One-Step Synthesis of 1,2,3,4-Tetrahydrobenzo[*g*]quinazoline-5,10-dione Derivatives from Vitamin K_3

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The reactions of 2-halogenonaphthoquinones (5, 13, 14 and 15) and 2-methyl-1,4-naphthoquinone (20; vitamin K_3) with primary and secondary amines were examined. 1,3-Dialkyl-1,2,3,4-tetrahydrobenzo[*g*]quinazoline-5,10-diones (9) were obtained in moderate yields by treating 20 with formaldehyde in primary amines. A plausible reaction path-way is also presented.

Keywords 2-methyl-1,4-naphthoquinone; 1,2,3,4-tetrahydrobenzo[*g*]quinazoline; formaldehyde; amination; quinone-methide; photochemical oxidation

Substituted 5-alkyl-5,8-dihydro-8-oxoquinoline-7-carboxylic acids (**1**) are well known anti-bacterial agents,[1] but recently the appearance of quinolone-resistant bacteria has been reported.[2] In the preceding paper, we reported attempts synthesize 3-amino-1,4-naphthoquinone-2-carboxylic acid derivatives (**2**) with the aim of obtaining new drugs, and we described a photo-chemical oxidative cyclization of 3-alkylamino-2-hydroxymethyl-1,4-naphthoquinones (**3**) to 1,4,5,10-tetrahydro-5,10-dioxo-2*H*-naphth[2,3-*d*][1,3]oxazine derivative (**4**).[3] When we reported the experiments of the preceding paper,[3] we newly obtained 1,3-dimethyl-1,2,3,4-tetrahydrobenzo[*g*]-quinazoline-5,10-dione (**9a**) in very low yield from a reaction mixture of 2-bromo-3-hydroxymethyl-1,4-naphthoquinone (**5**) with methylamine. In this paper, we present an improved preparation of **9** and discuss the reaction pathway from **5** to **9**.

In the preceding paper,[3] we reported that amination of the bromoquinone (**5**) with methylamine gave **6a** in 40.4% yield, but we did not isolate by-products of the reaction. This time we isolated three compounds [**7a** (12.8%), **8a** (17.6%), and **9a** (8.3%)] along with **6a** (42.0%) from the reaction mixture and determined their structures based on proton nuclear magnetic resonance (^{1}H-NMR) spectra and analytical data. In the ^{1}H-NMR spectrum of **9a**, signals at δ 3.97 ppm (s, 2H), 3.74 (s, 2H), 3.37 (s, 3H) and 2.49 (s, 3H) can be assigned to $-N(CH_3)C\underline{H}_2N(CH_3)-$, $=C-CH_2-N<$, $>NCH_3$ (3-position) and $>NCH_3$ (1-position), respectively. The signal of $>NCH_3$ at 2.49 ppm appears at relatively high magnetic field. The *N*-methyl group may be pushed out to the axial position of the tetrahydropyrimidine ring by peri-interaction with the

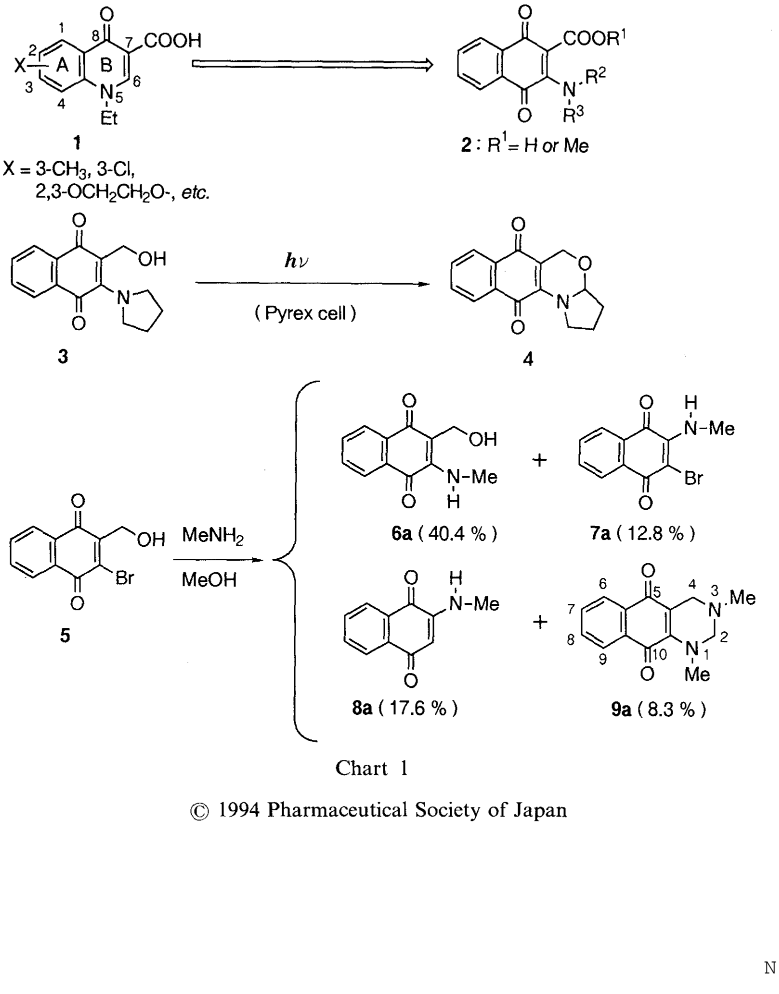

Chart 1

oxygen atom of the carbonyl group at the 10-position, and therefore, the *N*-methyl group may be located at the upper side of the quinone ring where diamagnetic anisotropy (shielding effect) of the quinone ring must be considered. These data support the proposed structure of **9a**. One carbon atom more is presented in the tricyclic product (**9a**) compared with the starting material **5**, while the products **7a** and **8a** lack one carbon atom of the hydroxymethyl group. We presumed that formaldehyde and a quinonemethide intermediate (see Charts 4, 5, and 6) might be involved. Thus, nitrogen gas was passed through the reaction mixture, and into a methanolic solution of dimedone (**11**); precipitation of methylenebisdimedone (**12**) reflects the presence in the reaction mixture of formaldehyde,[4] which might be produced by retro-hydroxymethylation. On the other hand, when the alcohol (**5**) was treated with propylamine in dichloromethane, the dimer (**10**) was obtained in 5.5% yield instead of the corresponding tetrahydroquinazoline derivative, together with **6b** (52.2%), **7b**[5] (11.6%), and **8b**[5] (19.2%). The structure of **10** was supported by the spectral and analytical data. The dimer (**10**) might be produced by condensation of the enamine **8b** with the alcohol (**6b**) or formaldehyde. The reaction of **5** with propylamine was examined in several solvents, and the results are summarized in Table I. Although the yields of the dimer (**10**) and the tetrahydroquinazoline (**9a**) were quite low in methanol and dichloromethane, interestingly the dimer (**10**) was obtained as the main product in *N*,*N*-dimethylformamide

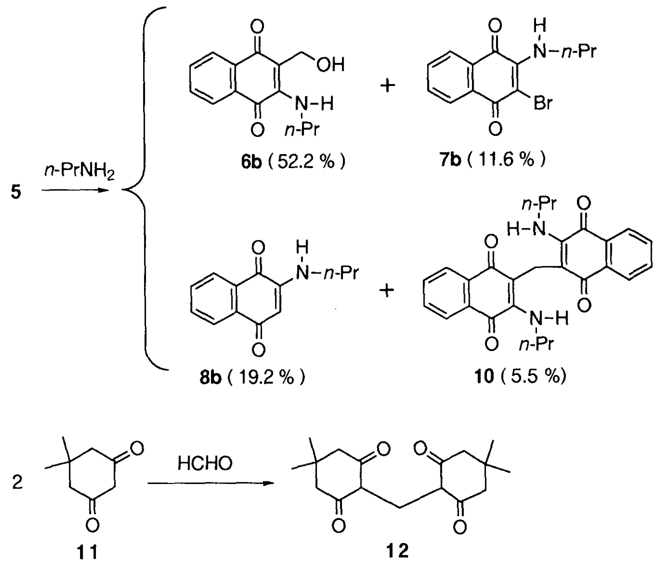

Chart 2

Table I. Reaction of **5** with *n*-Propylamine

Run	Solvent	Yield (%)[a]				
		6b	**7b**	**8b**	**10**	Total yield
1	MeOH	52.2	11.6	19.2	0	83.0
2	CH_2Cl_2	13.9	27.9	27.9	5.5	75.2
3	DMF	8.6	11.9	15.3	47.4	83.2

a) Isolated yield.

Table II. Reaction of **5**, **13**—**15** with 2 eq of *N*-Methylamine or Pyrrolidine

Run	Solv.	Starting materials				Yield (%)[a]				
			R^1	R^2	R^3					Total yield
1	MeOH	**15**	H	Me	H	**6a**: —	**7a**: 66.1	**8a**: 3.2	**9** : —	69.3
2	MeOH	**13**	Br	Me	H	**6a**: —	**7a**: 45.8	**8a**: 18.2	**9** : 6.2	70.2
3	MeOH	**14**	OAc	Me	H	**6a**: —	**7a**: 20.7	**8a**: 3.7	**9** : 45.5	69.9
4	MeOH	**5**	OH	Me	H	**6a**: 40.4	**7a**: 12.8	**8a**: 17.6	**9** : 8.3	80.1
5	MeOH	**15**	H	$-(CH_2)_4-$		**6b**: —	**7c**: 64.8	**8c**: 3.5	**16a**: —	68.3
6	MeOH	**13**	Br	$-(CH_2)_4-$		**6b**: —	**7c**: 37.1	**8c**: 7.0	**16a**: 18.7	62.3
7	MeOH	**14**	OAc	$-(CH_2)_4-$		**6b**: —	**7c**: 44.9	**8c**: 8.8	**16a**: 18.1	71.8
8	MeOH	**5**	OH	$-(CH_2)_4-$		**6b**: 75.0	**7c**: —	**8c**: —	**16a**: —	75.0
9	CH_2Cl_2	**15**	H	$-(CH_2)_4-$		**6b**: —	**7c**: 3.6	**8c**: 51.5	**16a**: —	55.1
10	DMF	**15**	H	$-(CH_2)_4-$		**6b**: —	**7c**: 6.5	**8c**: 64.2	**16a**: —	70.7

a) Isolated yield.

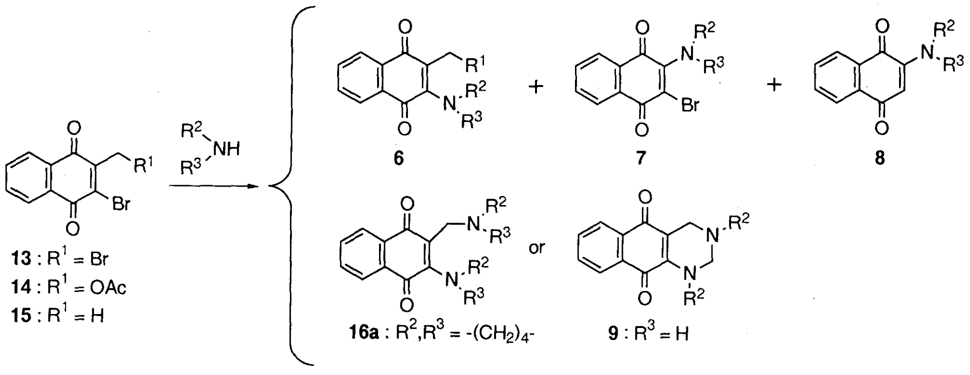

Chart 3

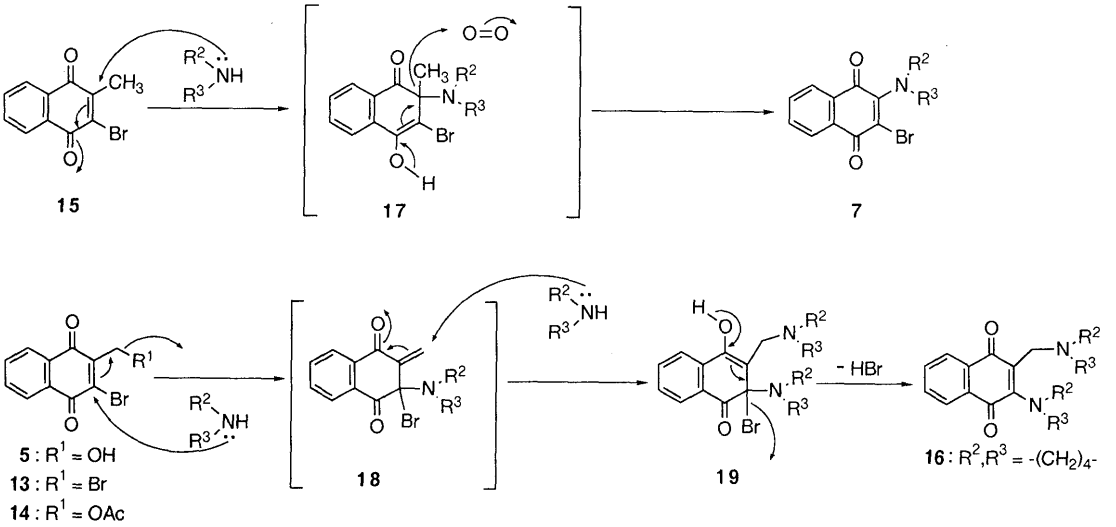

Chart 4

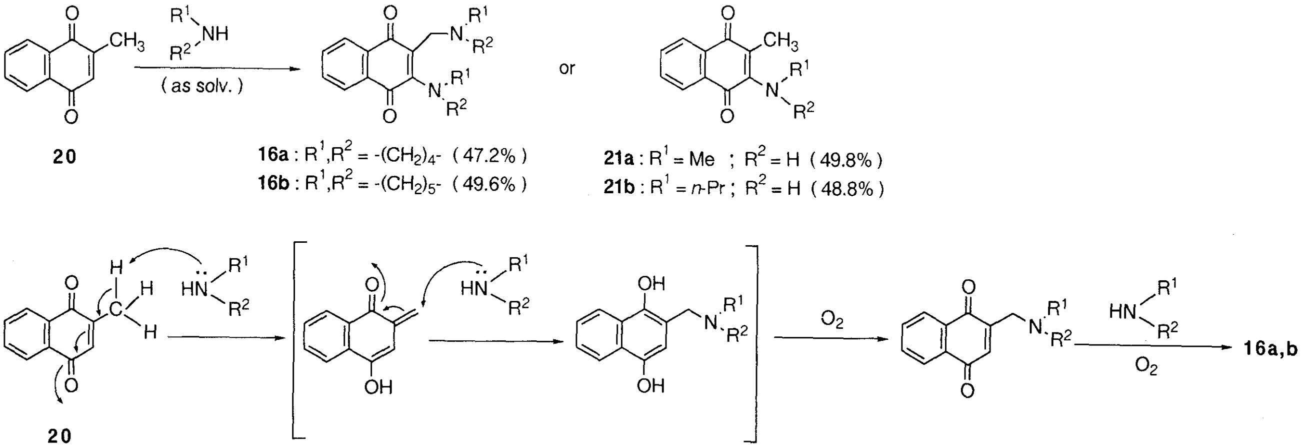

Chart 5

(DMF).

Next, we examined the reactivity of the substrates **13**—**15** with 2 eq of methylamine and pyrrolidine, and the results are summarized in Table II. Under the reaction conditions, however, bulky amines such as *sec*-butylamine, *tert*-butylamine and cyclohexylamine did not react at all. It is noteworthy that the methyl group of 3-bromo-2-methylnaphthoquinone (**15**) was lost in the reaction, but formaldehyde was not detected in the reaction mixture starting from **15**. In this case, it is presumed that in the addition-elimination reaction of the naphthoquinone system the methyl group behaves as an electron donor to oxygen, and a plausible mechanism is illustrated in Chart 4 (**15**→**17**→**7**). On the other hand, in the reactions starting from **5**, **13** and **14**, the quinonemethide (**18**) seems to be generated as a possible intermediate, which was subsequently converted to **16**.

A quinonemethide intermediate such as **18** may be similarly produced from 2-methyl-1,4-naphthoquinone (**20**; vitamin K_3) in the reaction with an amine, but the above-described results starting from **13**—**15** in Table II were disappointing (Chart 4). So the quinone (**20**) was treated with a large excess of amines. Reactions with cyclic and primary amines gave the diamino compounds (**16a** and **16b**[6]) and the monoamino compounds (**21a**[7] and **21b**), respectively, but the reactions with *tert*-butylamine and aniline did not proceed (Chart 5).

We presumed that the tetrahydroquinazolines (**9**) may be produced if formaldehyde is added to the mixture of **20** and primary amine as illustrated in Chart 6. Thus, 2-methyl-1,4-naphthoquinone (**20**) was treated with 17.5 eq of 37% formalin in a large excess of methylamine (35 eq) to give the expected product (**9a**) in 35.5% yield and 3-methyl-2-aminonaphthoquinone (**21c**)[7] in 39.8% yield. The results in the reactions of **20** with various primary amines are summarized in Table III.

Hans and his co-workers reported the two-step synthesis of **9** *via* 2-amino-1,4-naphthoquinone, starting from 1,4-naphthoquinone.[8] The present one-step, one-pot route for the synthesis of the 1,2,3,4-tetrahydroquinazoline derivatives (**9**) can be conveniently carried out starting from commercially available vitamin K_3 (**20**). The reaction mechanism is considered to include a quinonemethide intermediate (**22**) and an autooxidation step (Chart 6).

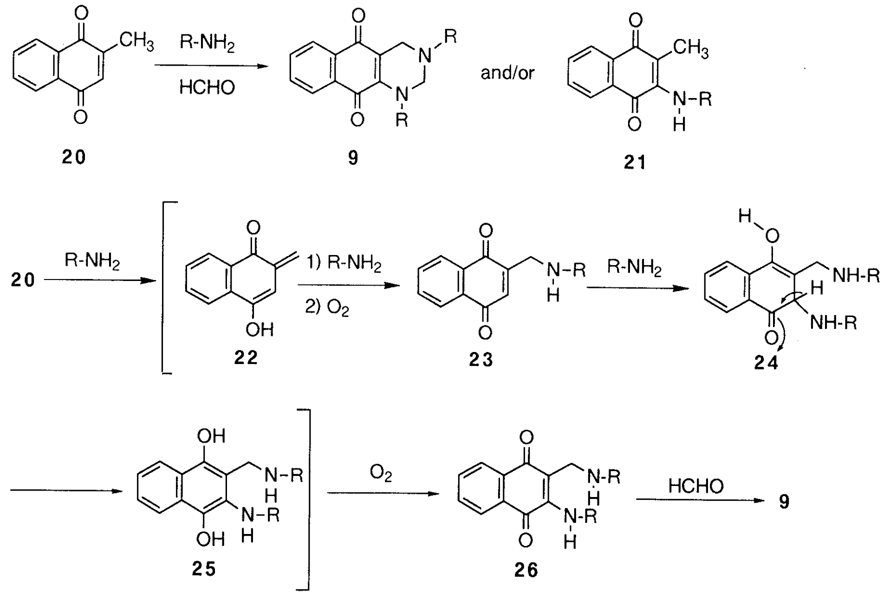

Chart 6

Table III. Reaction of **20** with a Mixture of a Large Excess of Amines and Formaline

Run	R	Yield (%)[a]			
		9		**21**	
1	H	—	—	—	—[b]
2	Me	**9a**	35.5	**21a**	39.8
3	*n*-Pr	**9b**	23.5	**21b**	35.8
4	iso-Pr	**9c**	23.1	**21c**	34.5
5	*n*-Bu	**9d**	20.8	**21d**	28.7
6	*sec*-Bu	—	0	**21e**	10.3
7	*tert*-Bu	—	—	—	—[b]
8	Cy	—	—	—	—[b]
9	$-CH_2CH_2OH$	—	—	—	—[c]
10	$-CH_2CH_2NH_2$	—	—	—	—[c]
11	Ph	—	—	—	—[b]

a) Isolated yield. *b*) No reaction. *c*) A complex mixture was obtained.

Experimental

All melting points are uncorrected. IR spectra were taken with a Shimadzu IR-435 spectrometer. ^{1}H-NMR were obtained at 270 MHz on a JEOL EX-270 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); quar (quartet); q (quintet); m (multiplet); br (broad); dd (double doublet); dt (double triplet). Low-resolution MS (LRMS) and high-resolution MS (HRMS) were obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure in the usual work-up procedure. Anhydrous sodium sulfate was used as a drying agent. A Kugel-Rohr apparatus was used for vacuum distillations of oily crude products. Silica gel (Merck Art. 7734) was used in column chromatography, and Silica gel 60PF$_{254}$ (Nacalai Tesque Ltd.) was used for preparative thin-layer chromatography (PTLC).

Reaction of 3-Bromo-2-hydroxymethyl-1,4-naphthoquinone (5) with Amine; Reaction of 5 with Methylamine as an Example A 30% methanolic solution of methylamine (1.0 ml, 8.7 mmol) was added dropwise to a solution of **5**[3] (267 mg, 1.0 mmol) in MeOH (15 ml) at room temperature, and the mixture was stirred for 1 h. The solvent was evaporated, and 10% Na_2CO_3 (10 ml) and CH_2Cl_2 (10 ml × 3) were added to the residue. The organic layer was dried and evaporated. The residue was purified by PTLC (solvent, AcOEt) to give four fractions. Evaporation of the first fraction gave **6a** as a crystalline residue,[3] which was recrystallized from AcOEt–*n*-hexane to give red needles. Yield, 94 mg (40.4%). mp 262.6—263.4 °C. Evaporation of the second fraction gave a crystalline residue of **7a**, which was recrystallized from *n*-hexane gave red needles. Yield, 34 mg (12.8%). mp 155.2—155.9 °C (lit. mp 156—157 °C).[9] IR ($CHCl_3$): 3351 (>NH), 1677 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 3.45 (d, 3H, $-NHC\underline{H}_3$, $J=5.6$ Hz), 6.08—6.21 (br, 1H, >NH), 7.62 (dt, 1H, C^6-H or C^7-H, $J=1.3$, 7.6 Hz), 7.71 (dt, 1H, C^7-H or C^6-H, $J=1.3$, 7.6 Hz), 8.03 (dd, 1H, C^5-H or C^8-H, $J=1.3$, 7.6 Hz), 8.15 (dd, 1H, C^8-H or C^5-H, $J=1.3$, 7.6 Hz). Evaporation of the third fraction gave a crystalline residue of **8a**, which was recrystallized from AcOEt to give red needles. Yield, 34 mg (17.6%). mp 232.4—234.1 °C (lit. mp 234 °C).[10] IR ($CHCl_3$): 3387 (>NH), 1676 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 2.93 (d, 3H, $-NHC\underline{H}_3$, $J=5.6$ Hz), 5.72 (s, 1H, >C=CH–), 5.86—6.02 (br, 1H, >NH), 7.61 (dt, 1H, C^6-H or C^7-H, $J=1.3$, 7.6 Hz), 7.73 (dt, 1H, C^7-H or C^6-H, $J=1.3$, 7.6 Hz), 8.04 (dd, 1H, C^5-H or C^8-H, $J=1.3$, 7.6 Hz), 8.11 (dd, 1H, C^8-H or C^5-H, $J=1.3$, 7.6 Hz). Evaporation of the fourth fraction gave **9a** as a crystalline residue, which was recrystallized from AcOEt to give red needles. Yield, 20 mg (8.3%). mp 131.3—132.9 °C. IR ($CHCl_3$): 1673 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 2.49 (s, 3H, $>NCH_3$), 3.37 (s, 3H, $>NCH_3$), 3.74 (s, 2H, $>NCH_2C=$), 3.97 (s, 2H, $>NCH_2N<$), 7.56—7.67 (m, 2H, C^6-H and C^9-H), 7.96—8.04 (m, 2H, C^7-H and C^8-H). *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.74; H, 5.87; N, 11.35. HRMS *m/z*: Calcd for $C_{14}H_{14}N_2O_2$, 242.1060. Found, 242.1044 (M$^+$).

Reaction of 5 with *n*-Propylamine in MeOH The reaction was carried out in a similar manner to that used for the reaction of **5** with methylamine except for the use of *n*-propylamine (173 μl, 2.1 mmol) in place of methylamine. The isolated products were **6b**[3] **7b** and **8b**.[5] **6b**: Red needles from AcOEt–*n*-hexane. Yield, 128 mg (52.2%). **7b**: Red needles from *n*-hexane. Yield, 34 mg (11.6%). mp 121.4—123.1 °C. IR ($CHCl_3$): 3331 (>NH), 1674 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.02 (t, 3H, $-CH_2C\underline{H}_3$, $J=7.3$ Hz), 1.73 (sex, 2H, $-C\underline{H}_2CH_3$, $J=7.3$ Hz), 3.80—3.88 (m, 2H, $>NCH_2-$), 6.04—6.18 (br, 1H, >NH–), 7.61 (dt, 1H, C^6-H or C^7-H, $J=1.3$, 7.6 Hz), 7.71 (dt, 1H, C^7-H or C^6-H, $J=1.3$, 7.6 Hz), 8.01 (dd, 1H, C^5-H or C^8-H, $J=1.3$, 7.6 Hz), 8.14 (dd, 1H, C^8-H or C^5-H, $J=1.3$, 7.6 Hz). *Anal.* Calcd for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.16; H, 4.04; N, 4.73. LRMS *m/z*: 293 (M$^+$), 295 (M$^+$+2). **8b**: Red needles from AcOEt. Yield, 41 mg (19.2%). mp 115.0—117.0 °C. IR ($CHCl_3$): 3370 (>NH), 1673 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.02 (t, 3H, $-CH_2C\underline{H}_3$, $J=7.6$ Hz), 1.73 (sex, 2H, $-C\underline{H}_2CH_3$, $J=7.6$ Hz), 3.15 (quar, 2H, $>NCH_2-$, $J=6.6$ Hz), 5.73 (s, 1H, >C=CH–), 5.82—6.02 (br, 1H, >NH–), 7.63 (dt, 1H, C^6-H or C^7-H, $J=1.3$, 7.6 Hz), 7.70 (dt, 1H, C^7-H or C^6-H, $J=1.3$, 7.6 Hz), 8.01 (dd, 1H, C^5-H or C^8-H, $J=1.3$, 7.6 Hz), 8.08 (dd, 1H, C^8-H or C^5-H, $J=1.3$, 7.6 Hz).

Reaction of 5 with *n*-Propylamine in CH_2Cl_2 The reaction was carried out in a similar manner to that used for the reaction in MeOH. The isolated products were **6b**[3] (35 mg, 13.9%), **7b** (82 mg, 27.9%), **8b** (60 mg, 27.9%) and **10** (11 mg, 5.5%). **10**: Red needles from AcOEt. mp

213.0—214.5 °C. IR ($CHCl_3$): 3280 (>NH), 1670 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.00 (t, 6H, $-CH_2C\underline{H}_3 \times 2$, J=7.3 Hz), 1.78 (sex, 4H, $-C\underline{H}_2CH_3 \times 2$), 3.75 (quar, 4H, $>NCH_2-$, J=6.6 Hz), 3.87 (s, 2H, $=C-CH_2-$), 7.55 (t, 2H, C^6-H or C^7-H, J=7.6 Hz), 7.67 (t, 2H, C^7-H or C^6-H, J=7.6 Hz), 7.91 (d, 2H, C^5-H or C^8-H, J=7.6 Hz), 8.07 (d, 2H, C^8-H or C^5-H, J=7.6 Hz), 8.31—8.38 (br, 2H, >NH × 2). *Anal.* Calcd for $C_{27}H_{26}N_2O_4 \cdot 1/4H_2O$: C, 72.30; H, 5.99; N, 6.25. Found: C, 72.42; H, 5.71; N, 6.04. LRMS *m/z*: 442 (M$^+$).

Reaction of 5 with *n*-Propylamine in DMF The reaction was carried out in a similar manner to that used for the reaction in MeOH. The isolated products were **6b**[3] (21 mg, 8.6%), **7b** (35 mg, 11.9%), **8b** (33 mg, 15.3%) and **10** (105 mg, 47.4%).

Reaction of 3-Bromo-2-methyl-1,4-naphthoquinone (15) with Methylamine in MeOH The reaction was carried out in a similar manner to that used for the reaction of **5** with methylamine in MeOH except for the use of **15** in place of **5**. The isolated products were **7a** (176 mg, 66.1%) and **8a** (8 mg, 3.2%).

Reaction of 3-Bromo-2-bromomethyl-1,4-naphthoquinone (13) with Methylamine in MeOH The reaction was carried out in a similar manner to that used for the reaction of **5** with methylamine in MeOH except for the use of **13** in place of **5**. The isolated products were **7a** (122 mg, 45.8%), **8a** (34 mg, 18.2%) and **9** (15 mg, 6.2%).

Reaction of 2-Acetoxymethyl-3-bromo-1,4-naphthoquinone (14) with Methylamine in MeOH The reaction was carried out in a similar manner to that used for the reaction of **5** with methylamine in MeOH except for the use of **14** in place of **5**. The isolated products were **7a** (55 mg, 20.7%), **8a** (7 mg, 3.7%) and **9** (110 mg, 45.5%).

Reaction of 15 with Pyrrolidine in MeOH The reaction was carried out in a similar manner to that used for the reaction of **15** with methylamine in MeOH. The isolated products were **7c**[5] (100 mg, 64.8%) and **8c**[5] (4 mg, 3.5%). **7c**: Red needles from isopropanol. mp 97.1—99.0 °C (lit. mp 97—100 °C).[5] IR ($CHCl_3$): 1664 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.90—2.05 (m, 4H, $>NCH_2C\underline{H}_2C\underline{H}_2-$), 3.90—4.00 (m, 4H, $-C\underline{H}_2NC\underline{H}_2-$), 7.59 (dt, 1H, C^6-H or C^7-H, J=1.5, 7.4 Hz), 7.67 (dt, 1H, C^7-H or C^6-H, J=1.5, 7.4 Hz), 7.90 (dd, 1H, C^5-H or C^8-H, J=1.5, 7.4 Hz), 8.09 (dd, 1H, C^8-H or C^5-H, J=1.5, 7.4 Hz). **8c**: Red needles from isopropanol. mp 157.7—159.6 °C (lit. mp 158—160 °C).[5] Spectral data of **8c** were listed in the preceding paper.[5]

Reaction of 13 with Pyrrolidine in MeOH The reaction was carried out in a similar manner to that used for the reaction of **15** with methylamine in MeOH except for the reaction time (1 h). The isolated products were **7c**[5] (57 mg, 37.1%), **8c**[5] (8 mg, 7.0%) and **16a** (29 mg, 18.7%). **16a**: Red viscous oil. IR ($CHCl_3$): 1674 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.80—2.00 (m, 8H, $>NCH_2C\underline{H}_2C\underline{H}_2-$), 2.78—2.88 (m, 4H, $-C\underline{H}_2NC\underline{H}_2-$), 3.85—3.94 (m, 4H, $-C\underline{H}_2NC\underline{H}_2-$), 4.12 (s, 2H, $=C-CH_2N<$), 7.57 (dt, 1H, C^6-H or C^7-H, J=1.3, 7.6 Hz), 7.67 (dt, 1H, C^7-H or C^6-H, J=1.3, 7.6 Hz), 7.87 (dd, 1H, C^5-H or C^8-H, J=1.3, 7.6 Hz), 8.03 (dd, 1H, C^8-H or C^5-H, J=1.3, 7.6 Hz). LRMS *m/z*: 241 (M$^+$ $-C_4H_7N$).

Reaction of 14 with Pyrrolidine in MeOH The reaction was carried out in a similar manner to that used for the reaction of **15** with methylamine in methanol except for the reaction time (1 h). The isolated products were **7c**[5] (69 mg, 44.9%), **8c**[5] (10 mg, 8.8%) and **16a** (28 mg, 18.1%).

Reaction of 15 with Pyrrolidine in CH_2Cl_2 The reaction was carried out in a similar manner to that used for the reaction in MeOH. The isolated products were **7c**[3] (6 mg, 3.6%) and **8c** (59 mg, 51.5%).

Reaction of 15 with Pyrrolidine in DMF The reaction was carried out in a similar manner to that used for the reaction in MeOH. The isolated products were **7c** (10 mg, 6.5%) and **8c** (73 mg, 64.2%).

Synthesis of 2-Pyrrolidino-3-(1-pyrrolidinylmethyl)-1,4-naphthoquinone (16a) from Vitamin K$_3$ (20) A solution of **20** (172 mg, 1.0 mmol) in pyrrolidine (3.0 ml, 35.9 mmol) was kept standing for 24 h in the dark. Pyrrolidine was evaporated and the residue was purified by PTLC (solv., AcOEt) to give a red viscous oil. Yield, 146 mg (47.2%). The product was identical with the above-described **16a** on the bases of a comparison of the spectral data.

Synthesis of 2-Piperidino-3-(piperidinylmethyl)-1,4-naphthoquinone (16b) from Vitamin K$_3$ (20) A solution of **20** (172 mg, 1.0 mmol) in piperidine (3.0 ml, 30.0 mmol) was kept standing for 24 h in the dark. Piperidine was evaporated and the residue was purified by PTLC (solv., AcOEt) to give a crystalline product, which was recrystallized from AcOEt to give red needles. Yield, 168 mg (49.6%). mp 70.7—72.0 °C (lit. mp 72 °C).[6] IR ($CHCl_3$): 1666 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.45—1.80 (m, 12H, $>NCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2- \times 2$), 2.33—2.48 (m, 4H, $-C\underline{H}_2NC\underline{H}_2-$), 3.42—3.62 (m, 4H, $-C\underline{H}_2NC\underline{H}_2-$), 3.50 (s, 2H, $=C-CH_2N<$), 7.44—7.66 (m, 2H, C^6-H and C^7-H), 7.92—8.14 (m, 2H, C^5-H and C^8-H).

Reaction of 20 with Methylamine This reaction was carried out in a similar manner to that used for the reaction of **20** and pyrrolidine, except for the use of 30% methylamine in MeOH (3.0 ml, 26.3 mmol) in place of pyrrolidine. Yield of **21a**, 100 mg (49.8%). Red needles from *n*-hexane. mp 132.1—132.4 °C (lit. mp 133 °C).[7]

Reaction of 20 with Propylamine This reaction was carried out in a similar manner to that used for the reaction of **15** and pyrrolidine except for the use of *n*-propylamine (3.0 ml, 36.5 mmol) in place of pyrrolidine. Yield of **21b**, 112 mg (48.8%). Red needles from *n*-hexane. mp 78.3—79.0 °C. IR ($CHCl_3$): 3340 (>NH), 1664 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.00 (t, 3H, $-CH_2C\underline{H}_3$, J=7.3 Hz), 1.64 (sex, 2H, $-C\underline{H}_2CH_3$, J=7.3 Hz), 2.23 (s, 3H, $=CCH_3$), 3.52 (quar, 2H, $>NCH_2-$, J=6.9), 5.70—5.78 (br, 1H, >NH), 7.56 (dt, 1H, C^6-H or C^7-H, J= 1.3, 7.6 Hz), 7.67 (dt, 1H, C^7-H or C^6-H, J=1.3, 7.6 Hz), 7.99 (dd, 1H, C^5-H or C^8-H, J=1.3, 7.6 Hz), 8.08 (dd, 1H, C^8-H or C^5-H, J=1.3, 7.6 Hz). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.49; H, 6.53; N, 6.11.

General Procedure for Synthesis of 1,2,3,4-Tetrahydro-1,3-dialkylbenzo[*g*]quinazoline-5,10-dione by Treatment of 2-Methyl-1,4-naphthoquinone (20) with a Mixture of a Large Excess of Amines and Formalin; Synthesis of 1,2,3,4-Tetrahydro-1,3-dimethylbenzo[*g*]quinazoline-5,10-dione (9a) as an Example The quinone (**20**, 172 mg, 1.0 mmol) was dissolved in a 30% methanolic solution of methylamine (4.0 ml, 35 mmol), and then 37% formalin (1.5 ml, 18 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The methanol was evaporated and the product was extracted by addition of CH_2Cl_2 (20 ml × 3) and water (20 ml). The organic layer was washed with saturated NaCl, dried, and evaporated. The residue was purified by chromatography (solvent, AcOEt then CH_2Cl_2). The AcOEt eluent was evaporated to give crystalline **9a**, which was recrystallized from AcOEt. Yield, 86 mg (35.5%). This product was identical with **9a** described above. The CH_2Cl_2 eluent was evaporated to give crystalline **21a**, which was recrystallized from AcOEt to give red needles. Yield, 80 mg (39.8%). This product was identical with **21a** described above. **9b** and **21b**: Obtained in a similar manner to that used for the reaction of **20** with methylamine except for the use of *n*-propylamine in place of methylamine. **9b**: Yield, 70 mg (23.5%). Red crystals from *n*-hexane. mp 21.3—23.1 °C. IR ($CHCl_3$): 1669 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 0.97 (t, 3H, $-CH_2C\underline{H}_3$, J=7.3 Hz), 1.60 (sex, 2H, $-C\underline{H}_2CH_3$, J=7.3 Hz), 1.72 (sex, 2H, $-C\underline{H}_2CH_3$, J=7.3 Hz), 2.50 (t, 2H, $>NC\underline{H}_2-$, J=7.6 Hz), 3.59 (t, 2H, $>NCH_2-$, J=7.6 Hz), 3.78 (s, 2H, $=CCH_2N<$), 4.04 (s, 2H, $>NCH_2N<$), 7.56 (dt, 1H, C^6-H or C^7-H, J=1.7, 7.6 Hz), 7.62 (dt, 1H, C^7-H or C^6-H, J=1.3, 7.6 Hz), 7.95 (d, 1H, C^5-H or C^8-H, J=1.3, 7.6 Hz), 8.01 (d, 1H, C^8-H or C^5-H, J=7.6 Hz). HRMS *m/z*: Calcd for $C_{18}H_{22}N_2O_2$, 298.1680. Found, 298.1660 (M$^+$). **21b**: 82 mg (35.8%). This product was identical with **21b** described above.

9c and **21c**: Obtained in a similar manner to that used for the reaction of **20** with methylamine except for the use of isopropylamine in place of methylamine. **9c**: Yield, 69 mg (23.1%). Red crystals from *n*-hexane. mp 49.7—51.8 °C. IR ($CHCl_3$): 1656 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.17 (d, 6H, $-CH(C\underline{H}_3)_2$, J=6.6 Hz), 1.29 (d, 6H, $-CH(C\underline{H}_3)_2$, J=6.6 Hz), 2.91 (hep, 1H, $>NC\underline{H}(CH_3)_2$, J=6.6 Hz), 3.72 (s, 2H, $=CCH_2N<$), 3.92 (s, 2H, $>NCH_2N<$), 4.88 (hep, 1H, $=CN(C\underline{H}(CH_3)_2)-$, J=6.6 Hz), 7.56 (dt, 1H, C^7-H or C^8-H, J=1.6, 7.4 Hz), 7.63 (dt, 1H, C^8-H or C^7-H, J=1.6, 7.4 Hz), 7.91 (dd, 1H, C^6-H or C^9-H, J=1.3, 7.6 Hz), 7.99 (dd, 1H, C^9-H or C^6-H, J= 1.3, 7.4). *Anal.* Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.38; H, 7.46; N, 9.44. **21c**: Yield, 79 mg (34.5%). Red crystals from *n*-hexane. mp 80.1—81.5 °C. IR ($CHCl_3$): 3330 (>NH), 1665 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 1.26 (d, 6H, $-CH(C\underline{H}_3)_2$, J=6.3 Hz), 2.21 (s, 3H, $=CCH_3$), 4.10—4.22 (m, 1H, $>NC\underline{H}(CH_3)_2$), 5.52—5.68 (br, 1H, >NH), 7.56 (t, 1H, C^7-H or C^6-H, J=6.7 Hz), 7.67 (t, 1H, C^6-H or C^7-H, J=6.7 Hz), 7.99 (d, 1H, C^8-H or C^5-H, J=6.7 Hz), 8.08 (d, 1H, C^5-H or C^8-H, J=6.7 Hz). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.39; H, 6.72; N, 6.05.

9d and **21d**: Obtained in a similar manner to that used for the reaction of **20** with methylamine except for the use of butylamine in place of methylamine. **9d**: Yield, 68 mg (20.8%). Red viscous oil. IR ($CHCl_3$): 1670 (>C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 0.88 (t, 3H, $-CH_2C\underline{H}_3$, J=7.3 Hz), 0.93 (t, 3H, $-C\underline{H}_2CH_3$, J=7.3 Hz), 1.26—1.68 (m, 8H, $-(C\underline{H}_2)_2CH_3 \times 2$), 2.48 (t, 2H, $>NC\underline{H}_2-$, J=7.8Hz), 3.57 (t, 2H, $>NCH_2-$, $J=7.4$ Hz), 3.72 (s, 2H, $=CC\underline{H}_2N<$), 3.98 (s, 2H, $>NCH_2N<$), 7.51 (t, 1H, C^7-H or C^8-H, $J=7.6$ Hz), 7.59 (t, 1H, C^8-H or C^7-H, $J=7.5$ Hz), 7.89 (d, 1H, C^6-H or C^9-H, $J=7.5$ Hz), 7.95 (d, 1H, C^9-H or C^6-H, $J=7.6$ Hz). HRMS *m*/*z*: Calcd for $C_{20}H_{26}N_2O_2$, 326.2000. Found, 326.1967 (M^+). **21d**: Yield, 70 mg (28.7%). Dark-red crystals from *n*-hexane. mp 64.6—66.1 °C. IR ($CHCl_3$): 3340 ($>NH$), 1664 ($>C=O$) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 0.88 (t, 3H, $-CH_2C\underline{H}_3$, $J=7.3$ Hz), 1.34 (sex, 2H, $-C\underline{H}_2CH_3$ or $-C\underline{H}_2CH_2CH_3$, $J=7.3$ Hz), 1.53 (q, 2H, $-C\underline{H}_2CH_2CH_3$ or $-C\underline{H}_2CH_3$, $J=7.3$ Hz), 2.14 (s, 3H, $=CCH_3$), 3.46 (quar, 2H, $>NCH_2-$, $J=6.6$ Hz), 5.59—5.67 (br, 1H, $>NH$), 7.46 (t, 1H, C^7-H or C^8-H, $J=7.6$ Hz), 7.57 (t, 1H, C^8-H or C^7-H, $J=7.6$ Hz), 7.86 (d, 1H, C^6-H or C^9-H, $J=7.6$ Hz), 7.97 (d, 1H, C^9-H or C^6-H, $J=7.6$ Hz). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.82; H, 7.14; N, 5.82.

21e: Obtained in a similar manner to that used for the reaction of **20** with methylamine except for the use of *sec*-butylamine (0.5 ml, 5.0 mmol) in place of methylamine. **21e**: Yield, 25 mg (10.3%). Red viscous oil. IR ($CHCl_3$): 3320 ($>NH$), 1663 ($>C=O$) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz): 0.95 (t, 3H, $-CH_2C\underline{H}_3$, $J=7.4$ Hz), 1.23 (d, 3H, $-CH(C\underline{H}_3)-$, $J=6.6$ Hz), 1.46—1.70 (m, 2H, $-C\underline{H}_2CH_3$), 2.19 (s, 3H, $=CC\underline{H}_3$), 3.90—4.05 (m, 1H, $>NCH-$), 5.62—5.70 (br, 1H, $>NH-$), 7.55 (t, 1H, C^7-H or C^8-H, $J=7.6$ Hz), 7.65 (t, 1H, C^8-H or C^7-H, $J=7.6$ Hz), 7.97 (d, 1H, C^6-H or C^9-H, $J=7.6$ Hz), 8.06 (d, 1H, C^9-H or C^6-H, $J=7.6$ Hz). HRMS *m*/*z*: Calcd for $C_{15}H_{17}NO_2$, 243.1260. Found, 243.1240.

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