

NOTE

SYNTHESIS OF 2-[4-(DIPHENYLMETHYL)-1-PIPERAZINYL]ETHYL METHYL
(±)-1,4-DIHYDRO-2,6-DIMETHYL-4-(*m*-NITROPHENYL)-3,5-
[6-¹⁴C]PYRIDINEDICARBOXYLATE DIHYDROCHLORIDE
([¹⁴C]CV-4093 (2HCl))

Norio Tada, Masahiro Kajino, Masazumi Watanabe*, and
Nobuyoshi Hayashi
Research and Development Division, Pharmaceutical Group
Takeda Chemical Industries, Ltd. 17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka 532, Japan.

SUMMARY

The carbon-14 labelled compound (5) of 2-[4-(diphenylmethyl)-1-piperazinyl]ethyl methyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate dihydrochloride (CV-4093 (2HCl)) was synthesized for the study of its metabolism and distribution in test animals. Starting from the commercially available ethyl[3-¹⁴C]acetoacetate (1), 5 was prepared by a modified Hantzsch synthesis, in an overall radiochemical yield of 23.7%.

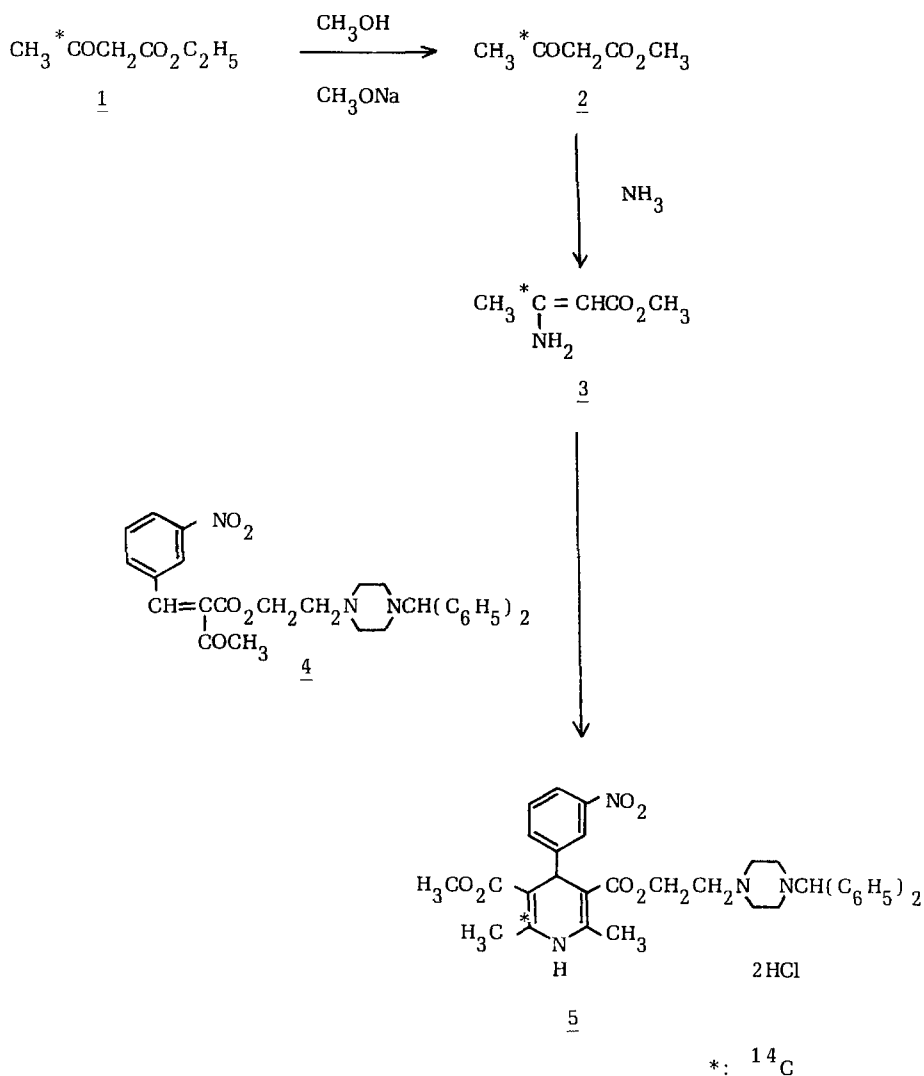
Key Words: [¹⁴C]CV-4093 (2HCl), 1,4-dihydropyridine derivative, calcium antagonist

INTRODUCTION

Calcium antagonists are used for the treatment of hypertension, angina pectoris, and peripheral and cerebral vascular disorders. The piperazinylalkyl ester analogue (CV-4093) of the 1,4-dihydropyridine calcium antagonist exhibits potent and long lasting hypotensive activity in spontaneously hypertensive rats (SHR).¹⁾

Carbon-14 labelled CV-4093 (2HCl) (5) was prepared for the studying its bioavailability, metabolism and distribution in test animals.

* To whom correspondence should be addressed.



Scheme

RESULTS

Ethyl[3- ^{14}C]acetoacetate (**1**, 740 MBq) was subjected to an ester exchange reaction with anhydrous methanol in the presence of sodium methoxide. The resulting methyl ester (**2**) of **1** was then condensed with methanolic ammonia to give methyl 3-amino[3- ^{14}C]crotonate (**3**). A modified Hantzsch²¹ synthesis of **3** with 2-(4-diphenylmethyl-1-piperazinyl)ethyl 2-(3-nitrobenzylidene)acetoacetate (**4**) afforded 2-[4-(diphenylmethyl)-1-

piperazinyl]ethyl methyl (±)-1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-[6-¹⁴C]pyridinedicarboxylate dihydrochloride (5, [¹⁴C]CV-4093 (2HCl)) in an one-pot condensation reaction.

EXPERIMENTAL

Ethyl[3-¹⁴C]acetoacetate (1) was purchased from Amersham Japan. 2-(4-Diphenylmethyl-1-piperazinyl)ethyl 2-(3-nitrobenzylidene)acetoacetate (4) was synthesized in these laboratories of Takeda Chemical Industries Ltd. High performance liquid chromatography (HPLC) analyses were performed on a Shimadzu LC-1 equipped with a UV-detector (254 nm), a Shimadzu chromatopac C-RIA integrator and a Nucleosil 5 C₁₈ column (4x150 mm) using a mobile phase of 0.1 M KH₂PO₄:MeCN:MeOH (10:12:3). The tR value of 5 was 7.4 min at a flow rate of 1.06 ml/min. Liquid scintillation counting was performed with an Aloka LSC-671 liquid scintillation spectrometer.

Methyl 3-amino[3-¹⁴C]crotonate (3)

To a solution of ethyl[3-¹⁴C]acetoacetate (1, 740 MBq, 2 mmol) in anhydrous MeOH (20 ml), a 0.05 M methanolic solution of NaOMe (6 ml) was added and the solution was stirred at room temperature under a stream of N₂ gas for 24 h. After refluxing on an oil bath for 20 min, the reaction solution was cooled and then neutralized with a solution of 78 mg of sulfuric acid in 4 ml of MeOH. Methanolic ammonia (1.35 g of ammonia gas was bubbled in 9 ml of MeOH) was added to the above reaction mixture and the mixture was kept in a refrigerator overnight. The reaction mixture was concentrated in vacuo and the residue was extracted three times with 8 ml of hot benzene. Insoluble materials were filtered off and the filtrate was concentrated in vacuo. The resulting residue was extracted twice with 6 ml of hot n-hexane. The combined n-hexane solution was concentrated in vacuo and the residue was triturated with n-hexane (1 ml) and stood for 1 h in an ice-bath. The crystals separated were filtered and washed with cold n-hexane (3 ml) and dried to yield pale yellow needles of 3 (60 mg, 26 %).

2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl Methyl (±)-1,4-Dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-[6-¹⁴C]pyridinedicarboxylate Dihydrochloride (5, [¹⁴C]CV-4093 (2HCl))

A solution of 3 (60 mg) and 2-(4-diphenylmethyl-1-piperazinyl)ethyl 2-(3-nitrobenzylidene)acetoacetate (4, 290 mg) in 2-propanol (5 ml) was

refluxed for 4 h on an oil bath. After removal of the solvent, the residue was dissolved in MeOH (1 ml). A solution of hydrogen chloride in MeOH (0.8 g of hydrogen chloride bubbled into 5 ml of MeOH) was added and then concentrated *in vacuo*. The residue was dissolved in acetone (4 ml) and stood for 15 h at room temperature. The precipitated crystals were filtered and dried *in vacuo* to give colorless crystals of **5** ($[^{14}\text{C}]\text{CV-4093}$ (2HCl), 248.3 mg, 175 MBq). The chemical and radiochemical purities of **5** were 99.9% and 99.8%, respectively, by HPLC analyses. The radiochemical yield of **5** was 23.7% based on **3**. The specific activity of **5** was 482 MBq/mmol.

REFERENCES

1. Meguro K., Aizawa M., Sohda T., Kawamatsu Y. and Nagaoka A.–
Chem. Pharm. Bull. **33**: 3787 (1985)
2. Bossert F. and Wehinger E.–Angew. Chem. Int. Ed. Eng. **20**:762 (1981)