Quinazolin-2-ones Having a Spirohydantoin Ring. II. Synthesis of Several Spiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-triones *via* 5-Hydroxyhydantoin Derivatives[1,2]

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Reaction of 1-ethoxycarbonylisatin (1b) with urea gave 5-(2-ethoxycarbonylaminophenyl)-5-hydroxyhydantoin (4b) in a good yield. Treatment of 4b with several amines directly gave the corresponding spiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione derivatives (7a—d) in moderate yields. 3-Unsubstituted and 3-methylspiroquinazolin-2-one derivatives 7a, b were also synthesized from 5-ethoxy and 5-ethylthiohydantoins 5a, d, which in turn were easily obtained by the reaction of either ethanol or ethylmercaptan with 4b in the presence of a catalytic amount of sulfuric acid.

Keywords 1-ethoxycarbonylisatin; urea; 5-(2-ethoxycarbonylaminophenyl)-5-hydroxyhydantoin; spirohydantoin; spiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione; spiroquinazolin-2-one

Several spirohydantoins which inhibit the enzyme aldose reductase are of potential value in the therapy of diabetic complications.[3–6] In connection with our interest in this field, we have studied the syntheses of quinazolin-2-ones having such a spirohydantoin ring.

In the previous paper,[1] we reported a new synthetic method for 3′-methylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (**7b**) which involves the reaction of 1-methylcarbamoylisatin (**1a**) with urea followed by cyclization of resulting 3,4-dihydro-4-hydroxy-3-methyl-4-ureidocarbonyl-2(1*H*)-quinazolinone (**3**) with hydrochloric acid (HCl). We proposed the following mechanism for the formation of the key intermediate **3**: the ring opening of **1a** with urea yields the oxalylurea **2** (X=NHMe),[7] in which the amino group of the carbamoylamino residue attacks one of the carbonyl groups of the oxalylurea group through path A in Chart 1. Meanwhile, the hydantoin derivative **4a** which would be formed from **2** (X=NHMe) through path B was not obtained in this reaction. We then examined the reaction of urea with 1-alkoxycarbonylisatin, not including a nucleophilic moiety instead of the carbamoyl group, in the expectation of finding an alternative route to the spiroquinazolin-2-ones **7** through path B. In this paper, we describe the synthesis of the hydantoins **4** (X=OR), and their transformation to the spiroquinazolin-2-ones **7**.

On treatment of 1-ethoxycarbonylisatin (**1b**)[8] with urea under reflux in tetrahydrofuran (THF) for 15 h, the desired 5-hydroxyhydantoin **4b** was obtained in one step in 81% yield. The structural assignment of the product **4b** was based on the following spectroscopic and elemental analyses. The infrared (IR) spectrum of **4b** showed absorption bands at 1780, 1725, and 1690 cm^{-1} due to three carbonyl groups. In the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **4b**, three carbonyl carbon signals appeared at δ 153.10, 155.39 and 174.86, and one quaternary sp^3 carbon signal appeared at δ 86.38. In a similar manner, **4c** was obtained from **1c** and urea in 75% yield. Considering the fact that the 1-methylcarbamoylisatin (**1a**) did not react with urea under these conditions,[1] the carbonyl group at the 2-position of **1b** appears to be more reactive than that of **1a**.

We then attempted the cyclization of the resulting 5-hydroxyhydantoins **4b** and **4c** with several amines to convert them into the spiroquinazolin-2-ones **7**. When **4b** was heated with methylamine in a sealed tube at 120 °C, the desired 3′-methylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (**7b**)[1] was obtained in 41% yield. Alternatively, compound **7b** was obtained by refluxing **4b** with methylamine in toluene–ethanol for 4 h. In the case of **4c**, however, the yield of **7b** was low.

In a similar manner, the reactions of **4b** with ammonia, hydrazine, and hydroxylamine gave the corresponding spiroquinazolin-2-ones **7a**, **c**, **d** as summarized in Table I. However, treatment of **4b** with benzylamine gave a complex mixture and the expected 3-benzylspiroquinazolin-2-one derivative was not isolated. A possible mechanistic interpretation for the formation of **7** is based on the assumption that **4b** is initially converted into the acyliminium ion

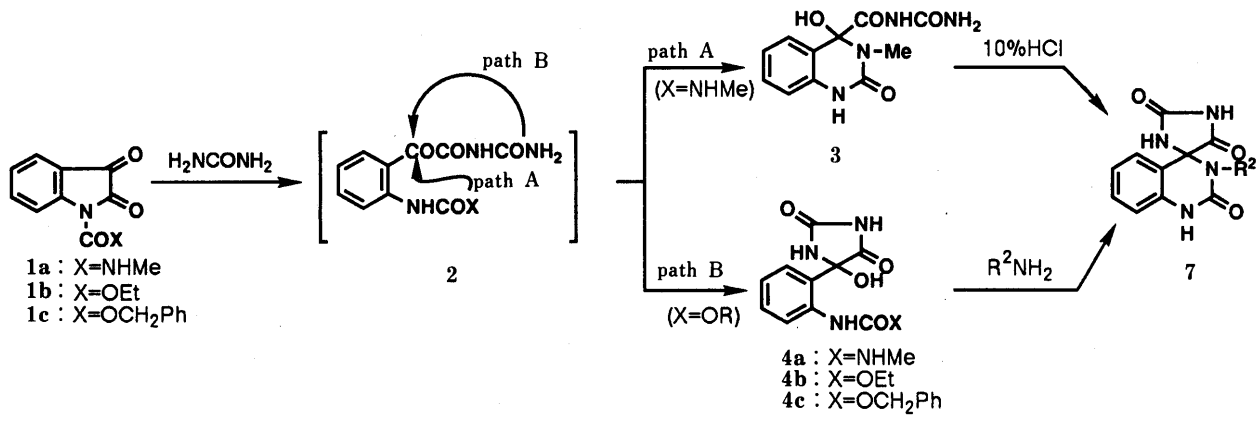


Chart 1

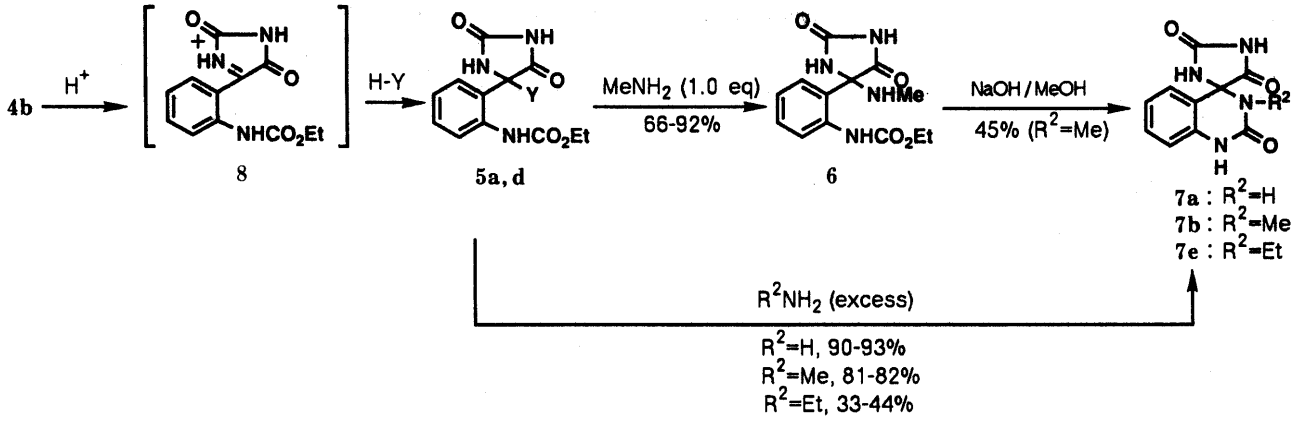
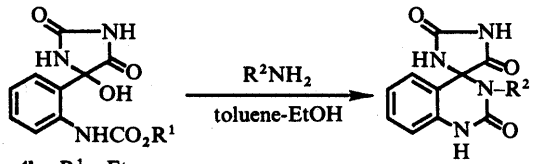


Chart 2

TABLE I. Reactions of 5-Hydroxyhydantoins **4** with Amines



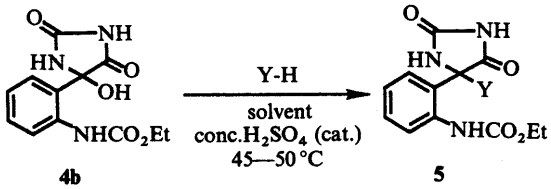
4b: R^1=Et
4c: R^1=CH_2Ph

7

Run	R^1	R^2	Method	Product	Isolated yield (%)
1	Et	H	A	7a	59
2	Et	Me	A	7b	41
3	Et	Me	B	7b	37
4	CH_2Ph	Me	B	7b	17
5	Et	NH_2	B	7c	57
6	Et	OH	B	7d	15

A: in a sealed tube at 120 °C for 4 h. B: reflux for 4 h.

TABLE II. Replacement of the 5-Hydroxy Group of **4b** with an Alkoxy or Alkylthio Group



4b **5**

Run	Y	Solvent	Time (h)	Product	Isolated yield (%)
1	EtO	EtOH[a]	5	5a	0
2	EtO	EtOH	1	5a	77
3	iso-PrO	iso-PrOH	2	5b	85
4	$PhCH_2O$	THF[b]	15	5c	90
5	EtS	THF[b]	3	5d	96
6	$PhCH_2S$	THF[b]	5	5e	90

a) No addition of concentrated H_2SO_4. *b*) Y-H (1.2—3.0 eq).

intermediate **8**. This step is followed by attack of the amines to give the 5-amino derivatives, which then undergo cyclization to yield **7**. If this mechanism is correct, it is expected that the replacement of the 5-hydroxy group of the hydantoins **4** (X = OR) by more effective leaving groups, such as 5-alkoxy or 5-alkylthio groups, may lead to an improvement in the yields of **7**. When **4b** was heated in ethanol for 17 h, no reaction proceeded and the starting material **4b** was recovered. However, in the presence of a catalytic amount of sulfuric acid or HCl,[9] the expected reaction took place to give **5a** in a good yield. In a similar way, **4b** was treated with various alcohols and mercaptans in the presence of a catalytic amount of sulfuric acid at 45 °C to give the corresponding 5-alkoxy and 5-alkylthiohydantoins **5b—e** in good yields. These results are summarized in Table II.

When the resulting 5-ethoxy- and 5-ethylthiohydantoins **5a, d** were treated with one equivalent of methylamine at 45 °C, the exchange of the substituent at the 5-position proceeded to afford 5-methylaminohydantoin **6** in good yields as shown in Chart 2. Compound **6** was successfully cyclized to the desired spiroquinazolin-2-one **7b** by treatment with sodium hydroxide (NaOH) in methanol. Interestingly, treatment of 5-ethoxy- or 5-ethylthiohydantoins **5a, d** with an excess of ammonia at 45 °C gave directly the desired 3-unsubstituted spiroquinazolin-2-one **7a** in a high yield. Being encouraged by this result, we then examined the reaction of **5a, d** with other amines. Thus, the reaction of **5a** or **5d** with methylamine gave the desired 3-methylspiroquinazolin-2-one **7b** in a high yield. In the case of ethylamine, 3-ethylspiroquinazolin-2-one **7e** was obtained in 33—44% yield. In contrast, the reaction with benzylamine did not proceed, and the desired 3-benzylspiroquinazolin-2-one derivative was not isolated.

In summary, we have found a facile and practical synthetic method for 3-unsubstituted or various 3-substituted quinazolin-2-ones having a spirohydantoin ring *via* 5-substituted hydantoin derivatives which can be readily derived from 1-alkoxycarbonylisatin with urea. However, this method would be limited to the synthesis of the spiroquinazolin-2-ones having relatively less bulky groups at the 3-position for steric reasons. Further attempts to develop versatile synthetic methods for the spiroquinazolin-2-ones and the assay of the biological activities of the compounds thus obtained are in progress.

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 proton nuclear magnetic resonance (^{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. Column chromatography was carried out with Kieselgel 60 (230—400 mesh, E. Merck) and analytical thin-layer chromatography (TLC) was performed with precoated Kieselgel $60F_{254}$ plates (0.25 mm thickness, E. Merck).

Material 1-Ethoxycarbonylisatin (**1b**) was prepared from isatin according to the reported procedure.[8]

1-Benzyloxycarbonylisatin (1c) Benzyloxycarbonyl chloride (8.19 g, 48 mmol) was added dropwise to a suspension of isatin (5.88 g, 40 mmol) and triethylamine (4.86 g, 48 mmol) in THF (60 ml) at 0 °C and the mixture was stirred at the same temperature for 30 min, then concentrated under reduced pressure. Water was added to the residue and the resulting crystals were collected, washed with water, and recrystallized from *N,N*-dimethylformamide (DMF) to give **1c** (9.56 g, 85%), mp 153—154 °C. IR (Nujol): 1795, 1785, 1740 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.46 (2H, s, CH_2Ar), 7.33—7.55 (6H, m, ArH × 6), 7.70—7.81 (2H, m, ArH × 2), 8.00 (1H, d, J = 8 Hz, ArH). MS *m/z*: 281 (M^+). *Anal.* Calcd for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.56; H, 4.07; N, 4.75.

5-(2-Ethoxycarbonylaminophenyl)-5-hydroxyimidazolidine-2,4-dione (4b) A suspension of **1b** (2.79 g, 12.7 mmol) and urea (1.15 g, 19.1 mmol) in THF (20 ml) was heated under reflux for 17 h. After cooling, the mixture was washed with water, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel using $CHCl_3$–methanol (9:1) as an eluent to give **4b** (2.88 g, 81%), mp 169—170 °C (dec.) (from AcOEt–*n*-hexane). IR (Nujol): 3300, 3200, 1780, 1725, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 4.03 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$), 6.8—7.35 (3H, m, ArH × 3), 7.70—7.90 (2H, m, ArH and OH), 8.90 (1H, s, NH), 9.10 (1H, s, NH), 10.70 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 14.40 ($CH_2\underline{C}H_3$), 60.35 ($\underline{C}H_2CH_3$), 86.38 (C-5), 121.13 (C-3′), 122.51 (C-5′), 125.93 (C-1′), 126.54 (C-6′), 129.62 (C-4′), 137.67 (C-2′), 153.10, 155.39, 174.86 (CO × 3). *Anal.* Calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.90; H, 4.97; N, 14.86.

5-(2-Benzyloxycarbonylaminophenyl)-5-hydroxyimidazolidine-2,4-dione (4c) This compound was synthesized from **1c** (5.0 g, 17.8 mmol) in the same manner as described for **4b**. Yield, 4.55 g (75%), mp 199—200 °C (dec.) (from AcOEt–*n*-hexane). IR (Nujol): 3300, 3230, 1790, 1730, 1705 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.17 (2H, s, CH_2Ar), 7.05—7.13 (1H, m, ArH), 7.31—7.44 (7H, m, ArH × 7), 7.98—8.04 (2H, m, ArH and OH), 9.16 (1H, s, NH), 9.45 (1H, s, NH), 10.97 (1H, s, NH). *Anal.* Calcd for $C_{17}H_{15}N_3O_5$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.52; H, 4.39; N, 11.99.

5-Ethoxy-5-(2-ethoxycarbonylaminophenyl)imidazolidine-2,4-dione (5a) Concentrated sulfuric acid (1.4 g) was added to a suspension of **4b** (27.9 g, 0.1 mol) in ethanol (100 ml) and the mixture was stirred at 45 °C for 1 h. After cooling, the resulting crystals were collected, washed with ethanol, and recrystallized from ethanol to give **5a** (23.6 g, 77%), mp 177—179 °C (dec.). IR (Nujol): 3400, 3210, 3110, 3080, 1790, 1740, 1720 cm^{-1}. MS *m/z*: 307 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 1.23 (3H, t, J = 7 Hz, $CO_2CH_2\underline{CH_3}$), 3.44 (2H, q, J = 7 Hz, OCH_2), 4.14 (2H, q, J = 7 Hz, CO_2CH_2), 7.00—8.00 (4H, m, ArH × 4), 9.03 (1H, s, NH), 9.41 (1H, s, NH), 11.38 (1H, s, NH). *Anal.* Calcd for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.68. Found: C, 54.66; H, 5.57; N, 13.72.

5-(2-Ethoxycarbonylaminophenyl)-5-isopropyloxyimidazolidine-2,4-dione (5b) This compound was synthesized from **4b** (0.56 g, 2 mmol) in isopropanol (10 ml) by a similar procedure to that described for **5a**. Yield, 0.55 g (85%), mp 217—218 °C (dec.) (from isopropanol–*n*-hexane). IR (Nujol): 3350, 3150, 3050, 1790, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.86—1.28 (9H, m, CH_3 × 3), 3.73—3.85 [1H, m, $C\underline{H}(CH_3)_2$], 4.05—4.21 (2H, m, CO_2CH_2), 7.08—7.16 (1H, m, ArH), 7.33—7.56 (2H, m, ArH × 2), 7.88—7.98 (1H, m, ArH), 9.13 (1H, s, NH), 9.41 (1H, s, NH), 11.34 (1H, s, NH). MS *m/z*: 321 (M^+). *Anal.* Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.95; N, 13.08. Found: C, 55.80; H, 5.95; N, 13.08.

5-Benzyloxy-5-(2-ethoxycarbonylaminophenyl)imidazolidine-2,4-dione (5c) This compound was synthesized from **4b** (0.98 g, 3.5 mmol) and benzyl alcohol (1.07 g, 10.3 mmol) in THF (5 ml) by a similar procedure to that described for **5a**. Yield, 1.16 g (90%), mp 182—183 °C (dec.) (from methanol–water). IR (Nujol): 3150, 3070, 1780, 1730, 1705 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 4.07 (2H, q, J = 7 Hz, OCH_2), 4.43 (2H, s, CH_2Ar), 7.13—7.48 (8H, m, ArH × 8), 7.89—7.93 (1H, m, ArH), 9.10 (1H, s, NH), 9.61 (1H, s, NH), 11.49 (1H, s, NH). *Anal.* Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.86; H, 5.04; N, 11.47.

5-(2-Ethoxycarbonylaminophenyl)-5-ethylthioimidazolidine-2,4-dione (5d) This compound was synthesized from **4b** (1.4 g, 5 mmol) and ethanethiol (1.1 ml, 15 mmol) in THF (10 ml) by a similar procedure to that described for **5a**. Yield, 1.56 g (96%), mp 174—175 °C (dec.) (from AcOEt–*n*-hexane). IR (Nujol): 3280, 3150, 3050, 1775, 1740, 1705 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t, J = 7.5 Hz, $SCH_2\underline{CH_3}$), 1.23 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 2.42—2.64 (2H, m, SCH_2), 4.13 (2H, q, J = 7 Hz, OCH_2), 7.16—7.68 (4H, m, ArH × 4), 9.42 (1H, s, NH), 9.56 (1H, s, NH), 11.57 (1H, s, NH). MS *m/z*: 262 ($M^+ - SEt$). *Anal.* Calcd for $C_{14}H_{17}N_3O_4S$: C, 52.00; H, 5.30; N, 12.99; S, 9.92. Found: C, 52.03; H, 5.31; N, 13.02; S, 9.76.

5-Benzylthio-5-(2-ethoxycarbonylaminophenyl)imidazolidine-2,4-dione (5e) This compound was synthesized from **4b** (0.98 g, 3.5 mmol) and benzylmercaptan (0.49 ml, 4.2 mmol) in THF (5 ml) by a similar procedure to that described for **5a**. Yield, 1.22 g (90%), mp 165—166 °C (dec.) (from AcOEt–*n*-hexane). IR (Nujol): 3180, 1770, 1730, 1705 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.72—3.82 (2H, ABq, J = 12 Hz, CH_2Ar), 4.12 (2H, q, J = 7 Hz, OCH_2), 7.19—7.65 (9H, m, ArH × 9), 9.53 (1H, s, NH), 9.57 (1H, s, NH), 11.54 (1H, s, NH). *Anal.* Calcd for $C_{19}H_{19}N_3O_4S$: C, 59.20; H, 4.97; N, 10.90; S, 8.32. Found: C, 59.04; H, 4.97; N, 11.02; S, 8.33.

5-(2-Ethoxycarbonylaminophenyl)-5-methylaminoimidazolidine-2,4-dione (6) (a) From **5a**: A 40% aqueous solution of methylamine (3.9 g, 50 mmol) was added to a solution of **5a** (15.4 g, 50 mmol) in methanol (100 ml), and the mixture was stirred at 45 °C for 6 h, then concentrated under reduced pressure. The residue was crystallized from diethyl ether, and recrystallized from ethanol to give **6** (9.8 g, 66%), mp 185—186 °C (dec.). IR (Nujol): 3340, 3230, 3140, 3080, 1785, 1735, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 2.18 (3H, d, J = 6 Hz, $NHC\underline{H_3}$), 3.81 (1H, q, J = 6 Hz, $N\underline{H}CH_3$), 4.12 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$), 6.9—7.5 (3H, m, ArH × 3), 8.0—8.2 (1H, m, ArH), 8.95 (1H, s, NH), 10.7 (2H, s, NH × 2). MS *m/z*: 261 ($M^+ - NH_2CH_3$). *Anal.* Calcd for $C_{13}H_{16}N_4O_4 \cdot 1/4H_2O$: C, 52.61; H, 5.60; N, 18.88. Found: C, 52.96; H, 5.52; N, 18.62.

(b) From **5d**: A 40% aqueous solution of methylamine (0.1 g, 1.3 mmol) was added to a solution of **5d** (0.32 g, 1 mmol) in THF (10 ml), and the mixture was stirred at 45 °C for 1 h. Work-up as described above gave **6** (0.27 g, 92%), mp 185—186 °C (dec.).

Spiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′5(3′*H*)-trione (7a) (a) From **4b**: A solution of **4b** (5.59 g, 20 mmol) and 10% ethanolic ammonia (13.6 g, 80 mmol) in toluene (150 ml)–ethanol (15 ml) was heated at 120 °C for 4 h in a sealed tube. After cooling, the precipitates were collected, washed with ethanol, and dissolved in water. This solution was acidified with 10% HCl to pH 2. The resulting crystals were collected, washed with water, and recrystallized from DMF–water to give **7a** (2.74 g, 59%), mp > 280 °C. IR (Nujol): 3270, 1790, 1730, 1670, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.84—7.31 (4H, m, ArH × 4), 7.97 (1H, s, NH), 8.95 (1H, s, NH), 9.67 (1H, s, NH), 10.92 (1H, br, NH). MS *m/z*: 232 (M^+). *Anal.* Calcd for $C_{10}H_8N_4O_3$: C, 51.72; H, 3.47; N, 24.13. Found: C, 51.39; H, 3.47; N, 23.84.

(b) From **5a**: A 28% solution of ammonium hydroxide (1.28 g, 21 mmol) was added to a suspension of **5a** (1.07 g, 3.5 mmol) in methanol (10 ml), and the mixture was heated at 45 °C for 15 h, then concentrated under reduced pressure. The residue was diluted with water and acidified with 10% HCl to pH 2. The resulting crystals were collected, washed with water, and recrystallized from DMF–water to give **7a** (0.75 g, 93%), mp > 280 °C.

(c) From **5d**: According to method (b) described above, **7a** was synthesized from **5d** (0.65 g, 2 mmol) in THF (5 ml). Yield 0.42 g (90%), mp > 280 °C (DMF–water).

3′-Methylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′5(3′*H*)-trione (7b) (a) From **4b**: According to method (a) described for **7a**, **7b** was synthesized from **4b** (2.51 g, 9 mmol) and 40% methanolic methylamine (2.71 g, 35 mmol). Yield, 0.91 g (41%), mp > 280 °C (from DMSO).

(b) From **4b**: A mixture of **4b** (1.40 g, 5 mmol) and 40% methanolic methylamine (0.85 g, 11 mmol) in toluene (33 ml)–ethanol (3.3 ml) was heated under reflux for 15 min. Then, 40% methanolic methylamine (1.55 g, 20 mmol) was added dropwise to the mixture under reflux over 1 h, and refluxing was continued for an additional 2.5 h. After cooling, the resulting precipitates were collected, and dissolved in water. This solution was acidified with 10% HCl to pH 2. The resulting crystals were collected, washed with water, and recrystallized from DMSO to give **7b** (0.46 g, 37%), mp > 280 °C.

(c) From **4c**: According to method (b) described for **7b**, **7b** was synthesized from **4c** (6.82 g, 20 mmol). Yield 0.85 g, (17%), mp > 280 °C (from DMSO).

(d) From **5a**: According to method (b) described for **7a**, **7b** was synthesized from **5a** (1.73 g, 5.6 mmol) and 40% aqueous methylamine

(2.0 g, 26 mmol). Yield 1.14 g (82%), mp > 280 °C (from DMSO).

(e) From **5d**: According to method (b) described for **7a**, **7b** was synthesized from **5d** (0.65 g, 2 mmol) in THF (5 ml). Yield 0.40 g (81%), mp > 280 °C (DMSO).

(f) From **6**: A mixture of **6** (2.92 g, 10 mmol) and NaOH (0.8 g, 20 mmol) in methanol (50 ml) was heated at 40 °C for 5 h, then concentrated under reduced pressure. The residue was dissolved in water and the solution was acidified with 10% HCl to pH 2. The resulting crystals were collected, washed with water, and recrystallized from DMSO to give **7b** (1.1 g, 45%), mp > 280 °C.

3'-Aminospiro[imidazolidine-4,4'(1'*H*)-quinazoline]-2,2',5(3'*H*)-trione (7c) A mixture of **4b** (2.79 g, 10 mmol) and hydrazine monohydrate (2.0 g, 40 mmol) in toluene (50 ml)–ethanol (50 ml) was heated under reflux for 4 h. After cooling, the precipitates were collected. The precipitates were diluted with water and acidified with 10% HCl to pH 2. The resulting crystals were collected, washed with water, and dried to give **7c** (1.44 g, 57%), mp > 280 °C. IR (Nujol): 3310, 3150, 1742, 1720, 1680, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.47 (2H, s, NH_2), 6.6—7.3 (4H, m, ArH × 4), 8.61 (1H, s, NH), 9.82 (1H, s, NH), 10.5—11.2 (11H, br, NH). *Anal.* Calcd for $C_{10}H_9N_5O_3 \cdot 1/4H_2O$: C, 47.71; H, 3.80; N, 27.82. Found: C, 47.52; H, 3.46; N, 27.90.

3'-Hydroxyspiro[imidazolidine-4,4'(1'*H*)-quinazoline]-2,2',5(3'*H*)-trione (7d) A mixture of hydroxylamine hydrochloride (5.56 g, 80 mmol) and potassium hydroxide (4.49 g, 80 mmol) in ethanol (50 ml) was stirred at 40 °C for 10 min. A suspension of **4b** (5.59 g, 20 mmol) in toluene (150 ml) was added to the mixture, and the whole was heated under reflux for 4 h. After cooling, the precipitates were collected. The precipitates were dissolved in water and acidified with 10% HCl to pH 2. The resulting crystals were collected, washed with water, and dried to give **7d** (0.77 g, 15%), mp 253 °C (dec.). IR (Nujol): 3220, 3080, 1782, 1735, 1680, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.6—7.3 (4H, m), 8.74 (1H, s), 9.63 (1H, s), 9.77 (1H, s), 10.83 (1H, br). *Anal.* Calcd for $C_{10}H_8N_4O_4 \cdot 1/2H_2O$: C, 46.69; H, 3.53; N, 21.78. Found: C, 46.58; H, 3.37; N, 21.92.

3'-Ethylspiro[imidazolidine-4,4'(1'*H*)-quinazoline]-2,2',5(3'*H*)-trione (7e) (a) From **5a**: According to method (b) described for **7a**, **7e** was synthesized from **5a** (1.54 g, 5 mmol) and 70% aqueous ethylamine (2.00 g, 31 mmol). Yield, 0.43 g (33%), mp > 280 °C (from DMF–water). IR (Nujol): 3450, 3120, 1790, 1720, 1665, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t, J = 7 Hz, CH_2CH_3), 2.8—3.6 (2H, m, CH_2CH_3), 6.7—7.5 (4H, m, ArH × 4), 9.13 (1H, s, NH), 9.84 (1H, s, NH), 11.17 (1H, s, NH). MS *m/z*: 260 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.22; H, 4.38; N, 21.72.

(b) From **5d**: According to method (b) described for **7a**, **7e** was synthesized from **5d** (0.65 g, 2 mmol) and 70% aqueous ethylamine (0.77 g, 12 mmol) in THF (5 ml). Yield 0.23 g (44%), mp > 280 °C (DMF–water).

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References and Notes

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