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Studies on 4(1*H*)-Quinazolinones. III.[1] Some Derivatizations of 2-Ethoxycarbonylalkyl-1-substituted-4(1*H*)-quinazolinones

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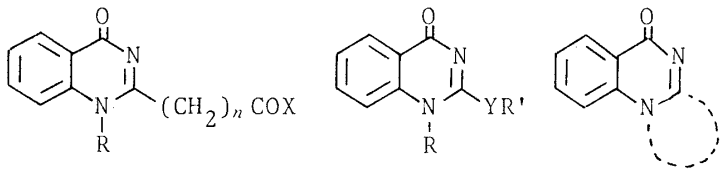
Reactions of 2-(substituted-amino)benzamide (**1**) with ethyl chloroformylformate (**2**), ethyl chloroformylacetate (**3**), and ethyl 2-chloroformylpropionate (**4**) gave 1-substituted 4(1*H*)-quinazolinones (**5**, **6**, and **7**, respectively) having an ethoxycarbonyl group on the substituent at position 2. 2-Ethoxycarbonyl-1-methyl-4(1*H*)-quinazolinone (**5b**) was converted to the carboxylic acid **14**, the hydroxamic acid **16**, the amide **18**, and the nitrile **19**. The nitrile **19** was allowed to react with various nucleophiles to give 1-methyl-4(1*H*)-quinazolinones (**17**, **20**, **21**, and **22**) having a substituted heteroatom at position 2. The reaction of **19** with sodium azide gave 1,2-dihydro-4-hydroxy-1-methyl-2-(5*H*-tetrazol-5-ylidene)-quinazoline (**25**) which is the 1,3-dipolar addition product to the cyano group. The intramolecular ring closures of **5**, **6**, and **7** having an alkoxycarbonylalkyl or chloroalkyl group at position 1 proceeded by using an appropriate base or heating to give the corresponding pyrrolo- or pyrido[1,2*a*]quinazolinones (**27**, **28**, **29**, **31**, and **32**).

Keywords——4(1*H*)-quinazolinone; ring closure; decarboxylation; Lossen rearrangement; substitution reaction; intramolecular Dieckmann condensation; pyrroloquinazolinone; pyridoquinazolinone

In recent years, we have investigated the synthesis and biological activity of 4(1*H*)-quinazolinones. During the course of this work, it was found that some of these quinazolinones showed potent antiinflammatory and/or antiallergic activity.[2] Therefore, our interest was extended to the synthesis of the following derivatives in a search for a more effective compound: (1) introduction of a carbonyl moiety into the substituent at position 2 (type I); (2) introduction of a substituted heteroatom directly into position 2 (type II); (3) interlinking of the substituents at position 1 and position 2 (type III). In addition, we expected that some of the type I 4(1*H*)-quinazolinones might be useful as starting materials for synthesis of the other types (type II and III) of 4(1*H*)-quinazolinones.



type I type II type III

Chart 1

Most of the type I 4(1*H*)-quinazolinones were prepared from the corresponding anthranilamides by the methods developed in our laboratory.[1a] Thus, the reaction of 2-(substituted-amino)-benzamides (**1**) with ethyl chloroformylformate (**2**) in chloroform gave 1-substituted 2-ethoxycarbonyl-4(1*H*)-quinazolinones (**5**) in good yields. The cyclization of **1** with ethyl chloroformylacetate (**3**) or ethyl 2-chloroformylpropionate (**4**) proceeded analogously to give 1-substituted 2,3-dihydro-2-ethoxycarbonylmethylidene-4(1*H*)-quina-

zolinones (**6**) or 2-(1-ethoxycarbonylethyl)-1-phenyl-4(1*H*)-quinazolinone (**7a**), respectively.

However, the reaction of 2-(2-chloroethylamino)benzamide (**1f**) with **4** gave an oily product, having the parent peak at *m/e* 418 in the mass spectrum (MS), instead of 1-(2-chloroethyl)-2-(1-ethoxycarbonylethyl)-4(1*H*)-quinazolinone (**7b**). The infrared (IR), nuclear magnetic resonance (NMR), and mass spectra of the oily product were identical with those of the *O*-acyl derivative **8** obtained by the reaction of 2-(2-hydroxyethylamino)-benzamide (**1g**) with **4**. It is likely that this reaction occurs *via* the intermediates **12** and **13**, as shown in Chart 3. The synthesis of **7b** was accomplished by treatment of **8** with sodium hydrogen carbonate, followed by chlorination with thionyl chloride. To avoid this, 1-(3-chloropropyl)-2-(1-ethoxycarbonylethyl)-4(1*H*)-quinazolinone (**7c**) was prepared from 2-(3-hydroxypropylamino)benzamide (**1h**) through **9** and **11**.

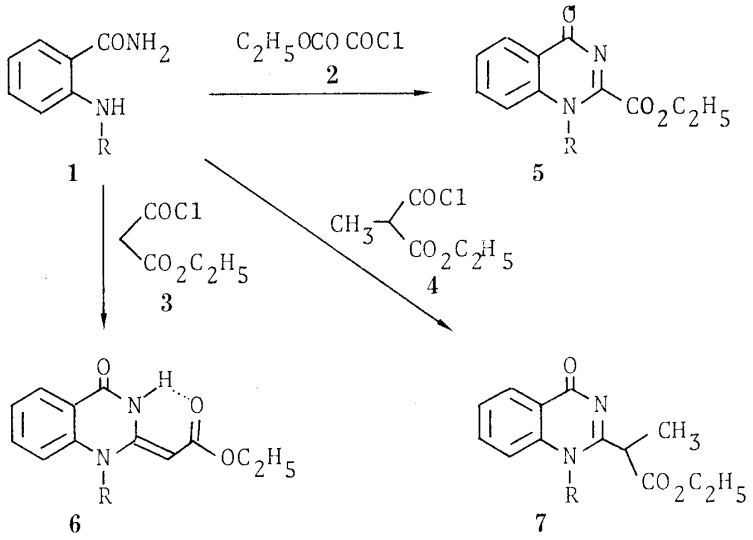


Chart 2

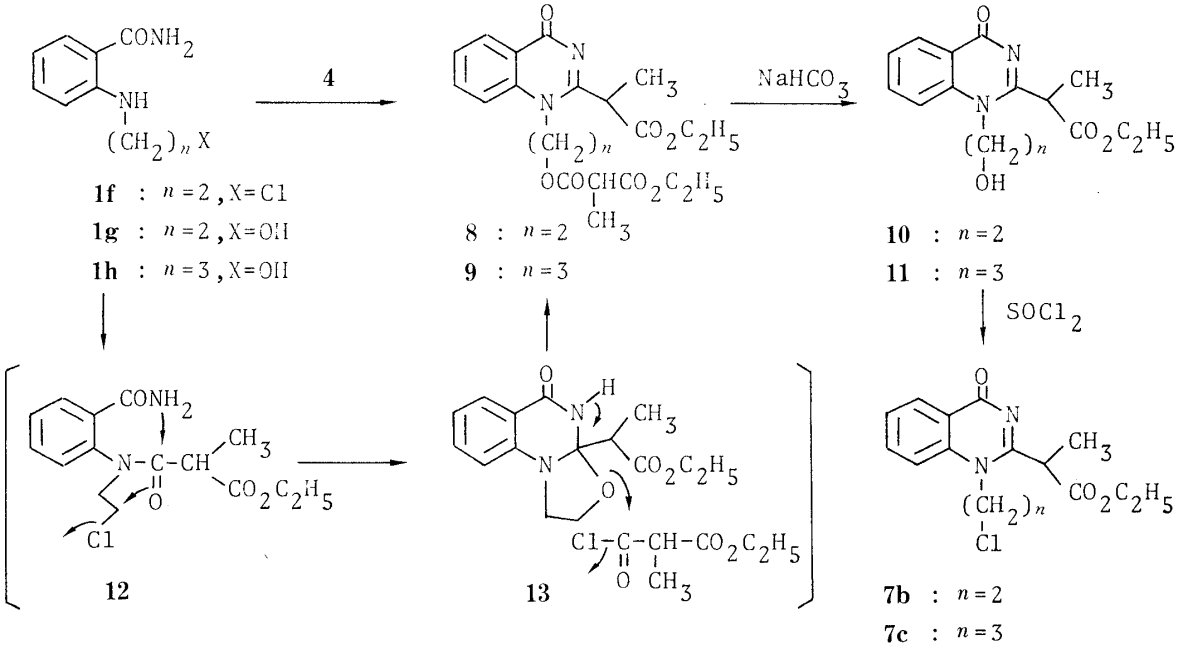
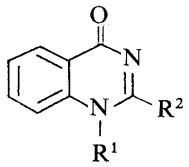


Chart 3

TABLE I. 2-Ethoxycarbonylalkyl-1-substituted-4(1*H*)-quinazolinones



Compd.	R^1	R^2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)			
						C	H	Cl	N
5a	C_6H_5	$CO_2C_2H_5$[a]	84	193—195					
5b	CH_3	$CO_2C_2H_5$	91	170—172	$C_{12}H_{12}N_2O_3$	62.06 (61.98	5.21 5.19		12.06 12.13)
5c	$(CH_2)_2CO_2CH_3$	$CO_2C_2H_5$	74	110—112	$C_{15}H_{16}N_2O_5$	59.20 (59.18	5.30 5.45		9.21 9.32)
5d	$(CH_2)_3CO_2C_2H_5$	$CO_2C_2H_5$	84	117—119	$C_{17}H_{20}N_2O_5$	61.43 (61.57	6.07 6.10		8.43 8.45)
6a	C_6H_5	$CH_2CO_2C_2H_5$[b]	92	235—237	$C_{18}H_{16}N_2O_3$	70.12 (69.78	5.23 5.15		9.09 9.19)
6b	$CH_2CO_2CH_3$	$CH_2CO_2C_2H_5$[b]	72	173—175	$C_{15}H_{16}N_2O_5$	59.20 (59.21	5.30 5.52		9.21 9.35)
6c	$(CH_2)_2CO_2CH_3$	$CH_2CO_2C_2H_5$[b]	50	160—162	$C_{16}H_{18}N_2O_5$	60.37 (60.25	5.70 5.81		8.80 8.91)
7a	C_6H_5	$CH(CH_3)CO_2C_2H_5$	84	186—188	$C_{19}H_{18}N_2O_3$	70.79 (70.54	5.63 5.74		8.69 8.47)
7b	$(CH_2)_2Cl$	$CH(CH_3)CO_2C_2H_5$	94	133—134	$C_{15}H_{17}ClN_2O_3$	58.35 (58.51	5.55 5.60	11.48 11.08	9.07 8.88)
7c	$(CH_2)_3Cl$	$CH(CH_3)CO_2C_2H_5$	87	138—140	$C_{16}H_{19}ClN_2O_3$	59.53 (59.53	5.93 5.92	10.98 10.74	8.68 8.75)

a) Reported in our preceding paper.[1a] *b*) Exomethylene structure.

The structures of **6** and **7** were determined by the following spectral data. The IR spectrum of **7a** showed an ester carbonyl stretching band at 1727 cm^{-1} and the NMR spectrum showed a doublet of 3H and a quartet of 1H at δ 1.55 and 3.56 owing to the protons of the $CH \cdot CH_3(CO_2Et)$ group, while an ester carbonyl stretching band in the IR spectrum of 2,3-dihydro-2-(ethoxycarbonylmethylidene)-1-phenyl-4(1*H*)-quinazolinone (**6a**) shifted to 1696 cm^{-1} due to the effects of the α,β-unsaturated double bond and intramolecular hydrogen bonding. The NMR spectrum of **6a** showed a sharp singlet signal of the exomethylene proton at δ 3.80 and a broad singlet signal of the position 3 proton at δ 12.32. A similar NMR spectrum has been observed in an analogous system by Blatter *et al.*[3]

2-Carboxy-1-methyl-4(1*H*)-quinazolinone (**14**) was prepared by alkaline hydrolysis of 2-ethoxycarbonyl-1-methyl-4(1*H*)-quinazolinone (**5b**), followed by acidification. When a suspension of **14** in chloroform was allowed to stand at room temperature, decarboxylation took place to give 1-methyl-4(1*H*)-quinazolinone (**15**).[4] Baker *et al.*[5] have already reported that similar decarboxylation proceeds in 4(3*H*)-quinazolinone-2-carboxylic acid. The hydroxamic acid **16** or the amide **18** was obtained by the reaction of **5b** with hydroxylamine or ammonia in good yield. The former, **16**, changed explosively to 2-amino-1-methyl-4(1*H*)-quinazolinone (**17**), the Lossen rearrangement product, on heating at the melting point (198 °C). This provided a simple method for the synthesis of **17**.

We next sought to develop a general synthetic method for the preparation of the type II 4(1*H*)-quinazalonones. It is known that a nitrile function bonded to a π-electron deficient

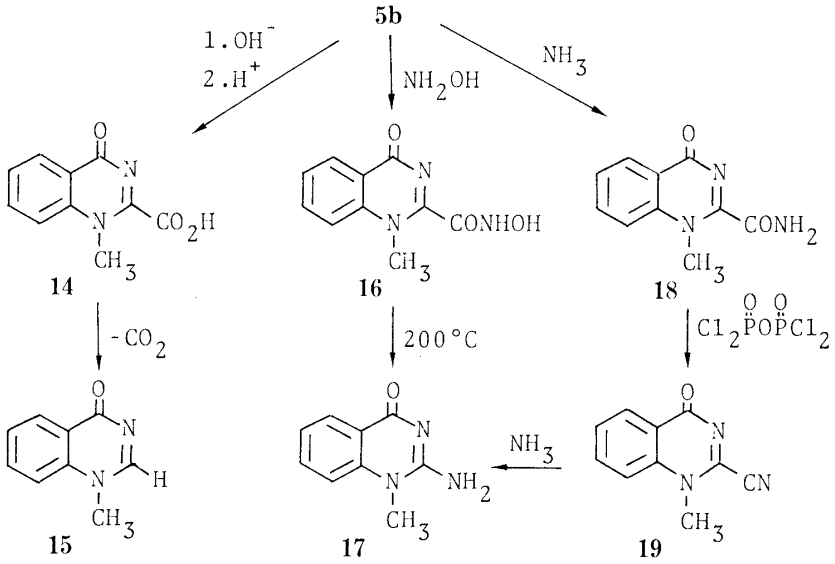


Chart 4

position in a heteroaromatic ring is susceptible to attack by various nucleophiles to give substitution[6] or addition[7] products. We thus attempted to synthesize 2-cyano-1-methyl-4(1*H*)-quinazolinone (**19**). Treatment of **18** with thionyl chloride or phosphoryl chloride gave a complex mixture and the nitrile **19** could not be isolated. Dehydration from **18** to **19** was therefore accomplished by using pyrophosphoryl chloride,[8] which is a mild dehydrating agent.[9] The nitrile **19** was treated with ammonia under ice cooling to afford **17**, the spectral data of which were identical with those of the sample obtained from **16**.

The investigation was extended to the reaction of **19** with various nucleophiles. Reaction of **19** with methylamine proceeded analogously to give 1-methyl-2-methylamino-4(1*H*)-quinazolinone (**20**). Treatment of **19** with β-mercaptopropionic acid or hydroxyacetic acid in the presence of triethylamine gave 2-(2-carboxyethylthio)-1-methyl-4(1*H*)-quinazolinone (**21**) or 2-carboxymethoxy-1-methyl-4(1*H*)-quinazolinone (**22**), respectively in fairly good yield. Further, **19** was allowed to react with the sodium salt of diethyl malonate to afford 2-bis(ethoxycarbonyl)methylidene-2,3-dihydro-1-methyl-4(1*H*)-quinazolinone (**23**) in 71% yield. As described above, the reaction of **19** with various nucleophiles resulted in the substitution reaction of the cyano group to afford the type II 4(1*H*)-quinazolinones.

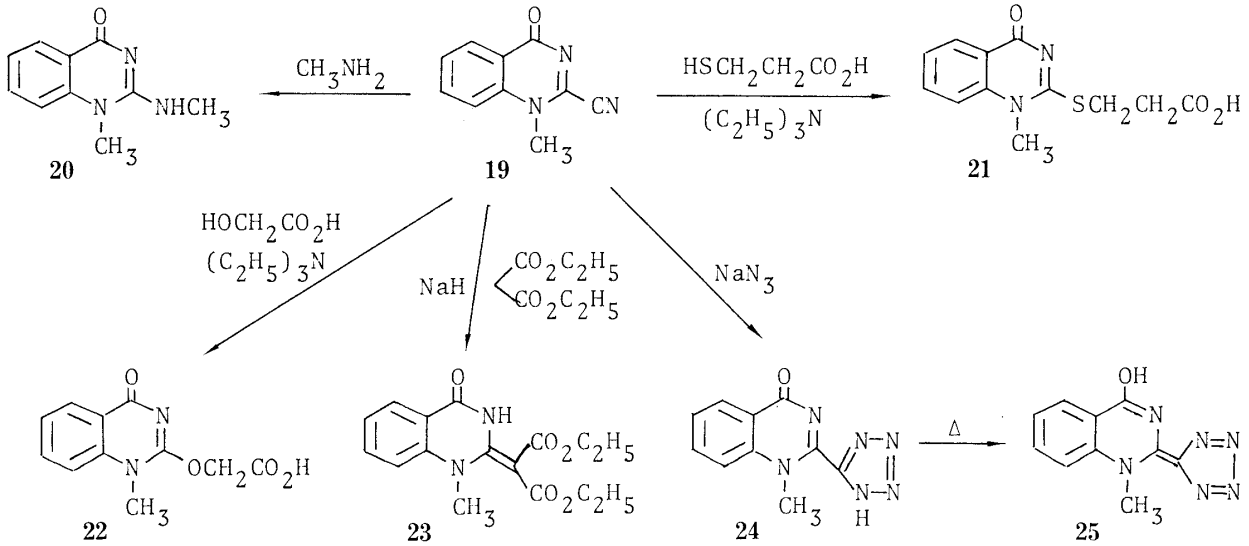


Chart 5

Higashino *et al.*[7] have reported that addition to the cyano group proceeded predominantly over substitution in the reaction of 4-isopropyl-2-quinazolinecarbonitrile with nucleophiles. The difference of results may be explained in terms of increased electrophilicity of position 2 in **19** owing to the mesomeric effect of the carbonyl group at position 4, compared with that of position 2 in Higashino's compound.

In contrast, reaction of **19** with sodium azide gave 1-methyl-2-(1*H*-tetrazol-5-yl)-4(1*H*)-quinazolinone (**24**), which resulted from 1,3-dipolar addition reaction to the cyano group. The product **24** was transformed to 1,2-dihydro-4-hydroxy-1-methyl-2-(5*H*-tetrazol-5-ylidene)-quinazoline (**25**) in hot dimethylformamide. The structures of **24** and **25** were determined from the IR spectra. In the IR spectra, **24** has a carbonyl stretching band at 1645 cm^{-1}, whereas **25** does not have any carbonyl band.

We next studied the synthesis of pyrrolo- and pyrido[1,2-*a*]quinazolinones (type III). Several methods for the synthesis of compounds of this type have been reported,[10] but most of the methods involve the formation of the quinazolinone skeleton at the last step. Our effort was directed toward the development of a synthetic route by intramolecular cyclization of the substituents at position 1 and position 2 of the type I 4(1*H*)-quinazolinones. The intramolecular Dieckmann condensation of 2-ethoxycarbonyl-1-(2-methoxycarbonylethyl)-4(1*H*)-quinazolinone (**5c**) occurred smoothly on treatment with sodium methoxide in methanol to give 2-methoxycarbonylpyrrolo[1,2-*a*]quinazoline-3,5(1*H*, 2*H*)-dione (**26**). This product was easily transformed into the tautomer **28** in hot dimethylformamide. The structures of **26** and **28** were determined from their spectral data. The IR spectrum of **26** showed three carbonyl stretching bands at 1720 (ester), 1698 (position 3) and 1648 cm^{-1} (position 5). On the other hand, the IR spectrum of **28** showed bands at 3350 (NH) and 3240 cm^{-1} (OH) and two carbonyl stretching bands at 1700 (ester) and 1670 cm^{-1} (position 5). The NMR spectrum of **28** exhibited the signals of five aromatic protons at δ 7.23—8.30 and two broad signals of OH and NH at δ 6.25 and 11.30. Similar condensation of 2-ethoxycarbonyl-1-(3-ethoxycarbonylpropyl)-4(1*H*)-quinazolinone (**5d**) with sodium hydride in dimethylformamide gave 3-ethoxycarbonyl-4-hydroxy-1*H*-pyrido[1,2-*a*]quinazolin-6(2*H*)-one (**27**). Further, the ring closure of 2,3-dihydro-2-ethoxycarbonylmethylidene-1-methoxy

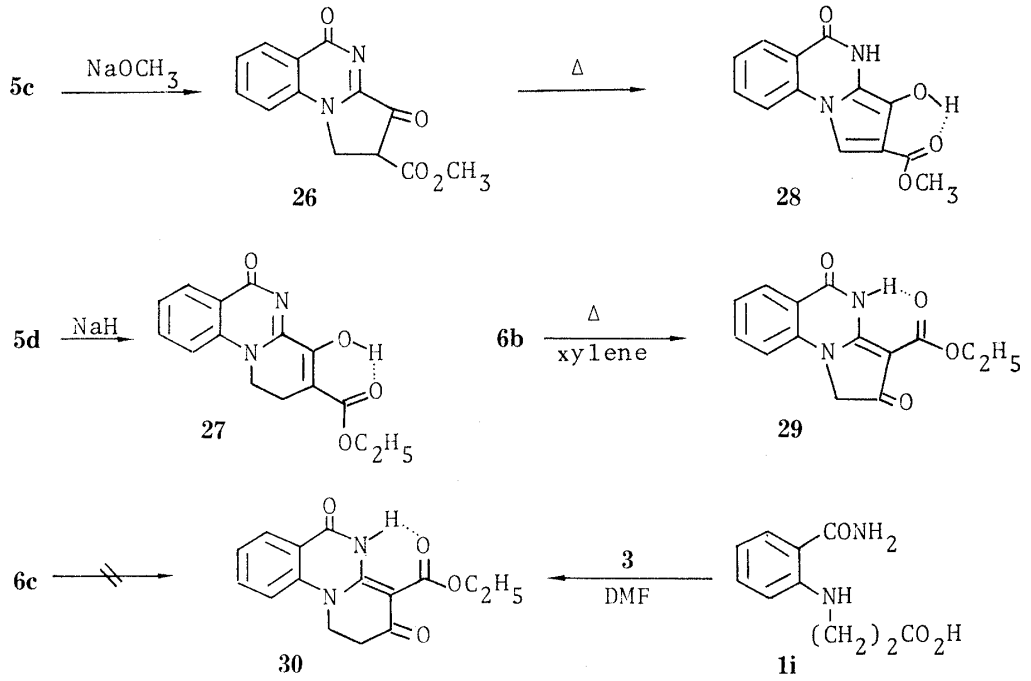


Chart 6

carbonylmethyl-4(1*H*)-quinazolinone (**6b**) proceeded smoothly under reflux in xylene to afford 3-ethoxycarbonylpyrrolo[1,2-*a*]quinazoline-2,5(1*H*,4*H*)-dione (**29**). In contrast, the ring closure of the 1-methoxycarbonylethyl derivative (**6c**) did not proceed in spite of extensive efforts (refluxing in xylene, treatment with sodium ethoxide or sodium hydride). Fortunately, 4-ethoxycarbonyl-1*H*-pyrido[1,2-*a*]quinazoline-3,6(2*H*,5*H*)-dione (**30**) could be obtained by the reaction of 2-(2-carboxyethylamino)benzamide (**1i**) with **3** in dimethylformamide (DMF) at 50 °C directly. Compound **30** might be expected to be obtained by the reaction of 2-(2-methoxycarbonylethylamino)benzamide (**1d**) with **3** under the same reaction conditions. To confirm this, we examined the reaction, but **6c** was the only isolable product. Further study on the formation mechanism of **30** from **1i** was not attempted.

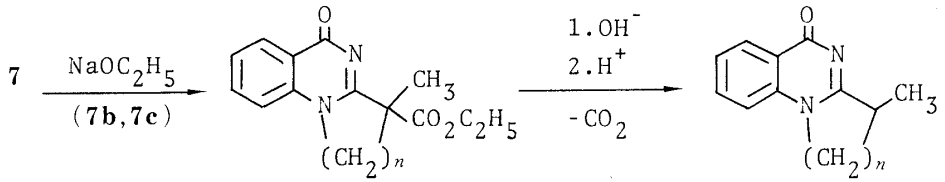


Chart 7

Finally, we investigated the synthesis of 3-methylpyrrolo[1,2-*a*]quinazolinone (**33**) and 4-methylpyrido[1,2-*a*]quinazolinone (**34**) from 1-chloroalkyl-2-(1-ethoxycarbonylethyl)-4(1*H*)-quinazolinones **7b** and **7c**. Treatment of **7b** or **7c** with sodium ethoxide at room temperature gave **31** or **32** in good yield. When the products were hydrolyzed with sodium hydrogen carbonate followed by acidification, decarboxylation took place spontaneously to give **33** or **34**.

Experimental

All melting points were determined on a Yamato MP-21 apparatus and are uncorrected. IR spectra were determined using a Shimadzu IR-27G spectrometer. NMR spectra were recorded on a Hitachi-Perkin Elmer R-20A instrument using tetramethylsilane (TMS) as an internal standard. MS were measured with a Hitachi M-60 mass spectrometer. Column chromatography was carried out on silica gel (Kieselgel 60, 0.063—0.200 mm, E. Merck).

2-(Substituted-amino)benzamides (1)——2-Phenylaminobenzamide (**1a**) and 2-methylaminobenzamide (**1b**) were prepared according to the reported method.[11,12]

2-Methoxycarbonylmethylaminobenzamide (**1c**) was obtained as colorless needles (EtOH, 92.8%, mp 151—152 °C) by the reaction of anthranilamide with methyl bromoacetate in the presence of $NaHCO_3$ in tetrahydrofuran (THF) at the reflux temperature for 24 h. *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.52; H, 5.87; N, 13.54.

2-(2-Methoxycarbonylethylamino)benzamide (**1d**) was obtained as colorless leaflets (EtOH–diisopropyl ether, 78.5%, mp 119—121 °C) by the reaction of 7% aqueous ammonia and 1-(2-methoxycarbonylethyl)isatoic anhydride, which was prepared from the corresponding anthranilic acid.[13] *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.32; H, 6.44; N, 12.73.

2-(3-Ethoxycarbonylpropylamino)benzamide (**1e**) was obtained as colorless needles (2-propanol–diisopropyl ether, 56.0%, mp 81—83 °C) by the reaction of 7% aqueous ammonia and the corresponding isatoic anhydride, which was prepared by the reaction of isatoic anhydride with ethyl 3-bromobutyrate. *Anal.* Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.32; H, 7.12; N, 11.34.

2-(2-Chloroethylamino)benzamide (**1f**) was obtained as colorless needles (2-propanol–diisopropyl ether, 49.2%, mp 126—127 °C) by the reaction of **1g** with $SOCl_2$ in $CHCl_3$ under reflux for 16 h. *Anal.* calcd for $C_9H_{11}ClN_2O$: C, 54.41; H, 5.58; Cl, 17.84; N, 14.10. Found: C, 54.24; H, 5.61; Cl, 17.70; N, 13.97.

2-(2-Hydroxyethylamino)benzamide (**1g**) was obtained as colorless needles ($CHCl_3$, 22.9%, mp 121—122 °C) by the reaction of anthranilamide, ethylene oxide and MeOH in a pressure bottle at 40—50 °C for 7 h. *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.75; H, 6.57; N, 15.25.

2-(3-Hydroxypropylamino)benzamide (**1h**) was obtained as colorless needles (2-propanol–diisopropyl ether, 67.0%, mp 122—124 °C) by reduction of **1d** with $LiBH_4$ in THF at room temperature for 20 h. *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.84; H, 7.08; N, 14.22.

2-(2-Carboxyethylamino)benzamide (**1i**) was obtained as colorless needles (DMF, 92.3%, mp 205—207 °C) by hydrolysis of **1d** with KOH. *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.75; H, 5.95; N, 13.55.

Ethyl chloroformylformate (**2**), ethyl chloroformylacetate (**3**), and ethyl 2-chloroformylpropionate (**4**) were prepared according to the reported methods.[14-16]

General Procedure for Preparation of 2-Ethoxycarbonyl-1-substituted-4(1*H*)-quinazolinones (5) (Table I). A Typical Example: 2-Ethoxycarbonyl-1-methyl-4(1*H*)-quinazolinone (5b)——The acyl chloride **2** (12.3 g, 0.09 mol) was added to a stirred suspension of **1b** (4.5 g, 0.03 mol) in $CHCl_3$ (30 ml) under ice cooling. After being stirred at room temperature for 22 h, the mixture was concentrated to dryness *in vacuo*. The residue was washed with diisopropyl ether and neutralized with aqueous $NaHCO_3$. The precipitate that had formed was collected by filtration to give **5b** (6.5 g, 93.4%), mp 168—171 °C. Recrystallization from 2-propanol gave a pure sample as colorless leaflets (6.3 g, 90.5%), mp 170—172 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1655. NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz), 3.76 (3H, s), 4.48 (2H, q, J=7 Hz), 7.29—7.96 (3H, m), 8.17—8.40 (1H, m).

General Procedure for Preparation of 2,3-Dihydro-2-ethoxycarbonylmethylidene-1-substituted-4(1*H*)-quinazolinones (6) (Table I). A Typical Example: 2,3-Dihydro-2-ethoxycarbonylmethylidene-1-phenyl-4(1*H*)-quinazolinone (6a)——A solution of **1a** (1.7 g, 0.008 mol) and **3** (3.6 g, 0.024 mol) in $CHCl_3$ (10 ml) was stirred at room temperature for 20 h. The mixture was worked up as described above. The crude product was recrystallized from EtOH–$CHCl_3$ to give **6a** (2.3 g, 93.3%) as colorless pillars, mp 235—236 °C. IR ν_{max}^{Nujol} cm^{-1}: 1696, 1645. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 3.80 (1H, s), 4.80 (2H, q, J=7 Hz), 6.17—6.45 (1H, m), 7.05—7.90 (7H, m), 9.05—9.32 (1H, m), 12.1—12.55 (1H, br s).

2-(1-Ethoxycarbonylethyl)-1-phenyl-4(1*H*)-quinazolinone (7a) (Table I)——A solution of **1a** (2.12 g, 0.01 mol) and **4** (4.93 g, 0.03 mol) in $CHCl_3$ (30 ml) was refluxed for 2.5 h. The mixture was worked up as described above. The product was recrystallized from 2-propanol to give **7a** (2.7 g, 83.9%), mp 186—188 °C. IR ν_{max}^{Nujol} cm^{-1}: 1727, 1641. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 1.55 (3H, d, J=7 Hz), 3.56 (1H, q, J=7 Hz), 4.07 (2H, q, J=7 Hz), 6.50—6.72 (1H, m), 7.23 (7H, m), 8.21—8.44 (1H, m).

Reaction of 1f with 4——A mixture of **1f** (1.0 g, 0.005 mol) and **4** (2.8 g, 0.017 mol) in $CHCl_3$ (20 ml) was refluxed for 3 h. The solvent was removed *in vacuo*. The residue was washed with diisopropyl ether, neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give an oily product. The product was subjected to silica gel column chromatography (30 g) using THF–benzene (3 : 7) to afford **8** as an oily product (1.6 g). NMR ($CDCl_3$) δ: 1.02—1.90 (12H, m), 3.20—3.68 (2H, m), 3.85—4.70 (8H, m), 7.10—8.03 (3H, m), 8.25—8.50 (1H, m). MS *m/e*: 418 (M^+), 373, 345, 273, 246, 132.

2-(1-Ethoxycarbonylethyl)-1-(2-hydroxyethyl)-4(1*H*)-quinazolinone (10)——The acyl chloride **4** (9.9 g, 0.06 mol) was added to a stirred suspension of **1g** (3.6 g, 0.02 mol) in $CHCl_3$ (100 ml) under ice cooling. After being stirred at the reflux temperature for 3.5 h, the mixture was concentrated *in vacuo*. The residue was washed with diisopropyl ether, neutralized with aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give crude **8** as an oily product. The spectral data and *Rf* value on TLC were identical with those of the sample obtained by the reaction of **1f** and **4**. A mixture of the oily product and $NaHCO_3$ (1.7 g, 0.02 mol) in EtOH–H_2O (30 ml–20 ml) was stirred at 70 °C for 5 h. After cooling, the mixture was extracted with $CHCl_3$ and the extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was subjected to silica gel column chromatography (30 g) using $CHCl_3$–MeOH (50 : 1) as an eluent to give **10** (1.9 g, 32.8%), mp 114—117 °C. Recrystallization from EtOH–diisopropyl ether gave a pure sample of **10** as colorless prisms, mp 123—125 °C. IR ν_{max}^{Nujol} cm^{-1}: 3360, 1739, 1630. NMR (DMSO-d_6) δ: 1.17 (3H, t, J=7 Hz), 1.54 (3H, d, J=7 Hz), 3.55—4.95 (7H, m), 5.20 (1H, t, J=6 Hz), 7.34—8.35 (4H, m). *Anal.* Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.86; H, 6.42; N, 9.50.

2-(1-Ethoxycarbonylethyl)-1-(3-hydroxypropyl)-4(1*H*)-quinazolinone (11)——By a procedure similar to that described above, reaction of **1h** (4.0 g, 0.021 mol) and **4** (9.9 g, 0.06 mol) in $CHCl_3$ (50 ml) gave **9** as an oily product, which was treated with aqueous $NaHCO_3$ to give **11** (2.5 g, 39.9%), mp 118—120 °C. Recrystallization from 2-propanol–diisopropyl ether gave pure **11** as colorless needles, mp 122—124 °C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1750, 1630. NMR (DMSO-d_6) δ: 1.19 (3H, t, J=7 Hz), 1.56 (3H, d, J=7 Hz), 1.75—2.38 (2H, m), 3.30—3.90 (3H, m), 3.92—4.75 (4H, m), 4.95 (1H, br), 7.37—8.30 (4H, m). *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.28; H, 6.77; N, 8.89.

General Procedure for Preparation of 1-Chloroalkyl-2-(1-ethoxycarbonylethyl)-4(1*H*)-quinazolinones (7b and 7c) (Table I). A Typical Example: 1-(2-Chloroethyl)-2-(1-ethoxycarbonylethyl-4(1*H*)-quinazolinone (7b)——A mixture of **10** (1.5 g, 0.0052 mol) and $SOCl_2$ (0.75 g, 0.0063 mol) in $CHCl_3$ (30 ml) was refluxed for 3 h. The solvent was removed *in vacuo*. The residue was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with 2-propanol–diisopropyl ether to give **7b** (1.5 g, 94.0%), mp 133—135 °C. Recrystallization from 2-propanol–diisopropyl ether gave

pure **7b** as colorless prisms, mp 134—135 °C. IR ν_{max}^{Nujol} cm^{-1}: 1733, 1635. NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz), 1.69 (3H, d, J=7 Hz), 3.72—4.92 (7H, m), 7.28—8.50 (4H, m).

2-Carboxy-1-methyl-4(1*H*)-quinazolinone (14)——A mixture of **5b** (1.16 g, 0.005 mol) and KOH (0.28 g, 0.05 mol) in EtOH–H_2O (20 ml–10 ml) was stirred at room temperature for 1.5 h. After removal of the solvent, the residue was acidified with 10% HCl to about pH 3 at 0 °C. The resulting crystals were isolated by suction to give pure **14** (0.93 g, 91.2%), mp 139—140 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1660. *Anal.* Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.89; H, 4.01; N, 13.93.

1-Methyl-4(1*H*)-quinazolinone (15)——A suspension of **14** (0.3 g) in $CHCl_3$ (5 ml) was stirred at room temperature for 3 h. The resulting clear solution was evaporated *in vacuo* to give **15** (0.22 g, 93.5%), mp 136—138 °C. The IR and NMR spectra of this product were identical to those of an authentic sample prepared according to the reported method.[4]

2-Hydroxyaminocarbonyl-1-methyl-4(1*H*)-quinazolinone (16)——A solution of KOH (0.4 g, 0.007 mol) in EtOH (40 ml) was added to a suspension of $NH_2OH \cdot HCl$ (0.49 g, 0.007 mol) in EtOH (20 ml). After the mixture had been stirred at room temperature for 0.5 h, potassium chloride that had formed was removed by filtration and **5b** (0.696 g, 0.003 mol) was added to the filtrate. The mixture was stirred at room temperature for 5 h and the solvent was removed *in vacuo*. The residue was dissolved in H_2O (20 ml) and acidified with AcOH to give a crystalline product (0.65 g, 98.9%), mp 198 °C (explosion). Recrystallization from DMF gave **16** as colorless prisms (0.4 g, 60.9%), mp 198 °C (explosion). IR ν_{max}^{Nujol} cm^{-1}: 3225, 1660. MS *m/e*: 219 (M^+). NMR (DMSO-d_6) δ: 3.36 (2H, s), 3.79 (3H, s), 7.40—8.23 (4H, m). *Anal.* Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.61; H, 4.18; N, 19.43.

2-Carbamoyl-1-methyl-4(1*H*)-quinazolinone (18)——A suspension of **5b** (2.32 g, 0.001 mol) in conc. NH_3 was stirred at room temperature for 1.5 h to give almost pure **18** (2.0 g, 98.5%), mp 247—249 °C. Recrystallization from AcOH gave **18** as colorless needles, mp 247—249 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3150, 1685, 1630. NMR ($CDCl_3$) δ: 3.76 (3H, s), 7.33—8.62 (6H, m). *Anal.* Calcd for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 58.74; H, 4.65; N, 20.44.

2-Cyano-1-methyl-4(1*H*)-quinazolinone (19)——Compound **18** (5.6 g, 0.028 mol) was added to pyrophosphoryl chloride (27 g) under ice cooling. After being stirred at 40 °C for 3 h, the mixture was poured into ice (200 ml) to give a crystalline product. The product was collected by filtration and neutralized with aqueous $NaHCO_3$ to give **19** (2.6 g, 50.9%), mp 236—239 °C. Recrystallization from DMF gave an analytical sample as colorless prisms, mp 242—245 °C. IR ν_{max}^{Nujol} cm^{-1}: 1657, 1604. MS *m/e*: 185 (M^+). NMR (DMSO-d_6) δ: 3.96 (3H, s), 7.10—8.20 (4H, m). *Anal.* Calcd for $C_{10}H_7N_2O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.51; H, 3.97; N, 22.67.

2-Amino-1-methyl-4(1*H*)-quinazolinone (17)——Method A: A mixture of **16** (1.0 g, 0.0046 mol) and naphthalene was stirred at 190—200 °C for 3 h. After cooling, the mixture was washed with $CHCl_3$ to give **18** (0.54 g, 67.6%), mp > 280 °C. Recrystallization from DMSO–MeOH gave pure **17** as colorless prisms (0.5 g, 62.6%), mp > 280 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1670. MS *m/e*: 175 (M^+). NMR (DMSO-d_6) δ: 3.58 (3H, s), 6.72—8.46 (6H, m). *Anal.* Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.53; H, 5.23; N, 24.08.

Method B: Ammonia was bubbled into a solution of **19** (1.5 g, 0.008 mol) in DMF (15 ml) under ice cooling for 1 h to give a crystalline product (0.9 g, 63.4%); mp > 280 °C. The IR spectrum of this product was identical with that of **17** obtained from **16**.

1-Methyl-2-methylamino-4(1*H*)-quinazolinone (20)——A suspension of **19** (0.5 g, 0.0027 mol) in 40% aqueous methylamine (20 ml) was stirred at room temperature for 3 h. The solvent was evaporated off *in vacuo* and the residue was triturated with H_2O to give crude **20** (0.5 g): mp > 280 °C (sintering at 248 °C). Recrystallization from DMSO gave **20** as colorless needles (0.33 g, 61.4%), mp > 280 °C. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1630. NMR (DMSO-d_6–CF_3COOD) δ: 3.10 (3H, s), 3.64 (3H, s), 7.22—8.25 (4H, m). *Anal.* Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.19; H, 5.77; N, 22.01.

2-(2-Carboxyethylthio)-1-methyl-4(1*H*)-quinazolinone (21)——A mixture of **19** (0.555 g, 0.003 mol), β-mercaptopropionic acid (0.424 g, 0.004 mol) and Et_3N (1 ml) in DMF (10 ml) was stirred at room temperature for 22.5 h. The solvent was removed *in vacuo* and the residue was triturated with MeOH to give a crystalline product (0.51 g), mp 238—241 °C (sintering at 188 °C). Recrystallization from DMF gave **21** as pale yellow prisms (0.37 g, 46.7%), mp 249—250 °C. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1610. NMR (DMSO-d_6) δ: 2.76 (2H, t, J=7 Hz), 3.39 (2H, t, J=7 Hz), 3.73 (3H, s), 7.18—8.17 (4H, m). *Anal.* Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.38; H, 4.62; N, 10.64; S. 11.89.

2-(Carboxymethoxy)-1-methyl-4(1*H*)-quinazolinone (22)——A mixture of **19** (0.86 g, 0.0046 mol), hydroxyacetic acid (0.46 g, 0.0061 mol) and Et_3N (1 ml) in DMF (5 ml) was stirred at 60 °C for 2 h. The solvent was removed *in vacuo* and the residue was triturated with H_2O to give a crystalline product (0.5 g), mp 246 °C (sintering at 193 °C). The crystals were dissolved in aqueous $NaHCO_3$ and an insoluble material was filtered off. The filtrate was acidified with 10% HCl to give a pure sample of **22** (0.45 g, 41.4%), mp 250 °C (sintering at 195 °C). IR ν_{max}^{Nujol} cm^{-1}: 1736, 1610. NMR (D_2O + NaOH) δ: 3.48 (3H, s), 4.71 (2H, s), 7.00—7.80 (4H, m). *Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.55; H, 4.53; N, 12.20.

Reaction of 19 with NaN_3——A mixture of **19** (0.55 g, 0.003 mol) and sodium azide (1.0 g, 0.015 mol) in DMF (20 ml) was stirred at 80 °C for 0.5 h. The solvent was removed *in vacuo* and the residue was dissolved in H_2O (20 ml)

and acidified with 10% HCl to about pH 3 to give 1-methyl-2-(1*H*-tetrazol-5-yl)-4(1*H*)-quinazolinone (**24**) as a crystalline product (0.46 g, 67.3%), mp 196—197 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1645, 1608. Recrystallization of **24** from DMF–H_2O gave 1,2-dihydro-4-hydroxy-1-methyl-2-(5*H*-tetrazol-5-ylidene)-quinazoline (**25**) as colorless needles (0.35 g, 51.2%), mp 209—210 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1590. MS *m/e*: 200 ($M^+ - 28$). NMR (DMSO-d_6) δ: 4.26 (3H, s), 7.50—8.47 (4H, m), 12.26 (1H, br s). *Anal.* Calcd for $C_{10}H_8N_6O$: C, 52.63; H, 3.53; N, 36.83. Found: C, 52.39; H, 3.69; N, 36.97.

2-Bis(ethoxycarbonyl)methylidene-2,3-dihydro-1-methyl-4(1*H*)-quinazolinone (23)——A solution of diethyl malonate (0.352 g, 0.0022 mol) and NaH (60% in oil, 0.088 g, 0.0022 mol) in THF (10 ml) was stirred for 0.5 h at room temperature. Compound **19** (0.37 g, 0.002 mol) was added to the solution and the mixture was stirred for 1 h at room temperature. The solvent was removed *in vacuo* and the residue was triturated with H_2O to give **23** (0.45 g, 70.8%), mp 160—162 °C. Recrystallization from EtOH gave a pure sample of **23** as colorless prisms, mp 164—165 °C. IR ν_{max}^{Nujol} cm^{-1}: 1705, 1690, 1630. NMR ($CDCl_3$) δ: 1.32 (6H, t, J=7 Hz), 3.43 (3H, s), 4.24 (4H, q, J=7 Hz), 7.00—7.82 (3H, m), 7.95—8.19 (1H, m), 12.72 (1H, br s). *Anal.* Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 59.97; H, 5.66; N, 8.70.

3-Hydroxy-2-methoxycarbonylpyrrolo[1,2-*a*]quinazolin-5(4*H*)-one (28)——A solution of NaOMe (0.54 g, 0.01 mol) in MeOH (10 ml) was added to a solution of **5c** (3.04 g, 0.01 mol) in MeOH (70 ml) under ice cooling. After the mixture had been stirred at room temperature for 1 h, the precipitate was collected by filtration. A suspension of the precipitate in 3% HCl (50 ml) was stirred at room temperature for 1 h to give 2-methoxycarbonyl pyrrolo[1,2-*a*]quinazoline-3,5-(1*H*,2*H*)-dione (**26**) as white crystals (2.0 g, 77.5%), mp 228—230 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1698, 1648. Recrystallization of the precipitate from DMF–H_2O gave **28** as yellow needles (1.6 g, 62.0%), 233—235 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3350, 3240, 1700, 1670. NMR (DMSO-d_6) δ: 3.80 (3H, s), 5.50—7.00 (1H, br), 7.23—8.30 (5H, m), 11.30 (1H, br s). *Anal.* Calcd for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90; N, 10.85. Found: C, 60.44; H, 3.98; N, 11.25.

3-Ethoxycarbonyl-4-hydroxy-1*H*-pyrido[1,2-*a*]quinazolin-6(2*H*)-one (27)——NaH (60% in oil, 0.16 g, 0.04 mol) was added to a stirred solution of **5d** (1.33 g, 0.04 mol) in DMF (10 ml) at room temperature and the mixture was stirred at 80 °C for 3 h. The solvent was evaporated off *in vacuo* to give a crude product (0.8 g). Recrystallization of the product from EtOH gave **27** as colorless needles (0.4 g, 35.0%), mp 198—199 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1660, 1648. MS *m/e*: 286 (M^+), 214, 185. NMR (DMSO-d_6) δ: 1.30 (3H, t, J=7 Hz), 2.81 (2H, t, J=7 Hz), 4.00—4.56 (4H, m), 5.28 (1H, br), 7.30—8.19 (4H, m). *Anal.* Calcd for $C_{15}H_{14}N_2O_4 \cdot 1/2H_2O$: C, 61.01; H, 5.12; N, 9.49. Found: C, 61.27; H, 4.86; N, 9.51.

3-Ethoxycarbonylpyrrolo[1,2-*a*]quinazoline-2,5(1*H*, 4*H*)-dione (29)——A suspension of **6b** (4.8 g, 0.015 mol) in xylene (70 ml) was stirred at reflux temperature for 28 h, then cooled. The precipitate that had formed was collected by filtration to give crude **29** (3.5 g, 81.5%), mp 235—238 °C (dec.). Recrystallization from DMF gave **29** as colorless needles (2.7 g, 62.9%), mp 240—243 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3210, 1730, 1683, 1641. NMR (DMSO-d_6) δ: 1.26 (3H, t, J=7 Hz), 4.20 (2H, q, J=7 Hz), 4.41 (2H, s), 7.16—8.27 (4H, m), 10.75 (1H, br s). MS *m/e*: 272 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.44; H, 4.61; N, 10.51.

4-Ethoxycarbonyl-1*H*-pyrido[1,2-*a*]quinazoline-3,6(2*H*, 5*H*)-dione (30)——The acyl chloride **3** (4.5 g, 0.03 mol) was added to a solution of **1i** (2.08 g, 0.01 mol) in DMF (20 ml) under ice cooling. After being stirred at 50 °C for 10 h, the mixture was concentrated *in vacuo*, and the residue was washed with diisopropyl ether, then neutralized with aqueous $NaHCO_3$. The precipitate that had formed was collected by filtration to give **30** (1.5 g, 52.4%), mp 227—228 °C (dec.). Recrystallization from DMF gave **30** as colorless needles (1.2 g, 41.9%), mp 230—232 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1700, 1655. NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7 Hz), 2.59 (2H, t, J=7 Hz), 4.21 (2H, q, J=7 Hz), 4.30 (2H, t, J=7 Hz), 6.95—8.27 (4H, m), 13.27 (1H, br s). *Anal.* Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.86; H, 4.89; N, 9.76.

3-Ethoxycarbonyl-3-methyl-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (31)——Compound **7b** (1.7 g, 0.0055 mol) was added to a solution of EtONa (0.23 g, 0.0056 mol) in EtOH (50 ml) under ice cooling. After being stirred at room temperature for 1 h, the mixture was acidified with AcOH and the solvent was evaporated off *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and then concentrated to dryness *in vacuo*. The residue was triturated with 2-propanol–diisopropyl ether to give **31** (1.0 g, 66.7%), mp 123—126 °C. Recrystallization from 2-propanol–diisopropyl ether gave pure **31** as colorless prisms (0.8 g, 53.4%), mp 125—127 °C. IR ν_{max}^{Nujol} cm^{-1}: 1738, 1645, 1600. NMR ($CDCl_3$ + DMSO-d_6) δ: 1.20 (3H, t, J=7 Hz), 1.68 (3H, s), 1.90—2.98 (2H, m), 3.94—4.70 (4H, m), 7.33—8.30 (4H, m). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.36; H, 5.92; N, 10.01.

4-Ethoxycarbonyl-4-methyl-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]quinazolin-6-one (32)——By a procedure similar to that described for the preparation of **31**, reaction of **7c** (2.3 g, 0.0071 mol) and NaOEt (0.31 g, 0.0078 mol) in EtOH (30 ml) provided **32** (1.2 g, 62.3%), mp 145—148 °C. Recrystallization from 2-propanol-diisopropyl ether gave a pure sample as colorless prisms, mp 150—152 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1641, 1608. NMR (DMSO-d_6) δ: 1.15 (3H, t, J=7 Hz), 1.68 (3H, s), 1.80—2.40 (4H, m), 3.90—4.55 (4H, m), 7.33—8.22 (4H, m). *Anal.* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.11; H, 6.48; N, 9.56.

3-Methyl-2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (33)——A mixture of **31** (0.8 g, 0.0029 mol) and KOH

(0.17 g, 0.003 mol) in EtOH–H_2O (10 ml–1 ml) was stirred at room temperature for 1 h. The solvent was evaporated off *in vacuo* and the residue was acidified with 10% HCl then extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was triturated with 2-propanol–diisopropyl ether to give a crystalline product (0.38 g, 64.6%), mp 157—160 °C. Recrystallization from 2-propanol–diisopropyl ether gave **33** as colorless needles (0.2 g, 34.0%), mp 168—171 °C. IR ν_{max}^{Nujol} cm^{-1}: 1638, 1610, 1600. NMR ($CDCl_3$) δ: 1.45 (3H, d, J=7 Hz), 1.68—3.55 (3H, m), 3.80—4.50 (2H, m), 7.00—8.35 (4H, m). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.59; H, 6.03; N, 13.84.

4-Methyl-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]quinazolin-6-one (34)——By a procedure similar to that described for the preparation of **33**, reaction of **32** (1.2 g, 0.0042 mol) and KOH (0.24 g, 0.0043 mol) in EtOH–H_2O (30 ml–10 ml) provided **34** (0.5 g, 52.6%, mp 143—146 °C), which was recrystallized from 2-propanol–diisopropyl ether to give a pure sample as colorless needles, mp 147—148 °C. IR ν_{max}^{Nujol} cm^{-1}: 1640, 1609. NMR (DMSO-d_6) δ: 1.50 (3H, d, J=7 Hz), 1.7—2.50 (4H, m), 2.70—3.40 (1H, m), 4.05 (2H, t, J=7 Hz), 7.23—7.89 (3H, m), 8.18—8.42 (1H, m). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.48; H, 6.65; N, 12.70.

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