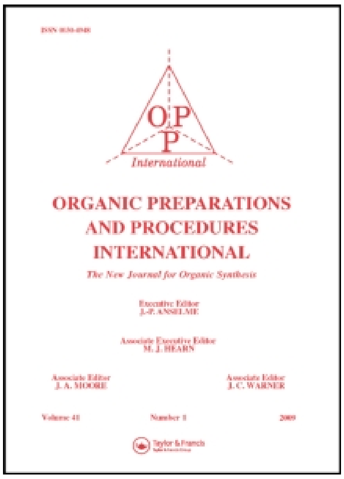

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A SIMPLE SYNTHESIS OF 1-HYDROXYALKYL-1,2,3,4-TETRAHYDROISOQUINOLINES

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A SIMPLE SYNTHESIS OF 1-HYDROXYALKYL-1,2,3,4-TETRAHYDROISOQUINOLINES[†]

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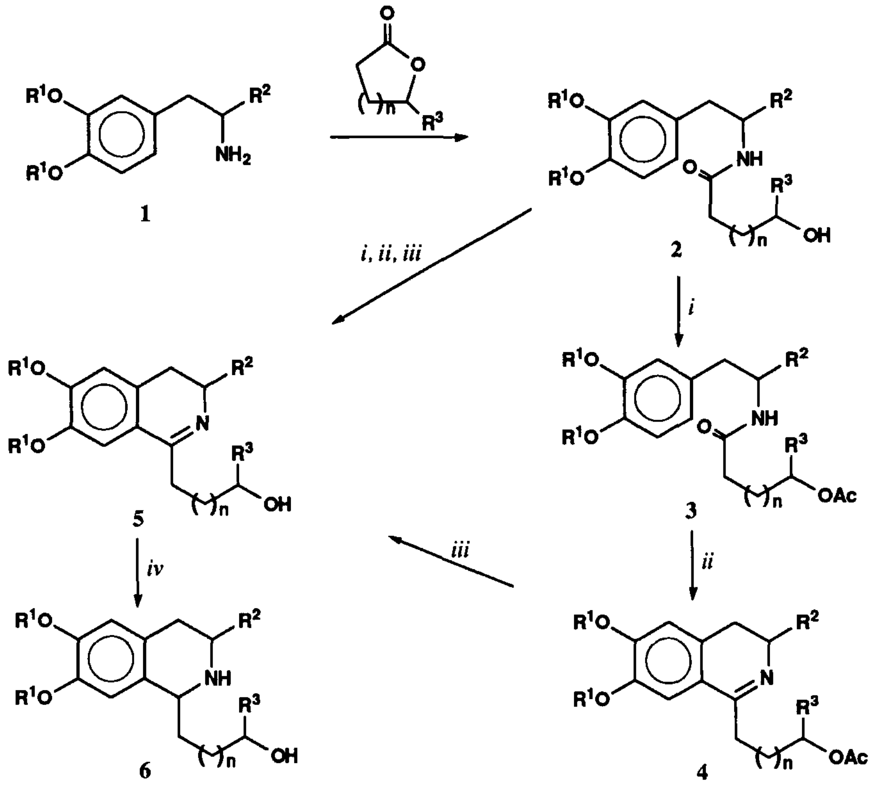
As difunctional aminoalcohol derivatives, 1-(ω-hydroxyalkyl)-1,2,3,4-tetrahydroisoquinolines provide the possibility of obtaining numerous isoquinoline derivatives of both chemical and pharmacological interest.[1-5] Although a number of procedures are available for the synthesis of calycotomine[6-8] and homocalycotomine,[2,3,9] there are only a few tedious methods for the preparation of higher homologs (**6a,e,f**).[5,10] This paper describes a convenient synthesis of compounds **6**.

Hydroxy amides **2** were obtained by the reaction of β-(3,4-dialkoxyphenyl)ethylamines **1** with different lactones.[11-14] Bischler-Napieralski cyclization of compounds **2a,d,e** was investigated previously; double ring-closure resulted in the formation of saturated benzo[*g*]indolizines or benzo[*a*]quinolizines.[11-14] After protection of the hydroxy group by *O*-acetylation, Bischler-Napieralski cyclization furnished 1-(acetoxyalkyl)-3,4-dihydroisoquinolines **4**. After ring-closure, the acetyl group can be readily removed by acid hydrolysis. This three-step process (acetylation, ring-closure and hydrolysis) can be carried out in a one-pot way. The intermediates were isolated only in the cases of **3a** and **4a**.

Sodium borohydride reduction of 1-(hydroxyalkyl)-3,4-dihydroisoquinolines **5** yielded the tetrahydro derivatives **6**. In the reduction of **5c** and **5d**, two diastereomeric products are possible. ^{1}H NMR measurements revealed that reduction of **5c** gave, after crystallization from diisopropyl ether, the (1*R**, 3*S**)[16] diastereomer of **6c**. The couplings of *H*-3 indicated that it is in the *axial* position. NOE measurements showed a clear effect between *H*-1 and *H*-3, as an indication of their 1,3-*diaxial* position. In the reduction of **5d**, a 3:2 mixture of the (1*R**, 3'*S**) and (1*R**, 3'*R**) diastereomers was formed. Assignments of the proton signals for the two **6d** diastereomers was based on 2D homonuclear COSY measurement, and the carbon spectrum was analysed by using heteronuclear COSY.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra were recorded in KBr pellets on a Spektromom 2000 spectrophotometer. ^{1}H NMR spectra were obtained on a JEOL



a) $R^1 = CH_3$, $R^2 = H$, $R^3 = H$, $n = 1$

b) $R^1 = CH_2CH_3$, $R^2 = H$, $R^3 = H$, $n = 1$

c) $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$, $n = 1$

d) $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$, $n = 1$

e) $R^1 = CH_3$, $R^2 = H$, $R^3 = H$, $n = 2$

f) $R^1 = CH_3$, $R^2 = H$, $R^3 = H$, $n = 3$

i) $AcCl/C_6H_6$; *ii*) $POCl_3/CHCl_3$; *iii*) HCl/H_2O; *iv*) $NaBH_4/MeOH$

GX 400 FT-NMR spectrometer in $CDCl_3$, with TMS as internal standard. For NMR measurements, the free bases were liberated from the HCl salts. Compounds **1c**[15], **2a**[13], **2d**[14] and **2e**[13] were prepared according to known methods. The physical and analytical data on the new compounds prepared are listed in Table 2.

General Procedure for Synthesis of Hydroxy Amides (2b,c,f).- A mixture of β-(3,4-dialkoxyphenyl)ethylamine **1** (0.10 mol) and the corresponding lactone (0.11 mol) was kept at 140-150° for 4-5 hrs. The oily product crystallized out on treatment with diisopropyl ether and EtOAc.

2b, IR: 1250, 1620, 3290 cm^{-1}; **2c**, IR: 1250, 1500, 1630, 3290 cm^{-1}; **2f**, IR: 1250, 1510, 1630, 3260 cm^{-1}.

General Procedure for the Synthesis of 6,7-Dialkoxy-1-(hydroxyalkyl)-3,4-dihydroisoquinolines (5a-f).- Acetyl chloride (0.30 mol, 21.3 mL) was added to hydroxy amide **2** (0.05 mol) dissolved in abs. benzene (150 mL). The mixture was refluxed for 2.5 hrs, and then evaporated. Evaporation was repeated twice after the addition of benzene (50 mL), and $POCl_3$ (10 mL) was added to the oily residue dissolved in $CHCl_3$ (80 mL). The solution was refluxed for 3 hrs, and then evaporated. The residue was dissolved in 15% HCl solution (80 mL) and refluxed for 3-5 hrs (monitored by TLC). After cooling, the solution was made alkaline (10 % NaOH) and extracted with $CHCl_3$ (4x50 mL). The combined extracts were dried with Na_2SO_4 and then evaporated. The oily product crystallized out on treatment with either diethyl ether or ethanolic HCl.

5a•HCl, yield 8.2 g (55%), mp. 164-166° (ethanol-ether), lit.[5] mp. 140-142°. IR: 1280, 1340, 1550, 1630, 3380 cm^{-1}; ^{1}H NMR: δ 1.99 (m, 2H, β-CH_2), 2.63 (t, 2H, 4-CH_2), 2.95 (tt, 2H, *J* = 7.6 Hz, 3-CH_2), 3.63 (tt, 2H, *J* = 1.5, 7.5 Hz, O-CH_2) 3.72 (t, 2H, *J* = 5.5 Hz, γ-CH_2), 3.91 and 3.92 (2s, 2x3H, 6-OCH_3 and 7-OCH_3), 6.70 (s, 1H, 5-CH), 7.04 (s, 1H, 8-CH).

5b, IR: 1260, 1330, 1550, 1640, 2690, 3370 cm^{-1}; ^{1}H NMR: δ 1.45, 1.48 (tt, 2x3H, *J* = 7.0 Hz, 6,7-CH_3), 1.97 (m, 2H, β-CH_2), 2.61 (t, 2H, *J* = 7.6 Hz, 4-CH_2), 2.91 (tt, 2H, *J* = 1.4, 6.4 Hz, O-CH_2), 3.62 (tt, 2H, *J* = 8.8, 1.4 Hz, 3-CH_2), 3.71 (m, 2H, γ-CH_2), 4.09, 4.13 (d q, 2x2H, *J* = 7.0 Hz, 6,7-OCH_2), 6.68 (s, 1H, 5-CH), 7.06 (s 1H, 8-CH).

5c, IR: 1260, 1340, 1500, 2840, 3280 cm^{-1}; ^{1}H NMR: δ 2.00 (m, 2H, β-CH_2), 2.43 (dd, 1H, *J* = 13.4, 0.7 Hz, 4-CH', 2.67 (dd, 1H, *J* = 15.7, 5.4 Hz, 4-CH"), 2.95 (m, 2H, O-CH_2), 3.56 (m, 1H, 3-CH), 3.71 (m, 2H, γ-CH_2), 3.90, 3.92 (2 s, 2x3H, 6,7-OCH_3), 6.68 (s, 1H, 5-CH), 7.03 (s, 1H, 8-CH).

5d, IR: 1260, 1270, 1490, 2670, 3280 cm^{-1}; ^{1}H NMR: δ 1.22 (*d*, 3H, δ-CH_3), 1.89 (m, 2H, *J* = 4.7, 6.2 Hz, β-CH_2), 2.63 (t, 2H, 4-CH_2), 2.87 (m, 1H, *J* = 6.4 Hz, O-CH'), 2.97 (m, 1H, *J* = 16.6 Hz, O-CH"), 3.60 (m, 1H, *J* = 7.5, 1.6 Hz, 3-CH') 3.64 (m, 1H, *J* = 15.1 Hz, 3-Hz, 3-CH"), 3.87 (m, 1H, *J* = 6.2 Hz, γ-CH), 3.91, 3.92 (2 s, 2x3H, 6,7-OCH_3), 6.70 (s, 1H, 5-CH), 7.04 (s, 1H, 8-CH).

5e, IR: 1250, 1320, 1540, 1620, 3280 cm^{-1}; ^{1}H NMR: δ 1.66 (m, 2H, *J* = 6.1, 7.0 Hz, γ-CH_2), 1.81 (q, 2H, *J* = 7.0 H, β-CH_2), 2.61 (t, 2H, *J* = 7.5 Hz, 4-CH_2), 2.75 (t, 2H, *J* = 7.0 Hz, O-CH_2), 3.60 (t, 2H, *J* = 7.5 Hz, 3-CH_2), 3.64 (t, 2H, *J* = 6.1 Hz, δ-CH_2), 3.91, 3.92 (2s, 2x3H, 6,7-OCH_3), 6.70 (s, 1H, 5-CH), 7.02 (s, 1H, 8-CH).

5f, IR: 1260, 1500, 2910, 3220 cm^{-1}; ^{1}H NMR: δ 1.45-1.54 (m, 2H, γ-CH_2), 1.53-1.66 (m, 2H, β-CH_2), 1.68-1.76 (m, 2H, δ-CH_2), 2.61 (t, 2H, 4-CH_2), 2.72 (tt, 2H, *J* = 7.3 Hz, 3-CH_2), 3.62 (tt, 2H, *J* = 7.5, 1.4 Hz, O-CH_2), 3.67 (t, 2H, *J* = 6.2 Hz, ε-CH_2), 3.91 (s, 3H, 6-OCH_3), 3.92 (s, 3H, 7-OCH_3), 6.70 (s, 1H, 5-CH), 7.00 (s, 1H, 8-CH).

1-(γ-Hydroxypropyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Hydrochloride (5a).- To a solution of **2a** (1.34 g, 5 mmol) in benzene (10 mL), acetyl chloride (2 mL) was added. The solution was evaporated after refluxing for 2 hrs, and the compound **3a** crystallized out on treatment with diethyl ether. Yield: 1.1 g (75%), mp. 82-83° (diisopropyl ether-EtOAc), lit[5] mp. 74-76°.

To a solution of **3a** (0.8 g, 2.6 mmol) in $CHCl_3$ (10 mL) $POCl_3$ (0.5 mL) was added. The mixture was refluxed for 2.5 hrs, and then evaporated. The residue was dissolved in cold water (25 mL) and the solution was made alkaline with ice-cold Na_2CO_3 solution and extracted with EtOAc (4x25 mL). The combined extracts were dried (Na_2SO_4), and then evaporated. The oily product (**4a**) crystallized out on treatment with hexane. Yield: 0.5 g (66 %), mp. 80-81° (*n*-hexane), formula (mw): $C_{16}H_{21}NO_3$ (291.35), analysis (calcd/found): C 65.96/65.73, H 7.27/7.44, N 4.81/4.69 %.

Compound **4a** (0.38 g, 1.3 mmol) was hydrolyzed into **5a** according to the general procedure written above, by using 10 mL 15 % HCl. Yield (HCl salt): 0.3 g (81 %).

General Procedure for the Synthesis of 6,7-Dialkoxy-1-(hydroxyalkyl)-1,2,3,4-tetrahydroisoquinolines (6). - To a stirred solution of compound **5** (0.05 mol) in methanol (150 mL), sodium borohydride (7.57 g, 0.20 mol) was added in small portions under ice cooling. The mixture was stirred at ambient temperature for 3 hrs, and then evaporated. The residue was dissolved in water (100 mL). The solution was acidified with cc HCl, then made alkaline with 10% NaOH solution under cooling and extracted with $CHCl_3$ (4x50 mL). The combined extracts were dried (Na_2SO_4), and then evaporated. The oily product crystallized out on treatment with either diethyl ether or ethanolic HCl.

6a, yield: 9.4 g (75%), mp. 81-84° (diisopropyl ether-EtOH), HCl mp. 166-169° (EtOH-ether), lit.[5] mp. 158-160°). IR: 1250, 1500, 2910, 3240 cm^{-1}; ^{1}H NMR: δ 1.76 (m, 2H, β-CH$_2$), 1.97 (m, 2H, α-CH$_2$), 2.65 (dt, 1H, 4-CH'), 2.78 (dt, 1H, *J* = 12.7 Hz, 4-CH"), 3.04 (m, 1H, *J* = 5.2, 6.1 Hz, 3-CH'), 3.19 (m, 1H, *J* = 12.8, 7.2, 5.2 Hz, 3-CH"), 3.55 (m, 1H, *J* = 3.0, 7.9 Hz, γ-CH'), 3.65 (m, 1H, *J* = 11.1, 3.3, 6.3 Hz, γ-CH"), 3.93 (dd, 1H, *J* = 3.5, 7.9 Hz, 1-CH), 3.85 (s, 3H, 6-OCH$_3$), 3.88 (s, 3H, 7-OCH$_3$) 6.56 (s, 1H, 5-CH), 6.59 (s, 1H, 8-CH).

6b, IR: 1250, 1510, 2910, 3260 cm^{-1}; ^{1}H NMR: δ 1.43, 1.43 (2x3H, *J* = 6.7, 6.4 Hz, 6,7-OCH$_2$C*H*$_3$), 1.68-1.82 (m, 2H, β-CH$_2$), 1.90-2.00 (m, 2H, α-CH$_2$), 2.64 (broad, 1H, 4-CH'), 2.74 (qt, 1H, *J* = 16.5, 6.8 Hz, 4-CH"), 3.04 (m, 1H, *J* = 5.5, 6.25, 12.8 Hz, 3-CH'), 3.18 (m, 1H, *J* = 5.2, 7.0, 12.8 Hz, 3-CH"), 3.54 (m, 1H, *J* = 2.9, 8.1, 11.0 Hz, γ-CH'), 3.65 (m, 1H, *J* = 3.1, 6.0, 11.1 Hz, γ-CH"), 3.91 (dd, 1H, *J* = 4.6, 7.2 Hz, 1-CH), 4.04, 4.05 (dq, 2x2H, *J* = 6.7, 6.4 Hz, 6,7-OCH$_2$), 6.62 (s, 1H, 5-CH), 6.64 (s, 1H, 8-CH).

6c, IR: 1210, 1510, 2910, 3240 cm^{-1}; ^{1}H NMR: δ 1.63 (m, 2H, β-CH$_2$), 1.95 (m, 1H, α-CH'), 2.10 (m, 1H, α-CH"), 2.56 (m, 1H, *J* = 15.0, 10.2 Hz, 4-CH'), 2.63 (m, 1H, *J* = 4.0 Hz, 4-CH"), 3.05 (m, 1H, *J* = 4.0, 6.1, 10.2 Hz, 3-CH), 3.55 (m, 2H, γ-CH$_2$), 3.84, 3.85 (2s, 2x3H, 6,7-OCH$_3$), 4.19 (d (broad), 1H, *J* = 5.5, <1 Hz, 1-CH), 6.53 (s, 1H, 5-CH), 6.56 (s, 1H, 8-CH).

6d, IR: 1250, 1510, 2910, 3390 cm^{-1}; ^{1}H NMR: δ of the major diastereomer: 1.19 (d, 3H, *J* = 6.3 Hz, δ-CH$_3$), 1.42-1.70 (m, 1H, α-CH'), 1.80-1.90 (m, 2H, β-CH$_2$), 1.96-2.04 (m, 1H, α-CH"), 2.69 (dt, 2H, *J* = 5.5, 6.5 Hz, 4-CH$_2$), 3.06 (dt, 1H, *J* = 13.4 Hz, 3-CH'), 3.17 (dt, 1H, *J* = 13.4 Hz, 3-CH"), 3.72-3.82 (m, 1H, γ-CH), 3.84 (s, 3H, 7-OCH$_3$), 3.85 (s, 3H, 6-OCH$_3$), 4.05 (d, 1H, *J* = 5.5 Hz, 1-CH), 6.55 (s, 1H, 5-CH), 6.58 (s, 1H, 8-CH).

^{1}H NMR: δ of the minor diastereomer: 1.14 (d, 3H, *J* = 6.25 Hz, δ-CH$_3$), 1.42-1.70 (m, 1H, α-CH'), 1.80-1.90 (m, 2H, β-CH$_2$), 2.08-2.17 (m, 1H, α-CH"), 2.63 (dt, 1H, *J* = 16.0, 4.6 Hz, 4-CH'), 2.85 (m, 1H, *J* = 5.0, 8.4 Hz, 4-CH"), 2.95 (m, 1H, *J* = 12.3 Hz, 3-CH'), 3.21 (m, 1H, *J* = 12.3 Hz, 3-CH"), 3.72-3.82 (m, 1H, γ-CH), 3.84 (s, 3H, 7-OCH$_3$), 3.85 (s, 3H, 6-OCH$_3$), 4.05 (d, 1H, J = 5.5 Hz, 1-CH), 6.57 (s, 1H, 5-CH), 6.59 (s, 1H, 8-CH).

6e, IR: 1250, 1510, 2920, 3410 cm-1; ^{1}H NMR: δ 1.50-1.78 (m, 2x2H, O,β-CH$_2$), 1.80-190 (m, 2H, γ-CH$_2$), 2.65 (dt, 1H, *J* = 16.0, 5.5, 5.0 Hz, 4-CH'), 2.74 (dt, 1H, *J* = 5.5, 7.6 Hz, 4-CH"), 2.95 (m, 1H, *J* = 5.0, 7.6, 12.6 Hz, 3-CH'), 3.20 (tt, 1H, *J* = 5.5, 5.5, 12.7 Hz, 3-CH"), 3.66 (m, 2H, δ-CH$_2$),

TABLE 1. ^{13}C NMR Chemical Shifts of Compounds **5a-f** and **6a-f**[a]

Cmpd	C-1	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	6,7-OCH$_3$	C-α	C-β	C-γ	C-δ	C-ε
5a	167.3	46.3	25.8	121.1	108.9	151.2	147.6	110.4	131.5	56.3 56.0	34.3	28.7	62.9	-	-
5b	167.6	46.2	25.8	121.9	111.9	151.9	147.0	111.9	131.7	65.4 64.5[b]	34.1	28.8	62.8	-	-
5c[c]	166.9	51.4	33.2	121.6	108.9	151.4	147.6	110.6	131.3	56.3 56.0	34.4	28.8	62.8	-	-
5d	167.4	46.2	25.7	122.0	108.8	151.1	147.5	110.4	131.4	56.3 56.0	35.0	32.7	67.5	23.8	-
5e	167.0	46.3	25.7	121.8	108.8	150.8	147.4	110.3	131.5	56.2 55.8	34.7	22.3	32.1	61.3	-
5f	166.8	46.7	25.9	122.0	108.9	150.9	147.6	110.5	131.7	56.3 56.0	35.4	25.9	25.4	32.2	62.3
6a	55.2	39.8	28.8	126.8	109.5	147.4	147.5	111.8	130.5	56.0 55.8	35.7	30.7	62.9	-	-
6b	55.5	39.9	28.9	127.1	112.2	147.1	147.5	113.9	130.7	65.0 64.6[e]	35.8	30.8	63.0	-	-
6c[f]	55.8	48.9	37.4	127.8	108.7	147.5	147.5	111.8	128.8		35.1	28.6	62.7	-	-
6d[g]	54.9	38.5	28.6	126.4	109.5	147.3	147.3	111.6	131.1	55.8 55.9	33.1	34.8	67.9	23.9	-
	54.9	41.0	29.0	127.2	109.1	147.3[d]	147.5[d]	111.8	121.8	56.1 55.9	35.2	38.7	67.1	23.5	-
6e	55.3	40.9	29.4	127.1	109.2	147.3	147.3	111.8	131.3	55.8 56.1	35.9	22.2	32.5	62.2	-
6f	55.3	41.0	29.4	127.1	109.2	147.2	147.2	111.7	131.5	55.8 56.0	36.5	25.8	25.8	32.5	62.4

a) In $CDCl_3$ solution. b) $O\underline{C}H_2CH_3$ lines; $OCH_2\underline{C}H_3$ lines: 14.9, 14.8. c) 3-CH_3 line: 21.8. d) Assignment may be reversed. e) $O\underline{C}H_2CH_3$ lines; $OCH_2\underline{C}H_3$: 15.0, 15.0. f) 3-CH_3 line: 22.3. g) Upper row: lines of the major isomer; lower row: lines of the minor isomer.

TABLE 2. Physical and Analytical Data on New Compounds

Cmpd No.	mp. (°C)	Yield (%)	Formula M.w.	Analysis: Calcd (Found) C	H	N
2b	62-63[a]	78	$C_{16}H_{25}NO_4$ 295.38	65.06 (65.01)	8.53 (8.80)	4.74 (5.07)
2c	79-81[a]	69	$C_{15}H_{23}NO_4$ 281.35	64.04 (64.12	8.24 (8.29)	4.98 (4.86)
2f	78-80[a]	74	$C_{16}H_{25}NO_4$ 295.38	65.06 (64.73)	8.53 (8.83)	4.74 (4.44)
5b[c]	172-174[d]	48	$C_{16}H_{24}NO_3$ 313.82	61.24 (61.51)	7.71 (7.55)	4.46 (4.73)
5c[c]	177-180[d]	45	$C_{15}H_{22}ClNO_3$ 299.80	60.10 (59.75)	7.40 (7.67)	4.67 (4.59)
5d[c]	183-185[d]	40	$C_{15}H_{22}ClNO_3$ 299.80	60.10 (59.75)	7.40 (7.65)	4.67 (4.87)
5e[c]	220-223[e]	45	$C_{15}H_{22}ClNO_3$ 299.80	60.10 (60.41)	7.40 (7.66)	4.67 (4.83)
5f	85-86[f]	52	$C_{16}H_{23}NO_3$ 277.36	69.29 (69.16)	8.36 (8.10)	5.05 (4.83)
6b	73-75[b]	70	$C_{16}H_{25}NO_3$ 279.38	68.79 (69.00)	9.02 (9.30)	5.01 (4.97)
6c	110-112[f]	65	$C_{15}H_{23}NO_3$ 265.34	67.90 (67.55)	8.74 (8.60)	5.28 (5.07)
6d[c]	160-163[f]	72	$C_{15}H_{24}ClNO_3$ 301.81	59.69 (59.34)	8.02 (8.33)	4.64 (4.84)
6e[c]	190-194[d]	60	$C_{15}H_{24}ClNO_3$ 301.81	59.69 (59.72)	8.02 (8.37)	4.64 (4.51)
6f[c]	161-166[d]	83	$C_{16}H_{26}ClNO_3$ 315.84	60.85 (60.84)	8.30 (8.22)	4.43 (4.53)

a) Diisopropyl ether-ethyl acetate. b) Hexane. c) Hydrochloride salt. d) Ethanol-diethyl ether. e) Ethanol. f) Diisopropyl ether.

3.84, 3.85 (2s, 2x3H, 6,7-OCH_3), 3.91 (dd, 1H, J = 2.9, 8.9 Hz, 1-CH), 6.56 (s, 1H, 5-CH), 6.61 (s, 1H, 8-CH).

6f, IR: 1250, 1500, 2910, 3420 cm^{-1}; ^{1}H NMR: δ 1.32-1.88 (m, 3x2H, O,β,γ-CH_2), 2.60-2.80 (m, 2H, δ-CH_2), 2.93 (q, 1H, J = 12.5 Hz, 4-CH'), 2.96 (q, 1H, J = 12.5 Hz, 4-CH"), 3.18 (t, 1H, J = 12.7, 5.5 Hz, 3-CH'), 3.22 (t, 1H, J = 12.7, 5.3 Hz, 3-CH"), 3.63 (t, 2H, J = 6.6 Hz, ε-CH_2), 3.84 (s, 3H, 7-OCH_3), 3.85 (s, 3H, 6-OCH_3), 6.56 (s, 1H, 5-CH), 6.60 (s, 1H, 8-CH).

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