

Institute for Drug Research, Budapest, P.O. Box 82, H-1325, Hungary
Received December 2, 1996

Dedicated to Professor Miha Tišler on the occasion of his 70th birthday

Reaction of 2-acetyl-4,5-dimethoxy-3'-chlorobenzophenone (**1**) with ethylenediamine afforded the imidazo[2,1-*a*]isoquinoline **2**, whereas 6-(3-chlorophenyl)-8,9-dimethoxybenzo[*b*]phenazine (**3**) and naphthol **4** were obtained with *ortho*-phenylenediamine.

J. Heterocyclic Chem., **34**, 1033 (1997).

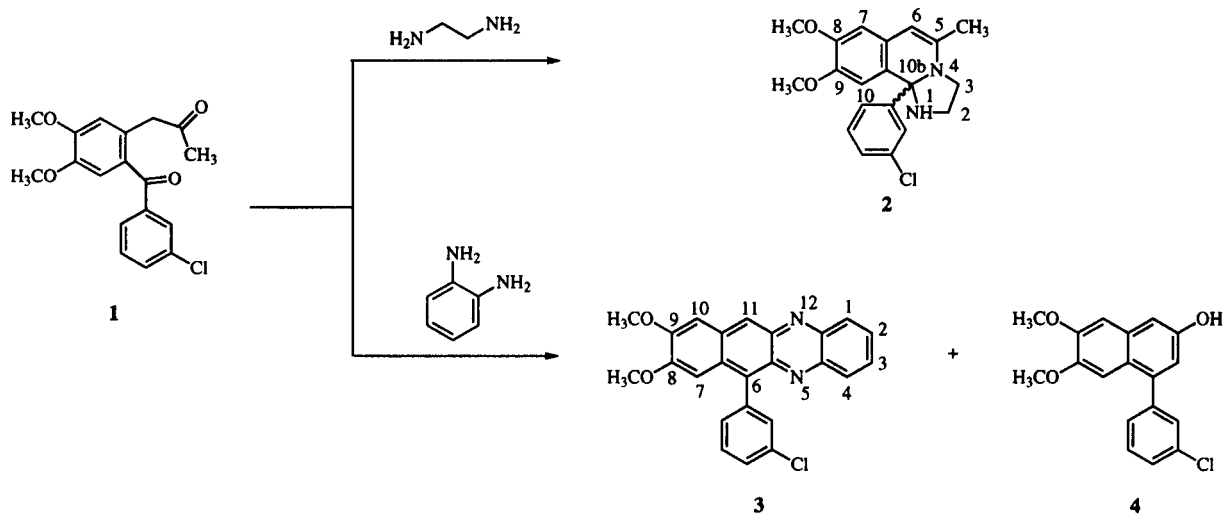
The discovery that some [2,3]benzodiazepines as selective non-competitive antagonists at the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors may have an important place in the treatments of various neurological disorders has recently stimulated extensive structure-activity relationship studies on this class of compounds [1].

A facile and powerful synthesis of 5*H*-[2,3]benzodiazepines was accomplished by cyclocondensation reaction of the easily available 1,5-benzodiketones with hydrazine hydrate [2]. With the aim of exploring the scope of this heterocyclization, in connection with our interest towards the structurally related [2,5]benzodiazonines [3], we report here on the reaction of diketone **1** with ethylenediamine and *ortho*-phenylenediamine.

Treatment of **1** with one equivalent of ethylenediamine in refluxing toluene in the presence of *p*-toluenesulfonic acid as a catalyst gave, instead of the expected benzodiazonine ring system, the imidazo[2,1-*a*]isoquinoline derivative **2** as only isolable product in 65% yield (Scheme 1). Structure of compound **2** was deduced from ¹H, ¹³C nmr, and ir spectra, and from microanalysis.

The ¹H nmr data showed one *C*-methyl, two methoxy and one olefinic singlets at δ 2.12, 3.80, 3.85 and 5.25 ppm, respectively. In the range of 2.9 to 3.5 ppm there was indication of four protons, two of which appeared as a multiplet centered at *ca.* 3.5 ppm, whereas the two remaining protons gave signals characteristic for an axial-equatorial proton-pair [*ax*, 2.90 (*J* = 12.4, 7.9, 7.9 Hz), and *eq*, 3.15 ppm (12.5, 6.9, 4.2)]. The aromatic protons could also be clearly assigned (see Experimental) by their multiplicity and NOE experiments (Figure 1). The NH proton also gave an identifiable signal at 2.40 ppm. In the ¹³C nmr spectrum, all signals appeared in the expected ranges. The methine, methylene and methyl signals were assigned unambiguously from the HETCOR spectrum. Assignments of quaternary carbons C-5, C-10a, C-6a and C-10b at 139.2, 121.7, 126.4 and 82.5 ppm, respectively, were fully proven by semiselective INEPT measurements [4] optimized to a heteronuclear coupling constant of 7 Hz. Finally, the ir spectrum, and microanalytical data were also consistent with the structure proposed.

Scheme 1



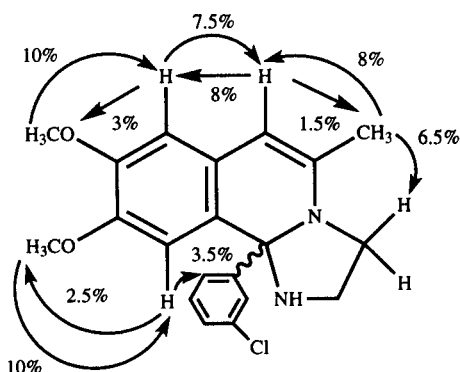


Figure 1. NOE Measurements for compound 2.

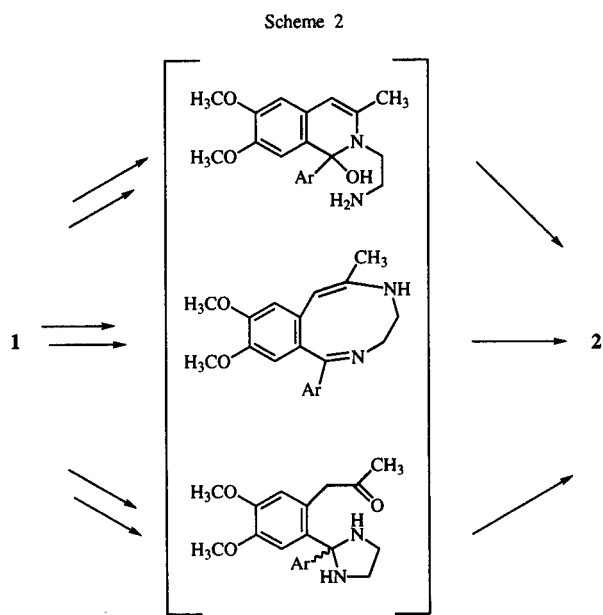
Next, compound **1** was treated with one equivalent of *ortho*-phenylenediamine, as a prototype of aromatic 1,2-diamines, under identical conditions as described above. In this case, however, the unreacted starting materials only could be recovered. Interestingly enough, when the reaction was carried out without any catalyst in refluxing methanol, a novel benzo[*b*]phenazine, compound **3**, and the naphthol derivative **4** were isolated in 17 and 56% yields, respectively, and no formation of a nine-member ring or an analogous structure to **2** could be detected.

For structure **3**, ^1H and ^{13}C nmr spectra provided valuable information. In ^1H nmr, two methoxy singlets at 3.90 and 4.30 ppm, and eleven aromatic protons appeared at 7.3–8.4 and 8.95 ppm, whereas no *C*-methyl proton signal was present. Eleven quaternary and eleven methine carbons as well as two methoxy signals were also identified in the ^{13}C nmr spectrum. These data together with microanalytical data fully support the structure of **3**. The 6-phenylbenzo[*b*]phenazine (having no other substituents) has already been synthesized by a completely different route, and the singlet at H11 of that compound was identified at 8.95 ppm [5]; such a signal was also present in the spectrum of **3**.

The structure of **4** could be deduced from the ^1H nmr which showed two methoxy singlets at 3.75 and 3.92 ppm, eight aromatic protons in the range of 6.9–7.5 ppm, and one singlet at 6.0 ppm corresponding to the 2-hydroxy proton. Furthermore, the ^{13}C nmr was also in agreement with this structure. Although, formation of **4** from **1** *via* an intramolecular aldol reaction has already been observed by others [6], apparently, it has not been characterized yet.

Formations of **2** and **3** need some mechanistic considerations. Three possible routes are depicted on Scheme 2.

In the first, most reasonable route (*cf.* [7]), an isoquinoline intermediate may be formed by cyclocondensation of the carbonyls with one of the nitrogens of ethylenediamine. In the subsequent nucleophilic attack of the other nitrogen onto the quaternary carbon could then lead to the final product. In the second route, a dihydrobenzodiazine



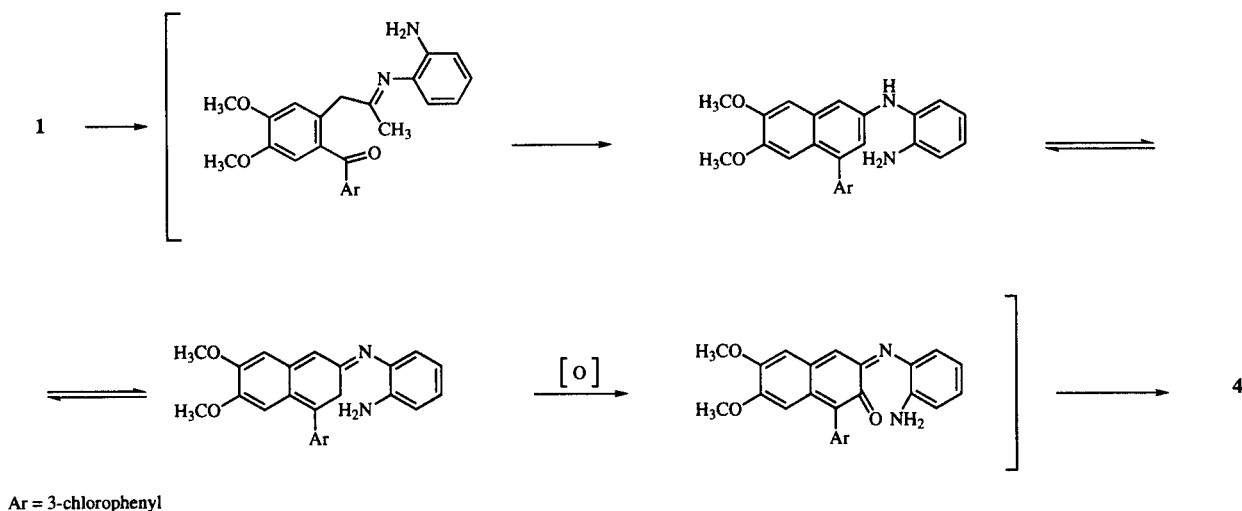
Ar = 3-chlorophenyl

none derivative (depicted in the 5*H*-tautomeric form) might be the intermediate from which **2** may be produced through a ring contraction. The third possible pathway involves a 2,2-diphenylimidazolidinyl aminal type intermediate formed by the reaction of diarylcarbonyl with ethylenediamine, which may be converted to the product by a nucleophilic attack of nitrogen onto the acetyl carbonyl followed by elimination of water. If such a mechanism operated, a linearly fused imidazo[1,2-*b*]isoquinoline isomer might have also been obtained in an analogous way by involvement of the acetyl carbonyl in the first step; such a compound could however be unambiguously excluded by spectroscopic data, and it is far less stable thermodynamically [8].

Formation of the benzo[*b*]phenazine derivative **3** may be interpreted *via* two different reaction pathways. Theoretically, the naphthol derivative **4** itself could have been served as a precursor by oxidation to a 2,3-naphthoquinone which upon reaction with *ortho*-phenylenediamine might yield **3**. But this route is of less if any significance, because in a separate experiment, when **4** was treated under identical conditions, formation of phenazine **3** could not be observed. Therefore, it is more reasonable that the oxidation step proceeds from the mono Schiff's base as proposed in Scheme 3.

The above findings indicate the need to elaborate another synthetic pathway and/or to incorporate a different substitution pattern for preparation of dihydro[2,5]-benzodiazines. On the other hand, reaction of diketone **1** with ethylenediamine represent a novel route to imidazo[2,1-*a*]isoquinolines, which may be of some value in the synthesis of derivatives substituted at position-10*b*.

Scheme 3



EXPERIMENTAL

All melting points were determined on a Boetius micro-melting point apparatus, and are uncorrected. The IR spectra were recorded on a Bruker IFS-85 FT-IR spectrometer in potassium bromide pellets, and frequencies are expressed in cm^{-1} . The NMR spectra were recorded on a Bruker AC-250 FT-NMR spectrometer at 250 MHz (^1H) and 62.9 MHz (^{13}C), at ambient temperature, in deuteriochloroform, using ^2H signal of the solvent as the lock and tetramethylsilane as the internal standard. Chemical shifts are given in ppm (δ) and J values in Hz. The signals are designated as follow: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; * and + symbols denote tentatively assigned and overlapping signals, respectively.

Elemental analyses (C,H,N) were performed on a Carlo Erba Elemental Analyzer Model 1012 apparatus. All analyses and spectroscopic measurements were done by the Analytical Department of Institute for Drug Research. Precoated silica gel plates (Merck) were used for thin layer chromatography. For column-chromatography silica gel 60 (Fluke No. 60738, size 0.035-0.070 mm, and No. 7734, size 0.063-0.200 mm for compounds **2**, **3** and **4**, respectively) was applied. Unless otherwise noted all reagents were purchased from commercial suppliers (Aldrich and Fluka) and used as received; solvents (Reanal, Hungary) were dried and distilled prior to use.

Compound **1** was prepared as reported [9].

10b-(3-Chlorophenyl)-8,9-dimethoxy-5-methyl-1,2,3,10b-tetrahydroimidazo[2,1-a]isoquinoline (**2**).

To a hot solution of *p*-toluenesulfonic acid (0.05 g) in toluene (120 ml), solutions of 2-acetyl-4,5-dimethoxy-3'-chlorobenzophenone (**1**) (1.00 g, 3.0 mmoles) in toluene (90 ml), and ethylenediamine (0.18 g, 3.0 mmoles) in toluene (90 ml) were simultaneously added. The reaction mixture was refluxed for 1.5 hours. The condenser was then supplied with a water trap, and the mixture was heated under reflux for an additional 2 hours.

Toluene was then decanted, and washed with water (2 x 20 ml), and dried over sodium sulfate. The yellow solution was evaporated to a final volume of ca. 10 ml in vacuum (2.6 x Pa) at 50°, and then it was purified by flash-column chromatography using a mixture of ethyl acetate:methanol:ammonium hydroxide (9:1:0.5) as eluting solvent under nitrogen atmosphere. The appropriate fractions were pooled and evaporated to dryness to obtain a yellow foam which upon trituration with petroleum ether (bp 40-70°) gave **2** as a yellow amorphous solid, yield 0.70 g (65%), mp 112-113°; ir: 3427, 1620, 1508, 1466, 1418, 1213; ^1H nmr: 2.12 (s, 3H, 5-CH₃), 2.40 (br, 1H, NH), 2.90 (ddd, J = 12.4, 7.9, 7.9, 1H, H_a2), 3.15 (ddd, J = 12.5, 6.9, 4.2, 1H, H_c2), 3.45-3.55 (m, 2H, H3), 3.80 (s, 3H, 8-OCH₃), 3.85 (s, 3H, 9-OCH₃), 5.25 (s, 1H, H6), 6.40 (s, 1H, H7), 7.00 (s, 1H, H10), 7.13 (dt, J = 7.3, 2.4, 1H, H4'), 7.18 (t, J = 7.3, 1H, H5'), 7.40 (dt, J = 7.3, 2.4, 1H, H6'), 7.50 (t, J = 2.4, 1H, H2'); ^{13}C nmr: 20.6 (C5-CH₃), 43.3 (C2), 48.7 (C3), 55.6 (8-OCH₃), 56.2 (9-OCH₃), 82.5 (C10b), 96.3 (C6), 105.6 (C7), 108.4 (C10), 121.7 (C10a), 123.4 (C6'), 125.2 (C2'), 126.4 (C6a), 127.1 (C4'), 129.4 (C5'), 133.9 (C3'), 139.2 (C5), 146.6 (C9), 148.1 (C1'), 148.6 (C8).

Anal. Calcd. for C₂₀H₂₁ClN₂O₂: C, 67.32; H, 5.89; N, 7.85. Found: C, 67.07; H, 6.04; N, 7.56.

6-(3-Chlorophenyl)-8,9-dimethoxybenzo[*b*]phenazine (**3**) and 4-(3-Chlorophenyl)-6,7-dimethoxy-2-naphthol (**4**).

To a solution of 1,5-diketone **1** (1.65 g, 5 mmoles) in methanol (15 ml) *ortho*-phenylenediamine (0.5 g, 5 mmoles) was added. The mixture was stirred under reflux for 16 hours. After cooling, the yellow precipitate was filtered and washed with methanol. The crude compound **3** (0.50 g) thus obtained was purified by column chromatography using a mixture of hexane:ethylacetate (1:1) as eluent, to give pure **3** (R_f = 0.8) as bright yellow solid, yield 0.35 g (18%), mp 215-220°; ir: 1605, 1504, 1273, 1213; ^1H nmr: 3.90 (s, 3H, OCH₃), 4.30 (s, 3H, OCH₃), 7.30 (s, 1H), 7.50-7.60 (m, 3H), 7.70 (br, 1H), 7.84-7.92 (m, 3H) (H2*, H3*, H7*, H10*, H2', H4', H5', H6'), 8.28 (m, 1H), 8.40 (m, 1H), (H1*, H4*), 8.95 (s, 1H, H11); ^{13}C nmr:

55.9, 56.3 (2 x OCH₃), 106.3, 107.3 (C7*, C10*), 125.7, (C11), 126.0, 127.1 (C6a*, C10a*), 127.6, 128.3, 129.2, 129.4, 129.6, 129.6, 129.7, 129.8 (C1*, C2*, C3*, C4*, C2', C4', C5*, C6'), 134.6 (C3'), 141.5, 141.6, 142.0, 142.5, 142.8, 142.9 (C4a*, C5a*, C6*, C1*, C11a*, C12a*).

Anal. Calcd. for C₂₄H₁₇ClN₂O₂: C, 71.90; H, 4.27; N, 6.99; Cl, 8.84. Found: C, 71.60; H, 4.14; N, 6.87; Cl, 8.92.

The mother liquor of crude **3** obtained above was evaporated to dryness in vacuum, and the residue was purified by column chromatography using a mixture of hexane:ethyl acetate (1:1) as eluent. Fractions (R_f = 0.7) were pooled, and evaporated to give pure **4** as white powder, yield 0.90 g (56%), mp 188-191°; ir: 3449, 1589, 1510, 1493, 1394, 1275, 1254, 1207; ¹H nmr: 3.75 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 6.00 (br, 1H, OH), 6.90 (d, J = 2.5, 1H, H3), 7.00 (s, 1H), 7.05 (s, 1H) (H5*, H8*), 7.10 (d, J = 2.5, 1H, H1), 7.30-7.45 (m, 3H, H4⁺, H5⁺, H6⁺), 7.48 (m, 1H, H2'); ¹³C nmr: 55.6, 55.7 (2 x OCH₃), 104.6, 105.6 (C5*, C8*), 109.1 (C1), 116.6 (C3), 121.9 (C4a), 127.4, 127.7, 129.5, 129.6 (C2', C4', C5', C6'), 131.1 (C8a), 134.2 (C3'), 139.0 (C4), 142.3 (C1'), 147.7 (C2), 149.8, 151.9 (C6*, C7*).

Anal. Calcd. for C₁₈H₁₅ClO₃: C, 68.60; H, 4.80. Found: C, 68.50; H, 4.62.

After complete removal of **4** from the column, a further elution gave the unreacted *ortho*-phenylenediamine (R_f = 0.3, 0.25 g, 46%).

Acknowledgment.

We thank Dr. F. Andrási (Pharmacological Department) for discussion, and appreciate his continuous interest in this work.

REFERENCES AND NOTES

- [1] E. S. Vizi, A. Mike and I. Tarnawa, *CNS Drug Rev.*, **2**, 91 (1996).
- [2] French Patent 2,566,774; *Chem. Abstr.*, **105** 133915k (1986).
- [3] A very few 2,5-benzodiazinones have been described thus far, see, US Patent 3,551,411; *Chem. Abstr.*, **75**, P 5976f (1971); US Patent 3,655,648; *Chem. Abstr.*, **77**, P 48637x (1972); T. Kitano, N. Shirai, M. Motoi and Y. Sato, *J. Chem. Soc. Perkin Trans. 1*, 2851 (1992); A. P. Kozikowski, D. Ma, Y.-P. Pang, P. Shum, V. Likic, P. K. Mishra, S. Macura, A. Basu, J. S. Lazo and R. G. Ball, *J. Am. Chem. Soc.*, **115**, 3957 (1993).
- [4] A. Bax, *J. Magn. Reson.*, **57**, 314 (1984).
- [5] E. J. Moriconi, R. E. Misner and T. E. Brady, *J. Org. Chem.*, **34**, 1651 (1969).
- [6] I. Hornyák, I. Kása, T. Hámori and J. Kőrösi, *Anal. Chim. Acta*, **227**, 311 (1989).
- [7] C. Germani, *Boll. Chim. Farm.*, **110**, 24 (1971).
- [8] The semiempirical AM1 calculations (SPARTAN, Wavefunction) gave $\Delta H_f^{\text{form}} = 14.77$ and 27.21 kcal/mol values for the fully optimized angular and linear isomers, respectively.
- [9] Hungarian Patent 194,529; *Chem. Abstr.*, **105**, 152712h (1986).