Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Synthesis of 9-Hydroxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole from 7-Methoxyindole

Francesco Santangelo [a] , Cesare Casagrande [a] , Gabriele Norcini [a] & Fulvio Gerli [a]
[a] Medicinal Chemistry Department, Zambon Group S.p.A., Via Lillo del Duca 10, 20091, Bresso (Milan), Italy
Published online: 23 Sep 2006.

To cite this article: Francesco Santangelo , Cesare Casagrande , Gabriele Norcini & Fulvio Gerli (1993): A Convenient Synthesis of 9-Hydroxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole from 7-Methoxyindole, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:19, 2717-2725

To link to this article: http://dx.doi.org/10.1080/00397919308013802

SYNTHETIC COMMUNICATIONS, 23(19), 2717-2725 (1993)

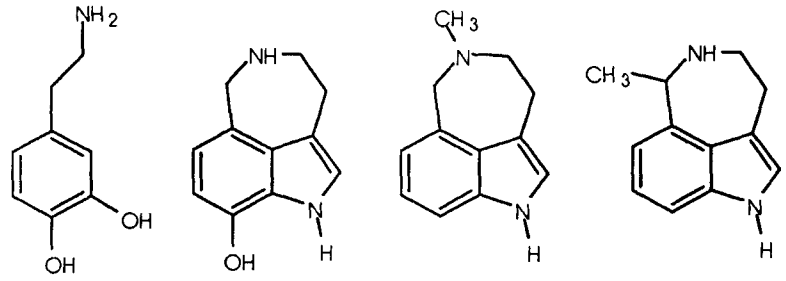
A CONVENIENT SYNTHESIS OF 9-HYDROXY-3,4,5,6-TETRAHYDRO-1H-AZEPINO [5,4,3-cd] INDOLE FROM 7-METHOXYINDOLE

Francesco Santangelo*, Cesare Casagrande, Gabriele Norcini and Fulvio Gerli
Medicinal Chemistry Department, Zambon Group S.p.A.
Via Lillo del Duca 10, 20091 Bresso (Milan) Italy

Abstract: *The title compound was prepared with a route which is characterized by selective carboxylation in position four of 7-methoxyindole. Brief biological results are reported.*

The azepino [5,4,3-cd] indole ring system has already been studied by other groups for its potential biological interest. Syntex Laboratories[1] have recently prepared a series of bridged 2,3,4,5-tetrahydro-1H-3-benzoazepines. Weak affinities on α_2 and $5HT_1$ receptors of 2 were reported. Azepine 3, prepared by Warner Lambert Laboratories, was tested to evaluate central and cardiovascular activies but no significant biological effect was found. We were prompted to synthesize 1 in order to verify whether the introduction of a hydroxyl group in position 9 may mimic the catechol system. In fact, the great importance of the catechol for substaining the biological activity[3,4], i.e. the hydroxyl group in position four, is essential for the dopamine activity.

*To whom correspondence should be addressed

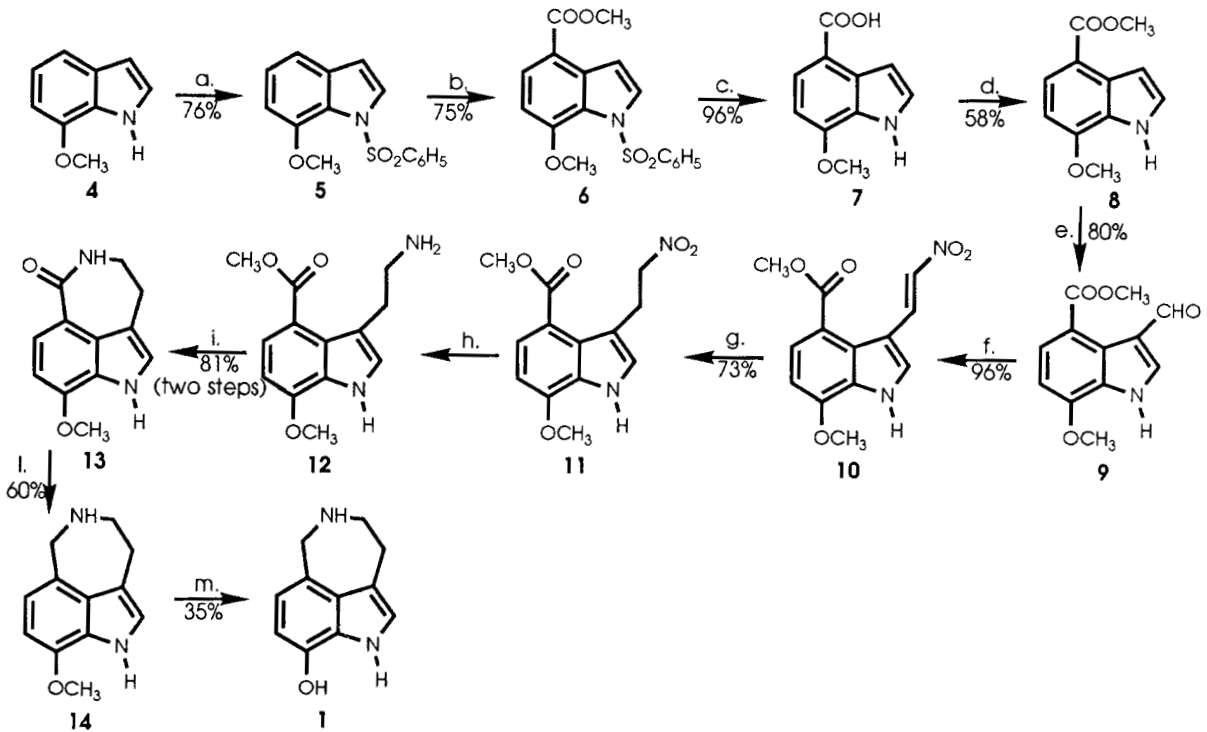


DOPAMINE 1 2 3

A convenient starting material is 7-methoxyindole[5] 4 which is easily protected to give 5 (scheme 1). The deactivation of the pyrrole ring, due to the electron withdrawing effect of the benzenesulphonyl group, allows selective carboxylation in position four in good yield. In fact, in the absence of this protection, or using t.butyloxycarbonyl group, the carboxylation goes selectively in good yield in position 3. Basic hydrolysis followed by esterification of the carboxyl leads to ester 8 which undergoes selective Vilsmeier formylation in position three. Knovenagael reaction with nitromethane under careful conditions in the presence of ammonium acetate gives the nitrostyrene 10. The double bond is reduced with $NaBH_4$ in methanol while the nitro group is reduced by hydrogenation in the presence of Pd catalyst. Partial spontaneous cyclization of tryptamine 12 accuris during the work-up of the reaction and is completed by heating in basic medium.

Reduction of amide with $LiAlH_4$ in tetrahydrofuran gives the amine 14 in good yield. Several attempts to cleave the ether linkage[6] were made but we managed to obtain 1 only in moderate yield by treatment with BBr_3 in CH_2Cl_2 at reflux temperature. Other unsuccessful reagents tried in this step are $AlCl_3$, BCl_3, hydrogen chloride or bromide in water or organic

SCHEME 1



Scheme 1 : a. $C_6H_5SO_2Cl$, NaH/DMF ; b. $(ClCO)_2$, $AlCl_3/CH_2Cl_2$ c. NaOH/CH_3OH d. HCl/CH_3OH e. $POCl_3$/DMF
f. CH_3NO_2, CH_3COONH_4 g. $NaBH_4$ /CH_3OH h. H_2, 10% Pd/C ,CH_3COOH i. NaOH/C_2H_5OH, reflux l. $LiAlH_4$/THF m. BBr_3/CH_2Cl_2

solvent, trimetylsilyl iodide, sodium thiocresolate or sodium thioethylate in polar aprotic solvent. Eventually, 1 was submitted to receptor binding studies for evaluating adrenergic, dopaminergic, serotoninergic or muscarinic affinities. However, 1 has not shown any significant affinities for any receptor investigated.

In conclusion, the introduction of a hydroxyl group in position 9 of azepine ring does not seem to improve the biological activity. However, we think it of interest to report the synthesis of 1, because not much information is known about this kind of ring substitution and moreover the inversion of reactivity when the pyrrole ring is protected with an electron withdrawing group is peculiar and has not been reported previously.

Experimental Section

Melting points were determined with a Büchi apparatus and were uncorrected. NMR spectra were run on Varian EM 360L or Varian XL 300 spectrometers and chemical shifts are given in δ units relative to Me_4Si. Multiplicities were designated as singlet (s), broad singlet (bs), double (d), triplet (t) or multiplet (m).

Mass spectra were performed on a Finningan 4006.

Analytical thin-layer chromatography was routinety performed on silica gel plates (Merck 60F - 254, 0.25 mm) precoated with a fluorescent indicator. Visualization was effected with ultraviolet light or iodine vapour.

All reactions were conducted under nitrogen atmosphere. Organic extracts were dried over Na_2SO_4.

N-Benzensulphonyl-7-methoxyindole 5

Benzensulphonyl chloride (123 ml, 0.96 mol) was added to a suspension

of 4[5] (94 g, 0.64 mol), and 55% sodium hydride (33.6 g, 0.77 mol) in mineral oil in dimethylformamide (1 l) so that the temperature was kept below 40°C. After 15 min the mixture was diluted with water and extracted with ethyl ether. The organic layer was washed with 5% $NaHCO_3$ and evaporated to dryness under vacuum.

The oily residue was crystallized from a mixture of cyclohexane and ethyl ether giving a first crop of 120 g. The mother solution was evaporated and purified by chromatography on silica gel (CH_2Cl_2/hexane = 1/1) with increasing amounts of CH_2Cl_2 up to 100%. A second crop of 20 g was combined with the former (76% overall) m.p. 87-89°C.

MS (chemical ionization, gas of ionization isobutane) m/e 288 (M^++1).

N-Benzensulphonyl-4-methoxycarbonyl-7-methoxyindole 6

Oxalyl chloride (215 ml, 2.5 mol) was added to a suspension of $AlCl_3$ (330 g, 2.5 mol) in CH_2Cl_2 (3 l) cooled at 0°C. After stirring at same temperature for 30 min, 5 (143 g, 0.5 mol) dissolved in CH_2Cl_2 was added and the mixture kept for 30 min at 20-25°C. Then it was poured into brine and extracted with CH_2Cl_2. The organic layer was washed with water, dried and evaporated to dryness.

The oily residue was dissolved in CH_3OH, heated at reflux temperature for 3 h and evaporated to dryness again. The resulting crude ester was purified by chromatography on silica gel (CH_2Cl_2) and then crystallized from 95% ethanol to give 130 g (75%) of 6 m.p. 208-211°C.

M.S. (chemical ionization, gas of ionization isobutane) m/e 346 (M^++1).

3-Carboxy-7-methoxyindole 7

A solution of 6 (34.5 g, 0.1 mol) in ethanol (0.5 l) and 40% w/v NaOH (60

ml) was refluxed for 3 h. After acidification with conc. HCl, the solid which precipitated, was collected by filtration and washed with water. The acid 7 (18.4 g, 96%) was used for the next step without purification. m.p. 250-255°C. ^{1}H NMR (60 MHz, DMSO-d_6) δ: 4.08 (s, 3H), 6.68 (1H, d), 7.00 (1H, d), 7.4 (1H, d), 7.80 (1H, d).

M.S. (chemical ionization, gas of ionization isobutane) m/e 192 (M^++1).

3-Methoxycarbonyl-7-methoxyindole 8

A solution of 7 (33 g, 0.17 mol) in methanol (300 ml) was acidified with a stream of anhydrous HCl and then heated to reflux temperature for 2 h. The solution was evaporated to dryness and the crude ester was first filtered on a bed of silica gel and then crystallized from a mixture of CH_2Cl_2/petroleum ether to give 20.5 g (58%) of 7. m.p. 96-98°C. ^{1}H NMR (60 MHz, $CDCl_3$) 4.0 (s, 6H), 6.7 (d, 1H), 7.08-7.38 (m, 2H), 8.02 (d, 1H). M.S. (chemical ionization, gas of ionization isobutane) m/e 206 (M^++1).

3-Formyl-4-methoxycarbonyl-7-methoxyindole 9

Phosphorus oxychloride (12 ml, 130 mmol) was dropped at 5°C on to a solution of 8 (20 g, 0.1 mol) in DMF (150 ml). After 1 h at room temperature the solution was diluted with water and heated at 70-80°C. The precipitated solid was collected by filtration, washed with water to yield 19 g (80%) of 9. m.p. 237-240°C. ^{1}H NMR (60 MHz, $CDCl_3$), δ: 3.92 (s, 3H), 4.12 (s, 3H), 6.88 (d, 1H), 7.40 (1H, d), 8.18 (1H, s), 10.6 (1H, s). MS (chemical ionization, gas of ionization isobutane) m/e 23 (M^++1), 202 (M^++ CH_3).

3-(2-Nitrovinyl)-4-methoxycarbonyl-7-methoxyindole 10

A solution of 9 (20 g, 85 mmol) and ammonium acetate (3 g) in

nitromethane (100 ml) was kept for 15 min at reflux temperature and then diluted with 50% ethanol (600 ml). The precipitated solid was collected by filtration and washed with 50% ethanol to yield 29.8 g (96%) of 10. m.p. 215-225°C (dec.). ^{1}H NMR (60 MHz, DMSO-d_6), δ: 3.99 (s, 3H), 4.12 (s, 3H), 6.82 (d, 1H), 7.84 (d, 1H), 8.04 (d, 1H), 8.40 (s, 1H), 9.46 (d, 1H).

MS (chemical ionization, gas of ionization isobutane) m/e 277 (M^++1).

3-(2-Nitroethyl)-4-methoxycarbonyl-7-methoxyindole 11

$NaBH_4$ (6.85 g, 0.18 mol) was added in portions to a solution of 10 (25 g, 9 mmol) in methanol (100 ml) at 40-50°C. After 1 h at the same temperature, the excess hydride was decomposed with acetic acid and then the mixture was evaporated to dryness. The crude residue was dissolved in CH_2Cl_2, washed with water, dried and evaporated. After purification by chromatography (eluent: CH_2Cl_2) on silica gel, pure 11 (19 g, 73%) was obtained. m.p. 140-141°C. ^{1}H NMR (60 MHz, $CDCl_3$), δ: 3.72 (t, 2H), 3.95 (s, 3H), 4.0 (s, 3H), 4.70 (t, 2H), 6.74 (d, 1H), 7.18 (d, 1H), 7.98 (d, 1H).

MS (chemical ionization, gas of ionization isobutane) m/e 279 (M^++1).

6-Oxo-9-methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole 13.

A suspension of 11 (20 g, 71 mmol), 10% Pd on charcoal (0.6 g) in acetic acid was submitted to hydrogenation at 40°C under a pressure of hydrogen (20 atm).

After 8 h at the same temperature, the theoretical amount of hydrogen had been absorbed. The catalyst was filtered off and the solution was evaporated to dryness. The residue was dissolved in CH_2Cl_2, washed with

dilute NaOH, dried and evaporated again. TLC analyses (n-butanol/water/acetic acid/acetone/toluene = 1/1/1/1/1) showed a mixture of 13 and tryptamine 12.

It was dissolved in 95% ethanol (340 ml) and basified with 10 N NaOH (13.7 ml). After 5 h at reflux temperature, the ethanol was evaporated and the solution was diluted with water, acidified with 37% HCl and finally cooled. The separated amide 13 was collected by filtration, washed with water to yield 12.5 g (81%). m.p. 280-285°C. ^{1}H NMR (300 MHz, DMSO-d_6), 2.89 (d, 2H), 3.35 (m, 2H), 3.95 (s, 3H), 6.77 (d, 1H), 7.14 (s, 1H), 7.77 (d, 1H).

MS (chemical ionization, gas of ionization isobutane) m/e 217 (M^++1).

9-Methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole hydrochoride 14

A mixture of 13 (11.7 g, 53 mmol), and $LiAlH_4$ (20.4 g, 0.53 mol) in THF (0.6 l) was kept at reflux temperature for 6 h. The excess hydride was decomposed by adding water (40 ml), 15% NaOH (20 ml) and water (100 ml) in that order. The salts were filtered off and the solution was evaporated to dryness. The residue was dissolved in 2N HCl, extracted with CH_2Cl_2 and then made basic with NaOH. The 14 which precipitated was then filtered, dissolved in CH_2Cl_2 and the solution acidified with a stream of anhydrous HCl in methanol to give a first crop of hydrochloride. From the mother liquor a second crop was collected to yield in all 8.7 g (60%) of 14 hydrochloride as a hygroscopic solid. ^{1}H NMR (60 MHz, DMSO-d_6 + D_2O) δ: 3.1-3.7 (m, 4H), 3.9 (s, 3H), 4.5 (s, 2H) , 6.6 (d, 1H), 6.8 (d, 1H), 7.2 (s, 1H). MS (electron impact) m/e 202 (M^+).

9-Hydroxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole hydrobromide 1

BBr_3 (2.4 ml, 25.8 mmol) in CH_2Cl_2 (10 ml) was added at -10°C to a solution of 14 (2.8 g, 11.7 mmol) in CH_2Cl_2 (60 ml). After 3 h at reflux temperature, the mixture was cooled and the solid filtered. After recrystallization from 95% ethanol, 1.1 g (35%) of 1 hydrobromide was obtained. m.p. 210-213°C. ^1H NMR (300 MHz, DMSO-d_6) 3.18 (t, 2H), 3.42 (bs, 2H), 4.22 (s, 2H), 6.50 (d, 1H), 6.74 (d, 1H), 6.62 (s, 1H); MS (chemical ionization, gas of ionization methane) m/e: 189 (M^++ 1).

References

1) Clark, R.D., Weinhardt, K.W., Berger, J., Fisher, L.E., Brown, C.M., MacKinnon, A.C., Kilpratick A.T. and Spedding, M., J. Med. Chem. 1990, 33, 633.

2) Von Strandtmann, M., Cohen M.P. and Shavel J., J. Med. Chem., 1965, 8, 200.

3) Kaiser, C. and Jain, Y., Med. Chem. Review 1985, 5, 145.

4) Cannon, J.G., "Progress in Drug Research", E. Jucker ed., Birkhäuser Verlag, Basel, 1985; pp. 303-314.

5) Kalir, A., Balderman, D., Edery H., and Porath, G., Israel J. Chem. 1967, 5, 129.

6) For review on ether cleavage see: Bhatt, M.V. and Kulkarni, S.V., Synthesis 1983, 249; ibid., 1988, 749.

(Received in UK 7 April 1993)