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A NEW SYNTHESIS OF 8-HYDROXY-2-DI-n-PROPYLAMINO-TETRALIN (8-OH-DPAT).

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ABSTRACT: *A new synthesis method for 8-OH-DPAT, a specific agonist at the 5-HT_{1A} serotonin receptor, is described. It employs the Curtius degradation of a tetralin carboxylic acid easily prepared from (2-methoxy benzyl) succinic acid by Friedel-Crafts cyclisation.*

The 5-HT_{1A} serotonin receptor is involved in an important number of regulation mechanisms in the central nervous system[1]. Recently the development of agonists for this type of receptor has generated considerable interest and some of them are of potential clinical interest as anxiolytics[2].

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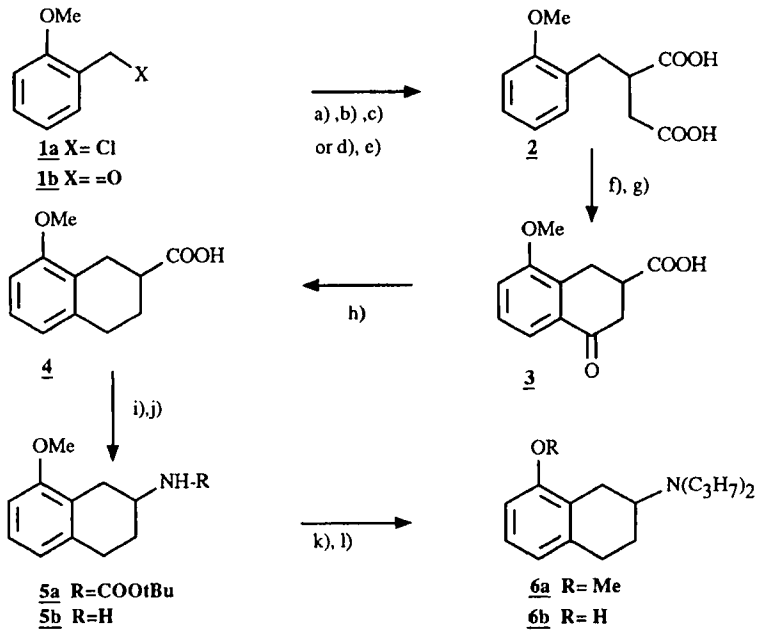
8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) **6b** is certainly the most thoroughly studied compound among the 5-HT_{1A} serotonin receptor agonists since it is particularly specific for this receptor subtype[3].

Several structure-activity relationships for **6b** have been published recently[4-6] and a number of compounds have been synthesized from 8-methoxy-2-tetralone. The introduction of a substituent in the 1 or 3 position of 8-OH-DPAT led to stereoselectivity rules for the molecular recognition by the 5-HT_{1A} serotonin receptor[7,8]. More recently, it was demonstrated that fluorine substitution in the 5 position resulted in a compound with antagonist properties[9] for the receptor suggesting the importance of this position for the pharmacological profile. In our research on the mapping of the 5-HT receptor we were interested in the activity of 8-OH-DPAT derivatives substituted in the 4 or 5 position. A synthetic method to prepare these compounds easily from 8-methoxy-2-tetralone, a starting material usually used in these series of compounds, was not available and a reappraisal of a synthetic route to synthesize 8-OH-DPAT was mandatory.

In the present communication we describe the first results for a new synthetic route to prepare 8-OH-DPAT based on the efficient Curtius degradation of a tetralin carboxylic acid in an amino compound prepared from an aromatic succinic acid derivative (scheme 1). The succinic acid derivative **2** was prepared in the routine way either by the acetoacetic ester method[10-11] from o-methoxy benzyl chloride **1a** or by condensation of the aromatic aldehyde **1b** with diethyl succinate followed by a hydrogenation[12]. This latter process provided the possibility to obtain an enantioselective synthesis of 8-OH-DPAT and its derivatives (by hydrogenation with a chiral catalyst[13]) which will be described in another paper.



Scheme 1

a) CH_3CO-CH(COOEt)CH_2COOEt, Na, toluene, 80°C; b) reflux, NaOH 2N, 18h; c) HCl conc, r.t.; d) $(CH_2$-$COOEt)_2$, Na, EtOH; e) Pd/C 10%, AcOH, H_2; f) $(CH_3CO)_2O$, reflux 2h; g) $AlCl_3$, $NO_2C_6H_5$; h) H_2, Pd/C 10%, AcOH, 70°C; i) diphenylphosphoryl azide, NEt_3, t.BuOH, reflux 18h; j) HCl 4N, AcOEt, 3h, r.t.; k) IC_3H_7, K_2CO_3, CH_3CN, 4 days, r.t; l) HBr 48%, 120-130°C, 2h.

The diacid **2** was transformed into an anhydride by heating with acetic anhydride and cyclised to a ketoacid **3** according to the Friedel-Crafts conditions in nitrobenzene[14]. The cyclisation was instantaneous since it was complete within 5 minutes, no improvement of yield could be obtained by a longer reaction time. The ketoacid **3** was hydrogenated at atmospheric pressure in 8-methoxy-2-tetralin carboxylic acid **4**. The best conditions in our hands for the Curtius reaction were the use of diphenylphosphoryl azide

(DPPA) in t.butanol at reflux[15] and the carbamate **5** was synthesized with a 74.5 % yield. By treatment with anhydrous HCl in ethyl acetate the hydrochloride of 8-methoxy-2-amino tetralin **5b** was directly prepared with a fairly good yield. The reaction of the hydrochoride with n-propyl iodide and K_2CO_3[16] gave the dipropylamino compound **6a** which was demethylated to 8-OH-DPAT[17] **6b**. Physicochemical and biological data for the compound which was obtained were identical to the reference product.

EXPERIMENTAL

Melting points were determined on a METTLER FP 61 melting point apparatus. ^1H and ^{13}C spectra were recorded using a BRUCKER AC200E spectrometer. The attribution of chemical shifts and coupling constants for the tetralins **4**, **5a**, **5b**, **6a** and **6b** was achieved by comparison with the reference product, 8-OH-DPAT[18]. Microanalyses were performed by the C.N.R.S. (department of microanalytical services), VERNAISON, FRANCE. All new compounds had satisfactory NMR and microanalytical data.

2-methoxy benzyl chloride 1a.

A solution of 64.7 g (0.54 mol) of thionyl chloride and 28.6 g (0.36 mol) of pyridine in 360 mL of toluene was cooled to 0°C in an ice bath. 50 g (0.36 mol) of 2-methoxy benzyl alcohol were added slowly while stirring vigourously. The reaction mixture was stirred at room temperature overnight and was poured onto ice. The solution was stirred for one hour more. The

organic layer was separated and washed twice with water, then with a saturated aqueous solution of $NaHCO_3$ and brine. It was dried over $MgSO_4$ and the solvent was evaporated to give an oil which was purified by distillation under reduced pressure, bp_{26mmHg} : 122- 124°C to afford 49.5 g of pure compound (86%).

^1H NMR ($CDCl_3$) δ : 3.9 (s, 3H, O-CH_3); 4.7 (s, 2H, CH_2); 6.9-7.0 (m, 2H, H_{ar}); 7.3-7.4 (m, 2H, H_{ar}).

^{13}C NMR ($CDCl_3$) δ : 41.6 (1C, CH_2Cl); 55.5 (1C, OCH_3); 110.7-120.6-125.7-130.0-130.5 (5C, C_{ar}); 157.3 (1C, $C_{ar\text{-}OCH3}$).

(2-methoxy benzyl) succinic acid 2.

A/ By the acetoacetic route.

6.1 g of sodium were added in small pieces to a solution of 60.1 g (0.278 mol) of diethyl acetyl succinate[10] in 200 mL of dry toluene and heated at 80°C. 49.5 g (0.316 mol) of 2-methoxy benzyl chloride were added slowly and the reaction mixture was refluxed for 18 hours. The cooled solution was acidified with acetic acid to pH 7 and evaporated. Water was added and the solution was extracted with ether. The combined organic layers were dried over $MgSO_4$ and the solvent removed. The residue was hydrolysed by boiling with 1400 mL of NaOH 2N for 18 hours. The cold alkaline solution was washed with ether and acidification with concentrated HCl delivered **2** as an oil which slowly solidified and was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The crude product was recrystallized in a mixture of acetone-toluene to provide after filtration 22.8 g (36%) of pure compound, mp : 144°C.

^{1}H NMR (CD_3OD) δ : 2.1-3.1 (m, 5H, CH_2-COOH, CH, C_6H_5-CH_2); 3.6 (s, 3H, O-CH_3); 6.6-6.7 (m, 2H, H_{ar}); 6.9-7.05 (m, 2H, H_{ar}).

^{13}C NMR (CD_3OD) δ : 33.3 (1C, CH_2-COOH); 35.9 (1C, CH); 42.7 (1C, C_{ar}-CH_2; 55.6 (1C, OCH_3); 111.4-121.3-129.1-131.8 (4C, C_{ar}); 127.8 (1C, C_{ar}-CH_2); 159.0 (1C, C_{ar}-OCH_3); 175.7-178.4 (2C, COOH).

B/ By the condensation of o-methoxy benzaldehyde **1b** and diethyl succinate.

A mixture of o-anisaldehyde (4.44 g, 40 mmol) and diethyl succinate (7.83 g, 45 mmol) was added slowly to a warm solution of sodium (2.23 g, 97 mmol) in anhydrous ethanol (50 mL). The reaction mixture was heated for 2 hours and the alcohol was removed. After water addition (50 mL), the solution was heated again for 2 hours. The solution was acidified with concentrated HCl. The yellow precipitate was filtered, washed with toluene and dried (4.42 g, 18.7 mmol, yield : 47%). The pale yellow product (2g, 8.5 mmol) was heated at 75°C overnight in 15 mL of acetic acid under H_2 with 0.25 g of 10% palladium on activated carbon. After cooling, the reaction mixture was filtered through celite and the acetic acid was evaporated. Water was added and a white solid precipitated. It was filtered, washed with water and dried to give pur o-methoxy benzyl succinic acid (1.76 g, 7.4 mmol, yield : 87.6%), mp : 142°C. The spectra were identical to those reported previously.

2 was converted to (2-methoxy benzyl) succinic anhydride by the following method : 8 g (33.6 mmol) of the acid **2** were refluxed for 2 hours with 80 g of acetic anhydride. The solution was evaporated to give a brown oil which gave 6.5 g of solid by cooling (88%).

5-methoxy-3-carboxy-1-tetralone 3.

5.6 g (25.5 mmol) of crude anhydride were dissolved in 60 mL of nitrobenzene and added slowly to a solution of 10 g (75.5 mmol) of $AlCl_3$ in 60 mL of nitrobenzene, cooled with an ice bath. The solution was stirred for 5 min. and a mixture of 40 g of ice in 40 mL of concentrated HCl was added. After standing overnight, nitrobenzene was removed by steam distillation. The cooled solution was extracted with ethyl acetate, the organic layer was dried over $MgSO_4$ and the solvent evaporated. The crude compound was purified by flash chromatography on silica gel (CH_2Cl_2-MeOH, 95/5) to give 3.03 g of pure compound, mp : 145°C, (54%).

^1H NMR ($CDCl_3$) δ : 2.6-3.3 (m, 5H, CH_2-CO, -CH-COOH, CH_2-Ar); 3.7 (s, 3H, O-CH_3); 6.9-6.95 (d, 1H, H_{ar}); 7.1-7.2 (t, 1H, H_{ar}); 7.5-7.55 (dd, 1H, H_{ar}).

^{13}C NMR ($CDCl_3$) δ : 24.9 (1C, Ar-CH_2); 39.2-39.7 (2 C, CH-COOH, CH_2-CO); 55.6 (1C, O-CH_3); 114.7-118.5-127.3 (3C, C_{ar}); 130.2 (1C, $C_{ar\text{-}CH2}$); 132.6 (1C, $C_{ar\text{-}CO}$); 156.6 (1C, $C_{ar\text{-}OCH3}$); 179.2 (1C, COOH); 196.1 (1C, CO).

8-methoxy tetralin 2-carboxylic acid 4.

2.44g (11.1 mmol) of the previous compound were reduced with H_2 under atmospheric pressure with 10% palladium on activated carbon (277 mg) in 50 mL of acetic acid and 1.4 mL of water by heating at 70-80°C overnight. The reaction mixture was filtered off through celite and evaporated to give the pure tetralin **4**. The yield was 2.2 g (96%), mp : 140°C.

^{1}H NMR ($CDCl_3$) δ : 1.8 (m, 1H, H_{3ax}); 2.1 (m, 1H, H_{3eq}); 2.65 (m, 2H, H_4); 2.8 (m, 2H, H_1); 3.0 (m, 1H, H_{2ax}); 3.7 (s, 3H, O-CH_3); 6.6 (t, 2H, H_{ar}); 7.05 (d, J= 7.9 Hz, 1H, H_{ar}); 11.0 (br s, 1H, COOH).

^{13}C NMR ($CDCl_3$) δ : 25.2-25.3 (2C, C_3-C_4); 28.5 (1C, C_1); 39.5 (1C, C_2); 55.9 (1C, O-CH_3); 107.0 (1C, C_7); 120.9 (1C, C_5); 123.7 (1C, C_9); ; 126.2 (1C, C_6); 136.9 (1C, C_{10}); 157.6 (1C, C_8); 182.0 (1C, COOH).

8-methoxy-2-terbutoxycarbonylamino tetralin 5a.

A solution of 1.55 g (7.5 mmol) of compound **4**, 2.17 g (7.9 mmol) of diphenylphosphoryl azide and 0.83 g (8.2 mmol) of triethylamine in 35 mL of terbutyl alcohol was refluxed for 18 hours. The reaction mixture was evaporated, 220 mL of toluene were added and this solution was successively washed with 5% citric acid solution (20 mL), water (20 mL), saturated $NaHCO_3$ solution (40 mL) and brine (20 mL). The solvent was removed under vacuum to provide the compound used without further purification in the following step, 1.55 g (75%).

^{1}H NMR ($CDCl_3$) δ : 1.4 (s, 9H, $C(CH_3)_3$); 1.6 (m, 1H, H_{3ax}); 1.95 (m, 1H, H_{3eq}); 2.3 (m(4), $J_{1ax\text{-}1eq}$= -17.3 Hz, $J_{1ax\text{-}2ax}$= 8.4 Hz, 1H, H_{1ax}); 2.8 (t, 2H, H_4); 3.7 (s, 3H, O-CH_3); 3.8 (m, 1H, H_{2ax}); 4.5 (br s ,1H, NH); 6.6 (2d, J= 7.8 Hz, 2H, H_7, H_5); 7.0 (t, J= 7.8 Hz, 1H, H_6).

^{13}C NMR ($CDCl_3$) δ : 27.5 (1C, C_4); 28.4 (3C, $(CH_3)_3$); 30.1 (1C, C_3); 45.7-46.9 (2C, C_1-C_2); 55.2 (1C, OCH_3); 80.0 (1C, $C(CH_3)_3$); 106.9 (1C, C_7); 120.9-123.3 (2C, C_9, C_5); 126.3 (1C, C_6); 136.0 (1C, C_{10}); 155.2-157.4 (2C, C_8-COOtBu).

8-methoxy-2-amino tetralin hydrochloride 5b.

To a solution of 0.3 g (1.1 mmol) of carbamate **5a** in 10 mL of ethyl acetate were added 10 mL of HCl 4N in ethyl acetate. The reaction mixture was stirred for 3 hours and then evaporated to give the crude hydrochloride which was purified by dissolution in ethanol and precipitation by addition of diethyl ether. The precipitate was filtered and dried to give the pure product, 0.17 g (74%), mp : 285°C.

^{1}H NMR (D_2O) δ: 1.55 (m, 1H, H_{3ax}); 1.9 (m, 1H, H_{3eq}); 2.3 (m(4), $J_{1ax\text{-}1eq}$= -16.8 Hz, $J_{1ax\text{-}2ax}$= 9.6 Hz, 1H, H_{1ax}); 2.6 (m, 2H, H_4); 2.9 (m(4), $J_{1ax\text{-}1eq}$= - 16.8 Hz, $J_{1eq\text{-}2ax}$= 5.3 Hz, 1H, H_{1eq}); 3.3 (m, 1H, H_{2ax}); 3.6 (s, 3H, O-CH_3); 6.6 (2d, J= 7.7 Hz, J= 7.3 Hz, 2H, H_7, H_5); 6.9 (t, J= 7.8 Hz, 1H, H_6)

^{13}C NMR (D_2O) δ: 27.4-28.3 (3C, C_1-C_3,C_4); 39.3 (1C, C_2); 56.8 (1C, O-CH_3); 109.6 (1C, C_7); 122.5 (2C, C_9, C_5); 128.7 (1C, C_6); 137.7 (1C, C_{10}); 158.1 (1C, C_8).

8-methoxy-2-(di-n-propylamino) tetralin 6a.

A suspension of 0.21 g (1 mmol) of 8-methoxy-2-amino tetralin hydrochloride **5b**, 0.2 mL of 1-iodopropane and 0.35 g of K_2CO_3 in 4 mL of acetonitrile was stirred for 4 days at room temperature. Ether was added and the precipitate was eliminated by filtration. The solution was concentrated by evaporation and purified by chromatography on an alumina column with ether as the eluant. The yield was 0.17 g (66%). The compound was converted to hydrochloride with HCl 4N in diethyl ether. After precipitation it was recrystallized in a mixture of ethanol-ether to deliver the pure hydrochoride, 0.08 g (41%), mp : 141°C.

^{1}H NMR (CD_3OD) δ : 1.2 (t,6H, 2xCH_3); 2.0 (m, 5H, 2xCH_2, H_{3ax}); 2.5 (m, 1H, H_{3eq}); 2.9 (m(4), $J_{1ax\text{-}1eq}$= -16.3 Hz, $J_{1ax\text{-}2ax}$= 11.3 Hz, 1H, H_{1ax}); 3.1-3.6 (m, 7H, H_{1ax}, H_4, 2xCH_2-N); 3.9 (m, 1H, H_{2ax}); 4.0 (s, 3H, O-CH_3); 6.9 (2d, 2H, H_7, H_5); 7.3 (t, 1H, H_6).

^{13}C NMR (CD_3OD) δ : 11.6 (2C, C_γ); 19.3-19.6 (2C, C_β); 24.5-24.6 (2C, C_1,C_3); 29.1 (1C, C_4); 53.6-53.9 (2C, C_α); 56.8 (1C, OCH_3); 61.1 (1C, C_2); 109.5 (1C, C_7); 122.1-122.2 (2C, C_9, C_5); 128.8 (1C, C_6); 137.9 (1C, C_{10}); 158.2 (1C, C_8).

8-hydroxy-2-(di-n-propylamino) tetralin hydrobromide 6b.

0.34 g (1.3 mmol) of 8-methoxy-2-(di-n-propylamino) tetralin was heated to 120-130°C in 10 mL of 48% HBr for 2 hours under nitrogen. The hydrobromic acid was evaporated and the residue was recrystallized from a mixture of ethanol-ether to yield pure 8-OH-DPAT, 0.36 g (84%), mp : 221°C. Physical data and spectra were identical to the reference compound.

^{1}H NMR (CD_3OD) δ : 1.1 (t, J= 7.4 Hz, 6H, 2xCH_3); 2.0 (m, 5H, 2xCH_2, H_{3ax}); 2.5 (m, 1H, H_{3eq}); 2.9 (m(4), $J_{1ax\text{-}1eq}$= -16.1 Hz, $J_{1ax\text{-}2ax}$= 11.2 Hz, 1H, H_{1ax}); 3.1 (m, 2H, H_4); 3.4 (m, 5H, 2xCH_2, H_{1eq}); 3.9 (m, 1H, H_{2ax}); 4.1 (s, 3H, O-CH_3); 6.8 (d, 2H, H_7, H_5); 7.0 (t, 1H, H_6).

^{13}C NMR (CD_3OD) δ : 11.4 (2C, C_γ); 19.75 (2C, C_β); 24.95-25.05 (2C, C_3,C_1); 29.4 (1C, C_4); 54.1 (2C, C_α); 62.0 (1C, C_2); 112.9 (1C, C_7); 120.4-120.5 (2C, C_9, C_5); 128.2 (1C, C_6); 137.4 (1C, C_{10}); 156.3 (1C, C_8).

References

1. Dourish, C. T., Ahlenius, S. and Hutson, P. H., "Brain 5-HT_{1A} receptors", VCH, Verlagsgelsellschaft mbH, Weinheim, 1987.

2. Traber, J. and Glaser, T., TIPS, 1987, *8*, 432.

3. Gozlan, H., El Mestikawy, S., Pichat, L., Glowinski, J. and Hamon, M., Nature, 1983, *305*, 140.

4. Björk, L., Höök, B. B., Nelson, D. L., Andén, N.-E. and Hacksell, U., J. Med. Chem., 1989, *32*, 779.

5. Mellin, C., Vallgarda, J., Nelson, D. L., Björk, L., Yu, H., Andén, N.-E., Csöregh, I., Arvidsson, L.-E. and Hacksell, U., J. Med. Chem., 1991, *34*, 497.

6. Liu, Y., Mellin, C., Björk, L., Svensson, B., Csöregh, I., Helander, A., Kenne, L., Andén, N.-E. and Hacksell, U., J. Med. Chem., 1989, *32*, 2311.

7. Arvidsson, L.-E., Johansson, A. M., Hacksell, U., Nilsson, J. L. G., Svensson, K., Hjorth, S., Magnusson, T., Carlsson, A., Andersson, B. and Wikström, H., J. Med. Chem., 1987, *30*, 2105.

8. Hancock, A. A., Meyer, M. D. and Debernadis, J. F., J. Receptor Research, 1991, *11*, 177.

9. Hillver, S.-E., Björk, L., Li, Y.-L., Svensson, B., Ross, S., Andén, N.-E. and Hacksell, U., J. Med. Chem. 1990, *33*, 1544.

10. Adkins, H., Isbell, N. and Wojcik, B., Organic synthesis, Coll. Vol. II, John Wiley and Sons, London, 1950, 262.

11. Haworth, R. D., Brynnor, J. and Way, Y. M., J. Chem. Soc., 1943, 10.

12. Cornforth, J. W.; Hughes, G. K.; Lions, F., J. Proc. Roy. Soc. N. S. Wales, 1939, *72*, 228.

13. Shao, L., Miyata, S., Muramatsu, H., Kawano, H., Ishii, Y., Saburi, M. and Uchida, Y., J. Chem. Soc. Perkin trans, 1990, 1441.

14. Huffman, J. W. and Mole, M. L., J. Org. Chem., 1972, *37*, 13.

15. Ninomiya, K., Shioiri, T. and Yamada, S., Tetrahedron, 1974, *30*, 2151.

16. Björk, L., Höök, B. B., Nelson, D. L., Andén, N.-E. and Hacksell, U, J. Med. Chem., 1989, *32*, 779

17. Arvidsson, L.-E., Hacksell, U., Johansson, A. M., Nilsson, J. L. G., Lindberg, P., Sanchez, D., Wikström, H., Svensson, K., Hjorth, S. and Carlsson, A., J. Med. Chem., 1984, *27*, 45.

18. Arvidsson, L. E., Karlén, A., Norinder, U., Kenne, L., Sundell, S. and Hacksell, U., J. Med. Chem., 1988, *31*, 212.

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