2000CC 192-5

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07F 9/645, 9/40 — A1

(11) International Publication Number: **WO 99/06417**

(43) International Publication Date: 11 February 1999 (11.02.99)

(21) International Application Number: PCT/US98/15841

(22) International Filing Date: 31 July 1998 (31.07.98)

(30) Priority Data:
08/905,091 1 August 1997 (01.08.97) US

(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

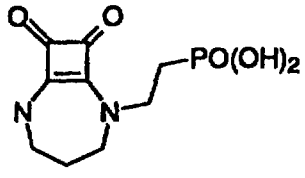
(72) Inventors: ASSELIN, Andre, Alfred; 64 Ackerman Drive, Mahwah, NJ 07430 (US). KINNEY, William, Alvin; Apartment IA, 811 Bustleton Pike, Richboro, PA 18954 (US). SCHMID, Jean; 17 Jeffrey Drive, Chester, NY 10918 (US).

(74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Patent Law Dept. – 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF [2-((8,9)- DIOXO-2,6-DIAZABICYCLO [5.2.0]-NON-1(7)-EN-2-YL)-ETHYL] PHOSPHONIC ACID



(I)

(57) Abstract

This invention relates to a process for the preparation of formula (I) compound [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]-non-1(7)-en-2-yl)ethyl]phosphonic acid, an NMDA antagonist useful as an anticonvulsant and neuroprotectant in situations involving excess release of excitatory amino acids. In the process of the present invention, 3-aminopropyl carbamic acid 1,1-dimethyl-ethyl ester is reacted with a dialkyl vinylphosphonate to obtain N-[3-(t-butyloxycarbonyl-amino)propyl]-2-aminoethylphosphonic acid dialkyl ester (d) in 80 % yield. Reaction of (d) with a 3,4-dialkoxycyclobut-3-en-1,2-dione gives [3-[[2-(dialkoxyphosphoryl)ethyl]-(2-alkoxy-3,4-dioxo-1,2-cyclobuten-1-yl)amino]propyl] carbamic acid 1,1-dimethylethyl ester (e) in 96 % yield. Deprotection and cyclization of (e) in trifluoroacetic acid gives [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]-non-1(7)-en-2-yl)ethyl]phosphonic acid dialkyl ester (c) in 58 % yield. The phosphonic acid diethyl ester (c) was treated with bromotrimethylsilane to give compound (I).