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Reaction of 4-Aroylquinazolines with Sodium Hydroxide: Aryl Migration to Give 4-Aryl-3,4-dihydro-4-quinazolinecarboxylic Acids and Formation of Quinazoline and Aroic Acids

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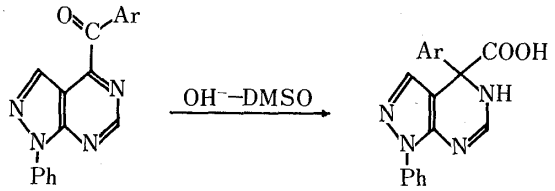
4-Aroylquinazolines (**3**) were prepared in good yields by alkaline hydrolysis of α-aryl-4-quinazolinylmethyl benzoates (**15**), followed by oxidation. The reaction of **3** with sodium hydroxide in dimethyl sulfoxide (DMSO) was found to proceed in two ways. One path is the aryl migration to lead to 4-aryl-3,4-dihydro-4-quinazolinecarboxylic acids (**4**), and the other is the fission of the C^4–CO bond to yield quinazoline (**5**) and aroic acids (**6**).

Potassium ferricyanide oxidized the carboxylic acids **4** to the corresponding 4-arylquinazolines (**14**) with elimination of carbon dioxide.

Reaction of 4-benzoylquinazoline (**3a**) with methylmagnesium iodide did not result in the migration, but instead yielded of α-methyl-α-phenyl-4-quinazolinemethanol (**18**) and 3,4-dihydro-α,4-dimethyl-α-phenyl-4-quinazolinemethanol (**19**).

Keywords——4-aroylquinazoline; 4-aryl-3,4-dihydro-4-quinazolinecarboxylic acid; 4-arylquinazoline; quinazoline; aroic acid; 4-quinazolinemethanol; aryl migration; benzilic acid rearrangement; fission

In the previous paper,[1] we reported that when a mixture of 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (**1**) and sodium hydroxide in dimethyl sulfoxide (DMSO) was stirred for 1 h, migration of the aryl group to the 4-position occurred, *i.e.*, the benzilic acid rearrangement, resulting in the formation of 4-aryl-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carboxylic acids (**2**).

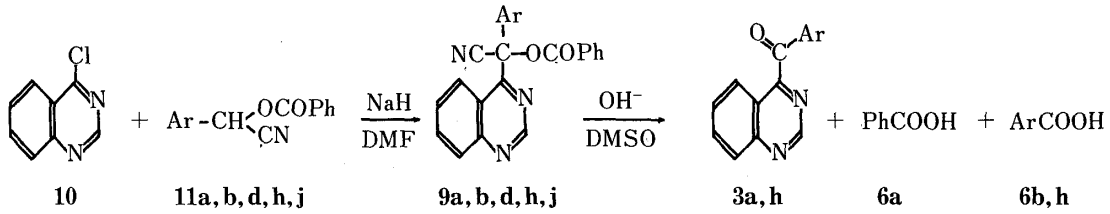


1 **2**

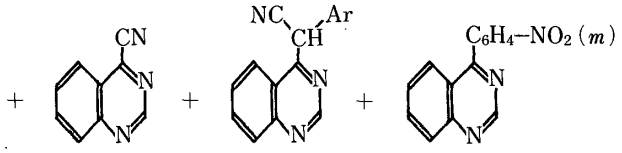
Chart 1

In the expectation that a similar migration would take place, we carried out the reaction of 4-aroylquinazolines (**3**) with sodium hydroxide in DMSO, and found that the reaction proceeded in two ways. One path is the expected aryl migration to lead to 4-aryl-3,4-dihydro-4-quinazolinecarboxylic acids (**4**), and the other is the fission of the C^4–CO bond to yield quinazoline (**5**) and aroic acids (**6**). In the present paper, we describe our detailed investigation of the aryl migration and the fission.

Hamana *et al.*[2] reported that α-aryl-α-benzoyloxy-2-quinolineacetonitriles (**7**) are easily convertible to the corresponding 2-aroylquinolines (**8**) by alkaline hydrolysis. When attempts

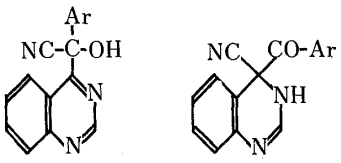


10 **11a, b, d, h, j** **9a, b, d, h, j** **3a, h** **6a** **6b, h**



12 **13b, h, j** **14j**

a: Ar = C_6H_5
b: Ar = C_6H_4–Cl (*p*)
d: Ar = C_6H_4–OMe (*p*)
h: Ar = C_6H_4–NO_2 (*p*)
j: Ar = C_6H_4–NO_2 (*m*)



A B

Chart 2

TABLE I. Reaction of **10** with **11** in the Presence of NaH in DMF

10	11	Reaction time (min)	Reaction temp. (°C)[a]	Product	
				9	Yield (%)
10	**11a**	10	r.t.	**9a**	45
10	**11b**	10	r.t.	**9b**	89
10	**11d**	7	80	**9d**	43
10	**11h**	5	r.t.	**9h**	56
10	**11j**	5	r.t.	**9j**	73

a) r.t. = room temperature.

TABLE II. Reaction of **9** with NaOH in DMSO[a]

9	Reaction time (h)	Product											
		3	Yield (%)	6a	Yield (%)	6	Yield (%)	12	Yield (%)	13	Yield (%)	14	Yield (%)
9a	0.5	**3a**	60		54				13	**13a**	—[b]	**14a**	—[b]
9b	1.0	**3b**	—[b]		29	**6b**	26		26	**13b**	29	**14b**	—[b]
9h	0.5	**3h**	57		30	**6h**	24		13	**13h**	20	**14h**	—[b]
9j	1.5	**3j**	—[b]		30	**6j**	—[b]		28	**13j**	24	**14j**	24

a) Reaction at room temperature. *b*) Not isolated.

were made to prepare the starting ketones **3** by application of Hamana's method to α-aryl-α-benzoyloxy-4-quinazolineacetonitriles (**9**), which were easily prepared by the reaction of 4-chloroquinazoline (**10**) with *O*-benzoylmandelonitriles (**11**)[3-5] in the presence of sodium

TABLE III. Melting Points and Elemental Analyses of **3h**, **4**, **9**, **13**, and **14**

Compd.	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
3h	179[a, j]	$C_{15}H_9N_3O_3$	64.51	3.25	15.05
			(64.57	3.33	14.95)
4a	176[b, k]	$C_{15}H_{12}N_2O_2 \cdot H_2O$	66.65	5.22	10.37
			(66.48	5.23	10.29)
4b	170[c, k]	$C_{15}H_{11}ClN_2O_2 \cdot H_2O$	59.12	4.30	9.19
			(58.99	4.40	9.16)
4c	165[c, k]	$C_{15}H_{11}ClN_2O_2 \cdot H_2O$	59.12	4.30	9.19
			(58.72	4.30	9.17)
4d	196[d, k]	$C_{16}H_{14}N_2O_3$	68.07	5.00	9.92
			(67.96	5.04	9.93)
4e	170[e, l]	$C_{16}H_{14}N_2O_3$	MS *m/e*: 238 ($M^+ - CO_2$)		
4f	176[e, h]	$C_{16}H_{14}N_2O_2 \cdot 1.5H_2O$	65.52	5.84	9.55
			(65.39	5.60	9.23)
9a	172[c, m]	$C_{23}H_{15}N_3O_2$	75.60	4.14	11.50
			(75.43	4.20	11.27)
9b	179[b, m]	$C_{23}H_{14}ClN_3O_2$	69.09	3.53	10.51
			(68.87	3.60	10.43)
9d	108[c, m]	$C_{24}H_{17}N_3O_3$	72.90	4.33	10.63
			(72.78	4.52	10.65)
9h	241[c, j]	$C_{23}H_{14}N_4O_4$	67.31	3.44	13.65
			(67.37	3.57	13.36)
9j	178[f, m]	$C_{23}H_{14}N_4O_4$	67.31	3.44	13.65
			(67.70	3.60	13.70)
13b	176[g, l]	$C_{16}H_{10}ClN_3$	68.70	3.60	15.02
			(68.18	3.74	14.97)
13h	234[h, l]	$C_{16}H_{10}N_4O_2$	66.20	3.47	19.30
			(65.91	3.53	19.16)
13j	212[g, l]	$C_{16}H_{10}N_4O_2$	66.20	3.47	19.30
			(66.44	3.66	18.96)
14b	122[b, l]	$C_{14}H_9ClN_2$	69.86	3.77	11.64
			(69.93	3.82	11.62)
14c	114[e, n]	$C_{14}H_9ClN_2$	69.86	3.77	11.64
			(69.69	3.80	11.57)
14d	82[e, n]	$C_{15}H_{12}N_2O$	76.25	5.12	11.86
			(76.23	5.24	11.84)
14e	—[i]	$C_{15}H_{12}N_2O$	MS *m/e*: 236 (M^+)		
14f	—[i]	$C_{15}H_{12}N_2$	MS *m/e* Calcd: 220.1001 (M^+) Found: 220.0972		
14h	190[b, m]	$C_{14}H_9N_3O_2$	66.92	3.61	16.73
			(66.66	3.70	16.59)
14j	174[c, l]	$C_{14}H_9N_3O_2$	66.92	3.61	16.73
			(66.67	3.65	16.68)

a) Pale yellow needles. *b*) Colorless needles. *c*) Colorless powder. *d*) Pale yellow prisms. *e*) Colorless prisms. *f*) Yellow needles. *g*) Yellow powder. *h*) Red powder. *i*) Colorless oil. *j*) Recrystn. from benzene. *k*) Recrystn. from H_2O. *l*) Recrystn. from MeOH. *m*) Recrystn. from benzene–petr. ether. *n*) Recrystn. from petr. ether.

hydride in *N*,*N*-dimethylformamide (DMF) (Table I), **3**, benzoic acid (**6a**), aroic acids (**6**), 4-quinazolinecarbonitrile (**12**), α-aryl-4-quinazolineacetonitriles (**13**), and 4-(*m*-nitrophenyl)quinazoline (**14j**, only in the case of **9j**) were obtained in poor yields (Table II).

TABLE IV. IR and ^{1}H-NMR Spectra of **3h**, **4**, **9**, **13**, and **14**

Compd.	IR ν_{max}^{KBr} cm^{-1}				^{1}H-NMR ($CDCl_3$) ppm		
	CO	NO_2	CN	CO_2H and NH	C^2-H (s)	Aromatic H (m)	OCH_3 (s)
3h	1680	1360, 1510			9.40	7.7—8.4 (8H)	
4a	1680			2400—3500			
4b	1680			2600—3600			
4c	1620			2200—3600			
4d	1680			2300—3300			
4e	1640			2700—3600			
4f	1620			2600—3600			
9a	1730				9.50	7.4—8.3 (14H)	
9b	1740				9.26	7.3—8.0 (13H)	
9d	1740				9.25	6.8—8.2 (13H)	3.82
9h	1750	1360, 1540			9.46	7.6—8.3 (13H)	
9j	1740	1360, 1520			9.35	7.2—8.6 (13H)	
13b[a]			2220		—[b]	7.0—8.0	
13h[a]		1340, 1500	2180		—[b]	7.0—8.5	
13j[a]		1350, 1520	2160		—[b]	7.1—8.9	
14b					9.24	7.3—8.2 (8H)	
14c					9.31	7.3—8.1 (8H)	
14d					9.22	6.9—8.3 (8H)	3.88
14e					9.22	6.8—8.0 (8H)	3.58
14f					9.12	7.0—8.1 (8H)	2.40 (CH_3)
14h		1360, 1520			9.32	7.2—8.6 (8H)	
14j		1340, 1530			9.43	7.2—8.7 (8H)	

a) ^{1}H-NMR in $(CD_3)_2SO$. *b*) Overlapping with aromatic H.

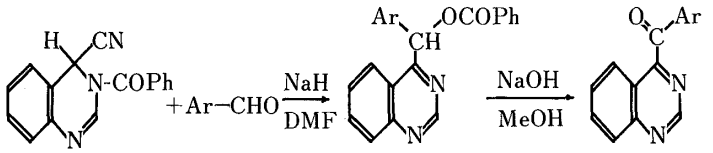
Thus, this method is not effective for the preparation of the starting **3**.

The initial step of the alkaline hydrolysis of **9** is undoubtedly the formation of the ketones **3** with the expulsion of cyanide ion. Subsequent nucleophilic attack of the resulting cyanide ion at the carbonyl carbon of **3** leads to an intermediate (A), while attack at C^4 forms an intermediate (B), as shown in Chart 2. Ready oxidation–reduction reaction between A and B may give **13**, **12**, and **6**. In fact, 4-(*p*-nitrobenzoyl)quinazoline (**3h**) reacted with cyanide ion in DMSO to give α-(*p*-nitrophenyl)-4-quinazolineacetonitrile (**13h**, 28%), **12** (46%), and *p*-nitrobenzoic acid (**6h**, 24%).

Even though the yield was low, compound **14j** might have been formed by the aryl migration of **3j**. This supported our expectation, described in the introduction, that the benzilic acid rearrangement of the ketones **3** would proceed.

Compounds **3a**,[6] **6a**, **b**, **h**, and **12**[7] showed undepressed melting points on admixture with the corresponding authentic samples. The structures of **3h**, **9a**, **b**, **d**, **h**, **j**, **13j**, and **14j** were suggested by their elemental analyses (Table III), and confirmed by analyses of their proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectra (Table IV). The IR spectra of **9** did not show any absorption band of the cyano group. This is compatible with the reported absence of the absorption band of a cyano group located at an electron-deficient carbon, such as in α-aryl-α-benzoyloxy-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-acetonitriles.[1] The melting points of α-(*p*-chlorophenyl)-4-quinazolineacetonitrile (**13b**) and **13h** were undepressed on admixture with the corresponding authentic samples prepared by the reaction of **10** with arylacetonitriles in the presence of sodium hydride in DMF.

The preparation of the starting **3** was eventually achieved by the following route in good



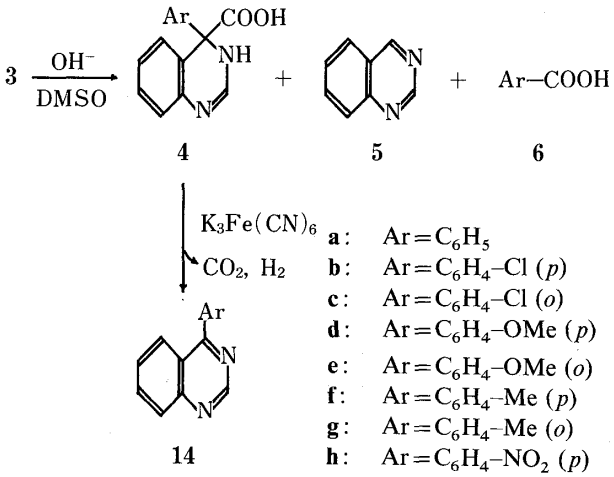
16 17a–i 15a–i 3a–h

a: Ar=C_6H_5 d: Ar=C_6H_4–OMe (*p*) g: Ar=C_6H_4–Me (*o*)
b: Ar=C_6H_4–Cl (*p*) e: Ar=C_6H_4–OMe (*o*) h: Ar=C_6H_4–NO_2 (*p*)
c: Ar=C_6H_4–Cl (*o*) f: Ar=C_6H_4–Me (*p*) i: Ar=C_6H_4–NO_2 (*o*)

Chart 3

TABLE V. Alkaline Hydrolysis of **15** in MeOH to **3**

	Product	
15	**3**	Yield (%)
15a	**3a**	88
15b	**3b**	88
15c	**3c**	73
15d	**3d**	89
15e	**3e**	92
15f	**3f**	85
15g	**3g**	72
15h	**3h**	26



a: Ar=C_6H_5
b: Ar=C_6H_4–Cl (*p*)
c: Ar=C_6H_4–Cl (*o*)
d: Ar=C_6H_4–OMe (*p*)
e: Ar=C_6H_4–OMe (*o*)
f: Ar=C_6H_4–Me (*p*)
g: Ar=C_6H_4–Me (*o*)
h: Ar=C_6H_4–NO_2 (*p*)

Chart 4

TABLE VI. Reaction of **3** with NaOH in DMSO

	Product					
3	**4**	Yield (%)	**5**	Yield (%)	**6**	Yield (%)
3a	**4a**	48		19	**6a**	47
3b	**4b**	60		15	**6b**	33
3c	**4c**	84		—[a]	**6c**	—[a]
3d	**4d**	21		15	**6d**	70
3e	**4e**	86		7	**6e**	6
3f	**4f**	38		13	**6f**	15
3h[b]	**4h**	—[a]		—[a]	**6h**	24

a) Not isolated. *b*) 4-(*p*-Nitrophenyl)quinazoline (**14h**) was obtained in 64% yield together with **6h**.

yields. Thus, α-aryl-4-quinazolinylmethyl benzoates (**15**), which were easily prepared by the reaction of quinazoline Reissert compound (3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile, **16**) with aromatic aldehydes (**17**) in the presence of sodium hydride in DMF,[8] were subjected to alkaline hydrolysis in methanol, followed by oxidation to yield the desired ketones **3** (Table V).

The ketones **3a**—**g** showed undepressed melting points on admixture with authentic samples[6] prepared by the cross benzoin condensation of quinazoline **5** with the corresponding aromatic aldehydes (**17a**—**g**) in the presence of cyanide ion, followed by oxidation.

When a mixture of the ketones **3** and sodium hydroxide in DMSO was stirred, migration

TABLE VII. Oxidation of **4** with $K_3Fe(CN)_6$ to **14**

	Product	
4	**14**	Yield (%)
4a	**14a**	85
4b	**14b**	69
4c	**14c**	83
4d	**14d**	72
4e	**14e**	65
4f	**14f**	70

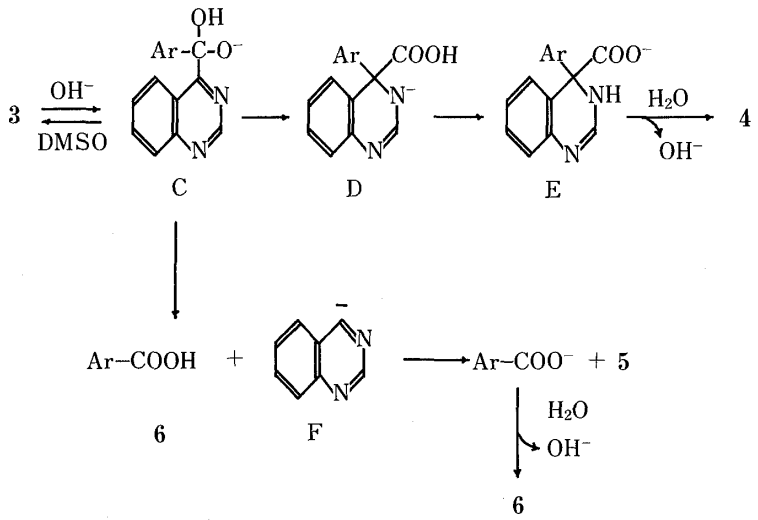


Chart 5

of the aryl group and fission of the C^4–CO bond occurred, giving the corresponding 4-aryl-3,4-dihydro-4-quinazolinecarboxylic acids (**4**), quinazoline **5**, and aroic acid **6** (Table VI). The carboxylic acids **4** formed the sodium salts with aqueous sodium carbonate, and were easily convertible to the corresponding 4-arylquinazolines (**14**) by potassium ferricyanide oxidation with elimination of carbon dioxide (Table VII). Based on the results obtained in the above experiments, as well as the elemental analyses (Table III) and the spectral data (Table IV), the structure of **4** was confirmed.

It was reported that the mechanism of the aryl migration of 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines **1** to 4-aryl-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carboxylic acids **2** is a type of benzilic acid rearrangement.[1] A similar mechanism may be involved in the formation of the carboxylic acids **4**. Thus, the aryl group of the anion (C), which is generated by equilibrium between the ketones **3** and a strong base such as hydroxide ion in DMSO,[9] undergoes a 1,2-shift, in which the migration terminus is the electron-deficient C^4-ring carbon,[6,7] leading to the salt of the carboxylic acids **4**, as shown in Chart 5. The influence of the strongly electron-deficient C^4-ring carbon causes the fission of C^4–C^α bond in C, giving quinazoline **5** and aroic acids **6**, as shown in Chart 5.

In the case of the *p*-nitrobenzoyl derivative (**3h**), however, the corresponding carboxylic acid (**4h**) was not isolated, and 4-(*p*-nitrophenyl)quinazoline (**14h**) was obtained together with *p*-nitrobenzoic acid **6h**. It is assumed that **14h** originates from the carboxylic acid **4h**, which could not be isolated due to its high susceptibility to oxidative decarboxylation. Although quinazoline **5** was not isolated, the acid **6h** seems to be formed by the fission of C^4–C^α bond in C.

It was reported that the aryl migration of **1** to **2** fails when methanolic NaOH is used instead of MDSO–NaOH.[1] However, the *p*-chlorobenzoyl derivative (**3b**) reacted with methanolic NaOH, and underwent the aryl migration and fission, giving **4b**, **5**, and **6b**. Many examples[10,11] have been reported where the reaction of benzil with a Grignard reagent proceeds with benzilic acid rearrangement. For example,[10] an aryl group migrates from one carbon to another in the reaction of *o*-tolylmagnesium bromide with benzil. In this case, the product is *o*-toluoyldiphenylcarbinol, formed by phenyl migration. When an attempt was made to form 4-acetyl-3,4-dihydro-4-phenylquinazoline, corresponding to **4a**, by means of the Grignard reaction using methylmagnesium iodide, **3a** yielded α-methyl-α-phenyl-4-quinazolinemethanol (**18**, 77%) as a main product together with 3,4-dihydro-α,4-dimethyl-α-phenyl-4-quinazolinemethanol (**19**, 19%) as a by-product, as shown in Chart 6.

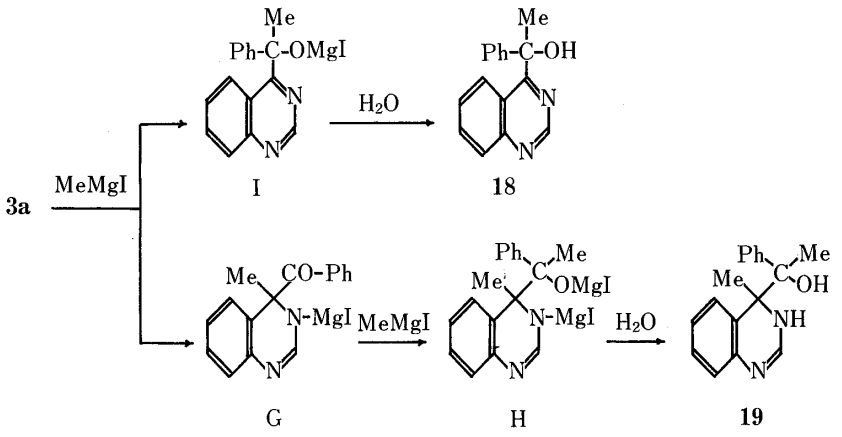


Chart 6

The addition of methylmagnesium iodide to the carbonyl group of **3a** in the initial step gives **18** by way of an adduct (I). It seems that compound **19** does not originate from **18**, as shown in Chart 6, for the following reasons. Methyl or aryl migration is not observed in the reaction of **18** under the aryl migration conditions using NaOH in DMSO or sodium hydride in DMF, and the reaction of methylmagnesium iodide with **18** does not afford **19**, resulting in the recovery of **18**. It was also reported that even if a methyl group is present at the 4-position, methylmagnesium iodide adds across the 3,4-bond of 4-methylquinazoline to give 3,4-dihydro-4,4-dimethylquinazoline.[12] Thus, the first step is undoubtedly addition of methylmagnesium iodide to the 3,4-bond of **3a** to give an adduct (G), followed by further addition to the carbonyl group, to form **19** by way of an adduct (H).

The structures of **18** and **19** were suggested by the elemental analyses, and confirmed by analyses of the IR and NMR spectra, as described in the experimental section. The ^{1}H-NMR spectrum of **18** showed a characteristic singlet at 9.23 ppm due to C^2-H of the aromatized quinazoline ring. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **19** showed two quartets due to C^α-Me (24.38 ppm) and C^4-Me (25.79 ppm), two singlets due to C^α or C^4 (60.14, 78.56 ppm), and a characteristic doublet due to C^2 (146.29 ppm). It was reported that alkyl 3,4-dihydro-4-quinazolinylmethyl ketone reacted with base to give quinazoline **5** and alkyl methyl ketone.[13] Similarly, although the yield was very poor, the reaction of **19** with methoxide ion in methanol gave **18**, supporting the conclusion that the phenyl group in **19** is present at the α-position.

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. Mass spectra (MS) were recorded on a Hitachi RMS-4 mass spectrometer. The exact mass measurements were made on a JEOL JMS-01SG-2 mass spectrometer combined with a JEC spectrum computer.

Preparation of α-Aryl-α-benzoyloxy-4-quinazolineacetonitriles (9)——A mixture of 4-chloroquinazoline (**10**, 1 mmol), an *O*-benzoylmandelonitrile (**11**, 1 mmol), and 50% NaH in oil (2 mmol) in DMF (10 ml) was stirred under the conditions described in Table I. The reaction mixture was poured onto an excess of ice-H_2O, and extracted with $CHCl_3$. The $CHCl_3$ 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 the corresponding **9** which was recrystallized from the appropriate solvent as shown in Table III. The yields of **9a**, **b**, **d**, **h**, **j** are given in Table I, melting points and elemental analysis data in Table III, and spectral data in Table IV.

Reaction of 9 with NaOH——A mixture of **9** (1 mmol) and 0.5 ml of 50% NaOH (in the cases of **9b** and **9j**, 0.1 ml of 50% NaOH was used) in DMSO (15 ml) was stirred under the conditions described in Table II. The reaction mixture was poured onto an excess of ice-H_2O, and extracted with $CHCl_3$. The $CHCl_3$ 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 4-quinazolinecarbonitrile (**12**), the second fraction gave the 4-aroylquinazolines (**3**), the third fraction afforded 4-arylquinazolines (**14**), and the fourth fraction gave α-aryl-4-quinazolineacetonitriles (**13**).

The aqueous layer was neutralized with AcOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave benzoic acid (**6a**), and the second fraction afforded aroic acids (**6**).

The yields of the reaction products, **12**, **3a**, **h**, **14j**, **13b**, **h**, **j**, and **6a**, **b**, **h** are given in Table II, melting points and elemental analysis data of **3h**, **13b**, **h**, **j**, and **14j** in Table III, and spectral data in Table IV.

α-(*p*-Chlorophenyl)- (13b) and α-(*p*-Nitrophenyl)-4-quinazolineacetonitrile (13h)——A mixture of **10** (1 mmol), an arylacetonitrile (1 mmol), and 50% NaH in oil (2 mmol) in DMF (15 ml) was stirred for 10 min. The reaction mixture was poured onto an excess of ice-H_2O, and neutralized with AcOH to separate the corresponding α-aryl-4-quinazolineacetonitrile (**13**) which was recrystallized from MeOH.

The reaction with *p*-chlorophenylacetonitrile gave α-(*p*-chlorophenyl)-4-quinazolineacetonitrile (**13b**) as a yellow powder, mp 176 °C, in 71% yield (198 mg).

The reaction with *p*-nitrophenylacetonitrile gave α-(*p*-nitrophenyl)-4-quinazolineacetonitrile (**13h**) as a red powder, mp 234 °C, in 36% yield (90 mg).

The elemental analysis data for **13b** and **13h** are shown in Table III, and spectral data in Table IV.

Reaction of 4-(*p*-Nitrobenzoyl)quinazoline (3h) with KCN——A mixture of **3h** (1 mmol, 279 mg) and 30% KCN (0.8 ml) in DMSO (15 ml) was stirred for 5 h. The reaction mixture was poured onto an excess of ice-H_2O, and 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 **12**,[7] mp 118—119 °C, in 46% yield (71 mg), and the second fraction gave **13h** in 28% yield (81 mg).

The aqueous layer was neutralized with AcOH, and extracted with $CHCl_3$. The $CHCl_3$ 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 *p*-nitrobenzoic acid (**6h**), mp 241 °C, in 24% yield (40 mg).

Preparation of 4-Aroylquinazolines (3)——A solution of an α-aryl-4-quinazolinylmethyl benzoate (**15**, 1 mmol) in 10% methanolic NaOH (5 ml) was refluxed for 30 min. The solvent was removed under reduced pressure. The residue was poured onto an excess of ice-H_2O, neutralized with AcOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and passed through a column of SiO_2 to remove impurities. Compounds **3a**—**h** obtained by this procedure were recrystallized from MeOH or petr. ether. The yields are shown in Table V. The melting points of **3a**—**g** were undepressed on admixture with authentic samples[6] prepared by benzoin condensation of **5** with the corresponding aromatic aldehydes in the presence of cyanide ion.

Reaction of 3 with NaOH in DMSO (Aryl Migration of 3 to 4-Aryl-3,4-dihydro-4-quinazolinecarboxylic Acids (4))——i) A mixture of **3** (1 mmol) and 50% NaOH (1 ml) in DMSO (15 ml) was stirred for 1 h. The reaction mixture was poured onto an excess of ice, and extracted with $CHCl_3$. The $CHCl_3$ 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 **5** (in the case of **3h**, the first fraction gave 4-(*p*-nitrophenyl)quinazoline (**14h**), mp 190 °C, in 64% yield (161 mg)).

The aqueous layer was neutralized with AcOH, and allowed to stand for 3 d. The separated crystals were filtered off, and recrystallized from H_2O or MeOH to give the carboxylic acids **4**. The filtrate was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4. Evaporation of the $CHCl_3$ gave aroic acids (**6**).

The yields of **5**, **4**, and **6** are shown in Table VI. The elemental analysis data and melting points of **4** are given in Table III, and spectral data in Table IV.

Benzoic acid (**6a**, mp 122 °C), *p*-chlorobenzoic acid (**6b**, mp 243 °C), *p*-anisic acid (**6d**, mp 184 °C), *o*-methoxybenzoic acid (**6e**, mp 101 °C), *p*-toluic acid (**6f**, mp 180 °C), and *p*-nitrobenzoic acid (**6h**, mp 241 °C) showed

undepressed melting points on admixture with the corresponding authentic samples.

ii) A mixture of **3b** (1 mmol, 268 mg) and 50% NaOH (1 ml) in MeOH (10 ml) was stirred for 3 h. The separated crysrals were filtered off, and recrystallized from MeOH to recover **3b** in 43% yield (115 mg). After removal of the MeOH from the filtrate under reduced pressure, the residue was poured onto an excess of ice-H_2O, and extracted with $CHCl_3$. The $CHCl_3$ 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 recovered **3b** in 7% yield (19 mg), and the second fraction gave **5** in 7% yield (9 mg).

The NaOH layer was neutralized with AcOH to separate **4b** in 25% yield (76 mg). The filtrate was extracted with $CHCl_3$. The $CHCl_3$ 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 **6b** in 10% yield (16 mg).

Oxidation of 4 with $K_3Fe(CN)_6$——A solution of $K_3Fe(CN)_6$ (576 mg) in H_2O (15 ml) was added to a mixture of **4** (100 mg), benzene (20 ml), and 33% KOH (0.4 ml), and the mixture was vigorously shaken for 1 h at room temperature. The benzene solution was dried over Na_2SO_4, and evaporation of the benzene gave 4-arylquinazolines (**14**), which were recrystallized from the appropriate solvent as described in Table III. The yields are listed in Table VII. Melting points and elemental analysis data in Table III, and spectral data in Table IV.

Reaction of 3a with MeMgI——A solution of MeMgI was prepared by the usual method from MeI (3 mmol, 426 mg) and Mg (6 mmol, 146 mg) in ether (5 ml). This solution was gradually added to a stirred solution of **3a** (1 mmol, 234 mg) in ether (10 ml), and the mixture was refluxed for 10 h. The solvent was removed under reduced pressure, and a solution of NH_4Cl (3 g) and 28% NH_3 (1.5 ml) in H_2O (7.5 ml) was added to the residue (adduct). The reaction mixture was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4, then chromatographed on a column of Al_2O_3 eluting with $CHCl_3$ and MeOH. The first fraction with $CHCl_3$ gave α-methyl-α-phenyl-4-quinazolinemethanol (**18**), which was recrystallized from MeOH to give colorless needles, mp 153 °C, in 77% yield (192 mg). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.67; H, 5.61; N, 11.15. IR ν_{max}^{KBr} cm^{-1}: 2900—3300 (OH). ^{1}H-NMR ($CDCl_3$): 9.23 (1H, s, C^2–H), 7.0—8.0 (9H, m, aromatic H), 6.24 (1H, br s, exchangeable with D_2O, C^{α}-OH), 2.10 (3H, s, C^{α}-CH_3).

The fraction with MeOH gave 3,4-dihydro-α,4-dimethyl-α-phenyl-4-quinazolinemethanol (**19**) which was recrystallized from MeOH to give colorless needles, mp 112—115 °C, in 19% yield (50 mg). *Anal.* Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.11; H, 6.75; N, 10.27. IR ν_{max}^{KBr} cm^{-1}: 2900—3260 (NH and OH). ^{1}H-NMR ($(CD_3)_2SO$): 6.5—7.1 (11H, m, aromatic H, C^2-H, and OH), 5.01 (1H, br s, exchangeable with D_2O, NH), 1.39 (3H, s, CH_3), 1.44 (3H, s, CH_3). ^{13}C-NMR ($(CD_3)_2SO$): 24.38 (q), 25.79 (q), 60.14 (s), 78.56 (s), 120.93 (d), 122.45 (d), 125.97 (d), 126.40 (s), 126.46 (d), 127.27 (d), 127.38 (d), 127.43 (d), 142.33 (s), 145.04 (s), 146.29 (d).

Reaction of 19 with Methoxide Ion——A solution of sodium methoxide was prepared from Na (19 mg) and MeOH (4 ml). Compound **19** (100 mg) was added to the sodium methoxide solution, and the mixture was refluxed for 12 h. After removal of the MeOH, the residue was neutralized with 5% AcOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and chromatographed on a column of Al_2O_3 with $CHCl_3$ and MeOH. The fraction eluted with $CHCl_3$ gave **18** (trace), and the fraction eluted with MeOH gave recovered **19** in 70% yield.

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