Synthesis of 8,9-Dialkoxybenzodiazepines and 7,8-Dialkoxyisoquinolines

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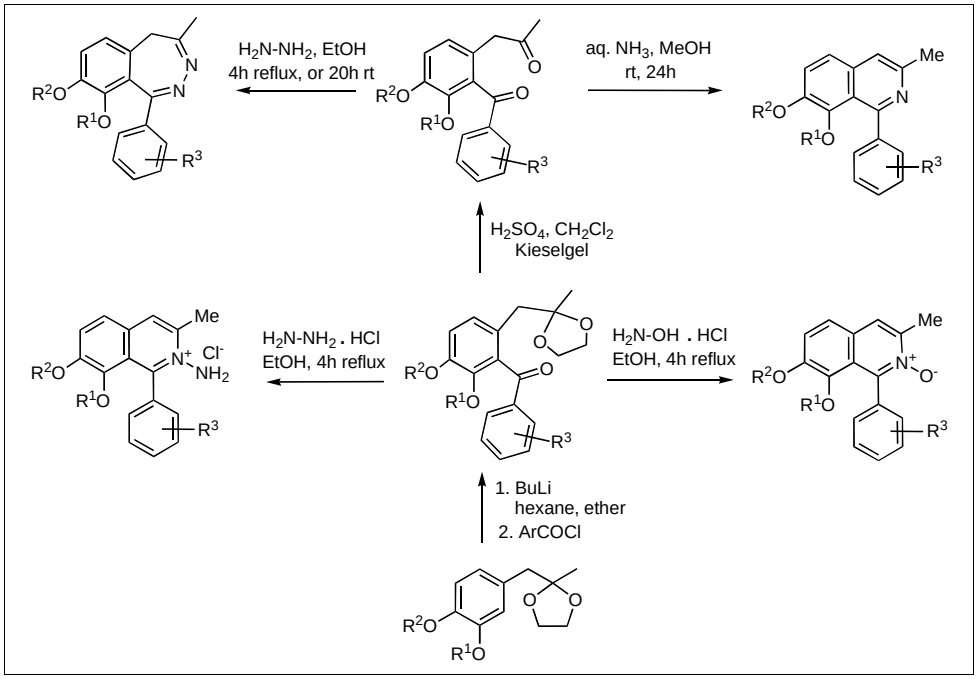
Received January 25, 2006

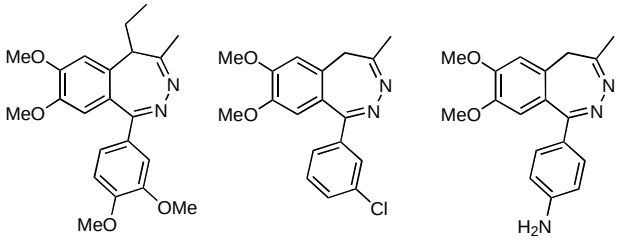


o-Aroylarylacetone type 1,5-diketone derivatives (5, 6) were synthesised from arylacetones (1) protected as 1,3-dioxolanes (4) through directed *ortho* lithiation followed by acylation with aroyl chlorides. 8,9-Dialkoxy-2,3-benzodiazepines 9 were obtained by cyclisation of diketones 6 with hydrazine. The reaction of diketones 6 with ammonia gave 7,8-dialkoxyisoquinolines 11. Reaction of ketals 5 with hydrazine hydrochloride and hydroxylamine hydrochloride afforded *N*-amino-7,8-dialkoxyisoquinolinium chlorides (10) and 7,8-dialkoxyisoquinolinium oxides (12), respectively.

J. Heterocyclic Chem., **43**, 1539 (2006).

7,8-Dialkoxy-2,3-benzodiazepines possess strong CNS activity [1-2]. Thus tofisopam (Grandaxin^R, Scheme 1) was introduced into market in 1975 as a psychovegetative regulator [3]. Follow-up compounds girisopam and nerisopam showed anxiolytic and atypical neuroleptic properties, respectively [4,5].

Scheme 1



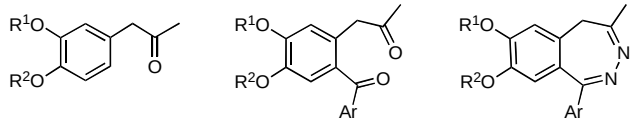
tofisopam
Grandaxin

girisopam

nerisopam

The synthesis of 7,8-dialkoxy-2,3-benzodiazepines **3** has been reviewed recently [6]. The *o*-aroylarylacetone type 1,5-diketone key intermediates **2** were prepared from arylacetones **1** by different procedures using electrophilic aromatic substitution reaction for the introduction of the new substituent to the benzene ring (Scheme 2). Cyclisation of diketones **2** with hydrazine hydrate afforded 2,3-benzodiazepines **3**.

Scheme 2



1 **2** **3**

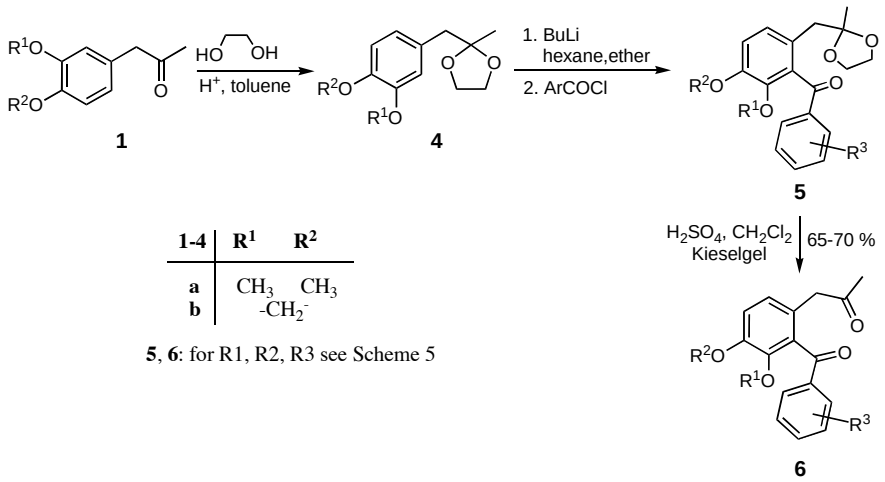
R^1,R^2: CH_3, $-CH_2-$ Ar: phenyl, substituted phenyl

In a continuation of the structure-activity relationship studies of 2,3-benzodiazepines and related isoquinoline

derivatives we decided to synthesize new 8,9-dialkoxy-2,3-benzodiazepines (**9**) and related 7,8-dialkoxyisoquinolines (**10-12**).

The synthesis of isomeric 1,5-diketones **6** required for the ring closure to derivatives **9-12** has been accomplished starting from arylacetones **1** by directed *ortho* lithiation reaction of ethylene ketals **4** at the doubly activated site and subsequent aroylation with aroyl chlorides to benzophenone ketals **5** which can be easily transformed to the required diketones **6** (Scheme 3).

Scheme 3

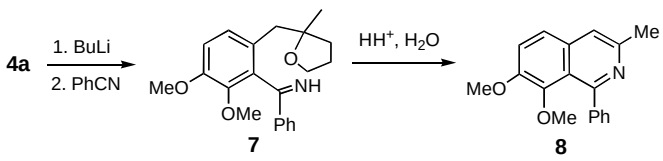


1-4	R1	R2
a	CH_3	CH_3
b	$-CH_2-$	

5, **6**: for R1, R2, R3 see Scheme 5

Aroylation of aryllithium compounds has been frequently achieved by reaction with benzonitriles as electrophiles and subsequent hydrolysis of the primarily formed ketimines. However, it is described in the literature that ketimine **7**, obtained by lithiation of **4a** followed by treatment with benzonitrile led to isoquinoline **8** upon hydrolysis, instead of diketone **6a** (Scheme 4) [7].Quenching of aryllithium compounds - obtained by lithiation of ketals **4** with aroyl chlorides instead of arylnitriles afforded benzophenone ketals **5**, which could be easily transformed to the required diketones **6** with acceptable to good yields.

Scheme 4



The reaction of 2-aroylarylacetones **6a-l** with hydrazine affords 8,9-dialkoxy-2,3-benzodiazepines **9a-l** in good yields (Scheme 5). However, treatment of the corresponding benzophenone ketals **5a-k** with hydrazine hydrochloride gave the isomeric *N*-amino-7,8-dialkoxyisoquinolinium chlorides (**10a-k**).

The distinction between compounds **9** and **10** was achieved by pmr spectroscopy [8,9]. The pmr spectrum of compounds **9** shows two doublets in the range of 2.98 and 3.45 ppm with coupling constants of J = 12.2–13.3 Hz characteristic for the non-equivalent protons of the CH_2 group of the 5*H*-2,3-benzodiazepine ring. The resonances of the 4-H protons of isoquinolines **10** are readily identified as singlets in the range of 8.40-8.61 ppm.

1-Aryl-3-methylisoquinolinium *N*-oxides **12a-h** were obtained when the 2-aroyldioxolanes **5a-h** were reacted with hydroxylamine hydrochloride (Scheme 5). On the other hand, diketones **6** are suitable starting materials also for the synthesis of new 1-aryl-3-methyl-8,9-dialkoxyisoquinolines as demonstrated by the preparation of compounds **11b,e,f** by the treatment of *o*-aroylarylacetones **6b,e,f** with aqueous ammonia.

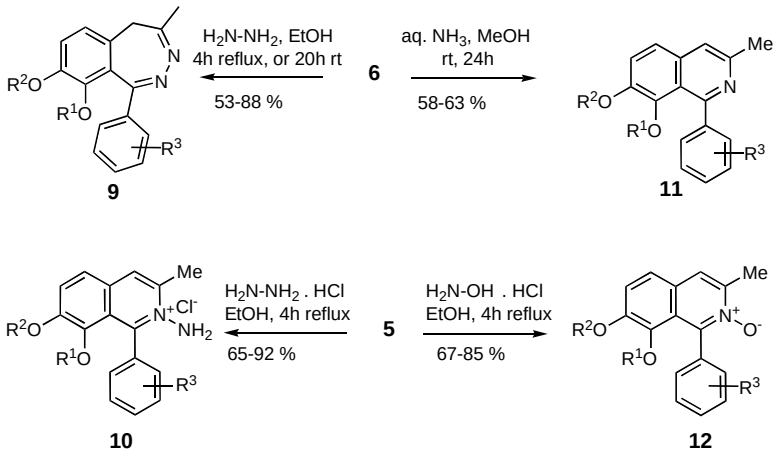
EXPERIMENTAL

Melting points were determined on a Kofler Boëtius micro apparatus and were not corrected. The ir spectra were recorded on an Aspect 2000 computer controlled Bruker IFS-113v vacuum optic FT spectrometer, using KBr pellets of solids or films of liquids. The pmr and cmr spectra were taken on a Bruker WM 250 FT, or a Varian Gemini-200, or a Varian Unity Inova 500 spectrometer, in deuteriochloroform and DMSO-d_6 as solvents. Chemical shifts were reported as δ values (ppm) downfield from internal tetramethylsilane.

2-[(3,4-Dimethoxyphenyl)methyl]-2-methyl-1,3-dioxolane (**4a**).

To a solution of **1a** (97.1 g, 0.5 mol) in toluene (700 ml) ethylene glycol (100 ml, 1.82 mol) and *p*-toluenesulfonic acid monohydrate (3 g) were added and the mixture was refluxed in a Dean-Stark apparatus for 12 h. After cooling the reaction mixture

Scheme 5



5,6,9-12	R^1	R^2	R^3
a	CH_3	CH_3	H
b	CH_3	CH_3	2-F
c	CH_3	CH_3	4-F
d	CH_3	CH_3	2-Cl
e	CH_3	CH_3	3-Cl
f	CH_3	CH_3	4-Cl
g	CH_3	CH_3	2,4-di-Cl
h	$-CH_2-$		H
i	$-CH_2-$		2-F
j	$-CH_2-$		4-F
k	$-CH_2-$		4-MeO
l	$-CH_2-$		4-NO_2

was made alkaline with an aqueous solution of sodium bicarbonate (10 %), extracted with water (3 x 200 ml) and dried (Na_2SO_4). After evaporation of the volatiles the residue was purified by bulb-to-bulb vacuum distillation to yield the title compound (89.5 g, 75 %) as colourless oil, bp 110-112 °C/0.15 mmHg. This compound was described as starting material in ref. [7] without giving any information about its synthesis and physical data; pmr (deuteriochloroform, 500 MHz): 6.84 (d, *J*=1.3 Hz, 1H), 6.79 (m, 2H), 3.89 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.74 (m, 2H), 2.87 (s, 2H), 1.31 (s, 3H); cmr (deuteriochloroform, 125 MHz): 148.2, 147.5, 129.4, 122.4, 113.6, 110.7, 109.6, 64.7, 55.7, 44.8, 24.2.

Anal. Calcd. for $C_{13}H_{18}O_4$ (238.29): C, 65.53; H, 7.61. Found: C, 65.57; H, 7.83.

2-Methyl-2-[(3,4-methylenedioxyphenyl)methyl]-1,3-dioxolane (**4b**).

This compound was prepared analogously to **4a** starting from **1b** (35.6 g, 0.2 mol) to give **4b** (39.5 g, 89 %) as colourless oil, bp 108 °C/0.4 mmHg; pmr (deuteriochloroform, 500 MHz): 6.79 (m, 1H), 6.72 (m, 1H), 6.70 (m, 1H), 5.91 (s, 2H), 3.90 (m, 2H), 3.79 (m, 2H), 2.82 (s, 2H), 1.29 (s, 3H); cmr (deuteriochloroform, 125 MHz): 147.1, 146.0, 130.5, 123.3, 110.7, 109.6, 107.7, 100.6, 64.7, 44.9, 24.1.

Anal. Calcd. for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.36. Found: C, 64.89; H, 6.44.

General Method for the Synthesis of *o*-Aroylarylacetone Ketals **5**.

Butyl lithium (29 ml of a 2.5 *M* solution in hexane, 0.072 mol) was added to a solution of the corresponding **4** (0.06 mol) in ether (120 ml) under argon. The temperature of the reaction mixture was kept below 5 °C during the addition of butyl lithium and it was then stirred for further 3 h at 0 °C. The appropriate aroyl chloride (0.063 mol) was added at 0-5 °C to the resulting suspension and the mixture was stirred for additional 2.5 hours at ambient temperature. Water (100 ml) was added under cooling with an ice–water bath, the pH of the mixture was adjusted to 7 with aqueous hydrochloric acid solution (1 %). The resulting layers were separated and the aqueous layer was extracted with ether (50 ml). The combined organic phases were washed with water, dried (Na_2SO_4) and evaporated to dryness to give *o*-aroylarylacetone ketals **5**. Compounds **5b** and **5l** were isolated in crystalline form and characterised. The oily products **5a** and **5c-h** were characterised by spectra (ir, pmr, cmr) and elemental analysis before transformation to derivatives **6**, **10** and **12** without further purification. Ketals **5i-k** were transformed directly to the corresponding diketons **6i-k** and *N*-amino-7,8-dialkoxyisoquinolinium chlorides **10i-k** without characterisation.

2-[(2-Benzoyl-3,4-dimethoxyphenyl)methyl]-2-methyl-1,3-dioxolane (**5a**).

This compound was obtained as an oil. Yield: 67 %; ir (potassium bromide): ν 1669 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.21 (s, 3H), 2.79 (s, 2H), 3.5-3.7 (m, 4H), 3.61 (s, 3H), 3.88 (s, 3H), 6.96 (d, *J*=8.5 Hz, 1H), 7.16 (d, *J*=8.5 Hz, 1H), 7.4-7.8 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 24.2, 40.5, 55.7, 61.2, 64.4, 109.5, 112.8, 127.0, 127.3, 128.1, 129.4, 132.9, 135.2, 138.0, 145.8, 150.9, 196.9.

Anal. Calcd. for $C_{20}H_{22}O_5$ (342.39): C, 70.16; H, 6.48. Found: C, 70.21; H, 6.53.

2-{[3,4-Dimethoxy-2-(2-fluorobenzoyl)phenyl]methyl}-2-methyl-1,3-dioxolane (**5b**)

This compound was obtained as colourless crystals, mp 60-61 °C (ether). Yield: 72 %; ir (potassium bromide): ν 1657 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.23 (s, 3H), 2.91 (s, 2H), 3.5-3.7 (m, 4H), 3.59 (s, 3H), 3.86 (s, 3H), 6.93 (d, *J*=8.5 Hz, 1H), 7.08 (d, *J*=8.5 Hz, 1H), 7.2-7.8 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 24.1, 40.1, 55.6, 60.9, 64.3, 109.5, 113.0, 116.3 (d, $^2J_{C\text{-}F}$=22.5 Hz), 123.6 (d, $^3J_{C\text{-}F}$= 3.9 Hz), 126.7, 127.4, 131.0, 134.0 (d, $^3J_{C\text{-}F}$=9.0 Hz), 136.3, 146.2, 150.7, 161.1 (d, $^1J_{C\text{-}F}$=258 Hz), 193.0.

Anal. Calcd. for $C_{20}H_{21}FO_5$ (360.38): C, 66.66; H, 5.87, F, 5.27. Found: C, 66.83; H, 5.91, F, 5.13.

2-{[3,4-Dimethoxy-2-(4-fluorobenzoyl)phenyl]methyl}-2-methyl-1,3-dioxolane (**5c**)

This compound was obtained as an oil. Yield: 74 %; ir (potassium bromide): ν 1670 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.20 (s, 3H), 2.80 (s, 2H), 3.6-3.9 (m, 4H,), 3.62 (s, 3H), 3.88 (s, 3H), 6.95 (d, *J*=8.5 Hz, 1H), 7.10 (d, *J*=8.5 Hz, 1H), 7.2-7.9 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 24.1, 40.7, 55.7, 61.5, 64.8, 111.2, 113.3, 115.8 (d, $^2J_{C\text{-}F}$=22.0 Hz), 123.0, 127.9, 129.4, 133.0 (d, $^3J_{C\text{-}F}$=9.1 Hz), 135.8, 146.4, 151.8, 165.9 (d, $^1J_{C\text{-}F}$=258 Hz), 196.4.

Anal. Calcd. for $C_{20}H_{21}FO_5$ (360.38): C, 66.66; H, 5.87; F, 5.27. Found: C, 66.91; H, 5.95; F, 5.20.

2-{[3,4-Dimethoxy-2-(2-chlorobenzoyl)phenyl]methyl}-2-methyl-1,3-dioxolane (**5d**).

This compound was obtained as an oil. Yield: 68 %; ir (potassium bromide): ν 1679 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.28 (s, 3H), 2.93 (s, 2H), 3.6-3.8 (m, 4H), 3.54 s, 3H), 3.85 (s, 3H), 6.94 (d, *J* = 8.5 Hz), 1H), 7.12 (d, *J*=8.5 Hz, 1H), 7.2-7.8 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 24.3, 40.1, 55.7, 61.0, 64.4, 109.6, 113.5, 126.0, 127.5, 127.6, 130.9, 131.7, 131.8, 132.6, 138.3, 151.0, 195.3.

Anal. Calcd. for $C_{20}H_{21}ClO_5$ (376.84): C, 63.75; H, 5.62; Cl, 9.41. Found: C, 63.84, H, 5.79; Cl, 9.35.

2-{[3,4-Dimethoxy-2-(3-chlorobenzoyl)phenyl]methyl}-2-methyl-1,3-dioxolane (**5e**).

This compound was obtained as an oil. Yield: 67 %; ir (potassium bromide): ν 1675 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.21 (s, 3H), 2.82 (s, 2H), 3.5-3.7 (m, 4H), 3.60 (s, 3H), 3.88 (s, 3H), 6.97 (d, *J*=8.5 Hz, 1H), 7.15 (d, *J*=8.5 Hz, 1H), 7.3-7.8 (m, 4H);(deuteriochloroform, 62.5 MHz): 24.2, 40.4, 55.6, 61.0, 64.3, 109.3, 113.0, 127.0, 127.5, 127.6, 129.1, 129.3, 132.6, 134.1, 134.3, 139.7, 145.8, 150.8, 195.5.

Anal. Calcd. for $C_{20}H_{21}ClO_5$ (376.84): C, 63.75; H, 5.62; Cl, 9.41. Found: C, 63.85; H, 5.65; Cl, 9.36.

2-{[3,4-Dimethoxy-2-(4-chlorobenzoyl)phenyl]methyl}-2-methyl-1,3-dioxolane (**5f**).

This compound was obtained as an oil. Yield: 75 %; ir (potassium bromide): ν 1671 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.22 (s, 3H), 2.82 (s, 2H), 3.6-3.8 (m, 4H), 3.63 (s, 3H), 3.89 (s, 3H), 6.96 (d, *J*=8.5 Hz, 1H), 7.14 (d, *J*=8.5 Hz), 1H), 7.39 (d, *J*=9.1 Hz, 2H), 7.77 (d, *J*=9.1 Hz, 2H); (deuteriochloroform, 62.5 MHz): 24.3, 40.5, 55.7, 61.1, 64.4, 109.7, 113.1, 122.6, 127.2, 127.7, 128.2, 130.9, 136.7, 139.1, 150.9, 195.6.

Anal. Calcd. for $C_{20}H_{21}ClO_5$ (376.84): C, 63.75; H, 5.62; Cl, 9.41. Found: C, 63.82; H, 5.67; Cl, 9.38.

2-{[3,4-Dimethoxy-2-(2,4-dichlorobenzoyl)phenyl]methyl}-2-methyl-1,3-dioxolane (**5g**).

This compound was obtained as an oil. Yield: 74 %; ir (potassium bromide): ν 1680 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.27 (s, 3H), 2.95 (s, 2H), 3.6-3.8 (m, 4H), 3.55 (s, 3H), 3.85 (s, 3H), 6.94 (d, *J*=8.5 Hz, 1H), 7.10 (d, *J*=8.5 Hz, 1H), 7.2-7.5 (m, 4H); (deuteriochloroform, 62.5 MHz): 24.1, 40.0, 55.6, 61.0, 64.3, 109.5, 113.6, 126.3, 127.7, 130.6, 132.5, 133.6, 136.7, 137.1, 146.7, 151.0, 194.1.

Anal. Calcd. for $C_{20}H_{20}Cl_2O_5$ (411.28): C, 58.41; H, 4.90; Cl, 17.24. Found: C, 58.47; H, 4.95; Cl, 17.17.

2-[(2-Benzoyl-3,4-methylenedioxyphenyl)methyl]-2-methyl-1,3-dioxolane (**5h**).

This compound was obtained as an oil. Yield: 85 %; ir (potassium bromide): ν 1676 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.21 (s, 3H), 2.90 (s, 2H), 3.4-3.6 (m, 4H), 3.55 (s, 3H), 3.90 (s, 2H), 6.99 (d, *J*=8.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz), 1H), 7.36 (d, *J*=8.9 Hz, 2H), 8.26 (d, *J*=8.9 Hz, 2H); (deuteriochloroform, 62.5 MHz): 24.3, 40.4, 55.7, 61.0, 64.2, 109.3, 113.5, 123.2, 127.4, 128.0, 130.1, 133.5, 143.1, 146.2, 149.8, 150.9, 195.2.

Anal. Calcd. for $C_{19}H_{18}O_5$ (326.35): C, 69.93; H, 5.56. Found: C, 69.71; H, 5.48.

2-[3,4-Methylenedioxy-2-(4-nitrobenzoyl)phenylmethyl}-2-methyl-1,3-dioxolane (5l).

This compound was obtained as pale yellow crystals, mp 145-146°C (ether). Yield: 64 %; ir (potassium bromide): ν 1667 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.21 (s, 3H), 3.08 (s, 2H), 3.45-3.61 (m, 4H), 5.84 (s, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.88 (d, *J*=8.1 Hz, 1H), 8.00 (d, *J*=8.9 Hz, 2H), 8.29 (d, *J*=8.9 Hz, 2H).

Anal. Calcd. for $C_{19}H_{17}NO_7$ (371.35): C, 61.45; H, 4.61; N, 3.77. Found: C, 61.43; H, 4.65; N, 3.81.

General Method for the Synthesis of 2-Aroylphenylacetones **6**.

To a suspension of silica gel (15 g, Kieselgel 60 for column chromatography, 0.063 – 0.2 mm) in dichloromethane (30 ml) aqueous sulphuric acid (15 %, 1.5 ml) was added at room temperature and it was stirred until the aqueous phase disappeared due to its adsorption on the silica gel surface (5 min). The corresponding *o*-aroylarylacetone ketal **5** (0.001 mol) was added to the mixture and the stirring was continued at room temperature for further 5 hours. The reaction mixture was then neutralised with sodium hydrogen carbonate (1 g), the silica gel was filtered off and washed with dichloromethane (2 x 15 ml). Evaporation of volatiles from the organic solutions yielded practically pure 2-aroylphenylacetones **6** that were recrystallised from an appropriate solvent or used directly to the synthesis of derivatives **9** and **11**.

1-(2-Benzoyl-3,4-dimethoxyphenyl)propan-2-one (**6a**).

This compound was obtained as an oil. Yield: 71 %; ir (potassium bromide): ν 1720, 1670 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 1.91 (s, 3H), 3.43 (s, 3H), 3.52 (s, 2H, CH_2)

3.78 (s, 3H), 6.88 (d, *J*=8.4 Hz, 1H), 6.92 (d, *J*=8.4 Hz, 1H), 6.8-7.7 (m, 5H); cmr (deuteriochloroform, 62.5 MHz): 29.4, 46.5, 55.7, 61.1, 113.3, 124.2, 126.4, 128.3, 129.3, 133.4, 134.2, 137.5, 146.0, 151.3, 197.0, 205.6.

Anal. Calcd. for $C_{18}H_{18}O_4$ (298.34): C, 72.47; H, 6.08. Found: C, 72.55; H, 6.12.

1-[3,4-Dimethoxyphenyl-2-(2-fluorobenzoyl)]propan-2-one (**6b**).

This compound was obtained as an oil. Yield: 65 %; ir (potassium bromide): ν 1720, 1675 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.10 (s, 3H), 3.55 (s, 3H), 3.66 (s, 2H), 3.86 (s, 3H), 6.94 (d, *J*=8.4 Hz, 1), 6.99 (d, *J*=8.4 Hz, 1H), 7.1-7.7 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 29.3, 46.7, 55.6, 60.7, 113.8, 116.3 (d, $^2J_{C\text{-}F}$= 22 Hz), 123.8 [d, $^4J_{C\text{-}F}$=3.8 Hz), 124.5, 126.5, 127.3 (d, $^3J_{C\text{-}F}$=9.6 Hz,), 131.0, 134.2 (d, $^3J_{C\text{-}F}$=9.0 Hz), 134.8, 146.6, 151.2, 161.1 (d, $^1J_{C\text{-}F}$=262 Hz), 193.8, 205.7.

Anal. Calcd. for $C_{18}H_{17}FO_4$ (316.33): C, 68.35; H, 5.42; F, 6.01. Found: C, 68.42; H, 5.48; F, 5.97.

1-[3,4-Dimethoxyphenyl-2-(4-fluorobenzoyl)]propan-2-one (**6c**).

This compound was obtained as an oil. Yield: 52 %; ir (potassium bromide): ν 1717, 1671 cm^{-1}; pmr (deuteriochloroform, 500 MHz): 2.03 (s, 3H), 3.55 (s, 3H), 3.63 (s, 2H), 3.89 (s, 3H), 6.95 (d, *J*=8.4 Hz, 1), 6.99 (d, *J*=8.4 Hz, 1H), 7.1-7.8 (m, 4H); cmr (deuteriochloroform, 125 MHz): 29.5, 46.7, 55.8, 61.2, 113.5, 115.6 (d, $^2J_{C\text{-}F}$= 22 Hz), 124.4, 126.6, 132.2 (d, $^3J_{C\text{-}F}$=9.8 Hz,), 134.0, 134.1, 146.1, 151.5, 165.9 (d, $^1J_{C\text{-}F}$=255,4 Hz), 195.5, 205.6.

Anal. Calcd. for $C_{18}H_{17}FO_4$ (316.33): C, 68.35; H, 5.42; F, 6.01. Found: C, 68.51; H, 5.47; F, 5.95.

1-[2-(2-Chlorobenzoyl)-3,4-dimethoxyphenyl]propan-2-one (**6d**).

This compound was obtained as an oil. Yield: 65 %; ir (potassium bromide): ν 1720, 1675 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.16 (s, 3H), 3.43 (s, 3H), 3.76 (s, 2H) 3.84 (s, 3H), 6.91 (d, *J*=8.4 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 1H), 7.3-7.7 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 29.5, 46.9, 55.6, 60.5, 114.4, 125.8, 126.3, 126.7, 130.4, 130.5, 131.7, 133.7, 139.2, 147.5, 151.5, 196.2, 205.9.

Anal. Calcd. for $C_{18}H_{17}ClO_4$ (332.78): C, 64.97; H, 5.15; Cl, 10.65. Found: C, 65.13; H, 5.21; Cl, 10.53.

1-[2-(3-Chlorobenzoyl)-3,4-dimethoxyphenyl]propan-2-one (**6e**).

This compound was obtained as an oil.Yield: 70 %; ir (potassium bromide): ν 1721, 1674 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.04 (s, 3H), 3.60 (s, 3H), 3.86 (s, 2H) 3.88 (s, 3H), 6.96 (d, *J*=8.4 Hz, 1H), 7.02 (d, *J*=8.4 Hz, 1H), 7.4-7.8 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 29.3, 46.5, 55.6, 60.9, 112.1, 113.6, 124.3, 126.5, 127.6, 128.7, 129.6, 133.0, 133.2, 134.4, 139.1, 146.1, 151.2, 195.7, 205.3.

Anal. Calcd. for $C_{18}H_{17}ClO_4$ (332.78): C, 64.97; H, 5.15; Cl, 10.65. Found: C, 65.11; H, 5.19; Cl, 10.54.

1-[2-(4-Chlorobenzoyl)-3,4-dimethoxyphenyl]propan-2-one (**6f**).

This compound was obtained as colourless crystals, mp 74-76 °C (2-propanol). Yield: 71 %; ir (potassium bromide): ν 1722, 1668 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.03 (s, 3H), 3.56 (s, 3H), 3.61 (s, 2H) 3.89 (s, 3H), 6.94 (d, *J*=8.4 Hz, 1H), 7.01 (d, *J*=8.4 Hz, 1H), 7.4-7.8 (m, 4H; cmr (deuteriochloroform, 62.5 MHz): 29.3, 46.5, 55.7, 61.0, 113.5, 124.3, 126.5, 128.6, 130.7, 133.6, 135.9, 139.6, 146.1, 151.3, 195.8, 205.4.

Anal. Calcd. for $C_{18}H_{17}ClO_4$ (332.78): C, 64.97; H, 5.15; Cl, 10.65. Found: C, 65.08; H, 5.18; Cl, 10.51.

1-[2-(2,4-Dichlorobenzoyl)-3,4-dimethoxyphenyl]propan-2-one (**6g**).

This compound was obtained as an oil. Yield: 65 %, not purified, used directly to the synthesis of **9g**; ir (potassium bromide): ν 1719, 1678 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.17 (s, 3H), 3.48 (s, 3H), 3.80 (s, 2H) 3.85 (s, 3H), 6.91 (d, *J*=8.4 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 1H), 7.2-7.5 (m, 3H); cmr (deuteriochloroform, 62.5 MHz): 29.4, 46.8, 55.5, 60.6, 114.5, 121.3, 125.8, 126.5, 126.7, 130.1, 131.4, 133.0, 136.9, 137.6, 147.5, 151.4, 195.0, 205.8.

Anal. Calcd. for $C_{18}H_{16}Cl_2O_4$ (367.23): C, 58.87; H, 4.39; Cl, 19.31. Found: C, 58.65; H, 4.33; Cl, 19.22.

1-(2-Benzoyl-3,4-methylenedioxyphenyl)propan-2-one (**6h**).

This compound was obtained as colourless crystals, mp. 112-113 °C (2-propanol). Yield: 38 %; ir (potassium bromide): ν 1722, 1652 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.11 (s, 3H), 3.78 (s, 2H), 5.84 (s, 2H), 6.71 (d, *J*=8.1 Hz, 1H), 6.89 (d, *J* = 7.7 Hz), 1H), 7.45-7.9 (m, 5H); cmr (deuteriochloroform, 62.5 MHz): 29.5, 47.3, 101.6, 110.0, 120.8, 124.6, 127.0, 128.4, 129.7, 133.4, 137.5, 146.2, 146.8, 194.2, 205.7.

Anal. Calcd. for $C_{17}H_{14}O_4$ (282.30): C, 72.33; H, 5.00. Found: C, 72.45; H, 5.13.

1-[2-(2-Fluorobenzoyl)-3,4-methylenedioxyphenyl]propan-2-one (**6i**).

This compound was obtained as colourless crystals, mp. 107-108 °C (2-propanol). Yield: 59 %; ir (potassium bromide): ν 1724, 1654 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.21 (s, 3H), 3.89 (s, 2H), 5.81 (s, 2H), 6.69 (d, *J*=7.7 Hz, 1H), 6.88 (d, *J* =8.1 Hz), 1H), 7.2-7.7 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 29.6, 47.8, 101.7, 110.8, 116.2 (d, $^2J_{C\text{-}F}$=22.5 Hz), 121.1, 124.1 (d, $^4J_{C\text{-}F}$=3.8 Hz), 124.8, 127.6 (d, $^3J_{C\text{-}F}$=15.2 Hz), 131.2 (d, $^4J_{C\text{-}F}$=1.9 Hz), 134.1 (d, $^3J_{C\text{-}F}$=8.8 Hz), 147.1, 147.5, 161.1 (d, $^1J_{C\text{-}F}$=256.4 Hz), 190.3, 205.9.

Anal. Calcd. for $C_{17}H_{13}FO_4$ (300.29): C, 68.00; H, 4.36; F, 6.33. Found: C, 67.91; H, 4.45; F, 6.28.

1-[2-(4-Fluorobenzoyl)-3,4-methylenedioxyphenyl]propan-2-one (**6j**).

This compound was obtained as colourless crystals, mp. 106-108 °C (2-propanol). Yield: 77 %; ir (potassium bromide): ν 1712, 1652 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.12 (s, 3H), 3.82 (s, 2H), 5.86 (s, 2H), 6.70 (d, *J*=8.1 Hz, 1H), 6.89 (d, *J*=8.1 Hz, 1H), 7.13 (t, *J*=8.6 Hz, 2H,), 7.90 (dd, *J*=8.4 and 5.5 Hz, 2H); cmr (deuteriochloroform, 62.5 MHz): 29.6, 47.3, 101.6, 110.1, 115.4, 115.8, 120.6, 124.6, 127.0, 132.3, 132.5, 133.9, 146.1, 146.8, 168.5, 192.7, 205.7.

Anal. Calcd. for $C_{17}H_{13}FO_4$ (300.29): C, 68.00; H, 4.36; F, 6.33. Found: C, 68.22; H, 4.35; F, 6.35.

1-[2-(4-Methoxybenzoyl)-3,4-methylenedioxyphenyl]propan-2-one (**6k**).

This compound was obtained as colourless crystals, mp. 102-103 °C (2-propanol). Yield: 56 %; ir (potassium bromide): ν 1712, 1650 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.10 (s, 3H), 3.75 (s, 2H), 3.87 (s, 3H), 5.88 (s, 2H), 6.71 (d, *J*=7.9 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H, 6.94 (d, *J*=8.4 Hz, 2H), 7.86 (d,

J=8.4 Hz, 2H); cmr (deuteriochloroform, 62.5 MHz): 29.6, 47.3, 55.5, 101.5, 109.7, 113.8, 121.4, 124.5, 126.8, 130.3, 132.2, 145.7, 146.7, 164.0, 192.6, 205.9.

Anal. Calcd. for $C_{18}H_{16}O_5$ (312.33): C, 69.22; H, 5.16. Found: C, 69.15; H, 5.22.

1-[3,4-Methylenedioxy-2-(4-nitrobenzoyl)phenyl]propan-2-one (**6l**).

This compound was obtained as yellow crystals, mp. 112-113 °C (ether). Yield: 78 %; ir (potassium bromide): ν 1723, 1666 cm^{-1}; pmr (deuteriochloroform, 250 MHz): 2.16 (s, 3H), 3.98 (s, 2H), 5.83 (s, 2H), 6.71 (d, *J*=7.9 Hz, 1H), 6.92 (d, *J*=7.9 Hz, 1H), 8.02 (d, *J*=9.0 Hz, 2H), 8.30 (d, *J*=9.0 Hz, 2H); cmr (deuteriochloroform, 62.5 MHz): 29.8, 47.3, 101.7, 110.9, 119.7, 123.5, 124.8, 127.3, 130.5, 142.8, 146.7, 147.1, 150.2, 192.9, 205.7.

Anal. Calcd. for $C_{17}H_{13}NO_6$ (327.30): C, 62.39; H, 4.00; N, 4.28. Found: C, 62.44; H, 4.12; N, 4.35.

General Method for the Synthesis of Benzodiazepines (**9**).

To a solution of 2-aroylphenylacetone (**6**, 0.01 mol) in ethanol (30 ml) hydrazine (95 %, 0.5 ml, 0.015 mol) was added and the mixture was refluxed for 30 min. After evaporation of the solvent *in vacuo* the residue was triturated with diethyl ether and the crystalline benzodiazepine (**9**) was collected by filtration and dried.

8,9-Dimethoxy-4-methyl-1-phenyl-5*H*-2,3-benzodiazepine (**9a**).

This compound was obtained as colourless crystals, mp. 127-129 °C (2-propanol). Yield: 75 %; pmr (deuteriochloroform, 250 MHz): 2.11 (s, 3H), 3.04 (d, *J*=12.4 Hz, 1H), 3.16 (d, *J*=12.4 Hz, 1H), 3.42 (s, 3H), 3.85 (s, 3H), 6.95 (d, *J*=8.4 Hz, 1H), 7.06 (d, *J*=8.4 Hz), 1H), 7.3-7.6 (m, 5H); cmr (deuteriochloroform, 62.5 MHz): 22.7, 37.4, 55.9, 60.9, 115.2, 121.0, 123.4, 127.6, 128.0, 129.1, 134.5, 139.3, 148.2, 152.0, 156.4, 157.4.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$ (294.35): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.54; H, 6.21; N, 9.45.

8,9-Dimethoxy-1-(2-fluorophenyl)-4-methyl-5*H*-2,3-benzodiazepine (**9b**).

This compound was obtained as colouirless crystals, mp. 94-96 °C (2-propanol). Yield: 84 %; pmr (deuteriochloroform, 250 MHz): 2.12 (s, 3H), 3.08 (d, *J*=12.4 Hz, 1H), 3.20 (d, *J*=12.4 Hz, 1H), 3.36 (s, 3H), 3.81 (s, 3H), 6.93 (d, *J*=8.4 Hz, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 6.9-7.8 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 22.8, 37.4, 55.8, 60.5, 115.1 (d, $^2J_{C\text{-}F}$=18.6 Hz), 121.0, 123.8 (d, $^3J_{C\text{-}F}$=4.2 Hz,), 124.8, 128.3 (d, $^2J_{C\text{-}F}$=11.3 Hz), 129.7 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 130.2 (d, $^3J_{C\text{-}F}$=8.5 Hz), 133.1, 147.5, 151.6, 153.3, 156.1, 160.2 (d, $^1J_{C\text{-}F}$=251 Hz).

Anal. Calcd. for $C_{18}H_{17}FN_2O_2$ (312.34): C, 69.22; H, 5.49; N, 8.97; F, 6.08. Found: C, 69.40; H, 5.52; N, 8.91; F, 6.02.

8,9-Dimethoxy-1-(4-fluorophenyl)-4-methyl-5*H*-2,3-benzodiazepine (**9c**).

This compound was obtained as colourless crystals, mp. 138-140 °C (2-propanol). Yield: 81 %; pmr (deuteriochloroform, 250 MHz): 2.10 (s, 3H), 3.02 (d, *J*=12.4 Hz, 1H), 3.16 (d, *J*=12.4 Hz, 1H), 3.44 (s, 3H), 3.85 (s, 3H), 6.95 (d, *J*=8.4 Hz, 1H), 7.08 (d, *J*=8.4 Hz, 1H), 7.5-7.6 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 22.7, 37.4, 55.8, 60.9, 114.8 (d, $^2J_{C\text{-}F}$=20.8 Hz), 115.2, 121.1, 122.9, 129.3 (d, $^3J_{C\text{-}F}$= 9.1 Hz), 134.1, 135.2, 147.8, 151.8, 156.0, 156.3, 163.3 (d, $^1J_{C\text{-}F}$ = 247 Hz).

Anal. Calcd. for $C_{18}H_{17}FN_2O_2$ (312.34): C, 69.22; H, 5.49; N, 8.97; F, 6.08. Found: C, 69.36; H, 5.54; N, 8.89; F, 6.01.

1-(2-Chlorophenyl)-8,9-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine (**9d**).

This compound was obtained as colourless crystals, mp. 123-125 °C (2-propanol). Yield: 78 %; pmr (deuteriochloroform, 250 MHz): 2.13 (s, 3H), 3.20 (d, *J*=12.4 Hz, 1H), 3.24 (d, *J*=12.4 Hz, 1H), 3.40 (d, *J*=12.4 Hz, 1H), 3.80 (s, 3H), 6.92 (d, *J*=8.4 Hz, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 7.3-7.8 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 22.9, 37.4, 55.8, 60.0, 115.4, 121.0, 124.9, 126.5, 129.2, 129.4, 130.7, 132.2, 133.8, 139.6, 147.2, 151.7, 156.0, 156.4.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$ (328.80): C, 65.75; H, 5.21; N, 8.52; Cl, 10.78. Found: C, 65.84; H, 5.28; N, 8.48; Cl, 10.71.

1-(3-Chlorophenyl)-8,9-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine (**9e**).

This compound was obtained as colourless crystals, mp. 108-110 °C (2-propanol). Yield: 76 %; pmr (deuteriochloroform, 250 MHz): 2.10 (s, 3H), 3.00 (d, *J*=12.4 Hz, 1H), 3.18 (d, J=12.4 Hz, 1H), 3.00 (d, *J*=12.4 Hz, 1H), 3.18 (d, *J*=12.4 Hz, 1H), 3.45 (s, 3H), 3.85 (s, 3H), 6.95 (d, *J*=8.4 Hz, 1H), 7.08 (d, *J*=8.4 Hz, 1H), 7.3-7.6 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 22.8, 37.4, 55.9, 60.8, 115.5, 121.1, 122.8, 125.8, 127.3, 128.9, 129.1, 133.8, 134.1, 141.1, 147.7, 151.8, 155.9, 156.2;

Anal. Calcd. For $C_{18}H_{17}ClN_2O_2$ (328.80): C, 65.75; H, 5.21; N, 8.52; Cl, 10.78. Found: C, 65.81; H, 5.26; N, 8.46; Cl, 10.70.

1-(4-Chlorophenyl)-8,9-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine (**9f**).

This compound was obtained as colourless crystals, mp. 129-130.5 °C (2-propanol). Yield: 87 %; pmr (deuteriochloroform, 250 MHz): 2.10 (s, 3H), 2.99 (d, *J*=12.4 Hz, 1H), 3.16 d, *J*=12.4 Hz, 1H), 3.44 (s, 3H), 3.85 (s, 3H), 6.96 (d, *J*=8.4 Hz), 1H), 7.07 (d, *J*=8.4 Hz, 1H), 7.3-7.5 (m, 4H); cmr (deuteriochloroform, 62.5 MHz): 22.8, 37.4, 55.9, 60.1, 115.3, 121.1, 122.8, 128.0, 134.1, 137.6, 147.8, 151.8, 156.0, 156.5.

Anal. Calcd. For $C_{18}H_{17}ClN_2O_2$ (328.80): C, 65.75; H, 5.21; N, 8.52; Cl, 10.78. Found: C, 65.80; H, 5.27; N, 8.49; Cl, 10.72.

1-(2,4-Dichlorophenyl)-8,9-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine (**9g**).

This compound was obtained as colourless crystals, mp. 125-127 °C (2-propanol). Yield: 88 %; pmr (deuteriochloroform, 250 MHz): 2.13 (s, 3H), 3.13 [d, *J*=12.4 Hz, 1H), 3.22 (d, *J*=12.4 Hz, 1H), 3.32 (s, 3H), 3.81 (s, 3H), 6.92 (d, *J*=8.4 Hz, 1H), 7.05 (d, *J*=8.4 Hz, 1H), 7.3-7.7 (m, 3H); cmr (deuteriochloroform, 62.5 MHz): 22.9, 37.4, 55.8, 60.8, 115.6, 121.1, 124.5, 126.9, 129.0, 131.5, 132.9, 133.7, 134.6, 138.2, 147.2, 151.7, 155.3, 156.0.

Anal. Calcd. For $C_{18}H_{16}Cl_2N_2O_2$ (363.24): C, 59.52; H, 4.44; N, 7.71; Cl, 19.52. Found: C, 59.58; H, 4.47; N, 7.68; Cl, 19.50.

4-Methyl-8,9-methylenedioxy-1-phenyl-5*H*-2,3-benzodiazepine (**9h**).

This compound was obtained as colourless crystals, mp. 214-216 °C (MeOH). Yield: 58 %; pmr (deuteriochloroform, 250 MHz): 2.12 (s, 3H), 3.05 (d, *J*=12.2 Hz, 1H), 3.23 (d, *J*=12.2 Hz, 1H, 5.74 (d, *J*=1.0 Hz, 1H), 5.83 (d, *J*=1.0 Hz, 1H), 6.72 (d, *J*=8.2 Hz, 1H), 6.95 (d, *J*=8.2 Hz, 1H), 7.4-7.7 (m, 5H); cmr

(deuteriochloroform, 62.5 MHz): 22.7, 38.0, 101.4, 110.8, 111.9, 118.5, 128.0, 129.6, 133.9, 137.2, 145.6, 147.2, 154.4, 155.8.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (278.31): C, 73.37; H, 5.07; N, 10.07. Found: C, 73.42; H, 5.23; N, 9.97.

1-(2-Fluorophenyl)-4-methyl-8,9-methylenedioxy-5*H*-2,3-benzodiazepine (**9i**).

This compound was obtained as colourless crystals, mp. 183-184 °C (2-propanol). Yield: 70 %; pmr (deuteriochloroform, 250 MHz): 2.13 (s, 3H), 3.07 (d, *J*=13.3 Hz, 1H), 3.27 (d, *J*=13.3 Hz, 1H), 5.72 (d, *J*=2.2 Hz, 2H) 6.70 (d, *J*=8.0 Hz, 1H), 6.91 (d, *J*= 8.0 Hz, 1H), 6.94-7.89 (m, 4H).

Anal. Calcd. for $C_{17}H_{13}FN_2O_2$ (296.30): C, 68.91; H, 4.42; N, 9.45; F, 6.41. Found: C, 69.03; H, 4.53; N, 9.38; F, 6.34.

1-(4-Fluorophenyl)-4-methyl-8,9-methylenedioxy-5*H*-2,3-benzodiazepine (**9j**).

This compound was obtained as colourless crystals, mp. 230-232 °C (MeOH). Yield: 53 %; pmr (deuteriochloroform, 250 MHz): 2.12 (s, 3H), 3.04 (d, *J*=12.2 Hz, 1H), 3.24 d, *J*=12.2 Hz, 1H), 5.77 (d, *J*=1.2 Hz, 1H), 5.86 (d, *J*=1.2 Hz, 1H), 6.74 (d, *J*=7.8 Hz), 1H), 6.97 (d, *J*=7.8 Hz, 1H,), 7.08 (t, *J*=8.7 Hz, 2H), 7.66 (dd, *J*=8.7 and 5.4 Hz), 2H).

Anal. Calcd. for $C_{17}H_{13}FN_2O_2$ (296.30): C, 68.91; H, 4.42; N, 9.45; F, 6.41. Found: C, 68.88; H, 4.40; N, 9.49; F, 6.39.

1-(4-Methoxyphenyl)-4-methyl-8,9-methylenedioxy-5*H*-2,3-benzodiazepine (**9k**).

This compound was obtained as colourless crystals, mp. 234-236 °C (EtOH). Yield: 72 %; pmr (deuteriochloroform, 250 MHz): 2.11 (s, 3H), 3.06 (d, *J*=12.3 Hz, 1H), 3.21 (d, J=12.3 Hz, 1H), 3.83 (s, 3H), 5.76 (d, *J*=1.2 Hz, 1H), 5.87 (d, *J*=1.2 Hz, 1H), 6.73 (d, *J*=7.9 Hz, 1H, 6.92 (d, *J*=7.9 Hz, 1H), 6.94 (d, *J*=9.1 Hz, 2H), 7.62 (dd, *J*=9.1 and 2.3 Hz), 2H).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$ (308.34): C, 70.12; H, 5.23; N, 9.09. Found: C, 70.20; H, 5.28; N, 9.06.

4-Methyl-8,9-methylenedioxy-1-(4-nitrophenyl)-5*H*-2,3-benzodiazepine (**9l**).

This compound was obtained as colourless crystals, mp. 226-228 °C (MeOH). Yield: 77 %; pmr (deuteriochloroform, 250 MHz): 2.16 (s, 3H), 3.02 (d, *J*=12.3 Hz, 1H), 3.31 (d, *J*=12.3 Hz, 1H), 5.80 (d, *J*=1.1 Hz, 1H), 5.89 (d, *J*=1.1 Hz, 1H), 6.79 (d, *J*=7.9 Hz, 1H), 7.02 (d, *J*=7.9 Hz, 1H), 7.83 (d, *J*=9.0 Hz, 2H), 8.24 (d, *J*=9.0 Hz, 2H).

Anal. Calcd. for $C_{17}H_{13}N_3O_4$ (323.31): C, 63.16; H, 4.05; N, 13.00. Found: C, 63.04; H, 4.21; N, 12.91.

General Method for the Synthesis of *N*-Aminoisoquinolinium chlorides (**10**).

To a solution of a corresponding *o*-aroylarylacetone ketal (**5**, 0.06 mol) in methanol (100 ml) and water (12 ml) hydrazine hydrochloride (8.2 g, 0.12 mol) was added and the reaction mixture refluxed with stirring for 1 hour. The methanol was evaporated *in vacuo*, water (300 ml) was added to the residue and the mixture extracted with dichloromethane (2 x 150 ml). The combined organic layers were evaporated *in vacuo* to dryness and the residue was recrystallised from an appropriate solvent to give *N*-aminoisoquinolinium chlorides (**10**).

N-Amino-7,8-dimethoxy-3-methyl-1-phenyl-isoquinolinium chloride (**10a**).

This compound was obtained as yellow crystals, mp. 132-134 °C (CH_3CN). Yield: 65 %; pmr (DMSO-d_6, 250 MHz): 2.88 (s, 3H), 3.13 (s, 3H), 3.96 (s, 3H), 7.24 (bs, 2H), 7.5-7.6 (m, 5H), 8.00 (d, *J* = 9.1 Hz, 1H), 8.11 (d, *J* = 9.1 Hz, 1H), 8.50 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 19.3, 57.0, 60.4, 122.4, 123.3, 124.5, 125.6, 128.1, 128.5, 129.8, 131.0, 132.7, 141.2, 142.9, 151.4, 152.2.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_2$ (330.81): C, 65.35; H, 5.79; N, 8.47; Cl, 10.72. Found: C, 65.43; H, 5.82; N, 8.38; Cl, 10.58.

N-Amino-7,8-dimethoxy-1-(2-fluorophenyl)-3-methyl-isoquinolinium chloride (**10b**).

This compound was obtained as yellow crystals, mp. 184-186 °C (2-propanol). Yield: 68 %; pmr (DMSO-d_6, 250 MHz): 2.95 (s, 3H), 3.20 (s, 3H), 3.99 (s, 3H), 7.49 (bs, 2H), 7.5-7.7 (m, 4H), 8.05 (d, *J* = 9.1 Hz, 1H), 8.17 (d, *J* = 9.1 Hz, 1H), 8.59 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 19.4, 57.0, 60.5, 115.3 (d, $^2J_{C\text{-}F}$ = 21 Hz), 121.2, 121.4, 122.4, 123.6, 124.4, 125.1, 126.4, 130.5, 131.3, 132.2 (d, $^3J_{C\text{-}F}$ = 8.9 Hz), 143.2 (d, $^3J_{C\text{-}F}$ = 13.4 Hz), 147.8, 152.1, 158.9 (d, $^1J_{C\text{-}F}$ = 244 Hz).

Anal. Calcd. for $C_{18}H_{18}ClFN_2O_2$ (348.80): C, 61.68; H, 5.20; N, 8.03; F, 5.45; Cl, 10.16. Found: C, 61.79; H, 5.28; N, 7.93; F, 5.41; Cl, 10.20.

N-Amino-7,8-dimethoxy-1-(4-fluorophenyl)-3-methyl-isoquinolinium chloride (**10c**).

This compound was obtained as yellow crystals, mp. 205-208 °C (2-propanol). Yield: 69 %; pmr (DMSO-d_6, 250 MHz): 2.89 (s, 3H), 3.18 (s, 3H), 3.97 (s, 3H), 7.43 (bs, 2H), 7.5-7.7 (m, 4H), 8.00 (d, *J* = 9.1 Hz, 1H), 8.11 (d, *J* = 9.1 Hz, 1H), 8.51 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 19.4, 57.0, 60.5, 115.6 (d, $^2J_{C\text{-}F}$ = 22.5 Hz), 122.6, 123.4, 124.5, 125.7, 129.1, 130.9 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 131.0, 141.4, 143.8, 150.7, 152.2, 162.0 (d, $^1J_{C\text{-}F}$ = 246 Hz).

Anal. Calcd. for $C_{18}H_{18}ClFN_2O_2$ (348.80): C, 61.68; H, 5.20; N, 8.03; F, 5.45; Cl, 10.16. Found: C, 61.81; H, 5.25; N, 7.91; F, 5.37; Cl, 10.21.

N-Amino-1-(2-chlorophenyl)-7,8-dimethoxy-3-methyl-isoquinolinium chloride (**10d**).

This compound was obtained as yellow crystals, mp. 203-206 °C (2-propanol). Yield: 68 %; pmr (DMSO-d_6, 250 MHz): 2.94 (s, 3H), 3.23 (s, 3H), 3.99 (s, 3H), 7.43 (bs, 2H), 7.6-7.7 (m, 4H), 8.05 (d, *J* = 9.1 Hz, 1H), 8.16 (d, *J* = 9.1 Hz, 1H), 8.58 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 19.0, 57.0, 60.6, 122.2, 123.5, 125.0, 126.3, 127.4, 129.2, 130.0, 131.1, 131.4, 131.6, 132.4, 149.4, 152.1.

Anal. Calcd. for $C_{18}H_{18}Cl_2N_2O_2$ (365.26): C, 59.19; H, 4.97; N, 7.67; Cl, 19.41. Found: C, 59.28; H, 5.03; N, 7.51; Cl, 19.29.

N-Amino-1-(3-chlorophenyl)-7,8-dimethoxy-3-methyl-isoquinolinium chloride monohydrate (**10e**).

This compound was obtained as yellow crystals, mp. 195-198 °C (H_2O). Yield: 71 %; pmr (DMSO-d_6, 250 MHz): 2.86 (s, 3H), 3.20 (s, 3H), 3.97 (s, 3H), 7.00 (bs, 2H), 7.5-7.7 (m, 4H), 8.02 (d, *J* = 9.1 Hz, 1H), 8.13 (d, *J* = 9.1 Hz, 1H), 8.51 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 19.2, 57.0, 60.4, 122.5, 123.4,

124.7, 125.8, 126.9, 128.1, 129.6, 130.1, 131.2, 133.1, 135.0, 141.7, 143.7, 150.6.

Anal. Calcd. for $C_{18}H_{18}Cl_2N_2O_2.H_2O$ (383.28): C, 56.41; H, 5.26; N, 7.31; Cl, 18.50. Found: C, 56.63; H, 5.38; N, 7.50; Cl, 18.45.

N-Amino-1-(4-chlorophenyl)-7,8-dimethoxy-3-methyl-isoquinolinium chloride monohydrate (**10f**).

This compound was obtained as yellow crystals, mp. 194-196 °C (H_2O). Yield: 75 %; pmr (DMSO-d_6, 250 MHz): 2.87 (s, 3H), 3.19 (s, 3H), 3.97 (s, 3H), 7.26 (bs, 2H), 7.6-7.7 (m, 4H), 8.01 (d, *J* = 9.1 Hz, 1H), 8.12 (d, *J* = 9.1 Hz, 1H), 8.50 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 19.3, 57.0, 60.5, 122.5, 123.4, 124.6, 125.8, 128.6, 130.3, 131.1, 131.8, 134.5, 141.6, 143.7, 150.8, 152.2.

Anal. Calcd. for $C_{18}H_{18}Cl_2N_2O_2.H_2O$ (383.28): C, 56.41; H, 5.26; N, 7.31; Cl, 18.50. Found: C, 56.58; H, 5.35; N, 7.48; Cl, 18.36.

N-Amino-1-(2,4-dichlorophenyl)-7,8-dimethoxy-3-methyl-isoquinolinium chloride monohydrate (**10g**).

This compound was obtained as yellow crystals, mp. 193-196 °C (H_2O). Yield: 78 %; pmr (DMSO-d_6, 250 MHz): 2.95 (s, 3H), 3.29 (s, 3H), 4.00 (s, 3H), 7.56 (bs, 2H), 7.7-7.9 (m, 3H), 8.05 (d, *J* = 9.1 Hz, 1H), 8.61 (s, 1H), 9.17 (d, *J* = 9.1 Hz, 1H); cmr (DMSO-d_6, 62.5 MHz): 19.3, 57.0, 60.7, 122.2, 123.6, 125.1, 126.6, 127.7, 128.8, 131.2, 131.5, 131.7, 132.7, 135.3, 142.5, 143.2, 148.5, 152.1.

Anal. Calcd. for $C_{18}H_{17}Cl_3N_2O_2.H_2O$ (417.72): C, 51.75; H, 4.58; N, 4.58; Cl, 25.46. Found: C, 51.93; H, 4.62; N, 4.44; Cl, 25.32.

N-Amino-3-methyl-7,8-methylenedioxy-1-phenyl-isoquinolinium chloride (**10h**).

This compound was obtained as yellow crystals, mp. 240-242 °C (EtOH). Yield: 92 %; pmr (DMSO-d_6, 250 MHz): 2.85 (s, 3H), 6.05 (dd, *J* = 5.8 and 0.8 Hz, 2H), 6.7 (b, 2H), 7.43-7.76 (m, 5H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 8.52 (s, 1H).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$ (314.77): C, 64.87; H, 4.80; N, 8.90; Cl, 11.26. Found: C, 64.95; H, 5.01; N, 8.87; Cl, 11.26.

N-Amino-1-(2-fluorophenyl)-3-methyl-7,8-methylenedioxy-isoquinolinium chloride (**10i**).

This compound was obtained as yellow crystals, mp. 238-240 °C (2-propanol). Yield: 70 %; pmr (DMSO-d_6, 250 MHz): 2.92 (s, 3H), 6.08 (dd, *J* = 5.8 and 0.8 Hz, 2H), 6.5 (b, 2H), 7.43-7.76 (m, 4H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 8.57 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}ClFN_2O_2$ (332.76): C, 61.36; H, 4.24; N, 8.42; F, 5.71; Cl, 10.65. Found: C, 61.44; H, 4.33; N, 8.30; F, 5.67; Cl, 10.69.

N-Amino-1-(4-fluorophenyl)-3-methyl-7,8-methylenedioxy-isoquinolinium chloride (**10j**).

This compound was obtained as yellow crystals, mp. 247-248 °C (2-propanol). Yield: 73 %; pmr (DMSO-d_6, 250 MHz): 2.85 (s, 3H), 6.03 (s, 2H), 7.36 (bs, 2H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.73 (dd, *J* = 5.4 and 3.5 Hz, 2H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 8.45 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}ClFN_2O_2$ (332.76): C, 61.36; H, 4.24; N, 8.42; F, 5.71; Cl, 10.65. Found: C, 61.32; H, 4.41; N, 8.38; F, 5.74; Cl, 10.61.

N-Amino-1-(4-methoxyphenyl)-3-methyl-7,8-methylenedioxy-isoquinolinium chloride hydrochloride (**10k**).

This compound was obtained as pale yellow crystals, mp. 220-222 °C (AcOH/EtOH). Yield: 65 %; pmr (DMSO-d_6, 250 MHz): 2.84 (s, 3H), 3.87 (s, 3H) 6.04 (s, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.32 (bs, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 8.40 (s, 1H).

Anal. Calcd. for $C_{18}H_{17}ClN_2O_3.HCl$ (381.25): C, 56.70; H, 4.76; N, 7.35; Cl, 18.60. Found: C, 56.63; H, 4.85; N, 7.33; Cl, 18.53.

General Method for the Synthesis of Isoquinolines **11**.

To a mixture of a 2-aroylphenylacetone (**6**, 0.033 mol) in methanol (40 ml) aqueous ammonium hydroxide (25 %, 20 ml, 0.15 mol) was added and refluxed with stirring for 1 hour. The solution obtained was evaporated *in vacuo* to dryness and the residue was chromatographed on a silica gel column (eluents: different mixtures of hexane and ether). After evaporation the solvents from the appropriate fractions the residue was triturated with hexane and the crystalline isoquinoline (**11**) was collected by filtration and dried.

7,8-Dimethoxy-1-(2-fluorophenyl)-3-methyl-isoquinoline (**11b**).

This compound was obtained as colourless crystals, mp. 80-82 °C. Yield: 58 %; pmr (deuteriochloroform, 250 MHz): 2.68 (s, 3H), 3.28 (s, 3H), 3.92 (s, 3H), 7.41 (s, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.0-7.5 (m, 4H), 7.53 (d, *J* = 9.0 Hz, 1H); cmr (deuteriochloroform, 62.5 MHz): 23.9, 56.7, 60.5, 114.4 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 118.3, 119.4, 121.6, 122.7, 123.2 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 129.0 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 130.1 (d, $^3J_{C\text{-}F}$ = 3.6 Hz), 131.8 (d, $^2J_{C\text{-}F}$ = 16.5 Hz), 133.6, 144.2, 148.5, 149.4, 152.0, 160.3 (d, $^1J_{C\text{-}F}$ = 252.5 Hz).

Anal. Calcd. for $C_{18}H_{16}FNO_2$ (297.33): C, 72.71; H, 5.42; N, 4.71; F, 6.39. Found: C, 72.85; H, 5.51; N, 4.68; F, 6.35.

1-(3-Chlorophenyl)-7,8-dimethoxy-3-methyl-isoquinoline (**11e**).

This compound was obtained as colourless crystals, mp. 89-91 °C. Yield: 61 %; pmr (deuteriochloroform, 250 MHz): 2.68 (s, 3H), 3.27 (s, 3H), 3.94 (s, 3H), 7.41 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.3-7.5 (m, 4H), 7.55 (d, *J* = 9.0 Hz, 1H); cmr (deuteriochloroform, 62.5 MHz): 23.8, 56.7, 60.4, 118.0, 119.3, 120.5, 122.7, 127.0, 127.1, 128.2, 128.6, 132.8, 133.9, 144.0, 145.2, 148.2, 149.5, 156.0.

Anal. Calcd. for $C_{18}H_{16}ClNO_2$ (313.78): C, 68.90; H, 5.14; N, 4.46; Cl, 11.30. Found: C, 69.03; H, 5.21; N, 4.47; Cl, 11.25.

1-(4-Chlorophenyl)-7,8-dimethoxy-3-methyl-isoquinoline (**11f**).

This compound was obtained as colourless crystals, mp. 92-94 °C. Yield: 63 %; pmr (deuteriochloroform, 250 MHz): 2.67 (s, 3H), 3.24 (s, 3H), 3.95 (s, 3H), 7.42 (s, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.3-7.5 (m, 4H), 7.56 (d, *J* = 9.0 Hz, 1H); cmr (deuteriochloroform, 62.5 MHz): 23.7, 56.7, 60.3, 117.7, 119.3, 120.3, 122.7, 125.4, 127.0, 130.1, 132.9, 133.9, 141.8, 144.0, 148.3, 149.4, 156.1.

Anal. Calcd. for $C_{18}H_{16}ClNO_2$ (313.78): C, 68.90; H, 5.14; N, 4.46; Cl, 11.30. Found: C, 68.97; H, 5.12; N, 4.50; Cl, 11.26.

General Method for the Synthesis of Isoquinolinium *N*-oxides (**12**).

To a solution of a corresponding *o*-aroylarylacetone ketal (**5,** 0.022 mol) in methanol (40 ml) hydroxylamine hydrochloride

(3.2 g, 0.05 mol) was added and the mixture was refluxed with stirring for 1 hour. The methanol was evaporated *in vacuo*, aqueous sodium hydrogen carbonate solution (10 %, 30 ml) was added to the residue and the mixture was stirred at room temperature for 2 h. The crystalline product was collected by filtration, washed with water and dried to give the corresponding isoquinolinium *N*-oxides (**12**).

7,8-Dimethoxy-3-methyl-1-phenyl-isoquinolinium-*N*-oxide (**12a**).

This compound was obtained as colourless crystals, mp. 149-151 °C (EtOH). Yield: 68 %; pmr (DMSO-d_6, 250 MHz): 2.60 (s, 3H), 3.17 (s, 3H), 3.91 (s, 3H), 7.32 (d, J = 8.9 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.4-7.5 (m, 5H), 7.60 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 17.7, 56.3, 60.2, 116.4, 122.2, 122.5, 123.7, 124.7, 127.2, 127.6, 128.3, 135.5, 141.4, 143.5, 143.6, 151.1.

Anal. Calcd. for $C_{18}H_{17}NO_3$ (295.34): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.38; H, 5.85; N, 4.68.

7,8-Dimethoxy-1-(2-fluorophenyl)-3-methyl-isoquinolinium-*N*-oxide (**12b**).

This compound was obtained as colourless crystals, mp. 170-173 °C (EtOH). Yield: 71 %; pmr (DMSO-d_6, 250 MHz): 2.60 (s, 3H), 3.25 (s, 3H), 3.92 (s, 3H), 7.31 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.2-7.4 (m, 5H), 7.61 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 17.5, 56.1, 60.1, 114.6 (d, $^2J_{C\text{-}F}$ = 22.1 Hz), 116.3, 122.7 (d, $^3J_{C\text{-}F}$ = 16 Hz), 123.2 (d, $^2J_{C\text{-}F}$ = 7 Hz), 123.4, 123.8, 124.4, 129.5 (d, $^3J_{C\text{-}F}$ = 9 Hz), 130.4 (d, $^4J_{C\text{-}F}$ = 3 Hz), 138.2, 140.8, 143.3, 151.0, 159.7 (d, $^1J_{C\text{-}F}$ = 240 Hz).

Anal. Calcd. for $C_{18}H_{16}FNO_3$ (313.33): C, 69.00; H, 5.15; N, 4.47; F, 6.06. Found: C, 69.17; H, 5.23; N, 4.35; F, 6.10.

7,8-Dimethoxy-1-(4-fluorophenyl)-3-methyl-isoquinolinium-*N*-oxide (**12c**).

This compound was obtained as colourless crystals, mp. 205-208 °C (CH_3CN). Yield: 73 %; pmr (DMSO-d_6, 250 MHz): 2.60 (s, 3H), 3.21 (s, 3H), 3.93 (s, 3H), 7.34 (d, J = 8.9 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.1-7.4 (m, 5H), 7.61 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 17.6, 56.2, 60.1, 114.5 (d, $^2J_{C\text{-}F}$ = 20.6 Hz), 116.3, 122.4, 122.6, 123.7, 124.7, 130.4, (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 131.2, 131.3, 141.1, 142.5, 143.5, 151.1, 162.0 (d, $^1J_{C\text{-}F}$ = 246 Hz).

Anal. Calcd. for $C_{18}H_{16}FNO_3$ (313.33): C, 69.00; H, 5.15; N, 4.47; F, 6.06. Found: C, 69.15; H, 5.21; N, 4.31; F, 6.13.

1-(2-Chlorophenyl)-7,8-dimethoxy-3-methyl-isoquinolinium-*N*-oxide (**12d**).

This compound was obtained as colourless crystals, mp. 187-189 °C (CH_3CN). Yield: 71 %; pmr (DMSO-d_6, 250 MHz): 2.61 (s, 3H), 3.29 (s, 3H), 3.92 (s, 3H), 7.32 (d, J = 8.9 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.4-7.5 (m, 5H), 7.62 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 17.6, 56.4, 60.5, 116.5, 122.5, 122.7, 123.8, 124.7, 126.4, 128.7, 129.0, 133.0, 135.0, 141.3, 141.4, 143.7, 151.1.

Anal. Calcd. for $C_{18}H_{16}ClNO_3$ (329.78): C, 65.56; H, 4.89; N, 4.25; Cl, 10.75. Found: C, 65.48; H, 4.91; N, 4.27; Cl, 10.83.

1-(3-Chlorophenyl)-7,8-dimethoxy-3-methyl-isoquinolinium-*N*-oxide (**12e**).

This compound was obtained as colourless crystals, mp. 203-205 °C (EtOH). Yield: 67 %; pmr (DMSO-d_6, 250 MHz): 2.60 (s, 3H), 3.24 (s, 3H), 3.93 (s, 3H), 7.33 d, J = 8.9 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.3-7.5 (m, 5H), 7.61 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 17.8, 56.5, 60.3, 116.7, 122.7, 123.8, 124.9, 126.9, 127.8, 128.7, 129.1, 133.7, 137.4, 141.3, 142.3, 143.8, 151.3.

Anal. Calcd. for $C_{18}H_{16}ClNO_3$ (329.78): C, 65.56; H, 4.89; N, 4.25; Cl, 10.75. Found: C, 65.59; H, 4.93; N, 4.19; Cl, 10.61.

1-(4-Chlorophenyl)-7,8-dimethoxy-3-methyl-isoquinolinium-*N*-oxide (**12f**).

This compound was obtained as colourless crystals, mp. 230-232 °C (EtOH). Yield: 75 %; pmr (DMSO-d_6, 250 MHz): 2.60 (s, 3H), 3.21 (s, 3H), 3.93 (s, 3H), 7.34 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.3-7.5 (m, 5H), 7.61 (s, 1H); cmr (DMSO-d_6, 62.5 MHz): 17.9, 56.5, 60.3, 116.6, 122.6, 122.7, 123.8, 124.9, 128.0, 130.2, 133.4, 134.1, 141.3, 142.5, 143.7, 151.3.

Anal. Calcd. for $C_{18}H_{16}ClNO_3$ (329.78): C, 65.56; H, 4.89; N, 4.25; Cl, 10.75. Found: C, 65.61; H, 4.94; N, 4.14; Cl, 10.57.

3-Methyl-7,8-methylenedioxy-1-phenyl-isoquinolinium-*N*-oxide (**12h**).

This compound was obtained as colourless crystals, mp. 228-230 °C (AcOH). Yield: 85 %; pmr (DMSO-d_6, 250 MHz): 2.60 (s, 3H,), 5.80 (s, 2H), 7.17 (d, J = 8.6 Hz), 7.29 (d, J = 8.6 Hz, 1H), 7.47 (s, 5H), 7.58 (s, 1H).

Anal. Calcd. for $C_{17}H_{13}NO_3$ (279.30): C, 73.11; H, 4.69; N, 5.01. Found: C, 73.07; H, 4.83; N, 4.89.

Acknowledgement.

The authors wish to express their thanks to Mrs. Dr. Sándorné Sólyom for recording the ir spectra, to Mrs. Magdolna Nagy and dr. István Kövesdi for recording the nmr spectra, to the late Mrs. Hirkóné Magdolna Csík for performing the elemental analyses and to Mrs. Éva Jóljárt, Mrs. Ildikó Szebelédi, Mrs. Tünde Jenei, Mrs. Birkásné Gyöngyi Mester and Mrs. Zsófia Vincze for technical help.

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