Nicotine Analogues: Synthesis of Pyridylazetidines[1a]

Henry V. Secor* and William B. Edwards, III*

Philip Morris Research Center, Richmond, Virginia 23261

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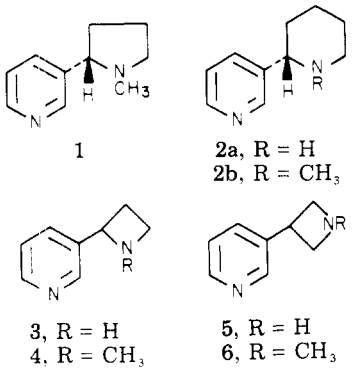
The synthesis of 2- and 3-(3-pyridyl)azetidines (**3** and **5**) and their *N*-methyl derivatives is reported. The key steps involve the preparation of 3-amino-2-(3-pyridyl)-1-propanol (**17b**) and the reductive detosylation of the *N*-(4-toluenesulfonyl) derivatives of **3** and **5**.

Despite the large body of work on the physiological and insecticidal properties of nicotine (**1**)[2,3] and nicotine-like agents,[2a,c,3a,c,4,5] a clear and complete understanding of their mode of action has remained elusive.[2b,4a,6] As part of our studies[7] on the alkaloids of *Nicotiana tabacum* L., we are interested in determining the pharmacological consequences of changing the size of nicotine's saturated ring. Studies involving this variation have previously been confined to the *Nicotiana* alkaloids, anabasine (**2a**) and *N*-methylanabasine (**2b**).[8] This article reports our synthesis of 2-(3-pyridyl)azetidine (**3**), 3-(3-pyridyl)azetidine (**5**), and their *N*-methyl derivatives (**4** and **6**). These pyridylazetidines might be expected to have nicotinic activity as recent studies on azetidine-2-carboxylic acid have shown that certain biological systems are unable to distinguish it from proline.[10]



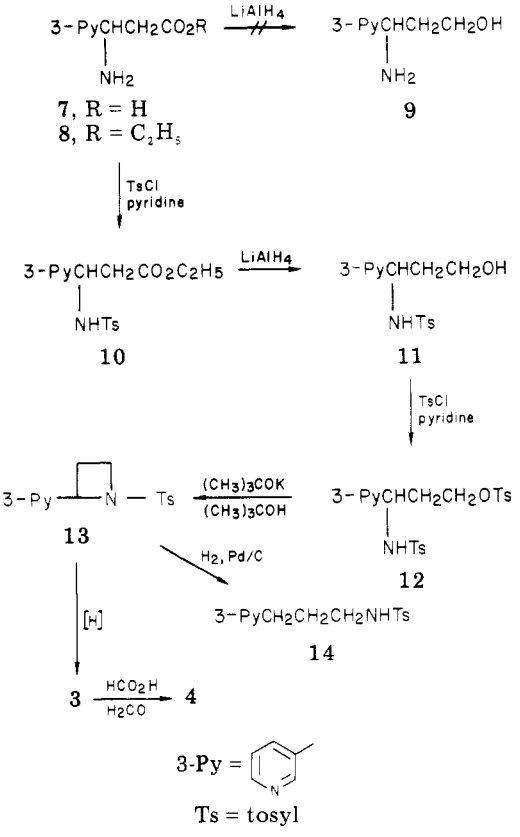
1

2a, R = H
2b, R = CH_3

3, R = H
4, R = CH_3

5, R = H
6, R = CH_3

Scheme I



Results and Discussion

Several methods have been developed for the synthesis of 4-substituted 2-azetidinones[11] which can be reduced to 2-substituted azetidines.[11b] These procedures, as well as ones developed for the preparation of pencillin and cephalosporin β-lactams,[12] were examined as routes to **3**. All, however, proved inapplicable.[13]

(1) (a) Experimental details of a portion of this work have appeared: H. V. Secor and E. B. Sanders, *J. Org. Chem.*, **43**, 2539 (1978). (b) The methylation of **4** has been reported: J. I. Seeman, H. V. Secor, J. F. Whidby, and R. L. Bassfield, *Tetrahedron Lett.*, 1901 (1978).

(2) (a) P. S. Larson, H. B. Haag, and H. Silvette, "Tobacco: Experimental and Clinical Studies", Williams and Wilkins Co., Baltimore, Md., 1961, and Supplements I–III; (b) R. W. Ryall in "Neuropoisons: Their Pathophysiological Actions", Vol. II, L. L. Simpson and D. R. Curtis, Eds., Plenum Press, New York, N.Y., 1974, Chapter 2; (c) U. S. Von Euler, Ed., "Tobacco Alkaloids and Related Compounds", Pergamon Press, Oxford, England, 1965.

(3) (a) L. Schmeltz in "Naturally Occurring Insecticides", M. Jacobson and D. G. Crosby, Ed., Marcel Dekker, New York, N.Y., 1971, Chapter 3; (b) R. D. O'Brien, "Insecticides: Action and Metabolism", Academic Press, New York, N.Y., 1967, Chapter 8; (c) R. L. Metcalf, "Organic Insecticides, Their Chemistry and Mode of Action", Interscience, New York, N.Y., 1955, Chapter 1.

(4) (a) I. Yamamoto in "Advances in Pest Control Research", Vol. 6, R. L. Metcalf, Ed., Interscience, New York, N.Y., 1965, pp 231–260; (b) T. Fujita, M. Nakajima, Y. Soeda, and I. Yamamoto, *Pest Biochem. Physiol.*, 1, 152 (1971); (c) T. Fujita, I. Yamamoto and M. Nakajima, in "Biochemical Toxicology of Insecticides", R. D. O'Brien and I. Yamamoto, Eds., Academic Press, New York, N.Y., 1970, pp 21–32; (d) I. Yamamoto et al., *Agric. Biol. Chem.*, **32**, 1341 (1968), and previous papers in this series.

(5) R. B. Barlow and J. T. Hamilton, *Br. J. Pharmacol.*, **18**, 510 (1962); R. E. Bowman, *J. Med. Chem.*, **16**, 1177 (1973), and previous papers in this series.

(6) R. L. Volle and G. B. Koelle in "The Pharmacological Basis of Therapeutics", 3rd ed, L. S. Goodman and A. Gilman, Eds., Macmillan, New York, N.Y., 1965, pp 578–585; L. Gyermek in "Drugs Affecting the Peripheral Nervous System", Vol. 1, A. Burger, Ed., Marcel Dekker, New York, N.Y., 1967, pp 180–183; P. G. Waser, Ed., "Cholinergic Mechanisms", Raven Press, New York, N.Y., 1975.

(7) D. F. Glenn and W. B. Edwards III, *J. Org. Chem.*, **43**, 2860 (1978); E. B. Sanders, H. V. Secor and J. I. Seeman, *ibid.*, **43**, 324 (1978); T. P. Pitner, W. B. Edwards III, R. L. Bassfield, and J. F. Whidby, *J. Am. Chem. Soc.*, **100**, 246 (1978).

(8) The insecticidal activity of **2a** and **2b** relative to **1** was found to be highly species dependent.[3a,4a,c,d] Studies on the mammalian colinergic effects of **2a** have shown it to be 50–80% less active than **1**,[9] while **2b** has essentially no nicotinic activity.[6]

(9) M. G. S. Clark, M. J. Rand, and S. Vanov, *Arch. Int. Pharmacodyn.*, **156**, 363 (1965).

(10) R. D. Norris and L. Fowden, *Phytochemistry*, 11, 292 (1972); H. Tristram and C. F. Thurston, *Nature (London)* **212**, 74 (1966).

(11) (a) E. Testa, A. Wittgens, G. Maffii, and G. Bianchi in "Research Progress in Organic-Biological and Medicinal Chemistry", Vol. I, U. Gallo and L. Santamaria, Ed., Societa Editoriale Farmaceutica, Milano, Italy, 1964, pp 478–583; (b) R. Graf, *Justus Liebigs Ann. Chem.*, **661**, 111 (1963).

(12) N. S. Isaacs, *Chem. Soc. Rev.*, **5**, 181 (1976), and references cited therein.

0022-3263/79/1944-3136$01.00/0

The successful synthesis of **3** (Scheme I) was based on the conversion of 3-amino-3-(3-pyridyl)propionic acid (**7**) to 2-(3-pyridyl)-*N*-(4-toluenesulfonyl)azetidine (**13**). A modified Fischer esterification of **7** gave ethyl 3-amino-3-(3-pyridyl)propionate (**8**), which was tosylated to afford ethyl 3-(3-pyridyl)-3-(4-toluenesulfonamido)propionate (**10**). Reduction of **10** followed by tosylation of the resulting alcohol **11** gave the ditosylate **12**. The shorter approach to **12** (**8** → **9** → **12**) could not be used as **8** was not reduced to **9** by $LiAlH_4$. The ditosylate was cyclized with potassium *tert*-butoxide to the prerequisite 2-(3-pyridyl)-*N*-(4-toluenesulfonyl)azetidine (**13**).

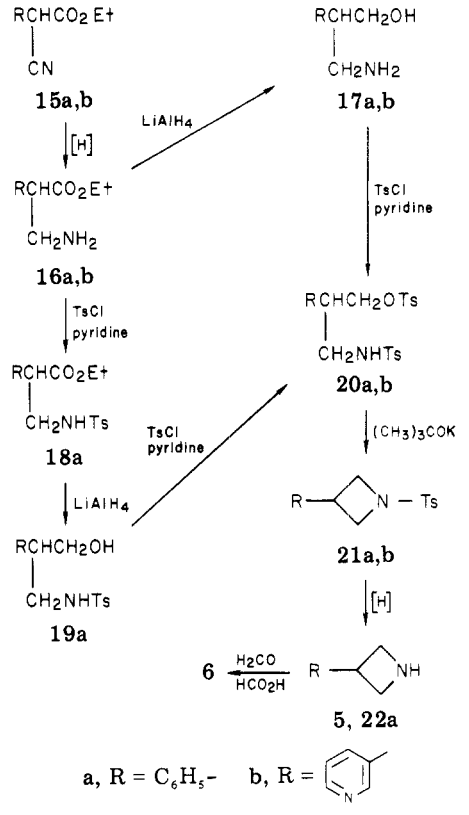
Because of the acid lability[15] of the azetidine ring, reductive rather than hydrolytic methods were examined for the detosylation of **13** to **3**. Sodium in alcohol, using mild conditions to avoid reduction of the pyridine ring,[16] gave only unreacted **13**. More rigorous conditions (Na/NH_3 at −33 °C) cleaved both the 4-toluenesulfonyl group and the azetidine ring, yielding 3-(3-pyridyl)-1-propylamine.[17] Sodium naphthalenide was then tried as a detosylating agent for this sensitive system. Our initial attempts to detosylate **13** with this reagent at 20 °C[18a] gave complex mixtures in which no **3** was detected.[19] Further experiments showed that the pyridine ring is reduced under these conditions. Using milder conditions (−60 °C),[18b] **3** was obtained in low yield[21] (~5% by GLC). The structural assignment was made on the basis of elemental and spectral analyses and confirmed by reaction of the product with 4-toluenesulfonyl chloride to give **13**.

The low yield of **3** could be due to the decomposition of its amide anion, initially formed in the reaction, or to the destruction of **13** by this anion.[22] These pathways should be minimized by carrying out the reactions in the presence of a proton source such as *tert*-butyl alcohol, which would quench the amide anion. Neither the *tert*-butyl alcohol nor **3** should interfere with the detosylation of **13**, since the rate of deprotonation of alcohols[23] and amines[18b] by sodium naphthalenide at −60 °C is considerably slower than that of tosylate cleavage.

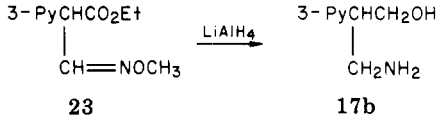
The detosylation reaction was run in the presence of varying amounts of *tert*-butyl alcohol. In all cases, substantial improvements in the yield and purity of the isolated **3** were realized with the optimum result obtained using 1 equiv of *tert*-butyl alcohol. The methylation of **3** under Eschweiler–Clark conditions gave **4**.

The synthesis of 3-(3-pyridyl)azetidine (**5**) along similar lines as those used for the preparation of **3** would require the cyclization of 2-(3-pyridyl)-3-(4-toluenesulfonamido)propyl 4-toluenesulfonate (Scheme II, **20b**). It seemed likely that this ditosylaminopropanol might, on reaction with base, undergo an E2 elimination rather than cyclization. To establish this point, the synthesis of a model compound, 3-phenylazetidine (Scheme II, **22a**), was undertaken.

Scheme II



Scheme III



The ditosylaminopropanol (**20a**) was prepared in 71% overall yield from ethyl 2-(3-phenyl)cyanoacetate (**15a**) in four steps (Scheme II, **15a** → **16a** → **18a** → **19a** → **20a**). The alternate route (**15a** → **16a** → **17a** → **20a**) was abandoned when it was found that reduction of **16a** gave a low yield of **17a**. The cyclization of **20a** with base was then attempted and afforded 3-phenyl-*N*-(4-toluenesulfonyl)azetidine (**21a**) in high yield. No β-elimination product was observed. The detosylation of **21a** with sodium naphthalenide was carried out as previously described and gave **22a** in similar yield.

The utility of our synthetic strategy as a route to 3-arylazetidines having been established, its applicability for the preparation of **5** was investigated. The prerequisite ethyl 2-(3-pyridyl)cyanoacetate (**15b**) was obtained by reaction of 3-pyridylacetonitrile with diethyl carbonate, but attempts to reduce **15b** to either ethyl 3-amino-2-(3-pyridyl)propionate (**16b**) or 3-amino-2-(3-pyridyl)-1-propanol (**17b**) were unsuccessful.[24] Consequently, an

(13) Attempted cyclization of 3-amino-3-(3-pyridyl)propionic acid (**7**) via acid-catalyzed or carbodiimide-promoted dehydration gave unreacted **7**. Reaction of **7** or its dihydrochloride with thionyl chloride, phosphorus tri- and pentachloride, or oxalyl chloride to give the acid chloride either returned **7** or gave intractable tars on treatment with base. Attempted ring closure of ethyl 3-amino-3-(3-pyridyl)propionate (**8**), with base or methyl magnesium iodide, gave complex mixtures in which the desired azetidinone could not be detected. Treatment of 5-methyl-3-vinylpyridine or 3-pyridinecarboxaldehyde with excess chlorosulfonyl isocyanate yielded only a 1:1 complex[14] which did not give an azetidinone.

(14) H. Ulrich, *Chem. Rev.*, **65**, 369 (1965).

(15) See ref 11a, pp 493–494.

(16) R. A. Barnes, *Chem. Heterocycl. Compd.*, **14**, 48–49 (1960).

(17) The structure of 3-(3-pyridyl)-1-propylamine was established from spectral data as well as by retosylation to give *N*-(3-(3-pyridyl)propyl)-4-toluenesulfonamide (**14**), which was identical with a sample prepared by Pd/C catalyzed hydrogenation of **13**.

(18) (a) S. Ji, L. B. Gortler, A. Waring, A. Battasti, S. Bank and W. D. Closson, *J. Am. Chem. Soc.*, **89**, 5311 (1967); (b) W. D. Closson, S. Ji, and S. Schulenberg, *J. Am. Chem. Soc.*, **92**, 650 (1970).

(19) After the completion of this work, White[20] reported that *N*-(4-toluenesulfonyl)azetidine can be detosylated to give azetidine using Closson's method[18a] with minor modification (warm glyme as the solvent).

(20) J. White and G. McGillivray, *J. Org. Chem.*, **39**, 1973 (1974).

(21) Varying temperature, dilution, and sodium naphthalenide addition rate for this reaction produced no discernible change in the yield of **3**.

(22) See ref 11a, p 494.

(23) Personal communication from W. D. Closson.

(24) Both catalytic (Pd/C, PtO_2, Raney Ni, and Rh/Al_2O_3) and metal hydride ($LiAlH_4$ and $LiAlH_4/AlCl_3$) reductions were tried under a wide variety of conditions.

alternate approach to **17b** was developed (Scheme III). Ethyl α-formyl-3-pyridylacetate was converted with *O*-methylhydroxylamine to the alkoximino ester **23**.[1a] Reduction of **23** proceeded smoothly to the desired **17b**, which could not be purified and was therefore reacted in situ with 4-toluenesulfonyl chloride to afford **20b**. Cyclization of **20b** to 3-(3-pyridyl)-1-(4-toluenesulfonyl)azetidine (**21b**) and its subsequent detosylation with sodium naphthalenide went as expected and gave the 3-(3-pyridyl)azetidine (**5**). Methylation of **5** gave the *N*-methyl derivative **6**.

Preliminary pharmacological evaluations of **3** and **4** for nicotine activity were carried out on isolated guinea pig ileum strips.[25] The data indicated that **4** is similar to *l*-nicotine (**1**) in potency and yields pharmacologically similar contractile responses which are blocked by large doses of morphine sulfate and atropine sulfate. However, **3** is approximately 20% as potent as **1** and yields contractile responses similar to methacholine, which are blocked by atropine sulfate but not by morphine sulfate. These results show that **4** probably acts as a ganglionic stimulatory agent to induce post-ganglionic cholinergic release of acetylcholine, whereas **3** may act as a post-ganglionic muscarinic type of stimulant similar to methacholine.

Experimental Section

Melting points (Thomas-Hoover apparatus) and boiling points are uncorrected. The ^1H NMR spectra were determined on either a Varian A60A or XL-100 spectrometer equipped with a Digilab data system using Me_4Si or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O solutions) as internal standards. The IR spectra were obtained on either a Perkin-Elmer 621 or a Digilab FTS-14 spectrophotometer. Low-resolution mass spectra were obtained on a CEC 21-104 spectrometer at 70 eV, 10 μA, 2000 V ion accelerating voltage and a source temperature of 250 °C. GLC analyses and preparative GLC (PGLC) were carried out using a Bendix Model 2300 chromatograph with 5 ft × 0.25 in. copper columns packed with 5% SE-30 on Chromosorb G-HP (80–100 mesh) with He carrier gas at 60 mL/min flow rate. TLC was performed on 250-μm thick SiO_2 GF plates. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3-Amino-3-(3-pyridyl)propionic Acid (7). A stirred mixture of 172.0 g (1.61 mol) of 3-pyridinecarboxaldehyde, 248.0 g (3.22 mol) of NH_4OAc, and 168.0 g (1.61 mol) of malonic acid in 1.35 L of EtOH was heated under reflux for 1 h. After cooling (10 °C), the precipitated solid was collected by filtration, washed with EtOH, and dried to give 172.8 g (47%) of a byproduct identified as 3-(2,2-dicarboxyvinyl)pyridine diammonium salt: mp 170–175 °C dec; IR (Nujol) 1550 cm^{-1}; NMR (Me_2SO-d_6) δ 7.35 (m, 1, 5-Py H, 7.77 (s, 1, CH), 7.9 (s, 8, 2 NH_4), 8.2 (m, 1, 4-Py H), 8.49 (m, 1, 6-Py H), 8.78 (m, 1, 2-Py H). Anal. $C_9H_{13}N_3O_4$: C, H, N.

The filtrate was heated under reflux for 20 min and concentrated [100 °C (1 mm)] to yield 218.0 g of a syrup which was dissolved in H_2O. The solution was allowed to stand for 12 h. The solid was collected by filtration and dried to give 14.7 g of 3-(3-pyridyl)acrylic acid, mp 230–232 °C, identical in all respects with an authentic sample.[26] The filtrate was concentrated to leave a gummy solid which was triturated with hot EtOH and the mixture was allowed to cool. The solid was collected by filtration and air dried to afford 65.4 g (24.5%) of **7** (mp 213–214 °C). Recrystallization from EtOH/H_2O gave an analytical sample: mp 216–218 °C (lit.[27] 205–206 °C); IR (Nujol) 1635 (C=O), 1585 cm^{-1}; NMR (D_2O) δ 2.91 (d, 2, J = 7 Hz, CH_2), 4.78 (t, 1, J = 7 Hz, CH), 7.57 (m, 1, 5-Py H), 8.02 (m, 1, 4-Py H), 8.57 (m, 2, 2- and 6-Py H).

Additional **7** was obtained by the following method. A mixture of 150.0 g (0.66 mol) of 3-(2,2-dicarboxyvinyl)pyridine diammonium salt and 150.0 g (1.95 mol) of NH_4OAc in 1 L of AcOH was heated on a steam bath until gas evolution ceased (~3.5 h), at which point TLC indicated only **7** and 3-(3-pyridyl)acrylic acid. The reaction solution was concentrated and the residue was dissolved in 500 mL of H_2O and allowed to stand overnight. The precipitated 3-(3-pyridyl)acrylic acid was removed by filtration and **7** was isolated as previously described, giving 48.0 g (43.7%), mp 200–201 °C. The overall yield of **7** based on starting 3-pyridinecarboxaldehyde was 45%.

Ethyl 3-Amino-3-(3-pyridyl)propionate (8). To a stirred, cooled (10 °C) suspension of 127 g (0.765 mol) of **7** in 2.8 L of EtOH was added 465 g (4.6 mol) of concentrated H_2SO_4 in 200 mL of EtOH. Stirring was continued until all material dissolved. The solution was allowed to stand at room temperature for 5 days and was concentrated to ~1 L [<50 °C (1 mm)]. This solution was added as rapidly as possible to a stirred, cooled (5 °C) mixture of 800 g (9.55 mol) of $NaHCO_3$ in 1.5 L of H_2O. The mixture was stirred for 15 min, treated with 750 mL of CH_2Cl_2, and stirred for 15 min. The insoluble salts were removed by filtration and washed with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 phases were dried (Na_2SO_4) in the cold. The CH_2Cl_2 was removed to leave 115 g (77.5%) of **8** which should be stored in the cold and used as soon as possible. Distillation on a small scale (~5 g) gave analytically pure **8**: bp 100–102 °C (0.1 mm); IR (neat) 3380 (NH_2), 3310 (NH_2), 1725 (C=O), 1187, 1018, 702 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3, J = 7 Hz, CH_2CH_3), 2.06 (s, 2, NH_2), 2.69 (d, 2, J = 7 Hz, $CHCH_2$), 4.18 (q, 2, J = 7 Hz, CH_2CH_3), 4.5 (t, 1, J = 7 Hz, $CHCH_2$)), 7.28 (m, 1, 5-Py H), 7.78 (m, 1, 4-Py H), 8.55 (m, 2, 2- and 6-Py H). Anal. $C_{10}H_{14}N_2O_2$: C, H, N.

Ethyl 3-(3-Pyridyl)-3-(4-toluenesulfonamido)propionate (10). To a stirred, cooled (5 °C) solution of 104 g (0.535 mol) of **8** in 950 mL of dry pyridine was added in portions 127 g (0.67 mol) of purified 4-toluenesulfonyl chloride.[28] After stirring for 2 h at 5 °C and standing overnight at room temperature, the solution was poured onto crushed ice and diluted with 3 L of H_2O. The solid product was collected, washed with water, and dried over KOH in vacuo to yield 180.3 g (81.7%) of **10** (mp 136–138 °C). Recrystallization from AcOEt gave analytically pure **10**: mp 137–138 °C; IR ($CHCl_3$) 3380 (NH), 1730 (C=O), 1349, 1162 cm^{-1}; NMR ($CDCl_3$) δ 1.11 (t, 3, J = 7 Hz, CH_2CH_3), 2.38 (s, 3, CH_3), 2.83 (d, 2, J = 7 Hz, $CHCH_2$), 4.05 (q, 2, J = 7 Hz, CH_2CH_3), 4.83 (q, 1, J = 7 Hz, CH), 6.33 (d, 1, J = 7 Hz, NH), 7.43 (m, 6, 4- and 5-Py and Ph H), 8.50 (m, 2, 2- and 6-Py H). Anal. $C_{17}H_{20}N_2O_4S$: C, H, N, S.

***N*-(3-Hydroxy-3-(3-pyridyl)propyl)-4-toluenesolfonamide (11).** To a cooled (5 °C), stirred suspension of 12.7 g (0.34 mol) of $LiAlH_4$ in 1.25 L of dry glyme was added 89.7 g (0.26 mol) of **10**. The stirred mixture was heated under reflux for 1.5 h, cooled (5 °C), slowly treated with 120 mL of saturated NaCl, heated under reflux for 30 min, and allowed to stand overnight. The insoluble solids were removed by filtration and washed with hot glyme, followed by hot EtOH. The pH of the combined filtrates was adjusted to pH 7.5–8.0 with 10% HCl and saturated $NaHCO_3$. The solution was concentrated and the solid was collected by filtration, washed with H_2O, and dried over KOH in vacuo to give 75.6 g (95%) of **11** (mp 152–153 °C). An analytically pure sample was obtained by recrystallization from H_2O: mp 153–154 °C; IR (Nujol) 3240, 1167, 1080, 715, 685 cm^{-1}; NMR (Me_2SO-d_6) δ 1.33 (m, 2, $CHCH_2$), 1.83 (s, 3, CH_3), 2.8 (m, 2, CH_2O), 3.97 (m, 1, CH), 7.42 (m, 6, 4- and 5-Py and Ph H), 8.42 (m, 2, 2- and 6-Py H), NH and OH resonances were not assignable. Anal. $C_{15}H_{18}N_2O_3S$: C, H, N, S.

3-(3-Pyridyl)-3-(4-toluenesulfonamido)propyl 4-Toluenesulfonate (12). To a stirred solution of 70.5 g (0.23 mol) of **11** in 750 mL of dry pyridine at 5 °C was added slowly 55.0 g (0.29 mol) of purified 4-toluenesulfonyl chloride.[28] The solution was refrigerated for 24 h and was then treated with 4 L of ice and H_2O containing 24.4 g (0.29 mol) of $NaHCO_3$. The solid which separated was collected by filtration, washed with H_2O followed by a small amount of cold EtOH, and dried over KOH in vacuo to yield 90.5 g (86%) of **12** (mp 156–158 °C). Recrystallization from CH_3CN afforded analytically pure **12**: mp 166–167 °C; IR (Nujol) 1361, 1190, 1180, 1160, 940 cm^{-1}; NMR (Me_2SO-d_6) δ 1.91 (m, 2, $CHCH_2$), 2.28 (s, 3, CH_3), 2.4 (s, 3, CH_3), 3.81 (m. 2, CH_2O), 4.3

(25) Carried out by Woodard Research Corporation, Herndon, Va.
(26) Obtained from Aldrich Chemical Co.
(27) R. N. Castle and A. Burger, *J. Am. Pharm. Assoc.*, **43**, 163 (1954).
(28) S. W. Pelletier, *Chem. Ind. (London)* 1034 (1953)

(q, 1, J = 7 Hz, CH), 7.41 (m, 10, 4- and 5-Py and Ph H), 8.31 (m, 2, 2- and 6-Py H), superimposed on the 8.31 multiplet at 8.31 (d, 1, J = 7 Hz, NH) which is removed by D_2O exchange. Anal. $C_{22}H_{24}N_2O_5S_2$: C, H, N, S.

2-(3-Pyridyl)-1-(4-toluenesulfonyl)azetidine (13). To 2.7 L of stirred, dry *tert*-butyl alcohol under N_2 was added 2.8 g (0.071 mol) of K, followed by heating under reflux until all of the metal reacted (~1.5 h). The solution was cooled (30 °C), treated with 30.0 g (0.065 mol) of **12**, heated under reflux for 10 h, decolorized with activated charcoal, and filtered hot through Celite which was then washed with hot CH_2Cl_2. The combined filtrates were concentrated and the residue was taken up in CH_2Cl_2. After filtration, the CH_2Cl_2 was removed to afford a solid which on recrystallization from AcOEt gave 17.2 g (92%) of analytically pure **13**: mp 141–142 °C; IR (Nujol) 1346, 1162, 812, 714 cm^{-1}; NMR ($CDCl_3$) δ 2.28 (m, 2, 3-azetidinyl H), 2.43 (s, 3, CH_3), 3.78 (m, 2, 4-azetidinyl H), 4.92 (m, 1, 2-azetidinyl H), 7.55 (m, 6, 4- and 5-Py and Ph H), 8.57 (m, 2, 2- and 6-Py H); mass spectrum m/e (rel intensity) 288 (44, M^+), 91 (100). Anal. $C_{15}H_{16}N_2O_2S$: C, H, N, S.

2-(3-Pyridyl)azetidine (3). A ~0.12 M solution of sodium naphthalenide was prepared under Ar in 2.0 L of dry glyme from 38.4 g (0.3 mol) of naphthalene and 5.75 g (0.25 mol) of Na.[18b] This solution was slowly added (~2 h) to a stirred solution of 15.0 g (0.052 mol) of **13** and 3.8 g (0.052 mol) of *tert*-butyl alcohol in 900 mL in dry glyme under Ar at 60 °C, in an all glass apparatus, until the persistence of a faint green color was noted. After adding 60 mL of MeOH, the mixture was allowed to warm to room temperature and stand overnight. The insoluble material was removed by filtration and washed with MeOH. The combined filtrates were concentrated to leave a gum which was treated with C_6H_6 and the insoluble material was removed by filtration. The solution was concentrated and the residue was taken up in petroleum ether (30–60 °C). After removal of the insoluble material by filtration, the solution was washed twice with H_2O. The H_2O washings were concentrated [30–50 °C (20 mm)] to leave an oil from which the remainder of the H_2O was removed by azeotropic distillation with C_6H_6/EtOH to give 3.2 g of an oil which was distilled to yield 2.4 g (35%)[29] of **3**: bp 70–74 °C (0.04 mm); GC and NMR showed >99% purity.[29] An analytically pure sample was obtained by PGLC: IR (neat) 3226 (NH), 1577, 1477, 800, 712 cm^{-1}; NMR ($CDCl_3$) δ 2.08 (s, 1, NH), 2.51 (m, 2, 3-CH_2), 3.41 (m, 1, 4-CH), 3.82 (m, 1, 4-CH), 5.0 (apparent t, 1, 2-CH), 7.18 (m, 1, 5-Py H), 7.72 (m, 1, 4-Py H), 8.44 (m, 2, 2- and 6-Py H); mass spectrum m/e (rel intensity) 134 (23, M^+), 133 (31), 105 (100), 79 (33), 78 (26), 52 (29), 51 (33).

Analysis was obtained on the dipicrate salt which was formed in EtOH and recrystallized from H_2O, mp 196–198 °C. Anal. $C_{20}H_{16}N_8O_{14}$: C, H, N.

1-Methyl-2-(3-pyridyl)azetidine (4). To a stirred, cooled (5 °C) solution of 920 mg (6.88 mmol) of **3** in 9 mL of H_2O was added 660 mg (8.83 mmol) of 40% H_2CO in 9 mL of H_2O followed by 755 mg (14.4 mmol) of 88% HCO_2H. The resulting solution was heated on a steam bath for 2 h, cooled (5 °C), treated with 1.21 g (14.4 mmol) of $NaHCO_3$, and concentrated [<80 °C (20 mm)] to ~7 mL. The turbid mixture was taken up in 125 mL of C_6H_6/EtOH (4:1). This solution was distilled at atmospheric pressure until the head temperature reached 80 °C. The remaining mixture was filtered and concentrated [<40 °C (20 mm)] to leave an oil which gave on distillation 400 mg (40%) of **4**: bp 49–50 °C (0.025 mm); GLC purity, >95%. An analytically pure sample was obtained by PGLC: IR (neat) 1575, 1479, 1425, 1027, 770, 713 cm^{-1}; NMR ($CDCl_3$) δ 2.08 (m, 2, 3-CH_2), 2.3 (s, 3, CH_3), 2.91 (m, 1, 4-HCH), 3.45 (m, 1, 4-HCH), 3.88 (t, 1, 2-CH), 7.05 (m, 1, 5-Py H), 7.73 (m, 1, 4-Py H), 8.44 (m, 2, 2- and 6-Py H); mass spectrum m/e (rel intensity) 148 (25, M^+), 147 (28), 119 (100). Anal. $C_9H_{12}N_2$: C, H, N.

***N*-(3-(3-Pyridyl)propyl)-4-toluenesulfonamide (14).** Hydrogenation of 1.0 g (3.5 mmol) of **13** was carried out at room temperature over 16 h in 100 mL of EtOH with 200 mg of 10% Pd/C catalyst using a Parr apparatus. The resulting mixture was filtered and the solvent was removed. The solid residue was recrystallized from C_6H_6 after decolorizing with charcoal and afforded 0.83 g (83%) of **14**, mp 106–107 °C. A second decolorization and recrystallization from C_6H_6 gave analytically pure **14**: mp 107–108 °C; IR 3370 (NH), 3290 (NH), 1330, 1161, 1095, 662 cm^{-1}; NMR ($CDCl_3$) δ 1.73 (pentet, 2, J = 7 Hz, $CH_2CH_2CH_2$–), 2.50 (s, 3, CH_3), 2.73 (t, 2 J = 7 Hz, Py-CH_2), 2.91 (q, 2, J = 7 Hz, –CH_2NH, which coalesces to a triplet on deuterium exchange of the NH), 5.60 (br s, 1, NH), 7.27 (m, 6, 4- and 5-Py and Ph H), 8.7 (m, 2, 2- and 6-Py H). Anal. $C_{15}H_{18}N_2O_2S$: C, H, N, S.

Ethyl 2-Phenyl-3-(4-toluenesulfonamido)propionate (18a). To a stirred, cooled (5 °C) solution of 10.0 g (44 mmol) of ethyl 3-amino-2-phenylpropionate hydrochloride (**16a**)[30] in 150 mL of dry pyridine was added 9.1 g (48 mmol) of purified 4-toluenesulfonyl chloride.[28] After stirring for 1 h at 5 °C and standing overnight in the cold, the solution was poured onto crushed ice and diluted with 1 L of H_2O. The crude, oily **18a** was extracted into CH_2Cl_2 and the solution was washed successively with cold (5 °C) 5% HCl, H_2O, and saturated NaCl. The solution was dried (Na_2SO_4), decolorized with charcoal, and concentrated to afford 13.0 g (86%) of **18a** as a viscous, colorless oil from which an analytically pure sample could not be obtained: TLC showed a single spot; IR (neat) 3270 (NH), 1720 (C=O), 1323, 1153, 810, 695 cm^{-1}; NMR (CCl_4) δ 1.13 (t, 3, J = 7 Hz, CH_2CH_3), 2.37 (s, 3, CH_3), 3.44 (m, 3, $CHCH_2$), 4.04 (q, 2, J = 7 Hz, CH_2CH_3), 5.45 (t, 1, J = 7 Hz, NH), 7.44 (m, 9, Ph H).

***N*-(3-Hydroxy-3-phenylpropyl)-4-toluenesulfonamide (19a).** To a cooled (5 °C), stirred suspension of 1.5 g (40 mmol) of $LiAlH_4$ in 300 mL of dry glyme was added over 10 min 12.7 g (36 mmol) of **18a**. The stirred mixture was heated under reflux for 30 min, cooled (10 °C), slowly treated with 20 mL of saturated NaCl, and heated under reflux for 1.5 h. The insoluble solids were removed by filtration and washed with hot glyme. The combined filtrates were concentrated, acidified (pH 2) with 10% HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O and saturated NaCl, dried (Na_2SO_4), and concentrated to yield 10.5 g (94%) of **19a** (mp 103–104 °C). Analytically pure **19a** was obtained by recrystallization from toluene: mp 104–105 °C; IR (Nujol) 3510 (OH), 3120 (NH), 1317, 1150, 1078, 660 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (br s, 1, OH), 2.42 (s, 3, CH_3), 3.5 (m, 3, $CHCH_2N$), 3.82 (d, 2, J = 7 Hz, CH_2O), 5.05 (br s, 1, NH), 7.33 (m, 9, Ph H). Anal. $C_{16}H_{19}NO_3S$: C, H, N, S.

2-Phenyl-3-(4-toluenesulfonamido)propyl 4-Toluenesulfonate (20a). To a stirred, cooled (5 °C) solution of 4.5 g (14.8 mmol) of **19a** in 80 mL of dry pyridine was added 3.5 g (18.4 mmol) of purified 4-toluenesulfonyl chloride.[28] After stirring for 1 h, the solution was refrigerated for 48 h and then concentrated [25 °C (1 mm)]. The oily residue was taken up in CH_2Cl_2 and the solution was washed with 5% $NaHCO_3$ and saturated NaCl. The solution was dried ($CaSO_4$) and decolorized with charcoal. The CH_2Cl_2 was removed and the resulting oil was triturated with Et_2O to afford 6.75 g (100%) of **20a** (mp 90–95 °C). Trituration of the pulverized product with H_2O followed by drying [80 °C (0.1 mm)] gave analytically pure **20a**: mp 101–103 °C; IR (KBr) 3280 (NH), 1350, 1170, 1088, 661 cm^{-1}; NMR ($CDCl_3$) δ 2.33 (s, 6, methyl H), 3.08 (m, 3, $CHCH_2N$), 4.08 (d, 2, J = 5 Hz, CH_2O), 4.88 (br s, 1, NH), 7.11 (m, 13, Ph H). Anal. $C_{23}H_{25}NO_2S_2$: C, H, N, S.

1-(4-Toluenesulfonyl)-3-phenylazetidine (21a) was prepared in 91% yield from **20a** by the method used to synthesize **13**: mp 133–134 °C (lit.[30] 133–136 °C). The product was identical in all respects with an authentic sample.

3-Phenylazetidine (22a) was prepared from **21a** using the method described for the synthesis of **3**. Yield was determined by GLC to be 48% and the product was confirmed as **22a** by comparison of its GLC and TLC with those of an authentic sample.[30]

3-Amino-2-(3-pyridyl)propanol (17b). To a stirred, cooled (5 °C) slurry of 24.5 g (0.65 mol) of $LiAlH_4$ in 1.2 L of dry glyme was added over 1.5 h a solution of 71.7 g (0.32 mol) of **23**[1a] in 500 mL of dry glyme. The mixture was stirred at room temperature

(29) The yield of **3** was variable (~30–50%). In some reactions traces of **13** and **14** were also isolated from the C_6H_6 insoluble material. At other times, the distilled product (**3**) was found by NMR to contain up to ~10% of an unidentified impurity which was not detected by GLC or TLC. The amounts of impurity and byproducts appeared to be due to difficulties in determining the end point for the reaction.

(30) E. Testa, L. Fontanella, L. Mariani, and G. F. Cristiani, *Justus Liebigs Ann. Chem.*, **639**, 157 (1961).

for 5 days, cooled (5 °C), and treated cautiously with 65 mL of saturated NaCl. After stirring overnight, the insoluble material was removed by filtration. The filter cake was stirred with a solution of 25 mL of saturated NaCl and 600 mL of glyme. This mixture was heated under reflux for 1 h and filtered hot. The combined filtrates were concentrated to give an oil which was dissolved in CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and removed to afford 37.4 g (76%) of crude **17b** as an oil. The IR and NMR of the crude product showed the absence of starting oxime and supported the proposed structure. TLC showed principally one component.

2-(3-Pyridyl)-3-(4-toluenesulfonamido)propyl 4-Toluenesulfonate (20b). To a stirred, cooled (0 °C) solution of 35.2 g (0.23 mol) of crude **17b** in 335 mL of dry pyridine was added in portions 96.9 g (0.51 mol) of purified 4-toluenesulfonyl chloride.[28] After stirring for 2 h, the solution was allowed to stand in the cold (5 °C) overnight and was then diluted to 3 L with H_2O and ice. After vigorous scratching, the precipitated gum solidified. It was collected, washed with H_2O, and dried over NaOH in vacuo to yield 66.5 g (48%, based on **23**) of **20b** which was of sufficient purity for subsequent reaction: mp 150–153 °C.

Analytically pure **20b** was obtained by column chromatography of the crude solid on SiO_2 (CH_2Cl_2 → 10% acetone/CH_2Cl_2), followed by two recrystallizations from CH_3CN: mp 167.5–168 °C; IR (Nujol) 3080 (NH), 1362, 1172, 1152, 1095, 985, 817, 660 cm^{-1}; NMR (Me_2SO-d_6) δ 2.43 (s, 3, CH_3), 2.48 (s, 3, CH_3), 3.13 (m, 3, $CHCH_2N$), 4.31 (d, 2, J = 5 Hz, CH_2O), 7.53 (m, 10, 4- and 5-Py and Ph H), 8.45 (m, 2, 2- and 6-Py H), NH resonance was not assignable. Anal. $C_{22}H_{24}N_2O_5S_2$: C, H, N, S.

3-(3-Pyridyl)-1-(4-toluenesulfonyl)azetidine (20b) was obtained as a semisolid (77%) from crude **20b** by the method described for the preparation of **13**. The crude product was chromatographed on SiO_2 (30:1, C_6H_6 → 10% acetone/C_6H_6) to yield a solid which was decolorized in boiling *tert*-butyl alcohol with charcoal. The *tert*-butyl alcohol was removed and the resulting solid was triturated with Et_2O to give analytically pure **20b** (38%): mp 95–96.5 °C; IR (Nujol) 1429, 1340, 1155, 1097, 709, 672 cm^{-1}; NMR ($CDCl_3$) δ 2.48 (s, 3, CH_3), 3.93 (m, 5, azetidinyl H), 7.47 (m, 6, 4- and 5-Py and Ph H), 8.21 (m, 2, 2- and 6-Py H); mass spectrum m/e (rel intensity) 288 (0.5, M^+), 105 (100), 91 (29.9). Anal. $C_{15}H_{16}N_2O_2S$: C, H, N, S.

3-(3-Pyridyl)azetidine (5) was prepared from **20b** in 27% yield using the method described for the synthesis of **3**: bp 93–97 °C (0.15 mm); GLC and NMR indicated >95% purity; IR (neat) 3295 (NH), 1577, 1482, 803, 713 cm^{-1}; NMR ($CDCl_3$) δ 2.04 (s, 1, NH), 3.91 (m, 5, azetidinyl H), 7.26 (1, m, 5-Py H), 7.72 (m, 1, 4-Py H), 8.50 (m, 2, 3- and 5-Py H); mass spectrum m/e (rel intensity) 134 (3.7, M^+), 105 (100), 104 (33.3), 78 (18).

Analysis was obtained on the dipicrate salt which was formed in EtOH and recrystallized from H_2O: mp 200–201 °C. Anal. $C_{20}H_{16}N_8O_{14}$: C, H, N.

1-Methyl-3-(3-pyridyl)azetidine (6) was prepared from **5** in 59% yield using the method described for the preparation of **4**: bp 63–65 °C (0.15 mm); IR (neat) 1577, 1483, 1429, 1025, 802, 711 cm^{-1}; NMR ($CDCl_3$) δ 2.37 (s, 3, CH_3), 3.17 (m, 2, azetidinyl H), 3.70 (m, 3, azetidinyl H), 7.22 (m, 1, 5-Py H), 7.66 (m, 1, 4-Py H), 8.48 (m, 2, 2- and 6-Py H); mass spectrum m/e (rel intensity) 148 (13.0, M^+), 106 (73.0), 105 (100), 104 (34.9).

Analysis was obtained on the dipicrate salt, which was formed in EtOH and recrystallized from H_2O, mp 191–192 °C. Anal. $C_{21}H_{18}N_8O_{14}$: C, H, N.

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Registry No. **3**, 62247-27-2; **3** dipicrate, 70892-01-2; **4**, 62247-28-3; **5**, 62247-32-9; **5** dipicrate, 70892-02-3; **6**, 62247-33-0; **6** dipicrate, 62247-34-1; **7**, 62247-21-6; **8**, 62247-22-7; **10**, 62247-23-8; **11**, 62247-24-9; **12**, 62247-25-0; **13**, 62247-26-1; **14**, 70892-03-4; **16a**, 29753-99-9; **17b**, 62247-29-4; **18a**, 70892-04-5; **19a**, 70892-05-6; **20a**, 70892-06-7; **20b**, 62247-30-7; **21a**, 70892-07-8; **21b**, 62247-31-8; **22a**, 4363-13-7; **23**, 62287-08-5; 3-pyridinecarboxaldehyde, 500-22-1; malonic acid, 141-82-2; 3-(2,2-dicarboxyvinyl)pyridine diammonium salt, 70892-08-9; 3-(3-pyridyl)acrylic acid, 1126-74-5.

The Chichibabin Reaction of Purines with Potassium Amide in Liquid Ammonia[1]

Nico J. Kos, Henk C. van der Plas,* and Beb van Veldhuizen

Laboratory of Organic Chemistry, Agricultural University, De Dreijen 5, 6703 BC Wageningen, The Netherlands

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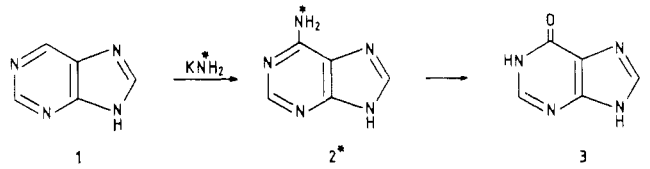
Reaction of purine and 2-methyl- and 8-methylpurine with potassium amide in liquid ammonia leads to the formation of adenine and 2-methyl- and 8-methyladenine, respectively. 6-Methyl- and 6,8-di-*tert*-butylpurine do not react. It was proven by applying ^{15}N-labeled potassium amide that the amination reactions do *not* involve opening of the pyrimidine ring. Low temperature NMR spectroscopy showed that in solutions of purine and 2-methylpurine in potassium amide–liquid ammonia an anionic σ complex at position 6 is formed. 8-Methylpurine on the contrary only showed the presence of a monoanion and a dianion.

It is well known that purines are in general more susceptible to nucleophilic than to electrophilic attack.[2] In basic medium, however, the reactivity toward nucleophiles is often strongly decreased due to deprotonation of the NH of the imidazole ring.[2] Deprotonation has as a further consequence that the pattern of addition of nucleophiles changes. Whereas in neutral purines both positions 6 and 8 are reactive in nucleophilic additions, in the anions of

Scheme I



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