Transformation of 1,4-Dihydropyridine Ring of Calcium Antagonist NZ-105 into Cyclohexenone Ring

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Received June 27, 1994; accepted September 26, 1994

On hydrolysis of the calcium antagonist, 2-(*N*-benzyl-*N*-phenylamino)ethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3-carboxylate hydrochloride ethanol (NZ-105 1·HCl·EtOH) in 35% hydrochloric acid, the 1,4-dihydropyridine ring was transformed to a cyclohexenone ring, affording the cyclohexenonephosphonates 2 and 3.

Key words calcium antagonist; 1,4-dihydropyridine; cyclohexenonephosphonate; ^{13}C-labeling; hydrolysis

A series of 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate derivatives show calcium antagonistic activity and are clinically useful vasodilators.[1] Recently a novel and structurally unique calcium antagonist, 2-(*N*-benzyl-*N*-phenylamino)ethyl 5-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3-carboxylate hydrochloride ethanol (NZ-105 **1**·HCl·EtOH)[2] was prepared, and its clinical evaluation has just been completed in Japan. In the development studies of NZ-105, the physical and chemical stability under various conditions, particularly in acidic media, was investigated. The present paper reports the hydrolytic transformation of the 1,4-dihydropyridine ring of NZ-105 into a cyclohexenone ring. The structures of the products, the cyclohexenonephosphonates **2** and **3**, were determined by chemical conversions and ^{13}C-labeling experiment.

Results and Discussion

During our studies on the stability of NZ-105 in acidic media, two cyclohexenonephosphonates **2** and **3** were obtained in 31% and 12% yields, respectively, when NZ-105 was treated with 35% hydrochloric acid. Compound **3** gave **2** quantitatively when treated with 1,3-dicyclohexylcarbodiimide (Chart 1).

Thus, these compounds were supposed to be the cyclic phosphonate **2** and its seco form **3**. However, it was difficult to determine whether they are the 4-methyl derivatives, **2-A** and **3-A**, or the 2-methyl isomers, **2-B** and **3-B**, only from the spectral data. In $CDCl_3$ solution (0.07—0.20 mol/l), **2** exists as a mixture of its keto and enol forms; the keto/enol ratio was 1/1, becoming 1/3—4 when the solution was left to stand for a week at room temperature. The transformation of **2** with diazomethane into the corresponding methyl enol ether was investigated. The oily product obtained was labile and gradually decomposed on standing at room temperature, giving the starting **2**. Methylenation of the cyclohexenonephosphonate **2** by the Horner–Emmons method afforded the expected methylenecyclohexenone **4** in 66% yield (Chart 2); it takes only the keto form.

In the ^{1}H-NMR spectrum of **4**, nuclear Overhauser effects (NOEs) were observed between methyl protons (H^4) and methylene protons (H^2 or H^3), and between H^4 and an olefinic proton (H^5), but not between H^4 and an *exo* methylene proton (H^6) (Fig. 1).

This fact indicates the structure of **4** to be **4-A**, and so that of **2** to be **2-A**. ^{13}C-Labeled NZ-105 (99 atom%), labeled at the 2-methyl group, was prepared from ^{13}C-acetyl chloride *via* **5** and **6** according to the reported method[3] and hydrolyzed, giving ^{13}C-containing cyclohexenonephosphonate **2**-^{13}C (Chart 3).

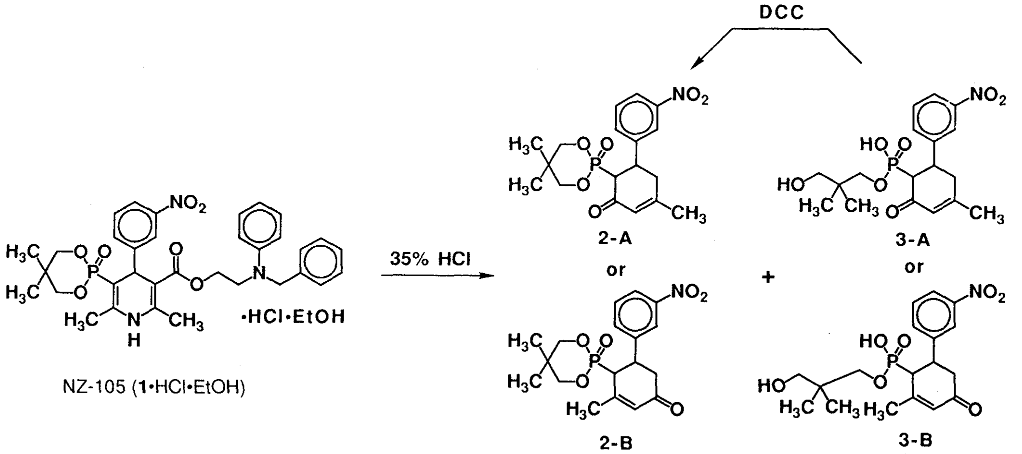

Chart 1

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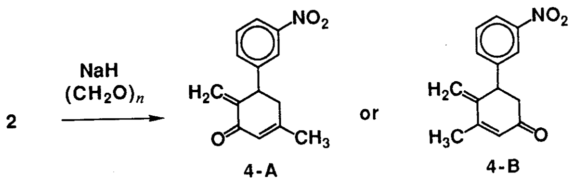

Chart 2

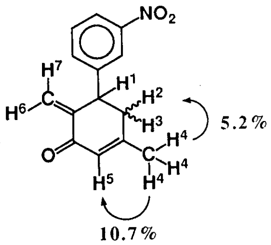

Fig. 1

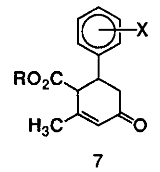

Fig. 2

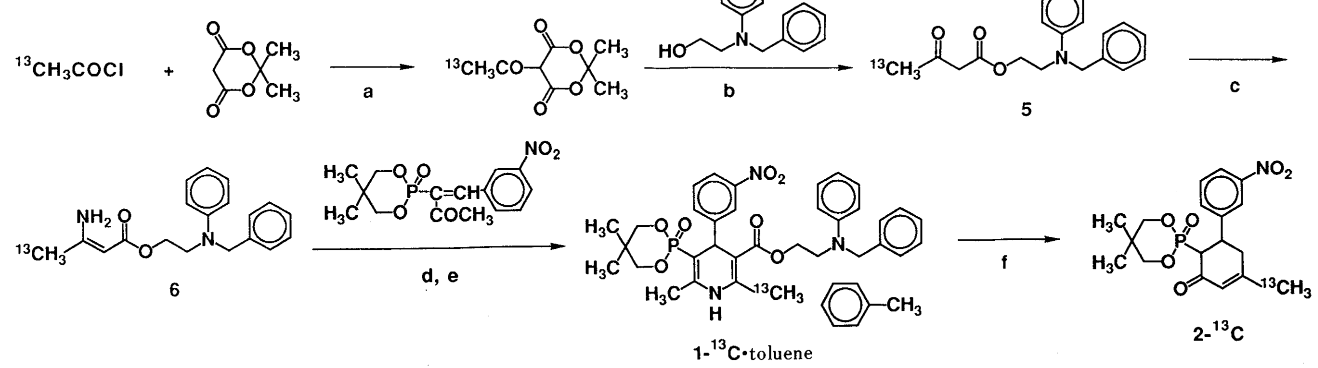

Chart 3

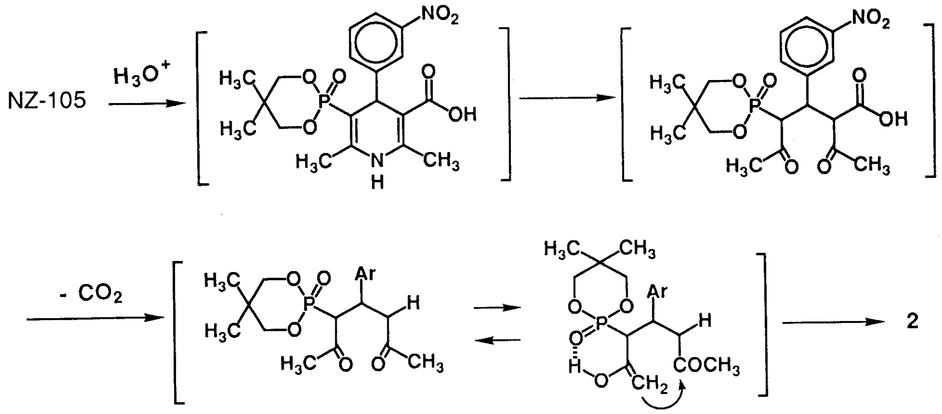

Chart 4

In the ^{1}H-NMR spectrum of **2**-^{13}C, two methyl groups ($\delta = 2.06$ and 2.12 ppm), assigned to the keto and the enol isomers, respectively, showed a large ^{13}C–H coupling constant ($J = 128$ Hz), while no olefinic proton showed a ^{13}C–H coupling constant. This result is consistent with the structure **2-A**, assigned above. Neither of the phosphonates **2-B** and **3-B** was detected in the hydrolysis products of NZ-105, though compounds **7**, which are the carboxylates of the corresponding phosphonates **2-B** and **3-B**, are known as hydrolysis products of 1,4-dihydropyridine-3,5-dicarboxylate derivatives (Fig. 2).[4-7]

The pathway of formation of **2** may be as illustrated in Chart 4. Hydrolysis of the ester function of NZ-105 gives the 1,4-dihydropyridine-3-carboxylic acid, the ring of which is cleaved to afford two acetyl groups. A decarboxylation of the β-ketocarboxylic acid intermediate is followed by specific cyclization to **2**. The hydrogen bonding between the enolic hydrogen and phosphoryl oxygen may be a factor in controlling the specific ring-closure to **2**.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on JEOL JMN-GSX 500 (500 MHz) and PMX 60 SI (60 MHz) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-DX 300. Column chromatography was carried out on silica gel (Merck, Type 60). TLC was performed on Merck Kieselgel 60F-245.

Hydrolysis of NZ-105 in 35% Hydrochloric Acid A solution of NZ-105 (14 g, 21 mmol) in 35% hydrochloric acid (50 ml) was heated under reflux for 1 h. After cooling, the reaction mixture was extracted with chloroform (50 ml × 1 and 20 ml × 3). The extract was dried (sodium sulfate) and concentrated to leave a residue, which was column-chromatographed. Elution with ethyl acetate afforded **2-A** (2.5 g, 31%, $Rf = 0.50$) and ethanol afforded **3-A** (1.0 g, 12%, $Rf = 0.50$).

6-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-3-methyl-5-(3-nitrophenyl)-2-cyclohexenone (2) 2-A Colorless crystals, mp 152—154 °C. *Anal.* Calcd for $C_{18}H_{22}NO_6P$: C, 56.99; H, 5.85; N, 3.69. Found: C, 56.72; H, 5.97; N, 3.61. ^{1}H-NMR ($CDCl_3$) δ: 0.86, 1.00, 2.06 (each s, CH_3), 1.08, 1.14, 2.12 (each s, CH_3), 2.35—4.35 (8H, m, $CH_2 \times 3$, Ar-CH, P-CH), 6.10 (1H, br s, CH=), 7.40—8.30 (4H, m, Ar-H). MS *m/z*: 379 (M^+), 229 ($O_2NC_6H_4$–C_6H_4O–CH_3), 151 ($(CH_3)_2C(CH_2O)_2$-PO).

Hydrogen 3-Hydroxy-2,2-dimethylpropyl 3-Methyl-5-(3-nitrophenyl)-2-cyclohexenone-6-phosphonate (3) 3-A Colorless oil. *Anal.* Calcd for $C_{18}H_{24}NO_7P$: C, 54.41; H, 6.09; N, 3.51. Found: C, 54.12; H, 6.33; N, 3.35. ^{1}H-NMR ($CDCl_3$) δ: 0.75—1.00 (6H, m, $CH_3 \times 2$), 2.03 (3H, br s, CH_3), 2.20—3.95 (8H, m, $CH_2 \times 3$, Ar-CH, P-CH), 6.00 (1H, br s, CH=), 7.20—8.30 (4H, m, Ar-H). MS *m/z*: 397 (M^+), 312 ($M^+ - OCHC(CH_3)_2CH_2$), 229 ($O_2NC_6H_4$–C_6H_4O–CH_3).

Conversion of 3 to 2 A solution of **3** (100 mg, 0.25 mmol) and 1,3-dicyclohexylcarbodiimide (400 mg, 1.9 mmol) in chloroform (2 ml) was allowed to stand at room temperature for 1 h. To this mixture, acetic acid (0.5 ml) and methanol (1 ml) were added. The whole was stirred at room temperature for 1 h, and the precipitates formed were filtered off. This filtrate was concentrated to give **2** (96 mg, 100%).

3-Methyl-6-methylene-5-(3-nitrophenyl)-2-cyclohexenone (4) A mixture of **2** (400 mg, 1.1 mmol) and sodium hydride (60 mg, 1.3 mmol, 50% oil dispersion) in benzene (20 ml) was allowed to stand at room temperature for 30 min. Paraformaldehyde (100 mg, 3.3 mmol) was added, and the whole was stirred at room temperature for 1 h. Water (5 ml) was added, and the mixture was acidified with 1 N hydrochloric acid and extracted with chloroform (50 ml × 1 and 20 ml × 3). The extract was dried (sodium sulfate) and concentrated to leave a residue which, on TLC developed with hexane–ethyl acetate (4 : 1), gave **3** (170 mg, 66%, *Rf* = 0.25). Colorless crystals, mp 107.5—108.0 °C. *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.99; H, 5.50; N, 5.93. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s, CH_3), 2.72 (1H, dd, $J = 17.4$, 6.3 Hz, H–CH), 2.86 (1H, dd, $J = 17.4$, 7.6 Hz, H–CH), 4.19 (1H, dd, $J = 7.6$, 6. Hz, CH), 4.93 (1H, s, =CH–H), 6.11 (1H, s, =CH–CO), 6.15 (1H, s, =CH–H), 7.52—7.62 (2H, m, Ar-H), 8.10—8.17 (2H, m, Ar-H). MS *m/z*: 243 (M^+), 226 ($M^+ - OH$), 215 ($M^+ - CO$).

2-(*N*-Benzyl-*N*-phenylamino)ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydro-2-[^{13}C]methyl-6-methyl-4-(3-nitrophenyl)pyridine-3-carboxylate (1-^{13}C) The previously reported method[2,3] was applied to the preparation of ^{13}C-labelled NZ-105 as follows.

1) A solution of [2-^{13}C]acetyl chloride (1.0 g, 12.6 mmol) in methylene chloride (5 ml) was added slowly to a stirred solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (1.8 g, 12.5 mmol) and pyridine (2.0 g, 25 mmol) in methylene chloride (20 ml) at 0 °C, and the mixture was stirred at room temperature for 1 h, then concentrated *in vacuo*. 2-(*N*-Benzyl)-*N*-phenylamino)ethanol (1.1 g, 4.8 mmol) and dioxane (20 ml) was added to the residue, and the mixture was heated under reflux for 2 h. After cooling, the solvent was evaporated off to leave a residue, which was subjected to column chromatography with hexane–ethyl acetate (4 : 1), giving **5** as a yellow oil (1.2 g, 31%, *Rf* = 0.33). Compound **5** was used without further purification.

2) A mixture of **5** (1.2 g, 3.8 mmol) and 10% ethanolic ammonia (10 ml) was stirred at room temperature for 16 h, and the reaction mixture was concentrated to leave a residue which was triturated with ethanol (10 ml), giving **6** as colorless crystals (0.80 g, 67%), mp 86.5—87.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (3H, d, $J = 12$, 6 Hz, $^{13}CH_3$), 3.61 (2H, t, $J = 6$ Hz, N–CH_2–C), 4.20 (2H, t, $J = 6$ Hz, O–CH_2–C), 4.42 (1H, d, $J = 4.5$ Hz, N–HC=C–CO), 4.53 (2H, s, CH_2-Ar), 6.50—7.30 (10H, m, Ar-H). MS *m/z*: 311 (M^+), 209 (CH_2=CH–N(C_6H_5)$CH_2C_6H_5$), 196 (CH_2–N(C_6H_5)$CH_2C_6H_5$CH), 91 ($C_6H_5CH_2$).

3) A mixture of **6** (0.70 g, 2.3 mmol) and 2-[1-acetyl-2-(3-nitrophenyl)ethenyl]-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan (0.76 g, 2.2 mmol) in isopropyl alcohol (15 ml) was heated under reflux for 2 h and the solvent was evaporated off to leave a residue which was triturated with toluene (5 ml), giving a 1 : 1 complex[8] (1.2 g, 74%) of **1**-^{13}C and toluene as yellow crystals, mp 152.0—153.0 °C. MS *m/z*: 632 (M^+), 209 (CH_2=CH–N(C_6H_5)$CH_2C_6H_5$), 196 (CH_2–N(C_6H_5)$CH_2C_6H_5$), 91 ($C_6H_5CH_2$). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, s, CH_3), 1.00 (3H, s, CH_3), 2.26 (3H, d, $J = 128$ Hz, $^{13}CH_3$–C=), 2.32 (3H, d, $J = 2.5$ Hz, CH_3–C=), 2.35 (3H, s, CH_3-Ar), 3.40—4.50 (8H, m, $CH_2 \times 4$), 4.35 (2H, s, CH_2-Ar), 4.90 (1H, d, $J = 11$ Hz, CH-Ar), 6.40—8.10 (15H, m, Ar-H and NH), 7.20 (5H, s, C_6H_5–CH_3).

Acknowledgement The authors are grateful to Dr. Shuntaro Mataka, Kyushu University, for valuable advice and discussions during this work.

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