2,3,8-TRIAZABICYCLO[3.3.1]NON-3-ENE. A NEW HETEROCYCLIC SYSTEM

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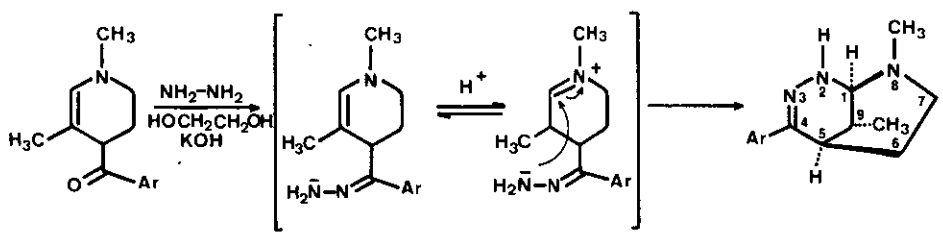
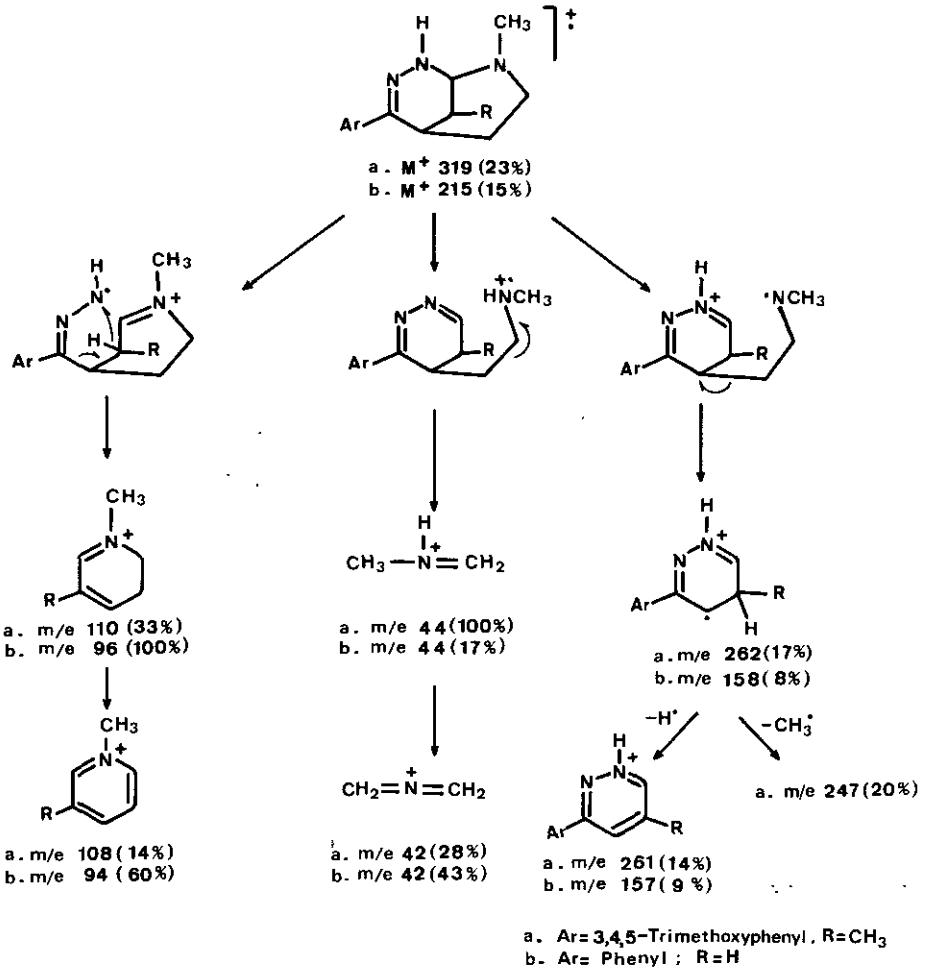
Abstract- The formation of 2,3,8-triazabicyclo[3.3.1]non-3-ene system by reaction of 4-acyl-1,2,3,4-tetrahydropyridines with hydrazine is described.

In the context of our studies about the synthesis of 7,8-benzomorphans by isomerization of 4-benzyl- and 4-benzoyl-1,2,3,6-tetrahydropyridines (2-piperideines), we attempted the Wolff-Kishner reduction of 3,4,5-trimethoxyphenyl 1,3-dimethyl-1,4,5,6-tetrahydro-4-pyridyl ketone (1), whose preparation has been already reported.[1] The treatment of 1 with hydrazine hydrate and potassium hydroxide in ethylene glycol under Wolff-Kishner conditions afforded a crystalline solid which was identified by its elemental analysis ($C_{17}H_{25}N_3O_3$) and spectroscopic data as the triazabicyclo[3.3.1]nonene 3.



The ir spectrum of 3 showed absorptions at 3450 and 1585 cm^{-1}, indicative of N-H and conjugated C=N bonds, respectively. The most significant signals in the ^1H nmr spectrum (200 MHz) were two broad singlets at δ 2.92 and 3.76 due to the bridgehead equatorial methine protons H-5 and H-1, respectively, and a doublet at δ 0.89 corresponding to the C-9 methyl group.[2] Other characteristic signals were the singlets corresponding to the aromatic protons, methoxy, and *N*-methyl groups. Besides, an exchangeable broad singlet at δ 6.36 corresponding to the N-H proton was observed. The mass spectrum of 3 showed a molecular peak at *m/e* 319 and a fragmentation

pattern consistent with the proposed structure.[3] The following scheme depicts the most characteristic fragmentations of triazabicyclo derivatives 3 and 10 (see later).

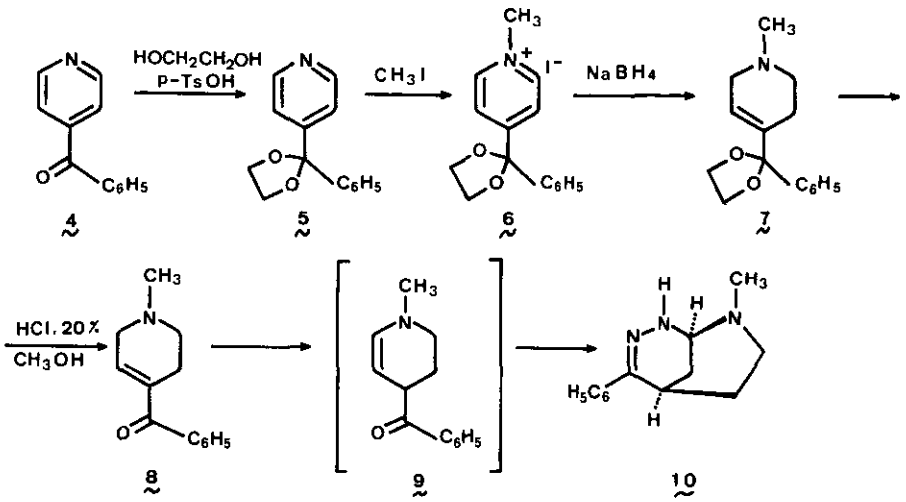


a. Ar= 3,4,5-Trimethoxyphenyl, R=CH_3
b. Ar= Phenyl ; R=H

The formation of 3 can be accounted for by considering that hydrazone 2 cyclizes by nucleophilic attack of the terminal nitrogen atom upon the iminium salt generated by protonation of the enamine function. Through a mechanistically similar process, i.e., the intramolecular attack of a carbonyl α-carbon upon a 2,3,4,5-tetrahydropyridinium salt, we have recently reported[4] the synthesis of 2-azabicyclo[3.3.1]nonan-7-ones.

To our knowledge there are not precedents on the synthesis of the 2,3,8-triazabicyclo[3.3.1]nonane system.[5] This prompted us to study a similar cyclization from a simplified model, such as 1,2,3,4-tetrahydropyridine 9, in order to evaluate if the observed cyclization could provide a general synthetic entry to this new heterocyclic system. As in the above enamine 1, initially we planned to prepare 9 by acid-

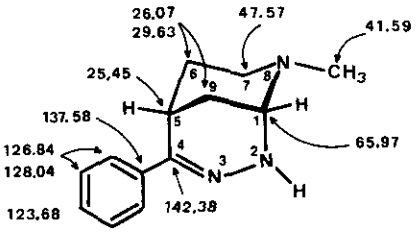
catalyzed isomerization of 1,2,3,6-tetrahydropyridine 8, which was obtained from 4-benzoylpyridine (4)[6] through the reaction sequence depicted in the scheme:



4 5 6 7 8 9 10

Although tetrahydropyridine 8 proved to be unstable and decomposed partially on chromatographic purification (silica gel), it was characterized by ^{1}H nmr. For this reason we attempted to effect the hydrolysis of acetal 7 and the isomerization of the double bond in a single step by refluxing in 50% acetic acid. As expected, further treatment of crude enamine 9 with hydrazine hydrate under Wolff-Kishner conditions afforded triazabicyclo system 10, but in very low yield (<10%) probably due to the sensitive character of the intermediate enamine.[7]

To avoid the manipulation of enamine 9 we decided to carry out the isomerization of tetrahydropyridine 8 under alkaline conditions (MeONa, MeOH) as described by Joule[8] and, without isolating enamine 9, to allow the entire reaction mixture to react with hydrazine hydrate. Operating in this manner the desired triazabicyclo 10 was obtained in pure form in 67% yield. The spectroscopic data were in full accord with the structural assignment. Thus, bands at 3100-3500 (NH) and 1590 (C=N) cm^{-1} were observed in the ir spectrum, whereas the most characteristic signals in the ^{1}H nmr spectrum were, as in compound 3, two broad singlets at δ 3.15 and 4.02 corresponding to the bridgehead methine protons H-5 and H-1, respectively. Finally, the chemical shift values in the ^{13}C nmr spectrum of 10 are summarized in the following figure. It is worth mentioning the deshielding (δ 65.97) and multiplicity (doublet) of C-1 indicative of a cyclized structure, as well as the shielding of C-7 as a consequence of a γ-gauche effect due to the axial substituents at C-1 and C-5.[9]



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EXPERIMENTAL

Ir spectra were taken on a Perkin-Elmer 577 spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. Nmr spectra were recorded in $CDCl_3$ with TMS (δ 0) as internal standard (^1H nmr, 60 MHz: Perkin-Elmer R-24B; ^1H nmr, 200 MHz and ^{13}C nmr: Varian XL-200). Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. Melting points were determined on a Büchi apparatus and are uncorrected. Column chromatography was carried out on SiO_2 (silica gel 60, Merck, 63-200 μm). Tlc was carried out on SiO_2 (silica gel HF_{254}, Merck) and the spots were located with uv light or iodoplatinate reagent. The developing solvent was ether-acetone-diethylamine (35:15:2). Preparative tlc were run on silica gel plates $60F_{254}$ (Merck), layer thickness 2 mm, using 9:1 ether-acetone as developing solvent. Microanalyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

Phenyl 4-Pyridyl Ketone Ethylene Acetal (5). A mixture of 4-benzoylpyridine[6] (9.15 g, 0.05 mol), ethylene glycol (25 ml, 0.45 mol), and *p*-toluenesulfonic acid monohydrate (9.9 g, 52 mmol) in anhydrous benzene (100 ml) was refluxed for 36 h with removal of water by a Dean-Stark trap. The resulting solution was poured into 10% sodium carbonate solution and extracted with benzene. The extracts were dried and evaporated to give 5 (9.1 g, 80%) as a brown gum which solidified on standing: mp 65-67 °C (ether); nmr: 3.90 (s, 4H, OCH_2), 7.0-7.5 (m, 7H, ArH), 8.40 (d, J=6 Hz, 2H, pyridine α-H); mass spectrum: *m/e* (relative intensity) 227 (M^+, 1), 183 (53), 150 (22), 149 (93), 106 (21), 105 (100), 78 (13), 77 (38), 51 (29), 50 (13). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 73.76; H, 5.73; N, 6.11.

4-(α,α-Ethylenedioxybenzyl)-1-methylpyridinium Iodide (6). To a solution of 5 (12.3 g, 54 mmol) in anhydrous acetone (100 ml) was added methyl iodide (10 ml, 0.16 mol) dropwise. The mixture was stirred at room temperature for 36 h. After filtration, a solid (17.5 g, 88%) was obtained. Recrystallization from acetone gave white crystals, mp 187-190 °C; nmr: 3.95 (s, 4H, OCH_2) , 4.50 (s, 3H, NCH_3), 7.0-7.4 (m, 5H, ArH), 7.90 (d, J=6 Hz, 2H, pyridine β-H), 9.21 (d, J=6 Hz, 2H, pyridine α-H). Anal. Calcd for $C_{15}H_{16}INO_2$: C, 48.79; H, 4.37; N, 3.79. Found: C, 48.41; H, 4.29; N, 3.75.

1-Methyl-1,2,3,6-tetrahydro-4-pyridyl Phenyl Ketone Ethylene Acetal (7). To an ice-cooled solution of 6 (8.5 g, 23 mmol) in absolute methanol (150 ml) was added sodium borohydride (1.89 g, 50 mmol) portionwise. The mixture was stirred at room tem-

perature for 4 h. The residue after evaporation was taken up in aqueous potassium carbonate solution and extracted with chloroform. The organic extracts were dried and evaporated to give 7 (5.5 g, 90%), bp 150-180 °C/0.1 mm Hg (oven temperature). Crystallization from ether-acetone gave a solid, mp 36-38 °C; nmr: 2.15 (s, 3H, NCH_3), 1.9-2.5 (m, 4H, NCH_2CH_2), 2.7-2.9 (m, 2H, $=CCH_2N$), 3.70 (br s, 4H, OCH_2), 5.60 (br s, 1H, =CH), 6.9-7.4 (m, 5H, ArH); mass spectrum: *m/e* (relative intensity) 245 (M^+, 4), 200 (3), 172 (11), 149 (100), 105 (47), 96 (98), 77 (26), 51 (9), 42 (15). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.14; H, 7.83; N, 5.68.

4-Phenyl-2,3,8-triazabicyclo[3.3.1]non-3-ene (10). Method A. A solution of acetal 7 (2 g, 8.16 mmol) in deoxygenated 50% acetic acid was refluxed under nitrogen for 2 h. The mixture was poured into ice-water, basified with potassium carbonate, and extracted with ether. The organic extracts were dried and evaporated to give an oil (1.5 g) which was dissolved in ethylene glycol (40 ml). To the resulting solution were added hydrazine hydrate (2 g, 32 mmol) and potassium hydroxide (2 g). The mixture was heated under nitrogen and distilled to raise the temperature to 140 °C. The remaining solution was stirred at 140 °C for 1 h, poured into water, and extracted with ether. The ethereal extracts were washed with water, dried, and evaporated to give a mixture of acetal 7 and triazabicyclo 10. Preparative tlc afforded 100 mg of the product 10 (lower Rf value).

Method B. A solution of 20% aqueous HCl (20 ml), methanol (10 ml), and acetal 7 (1 g, 4.1 mmol) was stirred at 60 °C for 30 min under nitrogen. The mixture was basified with potassium carbonate and extracted with ether. The organic extracts were dried and evaporated to give 8 (0.7 g, 85%); ir (NaCl): 1650 cm^{-1}; nmr: 2.30 (s, 3H, NCH_3), 2.55 (br s, 4H, NCH_2CH_2), 2.8-3.2 (m, 2H, $=CCH_2$), 6.30 (br s, 1H, =CH), 7.0-7.6 (m, 5H, ArH). Sodium metal (0.7 g, 30 mmol) cut into small pieces was added under nitrogen to 20 ml of anhydrous deoxygenated methanol. To this solution was added dropwise a solution of ketone 8 (1.5 g, 7.5 mmol) in deoxygenated methanol (10 ml), and the mixture was refluxed for 3 h. After cooling, ethylene glycol (30 ml) and 80% hydrazine hydrate (2 g, 32 mmol) were added. The mixture was heated, methanol, water, and excess of hydrazine hydrate were distilled under nitrogen for 3 h to raise the temperature to 140 °C, and the remaining solution was stirred at 140 °C for 15 h under nitrogen. The mixture was poured into water and extracted with ether. The ethereal extracts were washed with water, dried and evaporated to give 10 (1.1 g, 67%) which was purified by column chromatography (chloroform as eluent); ir (NaCl): 3100-3500 (NH), 1590 (C=N) cm^{-1}; nmr (200 MHz): 2.35 (s, 3H, NCH_3), 2.63 (m, 1H, 3-Heq), 3.15 (br s, 1H, 5-H), 4.02 (br s, 1H, 1-H), 6.60 (br s, 1H, exchangeable, NH), 7.3-7.4 (m, 3H, ArH), 7.6-7.7 (m, 2H, ArH); ^{13}C nmr: 25.45 (d, C-5), 26.07 and 29.63 (2t, C-6 and C-9), 41.59 (q, NCH_3), 47.57 (t, C-7), 65.97 (d, C-1), 123.68 (d, C-*para*), 126.84 and 128.04 (2d, C-*orto* and C-*meta*), 137.58 (s, C-*ipso*), 142.38 (s, C-4); mass spectrum: *m/e* (relative intensity) 215 (M^+, 15), 158 (8), 157 (9), 115 (23), 96 (100), 95 (37), 94 (60), 91 (23), 77 (22), 70 (31), 51 (13), 44 (17), 42 (43). The hydrochloride melted at 188-189 °C (acetone); ir (KBr): 3250 (NH), 1590 (C=N) cm^{-1}; nmr ($CDCl_3$-CD_3OD): 2.70 (s, 3H, $\overset{+}{N}CH_3$), 3.0-3.4 (m, 2H, 5-H and 7-Heq), 4.70 (br s, 1H, 1-H), 7.0-7.7 (m, 5H, ArH).

Anal. Calcd for $C_{13}H_{18}ClN_3$: C, 62.02; H, 7.21; N, 16.69; Cl, 14.08. Found: C, 62.48; H, 7.39; N, 17.06; Cl, 14.20.

8,9-Dimethyl-4-(3,4,5-trimethoxyphenyl)-2,3,8-triazabicyclo[3.3.1]non-3-ene (3). To a solution of potassium hydroxide (1.5 g) in ethylene glycol (35 ml) were added enamine 1[1] (1.5 g, 48 mmol) and 80% hydrazine hydrate (1.5 g, 24 mmol). The mixture was heated under nitrogen and distilled to raise the temperature to 140 °C. The resulting solution was stirred for 1 h at this temperature, cooled, poured into ice-water, and extracted with ether. The ethereal extracts were washed with water, dried, and evaporated to give a solid (0.44 g, 29%) which was recrystallized from acetone-hexane, mp 150-152 °C; ir (KBr): 3450 (NH), 1585 (C=N) cm^{-1}; nmr (200 MHz) 0.89 (d, J=7 Hz, 3H, 9-CH_3), 2.42 (s, 3H, NCH_3), 2.68 (br d, J=9 Hz, 2H, 7-H), 2.92 (br s, 1H, 5-H), 3.76 (br s, 1H, 1-H), 3.85 (s, 3H, OCH_3), 3.90 (s, 6H, OCH_3), 6.36 (br s, 1H, NH), 6.91 (s, 2H, ArH); mass spectrum: *m/e* (relative intensity) 319 (M^+, 23), 318 (11), 288 (23), 262 (17), 261 (14), 247 (20), 110 (33), 109 (14), 108 (15), 97 (14), 84 (49), 69 (17), 44 (100), 43 (20), 42 (28). Anal. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.93; H, 7.89; N, 13.16. Found: C, 63.62; H, 7.86; N, 12.87. Hydrochloride: nmr (DMSO-d_6): 0.80 (d, J=7 Hz, 3H, 9-CH_3), 1.8-2.5 (m, 4H, piperidine), 2.60 (br s, 3H, NCH_3), 3.20 (br s, 1H, =CCH), 3.68 (s, 3H, OCH_3), 3.90 (s, 6H, OCH_3), 4.65 (br s, 1H, 1-H), 6.96 (s, 2H, ArH). Anal. Calcd for $C_{17}H_{26}ClN_3O_3$: C, 57.38; H, 7.36; N, 11.81; Cl, 9.96. Found: C, 57.08; H, 7.43; N, 11.71; Cl, 9.98.

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