Synthesis of a Novel Heterocyclic System: 8-Fluoro-1,2,3,4,4a,10a-hexahydro-5*H*-[1]benzopyrano[2,3-*c*]pyridin-5-ol

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The synthesis of the title compound is described and its structure elucidated by ^{1}H nmr spectroscopy.

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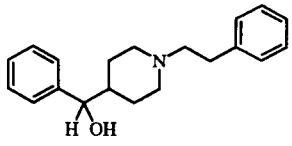
Introduction.

In order to get a similar compound to the serotonin (5 HT_{2a}) antagonist, α-(1-phenylethylpiperidin-4-yl)benzyl alcohol, (MDL 11,939), which has a minimum of potential pharmacophoric groups [1], the sterically fixed compound **8** was prepared. The purpose of steric fixation was to increase the selectivity to the 5 HT_{2a} receptor. The possible use of the previously unknown heterocyclic compound **8** as an amine component in other synthesized active substances is also conceivable (Figure 1).



MDL 11,939

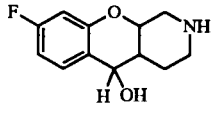


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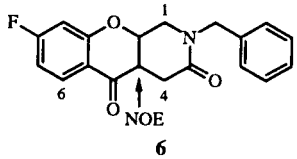
Figure 1.

Chemistry.

In order to synthesize compound **8**, carbonic acid **1** was first prepared reacting 3-fluorophenol and succinic anhydride by means of Friedel-Crafts acylation. *N*-Benzylaminoacetaldehyde diethyl acetal was then added to compound **1** in the presence of dicyclohexylcarbodiimide to yield carbonic acid amide **2**. Acetal cleavage was then induced by addition of trifluoroacetic acid at room temperature. The product, aldehyde **3**, was added to an equimolar quantity of pyrrolidine in dry toluene and subjected to an intramolecular Mannich-like reaction. This reaction is assumed to yield an intermediate compound **4.** The latter cyclizes to form **5**, which subsequently undergoes Michael-like addition to yield the novel tricyclic heterocycle **6**. Compound **6** is reduced by lithium aluminium hydride to yield compound **7**. Debenzylation of compound **7** using hydrogen and palladium on carbon yields the sterically fixed compound **8** (Scheme 1).

Structural Elucidation of Compounds **4** and **6.**

Compound **4** is synthesized by means of a Mannich-like reaction and subsequent Michael-like addition, which occurs in a stereospecific and diastereoselective manner. *Cis*-fusion of the two heterocyclic rings was demonstrated by means of an NOE experiment. When irradiated with the frequency of 4a-H, the signal intensity of 10a-H and 4-H increased. The only conceivable explanation for this is the *cis*-position of 4a-H relative to 10a-H and thus *cis*-fusion of the two heterocyclic rings. The constitution of the target compound **6** follows from the synthetic pathway and is in accordance with the ^{1}H nmr spectra. The configuration follows from the NOE experiments. Irridiation at 5-H produces enhancements of the signals of 4a-H, 10a-H, and 6-H and irridiation at 10a-H gives enhancements for 4a-H, 5-H, 1-$H_{ax.}$ and 1-$H_{equat.}$. These results are only compatible with an all-*cis*-configuration. The all-*cis*-configuration is confirmed and the conformation established through ^{3}J (H,H) coupling constants (see Experimental) (Figure 2).



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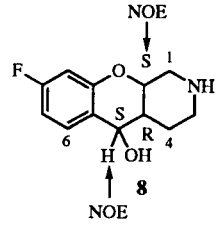


Figure 2.

The conformation derived from ^{3}J (H,H) values is identical to that computed by the MMC-based computer program „hyperchem" (Figure 3).

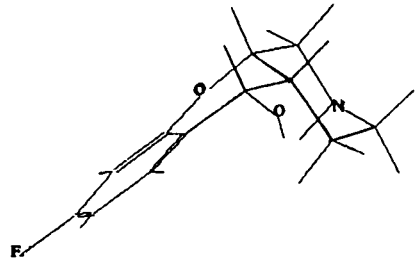
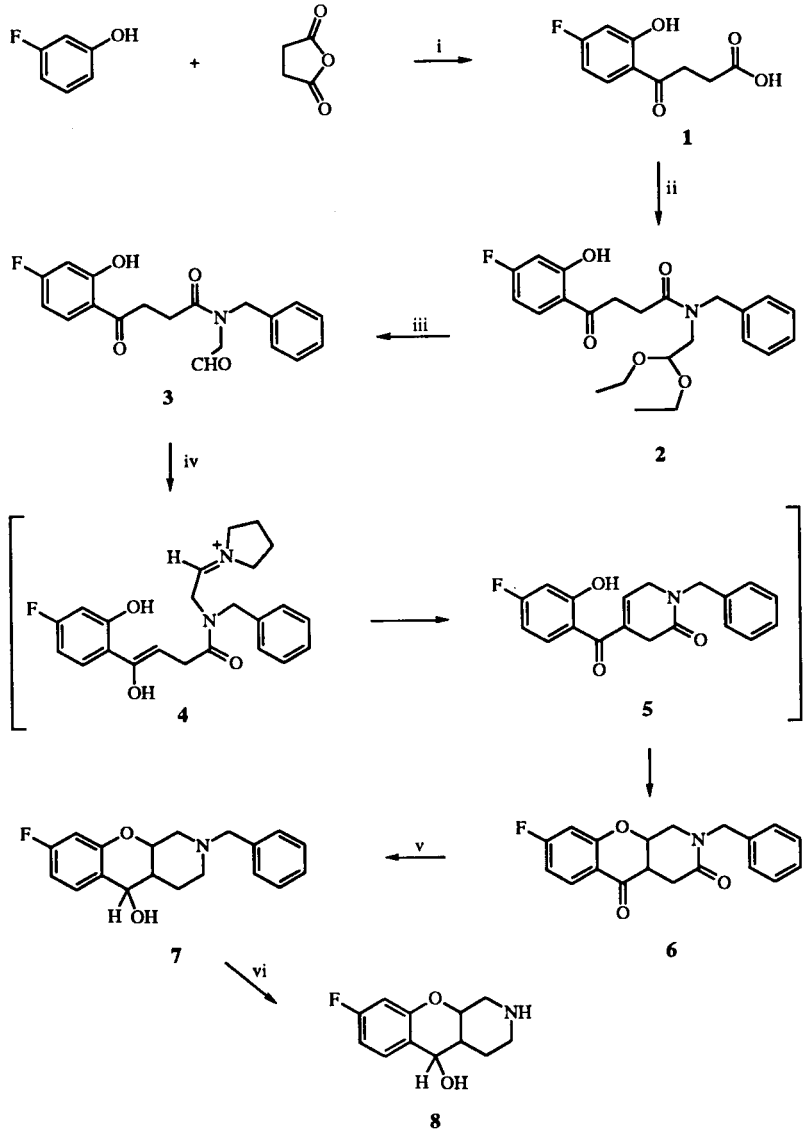


Figure 3.

Scheme 1



i, $AlCl_3$, dichloromethane; ii, DCC, *N*-benzylaminoacetaldehyde diethyl acetal, dichloromethane; iii, trifluoroacetic acid (20%), dichloromethane; iv, pyrrolidine, toluene; v, THF, $LiAlH_4$; vi, H_2, Pd/C, MeOH.

The conformation reveals that the ether oxygen and the NH are *gauche* oriented favoring complexation of guest like cation or molecules with complementary groups. Using the Cahn-Ingold-Prelog rule, *R/S* configurations were found in the three asymmetrical carbon atoms 4a-C, 5-C and 10a-C. Specifically, 4a-C was *R*-configurated, and the C-atoms 5-C and 10a-C were *S*-configurated.

EXPERIMENTAL

Melting points were determined on a Linström apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 297 spectrometer. The ^1H nmr spectra were recorded on a Bruker AC 300 and a JEOL GX 400 spectrometer. Mass spectra were obtained on a Finnigan MAT Bremen CH-7A spectrometer and Finnigan MAT Bremen CH-5DF. Elemental analyses were performed by the Institut für Pharmazie Analytical Service Laboratory.

4-(4-Fluoro-2-hydroxyphenyl)-4-oxobutanoic Acid (1).

To a stirred suspension of 3-fluorophenol (25.0 g, 223 mmoles) and succinic anhydride (22.5 g, 225 mmoles) in anhydrous 1,2-dichloroethane (200 ml) at 0° was slowly added aluminium chloride (59.5 g, 446 mmoles), and the resulting mixture was stirred for 24 hours under reflux. Hydrolysis was then carried out at room temperature using a mixture of ice water (100 ml) and concentrated hydrochloric acid (10 ml). The organic phase was separated, and the aqueous phase was extracted with 1,2-dichloroethane (3 x 100 ml). The combined 1,2-dichloroethane

solution was washed with water (2 x 100 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo* to afford a colorless solid, which was recrystallized from 20% aqueous acetic acid (150 ml) to give 14.5 g (30%) of **1** as colorless crystals, mp 134°; ir (potassium bromide): ν 1701 (COOH), 1635 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.57 (t, 2H), 3.24 (t, 2H), 6.81-6.86 (m, 2H), 8.01 (d, d, 1H), 12.18 (s, 2H); ms: m/z 212 (M^+).

Anal. Calcd. for $C_{10}H_9FO_4$: C, 56.60; H, 4.28. Found: C, 56.60; H, 4.27.

N-Benzyl-*N*-2,2-diethoxyethyl-4-(4-fluoro-2-hydroxyphenyl)-4-oxobutanoic Acid Amide (**2**).

To a stirred solution of compound **1** (3 g, 14.14 mmoles) and *N*-benzylaminoacetaldehyde diethyl acetal (3.16 g, 14.14 mmoles) in anhydrous dichloromethane (60 ml) at 0° was added *N,N'*-dicyclohexylcarbodiimide (2.92 g, 14.14 mmoles) and the mixture was stirred for 0.5 hours at this temperature. Stirring was continued for a further 3 hours at room temperature. After completation of the reaction, the mixture was filtered, the residue washed with dichloromethane (10 ml) and the filtrate was dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel with dichloromethane as an eluent to provide 4.38 g (74%) of a yellow oil of **2**; ir (sodium chloride): ν 1643 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15-1.25 (m, 12H), 2.81 (t, 2H), 2.98 (t, 2H), 3.28-3.40 (m,16H), 4.45-4.82 (m, 6H), 6.61-7.95 (m, 16H), 12.50 (d, 1H), 12.58 (d, 1H); ms: m/z 417 (M^+).

Anal. Calcd. for $C_{23}H_{28}FNO_5$: C, 66.17; H, 6.76; N, 3.36. Found: C, 65.97; H, 6.56; N, 3.29.

N-Benzyl-*N*-formylmethyl-4-(4-fluoro-2-hydroxyphenyl)-4-oxobutanoic Acid Amide (**3**).

To a stirred solution of compound **2** (2 g, 7.04 mmoles) in dichloromethane (20 ml) at 0° was added 20% aqueous trifluoroacetic acid (20 ml). The solution was gently warmed to room temperature and stirring was continued for a further 3 hours. The organic layer was separated, washed with saturated aqueous sodium chloride solution (3 x 30 ml), dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give an oily residue. The residue was purified by column chromatography on silica gel with a mixture of ethyl acetate/*n*-hexane 1:1 (v/v) as an eluent, 1.83 g (76%) of colorless crystals of **3** from petroleum benzin, mp 76°; ir (potassium bromide): ν 3437 (OH), 1733 (CHO), 1641 (CO), 1597 ($CONR_2$) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.98 (t, 2H), 3.42 (d, 2H), 4.10 (s, 2H), 4.69 (s, 2H), 6.60-6.75 (m, 2H), 7.20-7.42 (m, 5H), 7.82-7.92 (d, d, 1H), 9.55 (s, 1H), 12.48 (s, 1H); ms: m/z 343 (M^+).

Anal. Calcd. for $C_{19}H_{18}FNO_4$: C, 66.48; H, 5.29; N, 4.08. Found: C, 66.20; H, 5.41; N, 3.96.

2-Benzyl-8-fluoro-1,2,3,4a,10a-hexahydro-5*H*-[1]benzopyrano[2,3-*c*]pyridine-3,5-dione (**6**).

To a solution of **3** (1.2 g, 3.5 mmoles) in anhydrous toluene (40 ml) was slowly added pyrrolidine (256 mg, 3.6 mmoles) at room temperature. The resulting solution was stirred for 1 hour at this temperature and then heated under reflux for 45 minutes. After cooling to room temperature ethyl acetate (50 ml) was added to the mixture. The resulting solution was successively treated with 2 *N* hydrochloric acid (30 ml), 10% aqueous solution of sodium carbonate (2 x 30 ml) and then washed with water (30 ml). The organic phase was dried (magnesium sulfate) and evaporated. The crude product was purified by column chromatography on silica gel with a mixture of ethyl acetate/*n*-hexane 8:2 (v/v) as an eluent giving 120 mg (10%) of **4** as colorless crystals, mp 154°; ir (potassium bromide): ν 1687 (CO), 1633 ($CONR_2$) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.62 (m, 2H), 3.01-3.03 (m, 1H), 3.51-3.70 (m, 2H), 4.60-4.80 (m, 3H), 6.62-6.77 (d, d, 1H), 6.79-6.82 (d, t, 1H), 7.22-7.39 (m, 5H), 7.98 (d, d, 1H); ms: m/z 325 (M^+).

Anal. Calcd. for $C_{19}H_{16}FNO_3$: C, 70.15; H, 4.96; N, 4.31. Found: C, 69.85; H, 5.36; N, 4.13.

2-Benzyl-8-fluoro-1,2,3,4,4a,10a-hexahydro-5*H*-[1]benzopyrano[2,3-*c*]pyridin-5-ol (**7**).

To a suspension of lithium aluminium hydride (149 mg, 3.71 mmoles) in anhydrous tetrahydrofurane (40 ml) a solution of compound **6** in anhydrous tetrahydrofurane (40 ml) was added drop-by drop until weak boiling of the mixture was observed. After the addition was completed, the reaction mixture was stirred for 1 hour at room temperature, then hydrolyzed with water (10 ml) and filtrated. The filtrate was dried over magnesium sulfate and evaporated. The resulting crude oil was purified by column chromatography on silica gel with a mixture of ethyl acetate/*n*-hexane 1:1 (v/v) as an eluent giving 246 mg (21%) of **7** as colorless crystals, mp 160°; ir (potassium bromide): ν 3664 (OH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.78 (s, 1H), 2.03-2.22 (m, 4H), 3.02-3.12 (m, 1H), 3.39 (d, 1H), 3.70 (d, 1H), 4.12-4.20 (m, 2H), 4.70-4.92 (m, 3H), 6.52-6.58 (m, 1H), 6.61-6.71 (m, 1H), 7.18-7.42 (m, 5H); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{19}H_{20}FNO_2$: C, 72.84; H, 6.43; N, 4.47. Found: C, 71.28; H, 6.64; N, 4.36.

8-Fluoro-1,2,3,4,4a,10a-hexahydro-5*H*-[1]benzopyrano-[2,3-*c*]pyridin-5-ol (**8**).

A mixture of compound **7** (230 mg, 0.7 mmoles), glacial acetic acid/methanol 8:2 (v/v, 25 ml) and 10% palladium on carbon (0.1 g) was hydrogenated in a Parr apparatus at room temperature under an initial pressure of 14.5 psi until the calculated amount of hydrogen was absorbed (48 hours). After removal of the catalyst the solution was evaporated to dryness. Rotational chromatography on silca gel with dichloromethane/methanol 95:5 (v/v) as the eluent in the presence of ammonia yielded 96 mg (61%) of compound **8** as colorless crystals, mp 202°; ir (potassium bromide): ν 3396 (NH), 3294 (OH) cm^{-1}; ^1H nmr (deuteriochloroform; in order to facilitate assignment and recognition of coupling constants each of the 9 aliphatic protons was selectively irridiated): δ 1.25 (q, d; 12.5, 4.3 Hz; 1H, 4-H_{ax}), 1.6 (broad d, 13.4, 3.5, 3.5, 2 and 3.5 (w coupling to 10a-H), 1H, 4-H_e), 2.25 (m, 12.8, 6.1, 4.3, 2.1, 1H, 4a-H), 2.7 (t, d, 13.4, 12.2, 3.0, 1H, 3-H_{ax}), 2.85 (d, d, 14.3, 1.5, 1H, 1-H_{ax}), 3.2 (broad d, 13.4, 4.3, 2, 1H, 3-$H_{equat.}$), 3.25 (broad d, d, 14.3, 2.4, 3 (w coupling to 4-$H_{equat.}$), 1H, 1-H_e), 4.2 (broad s, 2.3, 2, 1.5, 1H, 10a-H), 5.0 (broad d, 6.1, <2 (coupling to 6-H), 1H, 5-H), 6.53 (d, d,11, 3, 1H, 9-H), 6.66 (t, d, 8.5, 8.5, 3, 1H, 7-H), 7.43 (pseudo t, d, 8.5, 7.5, <2, 1H, 6-H); ms: m/z 223 (M^+).

Anal. Calcd. for $C_{12}H_{14}FNO_2$: C, 64.50; H, 6.32; N, 6.27. Found: C, 63.91; H, 6.30; N, 6.26.

REFERENCES AND NOTES

[1] M. W. Dudley, N. L. Wiech, F. P. Miller, A. A. Carr, H. C. Cheng, L. E. Lawrence, E. Roebel, N. S. Doherty, H. I. Yamamura, R. C. Ursillo and M. G. Palfreyman, *Drug Develop. Res.*, **13**, 29 (1988).