Synthesis of Novel (Phenylalkyl)amines for the Investigation of Structure–Activity Relationships

Part 3[1])

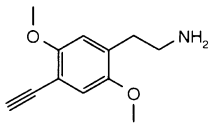
4-Ethynyl-2,5-dimethoxyphenethylamine (=4-Ethynyl-2,5-dimethoxybenzeneethanamine; 2C-YN)

by **Daniel Trachsel**

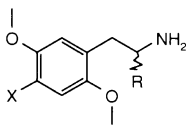
Rüttelistrasse 16, CH-4416 Bubendorf (e-mail: daniel_trachsel@gmx.ch)

An easy and efficient pathway for the preparation of 4-ethynyl-2,5-dimethoxyphenethylamine (=4-ethynyl-2,5-dimethoxybenzeneethanamine; 2C-YN; **1**) was developed, an ethynyl analogue of the potent 5-$HT_{2A/C}$ agonists, *e.g.*, 4-iodo-2,5-dimethoxy-amphetamine (DOI; **2b**). The ethynyl moiety was introduced by a Pd-catalyzed *Sonogashira* reaction of (trimethylsilyl)ethyne with *N*-(trifluoroacetyl)-protected 4-iodo-2,5-dimethoxyphenethylamine (**7**) in almost quantitative yield within only 1 h. Removal of the Me_3Si group was accomplished with Bu_4NF. Final *N*-deprotection by NaOH treatment afforded the novel phenethylamine **1** in an overall yield of 88%.

Introduction. – In continuation of the foregoing research [1][2], the aim was to find a convenient synthesis of 4-ethynyl-2,5-dimethoxyphenethylamine (=4-ethynyl-2,5-dimethoxybenzeneethanamine; **1**; 2C-YN). A large number of phenylalkylamines of the general structure **2** was prepared and investigated by numerous researchers [3a–j] including compounds with a wide variety of substituents at the 4-position (*e.g.*, halo, alkyl, alkylthio, alkoxy, nitro, CF_3, and others). At first, these phenylalkylamines were attractive due to the fact that they generally are potent hallucinogens (R = H or Me). Later, such compounds were found to be potent ligands for the serotonin 5-$HT_{2A/C}$ receptors, displaying low nanomolar affinity [4a–f], but none of them exhibited higher selectivity for 5-HT_{2A} *vs.* 5-HT_{2C} receptors [4e][4f]. The induction of hallucinogenesis seems to be principally mediated through the agonistic activation of the 5-HT_{2A} receptor [5].



1 (2C-YN)



2 R=H or Me
2a X=Br, R=Me (DOB)
b X=I, R=Me (DOI)
c X=CF_3, R=Me (DOTFM)
d X=CN, R=Me (DOCN)

[1]) Part 1, [1]; Part 2, [2].

Although numerous compounds of the general structure **2** have been described, an ethynyl group has not yet been introduced at position 4. From the geometric point of view, the ethynyl group can be considered isosteric with nitrile. They both are planar and linear and, therefore, in plane with the aromatic system. The *Table* summarizes some physicochemical data for the ethynyl group compared to other 4-substituents resulting in some of the most-potent 4-substituted 2,5-dimethoxy-α-methylbenzeneethanamines **2a**–**d** investigated in *in vitro* and *in vivo* studies [3j][6] (compound **2d** had considerably lower affinity at 5-HT_{2A}[2]) sites [4f][6] but is used for structural comparison). The hydrophobicity of the *para*-substituents of **2a**–**c** is considerably higher, but the ethynyl group has substantially higher hydrophobic character than the CN group. The ability to attract or repulse electrons (*Hammett* constant σ) of the ethynyl group is comparable to that of the Br- and I-atom, and the high electronegativity is in the range of that of the CF_3 group. The molar refraction is comparable to that of Br.

Table 1. *Some Physicochemical Data of 4-Substituents Used in 2,5-Dimethoxybenzenealkanamines* **2**

Substituent	Hydrophobicity π_x[a])	*Hammett* constant σ_p[b])	Electro negativity[c])	Molar refraction[d])
Br	0.86	0.23	2.8	8.88
I	1.12	0.18	2.5	13.94
CF_3	0.88	0.54	3.3–3.5	5.02
C≡N	−0.57	0.66	3.2–3.3	6.33
C≡CH	0.40	0.23	3.3	9.55

[a]) Relative partition coefficients of substituted benzenes is an octanol/H_2O solvent system [7]. [b]) Taken from [7] for *para*-substituted compounds. [c]) Values for Br and I are from the *Pauling* scale, for groups from [8]. Depending on its calculation method, several values are obtained. [d]) Approximate measure of steric bulk [7].

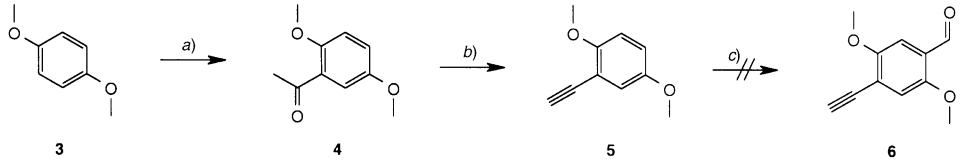
Although the corresponding α-methylphenethylamines **2** (=α-methylbenzeneethanamines = amphetamines; R = Me) are usually more potent and have longer duration of action *in vivo* [3j], only the phenethylamine derivative was prepared. Earlier *in vitro* studies showed that the presence of an α-methyl group has little effect on 5-$HT_{2A/C}$ affinity [4e][9][10]. Thus, phenethylamines have about the same affinity as their racemic α-methyl congeners (amphetamines) towards these binding sites. The increased *in vivo* potency seems to be due to the increased metabolic stability [4e][11]. In addition, the increased hydrophobicity [12] and the intrinsic activity on the receptor [3j] seems to play an important role.

Results and Discussion. – First attempts to introduce the ethynyl group with the aim to synthesize **1** were made by the method of *Buckle* and *Rockell* [13]. Thus, 1,4-dimethoxybenzene (**3**) was acetylated to give acetophenone **4** (*Scheme 1*). Compound **4** was chlorinated by treatment with PCl_5. Subsequent dehydrodehalogenation under basic conditions yielded 2-ethynyl-1,4-dimethoxybenzene (**5**). Different conditions were investigated to introduce the carboxaldehyde function by a *Vilsmeier* formylation. Probably due to the high reactivity of the nucleophilic ethynyl group, there was always immediate formation of a black tar, and the desired aldehyde **6** could not be isolated.

[2]) Note that the 5-HT_2 receptor has been renamed to 5-HT_{2A}.

Initially, it was planned to convert aldehyde **6** to the corresponding nitrostyrene by condensation with $MeNO_2$. Subsequent reduction with a hydride reagent (*e.g.*, alane (AlH_3)) should have afforded the desired phenethylamine **1**.

Scheme 1



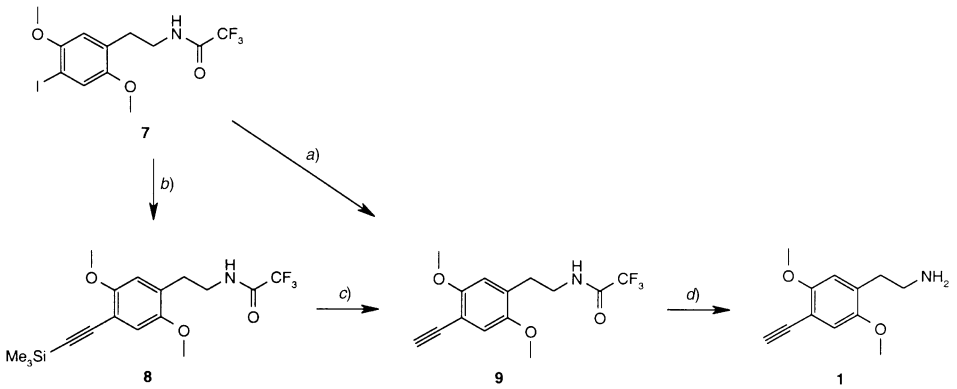
a) CH_3COCl, $AlCl_3$, CH_2Cl_2. *b*) 1. PCl_5, benzene; 2. KOH, EtOH. *c*) *N*-Methylformanilide, $POCl_3$.

To avoid the transformation of **5** into **6**, a cross-coupling (*Negishi*) route was chosen. *Negishi* and co-workers [14] developed a method for the direct introduction of an ethynyl group into iodoarenes with ethynylmetals and [$Pd(PPh_3)_4$] as catalyst. The reaction yields terminal alkynes and has the advantage that no protection-deprotection of the yne moiety is needed. Accordingly, *N*-(trifluoroacetyl)-protected 2,5-dimethoxy-4-iodophenethylamine **7** was treated with ethynylzinc bromide (generated *in situ* from ethynylmagnesium bromide and dry $ZnBr_2$ in THF) as shown in *Scheme 2*. The reaction was very slow, and only traces of the desired product **9** were formed. However, on application of the less-direct method (*Sonogashira* coupling) with ethynyltrimethylsilane as described by *Thorand* and *Krause* [15], the transformation was successfully accomplished. Thereby, ethynyltrimethylsilane was allowed to react with **7** in the presence of Et_3N and catalytic amounts of CuI and [$PdCl_2(PPh_3)_2$] in THF at room temperature (*Scheme 2*). The reaction to compound **8** was complete within 1 h, and no by-products were detected. As described in [15], it was not necessary to degas the solvent. Compound **8** could be used for further transformation without purification. The removal of the Me_3Si and CF_3CO protecting groups is well known and was achieved according to standard procedures (Bu_4NF and aq. NaOH solution, resp.). Starting from **7**, the overall yield for the preparation of **1** was 88%.

Compound **1** as well as **9** are important templates for the preparation of further derivatives. The ethynyl group can easily be converted into various other functionalities for structure-activity-relationship (SAR) studies, including to diyne or polyyne derivatives (by Pd-catalyzed coupling), to conjugated alkene derivatives (*via* hydroboration), and by further functionalization to esters, ethers, thioethers, and halogen compounds. Partial hydrogenation of **1** (which would afford the new compound 4-ethenyl-2,5-dimethoxyphenethylamine; 2C-V) or of an alkylated alkyne derivative (which would lead to (*Z*)- or (*E*)-alkene derivatives, depending on the hydrogenation method) is also an option. This remains to be investigated in future work.

It is important to note that the halide atom attached to the arene moiety of **7** was I. The *Sonogashira* coupling should as well be possible with the corresponding bromo derivative (*e.g.*, 4-bromo-2,5-dimethoxyphenethylamine; 2C-B, which is more easily available than the iodo compound) since the compounds described in [15] were all prepared from the corresponding bromoarenes. The α-methyl congener of **1**, DOYN,

Scheme 2



a) HC≡CZnBr, [Pd(PPh_3)$_4$], THF. *b*) [$PdCl_2$(PPh_3)$_2$ (2 mol-%), CuI (4 mol-%), Et_3N, $Me_3SiC{\equiv}CH$, THF. *c*) Bu_4NF, THF. d) 5M aq. NaOH, MeOH.

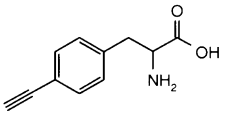
should be available *via* the same synthetic pathway from the corresponding iodo- or bromoarene derivative.

A *Hansch* analysis of a series of 4-substituted 2,5-dimethoxyamphetamines [6] gave a significant correlation between 5-HT_{2A} affinity and the hydrophobicity of the 4-substituents. The measured 5-HT_{2A} binding data for compound **2d** bearing the 4-CN substituent showed an affinity of approximately two orders of magnitude lower than that of **2a**,**b** [4f][6]. For the binding affinity at the 5-HT_{2A} receptor, the comparison of the physicochemical data for 4-substituents (*Table*) suggests that compound **1** should have substantially higher affinity than 4-cyano-2,5-dimethoxyamphetamine (**2d**; DOCN) or the α-demethyl congener thereof.

Due to the small size of the ethynyl group, **1** could have agonistic properties at the 5-HT_{2A} receptor, since the measurement of the functional activity of phenylalkylamines of type **2** bearing a large lipophilic 4-substituent (*e.g.*, hexyl, octyl, 3-phenylpropyl) showed that these ligands typically lead to antagonistic or at least partially agonistic effects, and phenylalkylamine analogs of **2** with a small lipophilic substituent at the 4-position exhibit agonistic behavior [6][10].

The ethynyl group is a substituent rarely seen attached to aromatic systems in pharmaceuticals, probably due to the only recently developed methods for its introduction, and the potential for metabolic instability due to its relatively acidic, terminal H-atom. However, several compounds bearing an ethynyl group were developed and investigated (*e.g.*, 4-ethynylphenylalanine (**10**) as a potent tryptophan-hydroxylase inhibitor [16][17], *Tarceva*™ (**11**) as a therapeutic antitumor agent [18], and the potent H_3-receptor antagonist **12** with high oral CNS activity [19]). Studies on the *in vitro* mechanism of the oxidation of π-bonds of *p*-substituted ethynylbenzenes by CYP450 [20] showed that the role of metabolite formation was strongly dependant on the electronic properties of additional substituents. An additional NO_2 group led to slow metabolism. With an additional Me group, the metabolism was fast. This suggests that 2C-YN (**1**) bearing two MeO groups and an alkyl side chain would be metabolized

quite fast. This and the above suggestions regarding the binding properties at the 5-HT_{2A} receptor remain to be investigated.



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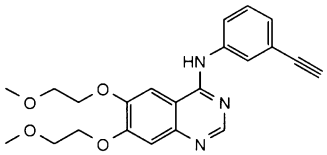

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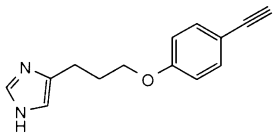

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Experimental Part

General. All compounds were commercially available and were used without further purification. Products were dried at 50-60°. TLC Monitoring: silica gel plates F_{254}, standard UV lamps for detection. M.p.: *Büchi 535*; uncorrected. IR Spectra: *Perkin-Elmer Spectrum-One* FT-IR system; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker AM-300* spectrometer; at 300 (^1H) and 75 MHz (^{13}C); δ in ppm, J in Hz.

N-*{2-{2,5-Dimethoxy-4-[2-(trimethylsilyl)ethynyl]phenyl}ethyl}-2,2,2-trifluoroacetamide* (**8**). A flame-dried apparatus was charged with 2,2,2-trifluoro-*N*-[2-(4-iodo-2,5-dimethoxyphenyl)ethyl]acetamide (**7**; 1.0 g, 2.48 mmol) [3j][9] (caution: **7** must not be contaminated by iodine monochloride from the previous reaction), CuI (20 mg, 0.1 mmol), [$PdCl_2(PPh_3)_2$] (35 mg, 0.05 mmol), and dry THF (5 ml) under Ar. Then Et_3N (1.0 g, 9.9 mmol) was added in one portion. After stirring for 1 min, ethynyltrimethylsilane (0.51 g, 5.2 mmol) in THF (1.0 ml) was added during 5 min (according to [15], slow addition prevents the formation of diynes). After stirring for 1 h, the conversion was complete, and the solvent was evaporated. The residue was taken up in AcOEt. Filtration through *Celite* and evaporation of the filtrate afforded a viscous oil which slowly crystallized: 0.90 g (97%) of **8**. Beige solid. M.p. 104–105°. ^1H-NMR ($CDCl_3$): 6.94 (*s*, 1 arom. H); 6.88 (br. *s*, NH); 6.63 (*s*, 1 arom. H); 3.84 (*s*, MeO); 3.82 (*s*, MeO); 3.55 (*q*, CH_2NH); 2.90 (*t*, $ArCH_2$); 0.30 (*s*, Me_3Si).

N-*[2-(4-Ethynyl-2,5-dimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide* (**9**). A soln. of **8** (0.87 g, 2.33 mmol) in THF (25 ml) was treated with 1M Bu_4NF in THF (11.0 ml) and stirred for 2 h. The mixture was quenched with sat. aq. NH_4Cl soln. (70 ml) and extracted with AcOEt (3 × 40 ml), the combined extract washed with brine, dried (Na_2SO_4), and evaporated, and the obtained viscous brownish oil further purified by flash chromatography (silica gel (50 g) hexanes/AcOEt 2:1 → 1:1): 0.64 g (91%) of **9**. Beige solid. M.p. 126–127°. ^1H-NMR ($CDCl_3$): 6.99 (*s*, 1 arom. H); 6.90 (br. *s*, NH); 6.67 (*s*, 1 arom. H); 3.87 (*s*, MeO); 3.82 (*s*, MeO); 3.59 (*q*, CH_2NH); 3.34 (*s*, HC≡C); 2.93 (*t*, $ArCH_2$).

4-Ethynyl-2,5-dimethoxybenzeneethanamine Hydrochloride (**1**·HCl; 2C-YN·HCl). A soln. of **9** (0.63 g, 2.09 mmol) in MeOH (120 ml) was treated with aq. 5M NaOH (35 ml) and stirred for 4 h. The mixture was diluted with Et_2O (150 ml), the aq. phase further extracted with Et_2O (3 × 50 ml), and the combined org. phase washed with H_2O (2 × 50 ml), dried (Na_2SO_4), and evaporated. The residual oil (reacts with CO_2 very quickly; should be stored under an inert gas if used as free base) was dissolved in anh. Et_2O (10 ml) and the soln. neutralized with anh. 1M HCl in Et_2O. The crystals were filtered off, washed with Et_2O, and dried: 0.44 g (88%) of **1**·HCl. Off-white crystals. M.p. 207–208°. IR (KBr): 3279, 2962, 2907, 2062, 1504, 1467, 1400, 1219, 1034, 859, 699. ^1H-NMR (D_2O): 6.97 (*s*, 1 arom. H); 6.80 (*s*, 1 arom. H); 3.71 (*s*, MeO); 3.66 (*s*, MeO); 3.61 (*s*, HC≡C); 3.10 (*t*, $CH_2NH_3^+$); 2.84 (*t*, $ArCH_2$). ^{13}C-NMR (D_2O): 154.04; 151.00; 127.64; 116.02; 114.02; 109.36; 83.03; 80.08; 56.36; 56.12; 39.72; 28.61.

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