The Thai Journal of Pharmaceutical Sciences

Volume 16
Issue 2 *1992*

Article 3

1-1-1992

SYNTHESIS OF MONOUREIDE ANALOGUES OF VALPROIC ACID (การสังเคราะห์โมโนยูรีดแอนะลอกของวัลโปรอิก แอซิด)

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Thai J. Pharm. Sci., 1992, Vol. 16, No. 2 pp. 145-150

SYNTHESIS OF MONOUREIDE ANALOGUES OF VALPROIC ACID

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Abstract

Two monoureide analogues of valproic acid were synthesized. N(2-propylpentanoyl) urea was synthesized by acylating urea with valproyl chloride. N(2-propylpentanoyl) thiourea was synthesized via the valproylisothio cyanate intermediate and concentrated ammonia. The structure of the two compounds were confirmed by IR, 'H-NMR, MS and elemental analysis

Key word index : Synthesis, Valproic Acid Analogues

Introduction

Epilepsy is a collection of seizure-disorders which had been defined as a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes of seizures in which there is a disturbance of movement, sensation, behavior, perception and consciousness. It has been estimated that one-half to one percent of the world population are affected by some forms of epilepsy (1). Antiepilepsy therapy with organic compounds began in 1912 when Hauptmann reported the clinical effectiveness of phenobarbital (2). Since then, several antiepileptic agents whose structures similar to that of phenobarbital were discovered, such as phenytoin, ethosuximide, trimethadione etc. At present, not so many drugs are effective in the treatment of epilepsy, among them valproic acid, (dipropylacetic acid) is the attractive one. Its molecular structure differs significantly from all other antiepileptic agents. However, valproic acid, considered to be a very safe drug exhibiting only moderately anticonvulsant action.

The successful use of phenobarbital in the treatment of epilepsy and the discovery of activity in phenacemide, acyclic structure which embodied a major part of the phenobarbital molecule (3), prompted the idea to synthesize monoureide and thioureide with 5-dipropyl side chain which resemble the partial structure of valproic acid. The above two monoureide analogues of valproic acid were expected to possess anticonvulsant activity.

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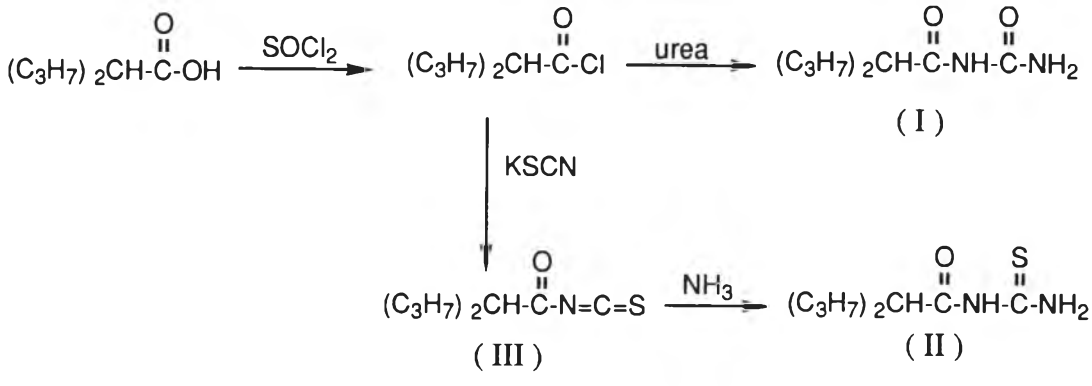
Scheme I described the synthetic pathways of monoureide (I) and thioureide analogues (II) of valproic acid.

Scheme I



Materials and Methods

Chemicals :

Valproic acid (Supported by Pharminar Co., Ltd.)

Thionyl chloride (Merck)

Urea (May & Baker Ltd.)

Potassium thiocyanate (BDH chemicals Ltd.)

Concentrated ammonia solution (Merck)

Instruments :

Elemental Analyzer : Perkin Elmer 240 L

Infrared Spectrophotometer : Shimadzu IR-440

Nuclear Magnetic Resonance Spectrometer : Jeol FX 90 Q (90 MHz)

Mass Spectrometer : Jeol FX 3000 double focusing

Melting point apparatus : Buchi, capillary melting point apparatus

N(2-Propylpentanoyl) Urea. (I)

A 5.76g (40 mmole) of valproic acid was dropwisely added to a solution of 5.20 g (3.19 ml.) of thionyl chloride, then the mixture was stirred at room temperature overnight. The excess thionyl chloride was removed *in vacuo* to yield the crude valproyl chloride, which was not further purified. The valproyl chloride was then added into a mixture of 2.40 g urea and 5.50 g of potassium carbonate in benzene. The mixture was refluxed for about 10 hours.

The mixture was filtered immediately and the white precipitate formed upon cooling was collected,then washed with cooled benzene and dried. Recrystallization from hexane yielded 5.65 g (76%) of product, mp 193-194°C. IR (KBr) cm^{-1} : 3400, 3340, 3240, 1700, 1680, 1590. ^{1}H-NMR ($CDCl_3$) : 0.90-0.97 (6H,m), 1.20-1.66 (8H, m), 2.24 (1H, m), 5.48 (1H,b), 8.39 (1H,b),9.20(1H,b).MS (EIMS) : m/z 187 (0.94), 157 (3.44),144 (55.93), 115 (100) Anal. Calcd for $C_9H_{18}N_2O_2$:), C 58.04; H 9.74; N 15.04. Found : C 57.92; H 9.97; N 15.39.

N(2-propylpentanoyl) thiourea (II)

A 5.76 g (40 mmole) of valproic 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* and the valproyl chloride obtained was added to 3.88 g of potassium thiocyanate in toluene. The mixture was stirred under reflux condition for about 12 hours. After cooling, the white solid was filtered off and the slightly yellow liquid was stirred, cooled in an ice bath. Then, a little excess of concentrated ammonia solution was added for a peroid of half an hour. The mixture was stirred for one hour. Then, the mixture was washed with H_2O (3 x 30 ml), the aqueous layer was discarded and the solvent was evaporated *in vacuo* to yield crude product. Purification was acheived by column chromatographic technique using silica gel as a stationary phase and hexane : ethyl acetate (5:1) as a mobile phase. The overall yield was 3.88 g (48%) of product, mp 81-82°C. IR (KBr) cm^{-1} : 3350, 1700, 1625, 1250. ^{1}H-NMR ($CDCL_3$) : 0.91-0.98 (6H, m) 1.20-1.83 (8H, m), 2.25 (1H, m), 7.35 (1H, b), 9.20 (1H, b), 10.02 (1H, b). MS (EIMS) : m/z 202 (50.52), 126 (22.18), 77 (38.39), 57 (100). Anal. Calcd for $C_9H_{18}N_2OS$: C 53.43; H 8.97; N 13.85. Found : C 53.17; H 8.68; N 13.57.

Results and Discussion

N(2-propylpentanoyl) urea (I)

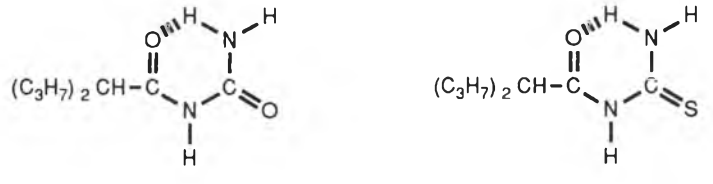
The synthesis of I was easily accomplished by the reaction of valproyl chloride and urea. The IR spectrum of I showed two carbonyl stretching vibration at 1680 and 1700 cm^{-1}, and the NH stretching at 3240, 3340 and 3400 cm^{-1}.

The ^{1}H-NMR spectrum of I showed the peak at chemical shift 0.90-1.66 ppm for alkyl side chains. The broad peak at 2.24 ppm represented methine proton. The broad peaks at chemical shift 5.48 ppm, 8.39 ppm and 9.20 ppm represented NH protons. The peak at 9.20 ppm showed at the most downfield should be the NH proton of imide NH. The two NH protons, which should be the NH protons of primary amide moiety, showed two separated signals at chemical shift 5.48

and 8.39 ppm due to the intramolecular hydrogen bonding. The peak at chemical shift 8.39 ppm represented NH proton forming intramolecular hydrogen bonding as shown in Figure 1a. From the mass spectrometer, the molecular ion peak (m/z 186) of I was not detected, however, the $(M+1)^+$ ions (m/z 187) was noted instead which may due to protonation of I by the ion-molecule reaction.

N(2-propylpentanoyl) thiourea (II)

The synthesis of II was accomplished *via* the reaction of valproylisothiocyanate intermediate and concentrated ammonia. The valproylisothiocyanate intermediate(III) was confirmed by its IR spectrum, which exhibited a very strong broad peak at 1985 cm^{-1} for the isothiocyanate functional group and at 1720 cm^{-1} for the c=o stretching vibration. The IR spectrum of II showed C=S stretching at 1250 cm^{-1}, the carbonyl stretching at 1700 $cm^{-1}$and three NH stretching at 3250,3300 and 3350 cm^{-1}. The 'H-NMR spectrum of II showed characteristic peaks of alkyl side chains at chemical shift 0.91-2.25ppm. The three broad peaks at chemical shift 7.35, 9.20 and 10.02 ppm represented NH protons. The chemical shift assignment of each NH proton was similar to that of I. Thus, the peak at 10.02 ppm which was the most deshielded should be the NH proton of thioimide. The peak of chemical shift 7.35 and 9.20 and ppm should be the NH proton of thioamide. The peak at chemical shift 9.20 ppm represented NH proton forming intramolecular hydrogen bonding as shown in Figure 1b



(a) (b)

Figure 1 : Proposed structures of monoureide analogues of valproic acid showing intramolecular hydrogen bonding

Nevertheless, the anticonvulsant activity of the two compounds must be further investigated.

Acknowledgements

We would like to thank Mr. Srichai Benjarungroj of Pharminar Co., Ltd. for sodium valproate. To the scientists of the Scientific and Technological Research Equipment Center, Chulalongkorn Universityfor spectroscopic data. To Graduate School Chulalongkorn University for granting partial financial support and to Department of Pharmaceutical Chemistry for providing of facilities.

References

1. Daniels, T.C. and Jorgensen, E.C. (1982) *Wilson and Gisvoldûs textbook of organic medicinal and pharmaceutical chemistry*, 8thed. J.B. Lippincott Co., Philadelphia.

2. Johns, G.L. and Woodbury, D.M. (1982) Anticonvulsant structure activity relationship : Historical development and probable causes of failure, *Drug Development Research* 2 : 333-355

3. Spinks, A and waring, W.S. (1963) Anticonvulsant agents, *Progress in medicinal chemistry* vol. 3 Butterworths, London.

ไทยเภสัชกร ปีที่ 16 ฉบับที่ 2, 2535 หน้า 145-150

การสังเคราะห์โมโนยูรีดแอนนะลอกของวัลโปรอิก แอซิด

บุญอรรถ สายศร, ชำนาญ ภัตรพานิช และ วิชาญ จันทร์วิทยานุชิต*

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บทคัดย่อ

ได้สังเคราะห์โมโนยูรีดแอนนะลอกของวัลโปรอิก แอซิด 2 ตัว คือ เอ็น (2-โพรพิลเพนทาโนอิล) ยูเรีย ซึ่งสังเคราะห์ได้จากปฏิกิริยาเอซิเลชั่นยูเรียด้วยวัลโปรอิล คลอไรด์ และ เอ็น (2-โพรพิลเพนทาโนอิล)ไทโอยูเรีย ซึ่งสังเคราะห์ได้จากปฏิกิริยาระหว่างสารมัธยันตร์วัลโปรอิลไอโซไทโอไซยาเนตและแอมโมเนียเข้มข้น การตรวจสอบ เอกลักษณ์ของสารใช้เทคนิคทางสเปกโทรสโกปี ได้แก่ อินฟราเรด สเปกโทรสโกปี นิวเคลียร์แมกเนติคเรโซแนนซ์ สเปกโทรสโกปี, แมสสเปกโทรเมตรีและการวิเคราะห์องค์ประกอบธาตุ

กุญแจคำ : การสังเคราะห์,แอนนะลอกของวัลโปรอิกแอซิด

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