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Synthesis of 1-(2-propylpentanoyl)-2-pyrrolidinone as Potential Anticonvulsant Agent.(การสังเคราะห์สาร 1-(2-โพรพิลเพนทาโนอิล)-2-ไพร์โรลิดิโนน ซึ่งมีแ...

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ORIGINAL ARTICLE

Synthesis of 1-(2-propylpentanoyl)-2-pyrrolidinone as Potential Anticonvulsant Agent.

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ABSTRACT

The target compound, 1-(2-propylpentanoyl)-2-pyrrolidinone, was synthesized by using 2-propylpentanoyl chloride and 2-pyrrolidinone sodium. The structure of the compound was determined by using ^{1}H-NMR ^{13}C-NMR and mass spectrometric technique. (Th.J.Pharm. Sci., Vol.15 No. 2, 87-92 (1990))

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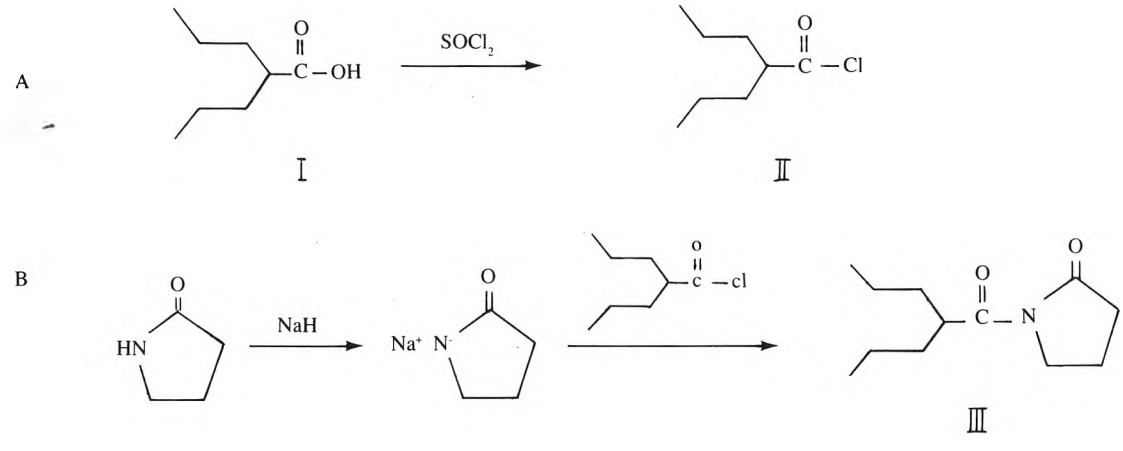
INTRODUCTION

Current available antiepileptic drugs are able to efficiently control seizures in about 50 percents of the patients (1), Furthermore, undesirable side effects from clinically used drugs often render treatment difficult. Notwithstanding the beneficial effects of the current drugs, there is still a need for new antiepileptic drugs with more selective anticonvulsant effects and less toxicity. As regards the widely used antiepileptic drug valproic acid (2-propylpentanoic acid, I) numerous derivatives of this drug have been tested for anticonvulsant action (2-6). Valproic acid, known as a broad spectrum anticonvulsant agent, exerts moderately anticonvulsant action, which is presumably secondary to the enhancing GABA-mediated inhibition, or acts directly on voltage-dependent Na^+ channels (7). The observations suggest that increased levels of GABA in the CNS may be useful in the treatment of epilepsy. Numerous derivatives of GABA, including alkyl ester of GABA, γ-acetylenic GABA, aliphatic and steroid esters of GABA have been developed in the hope of facilitating the uptake of GABA into the brain (8-10).

The most attractive study indicated that 2-pyrrolidinone, the lactam of GABA, penetrates readily into the CNS of mice and is converted enzymatically to GABA in the brain (11).

This paper was aimed to introduce an acyl function of 2-propylpentanoic acid to the position 1 of 2-pyrrolidinone, it is expected that hydrophobic part of the acid will enhance penetration of the molecule into the CNS and hydrolysis of this compound will obtain GABA and corresponding anticonvulsant valproic acid. The target compound was synthesized according to the typical procedure for preparing amides as shown in scheme I.



Scheme I Synthesis of 1-(2-propylpentanoyl)-2-pyrrolidinone

Materials and Methods

Instruments

1. Infrared Spectrophotometer : Shimaszu IR-440 (The Scientific and Technological Research Equipment Center, Chulalongkorn University.).
2. Nuclear Magnetic Resonance Spectrophotometer : Jeol FX 90Q (90 MHz) (The Scientific and Technological Research Equipment Center, Chulalongkorn University).
3. Mass spectrometer : Jeol FX 3000 double focusing (The scientific and Technological Research Equipment Center, Chulalongkorn University).

Chemicals

The starting materials used are, diethyl malonate (Fluka chemic Co.) propyl bromide (Fluka Chemic Co.), 2-pyrrolidinone. (Fluka AG.) All solvents used were B.P. and laboratory grade.

Synthesis : 2-propylpentanoic acid (Valproic acid) (I)

The method used for preparation of valproic acid was the same synthetic procedure as Porubek et al. (12) did. The overall yield was about 30%.

Synthesis : 1-(2-propylpentanoyl)-2-pyrrolidinone : (III)

A 5.76 g (40 mmole) of 2-propylpentanoic acid was dropwisely added to a solution of 5.20 g of thionyl chloride, then the mixture was stirred at room temperature overnight. The excess thionyl chloride was removed in vacuo to yield the crude acyl halide, which was not further purified. The acid chloride (II) was then added dropwisely into a suspension of pyrrolidinone sodium, which was prepared by treating 3.36 g (40 mmole) of pyrrolidinone with NaH in anhydrous benzene, the mixture was stirred at room temperature for 3 hours. The white solid was filtered off and the filtrate was evaporated. The oily product was added to a solution of $NaHCO_3$ (3 x 50 ml). The mixture was extracted with chloroform, washed with H_2O (2 x 50 ml) and the solvent was evaporated. The residual oily product was purified with a silica gel column, eluted with chloroform : hexane (3:1). The over all yield was about 7.60 g (90%). IR : 1740 (lactam C=O) ; 1680 (amide C=O) cm^{-1} ^{1}H-NMR : 0.92 (m,6H,2-CH_3) 1.38-1.61 (m, 8H, 2- CH_2-CH_2-) 2.01 (q, 2H), 2.61 (t, 2H), 3.81 (t, 3H) MS : m/e 212 $(M+1)^+$, 211 $(M)^+$, 126 $(M-C_4H_7NO)^+$.

Results and Discussions

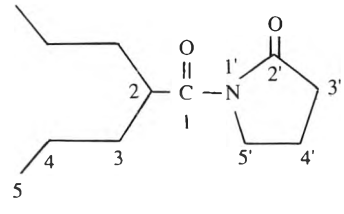
Syntheses and Structure Determination.

Synthesis of valproic acid has been described (12). In this paper, the starting material, diethylmalonate and propyl bromide, were refluxed in sodium ethoxide solution. After hydrolysis, the obtained compound was then undergone decarboxylation. The product obtained was confirmed by comparing with authentic sample.

The Synthesis of III was accomplished by the reaction of II and pyrrolidinone sodium. II was preferably prepared by the reaction of 2-propylpentanoic acid and thionyl chloride, the pyrrolidinone sodium was prepared by treating 2-pyrrolidinone with sodium hydride. Then, the target compound was obtained upon one-step reaction of the above reactants in dry benzene. With this method the yield obtained was about 90 percents (Scheme I).

The IR spectrum of III showed the C=O stretching 2 bands at 1680 cm^{-1} and 1740 cm^{-1} for amide carbonyl and lactam carbonyl respectively. The chemical shifts assignment of ^{1}H-NMR and ^{13}C-NMR was shown in Table 1.

Table 1. : Assignment of ^{1}H-NMR and ^{13}C-NMR chemical shifts of III.



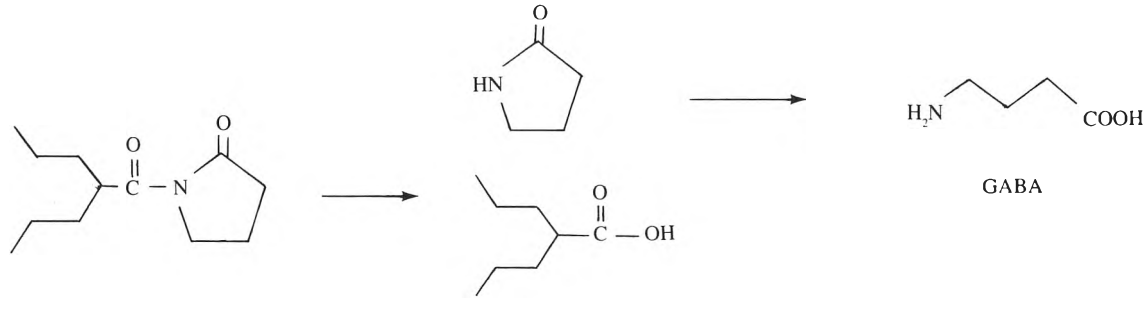
Position	^{13}C (ppm)	^{1}H (ppm)
1	174.67	-
2	43.08	3.81 (t, 3H)
3	34.04	1.38 (m, 4H)
4	20.17	1.61 (m, 4H)
5	13.83	0.92 (m, 6H)
1'	-	-
2'	179.63	-
3'	33.77	2.61 (t, 2H)
4'	16.70	2.01 (q, 2H)
5'	45.52	3.81 (t, 3H)

The fact that, intensity of protons ratio at 3.81 ppm is not corresponded for the methylene protons (it should be only two protons) the exceeding proton may be the methine proton at position 2 that showed broad peak (quintet, 1H) at about the same chemical shift. In order to prove this assumption, the spin-spin decoupling technique was used. Decoupling the two protons triplet at 2.02 ppm causes the triplet at 2.61 ppm to collapse to a sharp singlet and the triplet at 3.81 ppm to collapse to about five peaks. This investigation indicated that the chemical shift of the methine proton at the position 2 appears at about 3.8 ppm.

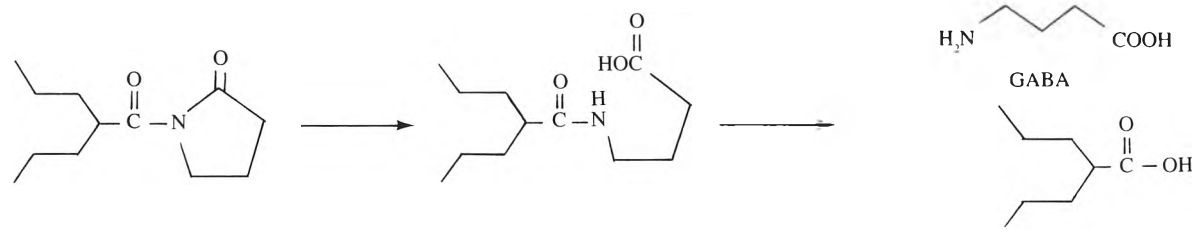
It is supposed that the inductive effect caused by the very strong electron withdrawing pyrrolidinone group and the additional strong hydrogen bonding deshielded the methine proton, which cause its peak much more down field. Recently, Sasaki et al. synthesized a series of 1-acyl-2-pyrrolidinone derivatives and evaluated the anticonvulsant activity of the compounds. All compounds were administered intraperitoneally into the mice and the results revealed that some derivatives possessing anticonvulsant action are probably due to the release of GABA by hydrolysis (13).

1-(2-propylpentanoyl) -2- pyrrolidinone acts possibly as a prodrug with dual anticonvulsant action. It is expected to be converted enzymatically to GABA and corresponding anticonvulsant valproic acid as shown in Scheme II.

pathway a



pathway b



Scheme II. Proposed hydrolytic pathways of III.

However, the mechanism of hydrolysis predominantly proceeded by which pathways must be elicited. In addition, pharmacological activity, kinetic study of the hydrolysis will be further investigated.

Acknowledgement

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การสังเคราะห์สาร 1-(2-โพรพิลเพนทาโนอิล)-2-ไพร์โรลิดิโนน ซึ่งมีแนวโน้มเป็นยาต้านอาการชัก

วิชาญ จันทร์วิทยานุชิต
*ชำนาญ ภัตรพานิช**

บทคัดย่อ

ได้สังเคราะห์สารเป้าหมาย 1-(2-โพรพิลเพนทาโนอิล) -2-ไพร์โรลิดิโนน โดยใช้ 2-โพรพิลเพนทาโนอิล คลอไรด์ และ 2-ไพร์โรลิดิโนน โซเดียม การตรวจสอบโครงสร้างของสารใช้เทคนิคทางสเปคโทรโฟโตมิเตอร์ ^{1}H-NMR ^{13}C-NMR และแมสสเปคโทรมิเตอร์ (ไทยเภสัชสาร ปีที่ 15(2) : หน้า 87-92 (2533))

* ภาควิชาเภสัชเคมี คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย