

The Sodium Borohydride Reduction of *N*-Iminopyridinium Ylides. I. Synthesis of *N*-Imino-1,2,3,6-tetrahydropyridines.

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Reaction of arylsulfonyl, pyridylcarbonyl and arylalkylhydrazines **2** with 2,4-dinitrophenylpyridinium chloride **1** affords *N*-iminopyridinium ylides **3**. The sodium borohydride reduction of ylides **3** to *N*-imino-1,2,3,6-tetrahydropyridines is described.

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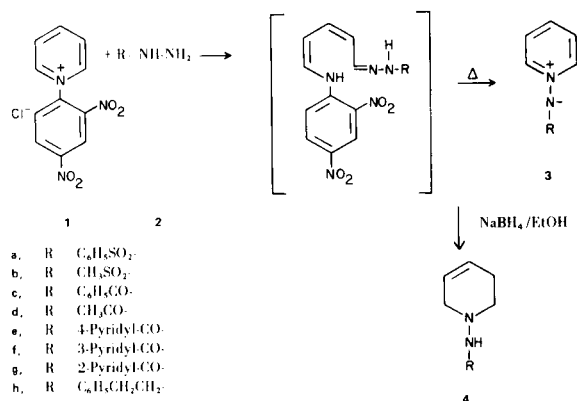
The use of *N*-iminopyridinium ylides as precursors for synthesis of pharmacologically active agents provides an attractive route to reduced pyridine heterocycles. Although the pharmacology of some *N*-alkylpiperidine and *N*-alkyl-1,2,3,6-tetrahydropyridine derivatives have been studied (1) the preparation of *N*-imino-1,2,3,6-tetrahydropyridines has not been reported. A program to develop synthetic methods has been initiated to prepare *N*-imino-1,2,3,6-tetrahydropyridines as model compounds for metabolic and pharmacological studies.

Treatment of 2,4-dinitrophenylpyridinium chloride **1** with arylsulfonyl, pyridylcarbonyl and arylalkylhydrazines **2** according to the procedure of Tamura (2) afforded *N*-iminopyridinium ylides **3**. The facile sodium borohydride reduction of ylides **3** now provides a convenient route to *N*-imino-1,2,3,6-tetrahydropyridines **4**.

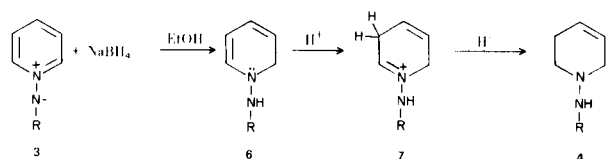
A typical procedure involves the reaction of **1** with benzenesulfonyl hydrazine **2a** to afford 5-(2,4-dinitroanilino)penta-2,4-dienal benzenesulfonylhydrazone which on heating gives rise to *N*-benzenesulfonyliminopyridinium

ylide **3a** (85.6%). Reduction of **3a** with sodium borohydride in ethanol at ice-bath temperature for 4 hours afforded *N*-benzenesulfonylimino-1,2,3,6-tetrahydropyridine **4a** (38.9%). The other pyridinium ylides **3b-h** and *N*-imino-1,2,3,6-tetrahydropyridyl derivatives **4b-h** described were prepared using similar procedures.

Phenylethylimino-1,2,3,6-tetrahydropyridine **4h** was found to undergo oxidation readily during purification and on storage to a compound which exhibits spectral data consistent with structure **5**. The high resolution mass spectrum exhibited a molecular ion at *m/e* 200.1316; (Mass calcd. for C₁₃H₁₆N₂: 200.1314). The nmr spectrum (deuteriochloroform) showed the following characteristic absorptions: a 5H multiplet at δ 7.15 due to phenyl hydrogens, a 1H triplet ($J_{\text{CH}=\text{CH}_2} = 6$ Hz) at δ 6.82 due to $-\text{N}=\text{CH}-$, a 2H multiplet at δ 5.68 attributed to C₄-H, C₅-H, a 2H doublet ($J_{\text{CH}=\text{CH}_2} = 6$ Hz) at δ 3.53 due to $-\text{CH}_2-$, a 2H multiplet at δ 3.38 assigned to the C₂-H, a 2H triplet ($J_{2,3} = 5.5$ Hz) due to the C₂-H and a 2H multiplet at δ 2.26 attributed to C₃-H. No change on addition of deuterium oxide was observed.



The mechanism for the reduction of pyridinium ylides **3** has not been investigated but it is expected to be analogous to that of pyridinium salts. Attack by hydride anion at carbon adjacent to the quaternary nitrogen would yield the dienamine **6** which on protonation and sub-



sequent reduction of the immonium species **7** would afford **4** (3).

Since other pyridinium ylides **3** can also be prepared (2) the above reaction should allow the synthesis of a variety of *N*-amino-1,2,3,6-tetrahydropyridine derivatives **4** with a wide selection of substituents on the tetrahydropyridyl, pyridyl and phenyl ring systems.

The reduction of functionalized pyridinium ylides **3** and biological screening of compounds **4** are presently under study.

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nmr spectra were determined for solutions of deuteriochloroform unless otherwise noted with TMS as internal standard with a Varian A-60 or HA-100 spectrometer. Infrared spectra were taken on a Unicam SP-1000 spectrometer. Mass spectra were measured with an AEI-MS-9 or MS-50 mass spectrometer and these exact mass measurements are used in lieu of elemental analyses.

N-Benzenesulfonyliminopyridinium Ylide (**3a**).

General Procedure A.

To an ice-cooled solution of **1** (3.26 g., 11.6 mmoles) in methanol (30 ml.) was added dropwise benzenesulfonylhydrazine (3.92 g., 22.8 mmoles) in methanol (40 ml.) and then triethylamine (0.9 ml.). The reaction mixture was allowed to stand at room temperature overnight. The solid which precipitated was filtered off and washed in succession with 60 ml. each of methanol, water, methanol and ether. A suspension of the solid obtained above in dioxane-water (4:1) (200 ml.) was heated under reflux for 12 hours to afford a clear solution. The solvent was removed *in vacuo* below 55°, water was added to the residue and the insoluble material removed by filtration. The filtrate was concentrated under reduced pressure to yield **3a**. Chromatography on a neutral alumina column (2.5 x 26 cm) using ether-methanol (1:1 v/v) (400 ml.) as eluant afforded pure **3a** (2.32 g., 85.6%), m.p. 150-152° (Lit. (4) m.p. 150-152°).

N-Benzenesulfonylimino-1,2,3,6-tetrahydropyridine (**4a**).

General Procedure B.

Sodium borohydride (100 mg.) was added to a solution of 95% ethanol (40 ml.) pre-cooled to 0°. A solution of **3a** (0.31 g., 1.32 mmoles) in 95% ethanol (40 ml.) was added dropwise during 20 minutes. After stirring for 4 hours at 0° the reaction mixture was poured onto crushed ice (150 ml.) and allowed to come to room temperature. Extraction with chloroform (4 x 75 ml.) drying (sodium sulfate) and removal of the solvent *in vacuo* gave a yellow semi-solid which was subjected to preparative tlc on four 8 x 8 inch silica gel GFP 254 plates, 0.5 mm in thickness, with benzene-ether (1:4 v/v) as the development solvent. Extraction with warm methanol (50 ml.) of the fraction with R_f of 0.78 gave **4a** (0.123 g., 38.9%), ir (neat): 1330 and 1165 cm^{-1}

(SO_2); nmr: δ 7.42-8.13 [m, 5, PH], 6.23 [2, 1, NH, exchanges with deuterium oxide], 5.22-5.82 [m, 2, $\text{C}_4\text{-H}$, $\text{C}_5\text{-H}$], 2.95-3.32 [m, 2, $\text{C}_6\text{-H}$], 2.7 [t ($J_{2,3} = 5.5$ Hz), 2, $\text{C}_2\text{-H}$], 1.82-2.23 [m, 2, $\text{C}_3\text{-H}$].

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 55.44; H, 5.92; N, 11.75. Found: C, 55.44; H, 6.16; N, 11.81.

N-Methanesulfonylimino-1,2,3,6-tetrahydropyridine (**4b**).

A solution of **3b** (0.21 g., 1.22 mmoles) in 95% ethanol (30 ml.) was added to a pre-cooled solution of sodium borohydride (0.2 g.) in 95% ethanol (40 ml.) and the reaction was completed as described under Procedure B above (5). The reaction product was subjected to preparative tlc on four 8 x 8 inch silica gel GF 254 plates, 0.5 mm in thickness, with benzene-ether (1:4 v/v) as development solvent. Extraction with warm methanol (50 ml.) of the fraction having R_f of 0.59 afforded **4b** (0.141 g., 65.0%), m.p. 68-70°; ir (chloroform): 1330 and 1165 cm^{-1} (SO_2); nmr: δ 6.0 [s, 1, NH, exchanges with deuterium oxide], 5.61 [m, 2, $\text{C}_4\text{-H}$, $\text{C}_5\text{-H}$], 3.25-3.52 [m, 2, $\text{C}_6\text{-H}$], 3.0 [t ($J_{2,3} = 6$ Hz), 2, $\text{C}_2\text{-H}$], 3.0 [s, 3, CH_3], 2.02-2.47 [m, 2, $\text{C}_3\text{-H}$]; Mass Calcd. for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: 176.0620. Found: 176.0621.

N-Benzenecarbonylimino-1,2,3,6-tetrahydropyridine (**4c**).

A solution of **3c** (1.43 g., 7.23 mmoles) in 95% ethanol (80 ml.) was added to a solution of sodium borohydride (0.4 g.) in 95% ethanol (40 ml.) pre-cooled to 0° and the reaction was completed as described under Procedure B above. The reaction product was purified on a 2.5 x 26 cm neutral alumina column. Elution with ether-methanol (5:1 v/v) 250 ml.) afforded **4c** (1.25 g., 85.5%), m.p. 137-139°; ir (chloroform): 3440 and 3350 (NH) and 1675 cm^{-1} (C=O); nmr: δ 9.93 [s, 1, NH, exchanges with deuterium oxide], 7.0-7.9 [m, 5, Ph], 5.32-5.87 [m, 2, $\text{C}_4\text{-H}$, $\text{C}_5\text{-H}$], 3.25-3.62 [m, 2, C_6H], 2.99 [t ($J_{2,3} = 6$ Hz), 2, $\text{C}_2\text{-H}$], 2.0-2.39 [m, 2, $\text{C}_3\text{-H}$]; Mass Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$: 202.1106. Found: 202.1095.

N-Methanecarbonylimino-1,2,3,6-tetrahydropyridine (**4d**).

A solution of **3d** (0.144 g., 1.06 mmoles) in 95% ethanol (30 ml.) was added to a solution of sodium borohydride (0.1 g.) in 95% ethanol (40 ml.) pre-cooled to 0° and the reaction was completed as described under Procedure B above (6). The reaction product was subjected to preparative tlc on four 8 x 8 inch silica gel GF 254 plates, 0.5 mm in thickness, using ether as the development solvent. Extraction with warm methanol (50 ml.) of the fraction having R_f of 0.29 afforded **4d** (0.057 g., 38.4%), m.p. 86-88°; ir (chloroform): 3430, 3350, 3315 and 3300 (NH) and 1665 cm^{-1} (C=O); nmr: δ 7.28 [s, 1, NH, exchanges with deuterium oxide], 5.65 [m, 2, $\text{C}_4\text{-H}$, $\text{C}_5\text{-H}$], 3.1-3.5 [m, 2, $\text{C}_6\text{-H}$], 2.98 [t ($J_{2,3} = 5.5$ Hz), 2, $\text{C}_2\text{-H}$], 1.83-2.5 [m, 2, $\text{C}_3\text{-H}$], 2.11 [s, 3, CH_3]; Mass Calcd. for $\text{C}_7\text{H}_{12}\text{N}_2\text{O}$: 140.0948. Found: 140.0950.

N-(4-Pyridylcarbonylimino)pyridinium Ylide (**3e**).

To an ice-cooled solution of **1** (6.52 g., 23.16 mmoles) in methanol (20 ml.) was added a suspension of isonicotinic acid hydrazide (6.2 g., 45.26 mmoles) in methanol (60 ml.) in five aliquots with stirring. Triethylamine (1.8 ml.) was then added and the reaction was completed with continuous stirring as described under Procedure A. The reaction product was then purified on a 2.5 x 26 cm neutral alumina column. Elution with ether-methanol (5:1 v/v) (625 ml.) gave **3e** (2.3 g., 50.0%) m.p. 219-221°; nmr (deuterium oxide): δ 8.33-8.83 [m, 4, $\text{C}_2\text{-H}$,

C₆-H (pyridine), C₂-H, C₆-H (pyridinium)], 7.71-8.33 [m, 5, C₃-H, C₅-H (pyridine), C₃-H, C₄-H, C₅-H (pyridinium)]; Mass Calcd. for C₁₁H₉N₃O: 199.0746. Found: 199.0747.

N-(4-Pyridylcarbonylimino)-1,2,3,6-tetrahydropyridine (**4e**).

A solution of **3e** (2.14 g., 10.7 mmoles) in 95% ethanol (30 ml.) was added to a solution of sodium borohydride (0.7 g.) in 95% ethanol (60 ml.) pre-cooled to 0° and the reaction completed as described under Procedure B. The reaction product was then purified on a 2.5 x 25 cm neutral alumina column. Elution with ether-methanol (5:1 v/v) (500 ml.) gave **4e** (2.0 g., 83.6%), m.p. 141-144°; ir (chloroform): 3430, 3340, 3290 (NH) and 1680, 1660 cm⁻¹ (C=O); nmr: δ 8.93 [s, 1, NH, exchanges with deuterium oxide], 8.66 [m, 2, C₂-H, C₆-H (pyridine)], 7.67 [m, 2, C₃-H, C₅-H (pyridine)], 5.62 [m, 2, C₄-H, C₅-H (tetrahydropyridine)], 3.22-3.65 [m, 2, C₆-H (tetrahydropyridine)], 3.07 [t (J_{2,3} = 5.5 Hz), 2, C₂-H (tetrahydropyridine)], 2.0-2.48 [m, 2, C₃-H (tetrahydropyridine)]; Mass Calcd. for C₁₁H₁₃N₃O: 203.1059. Found: 203.1056.

N-(3-Pyridylcarbonylimino)pyridinium Ylide (**3f**).

To an ice-cooled solution of **1** (3.26 g., 11.58 mmoles) in methanol (20 ml.) was added a suspension of nicotinic acid hydrazide (3.1 g., 22.63 mmoles) in methanol (60 ml.) in five aliquots with stirring. Triethylamine (0.9 ml.) was then added and the reaction completed with continuous stirring as described under Procedure A. The reaction product was then purified by elution from a 2.5 x 25 cm neutral alumina column using ether-methanol (6:1 v/v) (250 ml.) to afford **3f** (1.06 g., 46.2%) m.p. 167-169; nmr: δ 9.38 [d (J_{2,4} = 2 Hz) of d (J_{2,5} = 1 Hz), 1, C₂-H (pyridine)], 8.18-9.02 [m, 4, C₄-H, C₆-H (pyridine), C₂-H, C₆-H (pyridinium)], 7.0-8.18 [m, 4, C₅-H (pyridine), C₃-H, C₄-H, C₅-H (pyridinium)]; Mass Calcd. for C₁₁H₉N₃O: 199.0746. Found: 199.0750.

N-(3-Pyridylcarbonylimino)-1,2,3,6-tetrahydropyridine (**4f**).

A solution of **3f** (1.75 g., 8.8 mmoles) in 95% ethanol (30 ml.) was added to a solution of sodium borohydride (0.6 g.) in 95% ethanol (40 ml.) pre-cooled to 0° and the reaction was completed as described under Procedure B. The product was then purified by elution from a 2.5 x 25 cm neutral alumina column using ether-methanol (6:1 v/v) (300 ml.) to give **4f** (1.43 g., 80%) m.p. 119-121; ir (chloroform): 3480, 3440, 3345, 3290 (NH) and 1680, 1660 cm⁻¹ (C=O); nmr: δ 8.99 [d (J_{2,4} = 2 Hz), 1, C₂-H (pyridine)], 8.87 [s, 1, NH, exchanges with deuterium oxide], 8.6 [d (J_{5,6} = 5 Hz) of d (J_{4,6} = 2 Hz), 1, C₆-H (pyridine)], 8.14 [d (J_{4,5} = 8 Hz) of d (J_{4,6} = 2 Hz), 1, C₄-H (pyridine)], 7.28 [d (J_{4,5} = 8 Hz) of d (J_{5,6} = 5 Hz), 1, C₅-H (pyridine)], 5.6 [m, 2, C₄-H, C₅-H (tetrahydropyridine)], 3.28-3.63 [m, 2, C₆-H (tetrahydropyridine)], 3.07 [t (J_{2,3} = 5 Hz), C₂-H (tetrahydropyridine)], 2.0-2.41 [m, 2, C₃-H (tetrahydropyridine)]; Mass Calcd. for C₁₁H₁₃N₃O: 203.1059. Found: 203.1062.

N-(2-Pyridylcarbonylimino)pyridinium Ylide (**3g**).

To an ice-cooled solution of **1** (5.43 g., 19.29 mmoles) in methanol (30 ml.) was added a suspension of picolinic acid hydrazide (5.68 g., 41.4 mmoles) in methanol (60 ml.) in five aliquots with stirring. Triethylamine (1.8 ml.) was then added and the reaction completed with continuous stirring as described under Procedure A. The product was then purified by elution from a 2.5 x 25 cm neutral alumina column using ether-methanol (5:1 v/v) (600 ml.) to afford **3g** (2.1 g., 54.7%) m.p. 178-181°;

nmr: δ 8.37-9.03 [m, 3, C₆-H (pyridine), C₂-H, C₆-H (pyridinium)], 7.13-8.33 [m, 6, C₃-H, C₄-H, C₅-H (pyridine), C₃-H, C₄-H, C₅-H (pyridinium)]; Mass Calcd. for C₁₁H₉N₃O: 199.0746. Found: 199.0747.

N-(2-Pyridylcarbonylimino)-1,2,3,6-tetrahydropyridine (**4g**).

A solution of **3g** (0.21 g., 1.04 mmoles) in 95% ethanol (30 ml.) was added to a solution of sodium borohydride (0.3 g.) in 95% ethanol (30 ml.) pre-cooled to 0° and the reaction was completed as described under Procedure B. The reaction product was subjected to preparative tlc using four 8 x 8 inch silica gel PF 254 plates, 0.5 mm in thickness, with benzene-ether (1:4 v/v) as development solvent. Extraction with warm methanol (50 ml.) of the fraction having R_f 0.65 afforded **4g** (0.166 g., 78.2%), m.p. 82-83°; ir (chloroform): 3440, 3400, 3320 (NH) and 1680, 1675 cm⁻¹ (C=O); nmr: δ 8.9 [s, 1, NH, exchanges with deuterium oxide], 8.45 [d (J_{5,6} = 5 Hz) of d (J_{4,6} = 2 Hz), 1, C₆-H (pyridine)], 8.15 [d (J_{3,4} = 7.5 Hz) of d (J_{3,5} = 1 Hz), 1, C₃-H (pyridine)], 7.78 [d (J_{3,4} = J_{4,5} = 7.5 Hz) of d (J_{4,6} = 2 Hz), 1, C₄-H (pyridine)], 7.36 [d (J_{4,5} = 7.5 Hz) of d (J_{5,6} = 5 Hz) of d (J_{3,5} = 1 Hz), 1, C₅-H (pyridine)], 5.7 [m, 2, C₄-H, C₅-H (tetrahydropyridine)], 3.3-3.7 [m, 2, C₆-H (tetrahydropyridine)], 3.11 [t (J_{2,3} = 5.5 Hz), 2, C₂-H (tetrahydropyridine)], 2.02-2.52 [m, 2, C₃-H (tetrahydropyridine)]; Mass Calcd. for C₁₁H₁₃N₃O: 203.1059. Found: 203.1056.

Phenylethyliminopyridinium Ylide (**3h**).

To an ice-cooled solution of **1** (3.26 g., 11.58 mmoles) in methanol (20 ml.) was added a solution of phenylethylhydrazine (3.1 g., 22.79 mmoles) in methanol (100 ml.) with stirring. Triethylamine (0.9 ml.) was then added and the reaction completed with continuous stirring as described under Procedure A. The product was purified by elution from a 2.5 x 25 cm neutral alumina column using ether-methanol (1:1 v/v) (325 ml.) to give **3h** (0.81 g., 35.3%) as a reddish oil, nmr: δ 9.22 [d (J_{2,3} = J_{5,6} = 6 Hz) of d (J_{2,4} = J_{4,6} = 1.5 Hz), 2, C₂-H, C₆-H (pyridinium)], 7.7-8.3 [m, 3, C₃-H, C₄-H, C₅-H (pyridinium)], 7.11 [m, 5, Ph], 3.55 [m, 2, -N-CH₂-], 3.04 [m, 2, -CH₂-Ph]; Mass Calcd. for C₁₃H₁₄N₂: 198.1167. Found: 198.1156.

N-Phenylethylimino-1,2,3,6-tetrahydropyridine (**4h**).

A solution of **3h** (0.16 g., 0.81 mmole) in 95% ethanol (30 ml.) was added to a solution of sodium borohydride (0.06 g.) in 95% ethanol (30 ml.) pre-cooled to 0° and the reaction was completed as described under Procedure B. The reaction product was subjected to preparative tlc on four 8 x 8 inch silica gel GF 254 plates, 0.5 mm in thickness, using benzene-ether (2:3 v/v) as development solvent. Extraction with warm methanol (50 ml.) of the fraction having R_f of 0.51 afforded **4h** (0.081 g., 48.7%) as a very low melting solid, ir (film) 3350 cm⁻¹ (NH); nmr: δ 7.16 [m, 5, Ph], 5.6 [m, 2, C₄-H, C₅-H], 2.5-3.28 [complex m, 8, -CH₂-CH₂, C₂-H, C₆-H], 2.2 [m, 2, C₅-H] (7).

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(5) *N*-Methanesulfonyliminopyridinium ylide **3b** was prepared from the reaction of *N*-aminopyridinium iodide and methane-

sulfonyl chloride as reported; R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).

(6) *N*-Methanecarbonyliminopyridinium ylide **3c** was prepared from the reaction of *N*-aminopyridinium iodide and acetic anhydride; m.p. 168° (Lit. m.p. 168°, T. Okamoto, M. Hirobe, C. Mizushima and A. Osawa, *Yakugaku Zasshi*, **83**, 308 (1963); *Chem. Abstr.*, **59**, 5120b (1963).

(7) A satisfactory elemental analysis could not be obtained as **4h** undergoes oxidation to compound **5** during purification and on storage. Satisfactory analytical data was obtained for its oxidation product **5**.