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SYNTHESIS OF N-SUBSTITUTED PYRROLO[1,2-*a*][1,4]BENZODIAZEPINES

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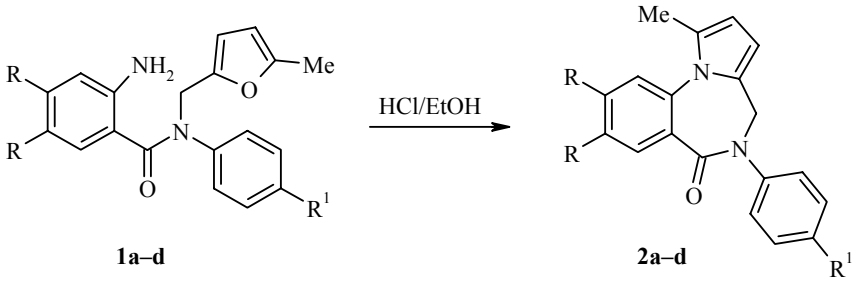
In the framework of our study on the use of furan-containing substrates in the synthesis of condensed heterocyclic systems, we continued our investigation of the transformations of N-furfurylanthranilamides in acid media. In an attempt to effect the recyclization of tertiary N-furfurylanthranilamides and 3-aminothieno-[2,3-*b*]pyridienecarboxamides by the action of a mixture of glacial acetic acid and hydrochloric acid, we found that the furfuryl fragment is lost rather than opening of the furan ring [1].

In the present communication, we show that the major reaction pathway upon treatment of amides **1** with ethanolic HCl is recyclization of the furan ring to form the pyrrolo[1,2-*a*]diazepine system.



1a–d **2a–d**

1, **2 a** R= H, R^1 = Br; **b–d** R = MeO, **b** R^1 = Br; **c** R^1 = Me; **d** R^1 = H

This reaction was carried out upon heating aminoamides **1** in an ethanolic solution of gaseous hydrogen chloride. The yields of N-substituted benzodiazepines **2a-d** were 52-62%.

The ^{1}H NMR spectra were taken on a Bruker DRX-500 spectrometer at 500 MHz for compounds **2a-c** and a Bruker AM-300 spectrometer at 300 MHz for compound **2d** in DMSO-d_6 with TMS as the internal standard. The electron impact mass spectra were taken on a MAT-112 mass spectrometer with direct inlet into the ion source. The ionizing energy was 70 eV.

Synthesis of Compounds 1a-d (General Method). Solution of gaseous hydrogen chloride in ethanol (20 ml) was added to a solution of aminoamide **1a-d** (0.5 mmol) in ethanol (20 ml) and the mixture obtained was maintained at 55-60°C until the starting reagent was entirely consumed as indicated by thin-layer

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chromatographic monitoring. The reaction mixture was poured into 100 ml ice water, neutralized by adding dry sodium carbonate to pH ~7, and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness in vacuum. The residue was separated by column chromatography using methylene chloride as the eluent for **2a** and 5.0:7.5 CCl_4-acetone as the eluent for **2c**. Product **2b** was recrystallized with silica gel from a mixture of ethyl acetate and petroleum ether. Product **2d** was recrystallized with silica gel from a mixture of acetone and petroleum ether.

5-(4-Bromophenyl)-1-methyl-4,5-dihydro-6H-pyrrolo[1,2-*a*][1,4]benzodiazepin-6-one (2a) was obtained in 54% yield as a white powder; mp 159-161°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.22 (3H, s, CH_3); 4.58 (2H, s, CH_2N); 6.06 (1H, d, *J* = 3.2, H pyrrole); 6.15 (1H, d, *J* = 3.2, H pyrrole); 7.28 (2H, d, *J* = 8.7, H arom.); 7.47-7.53 (1H, m, H arom.); 7.61 (2H, d, *J* = 8.7, H arom.); 7.66-7.72 (3H, m, H arom.); 7.87 (1H, d, *J* = 7.8, H arom.). Mass spectrum, *m/z* (I_{rel}, %): 367 $[M]^+$ (9), 366 (38), 354 (16), 353 (53), 352 (19), 351 (55), 196 (25), 184 (18), 183 (100), 182 (24), 169 (20), 168 (44), 167 (23), 155 (14), 154 (58), 127 (12), 107 (11), 101 (11), 76 (14), 65 (20), 59 (41), 58 (16), 57 (10), 52 (16), 51 (17), 43 (58), 42 (29). Found, %: C 62.18; H 4.03; N 7.70. $C_{19}H_{15}BrN_2O$. Calculated, %: C 62.14; H 4.12; N 7.63.

5-(4-Bromophenyl)-8,9-dimethoxy-1-methyl-4,5-dihydro-6H-pyrrolo[1,2-*a*][1,4]benzodiazepin-6-one (2b) was obtained in 60% yield as beige crystals; mp 177-179°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24 (3H, s, CH_3); 3.85 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 4.54 (1H, d, *J* = 15.9, CH_2N); 4.61 (1H, d, *J* = 15.9, CH_2N); 6.04 (1H, d, *J* = 3.3, H pyrrole); 6.11 (1H, d, *J* = 3.3, H pyrrole); 7.00 (1H, s, H arom.); 7.26 (2H, d, *J* = 8.7, H arom.); 7.33 (1H, s, H arom.); 7.60 (2H, d, *J* = 8.7, H arom.). Mass spectrum, *m/z* (I_{rel}, %): 427 $[M]^+$ (7), 426 (34), 414 (18), 413 (96), 412 (17), 411 (100), 256 (27), 244 (10), 243 (68), 240 (11), 228 (26), 214 (11), 200 (16), 174 (12), 154 (13), 101 (10), 82 (11), 76 (17), 59 (32), 58 (19), 57 (19), 55 (11), 43 (34). Found, %: C 59.12; H 4.39; N 6.54. $C_{21}H_{19}BrN_2O_3$. Calculated, %: C 59.03; H 4.48; N 6.56.

8,9-Dimethoxy-1-methyl-5-(4-methylphenyl)-4,5-dihydro-6H-pyrrolo[1,2-*a*][1,4]benzodiazepin-6-one (2c) was obtained in 62% yield as white crystals; mp 167-169°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH_3); 2.37 (3H, s, CH_3); 3.85 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 4.45 (1H, d, *J* = 15.7, CH_2N); 4.59 (1H, d, *J* = 15.7, CH_2N); 6.03 (1H, d, *J* = 3.2, H pyrrole); 6.11 (1H, d, *J* = 3.2, H pyrrole); 7.00 (1H, s, H arom.); 7.17 (2H, d, *J* = 8.2, H arom).; 7.20 (2H, d, *J* = 8.2, H arom.); 7.33 (1H, s, H arom.). Mass spectrum, *m/z* (I_{rel}, %): 362 $[M]^+$ (44), 348 (24), 347 (100), 256 (25), 243 (24), 228 (31), 101 (13), 59 (25), 57 (13), 43 (33), 42 (23). Found, %: C 73.00; H 6.19; N 7.76. $C_{22}H_{22}N_2O_3$. Calculated, %: C 72.91; H 6.12; N 7.73.

8,9-Dimethoxy-1-methyl-5-phenyl-4,5-dihydro-6H-pyrrolo[1,2-*a*][1,4]benzodiazepin-6-one (2d) was obtained in 53% yield as a beige powder; mp >130°C (dec.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 3.86 (3H, s, OCH_3); 3.90 (3H, s, OCH_3); 4.50 (1H, d, *J* = 15.7, CH_2N); 4.63 (1H, d, *J* = 15.7, CH_2N); 6.03 (1H, d, *J* = 3.2, H pyrrole); 6.11 (1H, d, *J* = 3.2, H pyrrole); 6.99 (1H, s, H arom.); 7.19-7.46 (6H, m, H arom.). Mass spectrum, *m/z* (I_{rel}, %): 348 $[M]^+$ (51), 334 (20), 333 (100), 280 (13), 308 (12), 266 (14), 256 (15), 244 (11), 243 (14), 241 (14), 240 (12), 228 (11), 200 (13), 198 (12), 186 (10), 183 (11), 170 (16), 154 (13), 101 (17), 93 (12), 76 (41), 69 (17), 60 (20), 59 (40), 57 (34), 55 (22), 53 (18), 44 (22), 41 (61). Found, %: C 72.49; H 5.70; N 8.10. $C_{21}H_{20}N_2O_3$. Calculated, %: C 72.40; H 5.79; N 8.04.

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