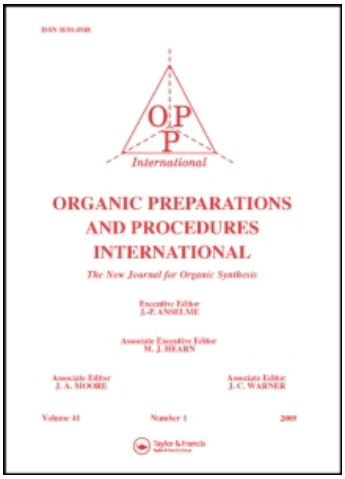


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

EFFICIENT REGIOSELECTIVE ALKYLATION OF 2-CARBOXAMIDOPIPERAZINE. APPLICATION TO THE SYNTHESIS OF THE NMDA COMPETITIVE ANTAGONIST ()-CPP

P. Pevarello[a]; G. Scappi[a]; M. Varasi[a]
[a] R&D/Farmitalia Carlo Erba, Milano, ITALY

To cite this Article Pevarello, P. , Scappi, G. and Varasi, M.(1994) 'EFFICIENT REGIOSELECTIVE ALKYLATION OF 2-CARBOXAMIDOPIPERAZINE. APPLICATION TO THE SYNTHESIS OF THE NMDA COMPETITIVE ANTAGONIST ()-CPP', Organic Preparations and Procedures International, 26: 3, 366 — 370
To link to this Article: DOI: 10.1080/00304949409458440
URL: http://dx.doi.org/10.1080/00304949409458440

4. J. E. McMurry and S. F. Donovan, *Tetrahedron Lett.*, 2869 (**1977**).

5. A. F. Cameron, F. D. Duncanson, A. A. Freer, V. W. Armstrong and R. Ramage, *J. Chem. Soc., Perkin 2*, 1030 (**1975**).

6. V. W. Armstrong, S. Coulton and R. Ramage, *Tetrahedron Lett.*, 4311 (**1976**).

7. a) A. G. M. Barrett, H. B. Broughton, S. V. Attwood and A. A. L. Gunatilaka, *J. Org. Chem.*, **51**, 495 (1986); b) A. G. M. Barrett and H. B. Broughton, *ibid.*, **49**, 3673 (1984).

8. D. B. Tongare and S. M. Babar, Unpublished results.

9. a) L. I. Smith and J. W. Opie, *Org. Syn. Coll. Vol.* **III**, 56 (1955); b) C. A. Fetscher, *ibid.*, **IV**, 735 (1962).

****

EFFICIENT REGIOSELECTIVE ALKYLATION OF 2-CARBOXAMIDOPIPERAZINE. APPLICATION TO THE SYNTHESIS OF THE NMDA COMPETITIVE ANTAGONIST (±)-CPP

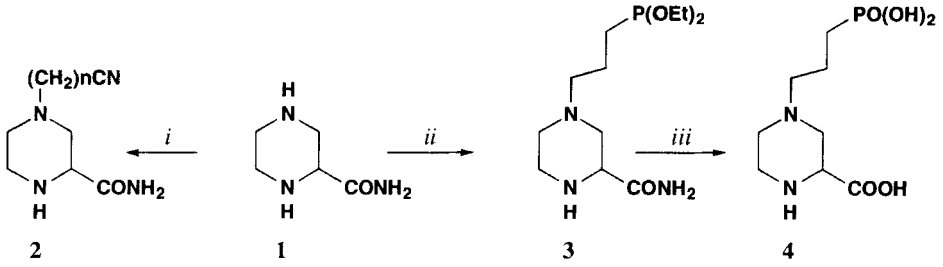
Submitted by (08/11/93) P. Pevarello*, G. Scappi and M. Varasi

R&D/Farmitalia Carlo Erba, Via Imbonati, 24 20159 Milano, ITALY

The search for selective competitive antagonists at the NMDA-subtype of the excitatory amino acid (EAA) receptors has lead in the recent past to the synthesis of several compounds having therapeutic potential as antiexcitotoxins.[1] Among the new compounds so far introduced 2-carboxy-4-(3-phosphonopropyl)piperazine (CPP; **4**) is one of the most frequently employed tools for biochemical and behavioral studies.[2-4] Very recently, a synthesis of CPP[5] overcame some of the problems of selectivity which had emerged in the first procedures.[6] Furthermore, new NMDA-antagonists have been presented which bear a tetrazole group linked through an alkyl chain to the N-4 piperazine nitrogen.[7]

Compounds **2a-d** (Scheme) were suitable intermediates for the synthesis of the NMDA-antagonists and were obtained in low yields (28-37%)[8] from the corresponding ω-bromoalkanenitrile and 2-carboxamidopiperazine. Under suitable experimental conditions (e. g. DMF, K_2CO_3, 50°, 3 hrs), the N-4 alkylation is nearly regiospecific[9] and can be accomplished in good yields (50-67%). This observation seems to be of general value in the N-4 alkylations of 2-carboxamidopiperazine.

Consequently, we were able to develop an improved synthesis of (±)-CPP consisting in only three steps starting from commercial reagents, without the need of employing protecting groups as shown below.



2 1 3 4

a) n = 1 (50%)
b) n = 2 (61%)
c) n = 3 (67%)
d) n = 4 (61%)

i) $Br(CH_2)_nCN$, K_2CO_3, DMF, 3 hrs, 50°
ii) $Br(CH_2)_3PO(OEt)_2$, K_2CO_3, DMF, 6 hrs, 50°
iii) 6N HCl, reflux, 6 hrs

This procedure which can be carried out on a gram-scale, also avoids the use of unsafe solvents such as benzene.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR Spectra were recorded on a Perkin-Elmer 297. ^1H NMR Spectra were acquired on a Bruker WP 80 SY or Varian VXR 200, respectively at 80 and 200 MHz. Chemical shifts are reported in ppm (δ) relative to the solvent signal (DMSO-d_5, 2.49 ppm). EI-MS spectra were recorded on a Varian MAT CH-7 mass spectrometer at 70 eV. FAB-MS spectra were recorded on a Finnigan MAT TSQ 70 mass spectrometer. Elemental analyses were performed by our analytical laboratories and agreed. Common reagent grade chemicals and starting materials purchased from commercial sources were used as received.

2-Carboxamidopiperazine (1).- A solution of 2-carboxamidopyrazine (5.0 g; 0.041 mol; Aldrich) in ethanol-water (1:1; 60 mL) was hydrogenated over 20% $Pd(OH)_2/C$ (2.5 g) at 50° and 50 psi until uptake of H_2 ceased (2 hrs). The mixture was filtered and the solvent was evaporated. The residue was flash-chromatographed on silica gel (CH_2Cl_2 60: CH_3OH 40: 30%NH_4OH 3) to yield 3.35 g (64%)[10] of **1** as a white solid, mp 134-136°, lit. 134-136°(dec.),[11] 143-144°[11] and 144-145°[12] (after recrystallization from ethanol).

^1H NMR (DMSO-d_6): δ 7.05 and 6.90 (2 bs, 2 H, $CONH_2$); 3.07 (dd, 1 H, J = 3.2Hz, J = 9.0Hz, H-2); 2.25-2.76 (m, 6 H, piperazine CH_2). EI-MS(m/z): 129 (9.1, $[M^+]$); 112 (9.9, $[M-NH_3]^+$); 100 (24, $[M-CH_2=NH]^+$); 85 (100, $[M-CONH_2]^+$). IR (Nujol): 1595, 1290, 1270, 1150, 995, 955, 800, 740 cm^{-1}.

Anal. Calcd. for $C_5H_{11}N_3O$: C, 46.50; H, 8.58; N, 32.53. Found: C, 46.75; H, 8.42; N, 32.72

4-Cyanomethyl-2-carboxamidopiperazine (2a).- To a stirred suspension of 2-carboxamidopiperazine **1** (1.0 g; 7.8 mmol) and anhydrous K_2CO_3 (1.08 g; 7.8 mmol) in dry DMF (40 mL), kept at 50°,

under nitrogen with stirring, was added in a single portion 0.75 g (6.25 mmol; 0.43 mL) of bromoacetonitrile. Stirring was continued for 3 hrs at 50°; then the mixture was evaporated *in vacuo* and the crude residue was flash-chromatographed on silica gel (eluent: CH_2Cl_2 98: CH_3OH 2; 30%NH_4OH 0.2; then 95:5:0.5) to give **2a** as a pale yellow solid (0.53 g; 50%); mp 172-174°.

^{1}H NMR(DMSO-d_6): 7.20 and 7.08 (2 bs, 2 H, $CONH_2$); 3.68 (s, 2 H, $\underline{CH_2}CN$); 3.16 (dd, J = 3.2Hz, J = 9.0Hz, 1 H, H-2); 2.45-2.90 (m, 4 H, H-6_{eq}, H-3_{eq}, H-6_{ax}, H-5_{eq}); 2.27 (bs, 1 H, NH); 2.06-2.21 (m, 2 H, H-3_{ax}, H-5_{ax}). IR(Nujol): 3300, 3110, 2240, 1655, 1375, 1315, 1255, 1140, 1110, 1040, 990, 940, 900, 860 cm^{-1}. FAB-MS(m/z): 169 (100, $[M+H]^+$); 142 (21.6, $[M-CN]^+$); 124 (18.9, $[M-\bullet CONH_2]^+$).

Anal. Calcd. for $C_7H_{12}N_4O\bullet 0.1\ H_2O$: C, 49.46; H, 7.23; N, 32.96. Found: C, 49.53; H, 7.23; N, 32.96

Under the same conditions, **2b-d** were obtained as white solids, starting from **1** and the corresponding ω-bromoalkanenitriles.

Compound 2b (61%; mp 148-150°).

^{1}H NMR(DMSO-d_6): δ 7.16 and 7.00 (2 bs, 2 H, $CONH_2$); 3.14 (dd, J = 3.2Hz, J = 9.0Hz, 1 H, H-2); 2.78-2.86 (m, 2H, H-6_{eq}, H-3_{eq}); 2.57-2.66 (m, 4 H, H-6_{ax}, H-5_{eq}, $CH_2\underline{CH_2}CN$); 2.52 (m, 2 H, $CH_2\underline{CH_2}N$); 2.18 (bs, 1 H, NH); 1.83-2.02 (m, 2 H, H-3_{ax}, H-5_{ax}).

FAB-MS (m/z): 183 (100, $[M+H]^+$); 138 (22.8, $[M-CONH_2]^+$). IR (Nujol): 3290, 3110, 2240, 1655, 1315, 1245, 1140, 1110, 1040, 990, 945, 900, 860 cm^{-1}.

Anal. Calcd. for $C_8H_{14}N_4O\bullet 0.15\ H_2O$: C, 51.96; H, 7.79; N, 30.30. Found: C, 51.81, H, 7.71; N, 30.05

Compound 2c (67%; mp 120-122°).

^{1}H NMR(DMSO-d_6): δ 7.18 and 7.02 (2 bs, 2 H, $CONH_2$); 3.13 (dd, J = 3.2 Hz, J = 9.0 Hz, 1 H, H-2); 2.4-2.9 (m, 6 H, H-6_{eq}, H-3_{eq}, H-5_{eq}, H-6_{eq}, CH_2CN); 2.28 (t, J = 6.9 Hz, 2 H, $CH_2\underline{CH_2}N$); 2.20 (bs, 1 H, NH); 1.86-2.02 (m, 2 H, H-3_{ax}, H-5_{ax}); 1.69 (m, 2 H, $NCH_2\underline{CH_2}CH_2CN$). FAB-MS (m/z): 197 (100, $[M+H]^+$); 152 (18, $[M-CONH_2]^+$). IR (Nujol): 3300, 3140, 2230, 1655, 1415, 1320, 1285, 1245, 1180, 1120, 1075, 1040, 1000, 990, 940, 890, 860, 830 cm^{-1}.

Anal. Calcd. for $C_9H_{16}N_4O$: C, 55.08 H, 8.22; N, 28.55. Found: C, 54.80; H, 8.15; N, 28.32

Compound 2d (61%; mp 121-123°)

^{1}H NMR(DMSO-d_6): δ 7.17 and 7.01 (2 bs, 2 H, $CONH_2$); 3.11 (dd, 1 H, J = 3.2 Hz, J = 9.2 Hz, H-2); 2.4-2.9 (m, 6 H, H-6_{eq}, H-3_{eq}, H-5_{eq}, H-6_{ax}, CH_2CN); 2.22 (t, J = 6.6 Hz, 2 H, $CH_2\underline{CH_2}N$); 2.18 (bs, 1 H, NH); 1.80-1.98 (m, 2 H, H-3_{ax}, H-5_{ax}); 1.4-1.6 (m, 4 H, $NCH_2\underline{CH_2}\underline{CH_2}CH_2CN$). FAB-MS (m/z): 211 (100, $[M+H]^+$); 166 (18, $[M-CONH_2]^+$). IR(Nujol): 3300, 3120, 2230, 1655, 1415, 1310, 1280, 1240, 1140, 1110, 1080, 1040, 980, 900, 855, 860 cm^{-1}.

Anal. Calcd. for $C_{10}H_{18}N_4O$: C, 57.12; H, 8.63; N, 26.64. Found: C, 56.96; N, 8.56; H, 26.50

(±)-2-Carboxamido-4-[3-(diethoxyphosphinyl)propyl]piperazine (3).- To a stirred mixture of (±)-2-carboxamidopiperazine (**1**; 1.0 g; 7.8 mmol), K_2CO_3 (1.08 g; 7.8 mmol) and anhydrous DMF (40 mL), kept under nitrogen at 50° was added dropwise a solution of diethyl 3-bromopropylphosphonate[13] (1.53 g; 5.9 mmol; 95%) in anhydrous DMF (5ml). The mixture was maintained at 50° for 6 hrs, then it was cooled, filtered and evaporated.The residue was flash-chromatographed on silica gel

(eluent CH_2Cl_2 97: CH_3OH 3: 30%NH_4OH 0.3) to afford **3** (1.38 g; 80%) as a colourless, thick oil. ^1H NMR (DMSO-d_6): δ 7.18 and 7.02 (2 bs, 2 H, $CONH_2$); 3.95 (m, 4 H, 2 $O\underline{CH_2}CH_3$); 3.11 (dd, J = 3.2 Hz, J = 9.2 Hz,1 H, H-2); 2.4-2.9 (m, 4 H, H-6_{eq}, H-3_{eq}, H-5_{eq}, H-6_{ax}); 2.26 (m, 2 H, CH_2N); 1.4-2.0 (m, 7 H, H-3_{ax}, H-5_{ax}, $NCH_2\underline{CH_2}\underline{CH_2}P$); 1.19 (t, J = 7.1 Hz, 6 H, $OCH_2\underline{CH_3}$). FAB-MS (m/z): 308 (100, $[M+H]^+$); 263 (19.2, $[M-CONH_2]^+$). IR (neat): 3450-3150 (broad), 2930, 2800, 1670, 1440, 1390, 1310, 1230, 1160, 1090, 1050, 1020, 960, 800 cm^{-1}.

Anal. Calcd. for $C_{12}H_{26}N_3O_4P$•0.8 H_2O: C, 44.80; H, 8.65; N 13.06. Found: C, 44.79; H, 8.62; N, 13.01

(±)-2-Carboxy-4-(3-phosphonopropyl)piperazine (CPP; 4)

The procedure[5] described as Method A was followed to give **4** (72%). Its ^1H NMR, MS, IR and TLC were in agreement with the literature data.[5]

REFERENCES

1. For some selected references: A. J. Hutchinson, M. Williams, C. Angst, R. De Jesus, L. Blanchard, R. H. Jackson, E. J. Wilsuz, D. E. Murphy, P. S. Bernard, J. Schneider, T. Campbell, W. Guida and M. A. Sills, *J. Med. Chem.*, **32**, 2171 (1989); B. Aebischer, P. Frey, H. P. Harter, P. L. Herrling, W. Müller, H. J. Olverman and J. C. Watkins, *Helv. Chim. Acta*, **72**, 1043, (1989); P. L. Ornstein, J. M. Schaus, J. W. Chambers, D. L. Huser, J. D. Leander, D. T. Wong, J. W. Paschal, N. D. Jones and J. B. Deeter, *J. Med. Chem.*, **32**, 827 (1989); C. F. Bigge, G. Johnson, D. F. Ortwine, J. J. Drummond, D. M. Retz, L. H. Brahce, L. L. Coughenour, F. W. Marcoux and A. W. Probert, *ibid.*, **35**, 1371 (1992); J. P. Whitten, D. Muench, R. V. Cube, P. L. Nyce, B. M. Baron and I. A. McDonald, *Bioorg. Med. Chemistry Lett.*, **1**, 441 (1991).

2. H. J. Olverman, D. T. Monaghan, C. W. Cotman and J. C. Watkins, *Eur. J. Pharmacol.*, **131**, 161 (1986).

3. D. E. Murphy, J. Schneider, C. Boehm, J. Lehmann and M. Williams, *J. Pharmacol. Exp. Ther.*, **240**, 778 (1987).

4. M. F. Jarvis, D. E. Murphy and M. Williams, *Eur. J. Pharmacol.*, **141**, 149 (1987).

5. D. A. Demaine, S. Smith and P. Barraclough, *Synthesis*, 1065 (**1992**).

6. a) C. F. Bigge, S. J. Hays, P. M. Novak, J. T. Drummond, G. Johnson and T. P. Bobovski, *Tetrahedron Lett.*, **30**, 5193 (1989); b) S. J. Hays, C. F. Bigge, P. M. Novak, J. T. Drummond, T. P. Bobovski, M. J. Rice, G. Johnson, L. J. Brahce and L. L. Coughenour, *J. Med. Chem.*, **33**, 2916 (1990).

7. P. L. Ornstein, M. Brian Arnold, D. Evrard, J. Daniel Leander, D. Lodge and D. D. Schoepp, *Bioorg. Med. Chem. Lett.*, **3**, 43 (1993).

8. Low yields refer to the overall two-step N-4 alkylation/ N-1-BOC derivatization of compounds **2a-d**. Since the N-1 BOC protection is nearly quantitative (BOC_2O, DMAP, CH_2Cl_2, r.t., 4 hrs), it can be safely assumed that the overall yields quoted in ref. 7 correspond to those of N-4 cyanoalkylation.

9. Small quantities (<10%) of N-1,N-4-disubstituted piperazines can be detected by TLC and isolated. The attribution of the N-4 regioisomer to the compounds **2a-d** was based on the Nuclear Overhauser Enhancement (NOE) of H-3_{eq} (3%), H-5_{eq} (2%) and H-3_{ax} /H-5_{ax} (1.5% overall) at 400 MHz (Varian VXR 400S) by irradiating the CH_2 in the side-chain of **2a**; structures **2b-d** were attributed by analogy.

10. A higher yielding hydrogenation procedure (PtO_2, 60 psi, 60°, 86%) is given in ref. 7.

11. E. Felder, S. Maffei, S. Pietra and D. Pitrè, *Helv. Chim. Acta,* **43**, 888 (1960).

12. F. L. Bach, Jr, S. Kushner and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 6049 (1955).

13. US 4,206,156; *CA* **93**:150378; see also ref. 6b.

****

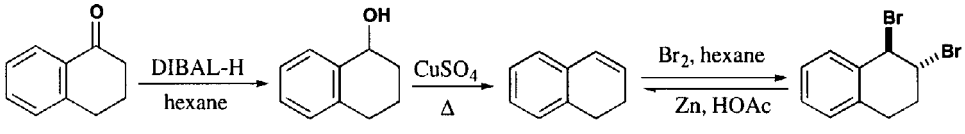
PURIFICATION OF 1,2-DIHYDRONAPHTHALENE- AN IMPORTANT INTERMEDIATE IN THE HYDROPROCESSING OF NAPHTHALENE

Submitted by (09/07/93)

Mike D. Cagle, Sharbil J. Firsan and E. J. Eisenbraun*

Department of Chemistry
Oklahoma State University, Stillwater, OK 74078

1,2-Dihydronaphthalene (**3**) is an important intermediate in the hydroprocessing of naphthalene which in turn, is a useful model in studies of the hydroprocessing of aromatic constituents of fossil fuels.[1] Knowledge of the precise thermochemical properties of **3** is essential for introducing improvements in refinery design and other petroleum processing technology.[2] Determination of these properties has been precluded thus far by the unavailability of **3** of the required purity. To meet this need, we prepared 68+ g of **3** (≥ 99.97% purity).[3]



While **3** and its 1-tetralol (**2**) precursor are commercially available,[4] they were synthesized starting with 1-tetralone (**1**) in order to minimize the presence of impurities boiling in the same range as **3**. Thus, treatment of freshly distilled **1** with DIBAL-H in hexane and dehydrating the resulting **2** by distilling from anhydrous copper(II) sulfate[5] afforded **3** in 98% initial purity. These reagents were