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THE FIRST EXAMPLE OF 3,7-DIAZABICYCLO[3.3.1]NONANE SYNTHESIS BY AMINOMETHYLATION OF GUARESCHI IMIDE SALTS

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2,6-Dioxopiperidine-3,5-dicarbonitriles (also known as Guareschi imides) and their salts are readily prepared by condensation of ketones, cyanoacetic ester, and ammonia [1-3] and have proved over more than a century to be convenient reagents for synthesizing derivatives of glutarimide, 3,3-disubstituted glutaric acids [4-6], azaspiranes [7], etc. A single method has been reported in the literature for the cyclization of Guareschi imides to bispidines (3,7-diazabicyclo[3.3.1]nonane derivatives) under conditions of acid hydrolysis of the nitrile groups [4, 8-11]. The compounds obtained are of interest as intermediate products in the preparation of substances with anti-ischemic activity [12] and of sparteine alkaloids [13].

We have previously reported a convenient method for the synthesis of 4-monosubstituted Guareschi imide salts by the reaction of 3-aryl-2-cyanoacrylamides with cyanoacetylpyrazole [14, 15]. These compounds, and other known 2,6-dioxopiperidine-3,5-dicarbonitriles are of general interest (as C-3/C-5 dinucleophilic reagents) for the preparation of substituted bispidines *via* a double aminomethylation reaction. The Mannich reaction of 3,5-dinucleophilic pyridine derivatives is one of the most generally applicable methods of preparing 3,7-diazabicyclo[3.3.1]nonanes [16, 17]. However, to this time there was no published evidence for the aminomethylation of Guareschi imides. We have found that the reaction of the glutarimide salt **1a** with benzylamine and an excess of formaldehyde occurred under mild conditions to give the 2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane salt ("bispidinate") **2**. Reaction of salt **1a** with β-phenethylamine and salt **1b** with benzylamine proceeded similarly. Acidification gave the expected bispidines **3a**,**b**.

These reactions serve as a first example of the synthesis of 3,7-diazabicyclo[3.3.1]nonane derivatives using Guareschi imides. The structure of compounds **2** and **3a**,**b** was confirmed by IR and ^{1}H NMR spectroscopy data, HPLC-MS, and elemental analysis. Optimization of the conditions, limits, and potential uses of the reaction will be the subject of future investigations.

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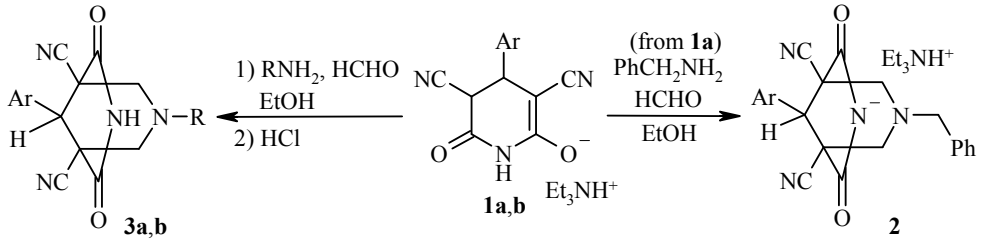

1 a Ar = 2-ClC_6H_4, **b** Ar = 2-MeC_6H_4; **2** Ar = 2-ClC_6H_4;
3 a Ar = 2-ClC_6H_4, R = CH_2CH_2Ph; **b** Ar = 2-MeC_6H_4, R = CH_2Ph

IR spectra were recorded on a Thermo Nicolet Magna IR 750 FTIR spectrometer for KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DPX-400 (400 MHz) instrument using DMSO-d_6 with TMS as internal standard. HPLC-MS analysis was carried out on a Shimadzu LC-10AD chromatograph with Shimadzu SP D-10A UV-Vis (254 nm) and Sedex 75 ELSD detectors combined with a PE SCIEX API 150EX mass spectrometer using ES-API ionization. Elemental analysis was performed on a Carlo Erba 1106 Elemental Analyzer instrument. Melting points were determined on an Electrothermal Mel-Temp 3.0 apparatus. Monitoring of the purity of the compounds obtained was carried out using TLC on Sorbfil PTSCh-AF-V-UV plates with acetone–hexane (1:1) as eluent and visualized with iodine vapor and UV radiation. The starting tetrahydropyridin-2-olates **1a** [15] and **1b** [14] were prepared by known methods.

Triethylammonium Salt of 7-Benzyl-9-(2-chlorophenyl)-2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (2). Tetrahydropyridin-2-olate **1a** (*Caution, irritant!*) (400 mg, 1.07 mmol), benzylamine (0.12 ml, 1.1 mmol), and 96% EtOH (10 ml) were placed in a 50 ml-beaker, and 37% formalin (1.00 ml, 13.3 mmol, free from paraformaldehyde) was added with stirring. The mixture was boiled for 1 min and then stirred for 1 h at about 20°C. The product precipitated upon cooling, and it was maintained for 24 h. The precipitate was filtered off, washed with EtOH and Et_2O. Yield 375 mg (69%). Colorless crystals; mp 225-227°C. IR spectrum, ν, cm^{-1}: 3441 (N–H), 2240 (C≡N), 1718, 1661 (C=O), 1608 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (9H, t, ^3J = 7.1, $3CH_2C\underline{H}_3$); 2.81 (6H, q, ^3J = 7.1, $3C\underline{H}_2CH_3$); 2.99 (2H, d, ^2J = 10.8) and 3.33 (2H, d, ^2J = 10.8, 6,8-CH_2); 3.72 (2H, br. s, $C\underline{H}_2Ph$); 4.36 (1H, s, 9-CH); 7.22-7.45 (8H, m, H Ar); 7.60-7.62 (1H, m, H Ar). The NH^+ signal was not observed due to deuterium exchange. Mass spectrum, *m*/*z*: 102.3 $[Et_3NH]^+$, 405.3 $[M\text{-}Et_3N+H]^+$, 809.0 $[2(M\text{-}Et_3N)+H]^+$. Found, %: C 66.50; H 6.49; N 13.92. $C_{28}H_{32}ClN_5O_2$. Calculated, %: C 66.46; H 6.37; N 13.84.

9-(2-Chlorophenyl)-2,4-dioxo-7-(2-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (3a). Tetrahydropyridin-2-olate **1a** (*Caution, irritant!*) (166 mg, 0.44 mmol), β-phenylethylamine (0.06 ml, 0.48 mmol), 96% EtOH (6 ml), and 37% formalin (0.50 ml, 6.66 mmol) were placed in a 25 ml-beaker. The mixture was boiled for 1 min, left for 48 h at 25°C, 96% EtOH (3 ml) was added, and then 10% HCl was added dropwise to pH 2. After 48 h, the precipitate was filtered off and washed with 50% EtOH and Et_2O. Yield 109 mg (59%). White powder; mp 251-253°C (decomp.). IR spectrum, ν, cm^{-1}: 3183 (N–H), 2262 (C≡N), 1734 sh, 1704 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.69-2.73 (2H, m, $NCH_2C\underline{H}_2Ph$); 2.79-2.83 (2H, m, $NC\underline{H}_2CH_2Ph$); 3.34-3.38 (2H, m) and 3.59 (2H, d, ^2J = 11.0, 6,8-CH_2); 4.93 (1H, s, 9-CH); 7.19-7.29 (6H, m, H Ar); 7.51-7.53 (2H, m, H Ar); 7.69-7.71 (1H, m, H Ar); 12.76 (1H, s, NH). Mass spectrum, *m*/*z*: 419.0 $[M+H]^+$, 837.3 $[2M+H]^+$. Found, %: C 65.82; H 4.68; N 13.43. $C_{23}H_{19}ClN_4O_2$. Calculated, %: C 65.95; H 4.57; N 13.38.

7-Benzyl-9-(2-methylphenyl)-2,4-dioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (3b) was prepared similarly to the bispidine **3a** from salt **1b** (300 mg, 0.85 mmol), benzylamine (0.1 ml, 0.93 mmol), and 37% formalin (1.0 ml, 13.3 mmol). Yield 126 mg (39%). Colorless crystals; mp 262-264°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.48 (3H, s, Me); 3.31 (2H, d, ^2J = 10.9) and 3.42 (2H, d, ^2J = 10.9, 6,8-CH_2); 3.78 (2H, br. s, $C\underline{H}_2Ph$); 4.38 (1H, s, 9-CH); 7.08 (1H, d, ^3J = 6.8, H Ar); 7.24-7.36 (8H, m, H Ar); 12.80 (1H, br. s, NH). Mass spectrum, *m*/*z*: 385.1 $[M+H]^+$, 769.8 $[2M+H]^+$. Found, %: C 71.68; H 5.37; N 14.70. $C_{23}H_{20}N_4O_2$. Calculated, %: C 71.86; H 5.24; N 14.57.

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