Chromium Trioxide Oxidation Products From 4-Spiro-1-phenylisochromans

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Chromium trioxide oxidation of 1-phenylisochroman-4-spiro-1′-cyclopentane (Ia) in acetic acid led to the expected 1-(2-benzoylphenyl)cyclopentanecarboxylic acid (IIa), while its 6,7-dimethoxy analogue Ib and 6,7-dimethoxy-1-phenylisochroman-4-spiro-4′-(1′-methyl)piperidine (Ic) under the same conditions gave a mixture of their related 1-hydroxy derivatives VIIIb and VIIIc and of the *p*-benzoquinones, 1-benzoyloxymethyl-1-(2,5-dioxo-4-methoxyphenyl)cyclopentane (IXb) and 1-benzoyloxymethyl-1-(2,5-dioxo-4-methoxyphenyl)-1-methylpiperidine (IXc). Cyclization of IIa with hydrazine or monomethylhydrazine led to the 5-spiro-substituted 1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones IIIa or XIa.

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An easy preparation of 2-benzoylphenylacetic acid, based on chromium trioxide oxidation of 1-phenylisochroman in acetic acid has been reported [1]. In order to obtain the corresponding 2-benzoylphenylacetic acids II as the starting materials for the synthesis of 5-spiro derivatives of 1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one (III), we submitted to this oxidation 1-phenylisochroman-4-spiro-1′-cyclopentane (Ia), its 6,7-dimethoxy derivative Ib and 6,7-dimethoxy-1-phenylisochroman-4-spiro-4′-(1′-methyl)-piperidine (Ic) (Figure 1).

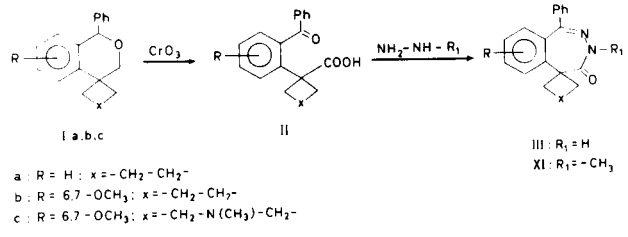


Figure 1

Compound Ia has been obtained from 1-hydroxymethyl-1-phenylcyclopentane (V) according to the synthetic pathway described for 1-phenylisochroman [2] (Figure 2).

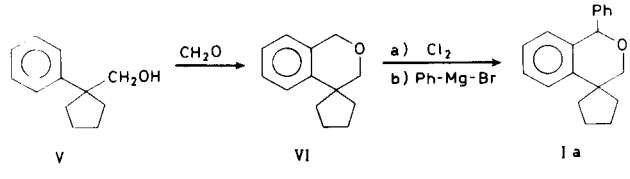


Figure 2

Compounds Ib and Ic have been prepared by condensation of benzaldehyde with 1-(3,4-dimethoxyphenyl)-1-hydroxymethylcyclopentane (VIIb) and with 4-(3,4-dimethoxyphenyl)-4-hydroxymethyl-1-methylpiperidine (VIIc) [3] in the presence of gaseous hydrogen chloride. (Figure 3).

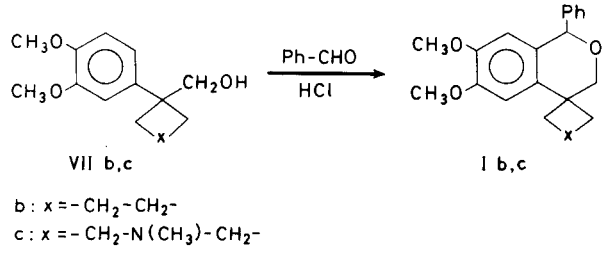


Figure 3

Among them, only Ia gave with chromium trioxide in acetic acid at 25-30° the expected 1-(2-benzoylphenyl)-cyclopentane carboxylic acid (IIa), while the same oxidation of Ib and Ic led to mixtures of the related 1-hydroxy derivatives VIIIb and VIIIc respectively, together with the quinone derivatives 1-benzoyloxymethyl-1-(2,5-dioxo-4-methoxyphenyl)cyclopentane (IXb) and 4-benzoyloxymethyl-4-(2,5-dioxo-4-methoxyphenyl)-1-methylpiperidine (IXc) (Figure 4).

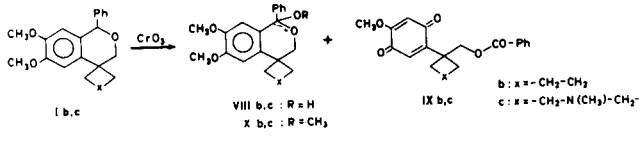
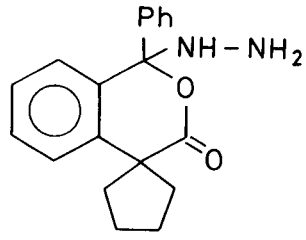


Figure 4

The structures of compounds VIII and IX are supported by chemical evidence and by ir and ^{1}H-nmr spectra. When refluxed in methanol, VIII gave smoothly the corresponding 1-methoxy derivatives X, while alkaline hydrolysis of IX led to benzoic acid. The ir spectra (nujol) of compounds VIII show the ν OH band at 3350 cm^{-1} while for compounds IX the ester ν CO band at 1720 cm^{-1} and the quinone ν CO bands at 1670 and 1640 cm^{-1} are present. The nmr and ms spectra are also in agreement with the proposed structures (see Experimental).

As expected, 1-(2-benzoylphenyl)cyclopentanecarboxylic acid (IIa) condensed with hydrazine or monomethylhydr-

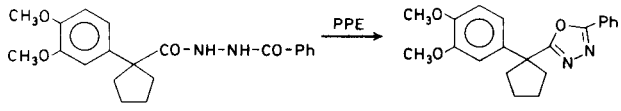
azine to give 1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one-5-spiro-1′-cyclopentane (IIIa) or its corresponding 3-methyl derivative XIa (Figure 1). From the reaction of IIa with hydrazine, in addition to IIIa, a by-product was isolated and identified as 1-hydrazino-1-phenyl-4-spiro-1′-cyclopentaneisochroman-3-one (XII). When XII was heated at 150° at 0.3 mm for 30 minutes, it was converted in nearly quantitative yield to the benzodiazepine IIIa (Figure 5).



XII

Figure 5

An attempted cyclization of 1-(3,4-dimethoxyphenyl)-cyclopentanecarboxylic acid benzoylhydrazide with polyphosphoric esters (PPE) aimed at preparing the 7,8-dimethoxy-2,3-benzodiazepin-4-one (IIIb) gave instead 1-(3,4-dimethoxyphenyl)-1-[2-(5-phenyl-1,3,4-oxadiazolyl)]-cyclopentane XIV (Figure 6).



XIII XIV

Figure 6

The nmr, ms and microanalytical data supported the structures of the above mentioned compounds (see Experimental).

The 2,3-benzodiazepin-4-ones IIIa and XIa have been submitted for preliminary pharmacological assay in order to check their ability to displace ^{3}H-diazepam from brain benzodiazepine binding sites. Concentrations ranging from 10^{-8} to $10^{-4}M$ have been employed according to a published method [4]. Under these conditions the two compounds did not inhibit specific ^{3}H-diazepam binding.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 580 spectrometer. The ^{1}H-nmr spectra were obtained using a Varian T-60 spectrometer with tetramethylsilane as an internal standard (deuteriochloroform solutions, ppm in δ units). Electron ionization ms were recorded on a LKB 2091 equipped with a digital PDP 11 data processing system, samples applied by direct inlet and probe usually heated from 25-200°, 70 eV. Column chromatography was carried out using Merck silica gel 70-230 mesh; tlc was performed on silica gel plates (Merck GF_{254}). Anhydrous sodium sulfate was used as drying agent.

1-Ethoxycarbonyl-1-phenylcyclopentane (IV).

To a stirred suspension of sodium hydride (50% in oil, 11.4 g, 0.24 mole) in anhydrous dimethylformamide (100 ml) a solution of ethyl phenylacetate (16.4 g, 0.1 mole) and 1,4-dibromobutane (23.8 g, 0.11 mole) in a mixture of anhydrous dimethylformamide (50 ml) and ethyl ether (50 ml) was added dropwise at a temperature of 30°. The reaction mixture was first stirred for 6 hours at room temperature, then cooled in ice water and 2-propanol (30 ml) added, then poured into water and extracted with ethyl acetate. After solvent removal, the oily residue was distilled and the fraction boiling at 140-147°/14 mm collected, yield 12.5 g (57%), lit [5] bp 121°/9 mm.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.82; H, 8.38.

1-Hydroxymethyl-1-phenylcyclopentane (V).

The product was obtained in 81% yield by lithium aluminum hydride reduction of IV in refluxing anhydrous ethyl ether for 3 hours as a colorless liquid, bp 147-151°/14 mm.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.60; H, 9.22.

Isochroman-4-spiro-1′-cyclopentane (VI).

A mixture of V (5 g), 40% formaldehyde (5 ml) and acetic acid (15 ml) was boiled for 1 hour. After cooling, the mixture was first made alkaline with diluted aqueous sodium hydroxide, then extracted with ethyl ether and the solvent removed. The resulting oily residue was distilled giving a colorless liquid, bp 145-150°/14 mm, yield 4.8 g (89%).

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.12; H, 8.56.

1-Phenylisochroman-4-spiro-1′-cyclopentane (Ia).

A gentle stream of chlorine was allowed to bubble into 10 g of VI cooled at −5° until a constant weight was obtained. Excess chlorine was removed at reduced pressure by heating at no more than 35-40°. The crude 1-chloroisochroman-4-spiro-1′-cyclopentane thus obtained was dissolved in anhydrous ethyl ether (50 ml) and added dropwise to a cooled (−10°) ether solution of phenyl magnesium bromide (prepared from 18.2 g of bromobenzene and 2.8 g of magnesium turnings). The mixture was stirred for 6 hours at room temperature and allowed to stand overnight, then cooled externally with ice water, and cautiously acidified with diluted hydrochloric acid. The separated ether layer after solvent evaporation gave an oily residue which was distilled and the fraction boiling at 147-150°/0.5 mm was collected, yield 9 g (64%) of a colorless viscous liquid; nmr: 7.32 (broad, aromatics, 5 H), 6.83 (m, aromatics, 4 H), 5.77 (s, -C*H*, 1H), 3.70 (AB system, CH_2, 2 H), 1.83 (m, cyclopentane, 8 H).

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.10; H, 7.72.

1-(3,4-Dimethoxyphenyl)-1-hydroxymethylcyclopentane (VIIb).

This compound has been prepared according to the procedure described for V by lithium aluminum hydride reduction of 1-(3,4-dimethoxyphenyl)-1-ethoxycarbonylcyclopentane (the latter compound, bp 120-125°/0.2 mm, has been obtained in a 64% yield from ethyl 3,4-dimethoxyphenylacetate and 1,4-dibromobutane in the same manner as its analogue IV), bp 128-130°/0.2 mm, yield 77%.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.92; H, 8.38.

6,7-Dimethoxy-1-phenylisochroman-4-spiro-1′-cyclopentane (Ib). 6,7-Dimethoxy-1-phenylisochroman-4-spiro-4′-(1′-methyl)piperidine (Ic).

A solution of each compound VII (0.02 mole) and benzaldehyde (2.6 g, 0.025 mole) in anhydrous dioxane (20 ml) was first saturated with gaseous hydrogen chloride, then refluxed for 1 hour. After cooling, the mixture was poured into water, made alkaline with diluted sodium hydroxide, and extracted with ethyl acetate. The solvent was removed, and the resulting residue distilled.

Compound Ib.

This compound had bp 155-160°/0.2 mm, mp 73-75° (from methanol), yield 89%; nmr: δ 7.37 (broad, aromatics, 5 H), 6.90 (s, aromatic, 1 H), 6.27 (s, aromatic, 1 H), 5.80 (s, C*H*-C_6H_5, 1 H), 3.98 and 3.73 (two s, -OCH_3, 6 H), 3.77 (AB system, -CH_2, 2 H), 1.95 (m, cyclopentane protons, 8 H).

Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.77; H, 7.46. Found: C, 77.94; H, 7.65.

Compound Ic.

This compound had bp 160-170°/0.05 mm, hydrochloride mp 300-305° (from ethanol), yield 83%; nmr of the hydrochloride (DMSO-d_6): δ 7.41 (broad, aromatics, 5 H), 7.27 (broad, aromatic, 1 H), 6.27 (s, aromatic, 1 H), 5.80 (s, -C*H*-C_6H_5, 1 H), 4.12 (AB system, isochroman -CH_2-, 2 H), 3.92 and 3.63 (two s, -OCH_3, 6 H), 2.92 (s, N-CH_3, 3 H), 3.80-1.60 (m, piperidine protons, 8 H).

Anal. (hydrochloride) Calcd. for $C_{22}H_{28}ClNO_3$: C, 67.76; H, 7.23; N, 3.59. Found: C, 68.01; H, 6.97; N, 3.60.

1-(2-Benzoylphenyl)cyclopentanecarboxylic Acid (IIa).

A solution of chromium trioxide (3 g, 0.03 mole) in a mixture of water (3 ml) and acetic acid (15 ml) was added dropwise under stirring to a solution of Ia (2.7 g, 0.01 mole) in acetic acid (30 ml), keeping the temperature at 30-35°. After 2 hours at room temperature, the mixture was poured into water and extracted with chloroform. The organic layer was shaken with 10% sodium hydroxide, and the separated alkaline aqueous phase was acidified with diluted hydrogen chloride and extracted with chloroform. Removal of the latter gave crude IIa, yield 2 g (67%), mp 187-189° (from ethanol): ir (nujol): ν CO (carboxyl) 1710 cm^{-1}, ν CO (ketone) 1670 cm^{-1}.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.30; H, 6.22.

6,7-Dimethoxy-1-hydroxy-1-phenylisochroman-4-spiro-1′-cyclopentane (VIIIb) and 1-Benzoyloxymethyl-1-(2,5-dioxo-4-methoxyphenyl)cyclopentane (IXb).

Compound Ib (3.2 g, 0.01 mole) was oxidized with chromium trioxide (3 g, 0.03 mole) in the same manner described for Ia. The crude product resulting from evaporation of the chloroform was chromatographed on a silica gel column with a 1:2 ethyl acetate-*n*-hexane mixture as the eluent. Compound IXb eluted first, followed by VIIIb.

Compound VIIIb.

This compound was obtained in a yield of 0.7 g (21%), mp 135-138° (from benzene-*n*-hexane); ms: 340 (M^+, 48), 323 (M − 17, 54), 264 (20), 263 (100), 245 (65), 217 (26), 195 (31), 105 (81), 91 (21), 77 (73), 51 (16).

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.30. Found: C, 73.87; H, 7.00.

Compound IXb.

This compound was obtained in a yield of 1.1 g (33%), yellow crystals mp 137-139° (from ethanol); nmr: δ 7.96 (m, aromatics, 2 H), 7.40 (m, aromatics, 3 H), 6.70 and 6.00 (two s, benzoquinone aromatics, 1 H each), 4.57 (s, -CH_2-OCO-, 2 H), 3.93 (s, -OCH_3, 3 H), 1.92 (m, cyclopentane protons, 8 H); ms: 340 (M^+, 3), 311 (M -CHO, 30), 218 (M -C_6H_5COOH, 21), 106 (18), 105 ($C_6H_5CO^+$, 100), 91 (12), 77 (89), 69 (25), 51 (21).

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.39; H, 6.08.

6,7-Dimethoxy-1-hydroxy-1-phenylisochroman-4-spiro-4′-(1′-methyl)piperidine (VIIIc) and 4-Benzoyloxymethyl-4-(2,5-dioxo-4-methoxyphenyl)-1-methylpiperidine (IXc).

Compound Ic (3.5 g, 0.01 mole) was oxidized with chromium trioxide (3 g, 0.03 mole) by the same procedure. The resulting reaction mixture was first cautiously added to 2-propanol (20 ml), concentrated under diminished pressure at 50-60°, made alkaline with diluted sodium hydroxide and extracted with chloroform. The residue obtained after solvent removal was chromatographed on a silica gel column eluting with ethyl acetate. Compounds IXc and VIIIc were thus successively collected.

Compound VIIIc.

This compound was obtained in a yield of 0.9 g (25%), mp 116-119° (from benzene-cyclohexane); ms: 369 (M^+, 25), 352 (M − 17, 21), 351 (M − 18, 42), 105 (40), 77 (36), 71 (59), 70 (100), 58 (27), 44 (70), 43 (51), 42 (59).

Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37. N, 3.79. Found: C, 71.71; H, 7.61; N, 3.49.

Compound IXc.

This compound was obtained in a yield of 1.5 g (40%), yellow crystals mp 149-151° (from ethanol); nmr: δ 7.90 (m, aromatics, 2 H), 7.38 (m, aromatics, 3 H), 6.66 and 5.98 (two s, benzoquinone aromatics, 1 H each), 4.70 (s, -CH_2-OCO, 2 H), 3.83 (s, -OCH_3, 3 H), 2.28 (s, N-CH_3, 3 H), 2.63-1.98 (m, piperidine protons, 8 H); ms: 369 (M^+, 28), 234 (M − 135, 14), 105 ($C_6H_5CO^+$, 48), 96 (21), 77 (51), 70 (100), 57 (18), 51 (13), 44 (23), 42 (43).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.30; H, 6.25; N, 3.57.

6,7-Dimethoxy-1-methoxy-1-phenylisochroman-4-spiro-1′-cyclopentane (Xb) and 6,7-Dimethoxy-1-methoxy-1-phenylisochroman-4-spiro-4′-(1′-methyl)piperidine (Xc).

These compounds were obtained by a 10 minute heating period at reflux of VIII (1 g) dissolved in methanol (10 ml) and crystallization from the methanolic mother liquor.

Compound Xb.

This compound was obtained in a yield of 0.9 g (88%), mp 95-97°; nmr: δ 7.60 (m, aromatics, 2 H), 7.37 (m, aromatics, 3 H), 6.73 and 6.60 (two s, aromatics, 1 H each), 3.85 and 3.53 (two s, -OCH_3 of positions 6 and 7, 3 H each), 3.60 (AB system, isochroman -CH_2-, 2 H), 3.33 (s, OCH_3 of position 1, 3 H), 1.85 (m, cyclopentane protons, 8 H).

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.82; H, 7.30.

Compound Xc.

This compound was obtained in a yield of 0.8 g (80%), mp 113-115°; nmr: δ 7.58 (m, aromatics, 2 H), 7.33 (m, aromatics, 3 H), 7.00 and 6.52 (two s, aromatics, 1 H each), 4.12 (s, isochroman -CH_2-, 2 H), 3.83 and 3.67 (two s, -OCH_3 of positions 6 and 7, 3 H each), 3.42 (s, OCH_3 of position 1, 3 H), 2.25 (s, -N-CH_3, 3 H), 3.00-1.30 (m, piperidine protons, 8 H).

Anal. Calcd. for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.65. Found: C, 71.88; H, 7.58; N, 3.64.

1-Phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one-5-spiro-1′-cyclopentane (IIIa), 3-Methyl-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one-5-spiro-1′-cyclopentane (XIa) and 1-Hydrazino-1-phenyl-4-spiro-1′-cyclopentane-isochroman-3-one (XII).

1-(2-Benzoylphenyl)cyclopentane carboxylic acid (IIa) (1 g) and 98% hydrazine hydrate or monomethylhydrazine (0.4 g) were refluxed for 3 hours in ethyleneglycol monomethyl ether (10 ml). After cooling the solvent was removed and the residue obtained was chromatographed on a silica gel column eluting with an ethyl acetate-*n*-hexane mixture (1:2). Compound IIIa was eluted first followed by XII.

Compound IIIa.

This compound was obtained in a yield of 0.6 g (61%), mp 165-167° (from ethanol); ms: 290 (M^+, 96), 261 (M − 29, 78), 233 (M − 57, 100), 191 (32), 165 (32), 155 (31), 129 (98), 115 (34), 91 (44), 77 (41).

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.38; H, 6.24; N, 9.63.

Compound XIa.

This compound was obtained in a yield of 0.8 g (77%), mp 130-132° (from 2-propanol-petroleum ether); ms: 304 (M^+, 54), 261 (M − 43, 47), 233 (M − 71, 51), 129 (100), 117 (32), 115 (57), 91 (40), 77 (31).

Anal. Calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found; C, 78.88; H, 6.49; N, 9.31.

Compound XII.

This compound was obtained in a yield of 0.2 g (20%), mp 133-135° (from benzene-*n*-hexane); nmr: δ 7.30 (m, aromatics, 9 H), 4.17 (broad, N*H*-NH_2, 3 H), 2.60 (m, cyclopentane, 2 H), 2.02 (m, cyclopentane, 6 H); ms: 308 (M^+, 3), 277 (M − 31, 62), 249 (M − 59, 100), 231 (20), 205 (16), 178 (20), 165 (17), 153 (24), 128 (16), 115 (25), 91 (26), 77 (38), 51 (15).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.71; H, 6.44; N, 9.07.

1-(3,4-Dimethoxyphenyl)cyclopentanecarboxylic Acid Benzoylhydrazide (XIII).

1-(3,4-Dimethoxyphenyl)cyclopentane carboxylic acid (5 g, 0.02 mole, obtained by alkaline hydrolysis of its ethyl ester IV, mp 141-143° from benzene) in anhydrous benzene (50 ml) was allowed to react for 3 hours at room temperature with thionyl chloride (10 ml). After removal of the solvent and excess thionyl chloride, the resulting residue was dissolved in absolute chloroform (20 ml) and added dropwise with stirring to a cooled solution of benzoylhydrazine (2.7 g, 0.02 mole) and triethylamine (2.1 g, 0.02 mole) in absolute chloroform (30 ml) and allowed to react at room temperature for 1 hour. The mixture was then washed successively with water, diluted hydrogen chloride, diluted sodium hydroxide and once more with water. Removal of the chloroform gave a residue which was crystallized from benzene, yield 5.8 g (79%), mp 143-145°.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.16; H, 6.50; N, 7.72.

1-(3,4-Dimethoxyphenyl)-1-[2-(5-phenyl-1,3,4-oxadiazolyl)]cyclopentane (XIV).

A mixture of 1 g of XIII and 4 g of polyphosphoric esters [6] in absolute chloroform (30 ml) was refluxed for 1 hour. After cooling, the reaction mixture was washed with water and the chloroform removed under the diminished pressure. The resulting crude product was chromatographed on a silica gel column eluting with an ethyl acetate-*n*-hexane mixture (1:2), yield 0.8 g (86%), mp 97-98° (from benzene-*n*-hexane); nmr δ 7.98 (m, aromatics, 2 H), 7.45 (m, aromatics, 3 H), 6.94 (m, aromatics, 3 H), 3.94 (s, OCH_3, 6 H), 2.94 (m, cyclopentane, 2 H), 2.04 (m, cyclopentane, 6 H).

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.86; H, 6.31; N, 7.77.

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