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Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t902189982>

AN IMPROVED PROCEDURE FOR THE ISOLATION OF 2-(N,N-DIETHYLAMINOMETHYL)-4-NITROPHENOL

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To cite this Article de Souza, M. C. B. V. , Bernardino, A. M. R. , Soares, M. C. and Retzlaff, M. G.(1992) 'AN IMPROVED PROCEDURE FOR THE ISOLATION OF 2-(N,N-DIETHYLAMINOMETHYL)-4-NITROPHENOL', *Organic Preparations and Procedures International*, 24: 3, 338 – 339

To link to this Article: DOI: 10.1080/00304949209355896

URL: <http://dx.doi.org/10.1080/00304949209355896>

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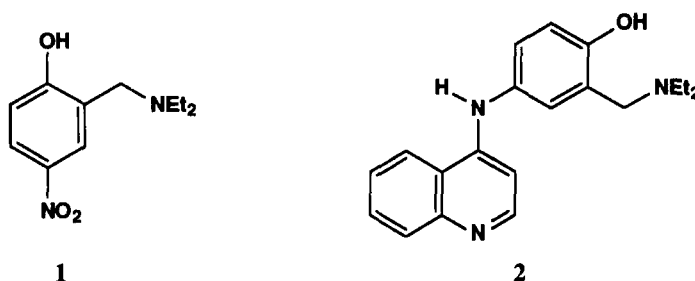
**AN IMPROVED PROCEDURE FOR THE ISOLATION OF
2-(N,N-DIETHYLAMINOMETHYL)-4-NITROPHENOL**

Submitted by
(08/16/91)

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2-(N,N-Diethylaminomethyl)-4-nitrophenol (**1**) is an important intermediate for the synthesis of amodiaquine (**2**), a therapeutic agent for the treatment of malaria. It has been prepared by Mannich reaction between *p*-nitrophenol, formaldehyde and diethylamine.¹ In our hands, however, the very tedious procedure using 10% hydrochloric acid and several extractions with ether never gave a yield higher than 7% (reported¹ 40%). We now describe an improved procedure utilizing hydrogen chloride gas and methylene chloride, which affords pure **1** in 58% yield cleanly and easily.



EXPERIMENTAL SECTION

¹H NMR spectra were recorded on a EM-360 60 MHz Spectrometer using TMS as internal standard.

Preparation of 2-(N,N-Diethylaminomethyl)-4-nitrophenol (1).- To *p*-nitrophenol (23.2 g, 0.166 mol) in a three-necked flask equipped with reflux condenser and addition funnel, was added slowly a mixture of diethylamine (19.1 mL, 0.183 mol) and formaldehyde (15.7 mL of a 30% solution in water) with stirring while the temperature was maintained at 20°. The mixture was then heated for 2 hrs at 80°. Evaporation under reduced pressure gave a red oil which was dissolved in 250 mL of dichloromethane. Then hydrogen chloride gas was bubbled to form the hydrochloride of **1**. The precipitated material was collected, washed with ethyl ether and dried under reduced pressure to yield 27.6 g (64%) of pale yellow crystals, mp. 223°, lit.^{1,2} mp. 223-224°.

¹H NMR (CDCl₃): δ 1.25 (t, 6H, CH₃), 2.75 (q, 4H, CH₂CH₃), 3.85 (s, 2H, ArCH₂), 6.6-6.9 (m, 1H, ArH), 7.8-8.2 (m, 2H, ArH).

Concentrated ammonium hydroxide (20 mL of a 33% aqueous solution in water) was added to the hydrochloride salt and the mixture was stirred for 15 min.. The resulting mixture was extracted with

dichloromethane, dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give **1**. Recrystallization from isopropyl alcohol gave 21.6 g (58%) of pure **1**, mp. 87°, lit.² mp. 87-89°.

¹H NMR (DMSO-d₆): δ 0.9-1.6 (m, 6H, CH₃), 2.5-3.3 (m, 4H, CH₂CH₂), 4.15 (s, broad, 2H, ArCH₂), 7.15 (d, 1H, ArH), 8.05 (d, 1H, ArH), 8.45 (d, 1H, ArH) ppm.

Acknowledgements.- We thank CNPq, FINEP and FAPERJ, for financial support and NPPN/UFRJ for providing the ¹H NMR spectra. We are grateful to Dr. Vitor Francisco Ferreira, Departamento de Química Orgânica, Universidade Federal Fluminense, for useful advice.

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SYNTHESIS OF 4-*trans*-[1-[4-[2-(5-CHLORO-2-METHOXYBENZAMIDO)ETHYL]BENZENESULFONYL]UREIDO]CYCLOHEXANOL HEMISUCCINATE ESTER

Submitted by Robert L. Stephon[†], R. Sam Niedbala^{††},
(09/05/91) Keith J. Schray[†], and Ned D. Heindel^{†*}

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Glyburide (**4**, R = H), 1-[4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonyl]-3-cyclohexylurea (**Micronase**, *The Upjohn Company*) is an orally active sulfonylurea drug used in treatment of type II (non-insulin dependent) diabetes mellitus. Assays for glyburide have included spectroscopic methods which lack the requisite sensitivity for detection of this drug in biological fluids.¹ Radioimmunoassay techniques are available for monitoring of the drug in plasma, using antisera raised to synthetic derivatives of the parent compound. The compound used to develop the existing radioimmunoassay contained a 4-acetic acid moiety as the attachment arm (**4**, R = CH₂COOH).² Synthesis of that target was accomplished by condensation of methyl 4-(isocyanato)cyclohexylacetate