

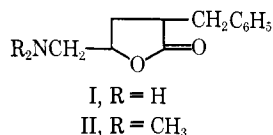
2-Benzyl-5-(N,N-dimethylamino)- γ -valerolactone, an Inhibitor of Plasma Cholinesterase^{1a}

SHERREL C. SMITH^{1b} AND FLOYD W. DUNN^{1c}

*Department of Biochemistry, University of Tennessee
College of Basic Medical Sciences, Memphis, Tennessee 38103*

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2-Benzyl-5-amino- γ -valerolactone (I) was prepared as a possible intermediate for the synthesis of 2-benzyl-5-aminolevulinic acid.² It was recognized that the N,N-dimethyl derivative of I might possess acetylcholine-like activity;³ therefore, 2-benzyl-5-(N,N-dimethylamino)- γ -valerolactone (II) was prepared and tested against isolated human plasma pseudocholinesterase system. II was found to have an I_{50} of 2.14×10^{-6} M in a previously described assay procedure.⁴



Experimental Section⁵

2-Benzyl-2-carboxy-5-bromo- γ -valerolactone.—A suspension of 34.3 g (0.193 mole) of N-bromosuccinimide in 200 ml of H₂O was added to a solution of 45 g (0.192 mole) of allylbenzylmalonic acid⁶ in 200 ml of Et₂O. After being stirred for 12 hr the Et₂O layer was removed and the H₂O layer was extracted twice with 25 ml of Et₂O. The combined ethereal extract was concentrated to a heavy oil; this was dissolved in 75 ml of Et₂O, and petroleum ether (bp 37–60°) was slowly added until precipitation was complete. The crystals were removed by filtration and recrystallized twice from Et₂O–petroleum ether (bp 37–60°); yield 27.3 g. Concentration of the mother liquor produced additional product which weighed 12.5 g after three recrystallizations. The total yield was 40.8 g (67.8%), mp 135° dec. *Anal.* (C₁₃H₁₃BrO₄) C, H.

2-Benzyl-5-phthalimido- γ -valerolactone.—2-Benzyl-2-carboxy-5-bromo- γ -valerolactone (20 g, 0.064 mole) was heated at 130° for 48 hr to effect decarboxylation. The resulting liquid showed its absorption bands as expected. It was used in a modified Gabriel synthesis,⁷ conducted at 90° for 24 hr. Isolation by the reported procedure and crystallization from C₆H₆–petroleum ether yielded 14.7 g (69%) of product, mp 130–135°. Five recrystallizations gave a product with mp 135–137°. *Anal.* (C₂₀H₁₉NO₄) H, N; C: calcd, 71.85; found, 71.42.

2-Benzyl-5-amino- γ -valerolactone Hydrochloride (I).—A 3.65-g sample of 2-benzyl-5-phthalimido- γ -valerolactone was added to 200 ml of 6 N HCl. The mixture was alternately refluxed and

cooled to room temperature four times. H₂O and HCl were removed in a rotary evaporator. Absolute EtOH was repeatedly added in 20-ml portions and evaporated to remove excess HCl. The residue was taken up in absolute EtOH, and Et₂O was added until precipitation was complete; yield 2.2 g (83.3%), mp 196–199° dec.

Compound I gave a purple color with ninhydrin. R_f values were, respectively, 0.38 in BuOH saturated with H₂O, 0.77 in MeOH–NH₃ (19:1), and 0.89 in pyridine–H₂O (65:35). *Anal.* (C₁₂H₁₈ClNO₂) C, H, N.

2-Benzyl-5-(N,N-dimethylamino)- γ -valerolactone Hydrochloride (II).—A solution of 2.0 g of I, 9.0 ml of 1 N NaOH, 5 ml of H₂O, 2 ml of 88% formic acid, and 2 ml of 40% CH₂O was heated for 6 hr at 100°. The mixture was concentrated to a heavy oil under reduced pressure. Absolute EtOH in 20-ml portions was added and was then evaporated four times. The oil was dissolved in 20 ml of anhydrous EtOH, and the NaCl was filtered off. Concentrated HCl (40 ml) was added to the filtrate and the solution was then concentrated to an oil. Absolute EtOH was added and evaporated four times. The dry crystals were thoroughly triturated with anhydrous Et₂O and filtered; yield 1.9 g (85.0%), mp 175–177°. *Anal.* (C₁₄H₂₀ClNO₂) C, H, N.

**N⁴,N^{4'}-Decamethylenebis-4-aminopyridine and
N⁹,N^{9'}-Decamethylenebis-9-aminoacridine**

JOHN P. PAOLINI, LOUIS J. LENDVAY, AND FRANK P. PALOPOLI

*The National Drug Company, Research Laboratories,
Division of Richardson-Merrell Inc.,
Philadelphia, Pennsylvania 19144*

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The title compounds (see Table I) are essentially the “ring removal” and “ring addition” compounds of N⁴,N^{4'}-decamethylenebis-4-aminoquinoline (1), a known antimicrobial agent.¹ The bisdecamethylene derivatives of 2- and 3-aminopyridine were also prepared. The compounds were tested *in vitro* according to methods previously described.² Table II contains the screening data for the amines, compound 1, and 9-aminoacridine (9), a compound whose antimicrobial activity is well documented.³

Experimental Section

N⁹,N^{9'}-Decamethylenebis-9-aminoacridine (2) was prepared from 9-chloroacridine (25 g, 0.11 mol) and 1,10-diaminodecane (8.6 g, 0.05 mol) according to the method of Strauss and Rosenstock.¹

N,N'-Bis(pyridyl)sebacylamides (6–8).—Sebacyl chloride (30 g, 0.125 mol) was added dropwise to a stirred mixture of the appropriate aminopyridine (23.5 g, 0.25 mol) and Et₃N (25 ml) in THF (250 ml). After about 10 ml of the chloride had been added, the mixture began to boil, and addition was continued at such a rate that reflux was maintained. After the addition was complete (about 10 min) stirring was continued for an additional 15 min. The solvent was then removed by evaporation *in vacuo*. The residue was triturated with 500 ml of 10% K₂CO₃ solution, filtered, washed with H₂O, and purified.

N,N'-Bis(pyridyl)decamethyleneamines (3–5).—A slurry of the appropriate diamide 6–8 (12.5 g, 0.035 mol) in warm THF (200 ml) was added, with stirring, to LAH (2.3 g, 0.06 mol) in THF (50 ml). The resulting mixture was heated under reflux for 1.5 hr. The reaction mixture was cooled in an ice bath and stirred during the successive dropwise additions of H₂O (3 ml), 15% NaOH solution (3 ml), and H₂O (20 ml). The mixture was

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(5) All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and M-H-W Laboratories, Garden City, Mich. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values. The cholinesterase inhibition study was kindly performed by Dr. James G. Beasley, Department of Medicinal Chemistry, University of Tennessee, Memphis.

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