SYNTHESIS OF *N*-(HALOGENATED) BENZYL ANALOGS OF SUPERPOTENT SEROTONIN LIGANDS

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ABSTRACT

In the last four years a group of extremely potent designer drugs, the *N*-benzylated phenylethylamines known as the NBOMe series, has surfaced on the street and in the news media. Although data documenting their high affinity and preference for 5-HT_2 serotonin receptors abound (5-HT_{2A} receptor activation is generally associated with the action of the "classical" hallucinogens), relatively little is known about the molecular basis of their potency and selectivity. In the setting of a project aiming to evaluate the possible involvement of halogen bonds in the binding of monoaminergic ligands to their receptors, we have begun to synthesize halogenated derivatives of known *N*-benzylated compounds for their pharmacological study. Here we report the synthesis of new phenylethylamine and tryptamine derivatives incorporating bromine atoms in their *N*-benzyl moiety.

Keywords: designer drugs, *N*-benzylphenylethylamine, *N*-benzyltryptamine, synthesis

INTRODUCTION

The last three years have seen the appearance on the informal market of a novel, extremely potent group of designer drugs commonly known as the NBOMe series. These compounds were first described in conference proceedings and in a Ph.D. thesis and shown to be at least partial agonists at the 5-HT_{2A} serotonin receptor,[1-5] the activation of which is generally associated with the action of the "classical" hallucinogens. They are *N*-2-methoxybenzyl derivatives, initially of mescaline and escaline (3,4,5-trimethoxy- and 3,5-dimethoxy-4-ethoxyphenylethylamine, respectively), and subsequently of the 4-substituted-2,5-dimethoxyphenylethylamines known as the 2C series:[6]

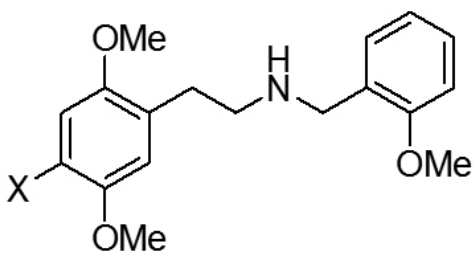

Figure 1.- NBOMe compounds: X = Cl, Br, I, small alkyl, CF_3, CN, etc.

As stated in the Erowid online psychoactive drug library, they "have become the defining psychedelics of 2013. Because they are strongly active below a milligram, are relatively easy to synthesize, and have effects and duration similar to LSD, they appear to be supplanting LSD on a significant portion of acid-style blotter... A number of stories about 25I and 25C indicate either an idiosyncratically stronger reaction in some people, or a sharp, non-linear increase in the intensity of effects as dose increases... The unusually high potency makes overdoses more likely. Unfortunately, the risks of 25I (and perhaps other NBOMes) at high doses seem to include delirious, dangerous behaviour (with some accidents resulting in death), as well as the possibility of death from direct pharmacological effects. Medically dangerous doses may be as low as 3-5 mg".[7]

Unidentified sources suggest that the most popular 25I-NBOMe [2-(2,5-dimethoxy-4-iodophenyl)-*N*-(2-methoxyphenyl)methylethanamine] appeared on the market in 2010 and was promptly offered on the online service Silk Road. In October 2011 the whole NBOMe series was made illegal in Russia, followed by some states in the US and Australia, New Zealand, Israel and Sweden, and "temporarily" scheduled by the DEA, while in the United Kingdom all *N*-benzylphenylethylamines would become class A drugs (those deemed most dangerous) in June, 2014. 25I-NBOMe and its chloro analog 25C-NBOMe have been seized by the Chilean police since early 2013. The relative ease of synthesis of this type of compound suggests, however, that new *N*-benzyl, not necessarily "NBOMe" derivatives, will surface posing a challenge to regulatory agencies. These, following their tradition, are likely to overreact placing obstacles in the path of scientific research on these interesting and potentially useful compounds.

In 2003, preliminary explorations led to the conclusion that *N*-2-methoxybenzyl substitution, not only of phenylethylamines but also phenylisopropylamines, tryptamines and 3-(2-aminoethyl)-(1*H*,3*H*) quinazoline-2,4-diones related to the typical 5-HT_2 receptor antagonist ketanserin, results in particularly high affinities for 5-HT_{2A} receptors.[5] Although other substitution patterns with an oxygen atom at the *ortho* position of the benzyl group exhibited similar potencies, as has been confirmed in later studies, the range of substituents on the benzyl moiety remains largely untapped. Consequently, it is difficult to rationalize the molecular basis of receptor affinity and functional potency and efficacy of this interesting family of drugs even though a π−π stacking interaction and a hydrogen bond, both involving the benzyl moiety, have been invoked as partial explanations.[8-10] Also, the pharmacological study of an expanded set of analogs is likely to reveal the causes of their suspected toxicity and uncover new substances with therapeutic potential.

In recent years we have begun a research program looking for halogen bonds in monoaminergic compounds. The halogen bond (C−X···Y, where Y is often a peptide backbone carbonyl oxygen in protein-drug binding) is a long-neglected interaction in medicinal chemistry. It can be about as strong as a hydrogen bond and equally directional, but its formation does not suffer from the drawback of the almost neutral net enthalpic change due to the necessary breakage of protein-water hydrogen bonds. Its strength is related to the electronegativity of the halogen, and usually increases in the order Cl < Br < I. As stated in a recent review, "the strength of the interactions they form makes iodinated or brominated fragments ideal candidates for lead discovery strategies, redefining halogen bonds as core interactions".[11] A recent example of compounds that may merit analysis in this context are cytotoxic oxadiazoles in which replacement of a methyl group by a bioisosteric chlorine or bromine atom results in an at least fourfold increase in potency which is greater for bromine than for chlorine.[12] Considering that, with only two exceptions,[9] benzyl-halogenated analogs of superpotent *N*-2-oxygenated benzyl monoamine derivatives have not been described, we view them as potentially valuable tools to probe the molecular basis of the sometimes remarkable increases in 5-HT_{2A} receptor affinity elicited by *N*-benzylation and to study possible qualitative differences in their actions. In this preliminary report we describe the synthesis of a number of phenylethylamine and tryptamine derivatives bearing halogenated 2-hydroxy- or methoxy *N*-benzyl substituents. Several previously reported compounds were prepared for comparative purposes,[5, 8] but they are not included in this communication. While the NBOMe nomenclature, is widespread and quite adequate to name the compounds presently found on the street, and has been extended to include 2-hydroxybenzyl (e.g. 25I-NBOH) and 2,3-methylenedioxybenzyl (e.g. 25I-NBMD) derivatives,[8] it is insufficient when attempting to name a broader range of derivatives. We therefore propose an extension of this nomenclature to include other substituents on the benzyl ring with appropriate numbering of the substituted positions. Thus, 25B-NBOMe would become 25B-NB2OMe, 25I-NBMD would become 25I-NB23MD, and so on.

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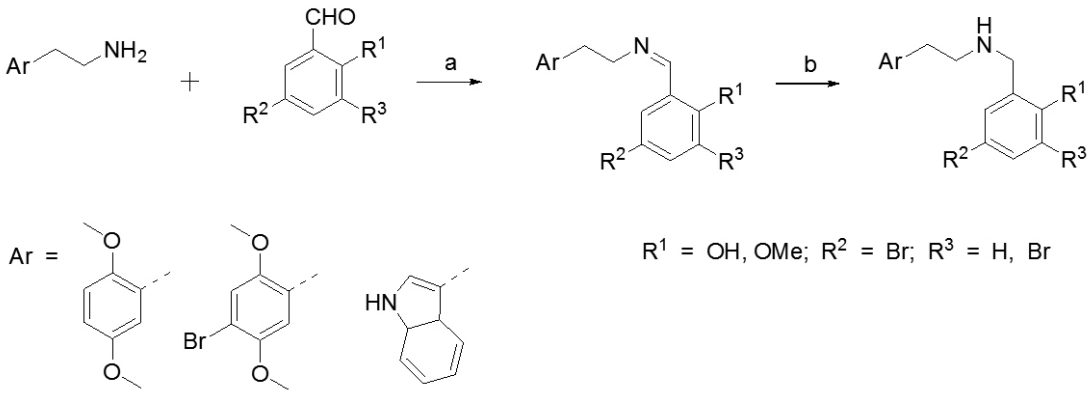
The procedures required to obtain aryl-brominated compounds are generally simpler than for their analogs with other halogens. As one of our goals is to explore the possibility that halogen bonding contributes to the pharmacological effects of some of these compounds, it is worth pointing out that, in spite of the often cited Cl < Br < I order in the stability of halogen bonds, bromine is near-optimal and occasionally associated with higher affinities than iodine.[11] Coincidentally, the affinities of a number of 25B compounds for 5-HT_{2A}R are almost invariably as high or higher than those of other 25Xs, with X = Me, F, Cl, I, Pr, SMe, SEt, SPr, CF_3 or CN, with the noteworthy exception of Et.[13]

In all cases the *N*-benzylated products were obtained by reductive amination of the appropriate substituted benzaldehydes. This was carried out by the "indirect" procedure in which the aldehyde and the amine are first allowed to react in order to generate the imine. Imine formation was almost instantaneous in the cases of the benzaldehydes bearing a 2-hydroxy group, and in the other cases required at most a couple of hours, but overnight stirring was adopted as a general procedure. Preliminary experiments comparing reductions with sodium acetoxyborohydride or borohydride showed no significant differences, and consequently the latter, less expensive reagent was used in all cases.

N-(Substituted)-benzyl-2-arylethylamines were prepared by sodium borohydride reduction of the corresponding imines, formed *in situ* in methanol solution from either 2-(2,5-dimethoxyphenyl)- or 2-(4-bromo-2,5-dimethoxyphenyl)ethanamine (2C-H and 2C-B, respectively) or tryptamine, and the appropriate aldehydes (Scheme 1).



Scheme 1. Preparation of 2-aryl-*N*-substituted benzylethanamines. a) MeOH, 12 h; b) $NaBH_4$, 24 h.

The *N*-benzylated phenylethylamines were isolated as their hydrochlorides. Although the ^{1}H NMR spectra of the hydrochlorides obtained in this way generally indicated ≥ 98% purity, with no indication of the presence of solvents of crystallization, when deemed necessary the salts were recrystallized in methanol.

EXPERIMENTAL

General. All solvents and reagents were of synthesis grade and were used without further purification. The phenylethylamines and substituted salicylaldehydes were prepared by standard literature methods. Melting points were determined using a Reichert Galen III hot plate microscope equipped with a thermocouple. NMR spectra were recorded with a Bruker Avance 400 spectrometer at 400 MHz (^{1}H) or 100 MHz (^{13}C), or with a Bruker ACP 200 instrument at 200 MHz (^{1}H), and referenced to the DMSO-d_6 residual signals (δ 2.50 or 40.45 ppm, respectively).

General procedure for the preparation of *N*-benzylated 2-arylethanamine hydrochlorides. The appropriate amine (5.5 mmol) and aldehyde (6.0 mmol) were dissolved in MeOH (90 mL) and stirred overnight at room temperature. Powdered $NaBH_4$ (24 mmol) was then added in small portions, with good stirring, over approximately 30 min, and the reaction was allowed to proceed for 24 h. The solvent was removed in a rotary evaporator and the cream-colored to light yellow residue was taken up with CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ solution. The organic phase was dried (Na_2SO_4), filtered, and concentrated to dryness. The light yellow oil was dissolved in 2-propanol (5 mL) to which was added 37% HCl (540 µL), and the solution was diluted with Et_2O (100 mL) to afford the salt, usually as a white crystalline powder.

***N*-(5-Bromo-2-hydroxyphenylmethyl)-2-(2,5-dimethoxyphenyl) ethanamine hydrochloride (25H-NB5Br2OH-HCl).** Obtained from 2C-H and 5-bromo-2-hydroxybenzaldehyde, overall yield 77%, colorless prisms, mp. 121-124 °C. ^{1}H NMR (200 MHz, D_2O) δ 7.48 (dd, *J* = 8.8, 2.4 Hz, 1H), 7,42 (d, *J* = 2.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.96 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.87 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 4.20 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.31 (t, *J* = 6.9 Hz, 2H), 3.01 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 154.0, 152.1, 134.7, 133.7, 127.0, 121.7, 118.5, 117.2, 113.3, 112.8, 110.6, 56.77, 56.28. 49.98, 45.09, 27.38.

***N*-(5-Bromo-2-methoxyphenylmethyl)-2-(2,5-dimethoxyphenyl) ethanamine hydrochloride (25H-NB5Br2OMe-HCl).** Obtained from 2C-H and 5-bromo-2-methoxybenzaldehyde, overall yield 81%, colorless clumps, mp. 133-135 °C. ^{1}H NMR (200 MHz, D_2O) δ 7.61 (dd, *J* = 8.8, 2.5 Hz, 1H), 7,45 (d, *J* = 2.6 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.97 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.86 (d, *J* = 2.6 Hz, 1H), 4.20 (s, 2H), 3.81 (s, 3H), 3.76 (s, 6H), 3.28 (t, *J* = 6.9 Hz, 2H), 2.99 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 159.0, 157.1, 139.7, 138.9, 132.1, 128.3, 122.12, 119.3, 118.2, 117.7, 117.5, 61.93, 61.73, 61.26, 51.88, 49.73, 32.56.

2-(4-Bromo-2,5-dimethoxyphenyl)- *N*-(5-bromo-2-hydroxyphenyl-methyl)ethanamine hydrochloride (25B-NB5Br2OH-HCl). Obtained from 2C-B and 5-bromo-2-hydroxybenzaldehyde, overall yield 83%, colorless parallelepipeds, mp. 162-165 °C. ^{1}H NMR (400 MHz, D_2O; very dilute) δ 7.44 (d, *J* = 8 Hz, 1H), 7.36 (brs, 1H), 7.24 (s, 1H), 6.92 (s, 1H), 6.77 (d, *J* = 8 Hz, 1H), 4.16 (s, 2H), 3.81 (s, 3H), 3.75 (s, 6H), 3.29 (brs, *J* = 2H), 2.95 (brs, 2H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (brs, 1H), 7,39 (d, *J* = 8.4 Hz, 1H), 7.19 (s, 1H), 7.02 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 4.08 (s, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.96 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 152.5, 150.4, 134.8, 133.8, 126.4, 121.7, 118.5, 116.9, 116.0, 110.7, 109.9, 57.59, 57.21, 46.77, 45.21, 27.29.

***N*-(5-Bromo-2-hydroxyphenylmethyl)-2-indolylethanamine hydrochloride (T-NB5Br2OH-HCl).** Obtained from tryptamine and 5-bromo-2-hydroxybenzaldehyde, yield 79%, yellowish crystals, mp. 260-264 °C. ^{1}H NMR (400 MHz, DMSO-d_6, free base) δ 10.83 (brs, 1H), 7.51 (d, ^3J = 7.6 Hz, 1H), 7.36 (d, ^3J = 7.6 Hz, 1H), 7.29 (d, ^4J = 2.0 Hz, 1H), 7.15 (s, 1H), 7.08 (dd, ^3J = 7.6 Hz, 1H), 6.98 (dd, ^3J = 7.6 Hz, 1H), 6.69 (d, ^3J =8.8 Hz, 1H), 3.87 (s, 2H), 2.90 (second order t, 2H), 2.85 (second order t, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, free base) δ 157.7, 137,2, 131.8, 131.2, 128.1, 129.0, 123.6, 121.8, 119.5 (2C), 118,4, 112.9, 112.3, 110.4, 50.46, 49.78, 25.90.

***N*-(3,5-Dibromo-2-hydroxyphenylmethyl)-2-indolylethanamine hydrochloride (T-NB5Br2OMe-HCl).** Obtained from tryptamine and 3,5-dibromo-2-hydroxybenzaldehyde, yield 86%, yellowish solid, mp. 243-248 °C. ^{1}H NMR (400 MHz, DMSO-d_6, free base) δ 10.94 (brs, 1H), 7.54 (dd,

^3J = 7.8 Hz, 1H), 7.36 (dd, ^3J = 8.1 Hz, 1H), 7.31 (d, ^4J = 2.5 Hz, 1H), 7.23 (dd, ^3J = 8.6, ^4J = 2.6 Hz, 1H), 7.09 (ddd, ^3J = 7.5, ^4J = 1.3, ^4J = 0.9 Hz, 1H), 7.00 (ddd, ^3J = 7.4, ^4J = 0.9 Hz, 1H), 6.65 (d, ^3J = 8.6 Hz, 1H), 3.35 (s, 2H), 3.05, 3.00 (second order multiplets, 4 H).

***N*-(3,5-Dibromo-2-methoxyphenylmethyl)-2-indolylethanamine hydrochloride (T-NB35diBr2MeO-HCl).** Obtained from tryptamine and 3,5-dibromo-2-methoxybenzaldehyde, yield 79%, glassy light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, free base) δ 11.0 (brs, 1H), 7.56 (dd, ^3J = 7.8 Hz, 1H), 7.45 (d, ^4J = 2.3 Hz, 1H), 7.36 (dd, ^3J = 8.1 Hz, 1H), 7.25 (d, ^4J = 2.4 Hz, 1H), 7.08 (ddd, ^3J = 7.1 Hz, 1H), 1H), 7.00 (ddd, ^3J = 7.4 Hz, 1H), 3.98 (s, 3H), 3.36 (s, 2H), 3.03 (second order multiplets, 4H).

RESULTS AND DISCUSSION

This preliminary communication reports the preparation of six previously unknown *N*-brominated and 2-oxygenated benzyl derivatives of 2,5-dimethoxyphenyl-ethylamine (2C-H), 4-bromo-2,5-dimethoxyphenylethylamine (2C-B), and tryptamine. The only known examples of halogenated 2-oxygenated phenylethylamine derivatives are 2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(4- or 5-bromo-2-methoxyphenylmethyl)ethanamine (25B-NB5Br2OMe and 25B-NB4Br2OMe in our nomenclature). These two compounds exhibited submicromolar affinities (against the antagonist [^{3}H] ketanserin) for human 5-HT$_{2A}$ receptors with pK_i values of 7.17 and 7.63, respectively, two orders of magnitude less than the closely related 25B-NBOMe (25B-NB2OMe).[9] However, functional results are lacking and it would be desirable to have 5-HT$_{2A}$ affinity values determined vs. an agonist such as [^{125}I] DOI, aside from the fact that nothing is known regarding their possible actions at other serotonin or non-serotonin receptors.

Pharmacological results available at this time seem to indicate that the *N*-benzylated phenylethylamines, phenylisopropylamines, tryptamines and quinazolinedione derivatives are quite selective for serotonin 5-HT$_2$ receptors (5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$). Two of the highest potency 5-HT$_{2A}$ partial agonists (25B-NBOMe and its "fly" analog) were also tested in different organ models against 5-HT$_3$, 5-HT$_4$, H$_1$, H$_2$ and H$_3$ (histamine), M$_3$ (muscarinic acetylcholine), α_{1D} and β_1 (adrenergic), and D$_2$ and D$_3$ (dopamine) receptors with the finding that nanomolar affinities (pA$_2$ values) were only observed toward 5-HT$_{2A}$ receptors, and at all the others the affinities were at best micromolar.[5] A study carried out by the NIMH PDSP (Psychoactive Drug Screening Programme) at the University of North Carolina on 48 related compounds including the NBOMe series against 12 different 5-HT receptor subtypes showed that high affinities only appear where the three 5-HT$_2$ subtypes are concerned. Furthermore, additional tests on 25I-NBOMe (as CIMBI-5) confirmed the low nanomolar affinities at the 5-HT$_2$ receptor subtypes and the micromolar or worse affinities at α_{2A}, M$_5$, D$_2$, 5-HT$_7$, 5-HT$_{5A}$, D$_1$, 5-HT$_{1B}$ and D$_5$ receptors and at the serotonin, norepinephrine and dopamine transporters. Nevertheless, significant pharmacological effects might still be elicited at 5-HT$_6$, 5-HT$_{1A}$, D$_3$, α_{2C}, and D$_4$ receptors (K_i values: 58, 85, 117, 348, and 647 nm, respectively).[9, 13, 14] Another indication that *N*-benzylated phenylethylamine derivatives are unlikely to interact with other targets than the 5-HT$_2$ receptors was found by us with 1-(4-methylthiophenyl)propan-2-amine (MTA), where *N*-substitution with benzyl or *p*-hydroxy, -methoxy, butoxy or benzyloxybenzyl groups resulted in a more than 400-fold reduction in its ability to inhibit rat monoamine oxidase A (MAO-A).[15]

It must be pointed out that the published pharmacological results suffer from two shortcomings: in the limited cases in which selectivity vs. different receptors was studied the compounds assayed were generally 2-methoxybenzyl derivatives, and when different substitution patterns were examined they were only assayed against 5-HT$_2$ receptors. Even if these choices are understandable in the context of the cited papers, they overlook potentially important differences that may arise with the introduction of a broader range of substituents. While potency at a particular biological target has often been a major goal, selectivity is also most important and it has been specifically addressed in this paper's most recent reference, although limited to the 5-HT$_2$ receptor subtypes.[13] If some of the differently substituted benzyl analogs should exhibit similar affinity for non-5-HT$_2$ receptor targets, it is reasonable to predict that their behavioral pharmacology will show qualitative and not only quantitative differences with regard to the NBOMe series. This, in turn, is likely to pose unforeseen dangers – and also present possible therapeutic advantages – if such new designer drugs reach the street or enter clinical tests. Our current research program aims to address some of these issues through a combination of *in vitro* and behavioral pharmacology of the compounds we have begun to synthesize, all in a medicinal chemical framework .

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