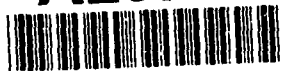


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**SYNTHESIS
OF N-(1-BENZYL)-4-METHOXYCARBONYL-4-PIPERIDINYL
N-PHENYLPROPANAMIDE**

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May 1993

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REPORT DOCUMENTATION PAGE

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Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE <p style="text-align: center;">1993 May</p>	3. REPORT TYPE AND DATES COVERED <p style="text-align: center;">Final, 91 May - 92 May</p>	
4. TITLE AND SUBTITLE <p style="text-align: center;">Synthesis of N-(1-Benzyl)-4-Methoxycarbonyl-4-piperidinyl N-phenylpropanamide</p>		5. FUNDING NUMBERS <p style="text-align: center;">PR-10161102A71A</p>	
6. AUTHOR(S) <p style="text-align: center;">McClure, Cynthia K.; Kiessling, Anthony J. (Univ. of DE); and Banks, Harold D. (ERDEC)</p>		8. PERFORMING ORGANIZATION REPORT NUMBER <p style="text-align: center;">ERDEC-TR-070</p>	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716 DIR, ERDEC,* ATTN: SCBRD-RTC, APG, MD 21010-5423		10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)		10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES *At the time this work was performed, ERDEC was known as the U.S. Army Chemical Research, Development and Engineering Center, and the ERDEC author was assigned to the Research Directorate.			
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.		12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) Conditions have been identified for optimization of the hydrolysis of the key alpha-aminonitrile intermediate in the synthesis of the title compound. An extensive search of the literature has discovered an unusual methoxycarbonyl anion equivalent which has been examined by means of a readily available model for addition to the corresponding imine.			
14. SUBJECT TERMS 4-methoxycarbonyl-4-anilidopiperidine Hydrolysis Alpha-aminonitrile Methoxycarbonyl anion synthon		15. NUMBER OF PAGES <p style="text-align: center;">15</p>	
17. SECURITY CLASSIFICATION OF REPORT <p style="text-align: center;">UNCLASSIFIED</p>		16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT <p style="text-align: center;">UNCLASSIFIED</p>	18. SECURITY CLASSIFICATION OF THIS PAGE <p style="text-align: center;">UNCLASSIFIED</p>	19. SECURITY CLASSIFICATION OF ABSTRACT <p style="text-align: center;">UNCLASSIFIED</p>	20. LIMITATION OF ABSTRACT <p style="text-align: center;">UL</p>

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PREFACE

The work described in this report was authorized under Project No. 10161102A71A, Research in Chemical Weapons/Chemical Biological Defense. This work was started in May 1991 and completed in May 1992.

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SYNTHESIS
OF N-(1-BENZYL)-4-METHOXYCARBONYL-4-PIPERIDINYL
N-PHENYLPROPANAMIDE

1. INTRODUCTION

Relief from excruciating pain has been a pursuit of mankind from time immemorial. An effective preparation, opium, derived from the unripe seed capsules of *Papaver somniferum* has been used for at least five millenia. Isolation and purification of its active principle, named morphine by Sertürner in 1806, launched the field of opiate analgesics. In 1832, an additional analgesic alkaloid, codeine, was isolated from the same source by Robiquet, many other analgesics have been subsequently found in natural products.

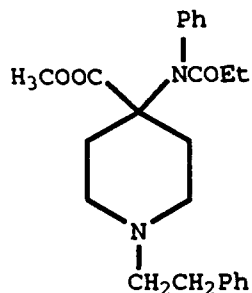
Over the past two centuries chemists have tackled the difficult problem of improving on naturally occurring drugs by discovering unnatural (or synthetic) compounds that are more effective than nature's gifts. While morphine is an extremely useful drug, it has adverse side effects, the most serious of which are respiratory and cardiovascular depression.

The strategy undertaken in drug discovery was to find compounds that were more potent than morphine, with the expectation that more potent drugs would be able to produce the desired analgesic effect at a much lower dosage than required for initiation of side reactions. This idea has an analogy in qualitative inorganic analysis where the concentration of a cation, for example, can be maintained low enough so that only one of a given group of anions will precipitate.

In the 1960's Janssen Pharmaceutica in Belgium discovered a drug they named fentanyl [N-1-(2-phenylethyl)-4-piperidinyl]-N-phenylpropanamide, and reported its pharmacological properties.¹ Its potency of almost 300 times that of morphine in animal studies translated into a significant reduction in the cardiovascular depression, and the use of fentanyl in clinical cardiovascular procedures. Regrettably, respiratory depression remains a significant complication, and the phenomenon of fentanyl rebound requires monitoring of patients well after analgesia has dissipated.

The partial success with fentanyl led to vigorous research efforts to prepare even more potent analgesics using fentanyl as a lead compound. This report is concerned with synthesis of one of the most interesting of these,

carfentanil, 1.² Its analgesic potency (animal studies) is ca. 28 times that of fentanyl. It has been used for the immobilization of large animals, but, to the best of our knowledge, no clinical trials have been reported.



1

2. DISCUSSION AND RESULTS

The published procedure for preparation of carfentanil reported by Janssen and coworkers² takes advantage of the reaction of readily available 1-(2-phenylethyl)-4-piperidone, aniline and KCN to produce the corresponding α -aminonitrile. Work in one of our laboratories improved the yield of this reaction to greater than 90%.³ For completion of the synthesis, the Belgian group sequentially hydrolyzed the cyano function to the amide and then to the carboxylic acid; deprotonation of the latter, nucleophilic substitution with CH_3I and acylation with propanoic anhydride provided the target molecule in a disappointing yield of 1%. No indication is given to the best of our knowledge as to whether the yields in this sequence were optimized.

The present investigation was directed toward studying the Janssen reaction sequence in more detail with a view to improving the overall yield of carfentanil, and toward exploring a new synthon for the methoxycarbonyl anion.

Synthesis of the α -aminonitrile from a commercially available ketone using the Janssen conditions was probed. The starting material chosen was 1-benzyl-4-piperidone, since the benzyl group is a convenient protecting group for a secondary amino function and also because the benzyl as opposed to 2-phenylethyl derivatives are pharmacologically inactive and safer to handle. It was discovered that this compound was rather sensitive to acid, and reverted easily to starting materials. When the reaction time was decreased

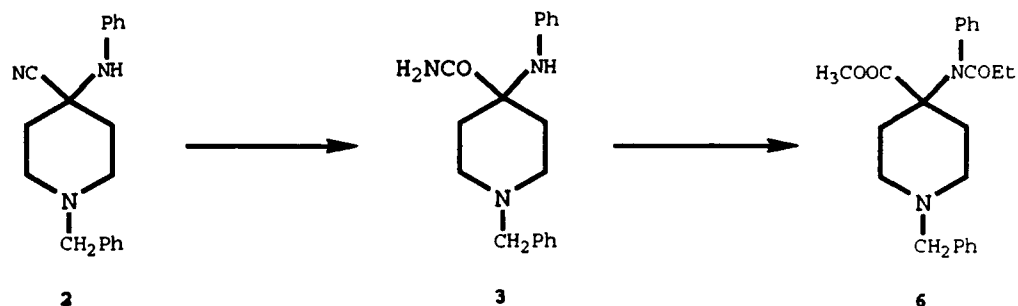
from 2 to 1 day, the yield increased from the reported 30% to almost 80%. Optimum reaction time was found to be 18 h. These results can be rationalized by assuming that because the forward reaction is favored by high concentration of cyanide ion, its depletion in the acidic reaction medium would promote reversion to the starting ketone.

The sensitivity of the α -aminonitrile to acid requires careful selection of reagents and conditions. It was determined that many such hydrolyses of the nitrile were unsatisfactory except when cold, concentrated H_2SO_4 was employed.⁴ In this case, a 73% yield of the carboxamide was obtained after two days of stirring at ambient temperature.

It should be noted that attempted base-catalyzed hydrolyses also led to reversion to the ketone, aniline and cyanide ion, due to either direct attack of hydroxide ion at C_4 or abstraction of the anilino hydrogen, followed by expulsion of cyanide ion and conversion of the resulting imine to the ketone. When the α -aminonitrile was reacted with 30% H_2O_2 and 20% NaOH (a Radziszewski-type reaction),⁵ a yield of only 15% was obtained. The starting material could be recovered in 80% yield, suggesting that this reaction has the potential for being a useful step in the synthesis, if the details of recycling the α -aminonitrile can be developed.

With the carboxamide in hand in good yield, methods for its transformation to the carboxylic acid were scrutinized. Moderate yields were obtained using the Janssen procedure, which was unattractive because of a tedious workup. Furthermore, the carboxylate salt, **5**, obtained by hydrolysis of the amide, was found to be an unwilling participant in the reported reaction with methyl iodide. Conducting the reaction in DMF at room temperature or 90° C produced no ester at varying reaction times as determined by GC/MS.

Attempts to convert the amide to the ester appeared to be more promising. Taber's⁵ recent results using tosylic acid and methanol encouraged us to pursue this approach. In our hands, the best conditions were found to be heating the reactants in a pressure bottle at 120° for 2 - 3 d. The ester was obtained in a modest yield of 45%. Unreacted amide was readily recovered, however, in yields up to 50% when the reaction mixture was subjected to flash column chromatography.



The second approach to the synthesis of carfentanil was considerably more ambitious. It envisioned applying the methoxycarbonyl anion synthon, dicyanotrimethylsiloxymethane in the presence of LDA, recently introduced by Yamamoto⁷ in a reaction with the phenylimino derivative of the ketone.⁸ In a feasibility study, malononitrile was deprotonated in THF with LDA at -78° . The amine was added after warming to room temperature. Analysis of the reaction product by GC/MS demonstrated that none of the expected 4-dicyanomethyl derivative was produced.

There are many examples in the literature of addition of nucleophiles to imines. Reactions of α -aminonitriles with NaBH_4 , LiAlH_4 , sodium metal, may be formally conceived as reactions of an intermediate imine with a hydride species. The Bruylants reaction is an addition of the alkyl group of a Grignard reagent to the intermediate imine.⁹ In addition, the preparation of an α -aminonitrile entails the addition of cyanide ion to the imine formed upon admixture of the ketone and amine. Previous studies in one of our laboratories have provided strong stereochemical evidence for imine intermediates in the NaBH_4 reduction of the α -aminonitrile.¹⁰ Addition of nucleophiles to imines is not nearly as straightforward as that for carbonyl compounds. Perhaps hard nucleophiles like hydride as opposed to the relatively soft dicyanomethyl anion are required for addition to imines.

3. EXPERIMENTAL METHODS

Propionic anhydride was distilled from P_2O_5 before use and stored under an argon atmosphere. Aniline was distilled from KOH immediately before use and stored under an argon atmosphere. The starting compound, 1-benzyl-4-piperidone, 1, was obtained from Aldrich Chemical Co., Inc. and used without further purification. Methylene chloride was distilled from calcium hydride.

^1H and ^{13}C NMR spectra were obtained on a Bruker AM-250 spectrometer as solutions in CDCl_3 . Chemical shifts are reported in ppm downfield from the internal standard, tetramethylsilane. Mass spectra (MS) were obtained on a Hewlett-Packard HP 5970 at 70 eV. Gas chromatography was performed on a Hewlett-Packard Model 5890A using an Allteck Econo-Cap column (SE-54, 30 m, 0.25 mm ID, 0.25 μ film thickness), He flow rate 1 mL/min, program [150 $^\circ$ C (10 min), ramp 10 $^\circ$ C/min to 250 $^\circ$ (hold until complete.)] Column chromatography was performed on Kiesel Gel 60 PF254. The solvent mixtures given below are volume/volume. R_f values indicated refer to thin layer chromatography on Analtech 2.5 x 10 cm, 250 M analytical plates coated with silica gel GF. Melting points were taken on a Lab Devices Mel-Temp and are uncorrected.

3.1 1-Benzyl-4-phenylamino-4-piperidinecarbonitrile (2)

Into a 250 mL round bottomed flask was placed 1-benzyl-4-piperidone (18.0 mL, 97 mmol), aniline (10.0 mL, 107 mmol) and glacial acetic acid (21.6 mL). While the mixture was stirring in an ice bath, an aqueous potassium cyanide solution was prepared by dissolving KCN (7.30g, 112 mmol) in water (21.6 mL). The KCN solution was added dropwise to the reaction mixture over a 30 min period. The mixture was allowed to stir at room temperature for 18 - 24 h, producing a copious precipitate. The reaction mixture was poured into a mixture of ice (100 g) and concentrated aqueous ammonia (100 mL). The resulting mixture was extracted three times with 30 mL portions of methylene chloride; the combined organic extracts were dried over MgSO_4 and the solvent removed in vacuo. The resulting oily solid was triturated with diethyl ether, and filtered under vacuum to provide 21.6 g (74.3 mmol, 76.4%) of a white crystalline solid, mp = 131 - 133 $^\circ$ C. R_f = 0.59 (5% MeOH/ CH_2Cl_2). ^1H NMR 7.42 - 7.21 (m, 7H, aromatic); 6.94 - 6.88 (m, 3H, aromatic); 3.64 (s, 1H, NH); 3.55 (s, 2H, PhCH_2); 2.81 (bd, 2H, J = 12.2 Hz); 2.46 (td, 2H, J = 11.4, 2.2 Hz); 2.33 (dd, 2H, J = 12.0, 2.4 Hz); 1.92 (td, 2H, J = 10.9, 3.3 Hz). ^{13}C NMR: 143.4, 138.1, 129.3, 129.0, 128.4, 127.3, 121.1, 120.8, 118.1, 62.6, 53.2, 49.3, 36.3. GC/MS: R_t = 14.46 min; mass calculated for $\text{C}_{19}\text{H}_{21}\text{N}_3$: 291.38; found: 263 ($M^{(\cdot+)} - \text{CN}$), 172, 144, 91, 77.

3.2 1-Benzyl-4-phenylamino-4-piperidinecarboxamide (3).

Into a 250 mL round bottomed flask was placed 2 (21.6 g, 74.3 mmol), and cooled in ice-water bath (5 °C). Concentrated sulfuric acid (100 mL) was added dropwise with stirring. Stirring was continued for 48 h, during which time the nitrile dissolved in the acid. The reaction mixture was cautiously added to 400 mL of NH₄OH and 200 g of wet ice while stirring. The precipitate was collected by suction filtration, washed with 100 mL of cold water, and dried under vacuum. The mother liquor was extracted three times with 30 mL of CHCl₃. The combined extracts were washed with 30 mL of water, dried over MgSO₄, and concentrated in vacuo to yield a white solid which was combined with the collected precipitate to provide 16.85 g (73.3%); m. p. = 186 - 188 °C. R_f = 0.01 (3% MeOH/CH₂Cl₂). ¹H NMR (DMSO-d₆): 7.29 - 7.14 (m, 7H, aromatic); 6.81 (s, 1H, CONH₂); 6.78 - 6.60 (m, 3H, aromatic); 5.50 (s, 1H, CONH₂); 4.01 (s, 1H, PhNH); 3.47 (s, 2H, CH₂-Ph); 2.73 (d, 2H, J = 12.0 Hz); 2.32 (td, 2H, J = 12.2, 2.74 Hz); 2.10 (t, 2H, J = 12.0 Hz); 1.91 (d, 2H, J = 12.5). ¹³C NMR (DMSO-d₆): 177.5, 145.3, 138.6, 128.5, 128.3, 128.0, 126.6, 116.5, 114.7, 62.1, 57.0, 48.4, 31.4. GC/MS: R_t = 22.66 min, mass calculated for C₁₉H₂₃N₃O: 309; found: 309, 265, 216, 146, 91, 77.

3.3 Methyl 1-Benzyl-4-phenylamino-4-piperidine-carboxylate (5).

Into a 500 mL screw cap pressure bottle was added 3 (2.00g, 6.47 mmol), methanol (50 mL) and p-toluenesulfonic acid monohydrate (4.0 g, 23.2 mmol). The bottle was sealed, and the mixture heated at 110° for 2 d. Upon cooling, the bottle was carefully opened and the methanol removed in vacuo. The purple solid was dissolved in CH₂Cl₂ (50 mL) and washed with saturated K₂CO₃ (20 mL), water (20 mL), dried (MgSO₄), and concentrated in vacuo. The crude solid was purified by flash chromatography (3% MeOH/CH₂Cl₂); R_f = 0.41 (5% MeOH/CH₂Cl₂). The desired product was obtained as a yellow oil (903 mg, 43.1%) in addition to recovered starting material (995 mg, 49.7%). ¹H NMR: 7.30 - 7.09 (m, 7H, aromatic); 6.75 - 6.53 (m, 3H, aromatic); 3.84 (s, 1H, NH); 3.66 (s, 3H, OCH₃); 3.49 (s, 2H, CH₂-Ph); 2.56 (2m, 2H); 2.38 (m, 2H); 2.23 (m, 2H); 2.03 (m, 2H). ¹³C NMR: 176.0, 145.0, 138.3, 129.2, 128.3, 127.7, 118.7, 115.4, 63.0, 58.3, 52.3, 49.0, 33.0. GC/MS: R_t = 17.48 min, mass calculated for C₂₀H₂₄N₂O₂: 324; found: 324, 231, 172, 91.

3.4 Methyl 1-Benzyl-4-[N-(1-oxopropyl)]-N-phenyl-amino-4-piperidinecarboxylate (6).

Into a 50 mL round bottomed flask was placed 5 (2.16 g, 6.65 mmol). After fitting with a reflux condenser, the flask was flushed with argon, freshly distilled propionic anhydride (10 mL) was added, and the mixture was refluxed for 12 h. The reaction mixture was cooled, and poured into a mixture of 30 mL of concentrated aqueous ammonia and 50 g of ice. The crude product was extracted three times with 15 mL portions of CHCl_3 , and the combined organic extracts were washed with water, and dried over MgSO_4 . Concentration in vacuo produced a yellow oil which was dissolved in 2-propanol (3 mL). A solution of 3.1 g of oxalic acid in 10 mL of 2-propanol was then added. The resulting precipitate was collected by suction filtration, washed with 3 mL of 2-propanol, suspended in 5 mL of H_2O and basified with 50% NaOH . The mixture was then extracted with CHCl_3 , dried over MgSO_4 , filtered and concentrated in vacuo to yield 2.019 g (5.31 mmol, 79.9%) of product as a yellowish oil. ^1H NMR: 7.40 - 7.24 (m, 10H, aromatic); 3.78 (s, 3H, CO_2CH_3) 3.66 (s, 2H, PhCH_2); 2.78 (m, 2H); 2.55 (m, 2H); 2.29 (m, 2H), 1.86 (q, 2H, COCH_2CH_3 , $J = 7.4$ Hz); 1.81 (m, 2H); 0.94 (t, 3H, COCH_2CH_3 , $J = 7.4$ Hz). ^{13}C NMR: 174.1, 173.9, 139.2, 130.6, 129.6, 129.3, 128.6, 128.3, 127.5, 62.3, 62.1, 53.3, 52.1, 49.4, 32.6, 28.9, 9.0. GC/MS: $R_t = 21.23$ min, mass calculated for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_3$: 380; found: 380, 231, 216, 140, 91.

4. CONCLUSIONS

The synthetic sequence for a formal preparation of carfentanil is a significant improvement of the method originally reported by Janssen and coworkers. It is not, however, quite as attractive as those of Taber⁶ and Feldman.¹¹, who report yields of the N-benzyl analog of carfentanil of 61 and 26% respectively starting from 1-benzyl-4-piperidone. While the initial experimentation in addition of a model for a methoxycarbonyl anion equivalent to 1-benzyl-4-phenyliminopiperidine was unsuccessful, this avenue of research should be pursued.

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