The Characterization and Cycloaddition Reaction of 5,6-Dihydro-1,3-dimethyl-6-methylene-5-[(substituted amino)methylene]-2,4(1*H*,3*H*)-pyrimidinediones[1)]

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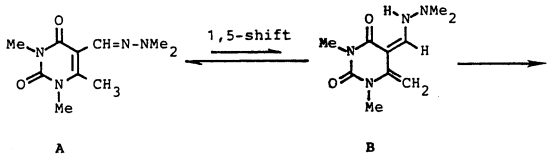
5,6-Dihydro-1,3-dimethyl-6-methylene-5-[(substituted amino)methylene]-2,4(1*H*,3*H*)-pyrimidinedione intermediates (**E**) were characterized spectroscopically and chemically. The cycloaddition reaction of **E** with olefinic dienophiles was carried out in highly regio- and stereoselective manners to give quinazoline derivatives.

Much attention has been focused on the heterocyclic compounds containing pyrimidine nuclei because of a broad range of pharmacological activities and industrial utilities.[2)] In a series of investigations on fused pyrimidine derivatives, we have reported the synthetic usefulness of 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione intermediates.[3)] More recently, the existence of a 5,6-dihydro-6-methylene-5-[(2,2-dimethylhydrazino)methylene]-2,4(1*H*,3*H*)-pyrimidinedione (**B**) from 6-methyl-5-[(dimethylhydrazono)-methyl]-2,4(1*H*,3*H*)-pyrimidinedione (**A**) was confirmed as a [4+2]cycloadduct to *N*-methylmaleimide.[4)]



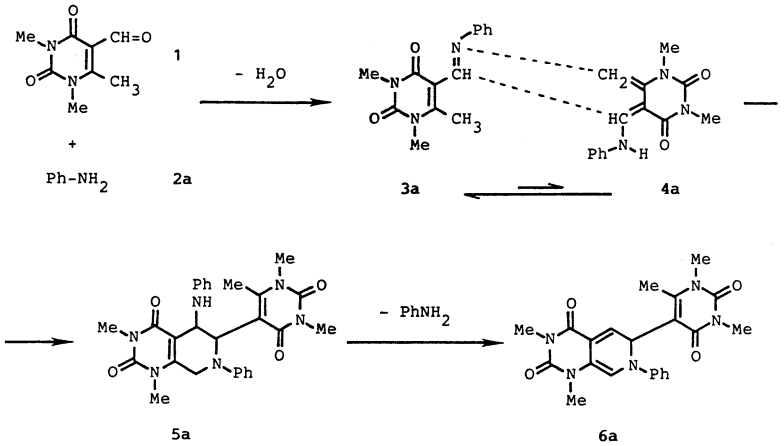
This prompted us to reinvestigate the reaction of 5-formyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinediones with primary amines.[3a,b)] In these reactions, the corresponding aldimines could not be isolated and the final products, pyrido[3,4-*d*]pyrimidine[3a)] and pyrrolo-[3,4-*d*]pyrimidine,[3b)] were obtained. In this paper the characterization of 5,6-dihydro-1,3-dimethyl-6-methylene-5-[(substituted amino)methylene]-2,4(1*H*,3*H*)-pyrimidinediones (**E**) and the profile of their cycloaddition reaction leading to quinazoline derivatives will be discussed.

Results and Discussion

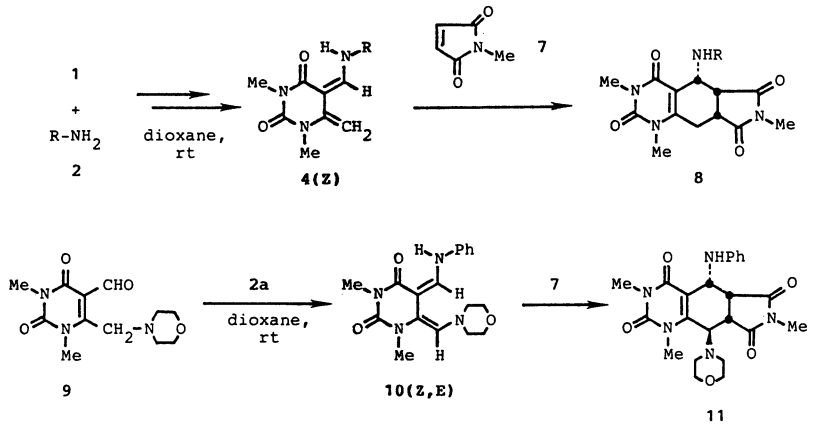
The reaction of 5-formyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**1**) with aniline (**2a**) (1.0 equiv) in deuteriochloroform ($CDCl_3$) was pursued by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of the reaction mixture exhibited the signals assignable to the aldimine **3a** and the final product **6a**,[3a)] but no other intermediates, e.g., **4a** and **5a**, were detected (Scheme 1). In order to elucidate the intermediate **4a**, **1** was allowed to react with **2a** (1.0 equiv) in dioxane at room temperature in the presence of *N*-methylmaleimide (**7**) (1.1 equiv). A sole product **8a**, a (1 : 1) adduct of the intermediate **4a** and **7**, was obtained in 90% yield.

The pyrrolo[3,4-*g*]quinazoline structure for **8a** was confirmed on the basis of analytical and spectral data. The cis-configuration between the 5- and 5a-H was deduced from the coupling constant ($J_{5\text{-}5a}$=5.5 Hz), which was consistent with that of the reported systems.[4,5)]

The reaction of **1** with cyclohexylamine (**2b**), benzylamine (**2c**), and ethyl glycinate (**2d**) in the presence of **7** was also examined. In these cases same type of



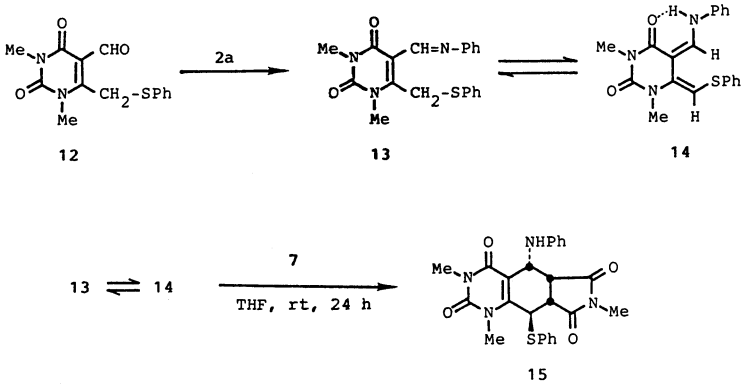
Scheme 1.



Scheme 2.

products **8b—d** were given in good yields. A similar reaction of 6-(morpholinomethyl) derivative **9** gave the corresponding cycloadduct **11**. The stereochemistries among the four methine protons (5-, 5a-, 8a-, and 9-H) of **11** were deduced to be cis, cis, and trans based on the consistence with the related system.[4] This means that the intermediate **10** has the 5*Z*,6*E*-configuration assuming the endo approach of **7** to the diene system of **10** (Scheme 2).

The aldimine **13** could be isolated as stable crystals in the reaction of 6-(phenylthiomethyl) derivative **12** with aniline (**2a**) in benzene. Interestingly, the aldimine **13** partly isomerized to 5,6-dihydro-5-anilinomethylene-1,3-dimethyl-6-(phenylthiomethylene)-



Scheme 3.

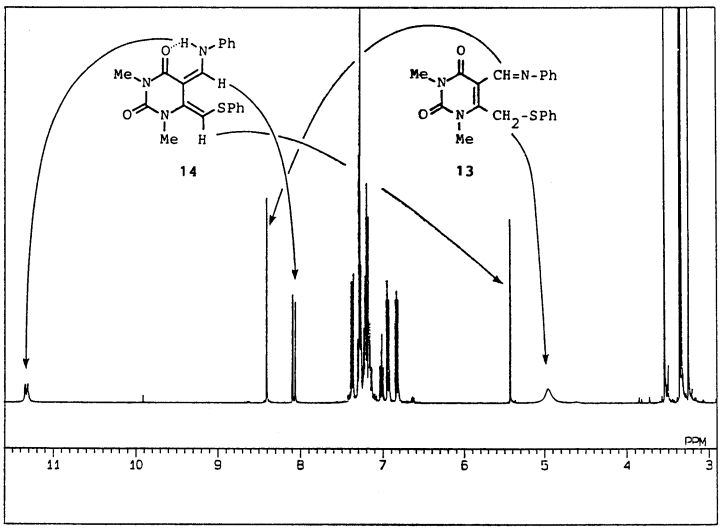


Fig. 1. Isomerization of imine **13** to 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione **14** in $CDCl_3$.

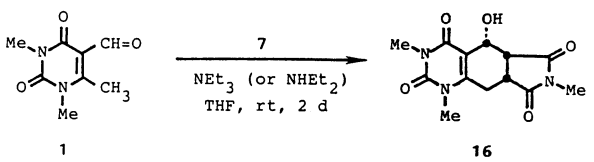
2,4(1*H*,3*H*)-pyrimidinedione (**14**) in $CDCl_3$ (Scheme 3). The ^1H NMR spectrum is demonstrated in Fig. 1. Therein, the signals of the methylene (δ=4.95, br s) and azomethine proton (δ=8.40, s) for **13**, and those of the vinyl protons of 6-methylene (δ=5.42, s) and 5-methylene (δ=8.07, d, J=12.8 Hz) and NH proton (δ=11.32, d, J=12.8 Hz) for **14** were observed. These assignments were confirmed by the treatment with deuterioxide. Three signals at δ=4.95, 5.42, and 11.32 disappeared and the signal at δ=8.07 (doublet) changed to singlet. The 5*Z*,6*E*-configuration for **14** was accomplished by the following evidence: the chemical shift of the NH proton of **14** means the intramolecular hydrogen bond between NH and carbonyl group at 4-position;[6] no NOE signal enhancement between the two vinyl protons at δ=5.42 and 8.07 was observed.

The equilibrium between **13** and **14** depended merely on the nature of solvents. On heating of **13** in dioxane-d_8 at 85 °C, the equilibrium leaned toward the aldimine **13**, but no other isomers, e.g., 5*Z*,6*Z*-isomer, were detected (Table 1).

The aldimine **13** reacted with **7** to give a cycloadduct **15**, which has the same stereochemistries concerning the four methine protons (Scheme 3). These mean that the [4+2]cycloaddition reaction of the 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione intermediates, **10** and **14**, and **7** proceeds with a high endo selectivity. Little solvent effect for the cycloaddition reaction of **13** and **7** was observed.

Table 1. Equilibrium between Imine **13** and 5,6-Dihydro-5-anilinomethylene-1,3-dimethyl-6-(phenylthiomethylene)-2,4(1*H*,3*H*)-pyrimidinedione (**14**) in Some Solvents

Solvent	Temp/ °C	Ratio of **13**:**14**
CD_2Cl_2	31	10:8.5
$CDCl_3$	31	10:9
$CDCl_3/CD_3CN$=1/3	31	10:8.8
Dioxane-d_8	31	10:9
	85	2:1



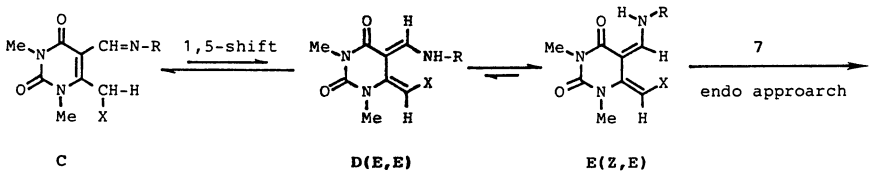
Scheme 4.

To obtain better understandings for the reaction profiles, the similar reaction of **1** with diethylamine or triethylamine in the presence of **7** was examined. In each case the 5-hydroxy derivative **16** was given in moderate yield, of which stereochemistry between the 5- and 5a-H was cis as same as that of **8** (Scheme 4).

This pyrrolo[3,4-*g*]quinazoline synthesis from **1**, **9**, and **12** is explainable as follows: the methyl or methylene group at 6- position of the aldimine **C** is activated, and the [1,5]hydrogen shift of **C** gives the 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione intermediate with 5*E*,6*E*-configuration (**D**), which is isomerized to more stable 5*Z*,6*E*-isomer **E**. The intramolecular hydrogen bond between the NH and carbonyl oxygen at 4-position of **E** would play an important role for the stabilization of the system.[7] The cycloaddition reacton of the intermediate **E** with **7** was carried out stereoselectively to give *endo*-adducts, **8**, **11**, and **15** (Scheme 5).

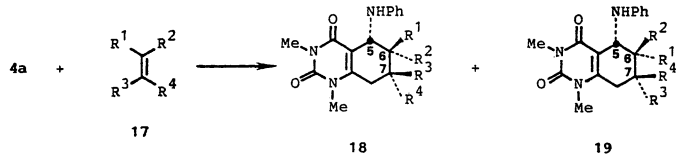
The reaction with other dienophiles was examined in order to elucidate the scopes and limitation of this reaction. The reaction of intermediate **4a**, generated from **1** and aniline (**2a**), with dimethyl fumarate (**17a**) in dioxane under reflux gave two (1:1) adducts **18a** and **19a**. From the analytical and spectral data, **18a** and **19a** were deduced to be stereoisomers of 5-anilino-5,6,7,8-tetrahydro-6,7-bis(methoxycarbonyl)-1,3-dimethyl-2,4(1*H*,3*H*)-quinazolinedione. The elaborate analysis of those ^1H NMR spectra showed that the major **18a** had the 5,6-*cis*-6,7-*trans* configuration and the minor **19a** had the 5,6-*trans*-6,7-*trans* one (See Experimental Section). A little different results were obtained from the reaction with fumaronitrile (**17b**). The major product **18b** with 5,6-*cis*-6,7-*trans* configuration was exclusively formed, which was converted to another product **20** with 5,6-*cis*-6,7-*cis* one. On the other hand, the reaction of **4a** with dimethyl maleate (**17c**) gave a (1:1) adduct **18c** in 28% yield together with a troublesome mixture of products. The regiochemistry of this reaction was elucidated by the reaction of **4a** with ethyl acrylate (**17d**). The 6-ethoxycarbonyl derivatives **18d** and **19d** were obtained, but another regioisomer, 7-ethoxycarbonyl derivative, was not detected. The intermediate **4a** reacted with methyl methacrylate (**17e**) to give the 6-methoxycarbonyl derivatives **18e** and **19e** together with a considerable amount of polymeric products (Table 2).

From the evidence for **14**, it is rationable to assume



Scheme 5.

Table 2. Preparation of Quinazoline Derivatives by the Reaction of 5,6-Dihydro-5-anilinomethylene-1,3-dimethyl-6-methylene-2,4(1*H*,3*H*)-pyrimidinedione (**4a**) with Olefinic Dienophiles (**17**)



	R^1	R^2	R^3	R^4	Reaction Conditions			Total yield/%	Ratio of **18**:**19**[d]
					Solvent	Temp	Time/h		
a	H	CO_2Me	CO_2Me	H	Dioxane	Reflux	20	99	7:2
b	H	CN	CN	H	Dioxane	Reflux	20	98[a]	1:—
c	H	CO_2Me	H	CO_2Me	Dioxane	Reflux	20	28[b]	—:—
d	H	CO_2Et	H	H	Dioxane	Reflux	20	74	5:1
d	H	CO_2Et	H	H	DME	Reflux	24	60	8:1
d	H	CO_2Et	H	H	THF	Reflux	24	39	11:1
d	H	CO_2Et	H	H	Dioxane	Rt	60	0	
e	Me	CO_2Me	H	H	Dioxane	Reflux	24	17[c]	3:2

a) Combined yield with another (1:1) adduct **20**. b) Yield of **18c**. More than five products were detected by TLC. c) Polymeric products were also obtained. d) Determined by isolated products or by ^{1}H NMR spectra of preliminarily separated products.

the *Z*-configuration for the intermediate **4a**. Therefore, the formation of the adducts **18** should be caused by the endo-approach of dienophiles **17** toward the anilinomethylene part of **4a** and, on the other hand, that of **19** by the exo one. The reaction conditions at an elevated temperature would lower the endo-selectivity of the [4+2]cycloaddition reaction of **4a** with **17**. In fact, the reaction of **4a** with **17d** in refluxing 1,2-dimethoxyethane (DME) or tetrahydrofuran (THF) showed an improved endo-selectivity (Table 2).

This paper described the characterization and reaction of 5,6-dihydro-1,3-dimethyl-6-methylene-5-[(substituted amino)methylene]-2,4(1*H*,3*H*)-pyrimidinedione (**E**), which have more reactive diene systems than 6-methylene-5-[(2,2-dimethylhydrazino)-methylene] derivative **B** as reported.[4] The [4+2]-cycloaddition reaction of **E** with olefinic dienophiles proceeded in high regio- and stereoselective manners to give quinazoline derivatives. The obtained diastereomeric products could be separated easily by a chromatography on silica gel. We believe that the cycloaddition reaction of **E** will give a powerful tool for the fused pyrimidine synthesis.

Experimental

General. All melting points are uncorrected. The IR spectra were measured on JASCO IRA-1 and/or IR-Report-100 spectrophotometers. The ^{1}H NMR spectra were obtained on JEOL GSX-400, 270, and/or JMN-MH-100 spectrometers. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal; ov, overlapping with each other. The ^{13}C NMR spectra were obtained on a JEOL GSX-400 or 270 spectrometer. The mass spectra were determined with a JEOL JMS-012G-2 or JMS-D spectrometer and at an ionization energy of 75 eV. The elemental analyses were performed on a Hitachi 026 CHN analyzer. All nonaqueous reactions were run under a positive pressure of argon. All solvents were dried by standard methods before use. The progress of most reactions was monitored by thin-layer chromatography (Silica Gel 60F-254, Merck). The visualization was made with ultraviolet light (254 and 365 nm). Chromatographic purification was performed with Wakogel C-200 (100—200 mesh, Wako Pure Chemical Industries) and/or Silica Gel 60 (230—400 mesh, Merck).

The Characterization of Aldimine 3a by ^{1}H NMR Spectroscopy. A solution of aniline (**2a**) (0.019g, 0.20 mmol) in $CDCl_3$ (0.2 ml) was added to a solution of **1**[8] (0.036 g, 0.20 mmol) in $CDCl_3$ (0.3 ml) in an NMR sample tube. The progress of the reaction was monitored at 31 °C. The ratio of **1**:**3a**:**6**[3a] was determined to be 10:3:0 (3 h), 9:6:1 (12 h), 11:8:8 (24 h), and 1:1.5:11 (55 h), respectively.

1,3,6-Trimethyl-5-[(phenylimino)methyl]-2,4(1*H*,3*H*)-pyrimidinedione (3a): ^{1}H NMR ($CDCl_3$) δ=2.93 (3H, s, $-CH_3$), 3.44, 3.58 (each 3H, 2s, N-CH_3), 6.6—7.4 (phenyl), 8.89 (1H, s, -CH=N-).

The Reaction of 1 with Primary Amines 2 in the Presence of *N*-Methylmaleimide (7). General Procedure: A solution of cyclohexylamine (**2b**) (0.114 ml; 1.0 mmol) in dioxane (1 ml) was added dropwise to a solution of **1** (1.0 mmol) and **7** (1.1 mmol) in dioxane (4 ml) for 10 min. The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated in vacuo to dryness. The crystallization from hexane-ethyl acetate and filtration gave the product **8b** and the filtrate was evaporated to dryness. Column chromatography of the residue on silica gel gave **8b** (hexane/ethyl acetate=1/3). The combined yield of **8b** was 80%.

5-Anilino-5a,8a-dihydro-1,3,7-trimethyl-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetrone (8a): Yield 90%; colorless prisms (ethanol); mp 242—243 °C; IR(KBr) cm^{-1}: 3360 (NH), 1780, 1690, 1650 (CO); ^{1}H NMR (DMSO-

d_6) δ=2.67, 3.14, 3.44 (each 3H, 3s, N-CH_3), 3.1—3.6 (total 4H, ov, 5a-, 8a-, and 9-H), 5.12 (1H, d, NH, $J_{NH\text{-}5}$=5.1 Hz), 5.22 (1H, dd, 5-H, $J_{NH\text{-}5}$=5.1 and $J_{5\text{-}5a}$=7.3 Hz), 6.5—6.7, 7.0—7.1 (total 5H, 2m, phenyl); ^{13}C NMR (DMSO-d_6) δ=22.1 (9-C), 24.1, 27.8, 31.2 (N-CH_3), 36.8 (8a-C), 45.0 (5a-C), 45.5 (5-C), 109.0 (4a-C), 113.2, 116.6, 128.3, 147.8 (phenyl-C), 150.9 (9a-C), 151.2 (2-C), 160.1 (4-C), 176.5, 178.8 (6- and 8-C); MS m/z: 368 (M^+). Found: C, 61.85; H, 5.66; N, 14.93%. Calcd for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47; N, 15.21%.

5-Cyclohexylamino-5a,8a-dihydro-1,3,7-trimethyl-1*H*-pyrrolo-[3,4-*g*]quinazoline-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetrone (8b): Yield 80%; colorless prisms (hexane-ethanol); mp 185—187 °C; IR(KBr) cm^{-1}: 3320 (NH), 1780, 1700, 1680 (CO); ^{1}H NMR ($CDCl_3$) δ=0.6—2.2 (total 12H, ov, cyclohexyl-H and NH), 2.92 (1H, dd, 5a-H, $J_{5\text{-}5a}$=4.0 Hz and $J_{5a\text{-}8a}$=9.2 Hz), 3.04 (3H, s, N-CH_3), 3.1—3.2 (total 3H, ov, 8a- and 9-H), 3.37, 3.51 (each 3H, 2s, N-CH_3), 4.88 (1H, d, 5-H, $J_{5\text{-}5a}$=4.0 Hz); ^{13}C NMR ($CDCl_3$) δ=23.0 (9-C), 24.8 (N-CH_3), 25.2 (cyclohexyl-3′- and -5′-C), 25.9 (cyclohexyl-4′-C), 28.5, 31.7 (N-CH_3), 34.2, 34.7 (cyclohexyl-2′- and -6′-C), 38.2 (8a-C), 46.2 (5a-C), 47.1 (5-C), 55.2 (cyclohexyl-1′-C), 111.3 (4a-C), 149.8 (9a-C), 151.8 (2-C), 160.7 (4-C), 177.0, 179.1 (6- and 8-C); MS m/z: 374 (M^+), 273 (M^+—cyclohexyl-NH_3). Found: C, 60.72; H, 6.95; N, 14.79%. Calcd for $C_{19}H_{26}N_4O_4$: C, 60.94; H, 7.00; N, 14.96%.

5-Benzylamino-5a,8a-dihydro-1,3,7-trimethyl-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetrone (8c): Yield 98%; pale yellow oil; IR (NaCl) cm^{-1}: 3320 (NH), 1780, 1700, 1650 (CO); ^{1}H NMR ($CDCl_3$) δ=3.05 (3H, s, N-CH_3), 3.0—4.5 (total 4H, ov, 5a-, 8a-, and 9-H and NH), 3.32, 3.34 (each 3H, 2s, N-CH_3), 3.46 (1H, dd, 9-H, $J_{8a\text{-}9}$=10.8 Hz and J_{gem}=18.1 Hz), 3.58, 3.75 (each 1H, 2d, -CH_2-Ph, J_{gem}=12.8 Hz), 5.00 (1H, d, 5-H, $J_{5\text{-}5a}$=4.4 Hz), 7.1—7.3 (5H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=23.3 (9-C), 24.9, 28.4, 31.5 (N-CH_3), 38.3 (8a-C), 45.6 (5a-C), 49.4 (5-C), 51.9 (-CH_2-Ph), 109.1 (4a-C), 126.7, 127.4, 128.0, 140.6 (phenyl-C), 150.3 (9a-C), 151.5 (2-C), 161.5 (4-C), 176.9, 178.7 (6- and 8-C); MS m/z: 282 (M^+), 275 (M^+—PhCH_2NH_2), 273 (275—H_2). Found: 383.17077. Calcd for $C_{20}H_{23}N_4O_4$ (M^++H): 383.17178.

5-(Ethoxycarbonylmethyl)amino-5a,8a-dihydro-1,3,7-trimethyl-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetrone (8d): Yield 73%; colorless prisms (ethanol); mp 180—182 °C; IR (KBr) cm^{-1}: 3300 (NH), 1780, 1730, 1700, 1640 (CO); ^{1}H NMR ($CDCl_3$) δ=1.22 (3H, t, -CH_3, J=7.0 Hz), 3.06, 3.35, 3.52 (each 3H, 3s, N-CH_3), 3.0—3.3 (total 7H, ov, 5a-, 8a-, and 9-H and NH and -CH_2-CO_2-), 4.09 (2H, q, -CH_2-, J=7.0 Hz), 4.83 (1H, d, 5-H, $J_{5\text{-}5a}$=4.8 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1 (CH_3), 23.3 (9-C), 24.9, 28.4, 31.8 (N-CH_3), 38.3 (8a-C), 45.4 (5a-C), 49.1, 49.2 (5-C and N-CH_2-), 60.9 (-CH_2-O-), 108.6 (4a-C), 151.1 (9a-C), 151.8 (2-C), 161.3 (4-C), 171.9 (COO), 176.6, 178.5 (6- and 8-C); MS m/z: 379 (M^++H), 276 (M^+—NHCH_2COOC_2H_5). Found: C, 53.89; H, 5.76; N, 14.75%. Calcd for $C_{17}H_{22}N_4O_6$: C, 53.96; H, 5.86; N, 14.81%.

The Reaction of 9[9] with Aniline (2a) in the Presence of 7. Similarly to the reaction of **1**, product **11** was obtained in 90% yield after a column chromatography on silica gel (hexane/ethyl acetate=1/1—1/3).

5-Anilino-5a,8a-dihydro-1,3,7-trimethyl-9-morpholino-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8(3*H*,5*H*,7*H*,9*H*)-tetrone (11): Colorless prisms (ethanol); mp 258—260 °C IR (KBr) cm^{-1}: 3340 (NH), 1780, 1700, 1640 (CO); ^{1}H NMR ($CDCl_3$) δ=2.5—2.7 (4H, m, morpholino methylene), 2.83, 3.27, 3.58 (each 3H, 3s, N-CH_3), 3.32 (1H, dd, 5a-H, $J_{5\text{-}5a}$=5.9 Hz and $J_{5a\text{-}8a}$=8.1 Hz), 3.42 (1H, dd, 8a-H, $J_{5a\text{-}8a}$=8.1 Hz and $J_{8a\text{-}9}$=1.7 Hz), 3.7—3.8 (4H, m, morpholino methylene), 4.37 (1H, d, 9-H, $J_{8a\text{-}9}$=1.7 Hz), 4.40 (1H, d, NH, $J_{NH\text{-}5}$=8.4 Hz), 5.61 (1H, dd, 5-H, $J_{NH\text{-}5}$=8.4 Hz and $J_{5\text{-}5a}$=5.9 Hz), 6.6—6.8, 7.1—7.2 (total 5H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=25.0, 28.5, 33.1 (N-CH_3), 39.4 (8a-C), 42.8 (5a-C), 47.4 (5-C), 49.4 (morpholino-2′- and -6′-C), 57.2 (9-C), 66.8 (morpholino-3′- and -5′-C), 109.4 (4a-C), 113.6, 118.7, 129.2, 146.2 (phenyl-C), 146.7 (9a-C), 151.8 (2-C), 160.6 (4-C), 175.8, 177.1 (6- and 8-C); MS m/z: 453 (M^+), 273 (M^+—PhNH_2—morpholine), 226.5, 93. Found: C, 61.61; H, 6.07; N, 15.24%. Calcd for $C_{23}H_{27}N_5O_5$: C, 61.91; H, 6.00; N, 15.44%.

The Isolation of Aldimine 13 and Its Cycloaddition Reaction with 7. A solution of the 6-(phenylthiomethyl) derivative **12**[9] (0.290 g, 1.0 mmol) and aniline (**2a**) (0.093 g, 1.0 mmol) in benzene (3 ml) was heated under reflux for 4 h. Evaporation of the solvent gave the aldimine **13** in almost quantitative yield. The reaction of **13** with **7** in dioxane at room temperature for 24 h gave the product **15** in 68% yield after a column chromatography on silica gel (hexane/ethyl acetate=1/1).

1,3-Dimethyl-5-[(phenylimino)methyl]-6-(phenylthiomethyl)-2,4(1*H*,3*H*)-pyrimidinedione (13): Yellow plates (hexane-ethanol); mp 120—122 °C; IR (KBr) cm^{-1}: 1680, 1620 (CO); MS m/z: 365 (M^+), 276 (M^+—Ph-N), 256 (M^+—Ph-S). Found: C, 65.88; H, 5.47; N, 11.66%. Calcd for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.24; N, 11.50%.

The ^{13}C NMR spectrum in $CDCl_3$ showed the signals corresponding to those of **13** and **14**: δ=27.6, 28.5, 32.0, 32.6, 32.7 (N-CH_3 and -CH_2-SPh), 90.2, 92.4, 108.3, 116.6, 121.1, 124.3, 126.1, 126.2, 126.8, 128.6, 129.0, 129.2, 129.3, 129.4, 129.8, 133.6, 138.5, 139.5, 141.7, 145.9 (-CH=N-), 151.1, 151.4 (2-C), 151.6 (2-C), 153.3, 155.9, 162.4 (4-C), 165.3 (4-C).

5-Anilino-5a,8a-dihydro-1,3,7-trimethyl-9-phenylthio-1*H*-pyrrolo[3,4-*g*]quinazoline-2,3,6,8(3*H*,5*H*,7*H*,9*H*)tetrone (15): Pale yellow prisms (ethyl acetate); mp 243—245 °C; IR (KBr) cm^{-1}: 3370 (NH), 1770, 1700, 1650 (CO); ^{1}H NMR ($CDCl_3$) δ=2.90, 3.27, 3.32 (each 3H, 3s, N-CH_3), 3.43 (1H, dd, 8a-H, $J_{5a\text{-}8a}$=8.8 Hz and $J_{8a\text{-}9}$=1.6 Hz), 3.59 (1H, dd, 5a-H, $J_{5\text{-}5a}$=6.0 Hz and $J_{5a\text{-}8a}$=8.8 Hz), 4.95 (1H, d, 9-H, $J_{8a\text{-}9}$=1.6 Hz), 5.63 (1H, dd, 5-H, $J_{NH\text{-}5}$=9.6 Hz and $J_{5\text{-}5a}$=6.0 Hz), 6.05 (1H, d, NH, $J_{NH\text{-}5}$=9.6 Hz), 6.7—6.8, 7.2—7.6 (total 10H, 2m, phenyl); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ=24.3, 27.5, 30.6 (N-CH_3), 41.4, 41.6, 43.8 (5a-, 8a-, and 9-C), 47.1 (5-C), 106.2 (4a-C), 112.4, 116.6, 128.4, 129.2, 129.7, 133.8, 146.0 (phenyl-C), 146.9 (9a-C), 150.5 (2-C), 159.9 (4-C), 175.0, 175.4 (6- and 8-C); MS m/z: 273 (M^+—PhSH—PhNH_2), 110, 93. Found: C, 63.00; H, 5.14; N, 11.59%. Calcd for $C_{25}H_{24}N_4O_4S$: C, 63.01; H, 5.08; N, 11.76%.

The Reaction of 1 with 7 in the Presence of Di- or Triethylamine. General procedure: Diethylamine (0.104 ml, 1.0 mmol) was added to a solution of **1** (0.182 g, 1.0 mmol) and **7** (0.166 g, 1.5 mmol) in THF (4 ml) and the reaction mixture was stirred at room temperature for 2 d. The resultant crystals **16** (0.119 g, 41%) were collected by filtration. Similarly, **16** was obtained in 39% yield from the reaction of **1** with **7** in the presence of triethylamine.

5a,8a-Dihydro-5-hydroxy-1,3,7-trimethyl-1*H*-pyrrolo[3,4-*g*]quinazoline-2,4,6,8(3*H*,5H,7*H*,9*H*)-tetrone (16): Colorless crystals; mp 245—249 °C; IR (KBr) cm^{-1}: 3460 (NH), 1780, 1690, 1650 (CO); ^{1}H NMR (DMSO-d_6) δ=2.7—3.0 (2H,

ov, 9-H), 2.85, 3.20, 3.43 (each 3H, 3s, N-CH_3), 3.2—3.5 (2H, ov, 5a- and 8a-H), 5.20 (1H, t, 5-H, J=3.7 Hz), 5.35 (br d, 1H, OH, J=3.7 Hz); ^{13}C NMR (DMSO-d_6) δ=22.4 (9-C), 24.1, 27.7, 31.0 (N-CH_3), 35.9 (8a-C), 45.7 (5a-C), 59.7 (5-C), 109.4 (4a-C), 151.3, 151.6 (2- and 9a-C), 160.1 (4-C), 176.5, 179.5 (6- and 8-C); MS m/z: 293 (M^+). Found: C, 53.50; H, 5.33; N, 14.50%. Calcd for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.16; N, 14.33%.

The Reaction of 4a with Olefinic Dienophiles 17. General Procedure: A solution of **2a** (1.0 mmol) in dioxane (1 ml) was added to a solution of **1** (1.0 mmol) and dimethyl fumarate (**17a**) (1.1 mmol) in dioxane (4 ml), and the reaction mixture was heated under reflux for 18 h. Evaporation of the solvent gave a residue, which was subjected to a column chromatography on silica gel to give the mixture of **18a** and **19a** (0.398 g, 0.99 mmol, **18a**/**19a**=7 : 2) as elution of hexane/ethyl acetate (1/2—1/3). Flash chromatography on silica gel of the mixture gave **18a** (hexane/ethyl acetate=1/2) and **19a** (1/3).

***c*-5-Anilino-5,6,7,8-tetrahydro-1,3-dimethyl-*r*-6,*t*-7-bis(methoxycarbonyl)-2,4(1*H*,3*H*)-quinazolinedione (18a):** Colorless needles (ethanol); mp 223—225 °C; IR (KBr) cm^{-1}: 3400 (NH), 1750, 1730, 1700, 1650 (CO); ^{1}H NMR ($CDCl_3$) δ=2.52 (1H, dd, 8-H, $J_{7\text{-}8}$=11.7 Hz and J_{gem}=17.6 Hz), 2.98 (1H, dd, 6-H, $J_{5\text{-}6}$=4.4 Hz and $J_{6\text{-}7}$=12.4 Hz), 3.04 (1H, dd, 8-H, $J_{7\text{-}8}$=6.2 Hz and J_{gem}=18.0 Hz), 3.28 (1H, ddd, 7-H, $J_{6\text{-}7}$=2.5 Hz and $J_{7\text{-}8}$=5.9 and 11.7 Hz), 3.31, 3.32, 3.38 (each 3H, 3s, N-CH_3 and O-CH_3), 3.2—3.4 (1H, br, NH), 3.78 (3H, s, O-CH_3), 5.31 (1H, d, 5-H, $J_{5\text{-}6}$=4.4 Hz), 6.6—6.9, 7.1—7.2 (total 5H, 2m, phenyl); ^{13}C NMR ($CDCl_3$) δ=28.3, 31.0 (N-CH_3), 29.3 (8-C), 37.0 (7-C), 45.6 (6-C), 47.4 (5-C), 51.8, 52.6 (O-CH_3), 109.5 (4a-C), 114.2, 118.5, 129.0, 146.2 (phenyl-C), 146.7 (8a-C), 151.8 (2-C), 161.4 (4-C), 171.4, 173.9 (COO); MS m/z: 401 (M^+). Found: C, 59.76; H, 5.78; N, 10.33%. Calcd for $C_{20}H_{23}N_3O_6$: C, 59.84; H, 5.78; N, 10.47%.

***t*-5-Anilino-5,6,7,8-tetrahydro-1,3-dimethyl-*r*-6,*t*-7-bis(methoxycarbonyl)-2,4(1*H*,3*H*)-quinazolinedione (19a):** Colorless needles (ethanol); mp 211—212 °C; IR(KBr) cm^{-1}: 3380 (NH), 1720, 1680, 1640 (CO); ^{1}H NMR ($CDCl_3$) δ=2.90 (1H, dd, 8-H, $J_{7\text{-}8}$=7.7 Hz, J_{gem}=18.3 Hz), 3.23 (1H, d, 8-H, $J_{7\text{-}8}$=0 Hz and J_{gem}=18.0 Hz), 3.34, 3.42, 3.48, 3.77 (each 3H, 4s, N-CH_3 and O-CH_3), 3.3—3.5 (2H, ov, NH and 7-H), 3.87 (1H, dd, 6-H, $J_{5\text{-}6}$=2.2 Hz and $J_{6\text{-}7}$=2.2 Hz), 5.05 (1H, br s, 5-H), 6.6—6.8, 7.1—7.2 (total 5H, 2m, phenyl); ^{13}C NMR ($CDCl_3$) δ=24.8 (8-C), 28.2, 30.9 (N-CH_3), 36.4 (7-C), 42.3 (6-C), 46.8 (5-C), 52.3, 52.7 (O-CH_3), 106.1 (4a-C), 112.9, 118.3, 129.3, 146.0 (phenyl-C), 149.4 (8a-C), 151.8 (2-C), 161.5 (4-C), 171.8, 174.2 (COO); MS m/z: 401 (M^+). Found: C, 59.91; H, 5.89; N, 10.33%. Calcd for $C_{20}H_{23}N_3O_6$: C, 59.84; H, 5.78; N, 10.47%.

The assignments of the proton signals for **18a** and **19a** were confirmed by their COSY spectra. More details of their structures were attained by the NOE measurements between the 5- and 6-H; the 8.5% signal enhancement for **18a** and the 8.2% one for **19a** were observed. These results mean that the configurations among the 5-, 6-, and 7-H are 5(eq)-6(ax)-6(ax) for **18a** and 5(eq)-6(eq)-7(eq) for **19a**, assuming that the cyclohexene rings of **18** and **19** have a pseudo chair form.

***c*-5-Anilino-*r*-6,*t*-7-dicyano-5,6,7,8-tetrahydro-1,3-dimethyl-2,4(1*H*,3*H*)-quinazolinedione (18b):** Colorless prisms (ethanol); mp 262—264 °C; IR (KBr) cm^{-1}: 3360 (NH), 2240 (CN), 1700, 1660 (CO); ^{1}H NMR (DMSO-d_6) δ=3.09 (1H, dd, 8-H, $J_{7\text{-}8}$=11.2 Hz and J_{gem}=17.9 Hz), 3.13, 3.35 (each 3H, 2s, N-CH_3), 3.35 (1H, dd, 8-H, $J_{7\text{-}8}$=5.9 Hz and J_{gem}=17.9 Hz), 3.57 (1H, dd, 6-H, $J_{5\text{-}6}$=3.4 Hz and $J_{6\text{-}7}$=12.2 Hz), 3.72 (1H, ddd, 7-H, $J_{6\text{-}7}$=12.2 Hz and $J_{7\text{-}8}$=5.9 and 11.2 Hz), 5.13 (1H, dd, 5-H, $J_{5\text{-}6}$=3.4 Hz and $J_{5\text{-}NH}$=8.0 Hz), 5.67 (1H, d, NH, $J_{NH\text{-}5}$=8.0 Hz), 6.6—7.1 (5H, m, phenyl); MS m/z: 335 (M^+). Found: C, 64.13; H, 5.28; N, 20.64%. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.46; H, 5.11; N, 20.89%.

***c*-5-Anilino-*r*-6,*c*-7-dicyano-5,6,7,8-tetrahydro-1,3-dimethyl-2,4(1*H*,3*H*)-quinazolinedione (20):** Colorless needles (ethanol); mp 281—284 °C; IR(KBr) cm^{-1}: 3400 (NH), 2240 (CN), 1700, 1650 (CO); ^{1}H NMR (DMSO-d_6) δ=3.17 (1H, dd, 8-H, $J_{7\text{-}8}$=7.0 Hz and J_{gem}=19.0 Hz), 3.28 (1H, dd, $J_{7\text{-}8}$=2.9 Hz and J_{gem}=19.0 Hz), 3.25, 3.44 (each 3H, 2s, N-CH_3), 3.79 (1H, dd, 6-H, $J_{5\text{-}6}$=2.9 Hz and $J_{6\text{-}7}$=3.3 Hz), 3.98 (1H, ddd, 7-H, $J_{6\text{-}7}$=3.3 Hz and $J_{7\text{-}8}$=2.9 and 7.0 Hz), 4.84 (1H, dd, 5-H, $J_{NH\text{-}5}$=5.5 Hz and $J_{5\text{-}6}$=2.9 Hz), 5.58 (1H, d, NH, $J_{NH\text{-}5}$=5.5 Hz), 6.6—6.7, 7.1—7.2 (total 5H, 2m, phenyl); ^{13}C NMR (DMSO-d_6) δ=23.0, 25.8, 29.1 (6-, 7-, and 8-C), 27.8, 30.9 (N-CH_3), 47.1 (5-C), 105.0 (4a-C), 112.4, 117.0, 129.0 (phenyl-C), 117.6, 118.9 (CN), 146.0, 146.7 (8a-C and phenyl-C), 151.2 (2-C), 160.7 (4-C); MS m/z: 335 (M^+). Found: C, 64.38; H, 5.20; N, 20.88%. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.46; H, 5.11; N, 20.89%.

The signal patterns and coupling constants of the ^{1}H NMR spectrum of **18b** were almost consistent with those of **18a**. Heating of the mixture of **18b** and **20** (1 : 1) in dioxane in the presence of a catalytic amount of aniline (**2a**) for 20 h gave the **18b** and **20** (5 : 1), but the heating without **2a** did not give any change.

***c*-5-Anilino-5,6,7,8-tetrahydro-*r*-6,*c*-7-bis(methoxycarbonyl)-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (18c):** Colorless needles (ethanol); mp 271—273 °C; IR (KBr) cm^{-1}: 3330 (NH), 1720, 1670 (CO); ^{1}H NMR ($CDCl_3$) δ=2.95 (1H, dd, 8-H, J_{gem}=18.3 Hz and $J_{7\text{-}8}$=6.2 Hz), 3.20 (1H, dd, 8-H, J_{gem}=18.3 Hz and $J_{7\text{-}8}$=11.4 Hz), 3.35, 3.48 (3H, 2s, N-CH_3), 3.67 (1H, dd, 6-H, $J_{5\text{-}6}$=2.4 Hz and $J_{6\text{-}7}$=3.3 Hz), 3.7 (total 8H, ov, OCH_3, 7-H, and NH), 5.06 (1H, d, 5-H, $J_{NH\text{-}5}$=2.4 Hz), 6.7—6.8, 7.2—7.6 (total 5H, 2m, phenyl); ^{13}C NMR ($CDCl_3$) δ=25.7, 31.0 (N-CH_3), 28.2 (8-C), 35.8 (7-C), 43.0 (5-C), 52.3, 52.4 (O-CH_3), 106.6 (4a-C), 113.5, 118.7, 129.5, 146.2 (phenyl-C), 149.8 (8-C), 151.8 (2-C), 161.6 (4-C), 171.3, 172.8 (COO); MS m/z: 401 (M^+). Found: C, 59.52; H, 5.90; N, 10.73%. Calcd for $C_{20}H_{23}N_3O_6$: C, 59.84; H, 5.78; N, 10.47%.

***c*-5-Anilino-*r*-6-ethoxycarbonyl-5,6,7,8-tetrahydro-1,3-dimethyl-2,4(1*H*,3*H*)-quinazolinedione (18d):** Colorless plates (ethanol); mp 218—221 °C; IR (KBr) cm^{-1}: 3350 (NH), 1720, 1690, 1630 (CO); ^{1}H NMR ($CDCl_3$) δ=1.04 (3H, t, -CH_3, J=7.0 Hz), 2.08, 2.24 (each 2H, 2m, 7-H), 2.45 (1H, ddd, 8-H, $J_{7\text{-}8}$=7.0 and 12.1 Hz and J_{gem}=18.3 Hz), 2.62 (1H, ddd, 6-H, $J_{6\text{-}7}$=3.3 and 13.2 Hz and $J_{5\text{-}6}$=4.0 Hz), 2.76 (1H, ddd, 8-H, $J_{7\text{-}8}$=1.2 and 5.7 Hz and J_{gem}=18.3 Hz), 3.32, 3.39 (each 3H, 2s, N-CH_3), 3.3—3.5 (1H, br, NH), 3.58, 3.90 (each 2H, dq, -CH_2-, J=7.0 Hz and J_{gem}=11.0 Hz), 5.27 (1H, d, 5-H, $J_{5\text{-}6}$=4.0 Hz), 6.6—7.2 (5H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=14.0 (CH_3), 18.6 (8-C), 25.9 (7-C), 28.2, 30.9 (N-CH_3), 43.6 (6-C), 47.4 (5-C), 110.2 (4a-C), 114.7, 118.6, 128.9 (phenyl-C), 147.3, 148.6 (phenyl-C and 8a-C), 151.9 (2-C), 161.9 (4-C), 172.0 (CO); MS m/z: 357 (M^+). Found: C, 63.90; H, 6.66; N, 11.75%. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.48; N, 11.76%.

***t*-5-Anilino-*r*-6-ethoxycarbonyl-5,6,7,8-tetrahydro-1,3-dimethyl-2,4(1*H*,3*H*)-quinazolinedione (19d):** Colorless prisms (ethanol); mp 198—199 °C; IR (KBr) cm^{-1}: 3360 (NH), 1720, 1690, 1640 (CO); ^{1}H NMR ($CDCl_3$) δ=1.28 (3H,

t, -CH_3, J=7.0 Hz), 2.08, 2.26 (each 1H, 2m, 7-H), 2.55 (1H, ddd, 8-H, $J_{7\text{-}8}$=5.7 and 0.6 Hz and J_{gem}=18.3 Hz), 2.83 (1H, ddd, 8-H, $J_{7\text{-}8}$=7.0 and 11.7 Hz and J_{gem}=18.3 Hz), 3.09 (1H, dd, 6-H, $J_{6\text{-}7}$=3.7 and 5.5 Hz), 3.34, 3.39 (each 3H, 2s, N-CH_3), 3.6—3.8 (1H, br, NH), 4.06—4.26 (2H, ov, -CH_2-), 5.02 (1H, br s, 5-H), 6.7—6.8, 7.1—7.3 (total 5H, 2m, phenyl); ^{13}C NMR ($CDCl_3$) δ=14.2 (CH_3), 18.3 (7-C), 23.4 (8-C), 28.2, 30.7 (N-CH_3), 39.9 (6-C), 47.3 (5-C), 60.9 (-CH_2-), 107.3 (4a-C), 113.4, 118.2, 129.4, 146.5 (phenyl-C), 150.5 (8a-C), 151.9 (2-C), 161.9 (4-C), 172.4 (COO); MS m/z: 357 (M^+). Found: C, 64.12; H, 6.61; N, 11.60%. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.48; N, 11.76%.

The NOE measurement between the 5- and 6-H for **18d** (6.8% signal enhancement) shows that the configurations of the 5- and 6-H are equatorial and axial, respectively. The configurations of the 5- and 6-H for **19d** are both equatorial, because the 5.5% signal enhancement was observed on the NOE measurement between the 5- and 6-H. These assignments were confirmed by the inspections of their molecular models; the anilino and ethoxycarbonyl groups for **18d** are crowded each other, and, therefore, the methylene and methyl protons of the ethoxyl group are shielded by the phenyl one. This upper-field shift effect due to phenyl group was available to the structural elucidation of adducts **18e** and **19e**.

***c*-5-Anilino-5,6,7,8-tetrahydro-*r*-6-methoxycarbonyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-quinazolinedione (18e):** Colorless needles (ethanol); mp 254—255 °C; IR (KBr) cm^{-1}: 3350 (NH), 1730, 1690, 1640 (CO); ^{1}H NMR ($CDCl_3$) δ=1.21 (3H, s, -CH_3), 2.04 (1H, dd, 5-H, $J_{7\text{-}8}$=7.3 Hz and J_{gem}=13.7 Hz), 2.25 (1H, ddd, 8-H, $J_{7\text{-}8}$=7.3 and 12.0 Hz and J_{gem}=13.7 Hz), 2.47 (1H, ddd, 7-H, $J_{7\text{-}8}$=7.3 and 11.7 Hz and $J_{7\text{-}8}$=18.8 Hz), 2.74 (1H, dd, 7-H, $J_{7\text{-}8}$=5.4 Hz and J_{gem}=18.8 Hz), 3.25, 3.32 (each 3H, 2s, N-CH_3), 3.35 (1H, br, NH), 3.42 (3H, s, -OCH_3), 4.91 (1H, br s, 5-H), 6.7—7.2 (5H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=19.5 (CH_3), 23.4, 23.9 (7- and 8-C), 28.9, 30.9 (N-CH_3), 44.8 (6-C), 51.5, 52.5 (5-C and OCH_3), 109.0 (4a-C), 114.3, 118.1, 128.9 (phenyl-C), 147.0, 147.3 (phenyl-C and 8a-C), 151.9 (2-C), 162.3 (4-C), 175.4 (COO); MS m/z: 358 (M^+). Found: C, 63.63; H, 6.55; N, 11.64%. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.48; N, 11.76%.

***t*-5-Anilino-5,6,7,8-tetrahydro-*r*-6-methoxycarbonyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-quinazolinedione (19e):** Colorless prisms (ethanol); mp 259—262 °C; IR (KBr) cm^{-1}: 3360 (NH), 1720, 1680, 1640 (CO); ^{1}H NMR ($CDCl_3$) δ=1.24 (3H, s, -CH_3), 2.0, 2.1, 2.6 (total 4H, ov, 7- and 8-H), 3.24, 3.36 (each 3H, 2s, N-CH_3), 3.67 (3H, s, OCH_3), 4.44 (1H, d, NH, $J_{NH\text{-}5}$=9.3 Hz), 5.08 (1H, br d, 5-H, $J_{NH\text{-}5}$=7.8 Hz), 6.6, 6.8, 7.1 (total 5H, 3m, phenyl); ^{13}C NMR ($CDCl_3$) δ=22.3, 23.5, 24.8 (CH_3 and 7- and 8-C), 26.9, 29.6 (N-CH_3), 45.4 (6-C), 47.8 (5-C), 51.0 (O-CH_3), 108.7 (4a-C), 111.5, 115.4, 127.9, 147.6 (phenyl-C), 147.9 (8a-C), 150.6 (2-C), 160.5 (4-C), 174.5 (COO); MS m/z: 358 (M^+). Found: C, 63.59; H, 6.47; N, 11.54%. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.48; N, 11.76%.

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