PREPARATION AND STEREOCHEMISTRY OF PHENOLIC 1-METHYL-3-ARYL-TETRAHYDROISOQUINOLINE DERIVATIVES

Dolores Badía, Esther Domínguez*, Carmen Iriondo, and Eduardo Martínez de Marigorta

Departamento de Química, Facultad de Ciencias,
Universidad del País Vasco, Bilbao, Spain

Abstract - The preparation of cis- and trans-1-methyl-3-(3,4-dimethoxyphenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5a) and (5b), and the stereochemistry of the isoquinoline system of these compounds are reported.

In recent years, interest has been focused on the 3-aryl-1,2,3,4-tetrahydroisoquinoline nucleus, since one of the methods[1,2] of choice for the synthesis of the protoberberine and benzophenanthridine skeleton involves the initial preparation of 3-aryltetrahydroisoquinoline derivatives.

In earlier papers[3], we have reported the synthesis of non-phenolic 6,7-dialkoxy-1-substituted 3-aryltetrahydroisoquinolines by means of the classical Pictet-Spengler reaction, but this method on our hands was unsuccessful when applied to phenolic 1,2-diarylethylamines, in order to obtain the corresponding 3-aryltetrahydroisoquinolines. Herein we wish to report an efficient method for the preparation of phenolic 6,7-disubstituted 3-aryltetrahydroisoquinolines (5a) and (5b) and to discuss the stereochemistry of the tetrahydroisoquinoline system on the basis of their spectroscopic data.

These compounds (5a) and (5b), were prepared by treating the phenolic 1,2-diarylethylamine (4a) with acetaldehyde. The mixture was heated at 80°C in a closed screw-cap test tube without acidic media[4], and the reaction was complete within 12 h furnishing the mixture (7:3) of phenolic isoquinolines (5a) and (5b), which were separated by column chromatography. The required ketone (3) was prepared according to the procedure described by Dyke[5], subsequent Leuckart reaction of (3) followed by the corresponding hydrolysis and debenzylation, afforded the expected 1,2-diarylethylamine (4a).

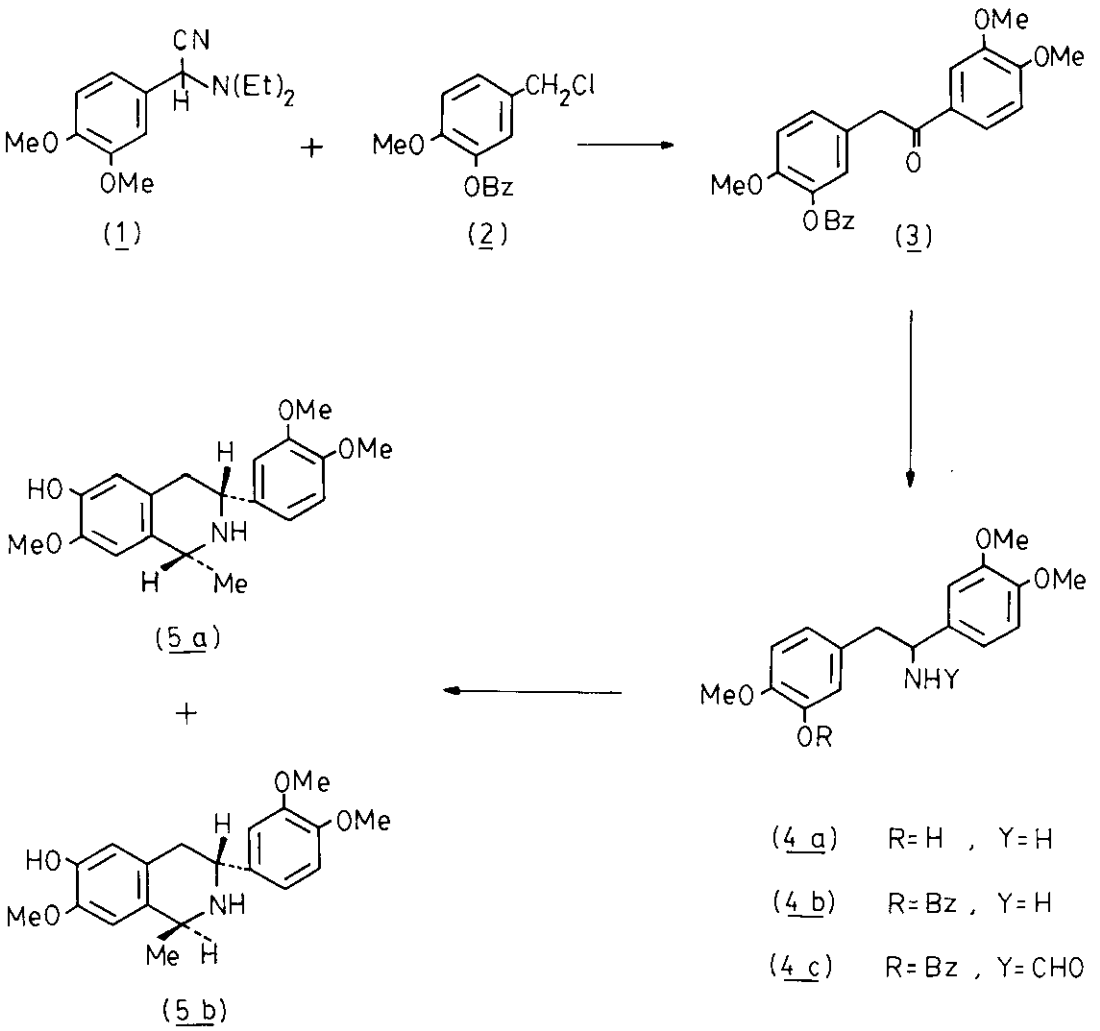
The pmr spectra (acetone-d_6) of (5a) and (5b) readily showed that the cyclization reaction had taken place. The two aromatic protons of the isoquinoline system appear in (5a) as uncoupled singlets at δ 6.51 and 6.81 ppm, while the corresponding aromatic protons in (5b) afford two singlets at δ 6.51 and 6.69 ppm.

The stereochemistry in structures (5a) and (5b) was assigned as follows:

Analysis of chemical shift ($CDCl_3$) (δ 1.50) reveals that the 1-methyl group in (5a) occupies the pseudoequatorial position, being slightly deshielded with respect to the pseudoaxial 1-methyl (δ 1.48) of (5b), while the corresponding pseudoaxial 1-proton of (5a) (δ 4.25) is shielded with respect to the pseudoequatorial 1-proton of (5b) (δ 4.30). Considerable precedent for this effect exists for nitrogen heterocycles[6], including tetrahydroisoquinolines[7].

On the other hand, the signal due to C_3-H in (5a) and (5b) shows an ABX splitting pattern, which is consistent with this proton being in an axial position in both compounds.

These data let us propose a cis configuration for compound (5a) and a trans configuration for (5b), thus showing that our method for phenolic cyclization is not diastereoselective.



EXPERIMENTAL

Melting points were determined on either Electrothermal IA 6304 or Buchi apparatus and are uncorrected. For thin-layer chromatography Merck Kieselgel GF 254 plates (0.2 mm thick) were used. Visualization was accomplished by uv light or by spraying with Dragendorff's reagent. Column chromatography was carried out on SiO_2 (silica gel 60 Merck, 230-400 mesh). Microanalyses were performed by the "Colegio Universitario de Alava". The ir spectra were recorded on a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (cm^{-1}) are listed. Pmr spectra were run on a Perkin-Elmer R-12 (60 MHz) and a Bruker WM-200-SY (200 MHz) instruments using TMS as internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. Mass spectra were measured with a Hewlett-Packard HP-5970 apparatus.

3-Benzyloxy-4-methoxybenzyl 3,4-Dimethoxyphenyl Ketone (3).
A solution of the 2-(N,N-diethylamino)-2-(3,4-dimethoxyphenyl)acetonitrile[5] (1.1 g, 4.4 mmole) in dry DMF (25 ml) was added to 0.25 g of sodium hydride (85% suspension in oil), washed with petroleum ether and suspended in dry DMF (10 ml) under N_2. The resulting suspension was stirred under N_2 for 3 h and the 3-benzyloxy-4-methoxybenzyl chloride (2) (1.07 g, 4.4 mmole), added over a further 3/4 h. After stirring overnight, the excess NaH was destroyed with MeOH and the solvent evaporated to yield an oil which was dried under 0.001 mm pressure at 90°C over 3 h. The resulting syrup was stirred in 6N HCl (15 ml) for 24 h. After dilution with water (15 ml) the aqueous solution was extracted with $CHCl_3$ (3x30 ml) and the combined organic extracts were washed with aqueous $NaHCO_3$ (2x15 ml) and H_2O (2x15 ml), dried (Na_2SO_4) and evaporated to leave an oil. The resulting oil was column chromatographed under pressure on silica gel by eluting with dichloromethane to afford a white solid. Crystallization from ethanol gave the ketone (3). Yield: 1.04 g (60%), mp 102-104 °C. Anal. Calcd. for $C_{24}H_{24}O_5$: C, 73.47; H, 6.12. Found: C, 73.40; H, 6.05%. Ir (KBr) ν_{max} cm^{-1}: 1675 (-CO-). Pmr ($CDCl_3$), δ: 7.6-7.3 (7H, m, Ph-H and Ar-H), 7.0-6.8 (4H, m, Ar-H), 5.15 (2H, s, $-CH_2-Ph$), 4.1 (2H, s, $-CH_2-CO-$), 3.92 (6H, s, $2xOCH_3$), 3.88 (3H, s, OCH_3).

N-1-(3,4-Dimethoxyphenyl)-2-(4-methoxy-3-benzyloxyphenyl)ethylformamide (4c).
A mixture of the ketone (3) (15.12 g, 0.04 mole), ammonium formate (25.20 g, 0.4 mole), 90% formic acid (4 ml) and formamide (4 ml) was heated at 185-190 °C for 3.5 h. Then, the reaction mixture was cooled to room temperature, water added and the resulting solid filtered off. Crystallization from ethanol gave the formamide (4c) as a white solid. Yield: 12.73 g (75%), mp 113-114°C. Anal. Calcd. for $C_{25}H_{27}O_5N$: C, 71.25; H, 6.41; N, 3.32. Found: C, 71.21; H, 6.37; N, 3.29%. Ir (KBr) ν_{max} cm^{-1}: 3340 (-NH-), 1665 (-CO-). Pmr ($CDCl_3$), δ: 8.0 (1H, s, -CHO), 7.3 (5H, s, Ph-H), 6.7-6.5 (6H, m, Ar-H), 5.9 (1H, broad d, -NH-), 5.15 (1H, m, $-\underline{CH}-CH_2-$), 5.0 (2H, s, $-CH_2-Ph$), 3.8 (6H, s, $2xOCH_3$), 3.65 (3H, s, OCH_3), 2.95 (2H, d, J=7 Hz, $-\underline{CH_2}-CH-$).

1-(3,4-Dimethoxyphenyl)-2-(4-methoxy-3-benzyloxyphenyl)ethylamine (4b).
To a well stirred solution of the ethylformamide (4c) (2.74 g, 6.53 mmole) in etha-

nol (25 ml) a solution (5 ml) of aqueous NaOH (40%) was added. The mixture was heated under reflux for 2 h, the solvent was evaporated, water was added and then extracted with chloroform (3 x 100 ml). Evaporation of the solvent from the combined dried extracts afforded an oil, which was crystallized from ethanol to give the ethylamine (4b). Yield: 2.03 g (79%), mp 108-109°C. Anal. Calcd. for $C_{24}H_{27}O_4N$: C, 73.28; H, 6.87; N, 3.56. Found: C, 73.26; H, 6.85; N, 3.61%. Ir (KBr) ν_{max} cm^{-1}: 3340 and 3280 ($-NH_2$). Pmr ($CDCl_3$), δ: 7.4 (5H, s, Ph-H), 7.0-6.6 (6H, m, Ar-H), 5.15 (2H, s, $-CH_2-Ph$), 4.1 (1H, m, $-\underline{CH}-CH_2-$), 3.9 (9H, s, $3xOCH_3$), 2.8 (2H, d, J=7.7 Hz, $-\underline{CH_2}-CH-$), 1.5 (2H, broad s, $-NH_2$).

1-(3,4-Dimethoxyphenyl)-2-(3-hydroxy-4-methoxyphenyl)ethylamine (4a).
A solution of the ethylamine (4b) (1.5 g, 3.8 mmole) in 95% ethanol (150 ml), was hydrogenated over 10% Pd/C at atmospheric pressure and room temperature for 3 h. Removal of the catalyst and solvent afforded the required amine (4a). Yield: 0.98 g (85%), mp 145-147°C (from methanol). Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.65; H, 6.96; N, 4.62. Found: C, 67.70; H, 6.94; N, 4.66%. Ir (KBr) ν_{max} cm^{-1}: 3345 and 3285 ($-NH_2$), 3200-2500 (-OH). Pmr ($CDCl_3$), δ: 7.1-6.7 (6H, m, Ar-H), 4.2 (1H, m, $-\underline{CH}-CH_2-$), 3.9 (6H, s, $2xOCH_3$), 3.85 (3H, s, OCH_3), 3.3 (3H, broad s, $-NH_2$ and -OH; exchangeable with D_2O), 2.9-2.7 (2H, d, $-\underline{CH_2}-CH-$). Ms, m/z (%): 303 (1.5) M^+, 186 (15.0), 164 (18.5), 149 (100), 135 (21.0).

cis- and trans-1-Methyl-3-(3,4-dimethoxyphenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5a) and (5b).
The phenolic amine (4a) (1.0 g, 3.3 mmole) and acetaldehyde (0.2 ml, 3.3 mmole) were mixed in 10 ml of ethanol. The mixture was heated at 80°C for 12 h in several closed screw-cap test tubes. After concentrating the so-obtained solution under vacuum, the resulting oil was treated with methanol to afford a white solid, containing two major components (tlc). Subsequent work-up and column chromatography (silica gel, eluting with $CHCl_3$ + 1.5% MeOH) gave the following compounds:
a) *Isomer* (5a): R_f=0.82 (silica gel, $CHCl_3$/MeOH, 9:1), yield: 610 mg (56%), colorless crystals of mp 164-165°C (from methanol). Anal. Calcd. for $C_{19}H_{23}O_4N$: C, 69.32; H, 6.99; N, 4.25. Found: C, 69.31; H, 7.01; N, 4.25%. Ir (KBr) ν_{max} cm^{-1}: 3320 (-NH-), 3100-2300 (-OH). Ir ($CHCl_3$): 3550 (free -OH), 3315 (-NH-). Pmr ($CDCl_3$), δ: 7.01 (1H, d, J_{meta}=2.0 Hz, H-2'), 6.93 (1H, dd, J_{meta}=2.0 Hz and J_{ortho}=8.2 Hz, H-6'), 6.83 (1H, d, J_{ortho}=8.2 Hz, H-5'), 6.67 (1H, s, H-5), 6.56 (1H, s, H-8), 4.25 (1H, q, J=6.9 Hz, H-1), 3.97 (1H, dd, J_{AX}= 3.5 Hz and J_{BX}=11.0 Hz, H-3), 3.88 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.90 (1H, dd, J_{BX}=11.0 Hz and J_{AB}= 15.5 Hz, H-4), 2.80 (2H, broad s, exchangeable with D_2O, -NH-, -OH), 2.75 (1H, dd, J_{AX}=3.5 Hz and J_{AB}=15.5 Hz, H-4), 1.50 (3H, d, J=6.9 Hz, $-CH_3$). Ms, m/z (%): 329 (22) M^+, 314 (97), 166 (92), 164 (100).
b) *Isomer* (5b): R_f=0.73 (silica gel , $CHCl_3$/MeOH, 9:1), yield: 250 mg (23%), mp 187-189°C (from methanol). Anal. Calcd. for $C_{19}H_{23}O_4N$: C, 69.30; H, 6.99; N, 4.25. Found: C, 69.31; H, 7.00; N, 4.26%. Ir (KBr) ν_{max} cm^{-1}: 3320 (-NH-), 3100-2300 (-OH). Ir ($CHCl_3$): 3550 (free -OH), 3315 (-NH-). Pmr ($CDCl_3$), δ: 7.01 (1H, d, J_{meta}=2.3 Hz, H-2'), 6.94 (1H, dd, J_{meta}=2.3 Hz and J_{ortho}=8.2 Hz, H-6'), 6.82 (1H, d, J_{ortho}=8.2 Hz, H-5'), 6.57 (1H, s, H-5), 6.56 (1H, s, H-8), 4.30 (1H, q, J=6.9 Hz, H-1), 4.20 (1H, t, J=6.7 Hz, H-3), 3.86 (6H, s, $2xOCH_3$), 3.81 (3H, s, OCH_3),

3.1-2.6 (2H, broad s, exchangeable with D_2O, -NH and -OH), 2.82 (2H, d, J=6.7 Hz, H-4), 1.48 (3H, d, J=6.9 Hz, $-CH_3$). Ms, m/z (%): 329 (19) M^+, 314 (100), 166 (76), 164 (81).

ACKNOWLEDGEMENT

We are grateful to the Spanish Ministry of Education and Science for the grant of a fellowship to one of us (E. Martínez de Marigorta).

REFERENCES

1. S. F. Dyke, D. W. Brown, M. Sainsbury and G. Hardy, Tetrahedron, 1971, 27, 3495.
2. S. F. Dyke and E. P. Tiley, Tetrahedron, 1975, 31, 561.
3. E. Domínguez and E. Lete, An. Quim., 1984, 80C, 13.
4. M. R. Falco, J. X. Vries, E. Marchelli, M.C de Lorenzo and G. Mann, Tetrahedron, 1972, 28, 5999.
5. S. F. Dyke, E. P. Tiley, A. W. C. White and D. P. Gale, Tetrahedron, 1975, 31, 1219.
6. F. Vierhapper, E. Eliel,and G. Zuñiga, J. Org. Chem., 1980, 45, 4844.
7. (a) A. Brossi, A. Focella and S. Teitel, Helv. Chim. Acta, 1972, 55, 15.
   (b) G. Grethe, M. Uskokovic, T. Williams and A. Brossi, Helv. Chim. Acta, 1967, 50, 2397.
   (c) H. A. Bates, J. Org. Chem., 1983, 48, 1932.

Received, 7th January, 1986