with an equimolar amounts of fatty acid and BOP reagent in dry THF. Addition of an excess of triethylamine at 0° followed by standard extractive work-up and purification by column chromatography, gave the desired amides **1-5** in good



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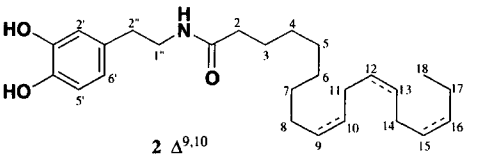

2 $\Delta^{9,10}$
3 $\Delta^{9,10}$, $\Delta^{12,13}$
4 $\Delta^{9,10}$, $\Delta^{12,13}$, $\Delta^{15,16}$

to excellent yields. Analysis including a high field NMR spectrometry, revealed the high purity of the products with no observable isomerization or/and oxidation-derived contamination. Our results are compared with those of the literature (Table).[1a] Arachidonic acid, which is becoming more important in medicinal chemistry assays,[4] was also used to test this method. Examination of the literature revealed that the *N*-arachidonyldopamine (**5**) is a new compound and some other dopamides previously described[1a] were not spectroscopically characterized.

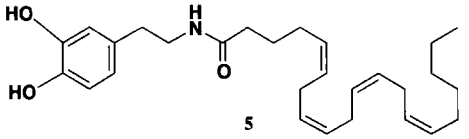

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TABLE. Yields of Compounds **1-5**

Compound	mp. (°C)[a]	Yield (%)[a]	mp. (°C)[b]	Yield (%)[b]
N-Stearyoyldopamine (**1**)	96-98	98	96-98.5	not given
N-Oleoyldopamine (**2**)	55-55.5	97	50.5-52	not given
N-Linoleoyldopamine (**3**)	oil	94	<20	46
N-Linolenoyldopamine (**4**)	< 20	89	oil	14
N-Arachidonyldopamine (**5**)	< 20	87	—	—

a) BOP-mediated coupling. b) Isobutyl chlorocarbonate method (ref. 1a).

EXPERIMENTAL SECTION

Melting points were determined with a Boetius apparatus and were not corrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a Varian Unity plus-500 spectrometer (500 MHz and 125 MHz respectively) with tetramethylsilane as the internal standard. Chemical shifts are reported in ppm (d) and coupling constants (J) are reported in Hz. The liquid secondary ion mass spectrometry (LSIMS-positive ion mode) spectra were accord using AMD-604 spectrometer. All reactions were carried out under argon atmosphere. Chromatographic purification of compounds was performed on silica gel MN Kieselgel 60 (100-200 mesh). TLC analyses were done on silica gel (Kieselgel 60 F_{254} Merck) plates, using 254 nm illumination or/and iodine vapor to visualize the spots. Tetrahydrofuran was purified and dried by distillation from sodium/benzophenone. Solvents for the column chromatography were redistilled. BOP-reagent was purchased from Chem-Impex Int. (Wood Dale, USA). **CAUTION**: Appropriate safety precautions should be exercised due to carcinogenic properties of HMPT, which is liberated during work with BOP reagent

General Procedure for Preparation of Acyl Dopamines.- The following procedure illustrates the preparation of all fatty acids dopamides.

N-Linolenoyldopamine (**4**).- To a stirred mixture of dopamine hydrochloride (2 g, 10.5 mmol) in 50 mL of dry THF was added BOP (4.7 g, 10.6 mmol) and linolenic acid (2.93 g, 10.5 mmol). The mixture was then stirred at room temperature for 10 min and then cooled to 5°. A solution of Et_3N (3.9 mL, 31.8 mmol) in 10 mL of dry THF was added dropwise with stirring to this mixture. The cooling-bath was then removed and the solution was stirred at room temperature for 12 h. The solu-

tion was then evaporated and 20 mL of brine and 150 mL of diethyl ether were added to the residue. The water layer was extracted with ether (2 x 20 mL) and the extracts were combined, washed with sodium bicarbonate solution, dried ($MgSO_4$) and rotary evaporated to dryness. The residue was then chromatographed using chloroform and chloroform-MeOH (9:1) mixture as eluents to give 4.13 g (95%) of **4** as colorless oil. Crystallization from diethyl ether-hexane gave 3.85 g (89%) of a colorless solid, mp. < 20°, lit.[1a] mp. (oil); ^{1}H NMR: δ 8.0 (br. s 2H, 2 x OH), 6.8 (d, J = 8.0 Hz, 1H-5'), 6.74 (s, 1H-2'), 6.55 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H-6'), 5.81 (t, J = 6.0 Hz, 1H-NH), 5.39 (m, 6H, H-9, H-10, H-12, H-13, H-15, H-16), 3.44 (q, J = 6.5 Hz, 2H-1"), 2.70-2.83 (m, 4H, H-11, H-14), 2.67 (t, J = 7.0 Hz, 2H-2"), 2.15 (t, J = 8.0 Hz, 2H-2), 1.95-2.10 (m, 4H, H-8, H-17), 1.53-1.62 (m, 2H-3), 1.20-1.39 (m, 8H, H-4, H-5, H-6, H-7), 0.97 (t, J = 7.5 Hz, 3H-18); ^{13}C NMR: δ 174.55, 144.45. 143.24, 131.97, 130.37, 130.24, 128.30, 128.24, 127.73, 127.10, 120.38, 115.48, 115.25, 41.02, 36.79, 34.87, 29.59, 29.20, 29.16, 29.11, 27.20, 25.74, 25.62, 25.53, 20.56, 14.29.

N-Stearoyldopamine (1).- Similarly to the procedure described for **4**, the title compound was prepared starting from stearic acid. After recrystallization from chloroform-methanol solution 3.25 g (yield 98%) of compound **1** was obtained as white semisolid: mp. 96-98.5°, lit.[1a] mp. 96-98.5° from chloroform-methanol; ^{1}H NMR: δ 7.47 (br. s, 2H, 2 x OH), 6.80 (d, J = 7.5 Hz, 1H-5"), 6.75 (s, 1H-2'), 6.55 (dd, J_1 = 7.5 Hz, J_2 = 2.0 Hz, 1H-6'), 5.59 (t, J = 2.5 Hz, 1H-NH), 3.49 (q, J = 6.5 Hz, 2H-1"), 2.70 (t, J = 7.0 Hz, 2H-2'), 2.15 (t, J = 8.0 Hz, 2H-2), 1.53-1.68 (m, 2H-3), 1.20-1.35 (m, 28H, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17), 0.89 (t, J = 7.0 Hz, 3H-18); ^{13}C NMR: δ 168.5, 149.2, 143.0, 126.5, 120.5, 115.38, 115.0, 36.87, 34.97, 34.59, 31.94, 29.72, 29.67, 29.64, 29.48, 29.37, 29.22, 29.13, 25.76, 22.70, 14.13; LSIMS(+) (m/z) (%): 442 (25.7) $(M+Na)^+$, 420 (75.5) $(M+H)^+$, 392 (68.6), 284, 270, 208, 95 (85.7), 91 (100).

N-Oleoyldopamine (2).- Similarly to the procedure described for **4**, the title compound was obtained starting from oleic acid. The crude colorless oil was chromatographed using chloroform as eluent and recrystallized from diethyl ether-pentane to afford 5.76 g (yield 97%) of compound **2** as a white prisms: mp. 55-55.5°, lit.[1a] mp. 50.5-52° from benzene-hexane; ^{1}H NMR: δ 6.82 (d, J = 7.8 Hz, 1H-5'), 6.74 (d, J = 2.0 Hz, 1H-2'), 6.53 (dd, J_1 = 7.8 Hz, J_2 = 2.0 Hz, 1H-6'), 5.82 (t, J = 6.0, 1H-NH), 5.29-5.38 (m, 2H, H-9, H-10), 3.46 (td, J = 6.8 Hz, 2H-1"), 2.67 (t, J = 6.80 Hz, 2H-2"), 2.15 (t, J = 8.0 Hz, 2H-2), 1.98-2.04 (m, 4H, H-8, H-11), 1.53-1.62 (m, 2H-3), 1.21-1.35 (m, 20H, H-4, H-5, H-6, H-7, H-12, H-13, H-14, H-15, H-16, H-17), 0.88 (t, J = 7.0 Hz, 3H-18); ^{13}C NMR: δ 174.68, 144.44, 143.23, 130.36, 130.02, 129.71, 120.38, 115.46, 115.22, 41.07, 36.80, 34.87, 31.91, 29.77, 29.72, 29.54, 29.34, 29.33, 29.22, 29.18, 29.13, 27.36, 27.18, 25.76, 22.69, 14.13; LSIMS (+) (m/z) (%): 835 $(2M+H)^+$ (6.5), 440 $(M+Na)^+$ (35.5), 418 $(M+H)^+$ (100), 282 (16.6).

N-Linoleoyldopamine (3).- Starting from linoleic acid the title compound was obtained as a colorless oil (5.13 g, yield 94%) following a procedure described for **4**, lit.[1a] mp. < 20° from benzene-acetone. ^{1}H NMR: δ 8.21 (br. s, 1H, OH), 7.60 (br. s, 1H, OH), 6.81 (d, J = 8.0 Hz, 1H-5'), 6.73 (d, J = 2.0 Hz, 1H-2'), 6.54 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H-6'), 5.73 (t, J = 5.5 Hz, 1H-NH), 5.29-5.41 (m, 4H, H-9, H-10, H-12, H-13), 3.45 (q, J = 6.5 Hz, 2H-1"), 2.67 (t, J = 7.0 Hz, 2H-2"), 2.13 (t, J = 7.5 Hz, 2H-2),

2.0-2.09 (m, 4H, H-8, H-14), 1.54-1.62 (m, 2H-3), 1.24-1.39 (m, 14H, H-4, H-5, H-6, H-7, H-15, H-16, H-17), 0.89 (t, J = 7.0 Hz, 3H-18); ^{13}C NMR: δ 174.04, 144.73, 143.39, 130.38, 130.22, 130.06, 128.02, 127.91, 120.28, 115.89, 115.68, 40.82, 36.81, 36.73, 36.69, 34.86, 31.52, 29.63, 29.35, 29.24, 29.21, 29.14, 25.76, 25.63, 22.58, 14.08.

N-Arachidonyldopamine (5).- Similarly to the procedure described for **4**, the title compound was prepared starting from arachidonic acid. Crystallization of the oil from diethyl ether-hexane mixture give **5** as white solid (1.25 g, yield 87%): mp. < 20°; ^{1}H NMR: δ 7.89 (s, 1H, OH), 6.80, (d, J = 8.0 Hz, 1H-5"), 6.77 (s, 1H, OH), 6.74 (d, J = 2 Hz, 1H-2'), 6.53 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H-6'), 5.81, (t, J = 6.0 Hz, 1H-NH), 5.28-5.43 (m, 8H, H-5, H-6, H-8, H-9, H-11, H-12, H-14, H-15), 3.46 (td, J_1 = 6 Hz, J_2 = 7 Hz, 2H-1'), 2.75-2.85 (m, 6H, H-7, H-10, H-13), 2.67 (t, J = 7 Hz, 2H-2"), 2.16 (t, J = 7.8 Hz, 2H-2), 2.01-2.10 (m, 4H, H-4, H-16), 1.67 (tt, J_1 = J_2 = 7.8 Hz, 2H-3), 1.21-1.38 (m, 6H, H-17, H-18, H-19), 0.88 (t, J = 6.9 Hz, 3H-20); ^{13}C NMR: δ 174.32, 144.42, 143.21, 130.54, 130.36, 128.97, 128.80, 128.63, 128.30, 128.07, 127.82, 127.50, 125.50, 120.40, 115.44, 115.23, 41.09, 36.13, 34.87, 31.51, 29.32, 27.22, 26.56, 25.64, 25.61, 25.61, 25.53, 22.58, 14.09; LSIMS(+) (m/z) (%): 462 $(M+Na)^+$ (56.3), 440 $(M+H)^+$ (100), 107 (23.8), 95 (32.5), 91 (44.4);

HR LSIMS: Calcd for $C_{28}H_{42}NO_3$ $(M+H)^+$ 440.31647. Found: 440.31824.

Anal. Calcd for $C_{28}H_{41}NO_3$: C, 76.50; H, 9.40; N, 3.19. Found: C 76.36, H 9.51, N 3.23

Acknowledgment.- This work was supported by grant BST-562/13/97 from the Department of Chemistry, University of Warsaw.

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