10*H*-Indeno[1,2,7,7a-*bcd*]pyren-10-ol (6c). Similar reaction of **6a** gave **6c** (74%), mp 240–43 °C (benzene): NMR δ 8.40 (s, 1, H_6), 8.37 (s, 1, H_{11}), 8.34 (dd, 1, H_7; $J_{7,8}$ = 7.8 Hz; $J_{7,9}$ = 3.2 Hz), 8.17 (dd, 1, H_1; $J_{1,2}$ = 8.1 Hz; $J_{1,3}$ = 3.2 Hz), 7.80–8.15 (m, 6, Ar), 6.63 (br s, 1, H_{10}), 2.38 (br s, 1, OH). Anal. Calcd for $C_{21}H_{12}O$: C, 89.98; H, 4.31. Found: C, 89.97; H, 4.34.

11*H*-Dibenz[*bc*,*l*]aceanthrylen-11-ol (7c). Similar reaction of **7a** gave **7c** (87%), mp 276–277 °C ($CHCl_3$): NMR δ 9.51 (d, 1, H_{12}; $J_{11,12}$ = 7.8 Hz), 8.37 (s, 1, H_6), 7.65–7.95 (m, 10, Ar), 6.89 (d, 1, H_{13}; J = 10.5 Hz), 2.26 (d, 1, OH, disappeared with D_2O; J = 10.5 Hz); HRMS calcd for $C_{23}H_{14}O$ m/z 306.1045, found m/z 304.1045.

4*H*-Fluoreno[4,4a,4b,5-*abc*]anthracen-4-ol (8c). Similar reaction of **8a** gave **8c** (82%), mp 270–72 °C: NMR δ 9.03 (s, 2, $H_{8,13}$), 8.34 (dd, 2, $H_{1,7}$; J = 8.0, 3.0 Hz), 8.14 (dd, 2, $H_{7,12}$; J = 9.5, 3.3 Hz), 7.81 (d, 2, $H_{3,5}$; J = 7.0 Hz), 7.59–7.73 (m, 4, Ar), 6.16 (br s, 1, H_4), 2.26 (br s, 1, OH, disappeared with D_2O). Anal. Calcd for $C_{23}H_{14}O$: C, 90.17; H, 4.61. Found: C, 90.09; H, 4.62.

7*H*-Dibenzo[*a*,*g*]fluoren-7-ol (9c). Similar reaction of **9a** gave **9c** (78%), mp 202–04 °C (lit.[32] mp 201–202 °C); NMR δ 8.74 (d, 1, H_8; J = 8.5 Hz), 8.44 (dd, 1, H_1; J = 8.2, 2.0 Hz), 8.40 (d, 1, Ar; J = 8.6 Hz), 7.46–7.98 (m, 9, Ar), 5.91 (d, 1, H_7; J = 10.3 Hz), 1.92 (d, 1, OH, disappeared with D_2O; J = 10.3 Hz).

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Supplementary Material Available: NMR spectral data for compounds **7c** and **5b–8b** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Preparation of Piperidinylpyridines via Selective Reduction of Bipyridines with Nickel–Aluminum Alloy

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Bipyridines were reduced to piperidinylpyridines in modest yield using nickel–aluminum alloy in potassium hydroxide solution. The reduction was selective, and 3-substituted rings were reduced in preference to 4-substitution in preference to 2-substitution. Thus 2,3-bipyridine gave only 2-(3′-piperidinyl)pyridine, 2,4-bipyridine gave only 2-(4′-piperidinyl)pyridine, and 3,4-bipyridine gave only 4-(3′-piperidinyl)pyridine. The symmetrical 2,2′- and 4,4′-bipyridines also gave the corresponding piperidinylpyridines, but the reduction of 3,3′-bipyridine was too sluggish to be practical. The products were identified using ^{13}C NMR spectroscopy, and the ^{13}C NMR spectra of the starting bipyridines were also recorded.

Substituted piperidines can be prepared using a variety of methods,[1] for example, cyclization reactions[2–4] which include reactions in which the initial product is an unsaturated piperidine (dihydro- or tetrahydropyridine)[5–10] or a piperidone[11–13] which can subsequently be reduced to a piperidine. Other approaches include alkylation of 2-piperideine[14] and reduction of the corresponding pyridines with tin and hydrochloric acid,[15] with sodium in alcohol,[16–19] or electrolytically.[18–20] These methods sometimes produce mixtures of unsaturated piperidines which require further reduction to the piperidine. Piperidinylpyridines have been prepared via cyclization,[10] alkylation of 2-piperideine,[14] reduction with tin and hydrochloric acid,[15] electroreduction,[20] and, in the case of 2-(2-piperidinyl)-pyridine, hydrogenation at high pressure over palladium.[21]

Scheme I

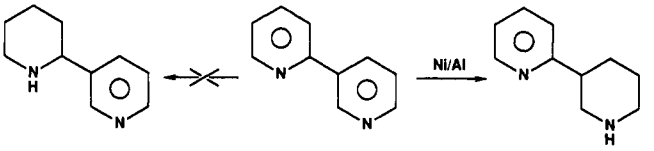

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Table I. Preparation of Piperidinylpyridine Dihydrochlorides by the Nickel–Aluminum Alloy Reduction of Bipyridines

starting material	product	reduction time (h)	yield (%)	mp (°C)	purity[a] (%)
2,2′-bipyridine	2-(2′-piperidinyl)pyridine·2HCl	5	9	198–9	93
2,3′-bipyridine	2-(3′-piperidinyl)pyridine·2HCl	78[b]	29	140–1	97
2,4′-bipyridine	2-(4′-piperidinyl)pyridine·2HCl	385	39	255-7 dec	96
3,4′-bipyridine	4-(3′-piperidinyl)pyridine·2HCl	771[c]	29	[d]	84
4,4′-bipyridine	4-(4′-piperidinyl)pyridine·2HCl	821[b]	12	276–8 dec	92

[a] Purity determined by GC. Isomeric purity determined by NMR (see text). [b] An extra batch of nickel–aluminum alloy was added in the course of the reaction. [c] Three extra batches of nickel–aluminum alloy were added in the course of the reaction. [d] The dihydrochloride could not be crystallized. The yield indicated is for the free base which distilled at 98–9 °C/0.5 mmHg.

The simplest procedure for the preparation of substituted piperidines is the reduction of the corresponding pyridine. In a previous paper[22] we have reported on the use of nickel–aluminum alloy in potassium hydroxide solution to effect this transformation. In a subsequent paper the method was extended to the reduction of other heterocycles.[23] We now wish to report that the nickel–aluminum alloy procedure can be used to selectively reduce bipyridines to piperidinylpyridines (Table I). Although the reaction is generally slow (probably for steric reasons),[22] it is very simple to carry out, particularly compared to the complex multistep cyclizations used to prepare some piperidines, as it is only necessary to stir the reaction mixture at room temperature until it is time to begin the workup procedure. We have found it helpful to monitor the reaction by GC. The components of the reaction always elute in the same order: bipiperidine, piperidinylpyridine, and bipyridine. When the concentration of the piperidinylpyridine reaches a maximum, the reaction is terminated before overreduction to the bipiperidine can occur. Recrystallization of the piperidinylpyridine dihydrochloride from aqueous ethanol gave products which were >90% pure in most cases.

The isomeric identities of the products were best determined by ^{13}C NMR, and it was found that only one reduction product was formed in each case (Table I). Thus 2,3-bipyridine gave only 2-(3′-piperidinyl)pyridine (isoanabasine). The other possible reduction isomer is 3-(2′-piperidinyl)pyridine, which was obtained commercially as anabasine. Inspection of the ^{13}C NMR spectra of the reduction product showed that <2% of the other compound was present (Scheme I). Similarly, 2,4-bipyridine gave only 2-(4′-piperidinyl)pyridine. The other possible product is 4-(2′-piperidinyl)pyridine, which was prepared using the method of Scully.[14] Inspection of the ^{13}C NMR spectra of the reduction product showed that <1% of the other compound was present. When 3,4-bipyridine was reduced, only 4-(3′-piperidinyl)pyridine was seen. The other possible reduction isomer was not available, but the ^{13}C NMR spectra of the reduction product was compared with that of anabasine, which also contains a 3-substituted pyridine ring, and it was found that <2% of the other compound was present. The symmetrical 2,2′- and 4,4′-bipyridines also gave the corresponding piperidinylpyridines, but the reduction of 3,3′-bipyridine was too sluggish to be practical.

It was found that the nature of the reduction depended on the substitution of the ring. 3-Substituted rings were reduced in preference to 4-substitution in preference to 2-substitution. In previous work[22] it was found that electron-supplying groups retarded the reaction while electron-withdrawing groups accelerated the reaction although electron-supplying groups in the 2-position also accelerated the reaction. In the current work competitive reductions of 2-, 3-, and 4-substituted *N*-methylpyridinecarboxamides with nickel–aluminum alloy showed that, in accord with the results for the bipyridines, *N*-methyl-3-pyridinecarboxamide was reduced slightly more readily than *N*-methyl-4-pyridinecarboxamide, which was reduced more readily than *N*-methyl-2-pyridinecarboxamide. All three compounds were reduced more readily than 2-methylpyridine. The products of the reduction of the *N*-methylpyridinecarboxamides were the corresponding *N*-methylpiperidinecarboxamides.

This procedure provides a facile method for the preparation of certain piperidinylpyridines which are analogues of the tobacco alkaloid anabasine. The reduction of 2,3-bipyridine gave 2-(3′-piperidinyl)pyridine, which is isoanabasine.[24]

Experimental Section

Materials. 2,2′-, 2,3′-, 2,4′-, 3,3′-, and 4,4′-bipyridine, (±)-anabasine, and all other reagents were obtained from Aldrich Chemical Co., Milwaukee, WI.

All compounds exhibited satisfactory mass spectral characteristics. A VG Analytical 7250 machine was used. HRMS data for 3,4-bipyridine and the piperidinyl pyridines (except for anabasine) are available as supplementary material. Compound purities were established by ^1H and ^{13}C NMR spectra and by GC analysis. Yields are mol % of the purified products.

N-Methyl-2-pyridinecarboxamide was prepared from 8.95 g of ethyl 2-pyridinecarboxylate and 15 mL of 40% methylamine in water (yield = 7.38 g (92%), bp 95–7 °C/1.2 mmHg, lit.[25] bp 128 °C/12 mmHg), and *N*-methyl-4-pyridinecarboxamide was prepared as previously described[22] by the method of Libermann et al.[26]

3,4′-Bipyridine was prepared by the method of Yamamoto et al.[27] from 3.00 g of 3-(trimethylstannyl)pyridine[28] and 2.63 g of 4-bromopyridine hydrochloride to give 1.36 g (70%) of 3,4′-bipyridine as a yellow oil, bp 116–9 °C/1 mmHg (lit.[29] bp 144–6 °C/15 mmHg). 4-Bromopyridine hydrochloride was converted to the free base by taking it up in ice-cold 1 M potassium hydroxide solution and extracting with ice-cold ether. The extracts were dried over $MgSO_4$ in the refrigerator and evaporated under reduced pressure to give the free base, which was used at once. This coupling reaction gave much better results than a classical Hantzsch synthesis,[30] which gave only low yields of impure material in our hands. A compound having a melting point of 61 °C prepared by the reaction of sodium in pyridine which was claimed to be 3,4-bipyridine[31] was shown to be 2,4-bipyridine.[32]

Analytical samples of the bipyridine dihydrochlorides were prepared by taking up the free base in ethanol and acidifying with

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Table II. ^{13}C NMR of Bipyridines

compound	pyridine ring carbons									
	2	3	4	5	6	2′	3′	4′	5′	6′
2,2′-bipyridine	156.01	120.97	136.81	123.61	149.07					
2,3′-bipyridine	154.34	120.20	136.62	122.50	149.54	149.67	134.44	133.90	123.22	147.88
2,4′-bipyridine	154.10	120.46	136.69	123.45	149.70	150.06	120.66	145.93	120.66	150.06
3,3′-bipyridine	148.95	133.05	134.00	123.42	147.80					
3,4′-bipyridine	149.93	133.52	134.10	123.61	147.88	150.30	121.32	144.92	121.32	150.30
4,4′-bipyridine	150.39	121.09	145.14	121.09	150.39					

Table III. ^{13}C NMR of Bipyridine Dihydrochlorides

compound	pyridine ring carbons									
	2	3	4	5	6	2′	3′	4′	5′	6′
2,2′-bipyridine·2HCl	146.09	123.89	145.68	127.41	143.72					
2,3′-bipyridine·2HCl	145.62	127.10	147.32	127.85	143.82	146.05	131.45	140.93	128.37	143.53
2,4′-bipyridine·2HCl	147.01	126.81	145.81	128.37	145.29	142.52	125.84	149.53	125.84	142.52
3,3′-bipyridine·2HCl	145.40	133.67	140.25	128.02	142.29					
3,4′-bipyridine·2HCl	148.08	137.32	144.46	130.73	146.67	145.20	128.55	154.36	128.55	145.20
4,4′-bipyridine·2HCl	142.61	126.36	151.92	126.36	142.61					

Table IV. ^{13}C NMR of Piperidinylpyridines

compound	pyridine ring carbons					piperidine ring carbons				
	2	3	4	5	6	2	3	4	5	6
2-(2′-piperidinyl)pyridine	163.53	120.40	136.43	121.82	148.88	62.37	33.02	24.91	25.97	47.07
3-(2′-piperidinyl)pyridine[a]	148.65	139.29	134.50	123.54	148.54	59.49	33.87	24.79	24.91	47.14
4-(2′-piperidinyl)pyridine	149.76	121.61	154.08	121.61	149.76	60.92	34.63	25.05	25.62	47.28
2-(3′-piperidinyl)pyridine	163.49	120.91	135.94	121.30	148.77	51.98	45.60	30.52	26.36	46.22
4-(3′-piperidinyl)pyridine	149.57	122.33	153.29	122.33	149.57	52.86	43.29	31.10	26.38	46.28
2-(4′-piperidinyl)pyridine	153.88	110.09	125.83	110.68	138.42	35.51	21.46	33.57	21.46	35.51
4-(4′-piperidinyl)pyridine	149.47	121.86	154.66	121.86	149.47	46.17	32.79	41.77	32.79	46.17

[a] Anabasine.

dilute HCl. This mixture was evaporated and dried by removing several portions of ethanol under reduced pressure. The resulting crystals were recrystallized from aqueous ethanol. 2,2′-Bipyridine dihydrochloride was also purified by sublimation. Mp: 2,2′-bipyridine dihydrochloride, 185–8 °C; 2,3′-bipyridine dihydrochloride, 227–8 °C; 2,4′-bipyridine dihydrochloride, 219–20 °C. The other dihydrochlorides sublimed without melting.

4-(2-Piperidinyl)pyridine was prepared from 1.58 g of 4-bromopyridine hydrochloride and 0.98 g of *N*-chloropiperidine using the method of Scully for the synthesis of anabasine.[14] 4-Bromopyridine was obtained as the free base as described above. 4-Lithiopyridine was prepared from 4-bromopyridine at −78 °C using *n*-butyllithium. The addition of piperideine (which was prepared from *N*-chloropiperidine and potassium superoxide in a 19-h reaction) was carried out at −78 °C, but in other respects the reaction is analogous to the previous procedure. 4-(2-Piperidinyl)pyridine (0.44 g, 33%) was obtained as a pale yellow oil, bp 120 °C/1 mmHg. 4-(2-Piperidinyl)pyridine dihydrochloride was also a yellow oil.

Analytical Procedures. The nickel–aluminum alloy reductions were followed by GC using a 1.8 m × 2 mm i.d. glass column packed with 2% Carbowax 20M + 1% KOH on 80/100 Supelcoport. The oven temperature was 200 °C, the injection temperature was 200 °C, the flame ionization detector temperature was 300 °C, and the carrier gas was nitrogen flowing at 30 mL/min. The reaction mixtures were analyzed by direct injection. The piperidinylpyridine dihydrochlorides were basified with 1 M KOH before analysis. It was found that the elution order was always bipiperidine (retention time 1.7–3.4 min), piperidinylpyridine (2.5–5.2 min), and bipyridine (4.0–9.9 min). For any given compound the peaks for the starting material and the reduction products were always well separated. The purities are given as area %. It should be noted that the response of the flame ionization detector (FID) is proportional to the number of carbons.[33] Since reduction does not change the number of carbons in the molecules, area % is equivalent to mol %, at least within the experimental error of the procedure. Other compounds were determined using the same GC system, retention times (min), and oven temperatures (°C) in parentheses: 2-methylpyridine (0.8, 80), *N*-methyl-2-pyridinecarboxamide (2.0, 200), *N*-methyl-3-pyridinecarboxamide (4.4, 225), and *N*-methyl-4-pyridinecarboxamide (4.3, 225).

Nickel–Aluminum Alloy Reductions. In a typical procedure 4.43 g of 2,4-bipyridine was taken up in 100 mL of methanol, and 100 mL of 1 M KOH solution was added. Nickel–aluminum alloy (25 g) was added in portions over 1 h, and the mixture was stirred at rt and monitored by GC. After 385 h the mixture was filtered through Celite 521 and washed through with 500 mL of CH_2Cl_2. The spent nickel (which is potentially pyrophoric) was allowed to dry on a metal tray away from flammable solids in a fume hood for 24 h and then discarded. The aqueous layer was extracted four times with CH_2Cl_2, and all CH_2Cl_2 layers were combined, dried over Na_2SO_4, and evaporated with dilute HCl to give a pink solid which was recrystallized twice from aqueous ethanol to give 2.67 g (39%) of 2-(4-piperidinyl)pyridine dihydrochloride as pink crystals, mp 255–7 °C dec. GC analysis showed that this material was 96% pure. Other reductions were carried out in a similar fashion with monitoring by GC (Table I). On occasion it was found necessary to add further batches of nickel–aluminum alloy to driven the reaction to completion. When GC monitoring indicated that the bipyridine was mostly reduced, the reaction was terminated to avoid overreduction to the bipiperidine. The dihydrochloride of 4-(3′-piperidinyl)pyridine could not be crystallized. The free base was a colorless oil which distilled at 98–9 °C/0.5 mmHg. The free bases were prepared by treating the dihydrochlorides with 1 M potassium hydroxide solution followed by extraction into CH_2Cl_2. The free bases were all oils except for 4-(4-piperidinyl)pyridine, which was a white crystalline solid, mp 86–7 °C (lit.[15] mp ~80 °C).

Competition experiments were carried out with 0.2 g of each pair of compounds in 10 mL of 0.5 M KOH solution. Nickel–aluminum alloy (1.25 g) was added, and the mixture was monitored by GC. *N*-Methyl-3-pyridinecarboxamide and *N*-methyl-4-pyridinecarboxamide could not be resolved by GC, so the reaction was monitored by ^{13}C NMR and it was found that the peaks for the 3-substituted isomer decreased at a slightly faster rate.

NMR Studies. ^{13}C NMR spectra were obtained at 50.1 MHz, and ^{1}H NMR spectra were obtained at 200 MHz. The bases were

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Table V. ^{13}C NMR of Piperidinylpyridine Dihydrochlorides

compound	pyridine ring carbons					piperidine ring carbons				
	2	3	4	5	6	2	3	4	5	6
2-(2′-piperidinyl)pyridine·2HCl	149.65	124.85	147.20	127.44	143.57	57.47	28.59	21.18	21.65	45.86
3-(2′-piperidinyl)pyridine·2HCl[a]	144.22	135.90	141.65	127.61	143.34	57.33	28.73	21.25	21.85	45.96
4-(2′-piperidinyl)pyridine·2HCl	145.07	128.29	159.23	128.29	145.07	61.88	32.36	24.12	24.78	48.62
2-(3′-piperidinyl)pyridine·2HCl	154.04	125.66	147.58	126.10	141.71	45.83	37.85	27.37	21.53	43.63
4-(3′-piperidinyl)pyridine·2HCl	141.22	126.24	161.78	126.24	141.22	46.58	39.43	28.11	21.77	43.71
2-(4′-piperidinyl)pyridine·2HCl	156.86	125.23	141.42	125.57	147.23	43.39	27.11	37.71	27.11	43.39
4-(4′-piperidinyl)pyridine·2HCl	141.17	125.72	164.53	125.72	141.17	43.64	27.76	39.21	27.76	43.64

[a] Anabasine dihydrochloride.

run in $CDCl_3$ using TMS for ^1H and chloroform for ^{13}C as internal standards. The hydrochlorides were run in D_2O using sodium 3-(trimethylsilyl)-1-propanesulfonate (TSP) for ^1H and dioxane or TSP for ^{13}C as internal standards. The spectra of the bipyridines and the piperidinylpyridines and their dihydrochlorides are available as supplementary material.

Assignment of ^{13}C NMR Resonances. APT (attached proton test[34]) experiments were conducted to identify the quaternary carbons and some carbons in symmetrically substituted rings could be identified by increased peak intensities. In general, the resonances for the bipyridines were tentatively assigned on the basis of the known resonances for substituted pyridines[35] with substituted carbons being shifted downfield most of all (Table II). The resonances of 2,2′-bipyridine were assigned on the basis of previously published work[36] although other workers have reversed the assignments of carbons 3 and 5.[37] Similarly, the resonances for 3,3′-bipyridine[37] and 4,4′-bipyridine[37,38] were assigned on the basis of previously published work. The resonances for 2,3′-bipyridine have also been published[37] and are in general agreement with our findings. However, we assign the resonance at 134.44 as carbon 3′ on the basis of an APT experiment. Additionally, we assign the resonance at 136.62 ppm as carbon 4, and we do not observe a resonance at 148.8 ppm as reported by these authors. Resonances for 2,4′- and 3,4′-bipyridine were assigned by analogy with these compounds.

Resonances for the bipyridine dihydrochlorides were assigned in a similar fashion using APT experiments and symmetry considerations (Table III). The chemical shifts for the 2 and 6 positions of pyridinium hydrochloride decrease relative to pyridine and the chemical shifts for the other positions increase (4 > 3, 5).[35]

Resonances for the piperidinylpyridines were established using APT experiments and symmetry considerations and by analogy with the assignments for the bipyridines (Table IV). Additionally, assignments for anabasine have been published,[39,40] and these assignments are similar to those for nicotine.[41] The piperidine ring carbons were assigned on the basis of studies of N-methylated 2-substituted piperidines which showed that the order was 4 < 5 < 3 < 6 < 2 (2 was also assigned by APT experiment)[42] and of N-methylated 3-substituted piperidines which showed that the order was 5 < 4 < 6 < 2 (3 was assigned by an APT experiment).[43] For the 4-substituted piperidines the 4 position was determined by an APT experiment and the lower values were assigned to the 3 and 5 carbons and the higher values to the 2 and 6 carbons by analogy with piperidine.[35]

Resonances for the piperidinylpyridine dihydrochlorides were established in a similar fashion (Table V). The resonances for anabasine dihydrochloride have been assigned by Leete.[40]

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Supplementary Material Available: HRMS data for 3,4′-bipyridine and the piperidinylpyridines (except for anabasine) and ^1H and ^{13}C NMR spectra for the bipyridines and the piperidinylpyridines and their dihydrochlorides (53 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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