Quinazolin-2-ones Having a Spirohydantoin Ring. I. Synthesis of Spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,2′,5′-trione by Reaction of 1-Carbamoylisatin with Urea or Guanidine[1)]

Masafumi YAMAGISHI, Ken-ichi OZAKI, Hiroshi OHMIZU, Yoshihisa YAMADA, and Mamoru SUZUKI*

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 16–89, Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan.
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Reaction of 1-methylcarbamoylisatin (4) with urea in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave 4-hydroxy-3-methyl-4-ureidocarbonyl-1,2,3,4-tetrahydroquinazolin-2-one (5), which was easily cyclized with 10% HCl to afford a spirohydantoin derivative; 3-methyl-spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,2′,5′-trione (6). In a similar manner, 2′-imino-3-methyl-spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,5′-dione (8) was prepared by the reaction of 4 with guanidine, and 8 was further converted to the spirohydantoin compound 6 by treatment with sodium nitrite in acetic acid.

Keywords 1-methylcarbamoylisatin; urea; guanidine; intramolecular cyclization; 4-hydroxy-1,2,3,4-tetrahydroquinazolin-2-one; spirohydantoin; spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,2′,5′-trione

Several spirohydantoins exhibit aldose reductase inhibitory activity, and may have great therapeutic potential for treating the chronic complications of diabetes.[2)] In the course of our studies on quinazolines,[3)] we became interested in the synthesis and biological activities of quinazolin-2-ones having the spirohydantoin skeleton. In this paper, we report a synthesis of the spirohydantoin compound (**6**) by the reaction of 1-methylcarbamoylisatin (**4**) with urea or guanidine.

Regarding the synthesis of quinazolin-2-ones, Capuano *et al.*[4)] and Petersen *et al.*[5)] have already synthesized 4-hydroxy-1,2,3,4-tetrahydroquinazolin-2-ones (**3**) by the reaction of 1-carbamoylisatin (**1**) with nucleophiles such as alcohols or amines, as shown in Chart 1. Based on these interesting reactions, we envisaged that quinazolin-2-ones having a spirohydantoin ring would be readily synthesized by the nucleophilic ring opening reaction of 1-carbamoylisatin (**1**) with urea or guanidine, followed by the formation of the spirohydantoin skeleton through an intramolecular cyclization of the corresponding quinazolin-2-one compound (**3**).

We firstly attempted the reaction of 1-methylcarbamoylisatin (**4**)[4a)] with urea under heating in tetrahydrofuran (THF) or *N*,*N*-dimethylformamide. However, the expected reaction did not proceed and the starting material (**4**) was recovered. Then, we tried the reaction under basic conditions. In the presence of sodium hydride or potassium *tert*-butoxide, the elimination of the carbamoyl group took place to afford isatin as a sole product. When **4** was refluxed in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF, several products including 4-hydroxy-3-methyl-4-ureidocarbonyl-1,2,3,4-tetrahydroquinazolin-2-one (**5**) were observed on thin-layer chromatography (TLC), and **5** was isolated in 30% yield from the reaction mixture. This product showed absorption bands at 1710 and 1648 cm^{-1} based on carbonyl groups in the infrared (IR)

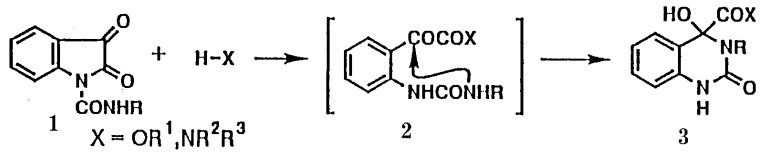

Chart 1

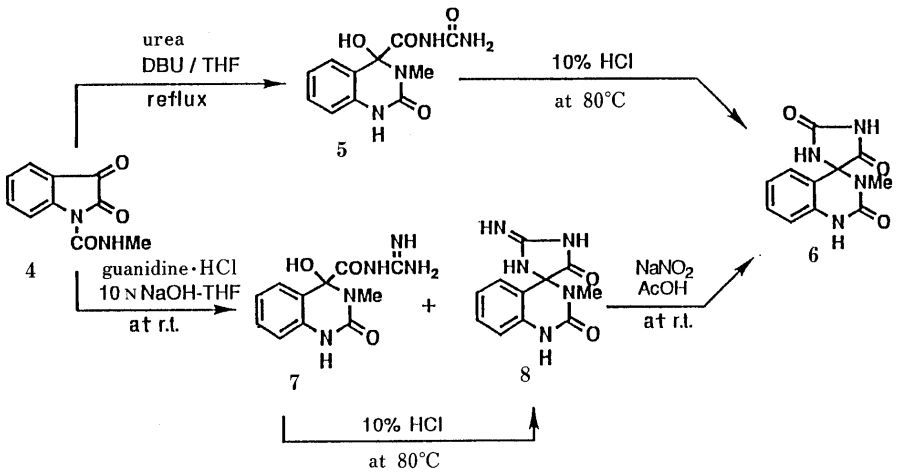

Chart 2

spectrum. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, a singlet signal at δ 2.74 due to a methyl group at the 3-position was exhibited. These spectroscopic results and the elemental analysis allowed us unequivocally to assign the structure of **5**. We assumed that **5** would be formed through an intramolecular cyclization of the oxalylurea compound **9a**, which was derived from **4** through the ring opening reaction induced by nucleophilic attack of urea on the 2-position, as shown by path A in Chart 3. On the other hand, the hydantoin compound **10a**, which might also be formed by the attack of the ureido group on the oxalyl carbonyl group of **9a** (path B in Chart 3), was not isolated in this reaction.

Then, we attempted an intramolecular cyclization of the quinazolin-2-one compound **5** to obtain the desired spirohydantoin compound (**6**).[6] The expected cyclization reaction took place under reflux in 1,2-dichlorobenzene to afford 3-methyl-spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,2′,5′-trione (**6**) in 57% yield, although the reaction did not proceed under reflux in benzene or toluene for 17 h. Moreover, **5** was readily cyclized to afford the spirohydantoin compound **6** in 85% yield by heating in 10% hydrochloric acid (HCl) at 80 °C for 3 h. The structure of the product **6** was elucidated by means of the following spectroscopic and elemental analyses. It showed absorption bands at 1780, 1735 and 1680 cm^{-1} due to three carbonyl groups in the IR spectrum. The ^{1}H-NMR spectrum of **6** exhibited a singlet signal based on a methyl group at the 3-position at δ 2.80 and three singlet signals based on three NH protons at δ 9.05, 9.91 and 11.31, respectively. Furthermore, in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **6**, three carbonyl carbon signals at δ 151.08, 155.29 and 172.97, and one quaternary sp^3 carbon signal at δ 78.09 were observed.

Thus, we found a new synthetic method for the spirohydantoin compound (**6**) in two steps from **4**. However, the yield in the first stage was not satisfactory. We presumed that this was due to the poor nucleophilicity of urea. Therefore, we examined the reaction of **4** with guanidine, having stronger nucleophilicity than urea. When **4** was treated with guanidine hydrochloride in the presence of 10 N sodium hydroxide (NaOH) in THF at room temperature, two products were observed on TLC, and they were isolated by column chromatography on silica gel. One of them, obtained in 32% yield, was assigned as 2′-imino-3-methyl-spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,5′-dione (**8**) on the basis of spectroscopic and elemental analyses. The ^{1}H-NMR spectrum of **8** exhibited a singlet signal due to a methyl group at the 3-position at δ 2.63 and four singlet signals due to four NH protons at δ 7.41, 7.90, 8.63 and 9.56, respectively. In the ^{13}C-NMR spectrum, two carbonyl carbon signals and one imino carbon signal at δ 151.63, 170.90 and 185.28, and one quaternary sp^3 carbon signal at δ 79.95 were observed. On the other hand, the other product, which was not sufficiently purified, showed the quasi-molecular ion peak at m/z 264 ($M^+ + 1$) in the liquid secondary ion spectrum (liquid SIMS), and exhibited a singlet signal at δ 2.68 due to a methyl group at the 3-position in the ^{1}H-NMR spectrum. Furthermore, this compound was converted to the spiro compound **8** by treatment with 10% HCl. Based on these results, we speculated that this product was 4-guanidinocarbonyl-4-hydroxy-3-methyl-1,2,3,4-tetrahydroquinazolin-2-one (**7**), which would be formed through an intramolecular cyclization of **9b** as shown by path A in Chart 3. When the reaction mixture containing **7** and **8** was treated with 10% HCl, **8** was obtained from **4** in 68% overall yield. Compound **10b** was not detected in this reaction, and this result was similar to that observed in the reaction of **4** with urea. Finally, **8** was successfully converted to the spirohydantoin compound **6** by treatment with sodium nitrite in acetic acid, in 33% yield.

A possible mechanism of the cyclization of **5** or **7** with acid is depicted in Chart 4. The acid-catalyzed elimination of water triggered by protonation of the hydroxy group at the 4-position of **5** or **7** would form the iminium compound **12** or the azaquinodimethane compound **13**,[7] which might be spontaneously converted to **6** or **8** by intramolecular cyclization.

Thus, a new synthetic method for quinazolin-2-ones having a spirohydantoin ring was established. Investigation of the scope and limitations of this new method, and its application to the synthesis of various quinazolin-2-ones having a spirohydantoin ring are under way.

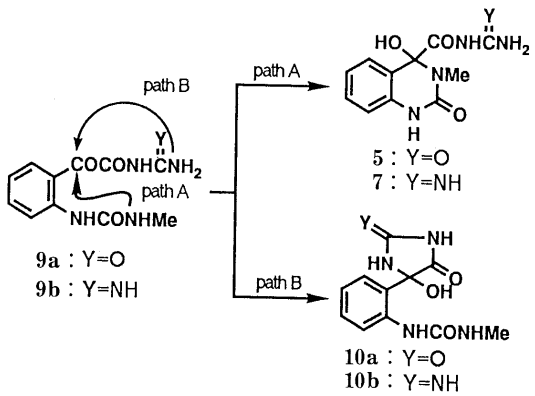

Chart 3

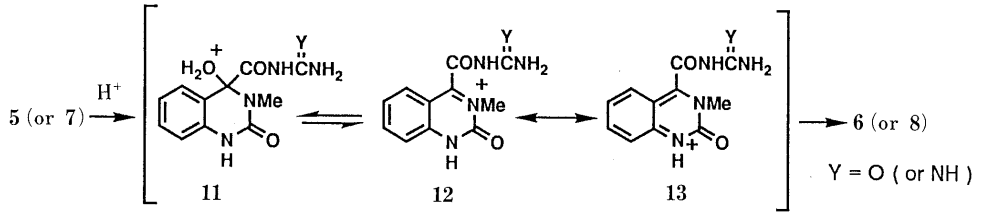

Chart 4

Experimental

All melting points were measured by the use of a Yamato MP-21 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-420 spectrometer. The ultraviolet (UV) spectra were recorded on a Shimadzu UV-250 spectrophotometer. ^{1}H-NMR spectra were obtained using a Hitachi R-40 (90 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were

determined on a Bruker AC-200 instrument (200 MHz) using TMS as an internal reference. Mass spectra (MS) were taken with a Hitachi M-60 mass spectrometer at an ionizing potential of 30 eV. The liquid SIMS were taken with a Hitachi M-2000A double-focusing mass spectrometer. The primary ion was Xe^+ and the accelerating voltages of primary and secondary ions were 6 and 3 eV, respectively. Column chromatography was carried out with Kieselgel 60 (230—400 mesh, E. Merck) and analytical TLC was performed with precoated Kieselgel $60F_{254}$ plates (0.25 mm thickness, E. Merck).

4-Hydroxy-3-methyl-4-ureidocarbonyl-1,2,3,4-tetrahydroquinazolin-2-one (5) Urea (4.5 g, 75 mmol) was added to a solution of **4** (10.2 g, 50 mmol) and DBU (0.3 g, 2 mmol) in THF (100 ml), and the mixture was refluxed for 10 h. After cooling, the resulting crystals were filtered off, washed with water and methanol, and recrystallized from dimethyl sulfoxide (DMSO)–ethanol to give **5** (4.0 g, 30%), mp >280 °C. IR (Nujol): 3380, 3190, 3110, 1710, 1648, 1602 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.74 (3H, s, CH_3), 6.64—7.96 (7H, m, ArH×4, NH×2, and OH), 9.50 (1H, s, NH), 9.68 (1H, s, NH). MS *m/z*: 246 ($M^+ - H_2O$). *Anal.* Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.60; H, 4.69; N, 21.44.

3-Methyl-spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,2′,5′-trione (6) (a) From **5**: A suspension of **5** (1.5 g, 5.7 mmol) in 1,2-dichlorobenzene (30 ml) was refluxed for 1.5 h. After cooling, the resulting crystals were filtered off and recrystallized from DMSO to give **6** (0.8 g, 57%), mp >280 °C. IR (Nujol): 3300, 3120, 3080, 1780, 1735, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.80 (3H, s, CH_3), 6.70—7.50 (4H, m, ArH×4), 9.05 (1H, s, NH), 9.91 (1H, s, NH), 11.31 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 27.64 (3-CH_3), 78.09 (C-4), 114.10 (C-8), 115.73 (C-4a), 121.87 (C-6), 125.20 (C-5), 130.39 (C-7), 136.54 (C-8a), 151.08 (C-2), 155.29 (C-2′), 172.97 (C-5′). UV $\lambda_{max}^{methanol}$ nm (log ε): 240 (4.07), 287 (3.30). MS *m/z*: 246 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.76. Found: C, 53.42; H, 3.99; N, 22.51.

(b) From **5**: A suspension of **5** (2.0 g, 7.6 mmol) in 10% HCl (20 ml) was heated at 80 °C for 3 h. After cooling, the resulting crystals were filtered off, washed with water, and recrystallized from DMSO to give **6** (1.58 g, 85%), mp >280 °C.

(c) From **8**: A suspension of sodium nitrite (52 mg, 0.75 mmol) in water (1 ml) was added dropwise to a solution of **8** (123 mg, 0.48 mmol) in acetic acid (1 ml)–water (2 ml) at 25 °C. The mixture was stirred at the same temperature for 1 h, and concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$–methanol (7:3) as an eluent to give **6** (39 mg, 33%), mp >280 °C. The product **6** obtained by method (b) or (c) was identical with the sample prepared by method (a) in terms of the IR and ^{1}H-NMR spectra.

Reaction of 1-Methylcarbamoylisatin (4) with Guanidine A 10 N NaOH solution (0.6 ml) was added to a suspension of guanidine hydrochloride (0.57 g, 6 mmol) in THF (5 ml), and the mixture was stirred at room temperature for 5 min. Then, a solution of **4** (1.02 g, 5 mmol) in THF (15 ml) was added and stirring was continued at room temperature for 4 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue was chromatographed on silica gel using $CHCl_3$–methanol (7:3) as an eluent. The first fraction gave **8** (0.41 g, 32%), mp 257—259 °C. IR (Nujol): 3250, 1710 (sh), 1670, 1660, 1615 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.63 (3H, s, CH_3), 6.60—6.82 (2H, m, ArH×2), 6.85—7.20 (2H, m, ArH×2), 7.41 (1H, s, NH), 7.90 (1H, s, NH), 8.63 (1H, s, NH), 9.56 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 27.75 (3-CH_3), 79.95 (C-4), 113.65 (C-8), 117.67 (C-4a), 121.35 (C-6), 125.03 (C-5), 129.36 (C-7), 136.73 (C-8a), 151.63, 170.90, 185.28 (C-2, C-2′, and C-5′). UV $\lambda_{max}^{methanol}$ nm (log ε): 240 (4.03), 287 (3.07). MS *m/z*: 245 (M^+). *Anal.* Calcd for $C_{11}H_{11}N_5O_2 \cdot 1/2H_2O$: C, 51.96; H, 4.76; N, 27.55. Found: C, 52.19; H, 4.53; N, 27.26. The second fraction gave **7** (0.64 g, 48%). mp 199 °C (dec.). IR (Nujol): 3350, 3200, 1670, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.68 (3H, s, CH_3), 6.56—6.83 (2H, m, ArH×2), 6.88—7.22 (2H, m, ArH×2), 7.3—7.65 (3H, m, NH×2 and OH), 9.32 (1H, br, NH). Liquid SIMS *m/z*: 264 ($M^+ + 1$).

2′-Imino-3-methyl-spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,5′-dione (8) (a) From **4**: A 10 N NaOH solution (0.6 ml) was added to a suspension of guanidine hydrochloride (0.57 g, 6 mmol) in THF (5 ml), and the mixture was stirred at room temperature for 5 min. Then, a solution of **4** (1.02 g, 5 mmol) in THF (15 ml) was added and stirring was continued at room temperature for 4 h. The reaction mixture was concentrated to dryness under reduced pressure and 10% HCl (10 ml) was added to the residue, then the mixture was heated on a steam bath for 1 h. After cooling, the resulting crystals were filtered off, washed with water and ethanol, and recrystallized from DMSO–water to give **8** (0.86 g, 68%), mp 258—259 °C. This compound was identical with **8** obtained by the method described above as judged from the IR and ^{1}H-NMR spectra.

(b) From **7**: A suspension of unpurified **7** (50 mg, 0.2 mmol) in 10% HCl was heated on a steam bath for 1 h. After cooling, the resulting crystals were filtered off to give **8** (12 mg, 25%). This product was identical with authentic **8** on TLC analysis.

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References and Notes

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5) S. Petersen, H. Heitzer, and L. Born, *Justus Liebigs Ann. Chem.*, **12**, 2003 (1974).
6) Capuano *et al.* reported that the reaction of 4-ethoxycarbonyl-1,2,3,4-tetrahydroquinazolin-2-ones with isocyanates gave the corresponding 1′,3-disubstituted, 1′,3,3′-trisubstituted, or 1,1′,3,3′-tetrasubstituted spiro[1,2,3,4-tetrahydroquinazoline-4,4′-imidazolidine]-2,2′,5′-trione.[4b,c] However, quinazolin-2-ones having an unsubstituted hydantoin ring have not been reported.
7) W. Metlesics, G. Silverman, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **31**, 1007 (1966).