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SYNTHESIS OF DL-α-^{15}N-TRYPTOPHAN FROM 1-^{15}N-HYDANTOIN#

Ganghua Tang*, Xiaolan Tang[1], Shihchen Wang, Guohui Jiang and Shuqin Wu
Department of Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100730, China; [1] Department of Applied Chemistry, Hunan Agricultural university, Changsha 410128, China.

SUMMARY

DL-α-^{15}N-Tryptophan was prepared by the use of Al-Ni alloy as reducing agent from 1-^{15}N-hydantoin and indole-3-aldehyde via three steps and 1-^{15}N-hydantoin was prepared from ^{15}N-glycine. The yield of 1-^{15}N-hydantoin based on ^{15}N-glycine was 89.3% and the yield of DL-α-^{15}N-tryptophan based on 1-^{15}N-hydantoin was 84%, giving an over-all yield from ^{15}N-glycine of 75%.
Keywords: DL-α-^{15}N-Tryptophan, 1-^{15}N-Hydantoin, Synthesis, ^{15}N-glycine

INTRODUCTION

For biochemical studies, ^{15}N-tryptophan is required. In our laboratory, we particularly need α-^{15}N-tryptophan, in order to investigate the metabolic transformation of perlolyrine in animals. Perlolyrine, a new active alkaloid, 1-(5-hydroxymethyl-furyl)-9H-pyrido[3,4-b]indole, has been isolated from *Lolium perenne L.*(Graminae), and synthesized from tryptophan [1]. Perlolyrine can be used to treat patients with coronary atherosclerotic heart disease [2].

One of the general methods for the preparation of α-amino acids was the reaction of the appropriate aldehyde with hydantoin. In order to synthesize DL-α-^{15}N-tryptophan, 1-^{15}N-hydantoin was prepared.

In this communication, convenient and efficient syntheses of DL-α-^{15}N-tryptophan (8) and 1-^{15}N-hydantoin (4) are described.

RESULTS AND DISCUSSION

There were many general methods for the preparation of tryptophan, one of which was the reaction of the indole-3-aldehyde with hydantoin via three steps, giving DL-tryptophan in better yield and purity than the method based on the reaction of the indole-3-aldehyde with azlactone[3,4]. We found out that the former method was also a satisfactory way for the preparation of DL-α-^{15}N-tryptophan (8).

1-^{15}N-Hydantoin (4) was prepared in three steps from ^{15}N-glycine (1) according to the method of Bond[5], as illustrated in Scheme 1. 1-^{15}N-Hydantoin was then allowed to react with indole-3-aldehyde (5) in piperidine to give 1-^{15}N-indolylidenehydantoin

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*Corresponding author: Dr Ganghua Tang, Department of Nuclear Medicine, Nan Fang Hospital, The First Military University, Guangzhou 510516, China.

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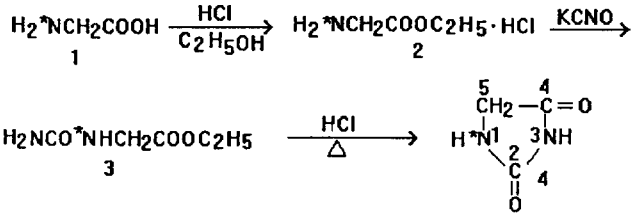
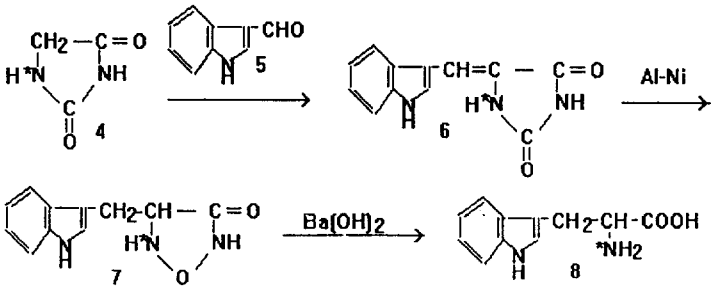
(6), which was first reduced by the use of the Al-Ni alloy in sodium hydroxide, giving indolylmethylhydantoin (7), and subsequently hydrolyzed in barium hydroxide, giving DL-α-^{15}N-tryptophan (8), as illustrated in Scheme 2. We should like to point out that the Al-Ni alloy was easy to handle, and its use also resulted in the same reducing efficiency as the Raney nickel.

Scheme 1



Scheme 2



The yield of 1-^{15}N-hydantoin based on ^{15}N-glycine was 89.3%. The yield of DL-α-^{15}N-tryptophan based on 1-^{15}N-hydantoin was 84%, giving an over-all yield from ^{15}N-glycine of 75%.

EXPERIMENTAL

^{15}N-Glycine was made in our own laboratory. TLC and other reagents were from Beijing Chemical Reagents Co.,China. Melting points were determined on a microscope melting pointing apparatus and were uncorrected. MS data were acquired with Hewlett-Packard 5971A/5890-II GC-MS. ^{1}H NMR spectra were recorded with varian XL-300 spectrometer, using TMS as an internal reference. UV spectra were detected by Beckman DU-600.

α-^{15}N-Glycine ethyl ester hydrochloride (2). ^{15}N-Glycine(1, 2.000g, 26.7 mmol) was covered with absolute ethanol (100ml) and dry hydrogen chloride was bubbled through the mixture in a container which was suspended in a 65-70 ℃ oil bath. The glycine slowly dissolved during the course of 30 minutes. Alcohol was added to replace that which evaporated. Treatment with hydrogen chloride was continued for an additional 15 minutes. The mixture was cautiously evaporated to dryness on a warm surface, giving 3.646g (98%) of α-^{15}N-glycine ethyl ester hydrochloride (2), mp 145-146 ℃.

α-^{15}N-Hydantoic ethyl ester (3). α-^{15}N-Glycine ethyl ester hydrochloride (2, 2.000g, 14.3mmol) was dissolved in water (80ml), and to it was added a slurry of

freshly prepared potassium cyanate[6](1.5g, 18.5mmol) in water (35ml). The mixture was stirred until precipitation started (4 to 5 minutes), and was then cooled at -5 ℃ for 2 hours, filtered,and dried, giving 1.938g (92.6%) of α-^{15}N-hydantoic ethyl ester (3), mp 128-129 ℃.

1-^{15}N-Hydantoin (4). α-^{15}N-Hydantoic ethyl ester (3, 1.900g, 7.8mmol) was covered with 25% hydrochloric acid (45ml) and evaporated to dryness on a steam bath overnight. Purification by alcohol extraction gave 1.280g (98.4%) of 1-^{15}N-hydantoin (4), mp 212-214 ℃.

1-^{15}N-Indolylidenehydantoin (6). 1-^{15}N-Hydantoin (4, 0.924g, 9.2mmol) was mixed with indole-3-aldehyde (5, 1.474g, 10.2mmol) and piperidine (45ml) in a 100ml flask equipped with a reflux condenser. The flask was lowered into an oil bath maitained at 150 ℃ for 20 minutes. The canary-yellow indolylidenehydantoin which formed was suepended in water (1000ml), acidified to Congo red paper with acetic acid, filtered, and washed with water, giving 1.993g (95%) of 1-^{15}N-indolylidenehydantoin (6), mp 315-317 ℃.

1-^{15}N-Indolylmethylhydantoin (7). 1-^{15}N-Indolylidenehydantoin (6, 1.000g, 4.4mmol) was suspended in 1N sodium hydroxide (10ml) and reduced at temperature in presence of the Al-Ni alloy (1.250g). The solid dissolved during the reduction, which was complete in 10 hours. The reducing agent was filtered off, and the filtrate acidified with dilute hydrochloric acid. The colourless crystalline precipitate had mp 213-214 ℃ and was sufficiently pure for hydrolysis to tryptophan. Crystallisation from water gave 0.988g (97.9%) of 1-^{15}N-indolylmethylhydantoin (7), mp 216-218 ℃.

DL-α-^{15}N-Tryptophan (8). 1-^{15}N-Indolylmethylhydantoin (7, 0.920g, 4.0mmol), barium hydroxide (2.750g) and water (28ml) were mixed and refluxed for 24 hours. Ammonia was evolved from the solution and barium carbonate was deposited. The condenser was then removed, and steam was allowed to escape to expel the last traces of ammonia. After dilution of the solution to 80ml, it was heated on the steam-bath, and a rapid stream of carbon dioxide passed in until the supernatant liquor was neutral to litmus. The barium carbonate, thus obtained in granular form, was filtered off and washed with boiling water. The filtrate was freed from the last trace of barium ions by addition of 2N sulphuric acid. After a further filtration the solution was evaporated to dryness at a reduced pressure. The residue of tryptophan was washed with alcohol and dried, giving 0.740g (90.3%) of DL-α-^{15}N-tryptophan (8), mp 281 ℃ (decomp.) with darkening from 260 ℃. The product was identical with authentic DL-tryptophan, as confirmed by paper chromatography (n-butyl acohol-acetic acid-water, 12:3:5) Rf=0.5; UV(H_2O): λ_{max}= 279 nm; MS: m/z 205; ^{1}H NMR(TMS): δ 4.6-4.9 (d, HC-N), 7.0-7.7 (m, indole CH).

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