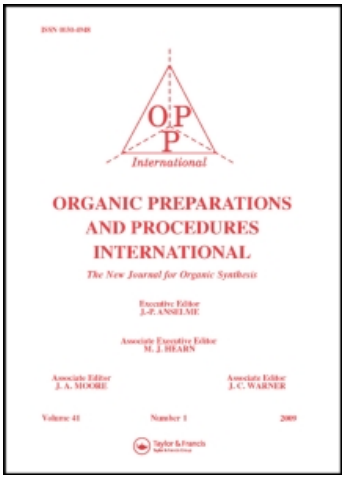


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

TWO IMPROVED SYNTHESES OF N,N'-*bis*(3,3-DIETHOXYPROPYL)SUCCINAMIDE

John T. Hortenstine[a]; John E. Mills[a]
[a] The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA

To cite this Article Hortenstine, John T. and Mills, John E.(1991) 'TWO IMPROVED SYNTHESES OF N,N'-*bis*(3,3-DIETHOXYPROPYL)SUCCINAMIDE', Organic Preparations and Procedures International, 23: 6, 757 — 760
To link to this Article: DOI: 10.1080/00304949109458253
URL: http://dx.doi.org/10.1080/00304949109458253

REFERENCES

1. a) H. A. El-Wakil and S. Abdel Baky, *Spectroscopy Lett.*, **23**, 497 (1990); b) R. Hanson and H. A. El-Wakil, *J. Org. Chem.*, **52**, 3687 (1987).

2. R. N. Hanson and H. A. El-Wakil and F. Murphy, *J. Labelled Comp. and Pharm.*, **27**, 615 (1989).

3. a) R. N. Hanson and H. A. El-Wakil, To be published; b) D. E. Seitz and H. A. El-Wakil and R. A. Millius, *Synth. Comm.*, **11**, 281 (1981).

4. Y. H. Lai, *Synthesis*, 585 (**1981**).

5. a) J. S. Buck and W. S. Ide, *J. Am. Chem. Soc.*, **54**, 3012 (1932); b) D. W. Robertson and J. A. Katzenellenbogen, *J. Org. Chem.*, **47**, 2387 (1982).

6. R. D. Reike and P. M. Hudnall, *J. Am. Chem. Soc.*, **94**, 7178 (1972).

7. W. C. Still, M. Kahn and A. Miltra, *J. Org. Chem.*, **43**, 2923 (1978).

8. J. W. Wilson, A. Burger, L. B. Turnbull, M. Peters and F. Milnes, ibid., **18**, 96 (1953).

9. The ^{1}H NMR spectrum was virtually indentical to the published spectrum of E and Z tamoxifen [G. R. Bedford and D. N. Richardson, Nature, **212**, 733 (1966)] with the obvious addition of the *O*-methyl peak.

****

TWO IMPROVED SYNTHESES OF N,N'-*bis*(3 ,3-DIETHOXYPROPYL)SUCCINAMIDE

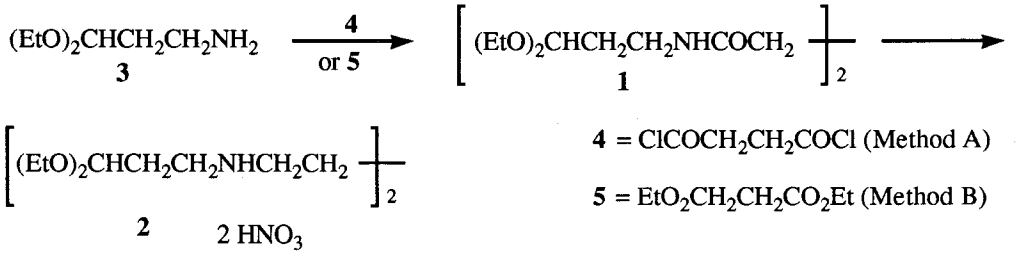
Submitted by (07/22/91) John T. Hortenstine* and John E. Mills

The R. W. Johnson Pharmaceutical Research Institute
Welsh and McKean Roads
Spring House, PA 19477-0776

The title compound (**1**) has been used as an intermediate in the four-step synthesis of spermine diacetal dinitrate (**2**),[1] an experimental immunosuppressive agent[2] of novel chemical structure. Interest in **2** led us to produce larger quantities of it. Succinamide **1** has previously been prepared in three steps by reaction of 3-chloropropionaldehyde diethyl acetal with potassium phthalimide to give N-(3,3-diethoxypropyl)phthalimide in 92% yield. The phthalimide was converted to 3,3-diethoxypropylamine (**3**), with hydrazine in 74% yield, and **3** was then reacted with succinyl chloride in methylene chloride at -50° to form **1** in 43% yield.[1] Unfortunately, upon scale-up

(1-2 moles), the yield of this last reaction was only 20%, and the required -50° temperature was impractical to achieve and maintain. The product was also contaminated with a large amount of an unknown orange viscous oil that could only be completely removed by column chromatography. The oil was difficult to identify using NMR or IR spectroscopy, but mass spectral evidence suggests it to be a mixture of oligomers produced through hydrolysis of the acetals and condensation of the resulting aldehyde with other molecules of the propylamine.

Since the purity of the crude succinamide prepared from succinyl chloride and **3** appeared to be a function of both temperature and acidity, efforts were directed toward developing reactions run at or near room temperature and toward insuring that the concentration of free hydrogen chloride was minimal. Using these criteria, two improved methods utilizing **3** as starting material have been developed. Method A involves treatment of the propylamine with succinyl chloride and sodium bicarbonate in *tert*-butyl methyl ether and water at 10-25°, while Method B involves



treatment of the propylamine with diethyl succinate at 110° for 72 hrs. The succinamide produced from both methods has been converted to **2** by lithium aluminum hydride reduction in tetrahydrofuran followed by nitric acid salt formation in ethanol/ether.[1] Samples produced by either method are identical by infrared, proton and carbon-13 NMR, mass spectra, and chromatographic methods to material produced using the method of Somayaji *et al.*[1] The yield of diamine 2 was 51% using **1** prepared from either method.

EXPERIMENTAL SECTION

Melting points were obtained in capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The proton and carbon-13 NMR spectra were recorded on a Bruker AM 400 instrument. The IR spectra were obtained on a Nicolet 60-SX instrument. Mass spectra were determined on a VG 70-250 mass spectrometer.

N,N'-Bis(3,3-diethoxypropyl)succinamide (1). Method A.- A rapidly stirred mixture of 3,3-diethoxypropylamine (**3**) (70 g, 0.47 mol) and sodium bicarbonate (78.4 g, 0.93 mol) in distilled water (126 mL) and *tert*-butyl methyl ether (450 mL) was cooled to 10° and a solution of succinyl chloride (37.5 g, 0.24 mol) in *tert*-butyl methyl ether (70 mL) was added dropwise over approximately 0.5 hr while the temperature was maintained below 20°. After stirring for 2 hrs at

room temperature (25°), the organic phase was separated and the aqueous phase washed once with *tert*-butyl methyl ether (140 mL). The organic phases were combined, dried over sodium sulfate and evaporated under reduced pressure. The crude orange-colored residue was dissolved in ethyl acetate (75 mL) and eluted through a flash silica gel column using a mixture of ethyl acetate:isopropanol:triethylamine (89.5:10:0.5). The solvent was evaporated under reduced pressure to yield 68 g (74%) of a cream-colored solid, mp. 78-81°. Recrystallization from a mixture of hexane (600 mL) and ethanol (18 mL) yielded 61.9 g (68%) of 1 as a white solid, mp. 89-91°, lit.[1] mp. 88-90°. IR (KBr): 3295, 2974, 1640, 1550, 1126, 1078 cm^{-1}; MS (CI): 377 (MH+); ^1H NMR ($CDCl_3$): δ 1.23 (t, 12H, $OCH_2O\underline{CH_3}$), 1.84 (m, 4H, $NHCH_2\underline{CH_2}CH$), 2.5 (s, 4H, $COCH_2\underline{CH_2}CO$), 3.36 (m, 4H, $NH\underline{CH_2}CH_2CH_2$), 3.55 (m, 4H, $O\underline{CH_2}CH_3$), 3.7 (m 4H, $O\underline{CH_2}CH_3$), 4.58 (t, 2H, $NHCH_2CH_2\underline{CH}$), 6.45 (br s, NH); ^{13}C NMR ($CDCl_3$): δ 15.3, CH_3; 31.8, CH_2; 33.0, CH_2; 35.6, CH_2; 61.8, CH_2; 102.2, CH; 171.8, C=O.

Method B. - A stirred mixture of 3,3-diethoxypropylamine (150 g, 1.01 mol) and diethyl succinate (87.1 g, 0.50 mol) was heated at 110° for 72 hrs while nitrogen was blown over the solution to remove ethanol. The nearly colorless liquid was treated with a mixture of hexane (1000 mL) and ethanol (30 mL). The title compound crystallized at room temperature. Filtration yielded 119.2 g (63.4%) of a white solid, mp. 89-91°. This material was identical in all respects to material prepared through method A.

Spermine Diacetal Dinitrate[3].- A solution of N,N'-*bis*(3,3-diethoxypropyl)succinamide (110 g, 0.29 mol) in dry THF (500 mL) was added dropwise, under nitrogen, to a stirred mixture of dry tetrahydrofuran (THF, 2800 mL) and lithium aluminum hydride (48.1 g, 1.26 mol) over 1 hr. The reaction was stirred and refluxed an additional 15 hrs, then cooled to room temperature. Saturated aqueous sodium sulfate (149 mL) was added dropwise over 1 hr, followed by the addition of solid sodium sulfate (600 g). The resulting mixture was stirred for 1 hr and filtered through Dicalite®. The filter cake was washed with THF (1000 mL) and the filtrate was concentrated under reduced pressure to yield 110.1 g (108%) of an amber colored oil. The oil was dissolved in absolute ethanol (500 mL) and diethyl ethyl ether (200 mL), stirred and cooled to -10°. Concentrated nitric acid (49.7 mL) was added over 0.5 hr. The resulting white solid was isolated by filtration. The filter cake was washed with cold absolute ethanol (3 x 100 mL) and diethyl ether (3 x 100 mL). and dried *in vacuo* at room temperature to yield 71.6 g (51%) of **2**, mp. 133-135°, lit.[1] mp. 134-135°. IR (KBr): 2975, 2872, 1410, 1382, 1298 cm^{-1}; MS (CI): 349 (MH^+); ^1H NMR (D_2O): δ 1.2 (t, 12H, $O\underline{CH_2}CH_3$), 1.77 (m, 4H), 2.04 (m, 4H), 3.16 (m, 8H), 3.66 (m, 4H, $O\underline{CH_2}CH_3$), 3.78 (m, 4H, $O\underline{CH_2}CH_3$), 4.78 (t, 2H, $\underline{CH}(OCH_2CH_3)$); ^{13}C NMR (D_2O): δ 17.0, CH_3; 25.5, CH_2; 32.7, CH_2; 46.0, CH_2; 49.6, CH_2; 66.2, CH_2; 103.6, CH.

Acknowledgments.- Discussions with Dr. Jeff Press and Mr. Lou Fitzpatrick concerning the purity of crude **2** and methods to improve that purity are gratefully acknowledged. Work performed by Mr. Phil Tao, Mr. John Masucci, and Ms. Diane Gauthier establishing the purity of **1** and of spermine

diacetal dinitrate, **2**, as well as work on the identification of process impurities is greatly appreciated. Our thanks to Ms. Barbara Baughman for assistance in the preparation of this manuscript.

REFERENCES

1. V. V. Somayaji, T. W. Hall, L. I. Wiebe, E. E. Knaus and J. P. Demers, *J. Labelled Compounds and Radiopharmaceuticals*, **27**, 449-455 (1989).

2. C. Y. Lau, Eur. Pat. Appl. EP366451A2, 2 May 1990 [*Chem. Abstr.* **113**, 91462t (1991)]

3. The procedure given here is essentially that of Somayaji *et al* (ref 1).

****

HEPTAFLUOROISOPROPOXIDE ION IN AROMATIC SUBSTITUTION

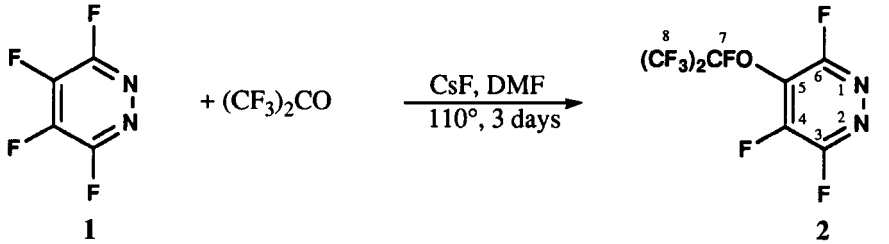
Submitted by (07/15/91) Keith E. Peterman* and Wojciech Dmowski†

Physical Sciences Department
York College of Pennsylvania
York, PA 17403-3426, USA

† *Institute of Organic Chemistry*
Polish Academy of Sciences
01-224 Warsaw, POLAND

As an activated perfluoro heteroaromatic, tetrafluoropyridazine (**1**) undergoes nucleophilic displacement reactions to form a variety of mono- and polysubstituted products. In early work, this precursor was reported to most easily substitute fluorine atoms at C-4 and C-5.[1] However, subsequent studies indicate that substituent orientations on the final products are more complex, citing the importance of both kinetic and thermodynamic control.[2] Kinetically favored C-4 and C-5 products are formed in the reaction of trifluoromethane thiolate ion with **1**.[3] We report here a similar reaction where substitution is accomplished utilizing a fluorinated alkoxide ion.

Hexafluoroacetone was found to react with tetrafluoropyridazine (**1**) in the presence of



1 **2**