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# Synthesis of *N*–alkylamides of 2–Oxopyrrolidine

*Zdravko Crnić* and Zlatko Vajtner*

*Research Institute PLIVA, Zagreb, Croatia*

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*N*–alkylamides of 2–oxopyrrolidine (**I**) were prepared by electrochemical reduction of previously undescribed 2,5–dioxopyrrolidine derivatives (**IV**), obtained by condensation of sodium succinimide (**II**) with $\omega$–halogen alkylamides (**III**). Some of the prepared compounds showed therapeutic activity, specially *N*–acetamide of 2–oxopyrrolidine, known under the generic name Piracetam.

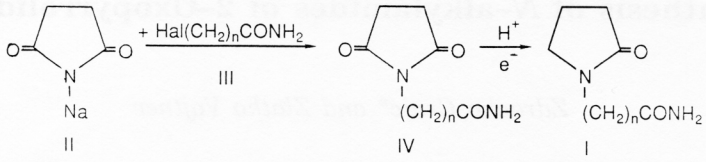
## INTRODUCTION

*N*–acetamide of 2–oxopyrrolidine was introduced into medicine, under the generic name Piracetam,[1–3] as a therapeutic agent for the improvement of brain metabolism (hyperkinesis, motion and memory diseases). The interesting neotropical activity of Piracetam stimulated synthesis of numerous related *N*–alkylamides of 2–oxopyrrolidine. It is known that compounds (**I**), in the following reaction scheme, were prepared by reaction of sodium 2–oxopyrrolidine with $\omega$–halogen alkylamides, as well as by reaction of esters or acidic chlorides of 2–oxopyrrolidine alykl acids with ammonia.[1] The preparation of *N*–alkylamides of 2–oxopyrrolidine was also carried out by the thermic decomposition of their ammonium salts[2] or by reaction of $\gamma$–butyrolactone with liquid ammonia at higher temperatures and pressures.[3] Finally, a new synthesis of *N*- alkylamides of 2–oxopyrrolidine *via* *N*–4–chlorobutyryl aminoacids was described.[4,5] On the other hand, 2–oxopyrrolidine and its *N*—methyl derivate may be prepared by electrochemical reduction of the corresponding 2,5–dioxopyrrolidine.[6,7] This paper reports a new procedure for the preparation of *N*–alkylamides of 2–oxopyrrolidine (**I**) by electrochemical reduction of *N*–alkylamides of 2,5–dioxopyrrolidine (**IV**).[8]

* To whom correspondence should be addressed.

## SYNTHESIS

The starting material, *N*–alkylamides of 2,5–dioxopyrrolidine (**IV**), the preparation of which had not been described, were prepared by condensation of sodium succinimide (**II**) with ω–halogen alkylamides (**III**) by heating under reflux for 2–5 hours. They were electrochemically reduced at 0–5 °C in a cell with a diaphragm using a lead cathode and a platinum or lead anode in the acidic medium ($H_2SO_4$) at a constant current of 0.1–0.2 A $cm^{-1}$.




Hal = Cl, Br ; n = 1-3

The electrochemical reduction was followed by thin layer chromatography. When the reduction was over, the catholyte was neutralized, filtered and the filtrate evaporated to dryness. Product isolation (extraction by hot isopropanol and recrystallization from ethanol/benzene) provided 50–80% of pure product.[8]

The results of preparative electrochemical reduction of *N*–acetamide of 2,5–dioxopyrrolidine at different experimental conditions are presented in Table I.

TABLE I

*Results of electrochemical reductions of N—acetamide of 2,5—dioxopyrrolidine (5 % solution), Pb cathode, Pb anode (anolyte 10 % $H_2SO_4$), 0—5 °C.*

| | Catholyte % $H_2SO_4$ | Current A $cm^{-1}$ | Yield % |
|---|---|---|---|
| 1 | 30 | 0.15 | 71.5 |
| 2 | 50 | 0.15 | 78.0 |
| 3 | 70 | 0.15 | 77.6 |
| 4 | 50 | 0.10 | 68.5 |
| 5 | 50 | 0.20 | 79.4 |
| 6* | 50 | 0.15 | 51.0 |

* Temperature 30 °C

The yields and the reaction conditions of other derivatives almost equal those of Piracetam.

It is obvious that the optimal reaction conditions for the preparation of *N*–alkylamides of 2–oxopyrrolidine by electrochemical reduction of *N*–alkylamides of 2,5–dioxopyrrolidine are 50% $H_2SO_4$ as the reaction solution, temperature of 0–50 °C and constant current densities of 0.15–0.20 A $cm^{-2}$.

In comparison with the procedures from the literature concerning the synthesis of *N*–alkylamides of 2–oxopyrrolidine, the one reported in this paper seems more convenient, giving satisfactory yields without problems in the isolation and purification of the final products.

## EXPERIMENTAL

Melting points were determined on the Fisher–Johns apparatus and are not corrected. The IR-spectra were recorded with a Model 257 G Perkin-Elmer spectrometer and reported in wave lengths followed by relative intensities in brackets. The $^1$H-NMR spectra were run on the Varian EM-390 NMR 90 mHz spectrometer in DMSO–$d_6$, with TMS as the internal standard. TLC was performed on silica gel plates (Merck, Kieselgel $HF_{254}$) using chloroform-methanol (9:1) as the eluent.

### *General Procedure for the Preparation of N–Alkylamides of 2,5–Dioxopyrrolidine (***IV***)*

A solution of sodium succinimide (2.44 g; 0.02 mol) and $\omega$–halogen alkylamide (0.022 mol) in ethanol (10 ml; dimethylformamide or toluene) was heated under reflux for 2–5 hours, and the formed crystals of sodium chloride filtered. The solvent, dimethylformamide or toluene, was evaporated, and dry residue suspended in ethanol or benzene-ethanol mixture (1:1; 10 ml). After stirring for 3 hours and standing in a refrigerator for 5 hours, the precipitate was filtered and dried. The crude product was recrystallized from ethanol or from ethanol-benzene mixture (1:1). Yield: 75–85%.

N–*Acetamide of 2,5—Dioxopyrrolidine*

M.p. 144–146 °C.

*Anal.* $C_6H_8N_2O_3$ (156,14) calc'd: C 46.15; H 5.16; N 17.94%
found: C 46.30; H 5.02; N 17.77%.

IR spectrum (KBr): 3455 (s) 3410 (m), 3310 (s), 3170 (s), 1780 (sh), 1710 (s), 1630–1690 (br.(s), $cm^{-1}$.

$^1$H NMR spectrum: 2,63 (s), 3.90 (s), 7.27 (d) ppm.

N–*β–Propionamide of 2,5—Dioxopyrrolidine*

M.p. 112–113 °C.

*Anal.* $C_7H_{10}N_2O_3$ (170,17) calc'd: C 49.40; H 5.92; N 16.46%
found: C 49.67; H 5.64; N 16.19%.

IR spectrum (KBr): 3395 (s), 3320 (sh), 3260 (sh), 3210 (s), 1770 (s), 1685 (vs), 1660 (vs), 1630 (sh) $cm^{-1}$.

$^1$H NMR spectrum: 2.28 (s), 2.62 (s), 3.56 (t), 7.01 (d) ppm.

N–*γ–Butyramide of 2,5—Dioxopyrrolidine*

M.p. 83–84 °C.

*Anal.* $C_8H_{12}N_2O_3$ (184.19) calc'd: C 52.16; H 6.57; N 15.21%
found: C 52.30; H 6.51; N 15.39%.

IR spectrum (KBr): 3415 (vs), 3350 (sh), 3290 (m), 3170 (vs) 1770 (sh), 1680 (vs), 1660 (sh), 1630 (sh) $cm^{-1}$.

$^1$H NMR spectrum: 1.5–2.2 (m), 2.60 (s), 3.36 (t), 6.88 (d) ppm.

### *General Procedure for the Preparation of N–Alkylamide of 2–Oxopyrrolidine (***I***) by Electrochemical Reduction*

*N*–alkylamides of 2,5–dioxopyrrolidine (5 mmol), dissolved in 30–70% $H_2SO_4$ (80 ml), were electrochemically reduced in a cell with a ceramic diaphragm (Fisher) using a lead cathode (50 ml) and a lead anode (anolyte 10% $H_2SO_4$). Electroreduction was carried out using a constant current density 0.1–0.2 A $cm^{-2}$, at 0.1–30 °C. The reaction was followed by the TLC method. After the reduction was completed, the catholyte was neutralized with a 40% solution of sodium hydroxide, at 0–5 °C, filtered, and the filtrate evaporated under reduced pressure to dryness. The pure product was obtained by extraction of dry residue with hot isopropanol, followed by recrystallization from ethanol or benzene-ethanol mixture (1:1). The results are listed in Table I. The reaction conditions and yields for the other derivatives are nearly the same as those for

Piracetam. Physical constants and spectra of the obtained *N*–alkylamides of 2–oxopyrrolidine correspond to those reported in the literature.[1–6]

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## SAŽETAK

### Sinteza *N*–alkilamida 2–oksopirolidina

*Zdravko Crnić i Zlatko Vajtner*

*N*–alkilamidi 2–oksopirolidina (**I**) su pripravljeni elektrokemijskom redukcijom do sada neopisanih 2,5–dioksopirolidinskih derivata (**IV**), koji su sintetizirani kondenzacijom sukcinimid-natrija (**II**) sa ω–halogen alkilamidima. Neki od navedenih spojeva pokazuju terapeutsko djelovanje, osobito *N*–acetamid 2–oksopirolidina, poznat pod generičkim imenom Piracetam.