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Reactions of the Anion of Quinazoline Reissert Compound (3-Benzoyl-3,4-dihydro-4-quinazolinecarbonitrile) with Electrophiles

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Reactions of the quinazoline Reissert compound (**2**) with various electrophiles in the presence of sodium hydride in *N*,*N*-dimethylformamide were investigated.

The reactions with aldehydes (**3**) and ketones (**12**) gave α-aryl (or alkyl)- (**7**) and α-alkyl-α-aryl (or alkyl)-4-quinazolinylmethyl benzoates (**16**), respectively. The reaction with π-deficient heteroaromatics (**10a—c**) gave 4-heteroarylquinazolines (**20a—c**). Alkylation (or arylation) with alkyl (or aryl) halides (**23a—c**) afforded 4-substituted 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitriles (**24a—c**). The reaction with dimethyl acetylenedicarboxylate proceeded in two ways, giving dimethyl 3-phenylpyrrolo[1,2-*c*]quinazoline-1,2-dicarboxylate (**27**) and dimethyl 3-benzoyl-4-cyano-1,2,3,4-tetrahydro-2,4-ethenoquinazoline-9,10-dicarboxylate (**28**). The reaction with 2-alkenonitriles (**29a, b**) resulted in the formation of 2-benzoyl-3-(4-quinanolinyl)alkanonitriles (**32a, b**).

Keywords——rearrangement; substitution; 1,3-dipolar addition; quinazoline Reissert compound anion; α-substituted 4-quinazolinylmethyl benzoate; 4-heteroarylquinazoline; 4-substituted 3,4-dihydro-4-quinazolinecarbonitrile; pyrrolo[1,2-*c*]quinazoline; 2,4-ethenoquinazoline; 2-benzoyl-3-(4-quinazolinyl)alkanonitrile

In the preceding paper,[1] it was reported that the anion (**1**) is generated by the treatment of 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile (**2**, quinazoline Reissert compound) with sodium hydride in *N*,*N*-dimethylformamide (DMF).

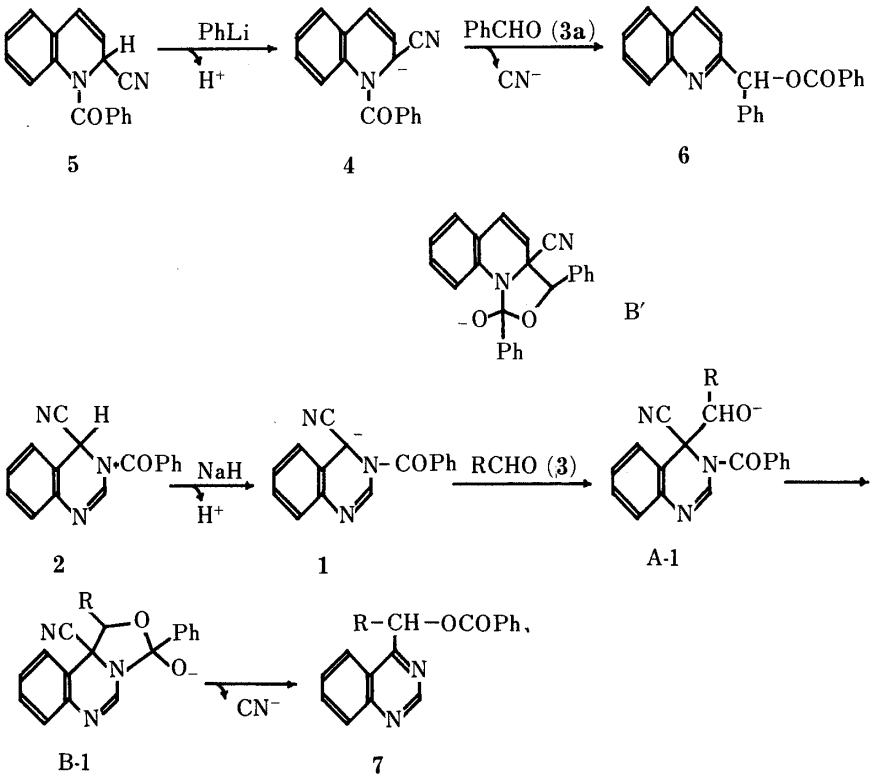
In order to elucidate the chemical properties of **1**, we examined the reactions of **2** with various electrophiles in the presence of sodium hydride in DMF. This paper describes the introduction of the corresponding substituents into the 4-position of the quinazoline ring by means of these reactions.

The Reaction with Aldehydes

It was reported[2] that the anion (**4**) of 1-benzoyl-1,2-dihydro-2-quinolinecarbonitrile (**5**, quinoline Reissert compound) reacts with benzaldehyde (**3a**) to form α-phenyl-2-quinolylmethyl benzoate (**6**).

When **2** reacted with aromatic (**3a—k**) and aliphatic (**3m—q**) aldehydes in the presence of sodium hydride in DMF, α-aryl- (**7a**[1]—**k**) and α-alkyl-4-quinazolinylmethyl benzoates (**7m—q**), respectively, were obtained. As shown in Table I, the yields of the esters **7** are decidedly better with aromatic aldehydes **3a—k** than with aliphatic aldehydes **3m—q**. However, as seen in the case of **3l**, the presence of a strongly electron donating *N*,*N*-dimethylamino group in the *p*-position of benzaldehyde caused the yield of the ester **7l** to drop to zero.

The formation of the esters **7** undoubtedly involves the initial addition of the anion **1** to the carbonyl carbon of the aldehydes **3** to form an intermediate (A-1), which then gives the esters **7** with the expulsion of a cyanide ion by way of an intermediate (B-1) that is similar to



a:	R=Ph	**g**:	R=*p*-C_6H_4Cl	**m**:	R=CH=CHMe
b:	R=*o*-C_6H_4Me	**h**:	R=*o*-$C_6H_4NO_2$	**n**:	R=CH=CH–Ph
c:	R=*p*-C_6H_4Me	**i**:	R=*p*-$C_6H_4NO_2$	**o**:	R=Et
d:	R=*o*-C_6H_4OMe	**j**:	R=3,4-$C_6H_3(OMe)_2$	**p**:	R=Pr
e:	R=*p*-C_6H_4OMe	**k**:	R=2-furyl	**q**:	R=$CH(Me)_2$
f:	R=*o*-C_6H_4Cl	**l**:	R=*p*-$C_6H_4N(Me)_2$		

Chart 1

TABLE I. Reaction of **2** with **3** in the Presence of NaH in DMF

		Product	
2	**3**	**7**	Yield (%)
2	**3a**	**7a**	82
2	**3b**	**7b**	72
2	**3c**	**7c**	90
2	**3d**	**7d**	94
2	**3e**	**7e**	57
2	**3f**	**7f**	75
2	**3g**	**7g**	80
2	**3h**	**7h**	65
2	**3i**	**7i**	73
2	**3j**	**7j**	62
2	**3k**	**7k**	72
2	**3l**	**7l**	0
2	**3m**	**7m**	27
2	**3n**	**7n**	33
2	**3o**	**7o**	45
2	**3p**	**7p**	69
2	**3q**	**7q**	39

TABLE II. Melting Points and Elemental Analyses of **7** and **8**

Compd.	mp (°C)	Formula	Analysis (%) Calcd (Found)		
			C	H	N
7a[h]	149[a]	$C_{22}H_{16}N_2O_2$	77.63	4.74	8.23
			(77.84	4.72	8.00)
7b[g]	94—95[d]	$C_{23}H_{18}N_2O_2$	77.95	5.12	7.91
			(77.89	5.10	7.85)
7c[h]	138[a]	$C_{23}H_{18}N_2O_2$	77.95	5.12	7.91
			(78.03	5.14	7.82)
7d[g]	122[a]	$C_{23}H_{18}N_2O_3$	74.58	4.90	7.56
			(74.35	4.96	7.50)
7e[g]	110[a]	$C_{23}H_{18}N_2O_3$	74.58	4.90	7.56
			(74.60	5.00	7.50)
7f[g]	95[a]	$C_{22}H_{15}ClN_2O_2$	70.50	4.03	7.47
			(70.16	4.03	7.53)
7g[h]	115[b]	$C_{22}H_{15}ClN_2O_2$	70.50	4.03	7.47
			(70.35	4.10	7.47)
7h[h]	168[a]	$C_{22}H_{15}N_3O_4$	68.56	3.92	10.91
			(68.40	3.97	10.89)
7i[h]	153[c]	$C_{22}H_{15}N_3O_4$	68.56	3.92	10.91
			(68.38	3.97	10.77)
7j[i]	141—142[a]	$C_{24}H_{20}N_2O_4$	71.98	5.03	7.00
			(72.04	5.09	6.69)
7k[h]	147[a]	$C_{20}H_{14}N_2O_3$	72.72	4.27	8.48
			(72.54	4.24	8.19)
7m	—[e]	$C_{19}H_{16}N_2O_2$	MS *m/e*: 304 (M^+)		
7n	—[e]	$C_{24}H_{18}N_2O_2$	MS *m/e*: 366 (M^+)		
7o	—[f]	$C_{18}H_{16}N_2O_2$	MS *m/e*: 292 (M^+)		
7p	—[f]	$C_{19}H_{18}N_2O_2$	MS *m/e*: 306 (M^+)		
7q[h]	96[a]	$C_{19}H_{18}N_2O_2$	74.49	5.92	9.15
			(74.68	5.92	9.07)
8d[g]	92[b]	$C_{16}H_{14}N_2O$	76.78	5.64	11.19
			(77.03	5.68	11.21)
8e[g]	66—67[b]	$C_{16}H_{14}N_2O$	76.78	5.64	11.19
			(76.91	5.74	11.03)
8f	—[f]	$C_{15}H_{11}ClN_2$	MS *m/e*: 254 (M^+), 256 ($M^+ + 2$)		
8g	—[e]	$C_{15}H_{11}ClN_2$	MS *m/e*: 254 (M^+), 256 ($M^+ + 2$)		
8k	—[e]	$C_{13}H_{10}N_2O$	MS *m/e*: 210 (M^+)		
8m	—[e]	$C_{12}H_{14}N_2$	MS *m/e*: 186 (M^+)		
8n	—[e]	$C_{17}H_{16}N_2$	MS *m/e*: 248 (M^+)		

a) Colorless prisms. *b*) Colorless needles. *c*) Yellow needles. *d*) Yellow prisms. *e*) Yellow oil. *f*) Colorless oil. *g*) Recrystallization from petr. ether. *h*) Recrystallization from MeOH. *i*) Recrystallization from benzene–petr. ether.

the cyclic intermediate (B′) observed in the reaction of the anion **4** with benzaldehyde **3a**.[2]

The ester **7a** showed an undepressed melting point on admixture with an authentic sample prepared by another route.[1] The structures of **7b**—**q** were suggested by the elemental analyses or molecular ion (M^+) peaks in mass spectral (MS) data (Table II), and confirmed by analyses of the infrared (IR) absorption and proton nuclear magnetic resonance (^{1}H-NMR) spectra (Table III). The IR spectra showed a carbonyl absorption peak in the 1700 to 1730 cm^{-1} region. The ^{1}H-NMR spectra showed a characteristic singlet due to C^2-H of the

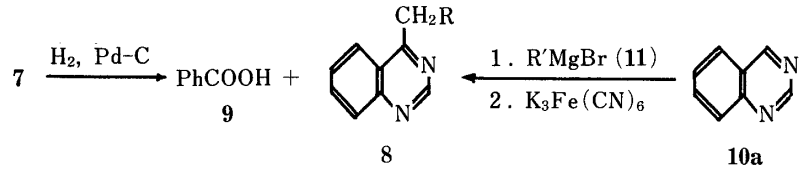
TABLE III. IR and ^{1}H-NMR Spectra of **7** and **8**

Compd.	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR ($CDCl_3$)			
	C=O	C^2–H (s)	CH–O	Aromatic H (m)	Other H
7a	1705	9.18	—[a]	7.70—8.33 (15H)	
7b	1700	9.11	—[a]	6.93—8.16 (14H)	2.25 (3H, s, CH_3)
7c	1730	9.15	—[a]	7.09—8.02 (14H)	2.47 (3H, s, CH_3)
7d	1720	9.20	—[a]	6.72—8.47 (14H)	3.82 (3H, s, OCH_3)
7e	1710	9.18	—[a]	6.70—8.30 (14H)	3.71 (3H, s, OCH_3)
7f	1730	9.23	—[a]	7.11—8.37 (14H)	
7g	1710	9.18	—[a]	7.08—8.26 (14H)	
7h	1725, 1360, 1530 (NO_2)	9.05	8.56 (s)	7.12—8.37 (13H)	
7i	1720, 1350, 1530 (NO_2)	9.15	—[a]	7.00—8.25 (14H)	
7j	1720	9.21	—[a]	6.66—8.31 (13H)	3.80 (6H, s, 2×OCH_3)
7k	1710	9.17	—[a]	7.14—8.31 (11H) 6.19—6.42 (2H)	
7m	1720	9.17	—[a]	6.96—8.48 (10H)	5.63—6.28 (2H, m, CH=CH), 1.25—2.28 (3H, m, =CHC$\underline{H}_3$)
7n	1730	9.20	6.72 (d, J=8.4 Hz)	7.00—8.40 (16H)	—[a]
7o	1720	9.16	6.48 (t, J=6.9 Hz)	7.14—8.37 (9H)	2.21 (2H, m, C$\underline{H}_2$Me), 1.10 (3H, t, J=6.6 Hz, $CH_2C\underline{H}_3$)
7p	1720	9.17	6.59 (t, J=6.6 Hz)	7.10—8.38 (9H)	2.18 (2H, m, C$\underline{H}_2$Et), 1.58 (2H, m, $CH_2C\underline{H}_2$Me), 1.00 (3H, t, J=6.2 Hz, $CH_2C\underline{H}_3$)
7q	1720	9.15	6.27 (d, J=8.4 Hz)	7.19—8.38 (9H)	2.66 (1H, m, C$\underline{H}$(Me)$_2$), 1.19 (3H, d, J=6.0 Hz, CH(C$\underline{H}_3$)$_2$), 0.92 (3H, d, J=6.0 Hz, CH(C$\underline{H}_3$)$_2$)
8a		9.12		6.98—8.13 (9H)	4.53 (2H, s, C^4–CH_2)
8d		9.09		6.59—8.23 (8H)	4.54 (2H, s, C^4–CH_2), 3.76 (3H, s, OCH_3)
8e		9.07		7.35—8.10 (4H), 6.06 (2H, d, J=7.0 Hz), 7.08 (2H, d, J=7.0 Hz)	4.47 (2H, s, C^4–CH_2), 3.66 (3H, s, OCH_3)
8f		9.09		6.94—8.07 (8H)	4.68 (2H, s, C^4–CH_2)
8g		9.10		7.04—8.16 (8H)	4.48 (2H, s, C^4–CH_2)
8k		8.61		5.49—5.78 (2H) 6.66—7.75 (5H)	4.08 (2H, s, C^4–CH_2)
8m		9.11		7.18—8.04 (4H)	3.09 (2H, t, J=7.5 Hz, C^4–C$\underline{H}_2$$CH_2$), 1.13—2.10 (4H, m, $CH_2C\underline{H}_2$Me), 0.91 (3H, t, J=6.6 Hz, $CH_2C\underline{H}_3$)
8n		9.06		7.00—8.02 (9H)	3.02 (2H, t, J=6.0 Hz, C^4–C$\underline{H}_2$$CH_2$), 2.75 (2H, t, J=6.0 Hz, $CH_2C\underline{H}_2$Ph), 1.99—2.44 (2H, m, $CH_2C\underline{H}_2CH_2$)

a) Overlapping with aromatic H.

quinazoline ring at 9.05 to 9.23 ppm.

Rosenmund *et al.*[3] reported that benzyl benzoate is easily convertible to toluene and benzoic acid by catalytic reduction over a palladium catalyst. The application of this reduction to the esters (**7a**, **d**—**g**, **k**, **m**, **n**) resulted in the formation of the corresponding 4-alkylquinazolines (**8a**, **d**—**g**, **k**, **m**, **n**) and benzoic acid (**9**) (Table IV).



8a: R=Ph
8d: R=*o*-C_6H_4OMe
8e: R=*p*-C_6H_4OMe
8f: R=*o*-C_6H_4Cl
8g: R=*p*-C_6H_4Cl
8k: R=2-furyl
8m: R=Pr
8n: R=CH_2CH_2Ph
11m: R'=Bu
11n: R'=$CH_2CH_2CH_2Ph$

Chart 2

TABLE IV. Catalytic Reduction of **7** over Pd Catalyst in Benzene–MeOH

	Product			
7	**8**	Yield (%)	**9**	Yield (%)
7a	**8a**	90		44
7d	**8d**	89		41
7e	**8e**	78		40
7f	**8f**	63		83
7g	**8g**	71		74
7k	**8k**	44		59
7m	**8m**	48		33
7n	**8n**	53		60

The picrate of **8a** showed an undepressed melting point on admixture with that of 4-benzylquinazoline prepared by another route.[4] The esters **8m** and **8n** were proved to be 4-butyl- and 4-phenylpropylquinazolines by comparison with authentic samples prepared by the reaction of quinazoline (**10a**) with the corresponding alkylmagnesium bromides (**11m**, **n**), followed by potassium ferricyanide oxidation. The structures of other 4-alkylquinazolines, **8d**—**g** and **8k**, were suggested by the elemental analyses or M^+ ion peaks in the MS (Table II), and confirmed by analyses of the ^{1}H-NMR spectra (Table III).

The Reaction with Ketones

It was reported that various ketones (**12**) react with 2-benzoyl-1,2-dihydro-1-isoquinolinecarbonitrile (**14**, isoquinoline Reissert compound) in the presence of 50% aqueous sodium hydroxide–acetonitrile containing triethylbenzylammonium chloride (TEBA) to give α,α-dialkyl-1-isoquinolylmethyl benzoates (**15**).[5]

Under the same conditions as used for the reaction with aldehydes **3**, the reaction with ketones **12** gave the desired α,α-dialkyl-4-quinazolinylmethyl benzoates (**16**). The yields of the esters **16** were reduced because of the occurrence of side reactions. Thus, acetophenone (**12a**), acetone (**12b**), and cyclohexanone (**12c**) gave the corresponding esters (**16a**—**c**) in less than 50% yield. In the case of **12a**, 2-(4-quinazolinyl)acetophenone (**17**)[6] was obtained together with the ester **16a**.

The mechanism of formation of the estes **16** is similar to that of the esters **7**, and involves

the initial formation of an intermediate (A-2) which then gives a cyclic intermediate (B-2); this in turn undergoes elimination–rearrangement to the esters **16**, as shown in Chart 3. Compound **17** may be formed by the nucleophilic attack of an acetophenone carbanion (E) at the 4-position of 4-quinazolinecarbonitrile (**18**),[7] which originates from the known self-decomposition of the anion **1**.[1]

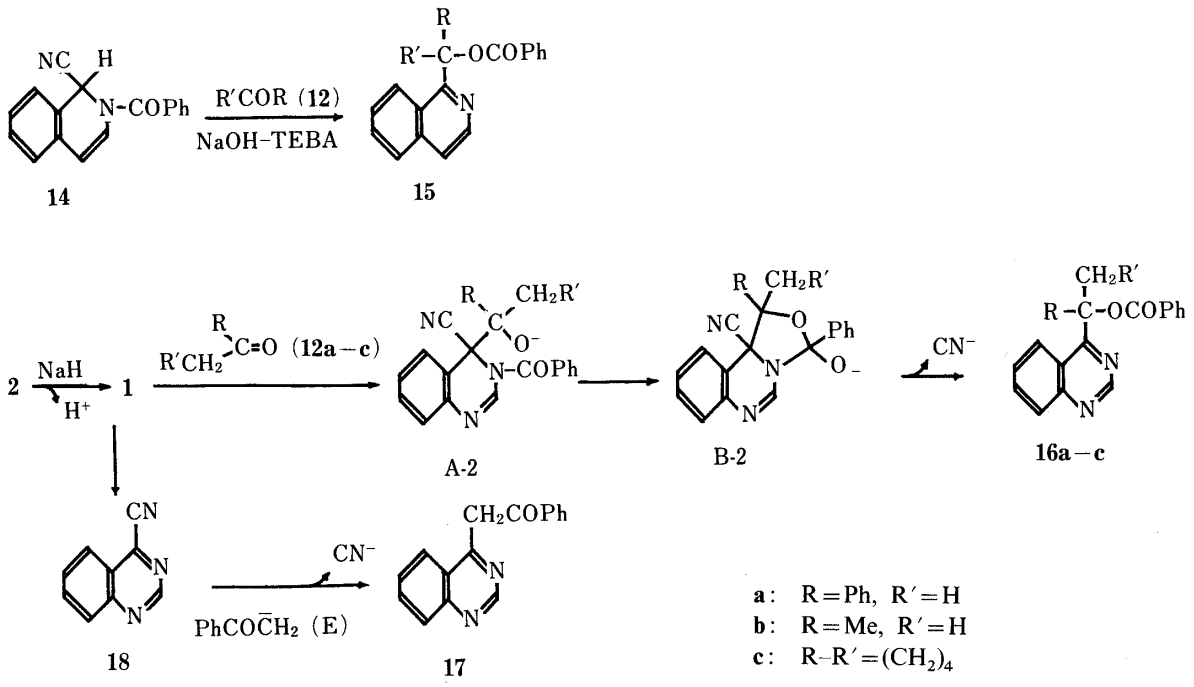


Chart 3

The structures of the esters **16a—c** were suggested by the elemental analyses, and confirmed by analyses of the IR and ^{1}H-NMR spectra. The IR spectra showed a carbonyl absorption peak in 1715 to 1730 cm^{-1} region. The ^{1}H-NMR spectra showed a singlet due to C^2-H at 9.10 to 9.30 ppm.

The Reaction with π-Deficient Heteroaromatics

It was reported that the chemical properties of C^4 of the quinazoline ring are equivalent to those of the carbonyl carbon of benzaldehydes.[8] For example, the benzoin-type condensation between quinazoline **10a** and aromatic aldehydes **3** in the presence of cyanide ion proceeded to give α-aryl-4-quinazolinemethanols.[8] In connection with this equivalence, it was expected that the anion **1** would also react with quinazoline **10a** to form 3-benzoyl-3,4-dihydro-4-(4-quinazolinyl)quinazoline (**19a**).

Under the same conditions as used for the reaction with **3**, **2** reacted with **10a** in the presence of sodium hydride in DMF to yield the expected product **19a** together with 4,4′-biquinazoline (**20a**).[9] In a similar manner, the reaction with 1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine (**10b**) and 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**10c**) gave the corresponding 4-heteroarylquinazolines (**20b**, **c**).

The formation of **19** can be explained by the addition of **1** to π-deficient heteroaromatics **10** to give an intermediate (A-3), which then leads to **19** *via* a cyclic intermediate (B-3), similar to the cyclic intermediate (B-1) proposed in the reaction with aldehydes **3**. The subsequent formation of an anion (F) by removal of the acidic methine hydrogen of the resulting **19** with sodium hydride, followed by aromatization with the expulsion of a benzaldehyde anion, leads to 4-heteroarylquinazolines **20**, as shown in Chart 4. In fact, **19a** reacted with sodium hydride

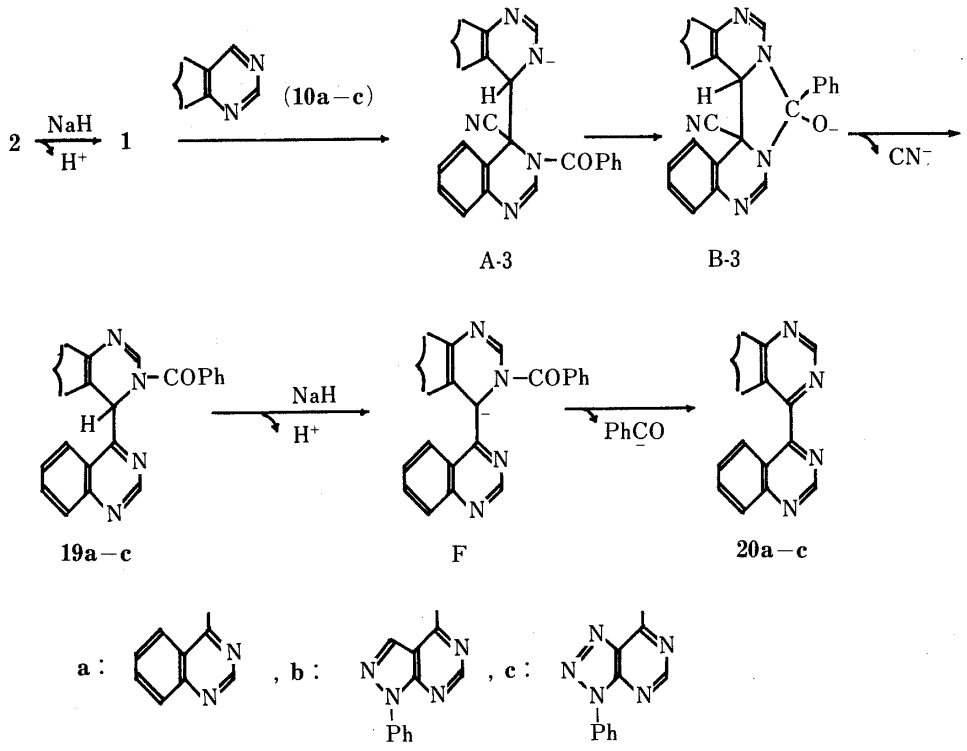


Chart 4

in DMF to give **20a** in 54% yield.

The structures of **20b**, **c** and **19a** were suggested by the elemental analyses, and confirmed by analyses of the IR and ^{1}H-NMR spectra, as described in the experimental section.

The Reaction with Alkyl (or Aryl) Halides

It was reported that the alkylation (or arylation) of the anion (**13**), generated by the action of sodium hydride on the isoquinoline Reissert compound **14**, with various alkyl (or aryl) halides in DMF gives the corresponding 1-alkyl (or aryl)-2-benzoyl-1,2-dihydro-1-isoquinolinecarbonitriles (**21**), which can then be hydrolyzed to the 1-alkyl (or aryl)-isoquinolines (**22**).[10,11]

The reactions of **2** with methyl iodide (**23a**), 2,4-dinitrochlorobenzene (**23b**), and 4-chloroquinazoline (**23c**) in the presence of sodium hydride in DMF proceeded in the same way as that of **13**, and resulted in the formation of the corresponding 4-alkyl (or aryl)-3-benzoyl-3,4-dihydro-4-quinazolinecarbonitriles (**24a**—**c**), which were easily convertible into the corresponding 4-alkyl (or aryl)-quinazolines (**8o**, **p**, **20a**) by alkaline hydrolysis.

However, in the cases of other alkyl (or aryl) halides (ethyl bromide (**23d**), ethyl iodide (**23e**), isopropyl bromide (**23f**), cyclohexyl bromide (**23g**), benzyl chloride (**23h**), *p*-nitrobenzyl chloride (**23i**), *p*-nitrochlorobenzene (**23j**), 2-chloropyridine (**23k**), and 9-chloroacridine (**23l**)), the alkylation (or arylation) did not proceed, and self-decomposition of the anion **1**[1] took place, giving **18**, **7a**, and *O*-benzoylbenzoin (**25**). Thus, the mesomeric effect of N^1 in the anion **1** as well as the N^3-benzoyl group may favor the expulsion of a benzaldehyde anion to yield the aromatic system rather than the formation of **24**. Therefore, the alkylation (or arylation) may take place only in the case of activated alkyl (or aryl) halides such as **23a**—**c**.

The structures of **24a**—**c** and **8p** were suggested by the M^+ ion peaks in the MS and elemental analyses, and confirmed by analyses of the IR and ^{1}H-NMR spectra, as described in the experimental section. The picrate of **8o** showed undepressed melting point on admixture with that of 4-methylquinazoline prepared by another route.[7]

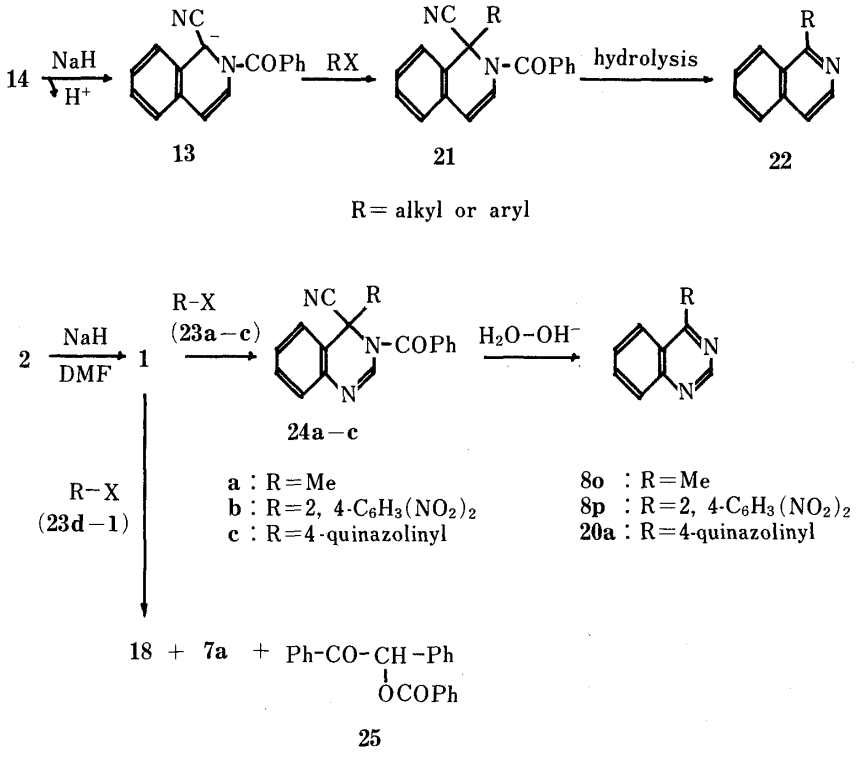


Chart 5

The Reaction with Dimethyl Acetylenedicarboxylate

It was reported by McEwen *et al.* that the reaction of the anion **13** with dimethyl acetylenedicarboxylate (DMAD) yields dimethyl 2-benzoyl-3-(1-isoquinolyl)butenedioate (**26**).[12] The reaction of **2** with DMAD in the presence of sodium hydride in DMF did not proceed in the same way as in the reaction of **13**, but took place in two ways, giving dimethyl 3-phenylpyrrolo[1,2-*c*]quinazoline-1,2-dicarboxylate (**27**) and dimethyl 3-benzoyl-4-cyano-1,2,3,4-tetrahydro-2,4-ethenoquinazoline-9,10-dicarboxylate (**28**).

The formation of these those products, **27** and **28**, may be rationalized in terms of paths A and B, as shown in Chart 6. The initial step is undoubtedly the formation of an intermediate (A-4) by the addition of the anion **1** to the triple bond of DMAD. The intramolecular addition of A-4 to the N^3-carbonyl carbon leads to an intermediate (B-4), which then gives **27** by way of a bridged intermediate (B-5) with the expulsion of an isocyanate ion (path A). On the other hand, another intramolecular addition of A-4 to the cyclic amidine carbon (C^2) leads to **28** by way of an intermediate (G) (path B).

The structures of **27** and **28** were suggested by the elemental analyses or M^+ ion peaks in the MS, and confirmed by analyses of the IR, ^{1}H-, and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra. The IR spectrum of **27** showed a carbonyl absorption peak at 1720 cm^{-1}, and the ^{1}H-NMR spectrum showed a characteristic singlet due to C^5-H of the pyrrolo[1,2-*c*]quinazoline ring at 8.45 ppm. The IR spectrum of **28** showed the ester and amide carbonyl absorption peaks at 1740 and 1670 cm^{-1}, and did not show any absorption peak due to a cyano group. The latter result is compatible with the reported absence of the absorption peak of the cyano group in the quinazoline Reissert compound **2**.[1] The ^{1}H-NMR spectrum showed a characteristic doublet (J=4.23 Hz; changed into a singlet with D_2O) due to C^2-H of the tetrahydroethenoquinazoline ring at 5.82 ppm, and the ^{13}C-NMR spectrum showed a doublet due to C^2 and a singlet due to C^4 at 72.44 and 62.25 ppm.

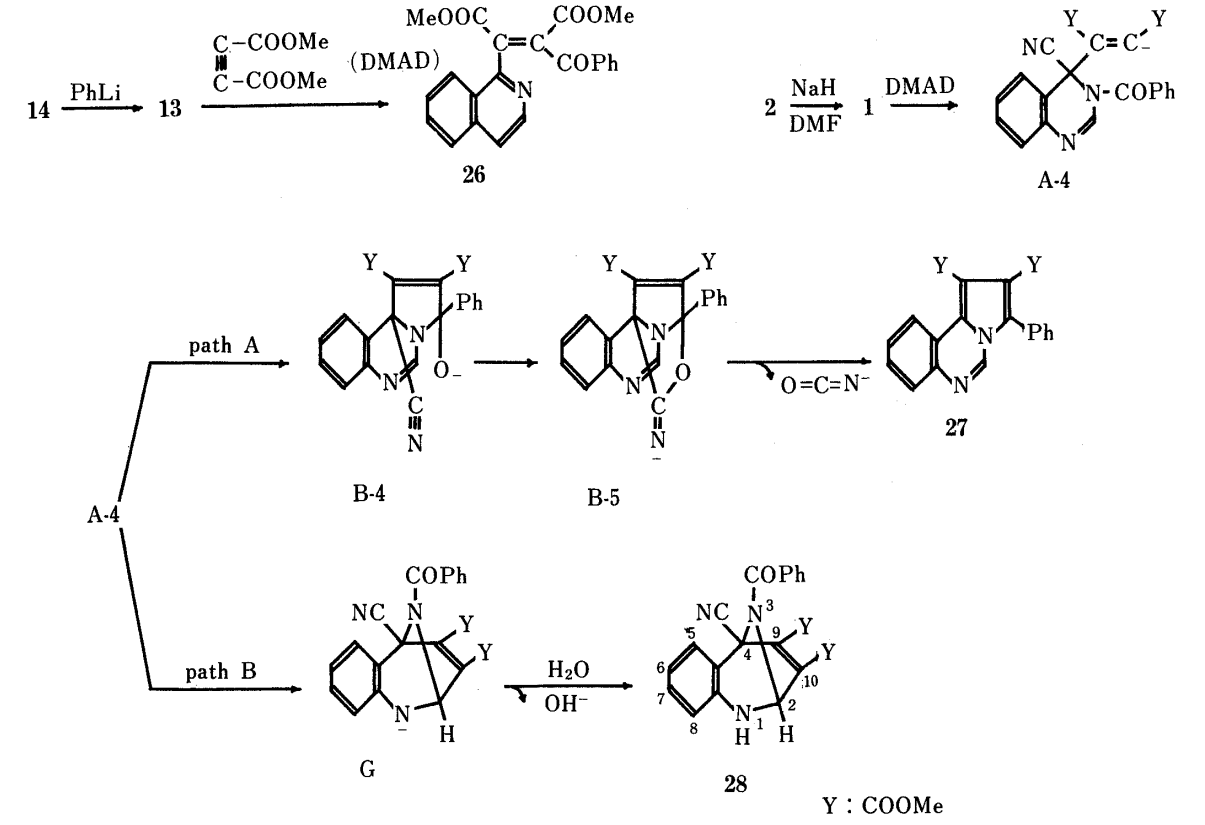


Chart 6

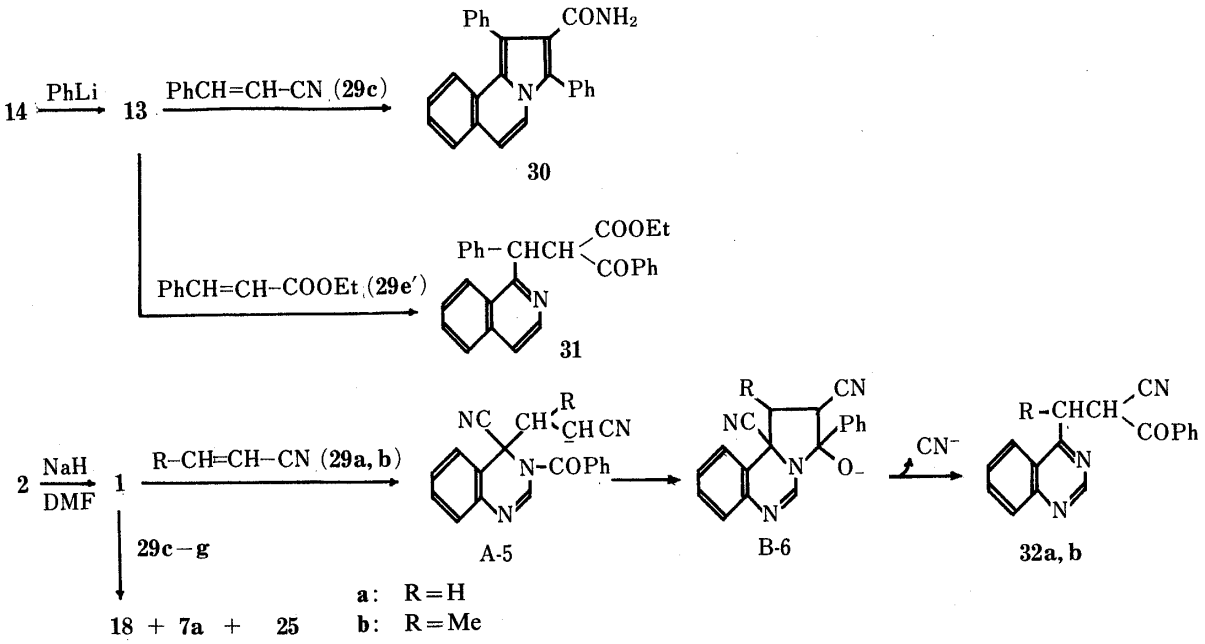


Chart 7

The Reaction with 2-Alkenonitriles

It was reported by McEwen *et al.* that the reaction of **13** with cinnamonitrile (**29c**) in dioxane gives rise to 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**30**), and the reaction with ethyl cinnamate (**29e'**) yields ethyl 2-benzoyl-3-(1-isoquinolyl)-3-phenylpropionate (**31**).[12] In the case of the quinazoline Reissert compound **2**, it was found that the

anion **1** could be used in a Michael-type reaction. Thus, **2** reacted with acrylonitrile (**29a**) and crotononitrile (**29b**) in the presence of sodium hydride in DMF to yield 2-benzoyl-3-(4-quinazolinyl)propionitrile (**32a**) and 2-benzoyl-3-(4-quinazolinyl)butyronitrile (**32b**), respectively. However, the use of cinnamonitrile (**29c**), methyl crotonate (**29d**), methyl cinnamate (**29e**), dimethyl maleate (**29f**), and maleic anhydride (**29g**) in this sequence did not lead to the corresponding reaction products (**32c—g**), but resulted in the formation of the known self-decomposition products[1] of the anion **1** (**18**, **7a**, and **25**).

The formation of **32** involves the initial addition of **1** to the β-carbon of **29** to form an intermediate (A-5), which gives **32** by way of a cyclic intermediate (B-6), similar to the cyclic intermediate[13] observed in the reaction of the anion **13** with acrylonitrile **29a**.

The structures of **32a**, **b** were suggested by the M^+ ion peaks in the MS, and confirmed by analyses of the IR and ^{1}H-NMR spectra, as described in the experimental section.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Jasco IRA-1 grating IR spectrometer. ^{1}H-NMR spectra were measured at 60 MHz on a Hitachi R-24 high-resolution NMR spectrometer, and ^{13}C-NMR spectra were taken at 90 MHz on a JEOL JNM-FX90Q FTNMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br s=broad singlet. MS were recorded on a Hitachi RMS-4 MS spectrometer. The exact mass measurements were made on a JEOL JMS-01SG-2 MS spectrometer combined with a JEC spectrum computer.

α-Aryl (or Alkyl)-4-quinazolinylmethyl Benzoates (7a—q)——NaH (50% in oil; 50 mg, 1 mmol) was slowly added to a solution of the quinazoline Reissert compound (**2**, 261 mg, 1 mmol) and an aldehyde (**3a—q**, 1 mmol) in DMF (2 ml) under ice cooling, and the mixture was then stirred for 30 min. The reaction mixture was poured onto an excess of ice, neutralized with AcOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave the corresponding products, **7a—q**. The yields are shown in Table I, melting points and elemental analysis data in Table II, and spectral data in Table III.

4-Alkylquinazolines (8a, d—g, k, m, n)——A catalyst, prepared from a 1% HCl solution of $PdCl_2$ (12 ml) and activated carbon (0.2 g), was added to a solution of one of **7a**, **d—g**, **k**, **m**, **n** (1 mmol) dissolved in benzene (6 ml) and MeOH (8 ml), and the mixture was shaken in an H_2 stream until the absorption of H_2 stopped. The catalyst was filtered off, the filtrate was evaporated, and the residue was extracted with benzene. The benzene layer was extracted with 10% NaOH, and the NaOH layer was neutralized with 30% HCl to give benzoic acid (**9**). The benzene layer was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave the corresponding 4-alkylquinazoline (**8**). The yields are shown in Table IV, melting points and elemental analysis data in Table II, and spectral data in Table III.

Preparation of 8m and 8n——BuMgBr (**11m**) was prepared by the usual method from BuBr (4.1 g, 30 mmol) and Mg (1.4 g, 60 mmol) in ether (10 ml). This solution was gradually added to a stirred solution of quinazoline (**10a**, 1.3 g, 10 mmol) in ether (15 ml), and the mixture was refluxed for 10 min. A solution of NH_4Cl (0.5 g) in 28% aqueous NH_3 (10 ml) was added to the reaction mixture, and whole was stirred for 10 min. The separated ether solution was dried over Na_2SO_4, and concentrated to dryness. A solution of $K_3Fe(CN)_6$ (9.9 g) in 20% KOH (8 ml) was added to the residue, and the mixture was vigorously shaken for 1 h, then extracted with benzene. The benzene extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave **8m** in 74% yield (1.38 g).

By the same procedure as described for the preparation of **8m**, **10a** (130 mg, 1 mmol), phenylpropyl bromide (600 mg, 3 mmol), and Mg (140 mg, 6 mmol) gave **8n** in 32% yield (80 mg).

α-Alkyl-α-alkyl (or aryl)-4-quinazolinylmethyl Benzoates (16a—c)——When **2** (261 mg, 1 mmol) was treated with acetophenone (**12a**, 120 mg, 1 mmol) in the same manner as described for **7**, the second fraction obtained by chromatography on a column of SiO_2 with $CHCl_3$ as the eluent gave α-methyl-α-phenyl-4-quinazolinylmethyl benzoate (**16a**, 23%, 81 mg), and the third fraction gave 2-(4-quinazolinyl)acetophenone[6] (**17**, 24%, 59 mg), mp 160—161 °C, pale green needles from petr. ether–benzene.

Compound **16a** was recrystallized from MeOH to give colorless prisms, mp 165 °C. *Anal.* Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.91. Found: C, 77.93; H, 4.94; N, 8.03. MS *m/e*: 354 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). ^{1}H-NMR ($CDCl_3$): 9.30 (1H, s, C^2-H), 6.90—8.30 (14H, m, aromatic H), 2.39 (3H, s, CH_3).

Similarly, the reaction with acetone (**12b**, 58 mg, 1 mmol) gave α,α-dimethyl-4-quinazolinylmethyl benzoate (**16b**, 48%, 140 mg), which was recrystallized from petr. ether to give colorless prisms, mp 118 °C. *Anal.* Calcd for

$C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.88; H, 5.47; N, 9.44. MS *m/e*: 292 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$): 9.16 (1H, s, C^2-H), 7.14—8.46 (9H, m, aromatic H), 2.06, (6H, s, $2 \times CH_3$).

Similarly, the reaction with cyclohexanone (**12c**, 98 mg, 1 mmol) gave 1-(4-quinazolinyl)cyclohexyl benzoate (**16c**, 30%, 100 mg), which was recrystallized from MeOH to give colorless prisms, mp 141 °C. *Anal.* Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 76.01; H, 6.09; N, 8.46. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). ^{1}H-NMR ($CDCl_3$): 9.10 (1H, s, C^2-H), 7.03—8.41 (9H, m, aromatic H), 1.15—2.99 (10H, m, alicylic H).

3-Benzoyl-4-(4-quinazolinyl)-3,4-dihydroquinazoline (19a) and 4-Heteroarylquinazolines (20a—c)——When **2** (261 mg, 1 mmol) was treated with a heteroaromatic (**10a—c**) in the same manner as described for **7**, the first fraction obtained by chromatography on a column of SiO_2 with $CHCl_3$ as the eluent gave **19a** (in the case of **10a**), and the second fraction gave the corresponding 4-heteroarylquinazoline (**20a—c**).

Compound **19a** (22%, 80 mg) was recrystallized from benzene–petr. ether to give colorless needles, mp 191 °C. *Anal.* Calcd for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 75.32; H, 4.55; N, 15.08. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). ^{1}H-NMR ($CDCl_3$): 9.04 (1H, s, $C^{2'}$-H), 6.92—8.70 (15H, m, aromatic H and C^4-H).

4,4′-Biquinazoline (**20a**, 14%, 36 mg) was recrystallized from benzene to give colorless needles, mp 246—247 °C, which showed undepressed melting point on admixture with an authentic sample prepared by another route.[9]

4-(1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)quinazoline (**20b**, 68%, 220 mg) was recrystallized from benzene to give slightly yellow needles, mp 200 °C. *Anal.* Calcd for $C_{19}H_{12}N_6$: C, 70.36; H, 3.73; N, 25.91. Found: C, 70.08; H, 3.74; N, 25.86. ^{1}H-NMR ($CDCl_3$): 9.44 (1H, s, C^2-H), 9.18 (1H, s, $C^{6'}$-H), 8.69 (1H, s, $C^{3'}$-H), 7.13—8.27 (9H, m, aromatic H).

4-(3-Phenyl-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-7-yl) quinazoline (**20c**, 49%, 159 mg) was recrystallized from benzene–petr. ether to give a slightly yellow powder, mp 188 °C. *Anal.* Calcd for $C_{18}H_{11}N_7$: C, 66.45; H, 3.41; N, 30.14. Found: C, 66.27; H, 3.43; N, 29.98. ^{1}H-NMR ($CDCl_3$): 9.46 (1H, s, C^2-H), 9.25 (1H, s, $C^{5'}$-H), 7.10—8.43 (9H, m, aromatic H).

4,4′-Biquinazoline (20a) from 19a——A mixture of **19a** (182 mg, 0.5 mmol) and 50% NaH in oil (25 mg, 0.5 mmol) in DMF (1 ml) was stirred for 1 h under ice cooling. The reaction mixture was poured into an excess of ice, neutralized with AcOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The second fraction gave **20a**[9] (54%, 70 mg), which was recrystallized from benzene to give colorless needles, mp 246—247 °C.

4-Alkyl (or Aryl)-3-benzoyl-3,4-dihydro-4-quinazolinecarbonitriles (24a—c)——When **2** (261 mg, 1 mmol) was treated with an alkyl (or aryl) halide (**23a—c**) in the same manner as described for **7**, the corresponding **24a—c** was obtained in the first fraction from a column of SiO_2 with $CHCl_3$ as the eluent.

MeI (**23a**) gave 3-benzoyl-3,4-dihydro-4-methyl-4-quinazolinecarbonitrile (**24a**, 36%, 96 mg), colorless oil. MS *m/e*: 275 (M^+). IR ν_{max}^{neat} cm^{-1}: 1700 (C=O), ^{1}H-NMR ($CDCl_3$): 7.17—8.18 (10H, m, aromatic H), 2.00 (3H, s, CH_3).

The reaction with 2,4-dinitrochlorobenzene (**23b**) gave 3-benzoyl-3,4-dihydro-4-(2,4-dinitrophenyl)-4-quinazolinecarbonitrile (**24b**, 44%, 188 mg), which was recrystallized from benzene–petr. ether to give a colorless powder, mp 120 °C (dec.). MS *m/e*: 427 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1360, 1540 (NO_2), 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 8.23—8.80 (3H, m, aromatic H), 6.60—7.80 (10H, m, aromatic H and C^2-H).

The reaction with 4-chloroquinazoline (**23c**) gave 3-benzoyl-3,4-dihydro-4-(4-quinazolinyl)-4-quinazolinecarbonitrile (**24c**, 36%, 140 mg), which was recrystallized from petr. ether to give a colorless powder, mp 225 °C. *Anal.* Calcd for $C_{24}H_{15}N_5O$: C, 74.02; H, 3.88; N, 17.99. Found: C, 74.14; H, 4.00; N, 17.93. IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O). ^{1}H-NMR ($CDCl_3$): 9.35 (1H, s, $C^{2'}$-H), 6.94—8.10 (14H, m, aromatic H and C^2-H).

Hydrolysis of 24a—c——A solution of one of **24a—c** (1 mmol) in MeOH (7 ml) and 10% NaOH (1 ml) was stirred for 30 min. The reaction mixture was neutralized with AcOH, and MeOH was removed under reduced pressure. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and chromatographed on a column of SiO_2 with benzene as the eluent. The first fraction gave benzoic acid (**9**), and the second fraction gave the corresponding 4-alkyl (or aryl)-quinazoline (**8o, p, 20a**).

The hydrolysis of **24a** gave **9** (70%, 85 mg) and 4-methylquinazoline (**8o**, 63%, 91 mg), picrate mp 182—183 °C, which showed undepressed melting point on admixture with the picrate of an authentic sample prepared by another route.[7]

The hydrolysis of **24b** gave **9** (64%, 78 mg) and 4-(2,4-dinitrophenyl)quinazoline (**8p**, 37%, 110 mg), which was recrystallized from benzene to give slightly yellow needles, mp 198 °C. *Anal.* Calcd for $C_{14}H_8N_4O_4$: C, 56.76; H, 2.72; N, 18.91. Found: C, 57.06; H, 2.68; N, 19.03. IR ν_{max}^{KBr} cm^{-1}: 1360, 1540 (NO_2). ^{1}H-NMR ($(CD_3)_2SO$): 9.27 (1H, s, C^2-H), 8.59—8.99 (2H, m, aromatic H), 7.62—8.20 (5H, m, aromatic H).

The hydrolysis of **24c** gave **9** (65%, 79 mg) and 4,4′-biquinazoline (**20a**, 31%, 80 mg).

Decomposition of 2 to 4-Quinazolinecarbonitrile (18), α-Phenyl-4-quinazolinylmethyl Benzoate (7a), and *O*-Benzoylbenzoin (25)——When **2** (261 mg, 1 mmol) was treated with an alkyl (or aryl) halide (EtBr (**23d**), EtI (**23e**), $(Me)_2CHBr$ (**23f**), cyclohexyl bromide (**23g**), $PhCH_2Cl$ (**23h**), p-$NO_2C_6H_4CH_2Cl$ (**23i**), p-$NO_2C_6H_4Cl$ (**23j**), 2-chloropyridine (**23k**), and 9-chloroacridine (**23l**)) in the same manner as described for **7**, the first fraction obtained by chromatography on a column of SiO_2 with $CHCl_3$ as the eluent gave **25**[14] in 15 to 20% yield, the second fraction gave **18**[7] in 20 to 25% yield, and the third fraction gave **7a** in 20 to 25% yield.

Dimethyl 3-Phenylpyrrolo[1,2-*c*]quinazoline-1,2-dicarboxylate (27) and Dimethyl 3-Benzoyl-4-cyano-1,2,3,4-tetrahydro-2,4-ethenoquinazoline-9,10-dicarboxylate (28)——When **2** (261 mg, 1 mmol) was treated with dimethyl acetylenedicarboxylate (DMAD, 142 mg, 1 mmol) in the same manner as described for **7**, the first fraction obtained by chromatography on a column of SiO_2 with $CHCl_3$ as the eluent gave **27** (6%, 22 mg), which was recrystallized from MeOH to give colorless prisms, mp 193 °C. *Anal.* Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.78; H, 4.37; N, 7.75. MS *m/e*: 360 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). ^{1}H-NMR ($(CD_3)_2SO$): 8.45 (1H, s, C^5-H), 7.31—7.79 (9H, m, aromatic H), 3.86 (3H, s, OCH_3), 3.65 (3H, s, OCH_3).

The second fraction gave **28** (30%, 121 mg), which was recrystallized from MeOH to give yellow needles, mp 198—200 °C. *Anal.* Calcd for $C_{22}H_{17}N_3O_5$: C, 65.50; H, 4.25; N, 10.42. Found: C, 65.56; H, 4.42; N, 10.38. MS *m/e*: 403 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1670, 1740 (C=O). ^{1}H-NMR ($(CD_3)_2SO$): 6.41—7.74 (10H, m, aromatic H and N^1-H), 5.82 (1H, d, changed into s with D_2O, J=4.2 Hz, C^2-H), 3.71 (3H, s, OCH_3), 3.68 (3H, s, OCH_3). ^{13}C-NMR ($(CD_3)_2SO$): 52.61 (q), 52.88 (q), 62.25 (s), 72.44 (d), 113.24 (s), 114.70 (s), 116.00 (d), 118.55 (d), 124.67 (d), 126.24 (s), 128.19 (d), 128.84 (d), 130.14 (d), 130.41 (s), 132.09 (s), 132.31 (d), 136.81 (s), 160.43 (s), 160.97 (s), 170.56 (s).

2-Benzoyl-3-(4-quinazolinyl)propionitrile (32a) and 2-Benzoyl-3-(4-quinazolinyl)butyronitrile (32b)——When **2** (261 mg, 1 mmol) was treated with acrylonitrile (**29a**, 53 mg, 1 mmol) in the same manner as described for **7**, the second fraction obtained by chromatography on a column of SiO_2 with $CHCl_3$ as the eluent gave **32a** (38%, 109 mg), yellow oil. MS *m/e*: 287 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O), 2240 (CN). ^{1}H-NMR ($CDCl_3$): 8.86 (1H, s, $C^{2'}$-H), 7.17—8.06 (9H, m, aromtic H), 5.41 (1H, dd, J_{ax}=7.8 Hz, J_{bx}=6.0 Hz, $\overset{H_a}{\underset{H_b}{C}}$–$CH_x$–CN), 4.17 (1H, dd, J_{ab}=17.4 Hz, J_{ax}=7.8 Hz, $\overset{H_a}{\underset{H_b}{C}}$–$CH_x$–CN), 3.83 (1H, dd, J_{ab}=17.4 Hz, J_{bx}=6.0 Hz, $\overset{H_a}{\underset{H_b}{C}}$–$CH_x$–CN).

Similarly, the reaction with crotononitrile (**29b**, 67 mg, 1 mmol) gave **32b** (72%, 217 mg), colorless oil. MS *m/e* Calcd for $C_{19}H_{15}N_3O$: 301.1218 (M^+). Observed: 301.1218 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O), 2240 (CN). ^{1}H-NMR ($CDCl_3$): 8.79 (1H, s, $C^{2'}$-H), 7.16—8.26 (9H, m, aromatic H), 5.49 (1H, d, J=7.8 Hz, CH–CH–CN), 4.63 (1H, m, Me–CH–CH–CN), 1.66 (3H, d, J=7.8 Hz, CH_3–CH–).

However, in the case of the reaction with cinnamonitrile (**29c**), methyl crotonate (**29d**), methyl cinnamate (**29e**), dimethyl maleate (**29f**), and maleic anhydride (**29g**), **25** (10—20%), **18** (10—15%), and **7a** (10—20%) were obtained from the first, second, and third fractions obtained by chromatography on a column of SiO_2 with $CHCl_3$ as the eluent.

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