THE SYNTHESIS OF A ROTATIONALLY RESTRICTED PHENOLIC ANALOG OF 5-METHOXY-3-(1,2,5,6-TETRAHYDROPYRID-4-YL)INDOLE (RU-24,969)

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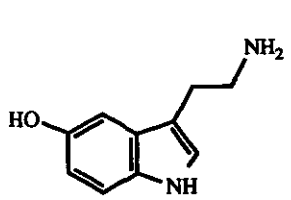
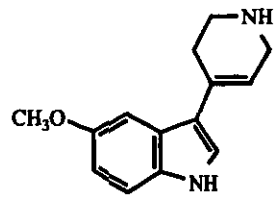
Abstract - Pyrrolo[3,2-b]pyrid-5-one represents a rotationally restricted phenolic analog of 5-hydroxyindole. The synthesis of the rotationally restricted phenolic analog of the serotonin agonist, 5-methoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole (RU-24,969), is presented. Protection of the 2-pyridone in this synthesis was achieved using its t-butyl ether.

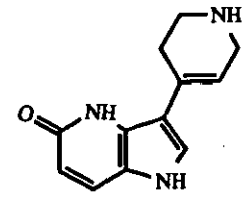
The synthesis of conformationally restricted analogs of biologically active molecules can lead to molecular probes used in the understanding of the particular molecular recognition requirements of a specific receptor or enzyme. These compounds can also be used to differentiate within a series of similar receptors or enzymes. Since the neurotransmitter serotonin (5-HT) has been implicated in disorders of appetite, memory, sleep, sexual behavior, and mood,[1] and since to date there are at least ten different serotonin receptors known (designated 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_2, 5-HT_3, etc.),[2] the study of conformationally restricted analogs of serotonin can lead to a better understanding of the specific functions of the individual serotonergic receptors. In this communication, we would like to present the synthesis of a rotationally restricted phenolic analog (**1**) of the serotonin agonist, 5-methoxy-3-(1,2,5,6-tetrahydropyrid-4-yl)indole (RU-24,969),[3] in which the 5-methoxy functionality (which acts as a hydrogen bond acceptor in



Serotonin (5-HT)



RU-24,969



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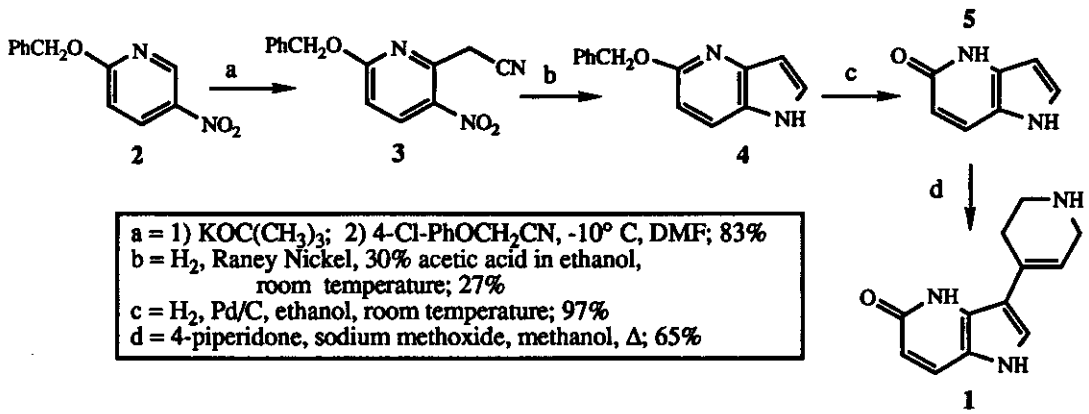
5-HT receptors) has been rotationally restricted in its potential hydrogen bond accepting interactions.

RU-24,969 is a very potent serotonin agonist claimed to be slightly selective for the 5-HT_{1B} receptor, but still active at 5-HT_{1A} and 5-HT_{1D} receptors.[4] Its direct analogy to serotonin can be simply seen through the replacement of the 3-aminoethyl sidechain of 5-HT for a 3-(1,2,5,6-tetrahydropyrid-4-yl) ring. Our objective was to examine the hydrogen bonding accepting role of the 5-methoxy substituent in RU-24,969. One approach to this problem was rotationally restricting the 5-oxygen substituent.

Since 2-hydroxypyridines are known to exist almost exclusively in the 2-pyridone [amide] tautomer,[5] a 2-pyridone could be viewed as a rotationally restricted analog of phenol. In a hydrogen bond accepting interaction, a 2-pyridone would only participate in bonding which can only occur in the plane of the aromatic ring since this molecule is locked in the amide tautomer. Therefore, to examine the potential for optimizing this type of interaction of RU-24,969 with specific 5-HT receptors, the synthesis of the pyrrolo[3,2-b]pyridone analog (**1**) of RU-24,969 was undertaken.

Scheme 1

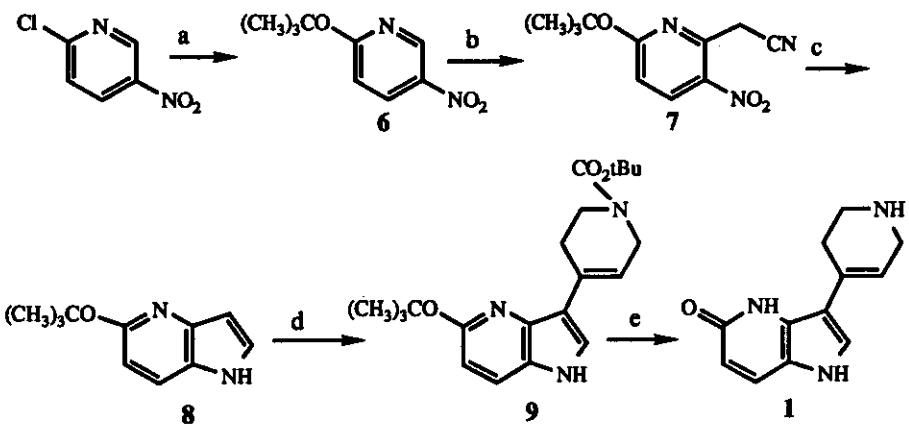


a = 1) $KOC(CH_3)_3$; 2) 4-Cl-$PhOCH_2CN$, -10° C, DMF; 83%
b = H_2, Raney Nickel, 30% acetic acid in ethanol, room temperature; 27%
c = H_2, Pd/C, ethanol, room temperature; 97%
d = 4-piperidone, sodium methoxide, methanol, Δ; 65%

Since indoles react with 4-piperidone under basic conditions to form 3-(1,2,5,6-tetrahydropyridyl)indoles,[3] the synthesis of **1** was seen as arising from a similar reaction using a 5-alkoxypyrrolo[3,2-b]pyridine. Through the use of a vicarious nucleophilic aromatic substitution reaction (VNASR) on 2-methoxy-5-nitropyridine, Makosza demonstrated a simple but elegant approach to pyrrolo[3,2-b]pyridines.[6] Since the desired VNASR would not work on a 5-nitro-2-pyridone because of the relatively acidic amide proton, the choice of an appropriate protecting group for the pyridone [amide] oxygen was needed. 2-Benzyloxy-5-nitropyridine (**2**)[7] was originally employed, and the VNASR was high yielding (83%)[8,9] (Scheme 1), but

the required reductive cyclization of the resulting 2-(6-benzyloxy-3-nitropyrid-2-yl)acetonitrile (3) was low yielding (27%) using Raney nickel, inconsistent on a large scale, and failed using Pd on carbon (Scheme 1). However, using the small amounts of the desired 5-benzyloxypyrrolo[3,2-b]pyridine (4) isolated from this sequence, pyrrolo[3,2-b]pyrid-5-one (5, 97%) was synthesized via straightforward hydrogenation (Pd/C) of the benzyloxy ether. Condensation of 5 with 4-piperidone in refluxing sodium methoxide/ methanol afforded our desired phenolic rotationally restricted analog of RU-24,969 (1) in 65% yield.

Scheme 2



a = $NaOC(CH_3)_3$, THF, room temperature; 54%
b = 1) $KOC(CH_3)_3$; 2) 4-Cl-$PhOCH_2CN$, -10° C, THF; 61%
c = H_2, Pd/C, room temperature to 60° C, ethanol; 72%
d = N-t-BOC-4-piperidone, sodium methoxide in methanol, Δ; 77%
e = HCl in methanol ; 86%

Since the low yield and inconsistency of the reductive cyclization limited the use of the sequence outlined in Scheme 1, an alternate ether to protect the pyridone functionality was sought. The use of a t-butyl ether was ideal (Scheme 2). 2-Chloro-5-nitropyridine was treated with sodium t-butoxide in anhydrous tetrahydrofuran to afford 2-t-butoxy-5-nitropyridine (6, 54%). VNASR on 6 yielded 61% of the acetonitrile (7). Reductive cyclization of (7) now using 10% Pd/C smoothly led to the desired 5-t-butoxypyrrolo[3,2-b]pyridine (8, 72%). This one pot cyclization occurred via the initial reduction of the aromatic nitro group to the aminopyridine derivative at room temperature,[10] followed by the intramolecular cyclization of the aromatic amine on the nitrile at 60° C with subsequent reduction of the intermediate amidine yielding 8.

The reaction of the pyrrolo[3,2-b]pyridine (**8**) with N-t-butoxycarbonyl-4-piperidone (N-t-BOC-4-piperidone) in refluxing sodium methoxide in methanol was analogous to the reaction of indoles with 4-piperidone under similar conditions.[3] The resulting 3-(N-t-butoxycarbonyl-1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyridine (**9**, 77%) was easily purified and crystalline. Deprotection of both the N-t-BOC and O-t-butyl groups was smoothly effected using standard conditions (HCl in methanol). While the resulting pyrrolo[3,2-b]pyrid-5-one (**1**) was somewhat water soluble, crystallization of this product could be slowly achieved from that solvent slightly above pH 7 to afford our desired target (**1**, 86%). This route using 5-t-butoxypyrrolo[3,2-b]pyridine (**8**, Scheme 2) was far superior to our initial approach to **1** (Scheme 1) since it was higher yielding and amenable to ten gram preparations of all intermediates.

Recrystallization of **1** in absolute methanol afforded crystals of sufficient quality for X-ray analysis. The pyridone [amide] C=O bond distance of 1.24Å, pyridone [amide] C-N bond length of 1.39Å, and location of the tautomeric proton on the nitrogen atom indicated that **1** did, in fact, exist almost exclusively in the pyridone [amide] tautomer. Therefore, **1** can be viewed as a phenolic rotationally restricted analog of RU-24,969, and pyrrolo[3,2-b]pyrid-5-one represents a rotationally restricted analog of 5-hydroxyindole. The pharmacological analysis of **1** is underway, and these results will be reported in an appropriate forum in due course.

ACKNOWLEDGEMENT

We would like to thank Dr. Jon Bordner (Pfizer) for the X-ray analysis of **1**.

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8. This yield represents a 10:1 mixture of the desired 2- and the 4-pyridyl regiomers.
9. All new compounds described in this communication have been characterized by ^{1}H and ^{13}C nmr, ir, lrms, hrms and/or elemental analysis.
10. 2-(3-Amino-6-t-butoxypyrid-2-yl)acetonitrile can be isolated if desired after room temperature hydrogenation of (**7**).

Received, 9th March, 1990