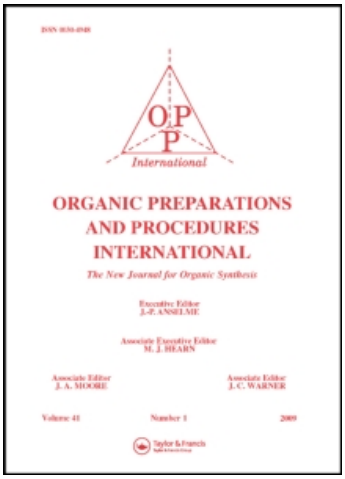

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Adamczyk, Maciej and Fino, James R.(1996) 'SYNTHESIS OF PROCAINAMIDE METABOLITES. N-ACETYL DESETHYLPROCAINAMIDE AND DESETHYLPROCAINAMIDE', Organic Preparations and Procedures International, 28: 4, 470 — 474
To link to this Article: DOI: 10.1080/00304949609356555
URL: http://dx.doi.org/10.1080/00304949609356555

SYNTHESIS OF PROCAINAMIDE METABOLITES. N-ACETYL DESETHYLPROCAINAMIDE AND DESETHYLPROCAINAMIDE

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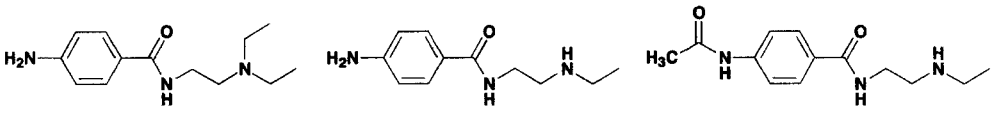
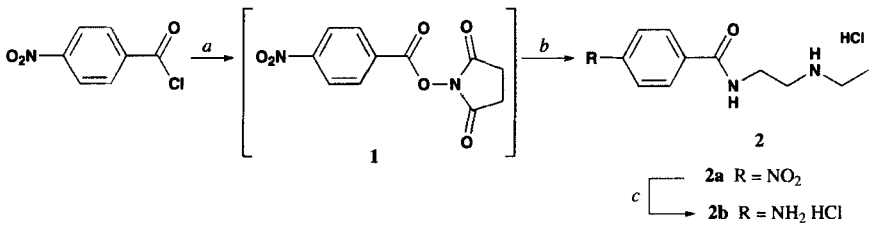
Procainamide is an antiarrhythmic drug that has several side effects, among which is induced lupus erythematosus.[1] To assure safe and effective treatment, the serum levels of procainamide must be monitored in patients.[2,3] Quantification of procainamide is routinely achieved by immunoassay. Antibodies used in the immunoassay must be assessed for cross-reactivity against the drug's metabolites to assure accurate quantification. Studies of procainamide metabolism by Ruo *et al.* resulted in the identification and characterization of N-ethyl-N'-(4-aminobenzoyl)ethylenediamine (desethylprocainamide, DEPA), a metabolite found in urine.[4,5] Taber *et al.* isolated and characterized N-ethyl-N'-(4-acetamido-benzoyl)ethylenediamine (N-acetyl desethylprocainamide, DENAPA) from human plasma.[6]



procainamide DEPA DENAPA

Neither DEPA nor DENAPA is commercially obtainable, therefore, the need for a well documented and facile procedure for their preparation is very important to both the research and clinical communities.[7] While the published syntheses for these metabolites provided a general description of the processes employed,[4-6,8,9] they lacked sufficient detail and product characterization for the production of materials suitable for our needs. We herein present descriptive procedures for the preparation and characterization of these important compounds.

As shown in Scheme 1, *p*-nitrobenzoyl chloride was converted to the N-hydroxy-

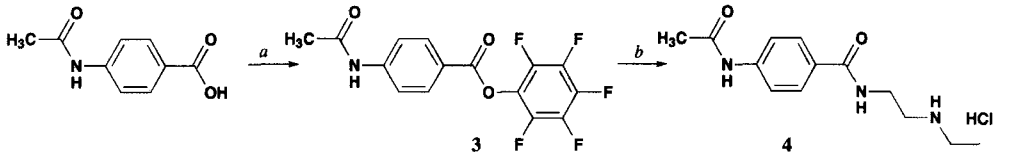


a) NHS, Et_3N, THF, DMF *b*) N-Ethylethylenediamine, Et_3N, THF, CH_2Cl_2 *c*) H_2, 10% Pd/C, EtOH, HCl

Scheme 1

succinimide (NHS) active ester (**1**). Selective acylation of unprotected N-ethylethylenediamine in the presence of triethylamine in THF yielded the nitrobenzamide **2a**. This intermediate was catalytically reduced then crystallized from ethanolic HCl to give pure DEPA (**2b**) as its bis HCl salt.

A two step synthesis of DENAPA was accomplished by converting 4-acetamidobenzoic acid to its pentafluorophenyl active ester (**3**) using pentafluorophenyl trifluoroacetate.[10] The subsequent addition of this active ester to unprotected N-ethylethylenediamine followed by extraction then crystallization from ethanolic HCl yielded DENAPA (**4**) as its HCl salt.



a) Pentafluorophenyl trifluoroacetate, pyridine, DMF *b*) N-Ethylethylenediamine, Et_3N, THF; then EtOH/HCl

Scheme 2

Several preparations of DEPA (**2b**) have been reported. One route employed the direct acylation of N-ethylethylenediamine with p-nitrobenzoyl chloride followed by reduction of the nitro group.[4] In our hands, this acylation was not selective, leading to a complex mixture which was difficult to purify. The same group reported a second route to **2b** which entailed acylation of N-ethylethylenediamine with N-Cbz-protected p-aminobenzoic acid NHS active ester, followed by hydrogenolysis[5]. The product was reported as the mono hydrochloride salt (mp. 172-174°) as compared to the bis hydrochloride salt for **2b** (mp. 212-216°) from the present route. A third route involved acylation of 2-(N-benzyl-N-ethyl)ethylenediamine with p-nitrobenzoyl chloride followed by simultaneous reduction of the nitro group and hydrogenolysis of the N-benzyl group.[8] The resulting material was reported as the hydrochloride (mp. 156°).

Several previous preparations of DENAPA (**4**) have also been reported. Based on our experience with **2b**, it was anticipated that acylation of N-ethylethylenediamine with N-acetamidobenzoyl chloride[5] or the acetylation of **2b**[4] would not be selective. The use of N-hydroxysuccinimide and N,N'-dicyclohexylcarbodiimide for making the active ester of *p*-acetamidobenzoic acid[9] was not attempted because of the difficulty in separation from the N,N'-dicyclohexylurea. These methods and an earlier one that used the potassium ferricyanide-mediated dealkylation of N-acetylprocainamide[6] were not investigated.

In summary, DEPA (**2b**) and DENAPA (**4**) were prepared efficiently and characterized as high purity solids. The procedures employ commercially available starting materials and reliably resulted in analytically pure materials suitable for use in metabolite cross reactivity studies.

EXPERIMENTAL SECTION

All melting points were taken with an Electrothermal capillary apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shifts (δ) are quoted in

ppm with tetramethylsilane (TMS) as an internal standard. Chemical ionization mass spectra were recorded using a Finnegan MAT SSQ700. Elemental analyses were made by Robertson Microlit Laboratories, Inc., Madison, NJ, USA. All chemicals were purchased from Aldrich Chemical Co. and were used as received unless otherwise specified.

4-Nitro-N-(2-aminoethylethyl)benzamide (2a).- A solution of 4-nitrobenzoyl chloride (10.0 g, 53.9 mmol) in THF (100 mL) was added dropwise over a 30 min period to a stirred solution of N-hydroxysuccinimide (6.2 g, 59 mmol), THF (200 mL) and triethylamine (15 mL, 108 mmol). After 6 hrs, DMF (40 mL) was added and stirring continued for 30 minutes. The solution was filtered, the precipitate washed with THF (100 mL) and the filtrate evaporated *in vacuo*. The residue was dissolved in dichloromethane (200 mL) and added dropwise over a 50 min period to a stirred solution of N-ethylethylenediamine (5.7 mL, 53.9 mmol), and triethylamine (15 mL, 108 mmol) in THF (200 mL). After 24 hrs, the precipitated product was isolated on a Buchner funnel and washed with THF (50 mL) then dried *in vacuo*. The solid was crystallized from ethanol/31% ethanolic HCl (100 mL/30 mL, respectively) and dried *in vacuo* to afford **2a** (11.3 g, 77%) as a light yellow solid, mp. 235.5-237.5° (dec.). ^{1}H NMR (d_6-DMSO): δ 9.29 (bs, 1H), 9.18 (bs, 2H), 8.30 (d, J = 8.8, 2H), 8.20 (d, J = 8.9, 2H), 3.66-3.61 (bm, 2H), 3.11 (bs, 2H), 3.05-2.90 (bm, 2H), 1.22 (t, J = 7.3, 3H). ^{1}H NMR (d_6-DMSO/D_2O): δ 8.26 (d, J = 8.9 Hz, 2H), 8.05 (d, J = 8.9 Hz, 2H), 3.44 (q, J = 5.8, 2H), 2.80 (t, J = 6.2, 2H), 2.66 (q, J = 7.0, 2H), 1.04 (t, J = 7.1, 3H). MS (DCI/NH_3) for $C_{11}H_{15}N_3O_3$: 238 $(M+H)^+$.

Anal. Calcd for $C_{11}H_{16}ClN_3O_3$: C, 48.27; H, 5.90; N, 15.36; Cl, 12.95
Found: C, 47.99; H, 5.92; N, 15.39; Cl, 13.32

Analytical sample of the intermediate N-hydroxysuccinimide active ester **1** was obtained by flash chromatography (silica gel, ethyl acetate/hexanes; 1:1) giving a light yellow solid, mp. 213.5-217.5° (no dec.). ^{1}H NMR (d_6-DMSO): δ 8.45 (d, J = 9.0 Hz, 2H), 8.35 (d, J = 9.0 Hz, 2H), 2.92 (s, 4H). MS (DCI/NH_3): 282 $(M+NH_4)^+$, 299 $(M+NH_4+NH_3)^+$.

Anal. Calcd for $C_{11}H_8N_2O_6$:C, 50.00; H, 3.06; N, 10.61. Found: C, 50.16; H, 3.07; N, 10.80

DEPA (2b).- To the nitrobenzamide **2a** (1.0 g) in ethanol (30 mL) and 6 N HCl (5 mL) was added 10 % Pd on carbon (200 mg). The mixture was hydrogenated at 45 psi of H_2 for 1 hour then the solution filtered through diatomaceous earth. The solvent was removed *in vacuo* and the solid dissolved in refluxing ethanol (25 mL). To this hot solution was added 31% ethanolic HCl (1 mL) and the solution allowed to cool to ambient temperature. The precipitate was isolated by filtration and dried *in vacuo* to give **2b** (0.65 g, 63%) as a light yellow solid, mp. 212-216°. ^{1}H NMR (d_6-DMSO): δ 9.09 (bs, 1.6H), 8.86 (t, J = 5.4, 1H), 8.65-8.00 (vb, 1.4H), 7.95 (d, J = 8.6, 2H), 7.21 (d, J = 8.5, 2H), 3.59 (q, J = 5.8, 2H),3.13-3.03 (bm, 2H),3.03-2.90 (bm, 2H), 1.22 (t, J = 7.2, 3H). ^{1}H NMR (d_6-DMSO/D_2O): δ 7.87 (d, J = 8.6, 2H), 7.17 (d, J = 8.5, 2H), 3.54 (m, 2H), 3.07 (t, J = 5.8, 2H), 2.96 (q, J = 7.3, 2H), 1.18 (t, J = 7.1, 3H). MS(DCI/NH_3) for $C_{11}H_{17}N_3O$: 208 $(M+H)^+$.

Anal. Calcd for $C_{11}H_{19}Cl_2N_3O$: C, 47.15; H, 6.85; N, 15.00; Cl, 25.30
Found: C, 47.02; H, 6.80; N, 15.00; Cl, 25.67

4-Acetamidobenzoic Acid Pentafluorophenyl Active Ester (3).- To 4-acet-amidobenzoic acid (5.0 g, 28 mmol) in pyridine (12 mL, 140 mmol) and DMF (100 mL) was added pentafluorophenyl trifluoroacetate (24 mL, 140 mmol) with stirring, under inert atmosphere. After 2 hrs, the solvent was removed *in vacuo* and the residue purified by vacuum flash chromatography (silica gel, ethyl acetate/hexanes, 1:1). Removing the solvent *in vacuo* afforded **3** (6.4 g, 66%) as a colorless solid, mp. 146.5-148.3°. ^{1}H NMR (d_6-DMSO): δ 10.50 (s, 1H), 8.13 (d, J = 8.6, 2H), 7.86 (d, J = 8.8, 2H), 2.13 (s, 3H). MS(DCI/NH_3): 346 $(M+H)^+$, 363 $(M+NH_4)^+$, 380 $(M+NH_4+NH_3)^+$.

Anal. Calcd for $C_{15}H_8F_5NO_3$: C, 52.18; H, 2.34; N, 4.06; F, 27.52
Found: C, 52.22; H, 2.09; N, 3.95; F, 27.71

DENAPA (4).- To a round-bottom flask equipped with magnetic stirrer was added THF (50 mL), N-ethylethylenediamine (1.5 mL, 14.5 mmol), and TEA (4.0 mL, 29 mmol). To this solution was added active ester **3** (5.0 g, 14.5 mmol) in THF (50 mL) dropwise over a 10 min period, under inert atmosphere. After 18h, the solvent was removed *in vacuo* and the residue dissolved in 1 N HCl (50 mL) and water (50 mL). The solution was extracted with ethyl acetate (4 x 200 mL) then the aqueous layer was brought to pH 12 with 1 N NaOH. This solution was extracted with chloroform (3 x 300 mL) and 10% ethanol in chloroform (2 x 300 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent removed *in vacuo* . The solid was dissolved in hot ethanol (50 mL) then 31% w/w HCl/ethanol (10 mL) was added. After 18 hours, the crystallized solid was isolated and dried in vacuo to give **4** (2.0 g, 48%) as a colorless solid, mp. 256-258° (dec.). ^{1}H NMR (d_6-DMSO): δ 10.31 (s, 1H), 8.96 (bs, 1H), 8.74 (t, J = 5.2, 1H), 7.88 (d, J = 8.4, 2H), 7.68 (d, J = 8.4, 2H), 3.57 (m, 2H), 3.08-2.93 (m, 4H), 2.07 (s, 3H), 1.21 (t, J = 7.0, 3H). ^{1}H NMR (d_6-DMSO/D_2O): δ 7.83 (d, J = 8.0, 2H), 7.65 (d, J = 8.2, 2H), 3.60 (t, J = 5.6, 2H), 3.14 (t, J = 5.6, 2H), 3.02 (q, J = 7.3, 2H), 2.12 (s, 3H), 1.23 (t, J = 7.2, 3H). MS (DCI/NH_3) for $C_{13}H_{19}N_3O_2$: 250 $(M+H)^+$.

Anal. Calcd for $C_{13}H_{20}Cl_2N_3O_2$: C, 54.63; H, 7.07; N, 14.71; Cl, 12.41
Found: C, 54.57; H, 7.08; N, 14.50; Cl, 12.49

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(±)-SEDAMINE AND (±)-ALLOSEDAMINE BY REDUTION OF N-METHYL-2-PHENACYLIDENEPIPERIDINE

Submitted by (01/09/95)

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Sedamine (**4**) is one of a series of α- and α,α'-substituted piperidine derivatives found in various *sedium* species.[1] Sedamine was the first of these alkaloids to be characterized and elucidated structurally.[2] Pyne and coworkers[3] have used the strategy of addition of nucleophiles to chiral vinyl sulfoxides for the asymmetric synthesis of chiral molecules and natural products such as sedamine. Vaultier and coworkers[4] have reported a stereoselective one-pot synthesis of γ-aminoalcohols and applied it in the synthesis of (±)-norsedamine and its pyrrolidino analogue. Stereoselective nucleophilic substitution of 6-methoxy-1-methoxycarbonylpipecolate also leads to an enantioselective route to (+)-sedamine.[5] We now report a novel approach for the synthesis of (±)-sedamine (**4**) and (±)-allosedamine (**5**) by reduction of N-methyl-2-phenacylidenepiperidine (**2**).

Thiolactam (**1**), readily prepared in 85% yield from the corresponding lactam and P_4S_{10}, was subjected to alkylative coupling *via* sulfide condensation[6] with phenacyl bromide to give (**2**) in 75% yield.

Reduction of **2** with LAH, i-Bu_2AlH and $NaCNBH_3$ gave **3** while hydrogenation in acidic medium or reduction by $NaBH_4$ in protic solvent (EtOH-H_2O) gave a 1:1 mixture of (±)-sedamine (**4**) and (±)-allosedamine (**5**) easily distinguished by ^1H nmr and separated by column chromatography. On the other hand, reduction of **3** with LAH and i-Bu_2AlH gave a mixture of **4** and **5** with the ratio of 70:30 and 0:100, respectively (Table 1).