REACTION OF 2-(2-AMINO-4-NITROANILINO)ETHANOL WITH 3-DIMETHYLAMINOPROPIOPHENONES

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Abstract: The reaction of 2-(2-amino-4-nitroanilino)ethanol **5** with 3-dimethylaminopropiophenones **6** is being investigated, aimed to obtain new 1,5-benzodiazepine derivatives. However, mixtures of unpredictable products are being obtained: 1-aryl-3-({2-[2-hydroxyethyl)amino]-5-nitrophenyl}amino)propan-1-ones **7**, hexahydroazeto[1,2-a][1,5]benzo-diazepines **8**, dihidrobenzimidazoles **9**, acetylated products **10** and tetrahydrobenzodiazepines **11**. All structures of the new compounds were determined on the basis of nmr measurements, especially by $^{1}H,^{1}H$- and $^{1}H,^{13}C$ COSY, DEPT, HSQC, HMBC and NOESY.

Introduction

Benzodiazepines are interesting compounds because of their pharmacological properties [1]. Many members of this family are nowadays widely used as tranquilizing and anticonvulsant agents. Condensation of α,β-unsaturated carbonyl compounds [2] and its precursors (such as dimethylaminopropiophenones) [3], reaction of β-haloketones [4] or condensation of methyl ketones in acidic media [5] with *o*-phenylenediamines have been reported as convenient methods for the synthesis of 1,5-benzodiazepines. Recently, we have described the synthesis of diazepine derivatives **1-4** in good yields [3c,6], starting from aromatic and hetero-aromatic 1,2-diamines and 3-dimethylaminopropiophenones **6** (fig. 1).

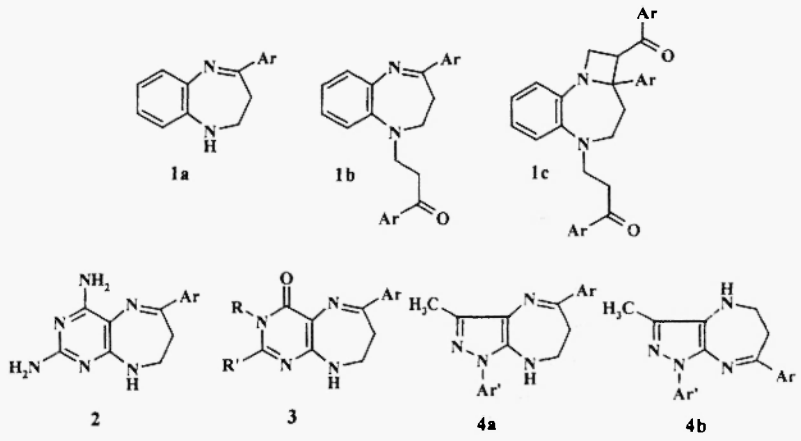
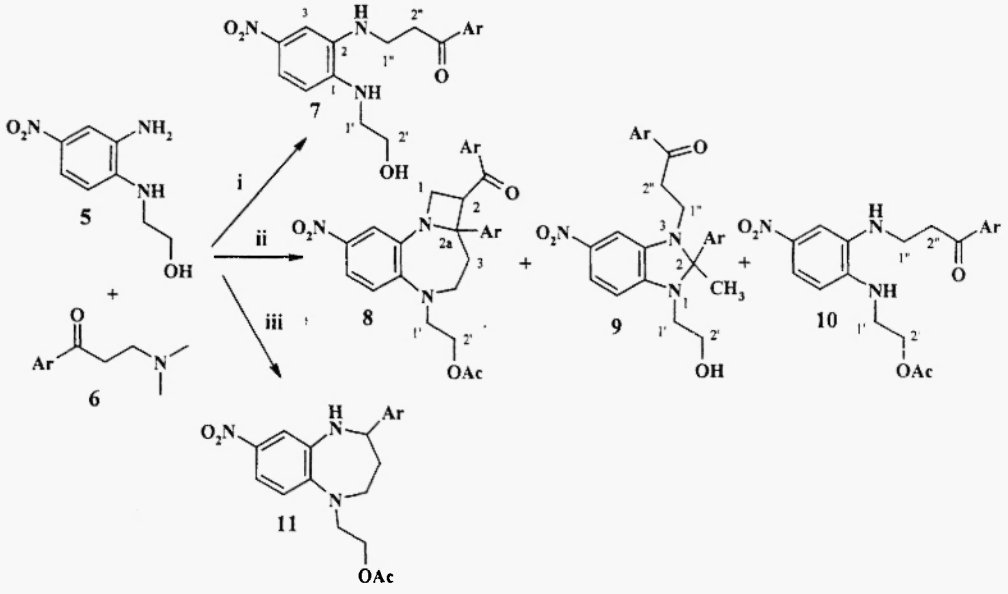


Figure 1. 1,5-Diazepine derivatives obtained from the reaction of 3-dimethylaminopropiophenones and aromatic 1,2-diamines

Results and Discussion

Continuing with our studies on the synthesis of fused diazepines from the reaction of *o*-diamines with 3-dimethylaminopropiophenones [3c,6], in this work, we are investigating the behavior of the *o*-phenylenediamine **5** (bearing the electronwithdrawing nitro and 2-

hydroxiethyl groups) in the reaction with 3-dimethylaminopropiophenones **6**. We are observing that this amine does not behave as simple as seems in the reaction proposed, and contrary, mixtures of unpredictable products are being obtained. A first experiment was carried out by refluxing the diamine **5** with one equivalent of *p*-methyl-3-dimethylaminopropiophenone hydrochloride **6a** in absolute ethanol during 30 min [7]. The product formed was characterized by nmr spectroscopy [7] as the N-alkylation product of the diamine **5**, 1-(*p*-methylphenyl)-3-({2-[2-hydroxyethyl)amino]-5-nitrophenyl}amino)-propan-1-one **7a** (Scheme 1). The subsequent cyclization to the expected benzodiazepine by continuous heating (6-10 hours) of compound **7a**, in different solvents (ethanol, acetic acid, DMF or DMSO) was unsucessful probably due to the low nucleophilicity of the secondary amino group.



Scheme 1. i) EtOH, 2 h; ii) glacial acetic acid, 30 min; iii) glacial acetic acid, 6 h.

Ar = a) $CH_3C_6H_4$, b) C_6H_5, c) 4-ClC_6H_4, d) 4-BrC_6H_4, e) 4-$O_2NC_6H_4$

A second experiment was carried out by refluxing diamine **5** with one equivalent of propiophenone **6a** in glacial acetic acid during 30 min [8] (Scheme 1). In this case three unpredicted products **8a** [9], **9a** [710] and **10a** [11] were obtained, separated by column chromatography and characterized by nmr spectroscopy. Compound **8a** corresponds to the expected 1,5-benzodiazepine which suffered (under our reaction conditions) the cycloaddition of a second molecule of the propiophenone **6a**. This process have already been described for us in a previous work [3c]. Compound **9a** apparentely corresponds to the product of the cyclocondensation of diamine with the carbonyl group of the propiophenone, losing a formaldehyde molecule (retro-Mannich reaction) and subsequent N-alkylation with a second molecule of propiophenone. While compound **10a** which is analogue to compound **7a** suffered an esterification process with participation of the solvent. The heating of the mixture of **5** and **6a** in glacial acetic acid during 6 hours carried out to formation of the unexpected tetrahydrobenzodiazepine **11a**, which was completly characterized by spectroscopical techniques [12]. Presumably, formation of this compound (although, it is not well stablished

yet) was carried out by a rupture of the 4-members ring from compound **8a**, accompanied by a reduction process under the reaction conditions.

In summary, until now, we are established that this unexpected behavior of amine **5** it is general for different *p*-substituents in propiophenones **6** (see scheme 1). Work is currently in progress to determine appropriate conditions of the reaction between **5** and **6**, to afford the targeted 1,5-benzodiazepines type **1a** (Fig. 1).

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7. Generai procedure for synthesis of compound **7a**: A solution of equimolar amounts of 2-(2-amino-4-nitroanilino)ethanol **5** (700 mg, 3.55 mmol) and 3-dimethylamino-*p*-methylpropiophenone **6** in 15 ml of absolute ethanol was heated to reflux for 2 hours. The precipitate formed was filtered, washed with ethanol and recrystallized from ethanol. This compound was obtained as red crystals, mp 164 °C, yield 55%. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 343 (10), 343 (26, M^+), 208 (20), 197 (35), 178 (45), 166 (63), 164 (15), 146 (30), 134 (12), 131 (14), 120 (44),119 (100), 118 (16), 105 (12), 93 (11), 92 (18), 91 (95), 78 (20), 65 (67), 55 (35), 51 (26), 43 (29), 39 (74). ^{1}H nmr (300 MHz, DMSO): 2.39 (s, CH_3), 3.28 (m, H-1'), 3.40-3.44 (m, H-1" and H-2"), 3.62 (m, H-2'), 4.83 (t, OH), 5.19 (t, NH"), 6.10 (t, NH'), 6.55 (d, H-6), 7.23 (d, H-3), 7.36 (d, H*o*), 7.62 (dd, H-5), 7.92 (d, H*m*). ^{13}C nmr: 21.2 (CH_3), 37.1 (C-2"), 38.5 (C-1"), 45.6 (C-1'), 59.0 (C-2'), 103.0 (C-3), 106.4 (C-6), 116.2 (C-5), 128.0 (C*m*), 129.3 (C*o*), 134.1 (C*i*), 134.7 (C-2), 136.8 (C-4), 143.2 (C*p*), 143.6 (C-1), 197.6 (C=O). Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.91; H, 6.22; N, 12.19.

8. General procedure for synthesis of compounds **8a**, **9a** and **10a**: A solution of equimolar amounts of 2-(2-amino-4-nitroanilino)ethanol **5** (700 mg, 3.55 mmol) and 3-dimethylamino-*p*-methylpropiophenone **2** in 15 ml of absolute ethanol was heated to reflux for 30 min and the reaction was monitored by TLC. After the solvent was removed, the products formed were separated by column chromatography on silica gel, using methylene chloride/ethyl acetate (3:2) as eluent. The compound obtained as the first fraction was **10a** (15 %, mp 141 °C), the second fraction (main product) was **8a** ((28 %, mp 99 °C) and the last fraction was compound **9a** (15 %, mp 116 °C).
9. Compound **8a** was obtained as yellow crystals. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 472 (7), 471 (20, M^+), 470 (10), 444 (13), 443 (36), 442 (18), 380 (29), 352 (12), 338 (30), 324 (17), 298 (25), 297 (51), 266 (33), 220 (35), 119 (87), 91(100), 76 (15), 65 (42), 55 (31). ^{1}H nmr (300 MHz, DMSO): 1.36 (m, H-4_a, 1H), 1.43 (m, H-3_a, 1H), 1.96 (m, H-3_b, 1H), 2.05 (m, H-4_b, 1H), 2.37 (s, CH_3), 2.38 (s, CH_3), 2.90 (m, H-1_a, 1H), 3.00-3.20 (m, H-1' and H-2'), 3.73 (m, H-2, 1H), 3.95 (m, H-1_b, 1H), 4.69 (t, OH), 6.31 (d, H-6), 7.15 (a, H-9), 7.64 (dd, H-7). ^{13}C nmr: 20.6 (CH_3), 21.0 (CH_3), 24.9 (C-3), 28.5 (C-4), 40.2 (C-2), 41.8 (C-1), 44.1 (C-1'), 58.7 (C-2'), 87.6 (C-2a), 96.6 (C-9), 100.5 (C-6), 118.9 (C-7), 138.3 (C-9a), 139.2 (C-8), 146.8. (C-5a), 200.5 (C=O). Anal. Calcd. for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20; N, 8.91. Found: C, 71.37; H, 6.09; N, 8.84.
10. Compound **9a** was obtained as orange-red crystals. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 459 (3, M^+), 444 (27), 368 (15), 299 (13), 298 (71), 252 (13), 222 (25), 208 (15), 147 (12), 146 (20), 129 (11), 119 (100), 118 (23), 117 (48), 105 (12), 91 (94), 77 (13), 65 (47), 63 (20), 55 (12). ^{1}H nmr (300 MHz, DMSO): 1.91 (s, CH_3-imidazole), 2.28 (s, CH_3), 2.36 (s, CH_3), 2.90-3.30 (m, H-1', H-1", H-2' and H-2"), 4.78 (t, OH), 6.31 (d, H-7), 6.89 (s, H-4), 7.63 (dd, H-6). ^{13}C nmr: 20.5 (CH_3), 21.0 (CH_3), 22.6 (CH_3-imidazole), 36.0 (C-2"), 38.1 (C-1"), 45.2 (C-1'), 58.8 (C-2'), 89.5 (C-2), 94.5 (C-4), 99.3 (C-7), 118.5 (C-6), 138.3 (C-3a), 139.5 (C-5), 146.5 (C-7a), 197.9 (C=O). Anal. Calcd. for $C_{27}H_{29}N_3O_4$: C, 70.57; H, 6.36; N, 9.14. Found: C, 70.52; H, 6.28; N, 9.21.
11. Compound **10a** was obtained as red crystals. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 385 (2, M^+), 239 (24), 166 (56), 164 (36), 146 (26), 144 (10), 120 (38), 119 (100), 118 (20), 92 (12), 91 (64), 89 (12), 76 (12), 65 (45), 63 (21), 55 (15). ^{1}H nmr (300 MHz, DMSO): 2.01 (s, $COCH_3$), 2.39 (s, CH_3), 3.40 (t, H-1'), 3.43-3.52 (m, H-1" and H-2"), 4.19 (t, H-2'), 5.13 (t, NH"), 6.21 (t, NH'), 6.60 (d, H-6), 7.24 (d, H-3), 7.36 (d, H*m*), 7.62 (d, H-5), 7.91 (d, H*o*). ^{13}C nmr: 20.6 (CH_3CO), 21.1 (CH_3), 36.9 (C-2"), 38.4 (C-1"), 41.5 (C-1'), 61.9 (C-2'), 103.1 (C-3), 106.5 (C-6), 115.9 (C-5), 127.9 (C*o*), 129.2 (C*m*), 134.0 (C*i*), 134.7 (C-2), 137.2 (C-4), 142.5 (C-1), 143.6 (C*p*), 170.4 ($COCH_3$), 197.8 (C=O). Anal. Calcd. for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.02; N, 10.90. Found: C, 62.29; H, 6.08; N, 10.84.
12. General procedure for the synthesis of compound **11a**: This compound was obtained following the above procedure for 6 h reaction time. The compound was obtained as yellow crystals, mp 80, yield 22%. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 343 (10), 343 (26, M^+), 208 (20), 197 (35), 178 (45), 166 (63), 164 (15), 146 (30), 134 (12), 131 (14), 120 (44),119 (100), 118 (16), 105 (12), 93 (11), 92 (18), 91 (95), 78 (20), 65 (67), 55 (35), 51 (26), 43 (29), 39 (74). ^{1}H nmr (300 MHz, DMSO): 1.83 (m, H-3_a, 1H), 2.03 (s, CH_3CO, 3H), 2.10 (m, H-3_b, 1H), 2.30 (s, CH_3, 3H), 3.30 (m, H-4_a, 1H), 3.50-354 (m, H-1_a', 1H), 3.69 (m, H-1_b', 1H), 3.94 (m, H-4_b, 1H), 4.23-4.28 (m, H-2', 2H), 4.49 (m, H-2, 2H), 5.34 (s, NH, 1H), 6.81 (d, H-6, 1H), 7.18 (d, H*m*, 1H), 7.29 (d, H*o*), 7.56 (dd, H-7, 1H), 7.71 (d, H-6, 1H). ^{13}C nmr: 20.6 (CH_3CO), 20.7 (CH_3), 33.9 (C-3), 49.2 (C-4), 50.9 (C-1'), 58.6 (C-2), 60.9 (C-2'), 113.7 (C-9), 114.5 (C-6), 116.7 (C-7), 126.7 (C*o*), 128.9 (C*m*), 136.3 (C*p*), 138.3 (C-8), 139.9 (C-9a), 140.3 (C*i*), 146.7 (C-5a), 170.3 (C=O). Anal. Calcd. for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.07; H, 6.20; N, 11.31.

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