# Synthesis of 6,7-Dimethoxy-1-halobenzyl-1,2,3,4-tetrahydroisoquinolines



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Some 6,7-dimethoxy-1-halobenzyl-1,2,3,4-tetrahydroisoquinolines were synthesized from 2-(3,4-dimethoxyphenyl)ethylamine and halophenylacetic acids in three steps in good yield.

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In a previous paper [1], we reported the pharmacological characterization of effects of verapamil and 1-(4'-methoxybenzyl)-6,7-dihydroxy-3,4-dihydroisoquinoline on the isolated guinea pig and on the rat terachesalis. In connection with our research program for the study on the pharmacological characterization of novel isoquinoline derivatives, we required some isoquinolines containing the mono- (or di-)halobenzyl moiety at the C-1 position.

In this paper, we would like to report the synthesis of 6,7-dimethoxy-1-halobenzyl-1,2,3,4-tetrahydroisoquinoilines.

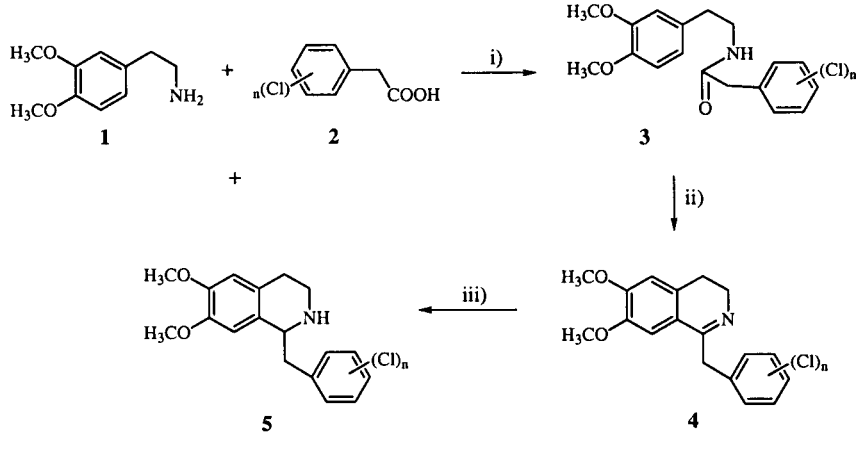
The synthesis of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-methoxyphenylacetamides from 2-(3,4-dimethoxyphenyl)ethylamine and phenylacetic acid (or phenylacetyl halide) has been reported [2]. Because of the convenience, we used halophenylacetic acid as the starting material for the preparation of **3**.

Reaction of **1** with halophenylacetic acid **2** in the presence of potassium carbonate gave the corresponding amides **3** in good yield. The structures of compounds **3** were established by ir, $^1$H nmr and elemental analyses.

The Bischler-Napieralski cyclization [2] of **3** with phosphorus oxychloride gave the corresponding 3,4-dihydroisoquinoline derivatives **4** in good yield. The infrared spectra of **4** did not show absorption bands of the carbonyl and NH groups. The $^1$H nmr spectra of **4** revealed proton signals of two $OCH_3$ (δ 3.75-3.90 ppm as singlets), two $CH_2$ of C-3 and C-4 positions (δ 3.36-3.78 ppm as triplets for C-3, δ 2.51-2.71 ppm as triplet for C-4) and one benzylic $CH_2$ at C-α position (δ 4.00-4.34 ppm as singlet) involving aromatic protons.

Reduction of **4** with sodium borohydride in methanol also afforded the corresponding 1,2,3,4-tetrahydroisoquinolines **5** in good yield, respectively. The infrared spectra of compounds **5** showed the absorption bands of NH in the 3322-3363 cm$^{-1}$ range. The $^1$H nmr spectra of **5** also showed proton signals of two $OCH_3$ at C-6 and C-7 (δ 3.77-3.87 ppm as a singlet), one NH of N-2 position (δ 1.67-2.12 ppm as a broad singlet), one CH of C-1 position (δ 3.97-4.67 ppm as a multiplet) and two $CH_2$ (δ 2.56-2.83 ppm as multiplets for $CH_2$ of α-position; δ 3.00-3.62

Scheme I



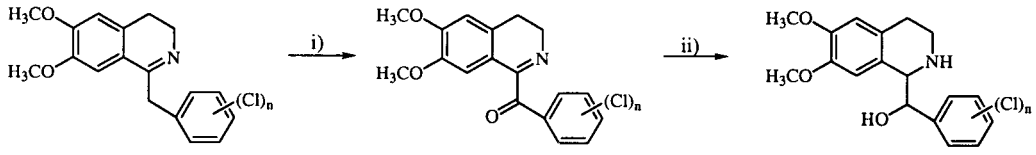

i) $K_2CO_3$, acetonitrile, reflux. ii) $POCl_3$, toluene, reflux. iii) $NaBH_4$, methanol.

| 2-5 | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| $(Cl)_n$ | 2-Cl | 3-Cl | 4-Cl | 3,4-$Cl_2$ | 2,4-$Cl_2$ | 2,6-$Cl_2$ |

ppm as a multiplet for the $CH_2$ of C-4). Whereas, the proton signals for the methylene group at the C-3 position were detected two multiplets in the δ 2.71-3.03 ppm range for axial proton and in the δ 2.80-3.30 ppm range for equatorial proton [3]. The proton signals of the α-methylene show as multiplet because it may be the diasteromeric protons.

**4c** were stirred in acetone or ethyl acetate for 3 days at room temperature to give the corresponding 1-benzoyl derivatives **6** in 64-75% yield. The infrared spectra of **6** showed the absorption band of the carbonyl group in the 1680-1704 $cm^{-1}$ range. The $^{13}C$ nmr spectra of **6** also showed carbon signals for the carbonyl group at the α-position in the δ 192.2-195.0 ppm range. Reduction of

Scheme II




**4** **6** **7**

i) Acetone or diethyl ether ii) $NaBH_4$, methanol.

| 6,7 | a | b | c |
|---|---|---|---|
| $(Cl)_n$ | 2-Cl | 3-Cl | 4-Cl |

On the other hand, we attempted the synthesis of 1-(α-hydroxybenzyl) derivatives **7** from the corresponding **4**. According to Kametani *et al.* [4], Weisbach *et al.* [5] and Martin *et al.* [6], the air oxidation of the α-methylene occurs readily in a suitable organic solvents such as methanol, ethanol or benzene. Therefore, compounds **4a**-**6** with sodium borohydride in methanol afforded the corresponding α-hydroxy derivatives **7** in good yield. The structures of **7** were established by ir, nmr and elemental analyses.

Further research including the pharmacological action are under way in our laboratory.

Table 1

Yields, Melting Points and Infrared Spectral Data for **3** and **4**

| Compound No. | Yield (%) | mp [a] | IR (potassium bromide) ($cm^{-1}$) |
|---|---|---|---|
| **3a** | 90 | 113-114 (D) | 3322, 3064, 2984, 2940, 2912, 2826, 1640, 1544, 1518, 1466, 1422, 1246, 1232, 1140, 1020, 800, 762 |
| **3b** | 86 | 88-89 (D) | 3340, 3102, 3024, 2960, 2852, 1660, 1560, 1532, 1464, 1456, 1430, 1344, 1278, 1248, 1150, 1036, 818, 778, 756 |
| **3c** | 84 | 124-125 (D) | 3320, 3100, 3032, 2964, 2944, 2856, 1656, 1560, 1530, 1476, 1434, 1270, 1248, 1156, 1100, 1040, 864, 820 |
| **3d** | 87 | 125-126 (DH) | 3310, 3100, 3045, 2970, 2862, 1654, 1566, 1530, 1482, 1435, 1386, 1350, 1276, 1250, 1212, 1156, 1040, 972, 894, 872, 818 |
| **3e** | 90 | 137-138 (DH) | 3092, 3032, 2956, 2844, 1636, 1584, 1522, 1480, 1454, 1360, 1256, 1212, 1184, 1108, 1052, 1020, 866, 820, 730 |
| **3f** | 82 | 155-156 (DH) | 3090, 3020, 2960, 2910, 2850, 1664, 1620, 1522, 1466, 1446, 1364, 1328, 1266, 1240, 1222, 1004, 1120, 1022, 940, 886, 784, 770 |
| **4a** | 91 | 73-74 (H) | 3090, 3046, 2954, 2858, 1608, 1576, 1528, 1488, 1478, 1356, 1314, 1260, 1252, 1220, 1172, 1064, 1040, 866, 834, 726 |
| **4b** | 83 | 67-68 (H) | 3106, 3044, 2948, 2860, 1618, 1543, 1486, 1426, 1368, 1272, 1210, 1160, 1056, 886, 853, 770 |
| **4c** | 86 | 104-105 (H) | 3040, 2986, 2846, 1612, 1578, 1510, 1374, 1330, 1300, 1244, 1220, 1164, 1098, 1060, 870, 862, 836, 640 |
| **4d** | 82 | 86-87 (DH) | 3060, 2952, 2854, 1616, 1582, 1544, 1470, 1378, 1306, 1280, 1246, 1164, 1066, 1048, 864, 820, 774 |
| **4e** | 90 | 131-132 (DH) | 3066, 2954, 2838, 1602, 1570, 1518, 1482, 1360, 1284, 1270, 1238, 1208, 1150, 1048, 860, 808 |
| **4f** | 89 | 93-94 (DH) | 3100, 3038, 2950, 2882, 2852, 1620, 1584, 1530, 1458, 1290, 1254, 1228, 1180, 1074, 982, 788 |

[a] Recrystallization solvent; D = Diethyl ether, DH = Diethyl ether/*n*-Hexane (1:1, v/v), H = *n*-Hexane.

Table 2

Yields, Melting Points and Infrared Spectral Data for **5**, **6** and **7**

| Compound No. | Yield (%) | mp [a] | IR (potassium bromide) ($cm^{-1}$) |
|---|---|---|---|
| **5a** | 85 | 62-63 (DH) | 3345, 3056, 2996, 2956, 2888, 1612, 1512, 1466, 1449, 1258, 1220, 1114, 853, 748 |
| **5b** | 87 | Liquid | 3336, 3012, 2922, 1594, 1512, 1457, 1262, 1220, 1104, 1024, 838, 766 |
| **5c** | 92 | Liquid | 3322, 3012, 2924, 2854, 1603, 1516, 1498, 1266, 1221, 1114, 1004, 845, 793 |
| **5d** | 90 | Liquid | 3363, 3026, 2963, 2864, 1622, 1527, 1482, 1272, 1239, 1129, 864, 794 |
| **5e** | 78 | 79-80 (DH) | 3350, 2952, 2847, 1619, 1520, 1478, 1365, 1263, 1277, 1222, 1112, 1020, 860, 782 |
| **5f** | 82 | 116-118 (DH) | 3348, 3082, 3021, 2950, 2912, 2837, 1619, 1520, 1440, 1362, 1263, 1225,1112, 1027, 857, 784 |
| **6a** | 67 | 98-99 (DH) | 3092, 3036, 2974, 2860, 1704, 1614, 1574, 1523, 1448, 1290, 1160, 1086, 1050, 920, 894, 818, 780 |
| **6b** | 64 | 119-120 (DH) | 3088, 3026, 2966, 2850, 1683, 1621, 1580, 1530, 1464, 1380, 1340, 1280, 1208, 1158, 1080, 864, 812, 770, 730, 700 |
| **6c** | 75 | 130-131 (DH) | 3040, 1680, 1620, 1580, 1532, 1462, 1380, 1340, 1286, 1216, 1158, 1100, 918, 816, 780 |
| **7a** | 86 | 147-148 (D) | 3491, 3230, 3060, 3006, 2843, 1634, 1526, 1457, 1262, 1238, 1120,1062, 856, 778 |
| **7b** | 84 | 92-93 (D) | 3268, 3006, 2910, 2838, 1610, 1526, 1476, 1258, 1144, 1112, 1010, 944, 752 |
| **7c** | 90 | 143-145 (D) | 3320, 3096, 2924, 2826, 1622, 1530, 1478, 1340, 1270, 1240, 1132,1130, 1070, 857, 784 |

[a] Recrystallization solvent; D = Diethyl ether, DH = Diethyl ether/*n*-Hexane (1:1, v/v).

Table 3

$^1$H NMR Spectral Data for **3** and **4**

| Compound No. | Solvent [a] | $^1$H NMR (δ, ppm) [b] N-H (bs) | 3' (or 6)-OMe (s) | 4' (or 7)-OMe (s) | 1 (or 3)-$CH_2$ (t) | 2 (or 4)-$CH_2$ (t) | α-$CH_2$ (s) | Ar-H (m) |
|---|---|---|---|---|---|---|---|---|
| **3a** | C | 5.51 | 3.80 | 3.82 | 3.31-3.61 | 2.66-2.68 | 3.61 | 6.60-7.25 |
| **3b** | D | 5.54 | 3.82 | 3.85 | 3.43-3.49 | 2.67-2.72 | 3.47 | 6.54-7.28 |
| **3c** | C | 5.55 | 3.83 | 3.87 | 3.42-3.46 | 2.67-2.71 | 3.48 | 6.51-7.29 |
| **3d** | D | 8.13 | 3.71 | 3.71 | 3.24-3.26 | 2.63-2.66 | 3.42 | 6.63-7.55 |
| **3e** | C | 5.50 | 3.71 | 3.73 | 3.65-2.69 | 3.69-2.80 | 4.54 | 6.77-7.36 |
| **3f** | C | 5.49 | 3.71 | 3.73 | 3.63-3.69 | 2.66-2.79 | 4.54 | 7.79-7.47 |
| **4a** | C | — | 3.79 | 3.88 | 3.70-3.75 | 2.65-2.70 | 4.18 | 6.66-7.39 |
| **4b** | C | — | 3.77 | 3.89 | 3.72-3.75 | 2.64-2.69 | 4.03 | 6.68-7.31 |
| **4c** | C | — | 3.75 | 3.87 | 3.69-3.72 | 2.62-2.67 | 4.00 | 6.66-7.23 |
| **4d** | C | — | 3.80 | 3.90 | 3.71-3.78 | 2.64-2.71 | 4.00 | 6.89-7.41 |
| **4e** | D | — | 3.76 | 3.79 | 3.43-3.48 | 2.52-2.57 | 4.14 | 6.89-7.57 |
| **4f** | D | — | 3.82 | 3.84 | 3.36-3.38 | 2.51-2.55 | 4.34 | 6.90-7.45 |

[a] D = Dimethyl-$d_6$ sulfoxide. C = Deuteriochloroform. [b] Abbreviations used: bs = broad singlet, s = singlet, t = triplet, m = multiplet and Ar = Aromatic. J = Hz unit. The proton signals of NH were exchangeable with deuterium oxide.

Table 4

$^1$H NMR Spectral Data of **5**

| Compound No. | Solvent [a] | $^1$H NMR (ppm) [b] 1-CH (m) | 2-NH (bs) | 3-$CH_2$ | 4-$CH_2$ (m) | 6-MeO (s) [c] | 7-MeO (s) [c] | α-$CH_2$ (m) | Ar-H |
|---|---|---|---|---|---|---|---|---|---|
| **5a** | D | 4.06-4.28 | 1.76 | 2.94-3.03 (m, $1H_a$) 3.22-3.30 (m, $1H_e$) | 3.38-3.62 | 3.87 | 3.82 | 2.74-2.78 | 6.60 (s, 1H) 6.68 (s, 1H) 7.17-7.29 (m, 3H) 7.38-7.44 (m, 1H) |
| **5b** | D | 4.09-4.15 | 1.98 | 2.83-2.88 (m, $1H_a$) 2.91-2.95 (m, $1H_e$) | 3.13-3.21 | 3.85 | 3.81 | 2.69-2.75 | 6.59 (s, 2H) 7.12-7.27 (m, 4H) |
| **5c** | D | 4.09-4.13 | 1.76 | 2.83-2.88 (m, $1H_a$) 2.91-2.93 (m, $1H_e$) | 3.13-3.20 | 3.83 | 3.81 | 2.67-2.74 | 6.59 (s, 1H) 6.60 (s, 1H) 7.15-7.28 (m, 4H) |
| **5d** | D | 3.97-4.00 | 2.12 | 2.71-2.79 (m, $1H_a$) 2.80-2.83 (m, $1H_e$) | 3.00-3.14 | 3.80 | 3.77 | 2.56-2.62 | 6.61 (s, 1H) 6.84 (s, 1H) 7.29-7.30 (m, 1H) 7.52-7.62 (m, 2H) |
| **5e** | D | 4.19-4.67 | 1.67 | 2.91-2.96 (m, $1H_a$) 2.98-3.02 (m, $1H_e$) | 3.20-3.44 | 3.87 | 3.83 | 2.72-2.76 | 6.60 (s, 1H) 6.66 (s, 1H) 7.21-7.42 (m, 3H) |
| **5f** | D | 4.13-4.18 | 1.71 | 2.84-2.88 (m, $1H_a$) 3.13-3.24 (m, $1H_e$) | 3.22-3.24 | 3.87 | 3.79 | 2.67-2.83 | 6.45 (s, 1H) 6.64 (s, 1H) 7.25-7.31 (m, 1H) 7.44-7.47 (m, 1H) |

[a] D = Dimethyl-$d_6$ sulfoxide. C = Deuteriochloroform. [b] Abbreviations used: bs = broad singlet, s = singlet, m = multiplet and Ar. = Aromatic, $H_a$ = axial hydrogen, $H_e$ = equatorial hydrogen. J = Hz unit. The proton signals of NH were exchangeable with deuterium oxide. [c] Assignment may be interchanged.

Table 5

$^1$H NMR Spectral Data of **6** and **7**

| Compound No. | Solvent [a] | 1H NMR (ppm) [b] 1-CH (d) (J) | 2-NH (bs) | 3-$CH_2$ | 4-$CH_2$ | 6-MeO (s) [c] | 7-MeO (s) [c] | α-$CH_2$ (d) (J) | Ar-H |
|---|---|---|---|---|---|---|---|---|---|
| **6a** | C | — | — | 3.82-3.87 (m) | 2.71-2.77 (t) | 3.93 | 3.88 | — | 6.74 (s, 1H) 7.27 (s, 1H) 7.35-7.45 (m, 3H) 7.68-7.71 (m, 1H) |
| **6b** | C | — | — | 3.92-3.97 (m) | 2.80-2.85 (t) | 3.96 | 3.81 | — | 6.77 (s, 1H) 6.97 (s, 1H) 7.40-8.03 (m, 4H) |
| **6c** | C | — | — | 3.91-3.94 (m) | 2.80-2.85 (t) | 3.95 | 3.81 | — | 6.77 (s, 1H) 6.96 (s, 1H) 7.45-7.48 (d, 2H, |

Table 5 (continued)

| Compound No. | Solvent [a] | $^1$H NMR (ppm) [b] 1-CH (d) (J) | 2-NH (bs) | 3-$CH_2$ | 4-$CH_2$ | 6-MeO (s) [c] | 7-MeO (s) [c] | α-$CH_2$ (d) (J) | Ar-H |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | J = 8.4), 7.98-8.01(d, 2H, J = 8.4) |
| **7a** | C | 4.59-4.60 (3.7) | 2.12 | 2.59-2.65 (m, 1$H_a$) 3.30-3.39 (m, 1$H_e$) | 2.82-3.00 (m) | 3.84 | 3.41 | 5.19-5.20 (3.9) | 5.85 (s, 1H) 6.59 (s, 1H) 7.22-7.42 (m, 4H) (OH not detect) |
| **7b** | C | 4.31-4.33 (4.4) | 1.78 | 2.55-2.59 (m) | 2.86-2.92 (m) | 3.86 | 3.70 | 4.97-4.98 (4.6) | 6.46 (s, 1H) 6.56 (s, 1H) 7.06-7.32 (m, 4H) (OH not detect) |
| **7c** | C | 4.25-4.26 (4.2) | 3.06 | 2.47-2.53 (m) | 2.79-2.80 (m) | 3.83 | 3.70 | 4.96-4.98 (5.0) | 4.82 (bs, OH), 6.47 (s, 1H), 6.52 (s, 1H), 7.10-7.22 (m, 4H) |

[a] D = Dimethyl-$d_6$ sulfoxide. C = Deuteriochloroform. [b] Abbreviations used: bs = broad singlet, d = doublet, s = singlet, m = multiplet and Ar. = Aromatic, $H_a$ = axial hydrogen, $H_e$ = equatorial hydrogen. J = Hz unit. The proton signals of OH and NH were exchangeable with deuterium oxide. [c] Assignment may be interchanged.

Table 6

Elemental Analytical Data of **3-5**

| Compound No. | Molecular Formula | Elemental Analyses (%) (Calcd/Found) C | H | N |
|---|---|---|---|---|
| **3a** | $C_{18}H_{20}NO_3Cl$ | 64.77 | 6.04 | 4.20 |
| | | 64.89 | 6.15 | 4.31 |
| **3b** | $C_{18}H_{20}NO_3Cl$ | 64.77 | 6.04 | 4.20 |
| | | 64.90 | 6.14 | 4.25 |
| **3c** | $C_{18}H_{20}NO_3Cl$ | 64.77 | 6.04 | 4.20 |
| | | 64.92 | 6.23 | 4.32 |
| **3d** | $C_{18}H_{19}NO_3Cl_2$ | 58.71 | 5.20 | 3.80 |
| | | 58.90 | 5.32 | 3.90 |
| **3e** | $C_{18}H_{19}NO_3Cl_2$ | 58.71 | 5.20 | 3.80 |
| | | 58.97 | 5.40 | 3.98 |
| **3f** | $C_{18}H_{19}NO_3Cl_2$ | 58.71 | 5.20 | 3.80 |
| | | 58.98 | 5.34 | 3.95 |
| **4a** | $C_{18}H_{18}NO_2Cl$ | 68.46 | 5.75 | 4.44 |
| | | 68.50 | 5.87 | 4.62 |
| **4b** | $C_{18}H_{18}NO_2Cl$ | 68.46 | 5.75 | 4.44 |
| | | 68.65 | 5.89 | 4.57 |
| **4c** | $C_{18}H_{18}NO_2Cl$ | 68.46 | 5.75 | 4.44 |
| | | 68.76 | 5.88 | 4.80 |
| **4d** | $C_{18}H_{17}NO_2Cl_2$ | 61.73 | 4.89 | 4.00 |
| | | 61.99 | 4.98 | 4.13 |
| **4e** | $C_{18}H_{17}NO_2Cl_2$ | 61.73 | 4.89 | 4.00 |
| | | 61.91 | 5.01 | 4.18 |
| **4f** | $C_{18}H_{17}NO_2Cl_2$ | 61.73 | 4.89 | 4.00 |
| | | 61.93 | 5.07 | 4.22 |

Table 6 (continued)

| Compound No. | Molecular Formula | Elemental Analyses (%) (Calcd/Found) C | H | N |
|---|---|---|---|---|
| **5a** | $C_{18}H_{20}NO_2Cl$ | 68.03 | 6.34 | 4.41 |
| | | 68.23 | 6.50 | 4.60 |
| **5b** | $C_{18}H_{20}NO_2Cl$ | 68.03 | 6.34 | 4.41 |
| | | 68.25 | 6.45 | 4.62 |
| **5c** | $C_{18}H_{20}NO_2Cl$ | 68.03 | 6.34 | 4.41 |
| | | 68.30 | 6.52 | 4.58 |
| **5d** | $C_{18}H_{19}NO_2Cl_2$ | 61.37 | 5.44 | 3.98 |
| | | 61.43 | 5.60 | 4.00 |
| **5e** | $C_{18}H_{19}NO_2Cl_2$ | 61.37 | 5.44 | 3.98 |
| | | 61.51 | 5.59 | 4.10 |
| **5f** | $C_{18}H_{19}NO_2Cl_2$ | 61.37 | 5.44 | 3.98 |
| | | 61.53 | 5.66 | 4.08 |

Table 7

Elemental Analytical Data of **6** and **7**

| Compound No. | Molecular Formula | Elemental Analyses (%) (Calcd/Found) C | H | N |
|---|---|---|---|---|
| **6a** | $C_{18}H_{16}NO_3Cl$ | 65.56 | 4.89 | 4.25 |
| | | 64.76 | 4.98 | 4.29 |
| **6b** | $C_{18}H_{16}NO_3Cl$ | 65.56 | 4.89 | 4.25 |
| | | 64.82 | 4.97 | 4.31 |
| **6c** | $C_{18}H_{16}NO_3Cl$ | 65.56 | 4.89 | 4.25 |

Table 7 (continued)

| Compound No. | Molecular Formula | Elemental Analyses (%) (Calcd/Found) | | |
|---|---|---|---|---|
| | | C | H | N |
| | | 64.87 | 4.99 | 4.33 |
| **7a** | $C_{18}H_{20}NO_3Cl$ | 64.77 | 6.04 | 4.20 |
| | | 64.98 | 6.14 | 4.27 |
| **7b** | $C_{18}H_{20}NO_3Cl$ | 64.77 | 6.04 | 4.20 |
| | | 64.97 | 6.21 | 4.30 |
| **7c** | $C_{18}H_{20}NO_3Cl$ | 64.77 | 6.04 | 4.20 |
| | | 64.90 | 6.26 | 4.35 |

## EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 or a Bruker FTNMR-DRX 500 spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. Open-bed chromatography was carried out on silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-halophenylacetamides **3**.

A mixture of **1** (39 mmoles), phenol derivatives **2** (40 mmoles), potassium carbonate (41 mmoles) and acetonitrile (80 ml) was refluxed for 6 hours. After cooling to room temperature, the mixture was filtered and washed with acetonitrile (10 ml x 2). The combined filtrate was evaporated under reduced pressure. The residue was triturated in water/diethyl ether (1:1, v/v; 100 ml) with stirring. The resulting crystals were filtered and washed with diethyl ether (10 ml x 2). The crude product was recrystallized to give compounds **3**.

6,7-Dimethoxy-1-halobenzyl-3,4-dihydroisoquinolines **4**.

A solution of **3** (20 mmoles), phosphorus oxychloride (22 moles) and dry toluene (80 ml) was refluxed for 4 hours. The mixture was evaporated under reduced pressure. Ammonia water (28%) was added to the residue. After stirring for 10 minutes, the mixture was filtered and washed with *n*-hexane (10 ml x 2). The resulting residue was applied to the top of an open-bed silica gel column (3 x 10 cm). The column was eluted with methylene chloride/ethyl acetate (10:3, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The crude product was recrystallized to afford compounds **4**.

6,7-Dimethoxy-1-halobenzyl-1,2,3,4-tetrahydroisoquinolines **5**.

A mixture of **4** (11 mmoles), sodium borohydride (12 mmoles) and methanol (50 ml) was stirred for 8 hours at room temperature. After evaporating the solvent, water (50 ml) and methylenechloride (50 ml) were added to the residue with stirring. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resulting residue was recrystallized to give **5**.

6,7-Dimethoxy-1-benzoyl-3,4-dihydroisoquinolines **6**.

Compounds **4a-4c** (20 mmoles) was dissolved in acetone (50 ml) or diethyl ether (50 ml). The solution was stirred for 3 days at room temperature. After evaporating the solvent under reduced pressure, the residue was applied to the top of an open-bed silica gel column (3 x 10 cm). The column was eluted with chloroform/ethyl acetate (10 : 3, v/v). Fractions involving the product were combined and evaporated under reduced pressure. The resulting residue was recrystallized from a suitable solvent to give the corresponding ketones **6**; $^{13}C$ nmr (deuteriochloroform): **6a,** δ 25.0, 47.9, 55.9, 56.0, 110.0, 110.2, 118.8, 126.9, 130.0, 130.8, 130.9, 131.5, 132.5, 138.0, 147.4, 151.5, 163.9, 195.0 ppm; **6b,** δ 25.2, 47.3, 55.9, 56.0, 109.5, 110.4, 119.0, 128.5, 129.7, 130.2, 131.1, 133.5, 134.6, 137.2, 147.6, 151.8, 163.6, 192.2 ppm; **6c,** δ 25.3, 47.3, 56.0, 56.1, 110.0, 110.5, 119.1, 128.7, 128.8, 134.0, 131.2, 131.8, 131.9, 140.3, 147.7, 151.8, 163.9, 192.5 ppm.

6,7-Dimethoxy-1-(α-hydroxyhalobenzyl)-1,2,3,4-tetrahydroisoquinolines **7**.

A mixture of **6** (11 mmoles), sodium borohydride (12 mmoles) and methanol (50 ml) was stirred for 8 hours at room temperature. After evaporating the solvent, water (50 ml) and methylenechloride (50 ml) were added to the residue with stirring. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resulting residue was recrystallized to give **7**.

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