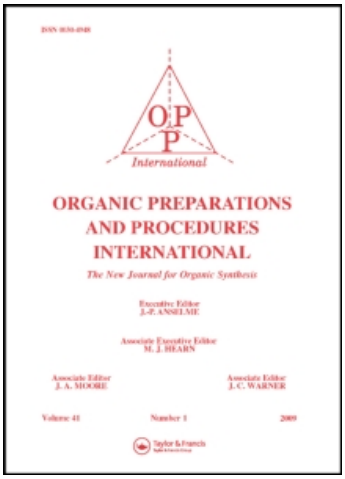

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THE PREPARATION OF AMIDE DERIVATIVES OF 3-AZABICYCLO-[3.3.1]NONANES AS NEW POTENTIAL ANTIARRHYTHMIC AGENTS

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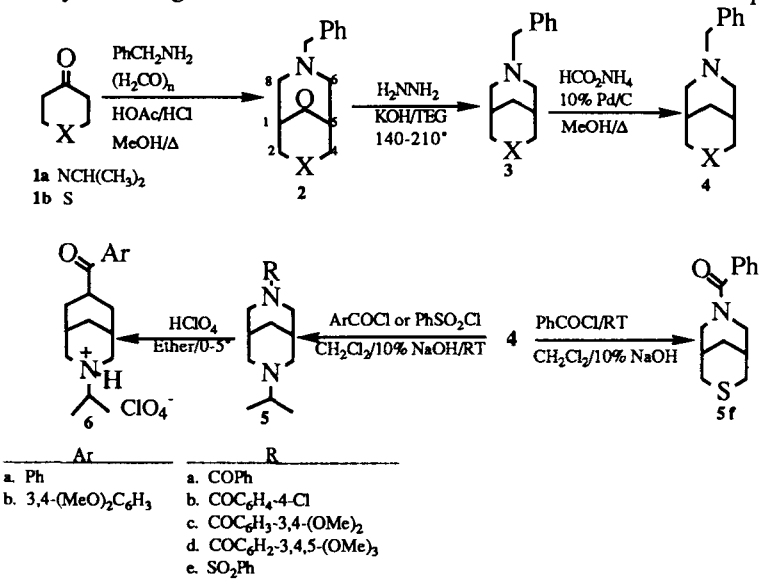
Members of the 3-azabicyclo[3.3.1]nonanes[1-7] and certain derivatives possess promising pharmacological properties as supported by a variety of assays. Several compounds have displayed superb antiarrhythmic action in animal models and slight alterations in structure effect significant changes in the observed activity.[2-5] A few isolated amide derivatives of this family have reported[3,4] antiarrhythmic activity also. We record herein a general synthesis of certain amide derivatives which not only exhibit antiarrhythmic characteristics but are also potential metabolites (which might be derived as *in vivo* degradation products) of members of the 3-azabicyclo[3.3.1]nonanes.[5]

A double Mannich condensation[8] of either 1-isopropyl-4-piperidinone (**1a**) or 4-thianone (**1b**) was utilized in the synthesis of the 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones **2a** and **2b**, respectively. Condensation of **1a** or **1b**, benzylamine, paraformaldehyde, and acetic acid/HCl in methanol gave ketones **2a** and **2b**. It was discovered that the ratio of acetic acid to HCl was critical in that the isolated yield of **2a**, for example, was increased from 20-50% to a consistent 56-57%. This pH dependence suggests that iminium ion intermediates formed in the reaction prior to cyclization to the product require a high acidity medium, and/or the reaction kinetics are altered in such a fashion to favor formation of the bicyclic ketones **2**. Wolff-Kishner reduction[9] of ketones **2** in the presence of hydrazine, KOH, and triethylene glycol at elevated temperature (140-210°) gave the amines **3** as oils (95%) which were characterized and used without further purification. Debenzylation of amines **3a** and **3b** was done in a boiling mixture of ammonium

formate, 10% Pd/C (catalytic), and methanol and gave the secondary amines **4a** (93%) and **4b** (57%), respectively. Although **4a** was isolated as an oil and used without further purification,



amine **4b** required chromatography and was isolated as a viscous gum. The use of ammonium formate as a hydrogen source (especially in debenzylation) has been recently examined and has proven to be a mild method for effecting $ArCH_2$-N cleavage.[10] However, it was suprising that hindered benzyl groups in **3** could be cleaved so readily. Amines **4** could then be acylated using a modified Schotten-Baumann procedure in which the amine was stirred at RT with the appropriate acylation agent in a biphase mixture of CH_2Cl_2/10% NaOH to give the crude amides **5**. Chromatography (neutral alumina) afforded **5a** as an oil (82.4%) while amides **5b-d** and **5f** were isolated (53-80%) as solids. Compounds **5a** and **5c** were then derivatized by conversion to the respective hydroperchlorate salts **6a** (91%) and **6b** (69%). Similarly, amine **4a** was converted to the sulfonamide **5e**.

Amide rotational barriers exhibited by similar benzamides have been found to be approximately 14-15 kcal/mol from ^1H and ^{13}C NMR spectral analyses in $DCCl_3$.[11,12] Thus, in amides **5**, nonequivalence is observed for the CH_3 carbons, C(1) and C(5), C(2) and C(4), and C(6) and C(8). Spectral data for salts **6a** and **6b** were accumulated at 80° in DMSO-d_6 solution (a higher temperature was necessary to obtain coalesced, intensified signals since the spectra at

room temperature displayed broadened, unresolved signals). This suggests that the rotational barrier for salts **6** is much lower than for the unprotonated amides **5**.[5] In summary, we report a convenient synthesis of amides of 3-azabicyclo[3.3.1]nonanes.

EXPERIMENTAL SECTION

All ^{1}H, ^{13}C, and ^{15}N spectral data were obtained on a Varian XL-300 NMR spectrometer operating at 299.94, 75.43, and 30.41 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C NMR spectra were recorded in δ or ppm values downfield from TMS [$(CH_3)_4Si$], while ^{15}N NMR signals were reported in ppm downfield from NH_3 *(liquid,* 0 ppm) using 8 M $^{15}NH_4NO_3$ (19.73 ppm) as an external reference. IR spectra were acquired on a Perkin Elmer 681 IR spectrometer. Melting points, which were uncorrected, were recorded on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Syntheses were executed, unless otherwise indicated, under an atmosphere of N_2 with magnetic stirring. All reagents were obtained commercially and used without further purification except for 4-thianone (**1b**) [prepared by known methods[13] and sublimed (45°/0.05 mm Hg)], 1-isopropyl-4-piperidinone (**1a**) (distilled: bp 38-41°/0.2 mm Hg), ammonium formate [recrystallized from methanol then dried (overnight, 0.2 mm Hg) in a dessicator prior to use (mp 118-120°)], and methanol (deoxygenated prior to use). Alumina (Merck, neutral, 70-230 mesh) and silica gel (Davison Chemical, "Davisil 62", 60-200 mesh) were employed in chromatographic separations with reagent grade solvents as eluants. *Caution: Although no diffculties were found with the hydroperchlorates cited herein, all work should be done in a hood and with extreme care .*

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**2a**).-In standard equipment was placed a mixture of benzylamine (10.71 g, 100 mmol), HCl (37%, 9.86 g, 100 mmol), glacial acetic acid (3.0 g, 50 mmol), and paraformaldehyde (6.31 g, 210 mmol) in deoxygenated CH_3OH (100 mL) which was stirred at reflux (15 min) . A solution of *N*-isopropyl-4-piperidinone (**1a**, 14.12 g, 100 mmol) and glacial acetic acid (6.0 g, 100 mmol) in CH_3OH (100 mL) was then added dropwise to the mixture (30 min), followed by stirring at reflux (18.5 hrs). Concentration of the solution gave an oil which was redissolved in H_2O (100 mL). An ether extract (100 mL) of this acidic solution was discarded. Basicification (pH~ 3, 10% NaOH) of the water layer produced a milky suspension which was extracted (ether, 4 x 60 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated to a viscous red oil, which, on distillation (175-185°/10^{-5} mm Hg), afforded a light yellow oil (15.6 g, 57.2%) which solidified when refrigerated; mp. 46-47.5°. Recrystallization (pentane) gave an analytical sample of **2a**, mp. 49-50°. IR (KBr): 3035, 2975, 2900, 2820 , 1745 (C=O) cm^{-1}; ^{1}H NMR

($DCCl_3$): δ 1.02 [d, 6 H, CH_3], 2.58 [bs, 2 H, H(1,5)], 2.87 [m, 5 H, ring protons and $CH(CH_3)_2$], 3.03 (dd, 4 H, ring protons), 3.53 (s, 2 H, $ArCH_2$), 7.30 (m, 5 H, Ar-H); ^{13}C NMR ($DCCl_3$): ppm 18.25 (CH_3), 46.93 [C(1,5)], 53.41 [$CH(CH_3)_2$], 53.71 [C(2,4)], 58.07 [C(6,8)], 61.25 ($ArCH_2$), 127.09, 128.25, 128.69, 138.67 (ArC), 215.20 (C=O); ^{15}N NMR ($DCCl_3$): ppm 39.25 [N(7)], 40.80 [N(3)].

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28.

Found: C, 75.18; H, 8.61; N, 10.24.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (**2b**).-Similar to **2a**, a mixture containing benzylamine (0.43 g, 4 mmol), paraformaldehyde (0.96 g, 32 mmol), CH_3OH (15 mL), HCl (37%, 0.20 g, 2 mmol), and glacial acetic acid (0.36 g, 6 mmol) was treated with 4-thianone (**1b**, 0.47 g, 4 mmol) and heated at reflux (6 hrs). Evaporation of the solvent gave a red oil which was diluted (H_2O, 30 mL), and the mixture was extracted (ether, 2 x 40 mL), the latter being discarded. Basification (pH~2, NaOH pellets 97%, 0.26 g, 6 mmol) of the aqueous layer produced a yellow suspension which was extracted (ether, 4 x 30 mL). Combined extracts were dried (Na_2SO_4), filtered, and concentrated to a yellow solid. This solid was digested (Skelly B, 300 mL, bp 60-68°) for 30 min, and the supernatant was decanted. Evaporation of the solvent gave **2b** which was then heated *in vacuo* (110°/0.1 mm) in a sublimation unit to give ketone **2b** (0.4 g, 40.4%); mp. 94.5-95.5° (lit.[2] mp. 91-93°).

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**3a**).-To a mixture of KOH pellets (85%, 13.6 g, 206 mmol) and ketone **2a** (7.0 g, 25.7 mmol) in triethylene glycol (120 mL) was added hydrazine (95%, 3.47 g, 103 mmol) in equipment with a lower take-off condenser and a jacketed flask (boiling tetralin in the jacket gave a temperature of 200-210°). After 4 hrs at reflux, the solution was cooled to RT and diluted (chilled water, 150 mL). Combined extracts (ether, 4 x 60 mL) of the suspension were washed with 10% NaOH (60 mL) and saturated NaCl (60 mL), dried (Na_2SO_4), filtered, and concentrated to a yellow oil (6.33 g, 95.3%). IR analysis showed no carbonyl and thus this oil **3a** was used directly.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane (**3b**).-To a mixture of KOH pellets (85%, 3.20 g, 48.5 mmol) and ketone **2b** (1.0 g, 4.04 mmol) in triethylene glycol (25 mL) was added,

hydrazine (95%, 1.36 g, 40.4 mmol) in a jacketed flask (*o*-xylene, bp 140-150°). Following the above procedure gave 0.90 g (95.4%) of a light yellow oil **3b** which displayed no C=O stretch in the IR spectrum and was used without further purification.

3-Isopropyl-3,7-diazabicyclo[3.3.1]nonane (**4a**).-In standard equipment was stirred a mixture of amine **3a** (5.53 g, 21.4 mmol) and 10% Pd/C (0.64 g, 30 mg/mmol of amine) in CH_3OH (80 mL). To this was added anhydrous HCO_2NH_4 (3.37 g, 53.5 mmol). Stirring the mixture at reflux (30 min), cooling the new mixture to RT, and filtering was followed by concentration to give a viscous oil. The oil was dissolved in H_2O (80 mL) and the pH was adjusted (~12, 10% NaOH). Combined extracts (CCl_4, 4 x 40 mL) of the aqueous solution were dried (Na_2SO_4), filtered, and concentrated to give yellow oil **4a** (3.35 g, 93.0%) which was used dir ;tly. IR (film): 3315 (N-H), 2965, 2900, 2850, 2790, 2760, 2725 cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.01 [d, 6 H, CH_3, J = 6.7 Hz], 1.60-1.67 [m, 3 H, H(1,5) and H(9)], 1.79-1.84 [m, 1 H, H(9)], 2.53-2.59 [m, 3 H, H(6,8)ax and $CH(CH_3)_2$], 2.90-3.06 [m, 4 H, H(6,8)eq, H(2,4)ax and H(2,4)eq], 3.56 (bs, 1 H, NH); ^{13}C NMR ($DCCl_3$): ppm 18.12 (CH_3), 30.04 [C(1,5)], 33.62 [C(9)], 52.86 [C(6,8)], 54.59 [$CH(CH_3)_2$], 54.65 [C(2,4)].

3-Thia-7-azabicyclo[3.3.1]nonane (**4b**).-In standard equipment was placed amine **3b** (0.90 g, 3.86 mmol) and 10% Pd/C (0.90 g) in anhydrous CH_3OH (25 mL), and anhydrous HCO_2NH_4 (1.11 g, 17.1 mmol) was added. With stirring, the mixture was brought to reflux (30 min), filtered, and concentrated to a gummy oil which was dissolved in CH_2Cl_2 (15 mL) and filtered. The filtrate was concentrated and placed in a diffusion chamber of ether. The mother liquor was decanted from the crude, oily **4b**. Chromatography of the oil was effected with CH_3OH/CH_2Cl_2 (300 mL of 10% CH_3OH/CH_2Cl_2, 50 mL of 20% CH_3OH/CH_2Cl_2, 100 mL of 50% CH_3OH/-CH_2Cl_2, and 100 mL of CH_3OH) on silica gel . This afforded 0.32 g (56.9%) of amine **4b** (Rf = 0.11, 10% CH_3OH/CH_2Cl_2) as a light, gummy solid (used without further purification). ^1H NMR ($DCCl_3$): δ 1.84, 2.04 [two bd, 2 H, H(9)], 2.31 [bs, 2 H, H(1,5)], 2.80 [bd, 2 H, H(2,4)ax,J = 12.3 Hz], 3.20 [bd, 2 H, H(2,4)eq, J = 13.7 Hz], 3.45 [m, 2 H, H(6,8)ax], 3.73 [bd, 2 H, H(6,8)eq, J = 13.2 Hz], 7.59 (bs, 1 H, NH); ^{13}C NMR ($DCCl_3$): ppm 24.88 [d, C(1,5)], 29.79 [t, C(9)], 32.17 [t, C(2,4)], 47.8 [t, C(6,8)].

3-Benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**5a**).-The following experiment will illustrate the general procedure used for most amides. In standard equipment was placed a solution of the amine **4a** (1.14 g, 6.77 mmol) and NaOH (10%, 6.80 g, 16.9 mmol) in CH_2Cl_2 (15 mL). Dropwise addition (15 min) of a solution of benzoyl chloride (1.05 g, 7.45 mmol) in CH_2Cl_2 (5 mL) was followed by stirring (2.75 hrs). Addition of H_2O (30 mL) and extraction (CH_2Cl_2, 3 x 25 mL) followed. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to a yellow oil. Chromatography of the oil (neutral alumina, EtOAc) gave fractions (Rf = 0.70) which were combined and concentrated to give 1.52 g (82.4%) of amide **5a** as an oil (used directly). IR (film): 3035, 2970, 2925, 2865, 2805, 2780, 2750, 1635 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 0.96 [d, 3 H, CH_3, J = 6.4 Hz], 1.07 [d, 3 H, CH_3, J = 6.6 Hz], 1.65-1.78, [m, 3 H, H(5) and H(9)], 1.97 [bs, 1 H, H(1)], 2.41 [d, 1 H, H(4)ax, J = 10.3 Hz], 2.50 [d, 1 H, H(6)ax, J = 11.0 Hz], 2.62 [m, 1 H, $CH(CH_3)_2$, J = 6.5 Hz], 2.72 [d, 1 H, H(6)eq, J = 10.6 Hz], 3.03-3.07 [m, 2 H, H(2)ax and H(4)eq], 3.30 [d, 1 H, H(8)ax, J = 13.2 Hz], 3.74 [d, 1 H, H(8)eq, J = 12.8 Hz], 4.77 [d, 1 H, H(2)eq, J = 13.9 Hz], 7.28-7.41 (m, 5 H, Ar-H); ^{13}C NMR ($DCCl_3$): ppm 16.30 [CH_3], 19.33 [CH_3], 29.06 [C(1)], 29.76 [C(5)], 32.29 [C(9)], 46.55 [C(2)], 52.19 [C(4)], 52.62 [C(8)], 54.34 [$CH(CH_3)_2$], 54.75 [C(6)], 126.75, 128.24, 128.67, 137.75 (Ar-C), 170.09 (C=O).

3-(4-Chlorobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**5b**).-A mixture of amine **4a** (0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was treated (15 min) with 4-chlorobenzoyl chloride (0.69 g, 3.92 mmol) in CH_2Cl_2 (5 mL). The usual procedure gave 0.86 g (80.4%) of **5b**; mp. 97-98°. IR (KBr): 2965, 2935, 2865, 2800, 2770 (C-H), 1630 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 0.95 [d, 3 H, CH_3, J = 6.5 Hz], 1.05 [d, 3 H, CH_3, J = 6.4 Hz], 1.63-1.75 [m, 3 H, H(5) and H(9)], 1.97 [bs, 1 H, H(1)], 2.41 [bd, 1 H, H(4)ax, J = 10.6 Hz], 2.50 [bd, 1 H, H(6)ax, J = 11.2 Hz], 2.59 [heptet, 1 H, $CH(CH_3)_2$, J = 6.5 Hz], 2.71 [bd, 1 H, H(6)eq, J = 11.0 Hz], 3.03-3.06 [m, 2 H, H(2)ax and H(4)eq], 3.31 [bd, 1 H, H(8)ax, J = 12.8 Hz], 3.71 [bd, 1 H, H(8)cq, 13.1 Hz], 4.77 [bd, 1 H, H(2)ax, J = 13.2 Hz], 7.27-7.37 (m, 4 H, Ar-H); ^{13}C NMR ($DCCl_3$): ppm 16.37, 19.35 [CH_3], 29.07 [C(1)], 29.80 [C(5)], 32.29 [C(9)], 46.68 [C(2)], 52.22 [C(4)], 52.56 [C(8)],

54.38 [$CH(CH_3)_2$], 54.79 [C(6)], 128.35, 128.51, 134.67, 136.11 (Ar-C), 169.03 (C=O).

Anal. Calcd. for $C_{17}H_{23}ClN_2O$: C, 66.55; H, 7.56. Found: C, 66.45; H, 7.71

3-(3-4-Dimethoxybenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**5c**).-A mixture of amine **4a** (0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was treated (15 min) with 3,4-dimethoxybenzoyl chloride (0.80 g, 3.92 mmol) in CH_2Cl_2 (10 mL). The usual procedure gave 0.87 g (73.1%) of off-white solid **5c**; mp. 67.5-69.5°. IR (KBr): 3055, 2950, 2915, 2845, 2820, 2770, 2750, 2710, 1625 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 0.96 [d, 3 H, CH_3, J = 6.4 Hz], 1.06 [d, 3 H, CH_3, J = 6.5 Hz], 1.62-1.75 [m, 3 H, H(5) and H(9)], 1.96 [bs, 1 H, H(1)], 2.43 [bd, 1 H, H(4)ax, J = 9.7 Hz], 2.51 [bd, 1 H, H(6)ax, J = 10.5 Hz], 2.62 [heptet, 1 H, $CH(CH_3)_2$, J = 6.4 Hz], 2.74 [bd, 1 H, H(6)cq, J = 9.9 Hz], 3.00-3.09 [m, 2 H, H(4)eq and H(2)ax], 3.32 [bd, 1 H, H(8)ax, J = 13.2 Hz], 3.83-3.94 [m, 7 H, H(8)eq and OCH_3], 4.77 [bd, 1 H, H(2)eq, J = 13.3 Hz], 6.84-6.94 (m, 3 H, Ar-H); ^{13}C NMR ($DCCl_3$): ppm 16.46, 19.15 [CH_3], 29.13 [C(1)], 29.86 [C(5)], 32.36 [C(9)[, 46.71 [C(2)], 52.25 [C(4)], 52.65[C(8)],54.35 [$CH(CH_3)_2$], 54.68 [C(6)], 55.88, 55.93 (OCH_3), 110.50, 119.64, 130.23, 148.78, 149.39 (Ar-C), 169.90 (C=O).

Anal: Calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49. Found: C, 68.58; H, 8.47

7-Isopropyl-3-(3,4,5-trimethoxybenzoyl)-3,7-diazabicyclo[3.3.1]nonane (**5d**).-A mixture of amine **4a** (0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was treated with 3,4,5-trimethoxybenzoyl chloride (0.92 g, 3.92 mmol) in CH_2Cl_2 (5 mL). This gave 1.02 g (79.1%) of off-white solid **5d**; mp. 67.5-69.5°. IR (KBr): 3055, 2985, 2955, 2910, 2890, 2780 (C-H), 1620 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 0.96 [d, 3 H, CH_3, J = 6.5 Hz], 1.09 [d, 3 H, CH_3, J = 6.7 Hz], 1.64-1.79 [m, 3 H, H(5) and H(9)], 2.05 [bs, 1 H, H(1)], 2.44 [bd, 1 H, H(4)ax, J = 10.6 Hz], 2.57 [bd, 1 H, H(6)ax, J = 10.8 Hz], 2.66 [heptet, 1 H, $CH(CH_3)_2$, J = 6.6 Hz], 2.71 [bd, 1 H, H(6)eq, J = 11.0 Hz], 3.02-3.07 [m, 2 H, H(4)eq and H(2)ax], 3.31 [bd, 1 H, H(8)ax, J = 13.2 Hz], 3.80-3.92 [m, 10 H, H(8)eq and OCH_3], 4.77 [bd, 1 H, H(2)eq, J = 13.5 Hz], 7.29 (s, 2 H, Ar-H); ^{13}C NMR ($DCCl_3$): ppm 15.87, 19.42 (CH_3), 29.02 [C(1)], 29.78 [C(5)], 32.35 [C(9)], 46.64 [C(2)], 51.73 [C(4)], 52.48 [C(8)], 54.39 [$CH(CH_3)_2$], 54.95 [C(6)], 56.13, 60.86 (OCH_3), 103.83,

133.32, 133.21, 138.22, 153.21 (Ar-C), 169.66 (C=O).

Anal. Calcd. for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34. Found: C, 66.04; H, 8.32

3-Benzenesulfonyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**5e**).-A stirred, ice cold (5°) mixture of amine **4a** (1.03 g, 6.12 mmol) and NaOH pellets (97%, 0.76 g, 18.4 mmol) in H_2O (7 mL) and CH_2Cl_2 (5 mL) was treated (30 min) with benzenesulfonyl chloride (2.16 g, 12.2 mmol) in CH_2Cl_2 (5 mL). Stirring (17.5 hrs) at RT gave a mixture which was partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL) followed by basification (pH~12, 10% NaOH) of the aqueous phase. Aqueous extracts (CH_2Cl_2, 3 x 30 mL) and the initial organic layer were combined and washed [10% NaOH (30 mL); saturated NaCl (30 mL)], dried (Na_2SO_4), filtered, and concentrated to a viscous oil. Chromatography (silica gel, 10% CH_3OH/CH_2Cl_2) gave fractions (Rf = 0.44) which were concentrated and rechromatographed (neutral alumina, EtOAc). Fractions (Rf = 0.53) were concentrated, and rechromatographed (silica gel, 5% CH_3OH/CH_2Cl_2). Fractions (Rf = 0.34) were concentrated to give 0.54 g (28.6%) of white solid **5e**; mp. 85.5-86.5°. IR (KBr): 3060, 2960, 2910, 2890, 2865, 2820, 1585, 1340, 1170 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.88 [d, 6 H, CH_3, J = 6.5 Hz], 1.40 [bs, 2 H, H(9)], 1.94 [bs, 2 H, H(1,5)], 2.35 [bd, 2 H, H(6,8)ax, J = 10.3 Hz], 2.53 [heptet, 1 H, $CH(CH_3)_2$, J = 6.5 Hz], 2.69 [bd, 2 H, H(6,8)cq, J = 10.3 Hz], 2.89 [dd, 2 H, H(2,4)ax, J = 11.2 Hz, J' = 4.5 Hz], 3.36 [d, 2 H, H(2,4)eq, J = 10.9 Hz], 7.58-7.75 (m, 5 H, Ar-H); ^{13}C NMR (DMSO-d_6): ppm 17.57 (CH_3), 27.39 [C(1,5)], 28.95 [C(9)], 48.88 [C(2,4)], 52.66 IC(6,8)], 53.42 [$CH(CH_3)_2$], 126.90, 129.01, 132.36, 136.79 (ArC).

Anal. Calcd. for $C_{16}H_{24}N_2O_2S$: C, 62.31; H, 7.85. Found: C, 62.48; H, 7.69.

7-Benzoyl-3-thia-7-azabicyclo[3.3.1]nonane (**5f**).-In the usual setup, a chilled (5°) solution of NaOH pellets (0.1 g, 2.38 mmol) in H_2O (1.7 mL) and amine **4a** (0.17 g, 1.19 mmol) in CH_2Cl_2 (1 mL) was treated (5 min) with benzoyl chloride (0.2 g, 1.43 mmol). Chromatography of the oil (alumina, EtOAc), afforded amide **5f** (Rf = 0.47) as white crystals (157 mg, 53.3%); mp. 95-96°. IR (KBr): 3065, 3045, 3000, 2985, 2940, 2910, 2855, 2835, 1635 (C=O); ^1H NMR ($DCCl_3$): δ 1.78-1.93 [m, 3 H, H(9) and H(1)], 2.15 [bs, 1 H, H(5)], 2.39 [d, 1 H, H(4)ax, J = 13.9 Hz], 2.77 [d, 1 H, H(6)ax, J = 12.3 Hz], 3.12-3.21 [m, 3 H,

H(4)eq and H(6)eq], 3.41 [d, 1 H, H(2)ax, J = 12.8 Hz], 3.89 [d, 1 H, H(2)eq, J = 13.4 Hz], 4.98 [d, 1 H, H(8)eq, J = 13.1 Hz], 7.38-7.44 (m, 5 H, Ar-H); ^{13}C NMR ($DCCl_3$): ppm 26.53 [C(1)],26.87 [C(5)], 31.73 [C(2)], 31.78 [C(9)], 32.34 [C(4)], 46.07 [C(8)], 52.12 [C(6)], 126.46,128.41,128.83, 137.35 (Ar-C), 170.38 (C=O).

Anal. Calcd. for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93. Found: C, 68.01; H, 7.07

3-Benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (**6a**).-A chilled (5°), stirred solution of the amide **5a** (1.52 g, 5.58 mmol) in ether (60 mL) was treated (10 min) with a solution of $HClO_4$ (60%, 1.17 g, 6.98 mmol) followed by stirring (10 min). Filtration gave salt **6a** which was washed(dry ether, 50 mL), stirred [hot CH_3OH (30 mL)] and refrigerated. Filtration and drying afforded 1.90 g (91.3%) of **6a**; mp. 226-227° (dec): IR (KBr): 3150 (NH), 2990, 2960, 2935, 2920, 2885, 1635 (C=O) cm^{-1}, 1100 (Cl-O);[14] ^1H NMR [DMSO-d_6]: δ 1.55 [d, 6 H, CH_3, J = 6.6 Hz], 1.97 [bd, 1 H, H(9), J = 13.0 Hz], 2.18 [bd, 1 H, H(9), J = 13.2 Hz], 2.51 [bs, 2 H, H(1,5)], 3.30[bd, 2 H, H(6,8)ax, J = 13.2 Hz], 3.65 [m, 2 H, H(2,4)ax], 3.83 [h, 1 H, $CH(CH_3)_2$, J = 6.8 Hz], 3.94 [bd, 2 H, H(6,8)eq, J = 12.3 Hz], 4.23 [bd, 2 H, H(2,4)eq, J = 13.2 Hz], 7.45-7.50 (m, 5 H, Ar-H), 7.85 (bs, 1 H, N-H); ^{13}C NMR (DMSO-d_6, 80°): ppm 16.34 [CH_3], 26.69 [C(1,5)], 27.62 [C(9)], 48.80 [C(2,4)], 52.31 [C(6,8)], 59.91 [$\underline{C}H(CH_3)_2$], 127.05, 128.30, 129.40, 136.40 (Ar-C), 172.86 (C=O).

Anal. Calcd. for $C_{17}H_{25}ClN_2O_5$: C, 54.76; H, 6.76. Found: C, 54.43; H, 6.78

3-(3,4-Dimethoxybenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (**6b**)-Amide **5c** (0.30 g, 0.90 mmol) in ether (30 mL) was treated with a solution of $HClO_4$ (60%, 0.18 g, 1.08 mmol) in $(H_3C)_2CHOH$ (1 mL). The usual procedure gave 0.27 g (69.2%) of white solid **6b**; mp. 235-236° (dec). IR (KBr): 3130 (NH), 3010, 2975, 2945, 2920, 1635 (C=O), 1095 (Cl-O) cm^{-1}; ^1H NMR (DMSO-d_6, 80°): δ 1.33 [d, 6 H, CH_3, J = 6.7 Hz], 1.74 [bd, 1 H, H(9), J = 12.8 Hz], 1.91 [bd, 1 H, H(9), J = 13.2 Hz], 2.27 [bs, 2 H, H(1,5)], 3.12 [bd, 2 H, H(6,8)ax, J = 13.7 Hz], 3.19-3.28 [m, 2 H, H(2,4)ax], 3.42-3.56 [m, 3 H, H(6,8)eq and $CH(CH_3)_2$], 3.78, 3.81 (two s, 6 H, OCH_3), 3.97 [bd, 2 H, H(2,4)eq, J = 13.6 Hz], 6.94-7.03 (m, 3 H, Ar-H), 7.81 (bs, 1 H, N-H); ^{13}C NMR (DMSO-d_6, 80°): ppm 16.34 (CH_3), 26.81 [C(1,5)], 27.80 IC(9)], 49.06 [C(2,4)], 52.40 [C(6,8)], 55.88, 55.92 (OCH_3),

59.97 [$CH(CH_3)_2$], 111.85, 112.10, 120.44, 128.68, 148.74, 150.26 (Ar-C), 172.97 (C=O).

Anal. Calcd. for $C_{19}H_{29}ClN_2O_7$: C, 52.72; H, 6.75. Found: C, 52.35; H, 6.77

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