# Aminoalkylpyridines 2[+]. Molecular Modification by N-Acylation of Amino Group and Effect on Anticonvulsant Activity

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**Abstract** - Several N-acetylaminoalkylpyridines (N-acetylAAPs) (**1a-4a**) were synthesized and tested for anticonvulsant activity in mice, ip, and rats, po. Several acetylating agents were investigated but excess acetic anhydride in refluxing benzene was the most effective. N-acetylation resulted in a decrease in the potent anticonvulsant activity of the parent AAPs, particularly by the oral route, and at the same time, a considerable increase in the neurotoxicity by the ip route.

## Introduction

Studies on the metabolism and pharmacology of the triazoline anticonvulsants [1-4] have led to the identification of the triazoline pharmacophore and the evolution of the aminoalkylpyridine (AAP) metabolite analogues as a new class of potent orally active anticonvulsants, far superior to the triazolines, with long duration of action and no apparent signs of neurotoxicity [4]. The AAPs are amenable to molecular modification at three sites -- the heterocyclic substituent, the alkyl grouping, and the amino-nitrogen. The synthesis and anticonvulsant testing of several N-acetyl AAPs, and the effects of acylation on the anticonvulsant activity and neurotoxicity are reported.

## Results and discussion

*Chemistry.*

Unlike anticipated, the acetylation of the secondary amino group in the AAP compounds proved difficult, and several acetylating agents had to be investigated. Conventional reagents such as acetyl chloride in the presence of dimethylaminopyridine (DMAP) and triethylamine, alone or in combination, led to incomplete reaction and in the presence of excess pyridine, an intractable mixture resulted. Acetic anhydride/sodium acetate and acetic anhydride/DMAP/ triethylamine combinations, as well as acetic anhydride in the presence of sodium hydride and DMSO or DMF, all failed at the acetylation. Acetic acid/DMAP in methylene chloride/DCC was also found unreactive. Finally, a combination of excess acetic anhydride in benzene was found to be the most promising reagent (Chart).

The acetylation reactions using *excess* acetic anhydride proceeded smoothly in refluxing benzene to give good yields (60-90%) of the N-acetyl compounds. Under these conditions, the acetylation of the monochlorophenylAAPs went to completion, but the dichlorophenylAAPs required *greater excess* of acetic anhydride and

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[+] Reference 4 is "Aminoalkylpyridines 1".

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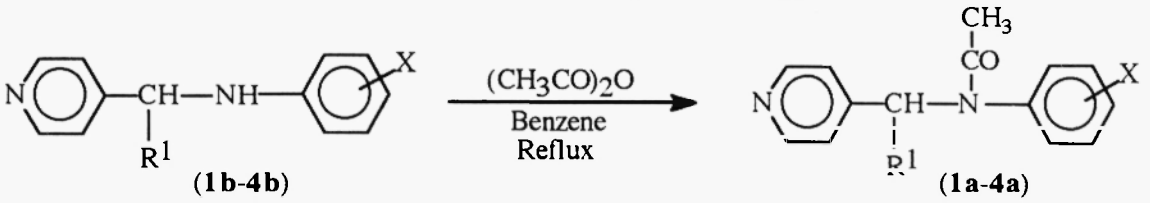
**Chart I** Synthesis of N-acetylaminoalkylpyridines




**(1b-4b)** **(1a-4a)**

**1a**,**1b**, $R^1$ = $CH_3$-, X = 4-Cl
**2a**, **2b**, $R^1$ = $CH_3$-, X = 3-Cl
**3a**, **3b**, $R^1$ = $CH_3$-, X = 3,4-$Cl_2$
**4a**, **4b**, $R^1$ = $CH_3CH_2$-, X = 3,4-$Cl_2$

more extended reflux periods. The latter compounds yielded dark brown reaction mixtures with some black insoluble material, which may account for their lower product yields (~60%). Column chromatography proved useful in purifying the products where fractional crystallization did not succeed.

The structures of the products were established by $^1$H- and $^{13}$C-NMR analysis. There was one interesting and striking feature in the $^1$H-NMR spectra of all the N-acetyl products; the 2,6-protons of the phenyl ring attached to the acetylated amino-nitrogen, displayed unusually characteristic broad peaks at ambient temperatures at which the spectra were obtained. This peak broadening of the 2,6-protons is unprecedented to the best of our knowledge. Although the broad peaks sharpened with much improved resolution, when the spectra were determined at temperatures that were either higher (80°C) or lower (-40°C) than the ambient (~20°C), it is difficult to offer a precise explanation for this phenomenon.

*Anticonvulsant and motor toxicity testing*

The compounds were evaluated for their anticonvulsant activity, neurotoxicity and potency, in mouse, ip, and rat, po, according to published procedures [5] using the maximal electroshock seizure (MES) test and the subcutaneous pentylenetetrazol seizure threshold (scMet) test.

N-acetylation of the AAPs generally resulted in a decrease in the anticonvulsant activity, particularly by the oral route in rats, and at the same time, a considerable increase in the neurotoxicity by the ip route in mice. Similar to the parent AAPs [4], the N-acetyl compounds also evinced greater effectiveness in the MES test showing activity at 100 mg/kg with little or no activity in the scMet test even at 300 mg/kg. However, unlike the potent orally active parents [4], none of the N-acetyl derivatives afforded more than 25% protection upon oral administration. None of the compounds showed toxicity by the oral route at the test dose of 30 mg/kg.

## Experimental

*Chemical synthesis*

Melting points were determined using a Thomas-Hoover capillary melting apparatus and are uncorrected. NMR spectra were recorded on a Varian VXR-300 spectrometer operating at 299.95 MHz for $^{1}H$ and 75.45 MHz for $^{13}C$, using $(CH_3)_4Si$ as the internal standard ($\delta = 0$). Elemental analyses for C, H and N were performed by Oneida Research Laboratory, One Halsey Road, Whitesboro, NY 13492. AAPs were prepared according to previously published procedures [4]. Column chromatography was performed on silica gel (70-230 mesh) (Aldrich) and thin-layer chromatograms were run on silica gel 60 $F_{254}$ plastic sheets (layer thickness, 0.25 mm) (Aldrich).

*General procedure for the synthesis of compounds 1a and 2a.*
To a solution of AAP (4.3 mmol) in 30 ml of benzene, was added 2.5 ml (26 mmol) of acetic anhydride. The solution was stirred magnetically and refluxed for 18 h. The mixture was cooled to room temperature, taken up in 100 ml of cold water, and neutralized with sodium bicarbonate. It was extracted with two 50 ml portions of methylene chloride. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure resulted in a yellowish oily residue, which solidified from a mixture of *tert*-butyl methyl ether (2-3 parts) and petroleum ether (1 part), to give pure crystalline materials in good yields.

*N-(4-Chlorophenyl)-1-(4-pyridyl)-N-ethylacetamide* ***1a.*** This was obtained as tannish crystals (1.0 g, 85 %); mp: 100-102 °C. Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; N, 10.20. Found: C, 65.73; H, 5.36; N, 10.19. $^{1}H$-NMR ($CDCl_3$), δ: 1.38 (3H, d, J = 7.5 Hz, $CH_3$), 1.78 (3H, s, $COCH_3$), 6.21 (1H, q, J = 7.2 Hz, CH), 6.69 (2H, br s, phenyl 2,6-H), 7.12 (2H, dd, $J_1$ = 4.8 Hz, $J_2$ = 1.5 Hz, pyridyl 3,5-H), 7.26 (2H, d, J = 8.1 Hz, phenyl 3,5-H), 8.51 (2H, dd, $J_1$ = 4.8 Hz, $J_2$ = 1.5 Hz, pyridyl 2,6-H). $^{13}C$-NMR ($CDCl_3$), δ: 16.5 ($CH_3$), 23.23 ($CH_3CO$), 50.9 (CH), 122.8 (pyridyl 3,5-C), 129.5 (phenyl-C), 131.3 (phenyl-C), 134.6 (phenyl 4-C), 137.2 (phenyl 1-C), 149.7 (pyridyl 4-C), 149.9 (pyridyl 2,6-C), 170.2 (CO).

*N-(3-Chlorophenyl)-1-(4-pyridyl)-N-ethylacetamide* ***2a.*** This was obtained as white crystals (0.98 g, 83 %); mp 108-109 °C. Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; N, 10.20. Found: C, 65.54; H, 5.63; N, 10.28. $^{1}H$-NMR ($CDCl_3$), δ: 1.41 (3H, d, J = 6.9 Hz, $CH_3$), 1.82 (3H, s, $COCH_3$), 6.20 (1H, q, J = 7.5 Hz, CH), 6.64 (1H, br s, phenyl 6-H), 6.85 (1H, br s, phenyl 2-H), 7.15 (2H, dd, $J_1$ = 4.5 Hz, $J_2$ = 1.5 Hz, pyridyl 3,5-H), 7.23 (1H, t, J = 8.9 Hz, phenyl 5-H), 7.33 (1H, d, J = 8.1 Hz, phenyl 4-H), 8.54 (2H, dd, $J_1$ = 4.5 Hz, $J_2$ = 1.5 Hz, pyridyl 2,6-H). $^{13}C$-NMR ($CDCl_3$), δ: 16.6 ($CH_3$), 23.3 ($CH_3CO$), 51.2 (CH), 122.8 (pyridyl 3,5-C), 128.3 (phenyl C), 128.9 (phenyl C), 130.2 (phenyl C), 130.3 (phenyl C), 134.7 (phenyl 3-C), 139.9 (phenyl 1-C), 149.6 (pyridyl 4-C), 149.9 (pyridyl 2,6-C), 170.1 (CO).

*Synthesis of compounds 3a and 4a.*
A solution of the *N-(3,4-dichlorophenyl)-1-(4-pyridyl)alkylamine* (7.5 mmol) in a mixture of 30 ml (318 mmol) of acetic anhydride and 20 ml of benzene was refluxed for 48 h. The mixture was evaporated to dryness in vacuo, to give an oily dark brown residue. The oil was taken up in 200 ml of cold water, neutralized with sodium bicarbonate, and extracted with two 100 ml portions of methylene chloride. The

combined extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent yielded a brown oil, which was purified by column chromatography using elution with hexanes to remove impurities and then with methylene chloride to give a pure fraction as indicated by TLC. It solidified from a mixture of *tert*-butyl methyl ether (2-3 parts) and petroleum ether (1 part) to afford the pure crystalline products.

*N-(3,4-Dichlorophenyl)-1-(4-pyridyl)-N-ethylacetamide 3a.* This was obtained as white crystals (1.2 g, 50 %); mp 73-76 °C. Anal. Calcd. for $C_{15}H_{14}Cl_2N_2O$: C, 58.27; H, 4.56; N, 9.06. Found: C, 57.99; H, 4.52; N, 9.03. $^1$H-NMR ($CDCl_3$), δ: 1.40 (3H, d, J = 7.2 Hz, $CH_3$), 1.82 (3H, s, $COCH_3$), 6.20 (1H, q, J = 7.2 Hz, CH), 6.59 (1H, br s, phenyl 6-H), 6.93 (1H, br s, phenyl 2-H), 7.13 (2H, dd, $J_1$ = 4.8 Hz, $J_2$ = 1.8 Hz, pyridyl 3,5-H), 7.36 (1H, d, J = 8.4 Hz, phenyl 5-H), 8.54 (2H, dd, $J_1$ = 4.8 Hz, $J_2$ = 1.8 Hz, pyridyl 2,6-H). $^{13}$C-NMR [$d_6$-DMSO], δ: 16.7 ($CH_3$), 23.2 ($CH_3CO$), 51.7 (CH), 122.6 (pyridyl 3,5-C), 130.4 (phenyl C), 131.0 (phenyl C), 131.2 (phenyl C), 131.4 phenyl C), 132.1 (phenyl C), 139.2 (phenyl 1-C), 149.7 (pyridyl 2,6-C), 149.8 (pyridyl 4-C), 169.1 (CO).

*N-(3,4-Dichlorophenyl)-1-(4-pyridyl)-N-propylacetamide 4a.* This was obtained as white crystals (1.6 g, 65 %); mp 98-99 °C. Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O$: C, 59.46; H, 4.99; N, 8.67. Found: C, 59.36; H, 4.68; N, 8.63. $^1$H-NMR [$d_6$-DMSO], δ: 0.90 (3H, t, J = 7.4 Hz, $CH_3$), 1.75 (3H, s, $COCH_3$), 1.81 (2H, q, J = 7.4 Hz, $CH_2$), 5.72 (1H, t, J = 7.2 Hz, CH), 6.90 (1H, br s, phenyl 6-H), 7.15 (2H, dd, $J_1$ = 4.5 Hz, $J_2$ = 1.5 Hz, pyridyl 3,5-H), 7.19 (1H, br s, phenyl 2-H), 7.62 (1H, d, J = 8.7 Hz, phenyl 5-H), 8.50 (2H, dd, $J_1$ = 4.5 Hz, $J_2$ = 1.5 Hz, pyridyl 2,6-H). $^{13}$C-NMR [$d_6$-DMSO], δ: 10.8 ($CH_3$), 22.8 ($CH_2$), 23.1 ($CH_3CO$), 57.7 (CH), 123.3 (pyridyl 3,5-C), 130.2 (phenyl C), 130.8 (phenyl C), 131.1 (phenyl C), 131.2 (phenyl C), 131.8 (phenyl C), 138.9 (phenyl 1-C), 147.9 (pyridyl 4-C), 149.8 (pyridyl 2,6-C), 169.2 (CO).

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