Synthesis and Spectral Properties of 6,7-Dimethoxy-1-[(*ortho*; and *para*-R)-phenyl]-3,4-dihydroisoquinoline

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The preparation of eleven novel 6,7-dimethoxy-1-[(*ortho*, and *para*-R)-phenyl]-3,4-dihydroisoquinolines with possible pharmacological activity is described. The structure of all products was corroborated by ir, ^{1}H-nmr, ^{13}C-nmr, and ms.

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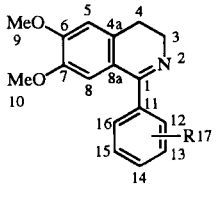
There have been several reports concerning biological and pharmacological interest for isoquinolines derivatives. Additionally, certain of the benzylisoquinolines are the synthetic and biosynthetic precursors of the morphine alkaloids [3-6]. Some tetrahydroisoquinolines derivatives are known to have activities as D_1 dopamine receptor ligands [7,8].

As a part of a program directed towards the synthesis and spectral property determination of heterocyclic derivatives with possible pharmacological activity, we describe in this report the synthesis of compounds **III**, **1-11** (Scheme 1), following the steps indicated in Scheme 2.

Scheme 1

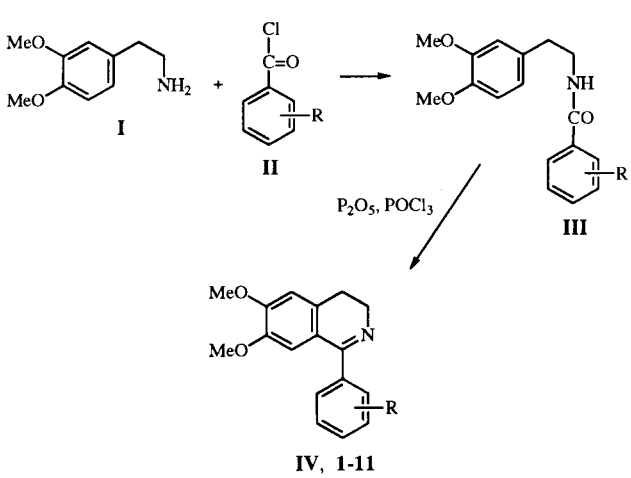


IV, **1-11**

1	H	**7**	*p*-CH_3
2	*o*-CH_3	**8**	*p*-OCH_3
3	*o*-OCH_3	**9**	*p*-Cl
4	*o*-Cl	**10**	*p*-Br
5	*o*-Br	**11**	*p*-NO_2
6	*o*-NO_2		

The 3,4-dimethoxyphenethyl amine **I** was dissolved in dry ether and treatment with the corresponding R-benzoyl chloride **II** in presence of aqueous sodium hydroxide solution under nitrogen atmosphere at room temperature overnight, afforded the compounds **III** in 85-95% yield.

Scheme 2



I **II** **III** **IV**, **1-11**

The corresponding compounds **III** were converted to the 6,7-dimethoxy-1-[(*ortho*, and *para*-R)-phenyl]-3,4-dihydroisoquinoline **IV**, **1-11** by refluxing in dry xylene in presence of phosphorus pentoxide and phosphorus oxychloride under nitrogen atmosphere for three hours with 65-80% yield.

The infrared spectrum of compounds **1-11** displayed absorptions at 1560-1570 cm^{-1} for -C=N stretching; at 1320 and 1357 cm^{-1} for C-O stretching; at 1275-1280 cm^{-1} for C-N stretching and the corresponding absortions for the R-substituent. In the ^{1}H-nmr spectra of derivatives **1-11** the presence of two proton signals at δ 2.7-2.8 triplet and δ 3.65-3.85 triplet were assigned to the methylene protons joined to C-4 and C-3; three proton signals at δ 3.65-3.75 singlet and δ 3.9-3.95 singlet were assigned to the methoxy protons joined to C-6 and C-7; one proton signal at δ 6.3-6.75 singlet and δ 6.75-6.8 singlet was assigned to the proton joined to C-8 and C-5. The aro-

Table 1

^{13}C NMR Spectral Data for Compounds **5** (R = *o*-Br) and **11** (R = *p*-NO_2)

Carbon	Chemical Shifts (ppm)	
	5(R = o-Br)	**11** (R = p-NO_2)
C-1 (C=N)	166.6	165.1
C-3(CH_2)	47.6	47.1
C-4 (CH_2)	25.5	25.9
C-4a (C-*C*=C)	121.8	120.7
C-5 (CH)	110.2	110.7
C-6 (*C*-OCH_3)	151.1*	151.5*
C-7 (*C*-OCH_3)	147.4*	147.3*
C-8 (CH)	110.6	110.7
C-8a (C-*C*=C)	131.1	132.7
C-9 (O-CH_3)	56.0	56.0
C-10 (O-CH_3)	56.0	56.0
C-11 (C-*C*=C)	140.3	145.3
C-12 (C-R) (R=H ó Br)	121.8	123.7
C-13 (CH)	132.8	130.0
C-14 (C-R) (R = H ó NO_2)	129.9	148.4
C-15 (CH)	127.4	130.0
C-16 (CH)	130.0	123.7

Table 2

Relative Abundances (%) of Principal Fragments in the Mass Spectra of 6,7-Dimethoxy-1-[(*ortho*, and *para*-R)-Phenyl]-3,4- dihydroisoquinoline

Compound	R	M+	[M-1]+	[M-R]+	[M-15]+	[M-17]+	[M-31]+	[102+R]+	251	220	208	192	180	152	102
1	H	90	100	100	5	18	20	15	8	5	12	12	20	18	8
2	*o*-CH_3	43	100	55	55	9	87	16	28	9	8	5	12	7	4
3	*o*-OCH_3	57	100	54	53	8	56	14	3	8	12	17	12	22	15
4	*o*-Cl	100	54	64	15	12	3	8	14	7	8	8	10	22	17
5	*o*-Br	49	22	100	5	2	3	9	12	10	13	12	19	36	27
6	*o*-NO_2	100	4	13	4	5	3	3	25	11	22	16	26	65	22
7	*p*-CH_3	55	100	18	18	12	17	3	5	3	3	2	4	7	5
8	*p*-OCH_3	97	100	37	25	22	37	12	13	3	2	3	7	15	10
9	*p*-Cl	89	100	9	15	13	16	13	4	4	3	6	5	28	4
10	*p*-Br	86	100	12	16	15	15	10	5	10	13	2	10	37	30
11	*p*-NO_2	84	100	7	4	5	8	2	8	5	5	8	13	25	20\

matic compounds appeared as an unresolved multiplet; AA'BB' system, or singlet at: δ 7.15-8.3.

The ^{13}C nmr spectra of compounds **5** and **11** are given in Table 1.

The mass spectrum of the compounds **1-11** exhibit an abundant molecular ion which probably reflects the stable nature of the 3,4-dihydroisoquinoline ring under electron impact. The relative abundance of the principal fragments ions of compounds **1-11** are given in Table 2. It can be seen that the compounds have some common features. The main fragmentation pathways of **1-11** include the elimination of a hydrogen atom from the molecular ion to produce the base peak for compounds **1-3** and **7-11**; the elimination of R-substituent from the molecular ion occurs in all the mass spectra given rise to the base peak only for **5**.

Further investigation on the synthesis of novel compounds from 1,2,3,4-tetrahydroisoquinoline *N*-methyl are presently being carried out.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet FT-55X Spectrophotometer. The ^1H-nmr spectra were recorded on a Varian Gemini-200 Spectrometer operating at 200 MHz and the ^{13}C-nmr spectra were recorded on a Varian VXR-300S Spectrometer operating at 300 MHz, in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts δ (ppm) expressed downfield from TMS. The mass spectra were measured on a Hewlett-Packard Model 5985A Quadrupole Mass Spectrometer and JEOL model JMS-SX102A High Resolution Mass Spectrometer with accurate mass determination of the molecular ion, using the direct inlet system. The spectra were recorded by electron impact at an ionization chamber temperature of 190° and ionizing electron energy of 70 eV.

Synthesis of *N*-(R-Benzoyl)-3,4-dimethoxyphenethylamine, **III**.

To a stirred solution of 3,4-dimethoxyphenethylamine **I**, 0.181 g (1 x 10^{-3} mole) in 15 ml of anhydrous ether under nitrogen atmosphere was added 0.5 ml of 20% aqueous sodium hydroxide solution. Freshly destilled R-benzoyl chloride **II** (1.5 x 10^{-3} mole) was added dropwise with stirring. A white precipitate formed immediately and the reaction was stirred at room temperature overnight. The colorless crystals were filtered, washed with ether and dried *in vacuo* to afford (75-95%) of *N*-(R-benzoyl)-3,4-dimethoxyphenethylamine **III**.

Synthesis of 6,7-Dimethoxy-1-[(*ortho*, and para-R)-phenyl]-3,4-dihydroisoquinoline **IV, 1-11**.

To a three-neck, round-bottom flask equipped with a magnetic stirrer, under a nitrogen atosphere was added compound **III** (1.0 x 10^{-3} mole) in 10 ml of dry xylene. Phosphorus pentoxide (0.204 g, 2 x 10^{-3} mole) was added in portions followed by the dropwise addition of freshly destilled phosphorus oxychloride (0.460 g, 3 x 10^{-3} mole). The mixture was stirred at reflux for 3.0 hours followed by cooling to room temperature and the xylenes were decanted. The solid residue was triturated with sufficient 10% aqueous sodium hydroxide solution to afford a suspension (*p*H 8-9). The suspension was extracted with methylene chloride (3 x 15 ml), the organic extracts were dried (sodium sulfate) and evaporated *in vacuo* to yield a reddish oil. The residual oil was purified on a silica gel chromatography column end elution with ethyl acetate to yield **IV, 1-11** (36-78%).

6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline (**1**).

This compound was obtained as colorless needles in 43% yield, mp 112-113°; ir (chloroform); ν -C=N- 1563, C-O- 1320 and 1357; C-N- 1277 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.7 (t, 2H, 4-H, J = 8.0 Hz), 3.8 (t, 2H, 3-H, J = 6.0 Hz), 3.7 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.75 (s, 1H, 8-H), 6.8 (s, 1H, 5-H), 7.35-7.65 (m, 5H, phenyl protons); ms: m/z 267 (M^+).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.37; H, 6.42; N, 5.26.

6,7-Dimethoxy-1-[(*ortho*-methyl)phenyl]-3,4-dihydroisoquinoline (**2**).

This compound was obtained as a reddish semisolid in 36% yield, ir (film): ν -C=N- 1565; C-O- 1320, and 1357. C-N- 1280 cm^{-1}; ^1H nmr (deuteriochloroform): δ; 2.15 (s, 3H, 17-H), 2.75 (t, 2H, 4-H, J = 8.0 Hz), 3.65 (t, 2H, 3-H, J = 6.3 Hz), 3.65 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.4 (s, 1H, 8-H), 6.75 (s, 1H, 5-H), 7.25 (s, 4H, phenyl protons); ms: m/z 281 (M^+).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.85; H, 6.82; N, 5.00.

6,7-Dimethoxy-1-[(*ortho*-methoxy)phenyl]-3,4-dihydroisoquinoline (**3**).

This compound was obtained as a yellow semisolid in 60% yield, ir (film): ν -C=N- 1567; C-O- 1357, 1322 and 1392; C-N- 1275 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.75 (t, 2H, 4-H, J = 8.1 Hz), 3.75 (t, 2H, 3-H, J = 6.2 Hz), 3.7 (s, 3H, 17-H), 3.65 (s, 3H, 9-H), 3.9 (s, 3H, 10-H), 6.5 (s, 1H, 8-H), 6.7 (s, 1H, 5-H), 7.0-7.35 (m, 4H, phenyl protons); ms: m/z 297 (M^+).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.71; H, 6.46; N, 4.71.

6,7-Dimethoxy-1-[(*ortho*-chloro)phenyl]-3,4-dihydroisoquinoline (**4**).

This compound was obtained as colorless needles, in 78% yield, mp 78-80°; ir (chloroform): ν -C=N- 1569; C-O- 1358 and 1323; C-N- 1279 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.8 (t, 2H, 4-H, J = 8.0 Hz), 3.7 (t, 2H, 3-H, J = 6.0 Hz), 3.7 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.4 (s, 1H, 8-H), 6.75 (s, 1H, 5-H), 7.4 (s, 4H, phenyl protons); ms: m/z 301 (M^+); 303 $[M+2]^+$.

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.35; N, 4.64. Found: C, 67.67; H, 5.37; N, 4.65.

6,7-Dimethoxy-1-[(*ortho*-bromo)phenyl]-3,4-dihydroisoquinoline (**5**).

This compound was obtained as yellow needles, in 42% yield, mp 65-66°, ir (chloroform): ν -C=N- 1569. C-O- 1357 and 1322; C-N- 1279 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.8 (t, 2H, 4-H, J = 8.1 Hz), 3.8 (t, 2H, 3-H, J = 6.2 Hz), 3.65 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.4 (s, 1H, 8-H), 6.75 (s, 1H, 5-H), 7.25-7.65 (m, 4H, phenyl protons). ms: m/z 345 (M^+); 347 $[M+2]^+$.

Anal. Calcd. for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05. Found: C, 58.95; H, 4.66; N, 4.02.

6,7-Dimethoxy-1-[(*ortho*-nitro)phenyl]-3,4-dihydroisoquinoline (**6**).

This compound was obtained as yellowish needles, in 64% yield, mp 110-112°; ir (chloroform): ν -C=N- 1570; C-O- 1358 and 1322; C-N- 1278; C-NO_2 1528 and 1355 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.8 (t, 2H, 4-H, J = 8.0 Hz), 3.8 (t, 2H, 3-H, J = 6.0 Hz), 3.65 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.65 (s, 1H, 8-H), 6.8 (s, 1H, 5-H), 7.4-8.15 (m, 4H, phenyl protons); ms: m/z 312 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.39; H, 5.15; N, 8.99.

6,7-Dimethoxy-1-[(*para*-methyl)phenyl]-3,4-dihydroisoquinoline (**7**).

This compound was obtained as colorless needles in 47% yield, mp 123-124°; ir (chloroform): ν -C=N- 1562; C-O- 1356 and 1321; C-N- 1277 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.4 (s, 3H, 17-H), 2.7 (t, 2H, 4-H, J = 8.0 Hz), 3.8 (t, 2H, 3-H, J = 6.0 Hz), 3.75 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.75 (s, 1H, 8-H), 6.8 (s, 1H, 5-H), 7.35 (AA'BB', 4H, J = 8.0, phenyl protons); ms: m/z 281 (M^+).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.84; H, 6.83; N, 4.97.

6,7-Dimethoxy-1-[(*para*-methoxy)phenyl]-3,4-dihydroisoquinoline (**8**).

This compound was obtained as colorless needles in 36% yield, mp 118-119°, ir (chloroform): ν -C=N- 1561. C-O- 1356 and 1320; C-N- 1277 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.7 (t, 2H, 4-H), J = 8.0 Hz), 3.75 (t, 2H, 3-H, J = 6.0 Hz), 3.75 (s, 3H, 9-H), 3.85 (s, 3H, 17-H), 3.95 (s, 3H, 10-H), 6.4 (s, 1H, 8-H), 6.75 (s, 1H, 5-H), 7.40 (AA'BB', 4H, J = 8.0, phenyl protons); ms: m/z 297 (M^+).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.72; H, 6.41; N, 4.74.

6,7-Dimethoxy-1-[(*para*-chloro)phenyl]-3,4-dihydroisoquinoline (**9**).

This compound was obtained as colorless needles in 64% yield, mp 120-122°; ir (chloroform): ν -C=N- 1562; C-O- 1356 and 1321; C-N- 1276 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.7 (t, 2H, 4-H, J = 8.0 Hz), 3.8 (t, 2H, 3-H, J = 6.0 Hz), 3.75 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.73 (s, 1H, 8-H), 6.77 (s, 1H, 5-H), 7.47 (AA'BB', 4H, J = 8.0 Hz, phenyl protons). ms: m/z 301 (M^+); 303 $[M+2]^+$.

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.35; N, 4.64. Found: C, 67.64; H, 5.35; N, 4.61.

6,7-Dimethoxy-1-[(*para*-bromo)phenyl]-3,4-dihydroisoquinoline (**10**).

This compound was obtained as yellowish needles in 75% yield, mp 138-140; ir (chloroform): ν -C=N- 1567; C-O- 1356 and 1320; C-N- 1277 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.75 (5, 2H, 4-H, J = 8.1 Hz), 3.8 (t, 2H, 3-H, J = 6.1 Hz), 3.75 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.7 (s, 1H, 8-H), 6.75 (s, 1H, 5-H), 7.5 (s, 4H, phenyl protons). ms: m/z 345 (M^+); 347 $[M+2]^+$.

Anal. Calcd. for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05. Found: C, 58.95; H, 4.68; N, 4.08.

6,7-Dimethoxy-1-[(*para*-nitro)phenyl]-3,4-dihydroisoquinoline (**11**).

This compound was obtained as yellowish needles in 73% yield, mp 150-152; ir (chloroform): ν -C=N 1560; C-O- 1320 and 1270; C-N 1278; C-NO_2 1510 and 1350 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.75 (t, 2H, 4-H, J = 8.0 Hz), 3.85 (t, 2H, 3-H, J = 6.0 Hz) 3.7 (s, 3H, 9-H), 3.95 (s, 3H, 10-H), 6.65 (s, 1H, 8-H), 6.8 (s, 1H, 5-H), 8.05 (AA'BB, 4H, J = 8.0 Hz, phenyl protons); ms: m/z 312(M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.37; H, 5.18; N, 8.99.

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