Chem. Pharm. Bull. 26(5)1623—1626(1978)

UDC 547.787.1.04 : 546.15.02.131.04

Synthesis of Radioiodinated Analog of Oxazolidine-2,4-dione

Tadatoshi Yamaguchi, Ken-ichi Ichiki, Hisao Sone, Minoru Maeda, and Masaharu Kojima

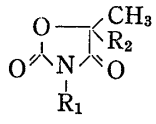
Faculty of Pharmaceutical Sciences, Kyushu University[1]

(Received October 22, 1977)

5-Iodomethyl-3,5-dimethyl-oxazolidine-2,4-dione-^{131}I (**6**) and 5-iodomethyl-5-methyl-oxazolidine-2,4-dione-^{131}I (**13**) were synthesized to evaluate their potential utility as pancreatic scanning agents.

Keywords——5-iodomethyl-3,5-dimethyl-oxazolidine-2,4-dione-^{131}I; 5-iodomethyl-5-methyl-oxazolidine-2,4-dione-^{131}I; PS-test; PS–DMO-test; pancreatic scanning agent

The pancreozymin-secretin test (PS-test) has been widely used as a clinically useful diagnostic tool for early detection of pancreas diseases.[2] Noda, *et al.* have recently found that the antiepileptic agent, 3,5,5-trimethyl-oxazolidine-2,4-dione (TMO) is converted by metabolic N-demethylation to 5,5-dimethyl-oxazolidine-2,4-dione (DMO), which is excreted into pancreatic juice in a high concentration after stimulation with secretine.[2] Moreover, the potential clinical application of DMO as a useful addition to the PS-test has been evaluated from the finding that pancreatic excretion of DMO depends on plasma DMO concentration and secretory volume.[2,3] On the other hand, despite the recent rapid advances in nuclear medicine, there is still no suitable radiopharmaceuticals available to aid in the diagnosis of pancreatic diseases except for selenomethionine-^{75}Se.[4] Thus the above information suggested that an appropriately radiolabeled analog of TMO or DMO might be the feature required for a pancreatic scanning and/or functional agent. Since none of the elements of TMO or DMO has a useful γ-emitting nuclide, it was necessary to introduce this feature into the molecule. Thus 5-iodomethyl-3,5-dimethyl- and 5-iodomethyl-5-methyl-oxazolidine-2,4-dione (**5** and **12**) were synthesized for radiolabeling with iodine-^{131}I.



1: $R_1=CH_3$, $R_2=H$
2: $R_1=CH_3$, $R_2=CH_2OH$
3: $R_1=CH_3$, $R_2=CH_2OSO_2-C_6H_4-CH_3$ (*p*)
4: $R_1=CH_3$, $R_2=CH_2OSO_2-C_6H_4-NO_2$ (*o*)
5: $R_1=CH_3$, $R_2=CH_2I$
6: $R_1=CH_3$, $R_2=CH_2-^{131}I$
10: $R_1=H$, $R_2=CH_2OH$
11: $R_1=H$, $R_2=CH_2OSO_2-C_6H_4-NO_2$ (*o*)
12: $R_1=H$, $R_2=CH_2I$
13: $R_1=H$, $R_2=CH_2-^{131}I$

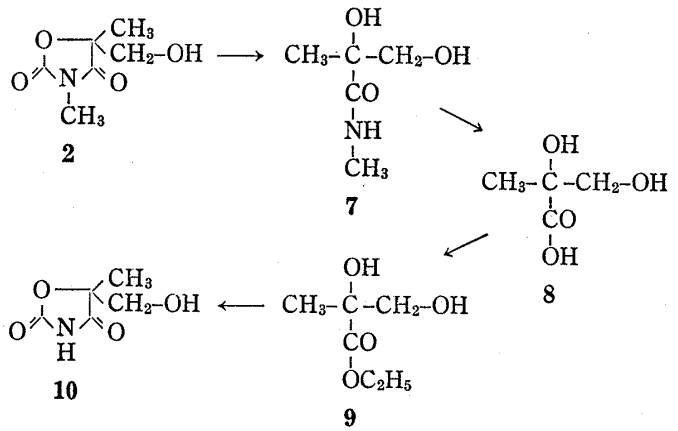


Chart 1

1) Location: *Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan.*
2) A. Noda and Y. Toda, *Igaku No Ayumi*, **85**, 577 (1973).
3) A. Noda, Y. Toda, T. Hayakawa, and S. Nakajima, *Am. J. Dig. Dis.*, **18**, 498 (1973); A. Noda, T. Hayakawa, S. Nakajima, T. Suzuki, and Y. Toda, *ibid.*, **20**, 1011 (1975); A. Noda, T. Hayakawa, I. Aoki, Y. Horiguchi, and Y. Toda, *ibid.*, **20**, 1019 (1975).
4) M. Blau and R.F. Manske, *J. Nucl. Med.*, **2**, 102 (1961); M. Blau and M.A. Beuder, *Radiology*, **78**, 974 (1962); D.L. Taben, J. Kearney, and A. Dolbow, *J. Nucl. Med.*, **6**, 726 (1965).

The synthetic approach to iodinated compounds (**5** and **12**) involved the nucleophilic displacement of the corresponding *o*-nitrobenzene sulfonates (**4** and **11**) with iodide. Attempts to iodinate the tosylate (**3**) were unsuccessful; the reaction with sodium iodide in refluxing acetone, acetonitrile, or DMF resulted in the recovery of the starting material. The required *o*-nitrobenzene sulfonate (**4**) was obtained in two steps from 3,5-dimethyl-oxazolidine-2,4-dione (**1**).[5] The *o*-nitrobenzene sulfonate (**4**) obtained thus reacted easily with sodium iodide in acetonitrile to give **5** in 93% yield. On the other hand, the suitable starting material for the successful synthesis of **12** appeared to be α,β-dihydroxyisobutyric acid (**8**). Although Powell and Glattfeld, *et al.* synthesized the acid (**8**) from 3-chloro-2-hydroxyisobutylic acid or 2,3-dihydroxyisobutyronitrile,[6] initial efforts were directed toward the conversion of the oxazolidine-2,4-dione (**2**) to **8**. The treatment of **2** with 5% NaOH underwent ring-opening to give N-methyl-α,β-dihydroxyisobutylamide (**7**). Subsequent esterification of **8** formed by heating of **7** with 10% HCl afforded **9**. Condensation of the ester (**9**) with urea according to Stoughton's procedure[7] gave 5-hydroxymethyl-5-methyl-oxazolidine-2,4-dione (**10**) in 31% yield. The NMR spectrum of **10** showed the great similarity of two proton signals due to the methylene at C_5 to that of **2**. The treatment of **10** with *o*-nitrobenzenesulfonyl chloride gave **11** which was readily converted to **12** by the action of sodium iodide in acetonitrile.

Radioiodine labeled compound (**6** and **13**) was obtained by isotope exchange with $Na^{131}I$ in DMF at 115—120° and in the molten state,[8] respectively. With the latter, the method consisted simply of melting **12** in the presence of $Na^{131}I$ in a test tube and, after cooling, extracting the product by TLC. Under this condition, approximately 100% exchange was usually achieved within 30 min.

The significant excretion of DMO-^{131}I (**13**) into the pancreatic juice was observed after secretin stimulation by intravenous administration to a dog of DMO-^{131}I (**13**).[9] This finding may imply the possibility of clinical usefulness of DMO-^{131}I (**13**) as a pancreatic functional agent. Other chemical approaches to design further radiopharmaceuticals are now under investigation.

Experimental

Melting points and boiling points are uncorrected. The infrared (IR) spectra were recorded with a JASCO IRA-1 spectrometer. The NMR spectra were obtained with a JNM PS-100 spectrometer with tetramethylsilane as internal reference. The thin-layer chromatography (TLC) was carried out on Silica gel $60F_{254}$ (0.5 mm layer, Merck). Column chromatography was carried out with Mallinckrodt Silica ARCC-4 (100 mesh). Chromatograms of radioiodinated compounds were scanned with a Aloka TRM-1B radiochromatogram scanner.

5-Hydroxymethyl-3,5-dimethyl-oxazolidine-2,4-dione (**2**)——A mixture of 3,5-dimethyl-oxazolidine-2,4-dione (**1**)[5] (495 mg), potassium carbonate (10 mg), and 37% formaldehyde solution (0.4 ml) was heated for 5 hr at 55°. After cooling, the mixture was diluted with water (1 ml) and extracted continuously with ether (50 ml) over 10 hr. The ether layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with chloroform to give a colorless syrup (500 mg, 88%). On standing, the syrup gradually crystallized to give colorless needles of **2**, mp 60°. *Anal.* Calcd. for $C_6H_7NO_4$: C, 45.29; H, 5.70; N, 8.35. Found: C, 44.91; H, 5.57; N, 8.35. IR ν_{max}^{Neat} cm^{-1}: 3460 (OH), 1830, 1750 (N–C=O). NMR ($CDCl_3$) δ: 1.46 (3H, s, C_5–CH_3), 2.84 (1H, b, OH), 3.05 (3H, s, N–CH_3), 3.79 (1H, d, J=11 Hz, CH_2OH), 3.89 (1H, d, J=11 Hz, CH_2OH).

5-Hydroxymethyl-3,5-dimethyl-oxazolidine-2,4-dione-5-*p*-toluene Sulfonate (**3**)——A mixture of **2** (1.10 g) and *p*-toluenesulfonyl chloride (2.2 g) in dry pyridine (10 ml) was allowed to stand overnight at room

5) M.A. Spielman, *J. Am. Chem. Soc.*, **66**, 1244 (1944).
6) J.E. Powell, H.R. Burkhold, and J.L. Farrell, *J. Chromatogr.*, **57**, 309 (1971); J.W.E. Glattfeld and L.P. Sherman, *J. Am. Chem. Soc.*, **47**, 1742 (1925).
7) R.W. Stoughton, *J. Am. Chem. Soc.*, **63**, 2376 (1941).
8) R. Ghanadian, S. Waters, M.L. Thakur, and G.D. Chisholm, *Int. J. appl. Radiat. Isotopes*, **26**, 343 (1975); H. Elias, E.H. Arnold, and G. Kloss, *ibid.*, **24**, 463 (1973).
9) Y. Oshiumi, K. Morita, I. Kamoi, C. Nakayama, I. Koga, K. Matsuura, M. Kojima, T. Yamaguchi, K. Ichiki, H. Sone, and M. Maeda, *Radioisotopes*, **26**, 469 (1977).

temperature, and worked up as usual to give **3** as colorless needles (1.34 g, 58%), mp 108°, after recrystallization from chloroform–*n*-hexane. *Anal.* Calcd. for $C_{12}H_{15}NO_6S$: C, 49.83; H, 4.83; N, 4.47. Found: C, 49.60; H, 4.92; N, 4.53. IR ν_{max}^{Nujol} cm^{-1}: 1330, 1320, 1190, 1180 (SO_2). NMR ($CDCl_3$) δ; 1.48 (3H, s, CH_3), 2.46 (3H, s, CH_3), 3.06 (3H, s, N–CH_3), 4.18 (1H, d, J=11 Hz, CH_2OSO_2), 4.25 (1H, d, J=11 Hz, CH_2OSO_2), 7.20—7.80 (4H, m, aromatic).

3,5-Dimethyl-5-*o*-nitrobenzenesulfonyloxymethyl-oxazolidine-2,4-dione (4)——A mixture of **2** (1.86 g) and *o*-nitrobenzenesulfonyl chloride (3.11 g) in dry pyridine was allowed to stand overnight at room temperature, and worked up as usual to give crystalline **4**. Recrystallization from chloroform–*n*-hexane gave colorless needles (1.19 g, 28%), mp 88°. *Anal.* Calcd. for $C_{12}H_{12}N_2O_8S$: C, 41.68; H, 3.51; N, 8.14. Found: C, 41.85; H, 3.40; N, 8.03. IR ν_{max}^{KBr} cm^{-1}: 1540, 1385 (NO_2), 1320, 1200 (SO_2). NMR ($CDCl_3$) δ: 1.50 (3H, s, C_5–CH_3), 3.10 (3H, s, N–CH_3), 4.50 (3H, s, CH_2), 7.80—8.20 (4H, m, aromatic).

5-Iodomethyl-3,5-dimethyl-oxazolidine-2,4-dione (5)——A solution of **4** (1.19 g) and sodium iodide (0.95 g) in acetonitrile (20 ml) was refluxed for 3 hr. The solvent was evaporated and the residue was diluted with H_2O (10 ml). The product was extracted with chloroform. Removal of the chloroform gave a colorless solid, which was recrystallized from chloroform–*n*-hexane to give **5** as colorless needles (926 mg, 93%), mp 54°. *Anal.* Calcd. for $C_6H_8INO_3$: C, 26.79; H, 3.00; N, 5.21. Found: C, 27.05; H, 3.06; N, 5.22. IR ν_{max}^{KBr} cm^{-1}: 1830, 1740 (N–C=O). NMR ($CDCl_3$) δ: 1.74 (3H, s, C_5–CH_3), 3.12 (3H, s, N–CH_3), 3.46 (1H, d, J=11 Hz, CH_2I), 3.56 (1H, d, J=11 Hz, CH_2I).

N-Methyl-α,β-dihydroxyisobutylamide (7)——A mixture of **2** (3.2 g) and 5% NaOH (20 ml) was stirred for 15 min at room temperature, and neutralized with 10% HCl. In order to remove the unchanged starting material the mixture was extracted with chloroform. The resulting aqueous layer was extracted with ethyl acetate. The ethyl acetate was removed and the residue was chromatographed on silica gel (chloroform) to give the amide (**7**) (2.4 g, 88%) as a colorless syrup. Further purification by sublimation (3.5 mmHg at 115°) for elemental analysis was performed. *Anal.* Calcd. for $C_5H_{11}NO_3$: C, 45.10; H, 8.32; N, 10.51. Found: C, 45.08; H, 8.21; N, 10.49. IR ν_{max}^{Neat} cm^{-1}: 3400 (OH), 3380 (NH), 1660, 1550 (N–C=O). NMR ($CDCl_3$) δ: 1.32 (3H, s, CH_3), 2.85 (3H, d, J=4 Hz, N–CH_3), 3.50 (1H, d, J=11 Hz, CH_2OH), 3.70 (2H, s, OH), 3.95 (1H, d, J=11 Hz, CH_2OH), 7.18 (1H, b, NH).

α,β-Dihydroxyisobutyric Acid (8)——A solution of **7** (3.0 g) in 10% HCl (17 ml) was refluxed for 9 hr and concentrated *in vacuo* to dryness. The residue was suspended in ethyl acetate and the undissolved solid was filtered. Evaporation of the filtrate left **8** (2.4 g, 88%) as syrup, which was used in the following reaction without further purification. IR ν_{max}^{Neat} cm^{-1}: 3410 (OH), 3000—2400 (COOH).

Ethyl α,β-Dihydroxyisobutyrate (9)——A solution of crude **8** (1.2 g) in ethanol (20 ml) and 35% HCl (0.05 ml) was refluxed for 10 hr. After removal of the solvent, distillation afforded the ester (**9**) as an oil, bp 118° (26 mmHg). Further purification by column chromatography (chloroform) gave 0.92 g of pure **9** as colorless syrup (62%). *Anal.* Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.71; H, 8.08. IR ν_{max}^{Neat} cm^{-1}: 3400 (OH), 1730, 1230 (O–C=O). NMR ($CDCl_3$) δ: 1.30 (3H, t, J=8 Hz, CH_3), 1.33 (3H, s, CH_3), 3.50 (1H, d, J=11 Hz, CH_2OH), 3.75 (1H, d, J=11 Hz, CH_2OH), 4.20 (2H, q, J=8 Hz, OCH_2).

5-Hydroxymethyl-5-methyl-oxazolidine-2,4-dione (10)——A mixture of the ester (**9**) (3.6 g), urea (1.46 g) and dry ethanol containing Na (0.56 g) was refluxed for 10 hr and concentrated to dryness. The residue was dissolved in ice-water (20 ml), neutralized with 35% HCl, and extracted with ether. The ether was removed and the residue was chromatographed on silica gel with chloroform–ethyl acetate (95: 5) to give **10** (1.1 g, 31%), mp 108°, after recrystallization from ethyl acetate–cyclohexane. *Anal.* Calcd. for $C_5H_7NO_4$: C, 41.83; H, 4.83; N, 9.65. Found: C, 41.61: H, 4.83; N, 9.54. IR ν_{max}^{Neat} cm^{-1}: 1840, 1740 (N–C=O). NMR [$(CD_3)_2CO$] δ: 1.42 (3H, s, C_5–CH_3), 3.20 (2H, b, NH and OH), 3.75 (1H, d, J=11 Hz, CH_2OH), 3.82 (1H, d, J=11 Hz, CH_2OH).

5-Methyl-5-*o*-nitrobenzenesulfonyloxymethyl-oxazolidine-2,4-dione (11)——A mixture of **10** (1.44 g), *o*-nitrobenzenesulfonyl chloride (532 mg) and dry pyridine (20 ml) was heated for 1 hr at 50°. Conventional treatment of the reaction mixture and recrystallization from ethyl acetate–cyclohexane gave **11** (770 mg, 23%) as colorless needles, mp 177°. *Anal.* Calcd. for $C_{11}H_{10}N_2O_8S$: C, 40.08; H, 3.05; N, 8.48. Found: C, 40.08; H, 3.01; N, 8.46. IR ν_{max}^{Nujol} cm^{-1}: 1540, 1350 (NO_2), 1310, 1190 (SO_2). NMR[$(CD_3)_2CO$] δ: 1.60 (3H, s, C_5–CH_3), 3.00 (1H, b, NH), 4.60 (2H, s, CH_2), 7.90—8.20 (4H, m, aromatic).

5-Iodomethyl-5-methyl-oxazolidine-2,4-dione (12)——A mixture of **11** (640 mg), sodium iodide (600 mg) and acetonitrile (20 ml) was refluxed for 7 hr and concentrated *in vacuo* to give a syrup which was eluted from silica gel to give crystalline **12**. Recrystallization from chloroform–cyclohexane gave colorless needles (254 mg, 51%), mp 58°. *Anal.* Calcd. for $C_6H_6INO_3$: C, 23.55; H, 2.37; N, 5.49. Found: C, 23.86; H, 2.52; N, 5.38. IR ν_{max}^{Neat} cm^{-1}; 1810, 1740 (N–C=O). NMR [$(CD_3)_2CO$] δ: 1.76 (3H, s, C_5–CH_3), 3.67 (1H, d, J=11 Hz, CH_2OH), 3.73 (1H, d, J=11 Hz, CH_2OH).

5-Iodomethyl-3,5-dimethyl-oxazolidine-2,4-dione-^{131}I (TMO-^{131}I) (6)——A solution of **5** (4.2 mg) and $Na^{131}I$ (4 mCi) in DMF(0.1 ml) was heated for 2 hr at 115—120°. The mixture was streaked on 0.5 mm thick silica gel glass plates and developed with chloroform. The separated **6** (*Rf* 0.53) was scraped and eluted with chloroform. Removal of the solvent afforded **6** (3 mg) with a specific activity of 0.5 mCi/mg. Chemical and radiochemical purity was established by TLC using chloroform as the eluent.

5-Iodomethyl-5-methyl-oxazolidine-2,4-dione-^{131}I (DMO-^{131}I) (13)——A methanol solution containing Na^{131}I (3 mCi) was placed in a test tube and evaporated to dryness at 100°. To the residue was added **12** (2 mg) and the mixture was heated for 30 min at 115—120°. After cooling, the product was dissolved in ethyl acetate (0.5 ml), which was streaked on 0.5 mm thick silica gel glass plates and developed with ethyl acetate. The separated DMO-^{131}I (*Rf* 0.62) was scraped and eluted with ethyl acetate. Removal of the solvent gave **13** (1.5 mg) with a specific activity of 1 mCi/mg. TLC as above gave a single spot coincident with the single radioactive area shown on a radiochromatoscannogram.

Acknowledgement The authors express their gratitude to the staffs of the Analytical Section of this Faculty for elemental analyses, IR, and NMR spectral measurement.