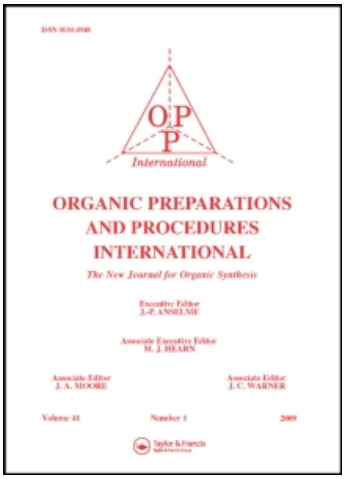


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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

M. C. B. V. de Souza[a]; A. M. R. Bernardino[a]; M. C. Soares[a]; M. G. Retzlaff[a]
[a] Departamento de Química Orgnica, Universedade Federal Fluminense Niterói, Rio de Janeiro, CEP, Brasil

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-DIETHYJAMINOMETHYL)-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

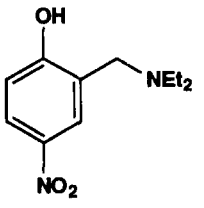
AN IMPROVED PROCEDURE FOR THE ISOLATION OF 2- (N,N-DIETHYLAMINOMETHYL)-4-NITROPHENOL

Submitted by (08/16/91)

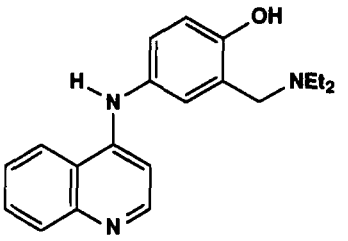
M. C. B. V. de Souza*, A. M. R. Bernardino, M. C. Soares, and M. G. Retzlaff

Departamento de Química Orgânica
Universedade Federal Fluminense
Niterói, Rio de Janeiro, CEP 24020, BRASIL

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% (reported[1] 40%). We now describe an improved procedure utilizing hydrogen chloride gas and methylene chloride, which affords pure **1** in 58% yield cleanly and easily.



1



2

EXPERIMENTAL SECTION

^{1}H 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°.

^{1}H NMR ($CDCl_3$): δ 1.25 (t, 6H, CH_3), 2.75 (q, 4H, $\underline{CH_2}CH_3$), 3,85 (s, 2H, AR$\underline{CH_2}$), 6.6-6.9 (m, 1H, Ar$\underline{H}$), 7.8-8.2 (m, 2H, Ar$\underline{H}$).

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°.

^{1}H NMR (DMSO-d_6): δ 0.9-1.6 (m, 6H, CH_3) , 2.5-3.3 (m, 4H, $\underline{CH_2}CH_3$), 4.15 (s, broad, 2H, Ar$\underline{CH_2}$), 7.15 (d, 1H, Ar$\underline{H}$), 8.05 (d, 1H,.Ar$\underline{H}$), 8.45 (d, 1H, Ar$\underline{H}$) ppm.

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

REFERENCES

1. a) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb and A. L. Rawlins, *J. Am. Chem. Soc.*, **70**, 1363 (1948); b) V. J. Stavrovskaya, *J. Gen. Chem. USSR*, 25, 915 (1955).

2. J. H. Burckhalter, *J. Am. Chem. Soc.*, **72**, 1308 (1950).

****

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

Submitted by (09/05/91)

Robert L. Stephon[†], R. Sam Niedbala[††], Keith J. Schray[†], and Ned D. Heindel[†*]

[†] *Department of Chemistry*
Lehigh University, Bethlehem, PA 18015

[††] *STC, 115 Research Dr., Bethlehem, PA 18015*

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 = CH_2COOH).[2] Synthesis of that target was accomplished by condensation of methyl 4-(isocyanato)cyclohexylacetate