Pergamon

Tetrahedron Letters, Vol. 36, No. 39, pp. 7019-7022, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01453-5

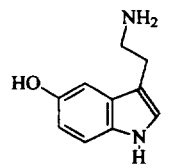
AN UNUSUAL BY-PRODUCT IN A CONCISE SYNTHESIS OF A ROTATIONALLY RESTRICTED PHENOLIC ANALOG OF SEROTONIN

John E. Macor

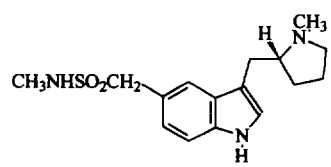
Fisons Pharmaceuticals, P.O Box 1710, Rochester, N.Y. 14603
PRESENT ADDRESS: Astra Arcus USA, P.O. Box 20890, Rochester, N.Y. 14602

Abstract: *An improved synthesis of a dihydropyrano[3,-2e]indole analog (4, CP-123,479) of serotonin has been accomplished. Starting with serotonin itself and utilizing a Claisen rearrangement/cyclization of a 5-propargyloxy-N-Cbz-tryptamine (2) to form the pyrano[3,2-e]indole in 3, the reaction sequence of four steps afforded a 36% overall yield of 4. In the conversion of 2 to 3, a unique tetracyclic by-product (5) was observed which arose from -NH- of the Cbz group adding across the olefin in the formed pyrano[3,2-e]indole. Conversion of 5 to the tertiary amine (6) added confirmation to the tetracyclic structure identification.*

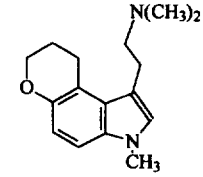
The design and synthesis of conformationally or rotationally restricted analogs of pharmacologically active compounds is a useful approach for determining the bioactive conformation of the molecule. This tack is especially relevant when the compound under study has multiple biochemical effects. Limiting the conformational or rotational freedom of components of that molecule can lead to increased specificity of biological action. The neurotransmitter serotonin (5-hydroxytryptophan, 5-HT) is an example of such a molecule whose multiplicitous pharmacological effects[1] could be limited by either conformational restriction of the 3-(2-aminoethyl) sidechain or by rotational restriction of the C5-hydroxyl group. We have been actively engaged in these studies[2] with some success. Conformational restriction of the 3-(2-aminoethyl) sidechain has led to CP-122,288,[2h, 3] a unique anti-migraine agent, while rotational restriction of the C5-hydroxyl group into a dihydro[3,2-e]pyranoindole (i.e. CP-132,484) has led to direct analogs of serotonin selective for 5-HT_2 receptors.[2f] This serotonin receptor family subtype has poor affinity for serotonin (when compared to other 5-HT receptors), and little is known about its pharmacological role in mammals. Compounds like CP-132,484 provide selective tools for examining 5-HT_2 receptors, but their long syntheses represent a challenge for acquiring large quantities of these agonists. Recent revelations[4] about 5-HT_2 receptors in primates have suggested that the indole



Serotonin (5-HT)



CP-122,288

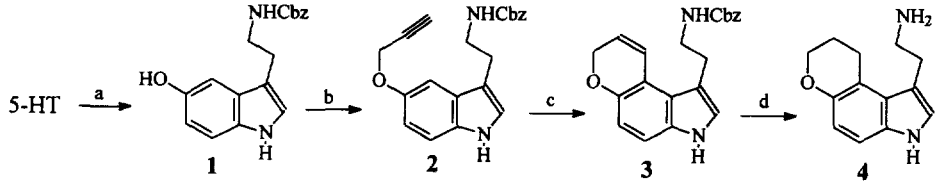


CP-132,484

-NH- analog of CP-132,484 (i.e. **4**, CP-123,479, Scheme 1) is the most relevant member of this family of tryptamines for study in higher mammals, but the original synthesis of **4** was eight steps (starting from 4-methyl-3-nitrophenol) with an overall yield of only 10%.[2e, 2f] In order to have access to significant quantities of **4**, we embarked on a new synthetic approach to this dihydropyrano[3,2-e]indole.

In this letter, we describe a four step synthesis of a direct analog of 5-HT and CP-132,484 (i.e. **4**, CP-123,479) in which an unusual multicyclic indole derivative was also observed. The original synthesis of **4** built the indolic heterocycle from a nitrotoluene derivative using the methodology of Batcho and Leimgruber.[2e, 2f] However, we had previously found a direct access to pyrano[3,2-e]indoles utilizing a Claisen rearrangement/cyclization of a 5-propargyloxyindole derivative.[2i] We sought to apply this methodology to a direct synthesis of **4** (Scheme 1), and we searched for an appropriate 5-hydroxyindole precursor.

Scheme 1



a) benzyl chloroformate, H_2O, Na_2CO_3, rt, 6 h (84%); b) propargyl bromide, Cs_2CO_3, acetone, rt, 22 h (76%); c) bromobenzene, Δ, 48 h (56%); d) H_2, $Pd(OH)_2/C$, EtOH, 72 h (100%)

After an examination of commercially available 5-hydroxyindoles, we concluded that, in fact, serotonin (5-HT) itself would serve as our best starting point. Accordingly, serotonin (as the creatinine sulfate) was protected using Schotten-Bauman conditions employing water as the reaction solvent. Direct extraction of the aqueous reaction mixture followed by silica gel filtration afforded an excellent yield (84%) of N-Cbz-5-HT (**1**). Alkylation of the C5-hydroxy group with propargyl bromide was accomplished using cesium carbonate as the base and acetone as solvent affording **2** (76%). In our hands, cesium carbonate has in the past reduced unwanted N1-alkylation in these reactions. The acetone was deoxygenated prior to reaction via copiously bubbling argon gas through the solvent for approximately 5 minutes. This appeared to reduce the dark colored impurities which arise during reactions with 5-hydroxyindoles.

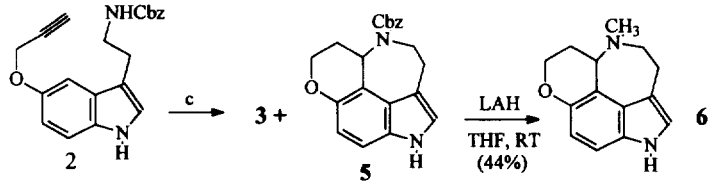
Heating the 5-propargyoxyindole (**2**) in refluxing bromobenzene for 48 hours effected the desired Claisen rearrangement/cyclization, affording the tryptamine (**3**, Scheme 1). Only the regiomer which resulted via rearrangement to C4 of the indole was detected (i.e. the pyrano[3,2-e]indole). No pyrano[2,3-f]indole (i.e. via rearrangement to C6 of the indole) was found. As noted above, this reaction also seemed to be improved if the reaction solvent was deoxygenated via copious application of argon gas through the reaction solution prior to the application of heat. With these conditions, the yield of this reaction was moderate (56%), and a significant

amount of decomposition could be seen as evidenced by the dark color of the resulting reaction solution. The use of Lewis acid catalysts to lower the reaction temperature necessary for this transformation has not as yet been explored.

Hydrogenation of the olefin and removal of the Cbz protecting group in **3** was accomplished using weight/weight quantities of Pearlman's catalyst under 3 atmospheres of hydrogen gas over 3 days. Although not studied rigorously, reduction of the olefin appeared to be sluggish. However, these conditions afforded a quantitative yield of the free base of **4**, which was physically and spectroscopically identical to the material we had previously obtained by alternate methods.[2f] And as before, the tryptamine (**4**, CP-123,479) was readily converted to a solid form as its maleate salt. Therefore, starting from serotonin itself, the synthesis of **4**, a rotationally restricted phenolic analog of 5-HT, was accomplished in four steps with an overall yield of 36%. This can be compared to the eight step, 10% overall yield in the original synthesis of **4**.[2f] Clearly, the utilization of 5-HT as the chemical starting point and the Claisen rearrangement/cyclization of the 5-propargyloxyindole (**2**) to afford the pyrano[3,2-e]indole (**3**) greatly improved the synthetic approach to the serotonin analog (**4**). We are presently exploring further the scope and utility of this approach for the general synthesis of dihydropyrano[3,2-e]indoles.

While there was substantial decomposition in the high temperature (156 °C) transformation of **2** to **3** (Scheme 1), a minor but significant by-product (**5**, 22% crude) which was slightly less polar on TLC than the desired product (**3**) was isolated. NMR and mass spectroscopy suggested that the by-product (**5**) arose from the addition of the -NH- of the -NH-Cbz into the olefin in the pyrano[3,2-e]indole of **3** (Scheme 2), however, the NMR spectrum of 5 was complicated by the slow (on NMR time scale) interconversion of the E and Z isomers of the carbamate. Therefore, reduction of the Cbz-group in **5** with lithium aluminum hydride in THF afforded the tertiary amine (**6**, 44%) whose spectral and physical data[5] (including $^{1}H/^{13}C$ heteroatom correlation and COSY NMR experiments) are entirely consistent with the tetracyclic structure which would have resulted from the addition of the -NH- of the -NH-Cbz into the olefin in the pyrano[3,2-e]indole of **3**.

Scheme 2

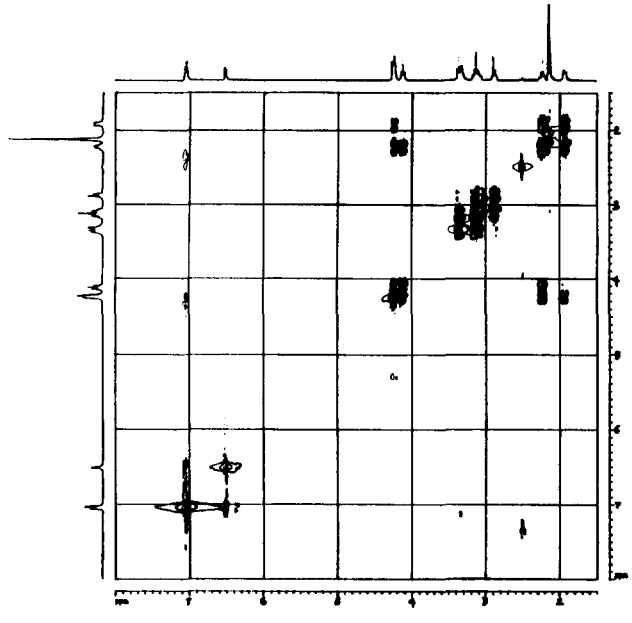


This unusual example of the addition of a weak nucleophile across an olefin is intriguing and warrants additional study. The heterocyclic ring system in **6** is novel, and it would appear to arise from the combination of a correctly orientated, polarized olefin in the presence of an intramolecularly disposed, reasonably soft nucleophile.

While the yield of **6** was low (22% crude), its presence as a by-product to the thermal rearrangement reaction suggests that its formation could be optimized through a proper choice of reaction conditions (i.e. presence of a base or olefin activating transition metal). Furthermore, the potential generality of this type of nucleophile addition to the olefin of pyrano[3,2-e]indoles would provide extraordinary access to a number of novel derivatives of indole natural products. Consequently, we are continuing to explore the potential for this reaction, and we will report our findings in due course.

REFERENCES:

1. For a review of the potential uses of serotonergics see: Glennon, R.A. *Neuroscience and Behavioral Reviews* **1990**, *14*, 35.
2. a) Macor, J.E.; Burkhart, C.A.; Heym, J.H.; Ives, J.L.; Lebel, L.A.; Newman, M.E.; Nielsen, J.A.; Ryan, K. Schulz, D.W.; Torgersen, L.K.; Koe, B.K. *J. Med. Chem.* **1990**, *33*, 2087; b) Macor, J.E.; Newman, M.E. *Heterocycles* **1990**, *31*, 805; c) Macor, J.E.; Ryan, K. *Heterocycles* **1990**, *31*, 1497; d) Macor, J.E.; Newman, M.E. *Tetrahedron Letters* **1991**, *32*, 3345; e) Macor, J.E.; Ryan, K.; Newman, M.E. *Tetrahedron* **1992**, *48*, 1039; f) Macor, J.E.; Fox, C.B.; Johnson, C.; Koe, B.K.; Lebel, L.A.; Zorn, S.H. *J. Med. Chem.* **1992**, *35*, 3625; g) Macor, J.E.; Blake, J.; Fox, C.A.; Johnson, C.; Koe, B.K.; Lebel, L.A.; Morrone, J.M.; Ryan, K.; Schmidt, A.W.; Schulz, D.W.; Zorn, S.H. *J. Med. Chem.* **1992**, *35*, 4503; h) Macor, J.E.; Blank, D.H.; Post, R.J.; Ryan, K. *Tetrahedron Letters* **1992**, *33*, 8011; i) Macor, J.E.; Blank, D.H.; Post, R.J. *Tetrahedron Letters* **1994**, *35*, 45; j) Macor, J.E. and Ryan, K. *Heterocycles* **1994**, *37*, 1447; k) Macor, J.E.; Blank, D.H.; Fox, C.B.; Lebel, L.A.; Newman, M.E.; Post, R.J.; Ryan, K.; Schmidt, A.W.; Schulz, D.W.; Koe, B.K. *J. Med. Chem.* **1994**, *37*, 2509; l) Macor, J.E.; Chenard, B.L.; Post, R.J. *J. Org. Chem.* **1994**, *59*, 7496.
3. Lee, W.S. and Moskowitz, M.A. *Brain Research* **1993**, *626*, 303.
4. Johnson, M.P.; Audia, J.E.; Nissen, J.S.; Nelson, D.L. *Eur. J. Pharmacol.* **1993**, *239*, 111.
5. The spectral and physical properties of **6** are: white solid; mp, decomposes 252-254 °C; IR (KBr) 1570, 1435, 1421 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) [$^1H/^{13}C$ heteroatom correlation assignment in brackets, δ] δ 10.70 (br s, NH), 7.05 (d, J=8.8 Hz, 1H [110.6]), 7.04 (d, J=3.6 Hz, 1H [122.6]), 6.51 (d, J=8.6 Hz, 1H [111.6]), 4.25-4.22 (m, 2H [65.8, 60.6]), 4.14-4.10 (m, 1H [65.8]), 3.38-3.32 (m, 1H [56.1]), 3.20-3.09 (m, 2H [56.1, 24.0]), 2.92-2.86 (m, 1H [24.0]), 2.27-2.19 (m, 1H [28.3]), 2.13 (s, 3H [30.9]), 1.93-1.90 (m, 1H [28.3]); ^{13}C NMR (DMSO-d_6) δ 148.1, 131.0, 125.9, 122.6, 115.9, 113.5, 111.6, 110.6, 65.8, 60.6, 56.1, 30.9, 28.3, 24.0; 2D COSY NMR at right; FAB LRMS (m/z, relative intensity) 230 (16), 229 (100, MH^+), 201 (33), 65 (16). Anal. calcd for $C_{14}H_{16}N_2O \cdot 0.5\ H_2O$: C, 70.85; H, 7.22; N, 11.81. Found: C, 70.61; H, 6.87; N, 11.65.



(*Received in USA* 19 *May* 1995; *revised* 24 *July* 1995; *accepted* 28 *July* 1995)