

1-Alkyl- and Azeto[1,2-*a*][1,5]benzodiazepine Derivatives in the Reaction of *o*-Phenylenediamine with 3-(Dimethylamino)propiophenones

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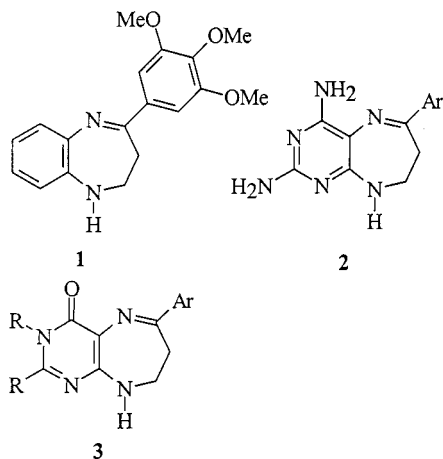
Keywords: 1,5-Benzodiazepines / Heterocycles / Azeto[1,2-*a*]-1,5-benzodiazepines / Cyclizations / Cycloadditions

The reaction of *o*-phenylenediamine (**4**) with one, two or three equivalents of *p*-substituted 3-dimethylaminopropiophenone hydrochlorides **5a–e** was studied. 4-Aryl-2,3-dihydro-1*H*-1,5-benzodiazepine derivatives **6a–e** were obtained in good yields, along with the 1:2-adducts **7c–e** and

the unexpected 1:3-adducts *rac*-**8c–e**. The type of adduct formed is determined by the molar ratio of the reactants **4** and **5** and by the nature of the substituent in the *para* position of the propiophenone **5**.

Introduction

The reaction of *o*-phenylenediamines with salts of 3-aminopropiophenones has been previously reported in the literature.^[1,2] Some 1,5-benzodiazepine derivatives thus obtained (e.g. compound **1** in Scheme 1) have been utilized as neoplasm inhibitors.^[2] Recently, our group has also reported the synthesis of diazepine derivatives **2** and **3** in good yields,^[3,4] starting from heterocyclic 1,2-diamines and 3-dimethylaminopropiophenone hydrochlorides **5**.



Scheme 1. 1,5-Diazepine derivatives formed from **4** and heterocyclic *o*-diamino compounds with 3-dimethylaminopropiophenones

Our interest in the synthesis and chemistry of fused diazepine ring systems^[5–8] led us to a more detailed study of this reaction, and to an analysis of the effect of the molar ratio of the reactants and the nature of the *para* substituent of the propiophenone on the reaction products.

Results and Discussion

A preliminary experiment was carried out by refluxing diamine **4** with one equivalent of *p*-nitropropiophenone hydrochloride (**5e**) in dry ethanol. The two products obtained were separated by column chromatography on silica gel, using ethyl acetate/hexane (1:2) as eluent, and were characterized by NMR spectroscopy. The compound obtained as the first fraction was the 1:2-adduct **7e**, while the second fraction (main product) was the expected compound **6e**. The reaction conditions (time and solvent) were then optimized to obtain only the products **6a–b** when reacting propiophenones **5a–b** with *o*-phenylenediamine (**4**). Similar conditions for the propiophenones **5c–e** led to the expected products **6c–e**, accompanied by small amounts of the compounds **7c–e**.

In a further experiment, aiming at the formation of the 1:2-adduct **7e** as the main product, more than two equivalents of propiophenone **5e** were used, and the reaction mixture was heated for a longer time. However, a mixture of two components was again obtained. The first fraction separated by column chromatography was the compound **7e** as the main product, followed by the 1:3-adduct **8e**. Several experiments under various reaction conditions showed that compounds of type **8** were accessible only for the propiophenones **5c–e** and not for **5a,b**.

We further established the best reaction conditions to obtain the compounds **6a–e** as major products by refluxing equimolar amounts of diamine **4** and the propiophenones **2a–e** for ca. 15 min. in an excess of dry ethanol. When a 1:2 ratio of diamine **4** and propiophenone **5c–e** was refluxed for ca. 2 h, compounds of type **7** were obtained as the main products. Finally, when a 1:3 mixture of diamine **4** and propiophenone **5c–e** was refluxed for 3 to 4 h, compounds **8c–e** were obtained as major products.

The structures of compounds **6a–e**, **7c–e** and **8c–e** were assigned by ¹H and ¹³C NMR spectra and confirmed by IR and mass spectrometric data (see Experimental Section). The most characteristic ¹H NMR signals for the com-

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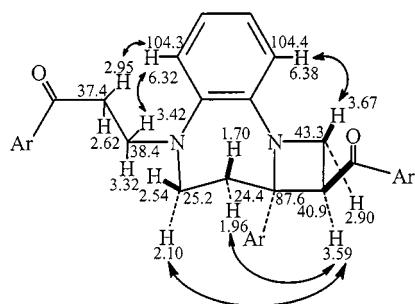
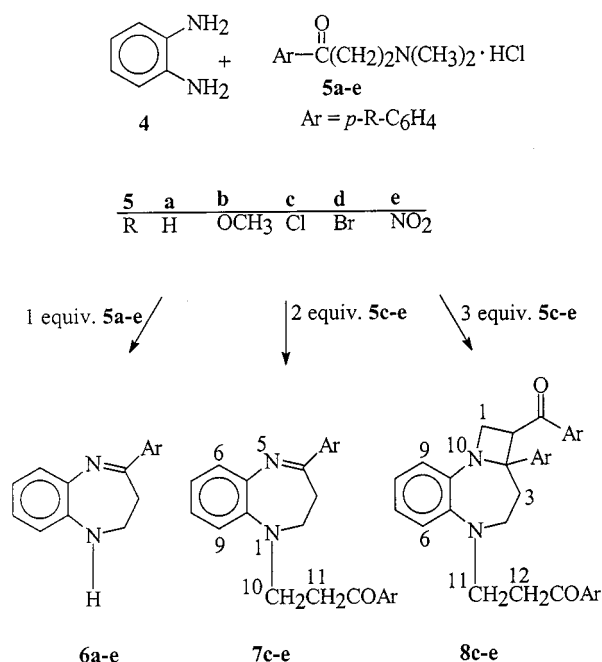


Figure 1. Correlation of the ^1H and ^{13}C NMR signals with certain positions of the ring skeleton of compound **8d**; arrows indicate the obtained nuclear Overhauser effects

pounds **6a–e** are represented by a broad singlet at $\delta = 3.55\text{--}3.95$ (deuterium exchangeable) corresponding to the N–H proton and a typical AA'BB' pattern for the building block 2-CH₂-3-CH₂. The spectra of the compounds **7c–e** show also the pattern for the building block 2-CH₂-3-CH₂ and additionally two multiplets for the CH₂–CH₂ segment in the side chain. The ^1H NMR spectra of compounds *rac*-**8c–e** show a complicated spin pattern at $\delta = 1.67\text{--}3.84$ owing to aliphatic protons. However, an extended study including DEPT and two-dimensional (COSY, NOESY and ^{13}C , ^1H shift correlation) measurements for *rac*-**8d** confirmed the proposed structure. Figure 1 depicts the correlation of the ^{13}C and the ^1H NMR signals with the nuclei of the tricyclic skeleton and the most important nuclear Overhauser effects (arrows). Apart from the *cis* fusion of the azete and the diazepine ring, the stereogenic center C-2 has to be considered. The geminal protons on C-1 can be assigned by the NOE between the aromatic 9-H ($\delta = 6.38$) and the lowfield signal of 1-H ($\delta = 3.67$). The latter proton and 2-H are in a *trans* position i.e. the (2*R*,2*aR*) configuration and its enantiomer (2*S*,2*aS*) were formed. Besides the ABM spin pattern of the protons on the azete ring, the spectrum contains an ABCD pattern for the protons on the diazepine ring and an ABCD pattern for the protons of the side chain attached on N-5. The individual correlation is again based on NOESY measurements (Figure 1). The ^{13}C NMR spectroscopic data were assigned by a ^1H , ^{13}C shift correlation measurement. The compounds *rac*-**8c** and **8e** gave very similar results (see Experimental Section).

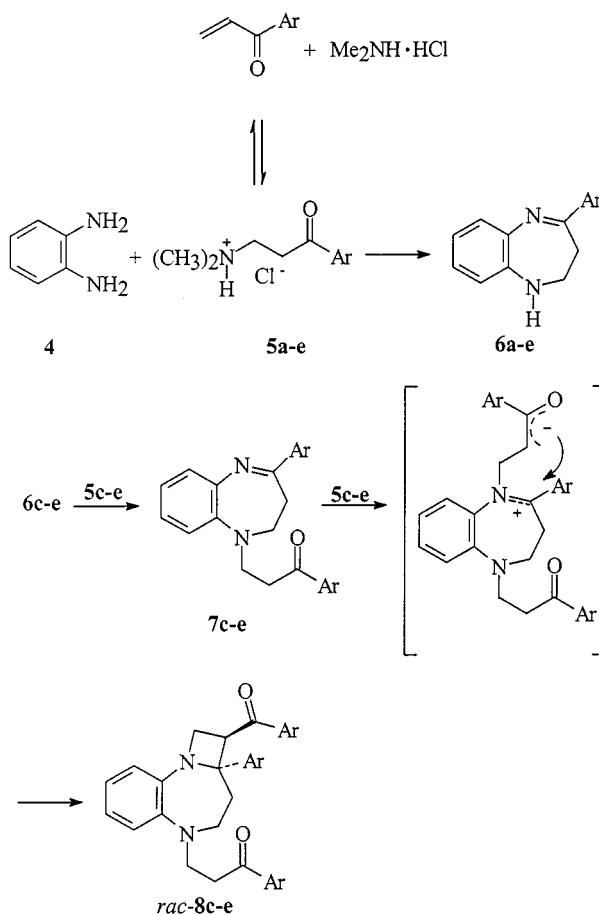
In the infrared spectra of the compounds **6a–e** the band characteristic for the N–H stretching vibration is present at 3401–3391 cm^{−1} together with a band at 1619–1625 cm^{−1}, assignable to the C=N group.^[9] In the compounds **7c–e**, a band assignable to the N–H stretching is not present; apart from the C=N stretching vibration an absorption at 1671–1676 cm^{−1} could be assigned to the C=O stretching vibration. Compounds *rac*-**8c–e** did not exhibit absorptions for N–H or C=N groups. However, a strong, broad band can be observed at 1676–1683 cm^{−1}; it is assigned to the two C=O groups.

As shown in Scheme 2, the 1:2- and 1:3 adducts were obtained only when the *p*-substituent in **5** is an electron-withdrawing group, such as nitro or halogen, while for Ar = C₆H₅ or C₆H₄–OCH₃ only diazepines of type **6** were obtained. This finding suggests that the reaction course is con-



Scheme 2. Reaction of *o*-phenylenediamine **4** with aryl-3-dimethylaminopropiophenones **5**

trolled by the reactivity of the propiophenones. According to Scheme 3, compounds **7c–e** were formed by an *N*-alkylation of the diazepines **6c–e** with a second equivalent of propiophenone **5c–e** or its well-known^[10] synthetic equiva-



Scheme 3. Stepwise formation of **6**, **7**, **8** and proposed intermediate

lent arylvinylketone, generated in situ from the corresponding propiophenone. On the other hand, formation of the compounds **rac-8** could occur by the attack of a third molecule of propiophenone **5** at the imino nitrogen of **7** (via the alkyliminium intermediate shown in Scheme 3), and subsequent cyclization to form the fused azete ring.

The structure and generation of the azeto[1,2-*a*][1,5]benzodiazepines are unprecedented; a somewhat related reaction was observed by Cortés et. al. when β -lactams were unexpectedly obtained in the reaction of some benzodiazepines with methoxyacetyl chloride.^[11]

As further support for the assertions in Scheme 3, the adducts **7c–e** and **8c–e** were alternatively obtained by the reaction of **6c–e** with one or two equivalents of the propiophenones **5c–e**.

Experimental Section

General: All melting points were taken with a Büchi melting point apparatus and are uncorrected. – IR: ATI-Mattson spectrophotometer. NMR: Varian-VXR-300S, Bruker ARX 400, CDCl₃ as solvent. – MS: Jeol SX-100 (70 eV). – Microanalyses: LECO CHNS-900 elemental analyzer.

General Procedure for the Preparation of the 2,3-Dihydro-1*H*-1,5-benzodiazepines (6a–e): A solution of **4** (300 mg, 2.77 mmol) and the corresponding ketone **5a–e** (2.77 mmol) in 50 mL of dry ethanol was heated for 15 min to reflux and the reaction was monitored by TLC. After the solvent was removed, the residue was purified by column chromatography on silica gel (3 × 80 cm) with chloroform as eluent.

2,3-Dihydro-4-phenyl-1*H*-1,5-benzodiazepine (6a): Yellow crystals, yield 370 mg, 60%, m.p. 129 °C. – ¹H NMR (CDCl₃): δ = 2.92 (t, *J* = 5.7 Hz, 2 H, 3-H), 3.55 (br. s, 1 H, NH), 3.74 (t, *J* = 5.7 Hz, 2 H, 2-H), 6.67 (d, 1 H), 6.90–6.99 (m, 2 H), 7.25 (d, 1 H), 7.36 (m, 3 H), 7.91 (br. t, 2 H, aromat. H). – ¹³C NMR (CDCl₃): δ = 30.6 (C-3), 49.3 (C-2), 116.8, 118.5, 123.5, 126.7, 126.8, 128.4, 129.5, 132.5, 136.2, 140.5 (aromat. C), 166.5 (C=N). – MS (70 eV): *m/z* (%) = 222 (100) [M⁺], 221 (88), 194 (43), 119 (47). – C₁₅H₁₄N₂ (222.3): calcd. C 81.09, H 6.30, N 12.60; found C 81.14, H 6.38, N 12.50.

2,3-Dihydro-4-(4-methoxyphenyl)-1*H*-1,5-benzodiazepine (6b): Yellow crystals, yield 315 mg, 45%, m.p. 155 °C. – ¹H NMR (CDCl₃): δ = 2.97 (t, *J* = 5.7 Hz, 2 H, 3-H), 3.60 (br. s, 1 H, NH), 3.83 (t, *J* = 5.7 Hz, 2 H, 2-H), 3.84 (s, 3 H, OCH₃), 6.71 (d, 1 H), 6.90–7.00 (m, 4 H), 7.32 (br. d, 1 H), 7.94 (d, 2 H, aromat. H). – ¹³C NMR (CDCl₃): δ = 28.6 (C-3), 50.3 (C-2), 52.9 (OCH₃), 111.2, 117.1, 118.2, 123.4, 126.0, 126.9, 129.4, 135.8, 137.2, 158.9 (aromat. C), 165.0 (C=N). – MS (70 eV): *m/z* (%) = 252 (100) [M⁺], 251 (27), 224 (48), 119 (35). – C₁₆H₁₆N₂O (252.3): calcd. C 76.21, H 6.35, N 11.10; found C 76.14 H 6.44, N 11.06.

4-(4-Chlorophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (6c): Orange crystals, yield 480 mg, 68%, m.p. 130 °C. – ¹H NMR (CDCl₃): δ = 2.96 (t, *J* = 5.7 Hz, 2 H, 3-H), 3.65 (br. s, 1 H, NH), 3.77 (t, *J* = 5.7 Hz, 2 H, 2-H), 6.67 (br. d, 1 H), 6.88 (m, 1 H), 6.95 (m, 1 H), 7.28 (d, 1 H), 7.33 (d, 2 H), 7.85 (d, 2 H, aromat. H). – ¹³C NMR (CDCl₃): δ = 31.9 (C-3), 52.1 (C-2), 119.5, 120.7, 126.7, 128.2, 128.6, 130.2, 130.4, 136.1, 137.5, 140.2 (aromat. C), 163.0 (C=N). – MS (70 eV): *m/z* (%) = 256/258 (100) [M⁺, Cl pattern], 255 (62),

228 (52), 119 (51). – C₁₅H₁₃ClN₂ (256.7): calcd. C 70.21, H 5.07, N 10.91; found C 70.14, H 5.12, N 10.86.

4-(4-Bromophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (6d): Orange crystals, yield 600 mg, 72%, m.p. 140 °C. – ¹H NMR (CDCl₃): δ = 3.00 (t, *J* = 5.7 Hz, 2 H, 3-H), 3.80 (br. s, 1 H, NH), 3.81 (t, *J* = 5.7 Hz, 2 H, 2-H), 6.71 (d, 1 H), 6.93 (m, 1 H), 7.02 (m, 1 H), 7.34 (d, 1 H), 7.54 (br. d, 2 H), 7.84 (br. d, 2 H, aromat. H). – ¹³C NMR (CDCl₃): δ = 32.1 (C-3), 54.1 (C-2), 119.8, 120.8, 124.6, 127.2, 128.8, 130.8, 131.7, 137.8, 138.7, 140.4 (aromat. C), 166.2 (C=N). – MS (70 eV): *m/z* (%) = 300/302 (100) [M⁺, Br pattern], 299 (68), 272 (30), 119 (65). – C₁₅H₁₃BrN₂ (301.2): calcd. C 59.84, H 4.32, N 9.30; found C 59.81, H 4.44, N 9.21.

2,3-Dihydro-4-(4-nitrophenyl)-1*H*-1,5-benzodiazepine (6e): Red crystals, yield 445 mg, 60%, m.p. 129 °C. – ¹H NMR (CDCl₃): δ = 3.10 (t, *J* = 5.7 Hz, 2 H, 3-H), 3.77 (t, *J* = 5.7 Hz, 2 H, 2-H), 3.95 (br. s, 1 H, NH), 6.72 (d, 1 H), 6.93 (m, 1 H), 7.05 (m, 1 H), 7.40 (d, 1 H), 8.10 (d, 2 H), 8.24 (d, 2 H). – ¹³C NMR (CDCl₃): δ = 33.3 (C-3), 49.8 (C-2), 119.1, 120.3, 123.5, 127.6, 127.8, 132.2, 135.9, 141.1, 145.7, 148.4 (aromat. C), 163.7 (C=N). – MS (70 eV): *m/z* (%) = 267 (100) [M⁺], 266 (89), 239 (24), 119 (55). – C₁₅H₁₃N₃O₂ (267.3): calcd. C 67.44, H 4.87, N 15.72; found C 67.38, H 4.84, N 15.66.

General Procedure for the Preparation of the 1-(2-Aroyl-ethyl)-2,3-dihydro-1*H*-1,5-benzodiazepines (7c–e): A solution of **4** (300 mg, 2.77 mmol) and the corresponding ketone (5.55 mmol) **5c–e** in 25 mL of dry ethanol was heated for 2 h to reflux and the reaction was monitored by TLC. The solid formed during the heating was filtered off and recrystallized from ethanol. A second crop of crystals was collected after cooling the reaction mixture and purified as mentioned previously.

1-[2-(4-Chlorobenzoyl)ethyl]-2,3-dihydro-1*H*-1,5-benzodiazepine (7c): Yellow crystals, yield 750 mg, 64%, m.p. 136 °C. – ¹H NMR (CDCl₃): δ = 2.81 (t, *J* = 6.3 Hz, 2 H, 3-H), 3.00 (t, *J* = 5.6 Hz, 2 H, 11-H), 3.52 (t, *J* = 6.3 Hz, 2 H, 2-H), 3.75 (t, *J* = 5.7 Hz, 2 H, 10-H), 6.90–7.41 (m, 4 H), 7.52–8.10 (m, 8 H, aromat. H). – ¹³C NMR (CDCl₃): δ = 29.9 (C-3), 37.5 (C-11), 47.0 (C-2), 63.4 (C-10), 119.4, 123.1, 124.9, 125.6, 127.0, 128.7, 129.0, 129.8, 131.1, 133.1, 135.1, 137.9, 140.3, 144.8 (aromat. C), 169.5 (C=N), 199.3 (C=O). – MS (70 eV): *m/z* (%) = 426/424/422 (75), [M⁺, Cl₂ pattern], 421 (25), 256 (100), 255 (78), 166 (55), 119 (48). – C₂₄H₂₀Cl₂N₂O (423.3): calcd. C 68.12, H 4.73, N 6.62; found C 68.18, H 4.84, N 6.66.

1-[2-(4-Bromobenzoyl)ethyl]-2,3-dihydro-1*H*-1,5-benzodiazepine (7d): Yellow crystals, yield 880 mg, 62%, m.p. 149 °C. – ¹H NMR (CDCl₃): δ = 2.82 (t, *J* = 6.4 Hz, 2 H, 3-H), 3.10 (t, *J* = 5.7 Hz, 2 H, 11-H), 3.56 (t, *J* = 6.3 Hz, 2 H, 2-H), 3.73 (t, *J* = 5.7 Hz, 2 H, 10-H), 6.85–7.38 (m, 4 H), 7.40–7.85 (m, 8 H, aromat. H). – ¹³C NMR (CDCl₃): δ = 30.7 (C-3), 737.0 (C-11), 47.3 (C-2), 63.5 (C-10), 119.3, 123.0, 125.1, 125.9, 126.6, 128.5, 128.8, 129.5, 131.8, 132.0, 135.6, 137.4, 139.2, 144.5 (aromat. C), 169.1 (C=N), 198.5 (C=O). – MS (70 eV): *m/z* (%) = 514/512/510 (63), [M⁺, Br₂ pattern], 509 (33), 300 (100), 299 (82), 210 (59), 119 (53). – C₂₄H₂₀Br₂N₂O (512.2): calcd. C 56.29, H 3.91, N 5.47; found C 56.18, H 3.84, N 5.53.

2,3-Dihydro-1-[2-(4-nitrobenzoyl)ethyl]-1*H*-1,5-benzodiazepine (7e): Red crystals, yield 840 mg, 68%, m.p. 213 °C. – ¹H NMR (CDCl₃): δ = 2.89 (t, *J* = 6.6 Hz, 2 H, 3-H), 3.16 (t, *J* = 5.9 Hz, 2 H, 11-H), 3.60 (t, *J* = 6.6 Hz, 2 H, 2-H), 3.78 (t, *J* = 5.9 Hz, 2 H, 10-H), 7.00–7.30 (m, 4 H), 7.88 (d, 2 H), 8.10 (d, 2 H), 8.18 (d, 2 H), 8.29 (d, 2 H, aromat. H). – ¹³C NMR (CDCl₃): δ = 29.9 (C-3), 37.4

(C-11), 47.1 (C-2), 63.4 (C-10), 119.2, 123.1, 123.8, 126.6, 127.2, 127.7, 128.9, 138.8, 141.1, 144.0, 148.9, 150.3 (aromat. C), 167.9 (C=N), 197.8 (C=O). – MS (70 eV): m/z (%) = 444 (60), $[M^+]$, 443 (22), 267 (100), 266 (91), 150 (48), 119 (53). – $C_{24}H_{20}N_4O_5$ (444.4): calcd. C 64.89, H 4.50, N 12.61; found C 64.81, H 4.64, N 12.53.

General Procedure for the Preparation of the (±)-Azeto[1,2-*a*][1,5]-benzodiazepines (*rac*-8c–e): A solution of **4** (300 mg, 2.77 mmol) and the corresponding ketone **5c–e** (8.35 mmol) in 50 mL of dry ethanol was heated for 4 h to reflux and the reaction was monitored by TLC. The products crystallized on cooling and were purified by column chromatography on silica gel (3 × 80 cm) with chloroform as eluent.

(±)-2-(4-Chlorobenzoyl)-5-[2-(4-chlorobenzoyl)ethyl]-2a-(4-chlorophenyl)-1,2,2a,3,4,5-hexahydroazeto[1,2-*a*][1,5]benzodiazepine (*rac*-8c): Pale yellow crystals, yield 910 mg, 56%, m.p. 210 °C. – 1H NMR ($CDCl_3$): δ = 1.71–1.79 (m, 1 H, 3-H), 1.97–2.01 (m, 1 H, 3-H), 2.09–2.15 (m, 1 H, 4-H), 2.55–2.58 (m, 1 H, 4-H), 2.61–2.69 (m, 1 H, 12-H), 2.92–2.96 (m, 1 H, 1-H), 2.98–3.03 (m, 1 H, 12-H), 3.29–3.37 (m, 1 H, 11-H), 3.42–3.49 (m, 1 H, 11-H), 3.60–3.66 (m, 1 H, 2-H), 3.69–3.72 (m, 1 H, 1-H), 6.35 (d, 1 H, 6-H), 6.42 (d, 1 H, 9-H), 6.68–6.75 (m, 2 H, 7-H, 8-H), 7.34 (d, 2 H), 7.37 (d, 2 H), 7.46 (d, 2 H), 7.61 (d, 2 H), 7.68 (d, 2 H), 7.86 (d, 2 H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 24.5 (C-3), 25.2 (C-4), 37.4 (C-12), 38.4 (C-11), 40.9 (C-2), 43.3 (C-1), 87.5 (C-2a), 104.3, 104.4 (C-6, C-9), 118.6, 119.2 (C-7, C-8), 128.8, 128.9, 129.0, 129.2, 129.4, 129.5, 129.7, 134.1, 134.7, 138.0, 139.0, 139.2, 139.7, 139.9 (aromat. C), 197.4, 199.6 (CO). – MS (70 eV): m/z (%) = 594/592/590/588 (25), $[M^+]$, Cl_3 pattern], 560 (17), 422 (100), 394 (15), 228 (29), 139 (62). – $C_{33}H_{27}Cl_3N_2O_2$ (589.9): calcd. C 67.21, H 4.58, N 4.75; found C 67.18, H 4.46, N 4.83.

(±)-2-(4-Bromobenzoyl)-5-[2-(4-bromobenzoyl)ethyl]-2a-(4-bromophenyl)-1,2,2a,3,4,5-hexahydroazeto[1,2-*a*][1,5]-benzodiazepine (*rac*-8d): Pale yellow crystals, yield 1.20 g, 60%, m.p. 208 °C. – 1H NMR ($CDCl_3$): δ = 1.67–1.71 (m, 1 H, 3-H), 1.94–1.97 (m, 1 H, 3-H), 2.06–2.12 (m, 1 H, 4-H), 2.51–2.55 (m, 1 H, 4-H), 2.58–2.66 (m, 1 H, 12-H), 2.88–2.93 (m, 1 H, 1-H), 2.95–2.99 (m, 1 H, 12-H), 3.27–3.33 (m, 1 H, 11-H), 3.39–3.45 (m, 1 H, 11-H), 3.56–3.60 (m, 1 H, 2-H), 3.65–3.73 (m, 1 H, 1-H), 6.32 (d, 1 H, 6-H), 6.39 (d, 1 H, 9-H), 6.66–6.72 (m, 2 H, 7-H, 8-H), 7.46 (d, 2 H), 7.53 (br.s, 4 H), 7.61 (d, 2 H), 7.62 (d, 2 H), 7.77 (d, 2 H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 24.4 (C-3), 25.2 (C-4), 37.4 (C-12), 38.4 (C-11), 40.9 (C-2), 43.3 (C-1), 87.6 (C-2a), 104.3 (C-6), 104.4 (C-9), 118.6, 119.2 (C-7, C-8), 123.0, 128.5, 128.6, 134.5, 135.1, 138.5, 138.9, 139.2 (aromat. C_q), 129.5, 129.6, 130.0, 131.7, 131.9, 132.2 (aromat. CH), 197.6, 199.9 (CO). – MS (70 eV): m/z (%) = 726/724/722/720 (18), $[M^+]$, Br_3 pattern], 692 (10), 510 (63),

482 (47), 272 (68), 183 (100). – $C_{33}H_{27}Br_3N_2O_2$ (723.3): calcd. C 54.82, H 3.73, N 3.87; found C 54.75, H 3.76, N 3.92.

(±)-1,2,2a,3,4,5-Hexahydro-2-(4-nitrobenzoyl)-5-[2-(4-nitrobenzoyl)ethyl]-2a-(4-nitrophenyl)azeto[1,2-*a*][1,5]benzodiazepine (*rac*-8e): Pale yellow crystals, yield 1.10 g, 64%, m.p. 192 °C. – 1H NMR ($CDCl_3$): δ = 1.69–1.73 (m, 1 H, 3-H), 1.92–1.96 (m, 1 H, 3-H), 2.09–2.13 (m, 1 H, 4-H), 2.50–2.57 (m, 1 H, 4-H), 2.58–2.65 (m, 1 H, 12-H), 2.86–2.92 (m, 1 H, 1-H), 2.96–2.99 (m, 1 H, 12-H), 3.25–3.32 (m, 1 H, 11-H), 3.39–3.44 (m, 1 H, 11-H), 3.67–3.76 (m, 1 H, 2-H), 3.80–3.84 (m, 1 H, 1-H), 6.37 (d, 1 H, 6-H), 6.47 (d, 1 H, 9-H), 6.56–6.66 (m, 2 H, 7-H, 8-H), 7.92 (d, 2 H), 7.98 (d, 2 H), 8.15 (d, 2 H), 8.23 (d, 2 H), 8.34 (d, 4 H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 24.4 (C-3), 24.6 (C-4), 37.4 (C-12), 38.3 (C-11), 40.7 (C-2), 42.1 (C-1), 87.2 (C-2a), 104.7, 104.9 (C-6, C-9), 118.6, 118.9 (C-7, C-8), 123.6, 123.7, 123.9, 128.3, 129.2, 129.4, 129.6, 139.0, 140.0, 140.1, 146.7, 147.2, 149.6, 149.9 (aromat. C), 197.4, 200.5 (CO). – MS (70 eV): m/z (%) = 621 (23), $[M^+]$, 593 (16), 444 (42), 416 (28), 239 (100), 150 (38). – $C_{33}H_{27}N_5O_8$ (621.6): calcd. C 63.80, H 4.35, N 11.27; found C 63.73, H 4.42, N 11.19.

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- [1] W. Werner, W. Jungstand, W. Gutsche, K. Wohlrabe, *Ger. (East)* 122,247 (*Cl. C07D53104*), 20 Sept. 1976, *Appl.* 188,678, 02 Oct. 1975; *Chem. Abstr.* 1976, 87, 39550a.
- [2] K. Hideg, H. O. Hankovszky, *Acta Chim. (Budapest)* 1968, 57, 213–217; *Chem. Abstr.* 1969, 70, 4082w.
- [3] B. Insuasty, H. Insuasty, J. Quiroga, C. Saitz, C. Jullian, *J. Heterocycl. Chem.*, in press.
- [4] B. Insuasty, J. C. Argoti, S. Gómez, J. Quiroga, R. Martínez, E. Angeles, R. Gabiño, M. Nogueras, A. Sánchez, *J. Heterocycl. Chem.* 1998, 35, 1397–1399.
- [5] B. Insuasty, R. Abonia, J. Quiroga, *Ann. Quim.* 1992, 88, 718–720.
- [6] B. Insuasty, J. Quiroga, H. Meier, *Trends Heterocycl. Chem.* 1997, 5, 83–89.
- [7] B. Insuasty, R. Abonia, J. Quiroga, H. Meier, *J. Heterocycl. Chem.* 1993, 30, 229–231.
- [8] A. R. Katritzky, R. Abonia, B. Yang, M. Qi, B. Insuasty, *Synthesis* 1998, 1487–1490.
- [9] L. H. Sternbach, E. Reeder, *J. Org. Chem.* 1961, 26, 1111–1118.
- [10] S. Piroëlle, P. Rollin, *Bull. Soc. Chim. Fr.* 1973, 2543–2546.
- [11] E. Cortés, R. Martínez, I. Ceballos, *J. Heterocycl. Chem.* 1989, 26, 119–124.

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