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Reactions of 3-Benzoyl-3,4-dihydro-2-methyl-4-quinazolinecarbonitrile (2-Methylquinazoline Reissert Compound) with Acid, Base, Sodium Hydride, and Electrophiles

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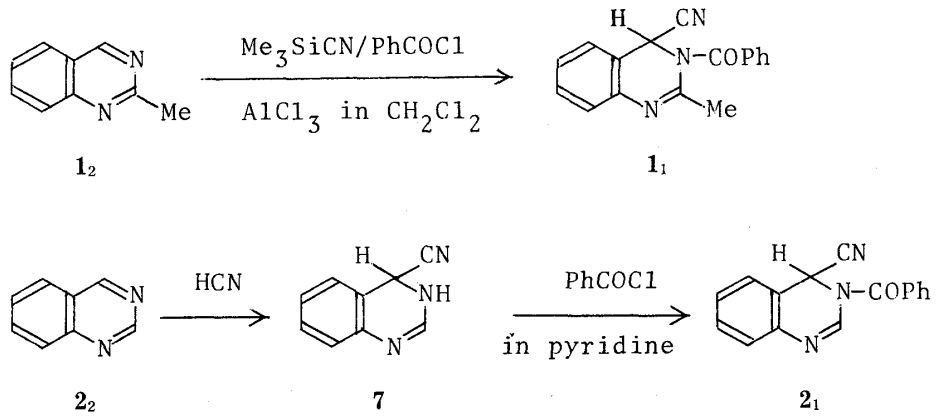
Acid hydrolysis of 3-benzoyl-3,4-dihydro-2-methyl-4-quinazolinecarbonitrile ($\mathbf{1}_1$, 2-methylquinazoline Reissert compound) resulted in the formation of the oxazole ($\mathbf{1}_3$). Alkaline hydrolysis gave 2-methylquinazoline ($\mathbf{1}_2$) and benzoic acid (**8**). The anion (D^1), generated from $\mathbf{1}_1$ and NaH in dimethylformamide (DMF), underwent decomposition to give the ketone ($\mathbf{1}_4$) and the cyanoquinazoline ($\mathbf{1}_5$) together with by-products $\mathbf{1}_2$ and *O*-benzoylbenzoin (**9**). Compound $\mathbf{1}_1$ reacted with aromatic aldehydes (**10a—c**) in the presence of NaH to give the benzoates ($\mathbf{1}_6$**a—c**) and by-products $\mathbf{1}_2$ and $\mathbf{1}_5$. Alkylation (or arylation) with alkyl (or aryl) halides (**11a, b**) afforded the corresponding 4-substituted derivatives ($\mathbf{1}_9$**a, b**) and a by-product $\mathbf{1}_4$.

The reactivities of $\mathbf{1}_1$ and 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile ($\mathbf{2}_1$, quinazoline Reissert compound) are compared.

Keywords——Reissert compound; quinazoline; hydrolysis; Reissert compound anion; rearrangement; aromatization; electronic effect; electrophilic substitution

In the preceding paper[1] we reported a preparation of 3-benzoyl-3,4-dihydro-2-methyl-4-quinazolinecarbonitrile ($\mathbf{1}_1$, 2-methylquinazoline Reissert compound). Recently we also obtained for the first time 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile ($\mathbf{2}_1$, quinazoline Reissert compound) through an indirect two-step procedure, as shown in Chart 1.[2a]

In order to elucidate the reactivity of $\mathbf{1}_1$ with regard to the electronic effect of the methyl substituent, we examined the following reactions of $\mathbf{1}_1$; (a) acid hydrolysis, (b) alkaline hydrolysis, (c) reaction with sodium hydride, and (d) reaction with electrophiles in the presence



$\mathbf{1}_2$ $\mathbf{1}_1$ $\mathbf{2}_2$ **7** $\mathbf{2}_1$

Chart 1

of sodium hydride. In the present paper, we describe the results obtained from the above reactions (a) to (d) in detail, comparing the reactivity of $\mathbf{1}_1$ with that of $\mathbf{2}_1$ which has already been reported.[2)]

(a) Acid Hydrolysis

We reported that quinazoline Reissert compound $\mathbf{2}_1$ was hydrolyzed in an acid medium to give the ring fission product, 2-(2-aminophenyl)-2-benzamidoacetonitrile ($\mathbf{2}_3$) together with $\mathbf{2}_2$ and benzoic acid (**8**) by way of the cyclic amidinium salt (A^2).[2a)]

On the other hand, $\mathbf{1}_1$ reacted with acid in a different way from that of $\mathbf{2}_1$, resulting in the formation of 4-(2-acetamidophenyl)-5-amino-2-phenyloxazole ($\mathbf{1}_3$).

The mechanism of the formation of the oxazole $\mathbf{1}_3$ is assumed to involve sequential quaternization, ring closure, and ring fission, as shown in Chart 2. Because electronic effects

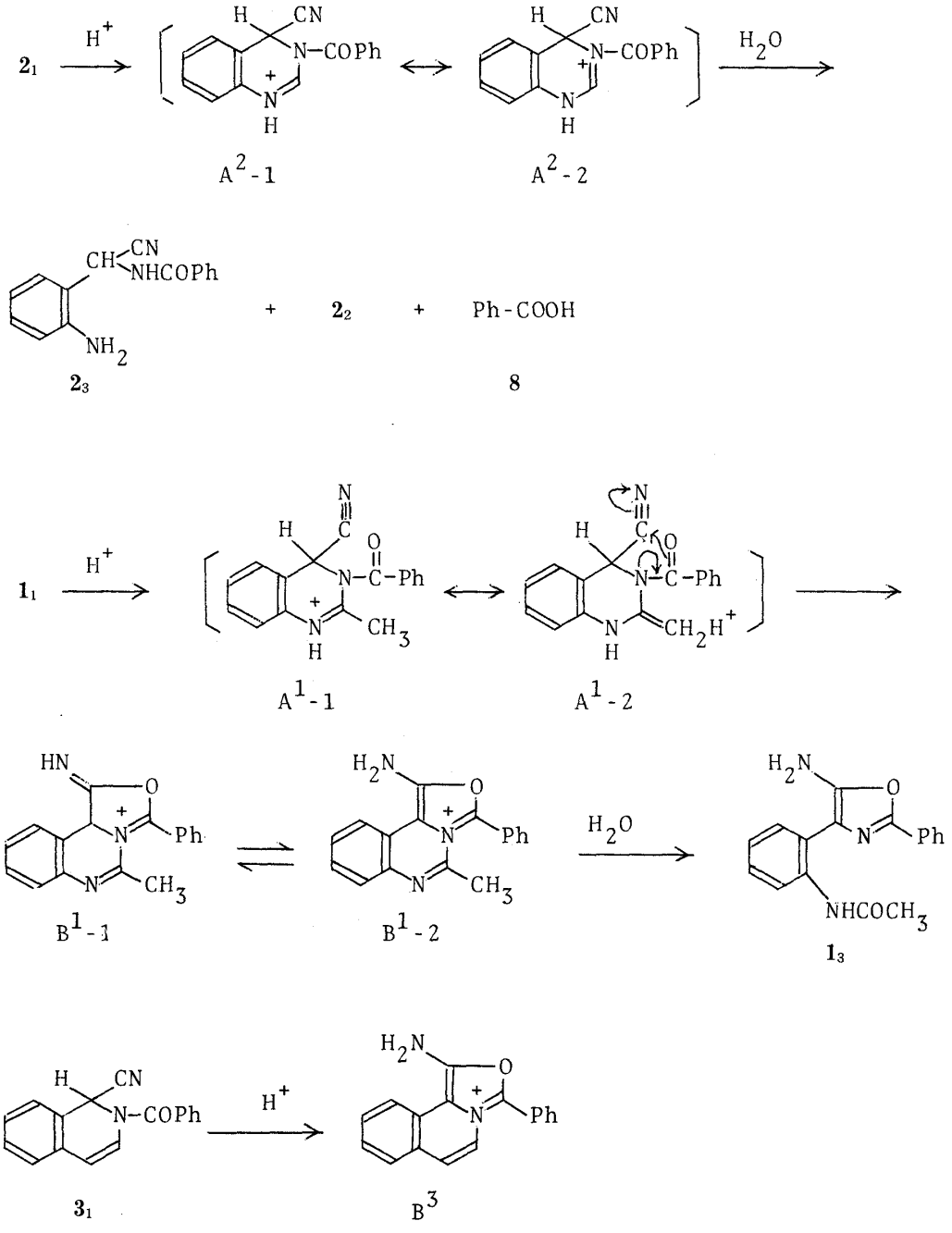


Chart 2

of the N^1-atom and the methyl substituent of the initially formed quaternary salt (A^1) reinforce each other, we can write resonance structures A^1-1 and A^1-2, in which there is no charge separation at the N^3-atom. This absence of charge separation enhances ring closure, leading to the oxazolo[3,4-*c*]quinazolinium salt (B^1). Subsequent nucleophilic attack of water at the carbon of the cyclic amidinium moiety in B^1, followed by ring fission, gives the oxazole $\mathbf{1}_3$. The intermediate B^1 corresponds to the oxazolo[4,3-*a*]isoquinolinium salt (B^3)[3,4] observed in acid hydrolysis of 2-benzoyl-1,2-dihydro-1-isoquinolinecarbonitrile ($\mathbf{3}_1$, isoquinoline Reissert compound).

On the other hand, in acid hydrolysis of $\mathbf{2}_1$, the initially formed quaternary salt (A^2) can not cyclize to the oxazolo[3,4-*c*]quinazolinium salt (B^2), because of a positive charge at the N^3-atom. Eventually, A^2 is hydrolyzed in acid medium, giving the ring fission product $\mathbf{2}_3$.

(b) Alkaline Hydrolysis

It is well known that hydrolysis of $\mathbf{2}_1$ in an alkaline medium resulted in the formation of $\mathbf{2}_2$ and **8**.[2a] We also reported that in the case of $\mathbf{3}_1$ a similar hydrolysis proceeded, and isoquinoline ($\mathbf{3}_2$) and **8** were obtained.[2a]

Similarly, $\mathbf{1}_1$ was hydrolyzed to $\mathbf{1}_2$[5] and **8** by alkali. The reaction may well occur by the initial formation of an adduct (C^1) of the hydroxide ion at the carbonyl carbon, followed by the ready loss of a cyanide ion, leading to $\mathbf{1}_2$ and **8**, as shown in Chart 3.

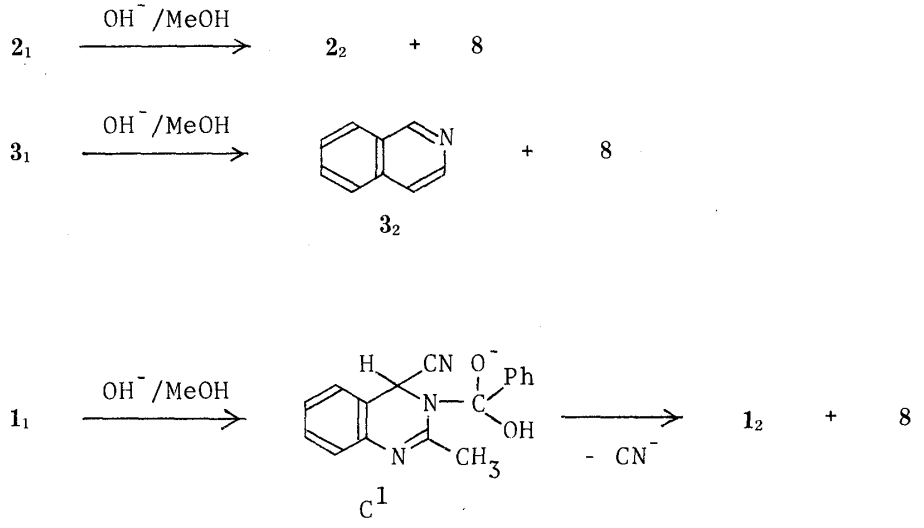


Chart 3

(c) Reaction with Sodium Hydride

Boekelheide and Weinstock reported that the anion (D^3) of $\mathbf{3}_1$ underwent rearrangement, giving 1-benzoylisoquinoline ($\mathbf{3}_4$) with expulsion of a cyanide ion.[6] Moreover, McEwen and Cobb proposed a mechanism in which the rearrangement of the anion (D^4) of 1-benzoyl-1,2-dihydro-2-quinolinecarbonitrile ($\mathbf{4}_1$, quinoline Reissert compound) to 2-benzoylquinoline ($\mathbf{4}_4$) proceeded through the aziridine intermediate (E^4) in an intramolecular process.[7]

On the other hand, recently we reported that the anion (D^2) of $\mathbf{2}_1$ underwent aromatization, which is different from the behavior of D^3, resulting in the formation of 4-quinazolinecarbonitrile ($\mathbf{2}_5$) and a benzaldehyde anion (F), together with α-phenyl-4-quinazolinylmethyl benzoate ($\mathbf{2}_6$**a**) and *O*-benzoylbenzoin (**9**)[8] as by-products which were formed by further reaction of the resulting anion F with another molecule of $\mathbf{2}_1$.[2a]

In the case of $\mathbf{1}_1$, the anion (D^1), generated from the reaction of $\mathbf{1}_1$ with sodium hydride, underwent both rearrangement and aromatization, resulting in the formation of 4-benzoyl-2-methylquinazoline ($\mathbf{1}_4$)[9] and 2-methyl-4-quinazolinecarbonitrile ($\mathbf{1}_5$)[10] together with $\mathbf{1}_2$ and

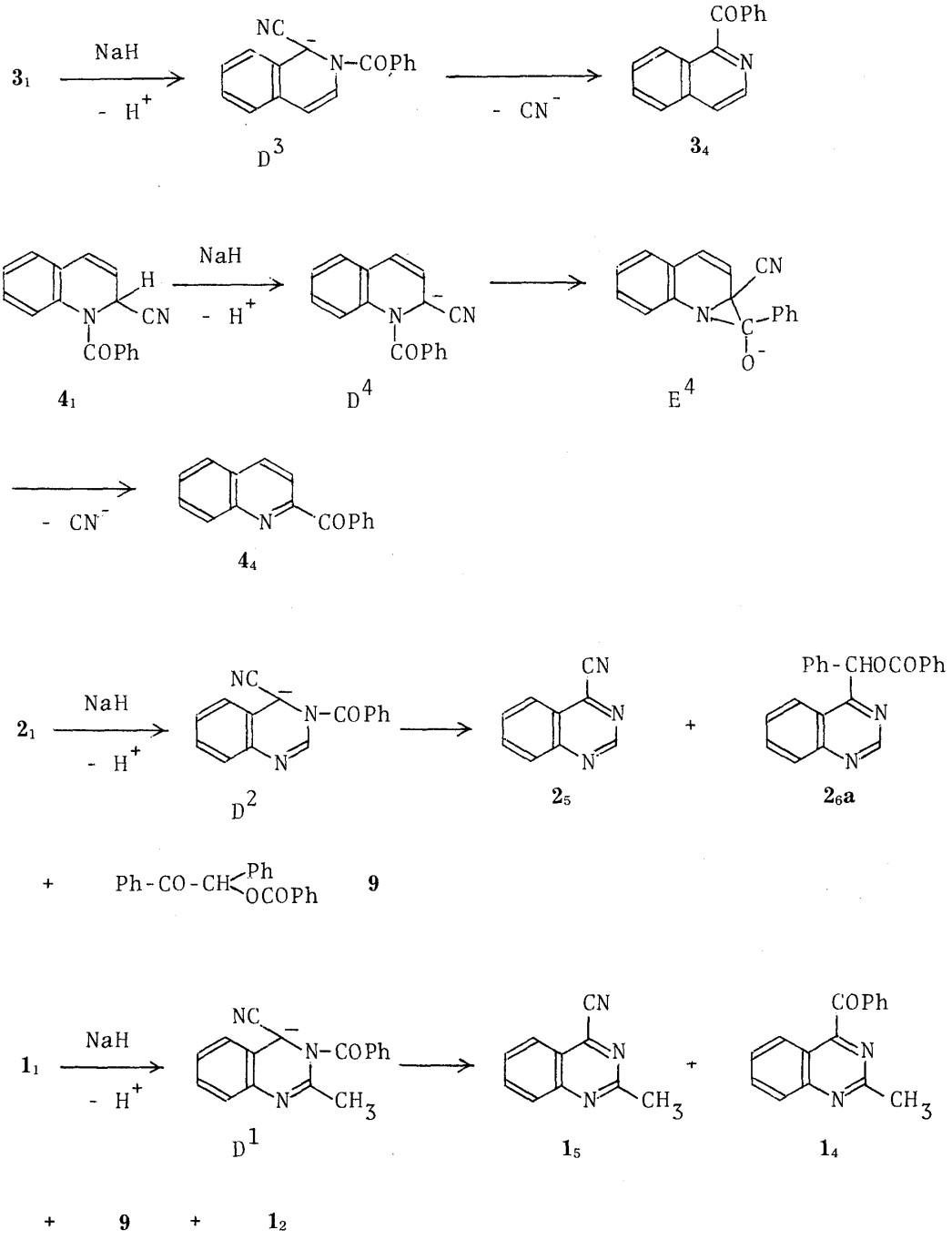


Chart 4

9.

The rearrangement and aromatization may be explained as follows (Chart 5). In a resonance structure D^1-3, a positive charge at the N^3-atom, due to the electronic effect of the N^1-atom as well as a positive charge at the neighboring carbonyl carbon decreases the stability of the N^3–CO bond, favoring aromatization to $\mathbf{1}_5$ with expulsion of the anion F rather than the formation of the aziridine intermediate E^1. On the other hand, resonance structures D^1-1 and D^1-2, in which the electron-withdrawing effect of the N^1-atom and electron-releasing effect of the methyl substituent overlap each other, do not bear a positive charge at the N^3-atom, favoring ring closure to the aziridine intermediate E^1 rather than aromatization. The intermediate E^1 leads to $\mathbf{1}_4$ with expulsion of a cyanide ion.

By-products, **9** and $\mathbf{1}_2$, are assumed to be formed by further reactions of the resulting

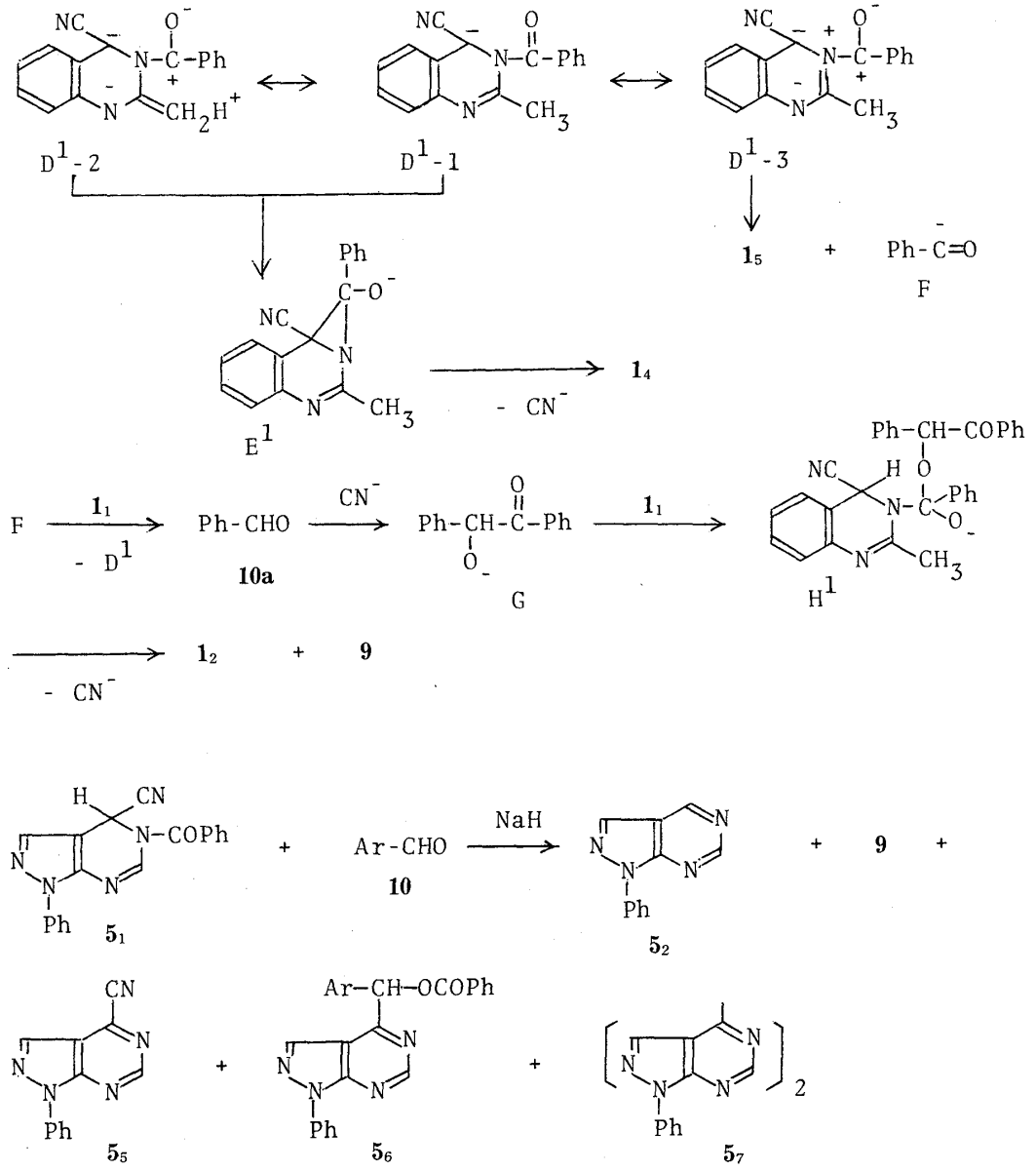


Chart 5

anion F involving sequential formation of benzaldehyde (**10a**), benzoin condensation, and nucleophilic attack of the O-anion (G) of benzoin on the carbonyl carbon of $\mathbf{1}_1$, as shown in Chart 5. A similar mechanism has been proposed by us[11] for the formation of **9** and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine ($\mathbf{5}_2$) in the reaction of 5-benzoyl-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile ($\mathbf{5}_1$) with aromatic aldehydes (**10**).

On the basis of our mechanism, it can be assumed that the introduction of an electron-withdrawing group into the 4-position of $\mathbf{3}_1$ might cause the aromatization as observed in $\mathbf{2}_1$.[2a] In fact, 2-benzoyl-1,2-dihydro-1,4-isoquinolinedicarbonitrile ($\mathbf{6}_1\mathbf{a}$), which was prepared by application of Ruchirawat's method[12] to 4-isoquinolinecarbonitrile ($\mathbf{6}_2\mathbf{a}$),[13] reacted with sodium hydride, giving the anticipated dicarbonitrile ($\mathbf{6}_5\mathbf{a}$).[14] In the case of 2-benzoyl-4-bromo-1,2-dihydro-1-isoquinolinecarbonitrile ($\mathbf{6}_1\mathbf{b}$) having an electronegative bromine atom at the 4-position, a similar aromatization occurred, resulting in the formation of 4-bromo-1-isoquinolinecarbonitrile ($\mathbf{6}_5\mathbf{b}$) and 4′-bromo-4,1′-biisoquinoline-1-carbonitrile ($\mathbf{6}_8\mathbf{b}$), which may be formed by nucleophilic substitution of the bromine atom of the resulting $\mathbf{6}_5\mathbf{b}$ with the anion D^6, as shown in Chart 6.

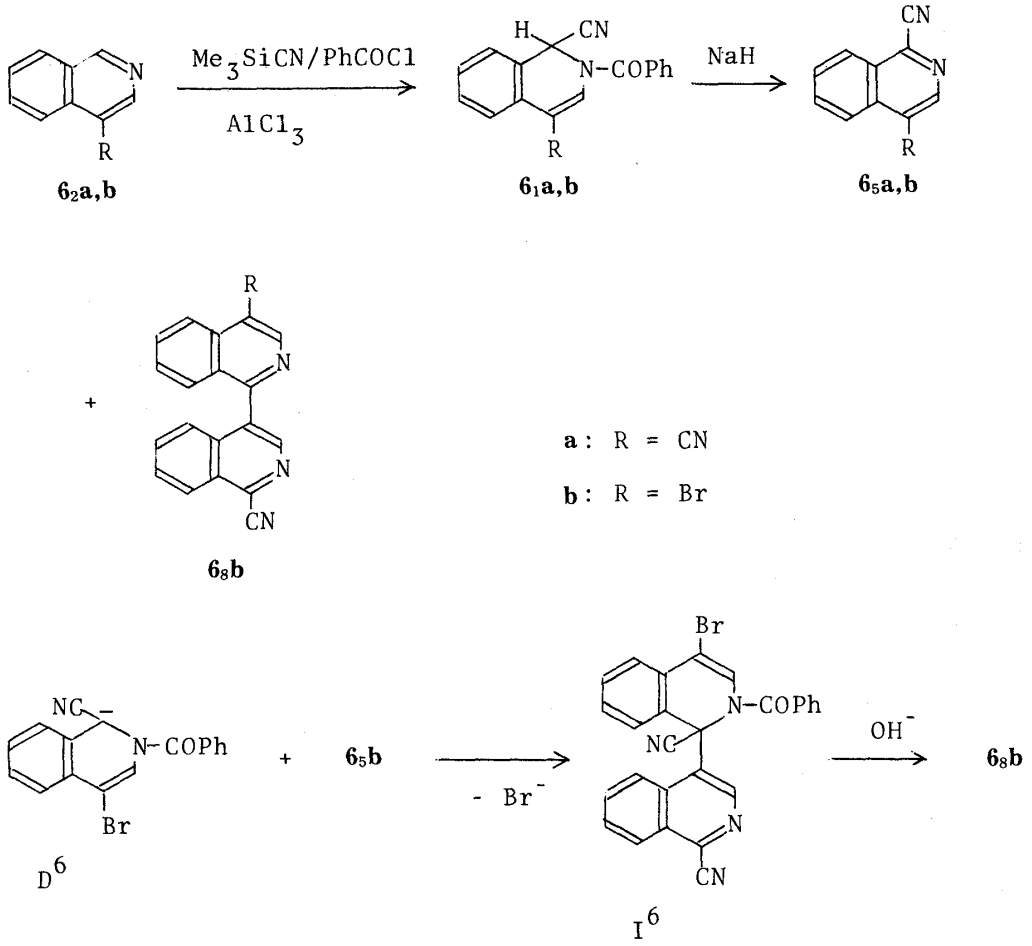


Chart 6

(d) Reaction with Electrophiles

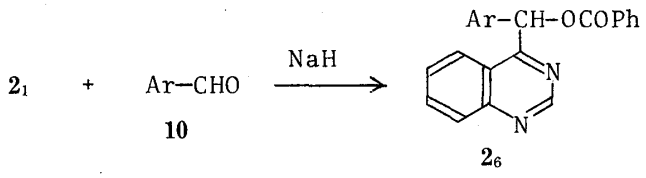
The reactions of aromatic aldehydes (**10**) and alkyl (or aryl) halides (**11**) with $\mathbf{2}_1$ were reported in the previous paper.[2b]

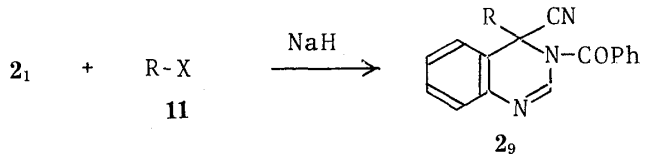
A similar reaction proceeded in the reaction of $\mathbf{1}_1$ with **10a—c** in the presence of sodium hydride, giving the benzoates ($\mathbf{1}_6$**a—c**) and by-products $\mathbf{1}_2$ and $\mathbf{1}_5$, as shown in Chart 7. Formation of the benzoates $\mathbf{1}_6$ may be explained by the mechanism involving sequential formation of intermediates J^1 and K^1, similar to the intermediates observed in the reaction of the anions D^2 and D^4 with **10**,[2b,15] as shown in Chart 7.

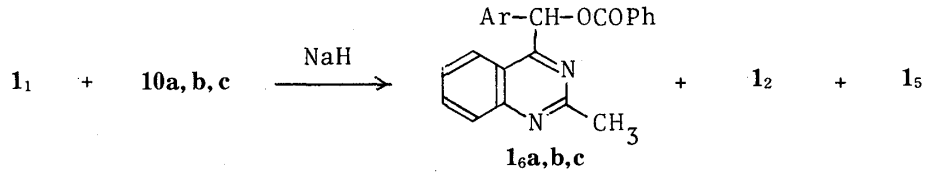
Alkylation (or arylation), similar to that of $\mathbf{2}_1$, occurred in the reaction of $\mathbf{1}_1$ with methyl iodide (**11a**) and 2,4-dinitrochlorobenzene (**11b**) in the presence of sodium hydride, yielding 4-methyl- ($\mathbf{1}_9$**a**) and 4-(2,4-dinitrophenyl)-3-benzoyl-3,4-dihydro-2-methyl-4-quinazolinecarbonitriles ($\mathbf{1}_9$**b**), respectively, together with $\mathbf{1}_4$ as a by-product, as shown in Chart 7.

In connection with reactions involving the formation of the anion of Reissert compounds, we examined the reaction of $\mathbf{6}_1$ with **10a** in the presence of sodium hydride. Thus, $\mathbf{6}_1$**a** and $\mathbf{6}_1$**b** reacted with **10a** in the same way as that of $\mathbf{1}_1$, affording the corresponding benzoates $\mathbf{6}_6$**a** and $\mathbf{6}_6$**b**, respectively, together with by-products **9** and the corresponding isoquinolines ($\mathbf{6}_2$**a** and $\mathbf{6}_2$**b**). The benzoates $\mathbf{6}_6$**a** and $\mathbf{6}_6$**b** were converted into the ketone ($\mathbf{6}_4$**a**) or the alcohol ($\mathbf{6}_{10}$**b**) by alkaline hydrolysis, as shown in Chart 8.

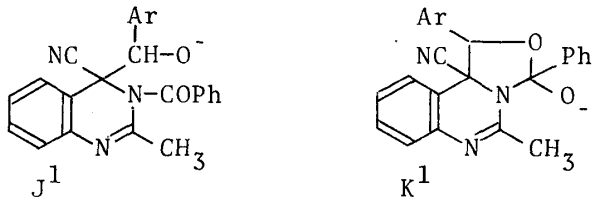
The experimental results may be summarized as follows. i) In the reaction (a), $\mathbf{1}_1$ reacts differently from $\mathbf{2}_1$, and the oxazole $\mathbf{1}_3$ is formed by way of the oxazolo[3,4-*c*]quinazolinium cation B^1. ii) In the reaction (c), $\mathbf{1}_1$ undergoes both aromatization and rearrangement (the latter did not take place in the case of $\mathbf{2}_1$[2b]), resulting in the formation of the cyanoquinaz-

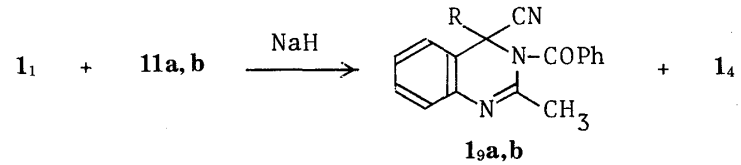






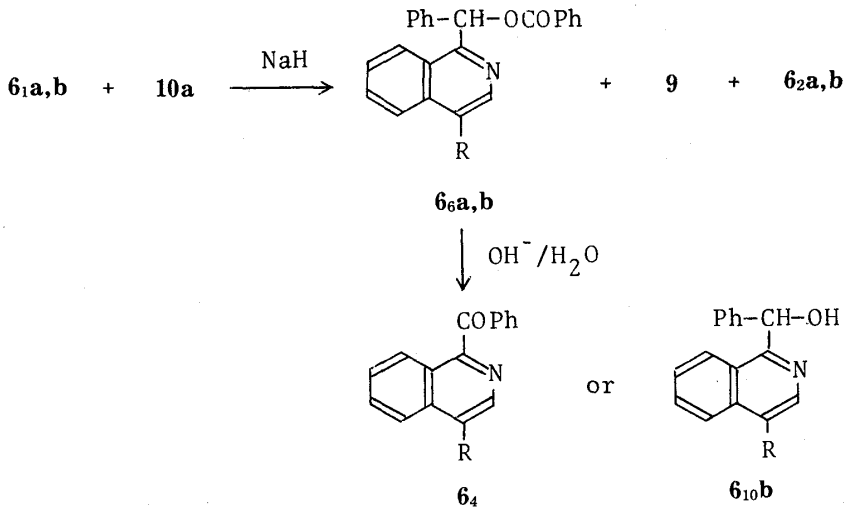
a: Ar = Ph, **b**: Ar = *p*-C_6H_4OMe, **c**: Ar = *p*-C_6H_4Me





a: R = Me, X = I; **b**: R = 2,4-$(NO_2)_2C_6H_3$, X = Cl

Chart 7



a: R = CN, **b**: R = Br

Chart 8

oline $\mathbf{1}_5$ and ketone $\mathbf{1}_4$, respectively. iii) In the reaction (c), the isoquinoline Reissert compounds $\mathbf{6}_1\mathbf{a}$ and $\mathbf{6}_1\mathbf{b}$, having an electron-withdrawing cyano group and an electronegative bromine atom at the 4-position, respectively, undergo aromatization, similar to that of $\mathbf{2}_1$, resulting in the formation of the cyanoisoquinolines $\mathbf{6}_5\mathbf{a}$ and $\mathbf{6}_5\mathbf{b}$, respectively, with elimination of the anion F. iv) The formation of the benzoates $\mathbf{1}_6$ and the alkylation products $\mathbf{1}_9$ in the reaction (d) indicates that $\mathbf{1}_1$ is potentially available as a synthetic intermediate for introduction of a functionalized carbon group at the 4-position by the use of electrophiles.

Experimental

All melting points are uncorrected. Infrared absorption (IR) spectra were recorded on a Jasco A-102 diffraction grating IR spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 60 MHz on a Hitachi R-24B 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, and coupling constants (J) are given in hertz (Hz). The following abbreviation are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br s = broad singlet. Mass spectra (MS) were recorded on a JEOL JMS D-100 mass spectrometer. Samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2, Wakogel C-200 (200 mesh).

Acid Hydrolysis of $\mathbf{1}_1$——A mixture of $\mathbf{1}_1$ (1 mmol, 275 mg) and 20% HCl (4 ml) was stirred for 10 h. On cooling, crystals separated. They were collected by suction, washed with 2 N Na_2CO_3, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. Recrystallization of the residue from benzene–MeOH gave $\mathbf{1}_3$ as colorless needles, mp 161—163 °C, in 40% yield (116 mg). *Anal.* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.65; H, 5.17; N, 14.24. MS m/z: 293 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3300, 3380 (NH), 1700 (CO). ^{1}H-NMR ($(CD_3)_2SO$): 2.07 (3H, s, CH_3), 5.10—6.12 (2H, br s, NH_2), 6.38—8.10 (9H, m, aromatic H), 10.22—10.56 (1H, br s, NH). ^{13}C-NMR ($(CD_3)_2SO$): 23.84 (q, CH_3), 114.32 (s), 117.14 (d), 127.00 (d), 127.81 (s), 129.38 (d), 130.41 (d), 131.99 (d), 133.01 (s), 139.62 (s), 147.81 (s), 157.83 (s), 172.08 (s, CO).

Alkaline Hydrolysis of $\mathbf{1}_1$——A mixture of $\mathbf{1}_1$ (1 mmol, 275 mg) and 10% NaOH (2 ml) in MeOH (5 ml) was stirred for 1 h. The reaction mixture was neutralized with AcOH, and the solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2. The fraction eluted with benzene–$CHCl_3$ (1 : 1) gave $\mathbf{1}_2$ in 76% yield (110 mg). The fraction subsequently eluted with $CHCl_3$ gave **8** in 72% yield (88 mg).

Compound $\mathbf{1}_2$ was identified by comparison with an authentic specimen prepared by another route.[5]

Reaction of $\mathbf{1}_1$ with NaH——NaH (60% in oil, 1 mmol, 40 mg) was added to a stirred solution of $\mathbf{1}_1$ (1 mmol, 275 mg) in *N*,*N*-dimethylformamide (DMF, 1 ml) under ice cooling, and the whole was stirred for a further 5 min. The reaction mixture was poured onto a large amount of ice, neutralized with AcOH, and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2. The fraction eluted with benzene gave **9**[8] in 33% yield (35 mg). The first, second, and third fractions subsequently eluted with $CHCl_3$ gave $\mathbf{1}_5$,[10] $\mathbf{1}_4$,[9] and $\mathbf{1}_2$ in 20% (32 mg), 32% (80 mg), and 7% yields (10 mg), respectively.

Compounds **9**, $\mathbf{1}_5$, and $\mathbf{1}_4$ were identified by comparison with the corresponding authentic specimens prepared by other routes.[8-10]

Preparation of $\mathbf{6}_1$——A solution of benzoyl chloride (22 mmol, 3.11 g) was added to a well stirred solution of $\mathbf{6}_2$ (20 mmol) and TMSCN (20 mmol, 2.23 g) in CH_2Cl_2 (30 ml), and the mixture was stirred for 5 min. $AlCl_3$ (2 mmol, 267 mg) was added to the mixture and the whole was stirred for 22 h at room temperature. The solution was washed with H_2O, 5% HCl, H_2O, 5% NaOH, and H_2O. The CH_2Cl_2 solution was dried over Na_2SO_4 and concentrated. The residue was recrystallized from benzene–petroleum benzin to give $\mathbf{6}_1$.

From $\mathbf{6}_2\mathbf{a}$, 2-benzoyl-1,2-dihydro-1,4-isoquinolinedicarbonitrile ($\mathbf{6}_1\mathbf{a}$) was obtained as colorless prisms, mp 197—199 °C, in 87% yield (4.94 g). *Anal.* Calcd for $C_{18}H_{11}N_3O$: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.52; H, 3.86; N, 14.73. IR ν_{max}^{KBr} cm^{-1}: 2210 (CN), 1680 (CO). ^{1}H-NMR ($(CD_3)_2SO$): 6.71 (1H, s, C^1-H), 7.19—7.78 (10H, m, aromatic H). ^{13}C-NMR ($(CD_3)_2SO$): 44.5 (d, C^1), 92.9 (s, C^4), 115.3 (s, CN), 116.3 (s, CN), 123.2 (d), 123.5 (s), 125.7 (s), 127.7 (d), 128.8 (d), 129.5 (d), 129.8 (d), 130.5 (d), 130.8 (s), 132.7 (d), 138.5 (d), 168.4 (s, CO).

From $\mathbf{6}_2\mathbf{b}$, 2-benzoyl-4-bromo-1,2-dihydro-1-isoquinolinecarbonitrile ($\mathbf{6}_1\mathbf{b}$) was obtained as colorless needles, mp 166—168 °C, in 82% yield (5.56 g). *Anal.* Calcd for $C_{17}H_{11}BrN_2O$: C, 60.20; H, 3.27; N, 8.26. Found: C, 60.18; H, 3.24; N, 8.26. IR ν_{max}^{KBr} cm^{-1}: 1660 (CO). ^{1}H-NMR ($CDCl_3$): 6.46 (1H, s, C^1-H), 6.91 (1H, s, C^3-H), 7.21—7.70 (9H, m, aromatic H). ^{13}C-NMR ($CDCl_3$): 45.2 (d, C^1), 104.9 (s, C^4), 115.9 (s, CN), 124.6 (s), 126.0 (d), 126.5 (d), 128.8 (d), 129.2 (d), 129.7 (d), 130.5 (d), 131.5 (s), 132.4 (d), 167.7 (s, CO).

Reaction of $\mathbf{6}_1$ with NaH——NaH (3.6 mmol, 86.4 mg) was added to a well stirred solution of $\mathbf{6}_1$ (3 mmol) in DMF (10 ml) under ice cooling, then the whole was stirred for 1 h at room temperature. The reaction mixture was

poured onto a large amount of ice, neutralized with AcOH, and extracted with AcOEt. The insoluble crystalline material was collected by suction and recrystallized from benzene–petroleum benzin to give the dimer **6**$_8$. The extract was dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on a column of SiO_2. The fraction eluted with benzene gave **6**$_5$. The fraction subsequently eluted with $CHCl_3$ gave **6**$_8$.

From **6**$_1$**a**, 1,4-isoquinolinedicarbonitrile (**6**$_5$**a**)[14] was obtained as slightly yellow needles from MeOH, mp 179—180.5 °C, in 71% yield (380 mg). IR ν_{max}^{KBr} cm^{-1}: 2225 (CN). ^{1}H-NMR ($CDCl_3$): 7.65—8.48 (4H, m, aromatic H), 8.77 (1H, s, C^3-H). Compound **6**$_5$**a** was identified by comparison with an authentic sample prepared from another route.[14]

From **6**$_1$**b**, 4-bromo-1-isoquinolinecarbonitrile (**6**$_5$**b**; colorless needles from petroleum benzin, mp 124—126 °C) and 4′-bromo-4,1′-biisoquinoline-1-carbonitrile (**6**$_8$**b**; colorless needles from benzene–petroleum benzin, mp 233—235 °C) were obtained in 35% (211 mg) and 14% yields (146 mg), respectively.

Compound **6**$_5$**b** was identified by comparison with an authentic sample prepared by application of an improved Henze reaction[17] to 4-bromoisoquinoline 2-oxide.[18] *Anal.* Calcd for $C_{10}H_5BrN_2$: C, 51.53; H, 2.16; N, 12.02. Found: C, 51.78; H, 2.16; N, 12.25. MS *m/z*: 234 (M^++2), 232 (M^+). ^{1}H-NMR ($CDCl_3$): 7.71—8.33 (4H, m, aromatic H), 8.71 (1H, s, C^3-H).

Compound **6**$_8$**b**: *Anal.* Calcd for $C_{19}H_{10}BrN_3$: C, 63.35; H, 2.80; N, 11.67. Found: C, 63.18; H, 2.79; N, 11.61. MS *m/z*: 361 (M^++2), 359 (M^+). ^{1}H-NMR ($CDCl_3$): 8.82 (1H, s, C^3-H), 8.52 (1H, s, C$^{3'}$-H), 8.30—7.15 (8H, m, aromatic H).

Preparation of 6$_5$**b**——Compound **6**$_5$**b** was prepared by application of an improved Henze[19] reaction reported by Fife[17] to 4-bromoisoquinoline 2-oxide.[18] *N,N*-Dimethylcarbamoyl chloride (6 mmol, 645 mg) was added to a solution of 4-bromoisoquinoline 2-oxide (5 mmol, 1120 mg) and TMSCN (6 mmol, 606 mg) in dry CH_2Cl_2 (20 ml), and the whole was stirred for 24 h. The reaction mixture was washed with 10% K_2CO_3 (10 ml), dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2. The fraction eluted with benzene gave **6**$_5$**b** in 62% yield (720 mg).

Reaction of 1$_1$ **with 10 in the Presence of NaH**——NaH (60% in oil, 1 mmol, 40 mg) was added to a well stirred solution of **1**$_1$ (1 mmol, 275 mg) and **10** (1 mmol) in DMF (2 ml) under ice cooling, and the whole was stirred for 30 min. The reaction mixture was poured onto a large amount of ice, neutralized with AcOH, and extracted with benzene. The extract was dried over Na_2SO_4, concentrated, and chromatographed on a column of SiO_2. The first, second, and third fractions eluted with $CHCl_3$ gave **1**$_5$,[10] **1**$_6$, and **1**$_2$,[5] respectively.

From the reaction with **10a**, the benzoate **1**$_6$**a** (colorless prisms from benzene–petroleum benzin, mp 112 °C) in 78% yield (277 mg), **1**$_2$ in 10% yield (15 mg), and a trace of **1**$_5$ (2 mg) were obtained. Compound **1**$_6$**a**: *Anal.* Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.91. Found: C, 77.76; H, 5.18; N, 7.76. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO). ^{1}H-NMR ($CDCl_3$): 2.85 (3H, s, C^2-CH_3), 7.18—8.34 (15H, m, aromatic and methylidyne H).

From the reaction with **10b**, the benzoate **1**$_6$**b** was obtained as colorless prisms from benzene–petroleum benzin, mp 120—122 °C, in 65% yield (227 mg), together with a trace of **1**$_5$. Compound **1**$_6$**b**: *Anal.* Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.86; H, 5.24; N, 7.31. IR ν_{max}^{KBr} cm^{-1}: 1710 (CO). ^{1}H-NMR ($CDCl_3$): 2.84 (3H, s, C^2-CH_3), 3.70 (3H, s, OCH_3), 6.70—8.30 (14H, m, aromatic and methylidyne H).

From the reaction with **10c**, the benzoate **1**$_6$**c** was obtained as colorless needles from benzene–petroleum benzin, mp 145 °C, in 53% yield (195 mg), together with **1**$_2$ in 15% yield (22 mg) and **1**$_5$ in 7% yield (12 mg). Compound **1**$_6$**c**: *Anal.* Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.11; H, 5.48; N, 7.54. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO). ^{1}H-NMR ($CDCl_3$): 2.28 (3H, s, CH_3), 2.85 (3H, s, C^2-CH_3), 6.98—8.33 (14H, m, aromatic and methylidyne H).

Reaction of 1$_1$ **with 11 in the Presence of NaH**——NaH (60% in oil, 1 mmol, 40 mg) was added to a well stirred solution of **1**$_1$ (1 mmol, 275 mg) and **11** (1 mmol) in DMF (2 ml) under ice cooling, and the whole was stirred for 1 h. The reaction mixture was poured onto a large amount of ice, neutralized with AcOH, and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2. The first and second fractions eluted with benzene gave **1**$_9$ and **1**$_4$, respectively.

From the reaction with **11a**, **1**$_9$**a** was obtained as a yellow oil in 51% yield (148 mg), together with **1**$_4$ in 20% yield (50 mg). Compound **1**$_9$**a**: MS *m/z*: 289 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1680 (CO). ^{1}H-NMR ($CDCl_3$): 1.94 (6H, s, C^2-CH_3 and C^4-CH_3), 7.22—7.83 (9H, m, aromatic H).

From the reaction with **11b**, **1**$_9$**b** was obtained as yellow needles from benzene–petroleum benzin, mp 106—107 °C, in 57% yield (251 mg). MS *m/z*: 441 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1350, 1530 (NO_2), 1680 (CO). ^{1}H-NMR ($CDCl_3$): 2.00 (3H, s, C^2-CH_3), 6.47—8.60 (12H, m, aromatic H).

Reaction of 6$_1$**a with 10a in the Presence of NaH**——NaH (1.8 mmol, 43 mg) was added to a well stirred solution of **6**$_1$**a** (1.5 mmol, 428 mg) and **10a** (1.8 mmol, 191 mg) in DMF (8 ml) under ice cooling, and the whole was stirred for 15 min. The reaction mixture was poured onto a large amount of ice, neutralized with AcOH, and extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, concentrated, and chromatographed on a column of SiO_2. The first and second fractions eluted with benzene gave **9**[8] and the benzoate **6**$_6$**a** in 27% (130 mg) and 48% yields (260 mg), respectively. The fraction subsequently eluted with $CHCl_3$ gave **6**$_2$**a**[13] as colorless needles from petroleum benzin, mp 103—104.5 °C, in 22% yield (50 mg).

Compound **6**$_6$**a** was obtained as colorless needles from benzene-petroleum benzin, mp 126—128 °C. *Anal.* Calcd for $C_{24}H_{16}N_2O_2$: C, 79.11; H, 4.43; N, 7.69. Found: C, 79.02; H, 4.46; N, 8.19. MS *m/z*: 364 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1710

(CO), 2215 (CN). ^{1}H-NMR ($CDCl_3$): 7.21—8.53 (15H, m, aromatic and methylidyne H), 8.89 (1H, s, C^3-H).

Reaction of 6_1b with 10a in the Presence of NaH——The similar reaction of **6_1b** (2 mmol, 678 mg) and **10a** (2.4 mmol, 255 mg) in the presence of NaH (2.4 mmol, 58 mg) in DMF (8 ml) with stirring for 1 h gave the benzoate (**6_6b**) as colorless needles from benzene–petroleum benzin, mp 121—124 °C, in 51% yield (263 mg) and **6_2b**[16] as an oil in 17% yield (70 mg).

Compound **6_6b**: *Anal.* Calcd for $C_{23}H_{16}BrNO_2$: C, 66.04; H, 3.85; N, 3.35. Found: C, 67.27; H, 4.01; N, 3.11. MS *m/z*: 417 (M^+), 419 ($M^+ + 2$). IR ν_{max}^{KBr} cm^{-1}: 1710 (CO). ^{1}H-NMR ($CDCl_3$): 7.20—8.27 (15H, m, aromatic and methylidyne H), 8.71 (1H, s, C^3-H).

Alkaline Hydrolysis of 6_6——i) A solution of **6_6a** (100 mg) in a mixture of 10% NaOH (1 ml) and MeOH (10 ml) was refluxed for 30 min. After removal of the MeOH under reduced pressure, H_2O was added to the residue, and the separated oily material was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated to dryness. The extract was dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from MeOH to give the ketone **6_4a** as pale yellow needles, mp 157—159 °C, in 85% yield (60 mg). *Anal.* Calcd for $C_{17}H_{10}N_2O$: C, 79.06; H,3.90; N, 10.85. Found: C, 78.60; H, 4.19; N, 10.66. MS *m/z*: 258 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1660 (CO), 2220 (CN). ^{1}H-NMR ($CDCl_3$): 7.15—8.29 (9H, m, aromatic H), 8.85 (1H, s, C^3-H).

ii) The similar alkaline hydrolysis of **6_6b** (270 mg) in a mixture of 10% NaOH (1 ml) and MeOH (10 ml) by refluxing for 20 min gave the alcohol **6_{10}b** as slightly yellow prisms from MeOH, mp 136—139 °C, in 34% yield (68 mg). *Anal.* Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46. Found: C, 61.17; H, 3.84; N, 4.55. IR ν_{max}^{KBr} cm^{-1}: 3360 (OH). ^{1}H-NMR ($CDCl_3$): 5.79 (1H, d, J=6 Hz, CHOH), 6.42 (1H, d, J=6 Hz, CHOH), 7.15—8.30 (9H, m, aromatic H), 8.77 (1H, s, C^3-H).

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