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Preparation and Reactions of Quinazoline Reissert Compound (3-Benzoyl-3,4-dihydro-4-quinazolinecarbonitrile)

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The benzoylation of 3,4-dihydro-4-quinazolinecarbonitrile (**3**) with benzoyl chloride in pyridine gave quinazoline Reissert compound (**1**, 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile) in 82% yield.

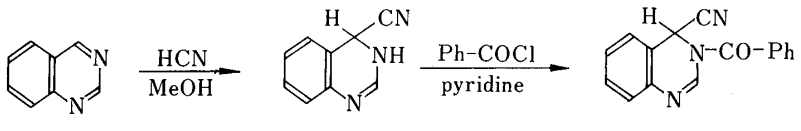
The alkaline hydrolysis of **1** in methanol resulted in the formation of quinazoline (**2**) and benzoic acid (**4**). Acid hydrolysis gave 2-benzamido-2-(2-aminophenyl)acetonitrile (**6**), **4**, and **2**. The HCl salt of **1** existed predominantly in the cyclic amidinium structure of the type **8**. Compound **1** reacted with sodium hydride in dimethylformamide to yield 4-quinazolinecarbonitrile (**9**), α-phenyl-4-quinazolinylmethyl benzoate (**10**), and *O*-benzoylbenzoin (**11**).

In the present paper we compare the chemical properties of **1** with those of isoquinoline Reissert compound (**13**, 2-benzoyl-1,2-dihydro-1-isoquinolinecarbonitrile).

Keywords——quinazoline Reissert compound; cyclic amidinium cation; alkaline hydrolysis; acid hydrolysis; quinazoline Reissert compound anion; acetonitrile derivative; 4-quinazolinecarbonitrile; 4-quinazolinylmethyl benzoate derivative

It is well known that 2-benzoyl-1,2-dihydro-1-isoquinolinecarbonitrile,[1] so-called isoquinoline Reissert compound (**13**), is easily prepared by the reaction of isoquinoline (**14**) with benzoyl chloride in aqueous potassium cyanide.[2] Since **13** can be used as the starting key compound in the synthesis of isoquinoline alkaloids such as papaverine,[3] much work has been done on **13**. Results on the chemistry of the Reissert compounds up to 1978 have been summarized in three comprehensive reviews.[2]

In the quinazoline area, it was reported that when attempts were made to form 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile (**1**, quinazoline Reissert compound) by the standard method[2] using benzoyl chloride and aqueous potassium cyanide, quinazoline (**2**) underwent a ring fission to give 2′-formylbenzanilide, *o*-aminobenzaldehyde, and *N*-formylbenzamide.[4] Thus, the method in aqueous media is not effective for the preparation of **1**. Recently, Popp *et al.* carried out Reissert compound formation on **2** in anhydrous media using benzoyl chloride and trimethylsilyl cyanide in methylene chloride, and succeeded in obtaining 1,3-dibenzoyl-1,2,3,4-tetrahydro-2,4-quinazolinedicarbonitrile.[5] This compound is one of the quinazoline Reissert compounds, but not the desired one (**1**). Compound **1** has not been described in the literature. In the present paper, we describe the preparation and some reactions of **1**, and compare the chemical properties of **1** with those of **13**.



2 3 1

Chart 1

The preparation of **1** was achieved by the following route in an overall yield of 55%. Thus, 3,4-dihydro-4-quinazolinecarbonitrile (**3**), which was easily prepared by the addition of hydrogen cyanide to **2** in methanol,[6] was subjected to benzoylation with benzoyl chloride in pyridine, yielding the desired compound (**1**).

The infrared absorption (IR) spectrum of **1** showed a carbonyl absorption peak (1690 cm^{-1}), and did not show any absorption due to the cyano group. The latter result is compatible with the reported absence of the absorption peak of a cyano group located at an electron-deficient carbon, such as in *O*-benzoylmandelonitriles.[7] The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum showed two singlets of C^4–H (6.18 ppm) and C^2–H (7.65 ppm). Moreover, the ^{13}C-NMR spectrum showed two doublets due to C^4 (42.53 ppm) and C^2 (141.39 ppm) and two singlets due to the cyano (115.75 ppm) and carbonyl (168.79 ppm) carbons. The elemental analyses were consistent with the structure of 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile (**1**).

The alkaline hydrolysis of **1** in methanol resulted in the formation of **2** and benzoic acid (**4**). The reaction may well occur by initial attack of hydroxide ion at the carbonyl carbon, followed by the ready loss of a cyanide ion, leading to **2** and **4**.

Similarly, **13** gave **14**, **4**, and isoquinaldamide (**15**) under the same conditions.

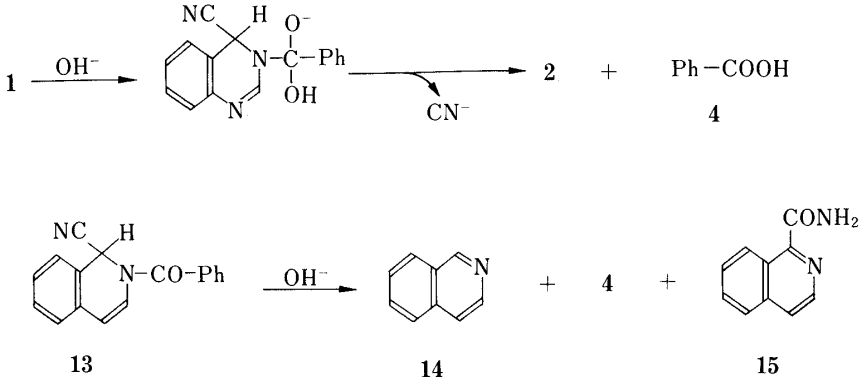


Chart 2

It was reported by Reissert that **13** was hydrolyzed in an acid medium to give benzaldehyde (**5**) plus **15** and 1-isoquinolinecarboxylic acid (**16**).[8] Moreover, Katritzky *et al.* reported that the salt (**17**) isolated by the treatment of **13** with acid should be regarded as having the oxazolo[4,3-*a*]isoquinolinium structure, as shown in Chart 3.[9]

On the other hand, the reaction of **1** with acid proceeded in a different way from that of **13**, and resulted in the formation of 2-benzamido-2-(2-aminophenyl)acetonitrile (**6**), **4**, and **2**. The structure of **6** was suggested by its elemental analysis, and confirmed by analyses of its IR and ^{1}H-NMR spectra, as described later. Compound **6** was easily converted into 2-benzamido-2-(2-acetamidophenyl)acetonitrile (**7**) by acetylation with acetic anhydride.

The salt **8**, having the cyclic amidinium structure as shown in Chart 3, was prepared by the introduction of hydrogen chloride gas into a solution of **1** in benzene, and it reacted with water in the same way as **1**, giving **6**, **4**, and **2**. Thus, the nucleophilic attack of water at the carbon of the cyclic amidinium moiety, followed by ring opening, leads to **6**, while attack at the carbonyl carbon, followed by the elimination of hydrogen cyanide, gives the acid (**4**) and quinazoline (**2**).

The IR spectrum of **8** showed a carbonyl absorption peak (1720 cm^{-1}). The ^{1}H-NMR spectrum showed two characteristic singlets due to C^4–H (6.68 ppm) and C^2–H (8.65 ppm). The ^{13}C-NMR spectrum showed two doublets due to C^4 (41.88 ppm) and C^2 (149.64 ppm), and two singlets due to the cyano (114.05 ppm) and carbonyl carbons (167.25 ppm). This

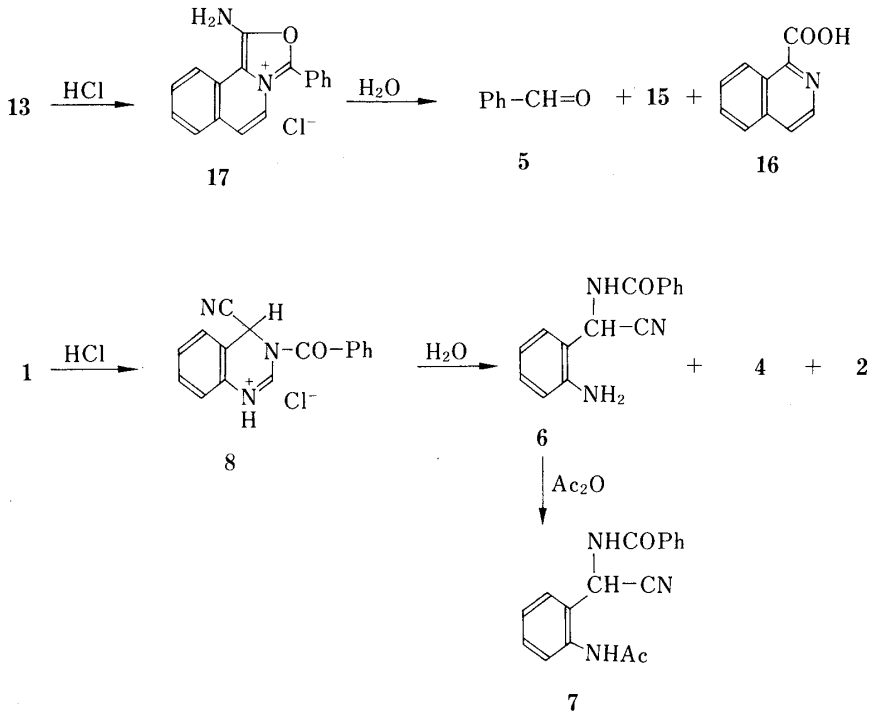


Chart 3

showed that **8** exists predominantly in the cyclic amidinium structure.

On the other hand, the IR, ^{1}H-, and ^{13}C-NMR spectra of isoquinoline Reissert salt (**17**), which was prepared in the same manner as of **8**, did not show any absorption peak due to a carbonyl or cyano group, or sp^3-hybridized carbon, supporting Katritzky's structure (**17**).

It was reported by Boekelheide *et al.* that the anion (A), which was generated by the removal of the hydrogen at the 1-position of **13** with sodium hydride, rearranged to 1-benzoylisoquinoline (**18**) with the expulsion of a cyanide ion.[10] Moreover, McEwen *et al.* proposed a mechanism whereby 2-benzoylquinoline (**20**) arose from the anion (A′) of quinoline Reissert compound (**19**) by way of the aziridine intermediate (B′) in an intramolecular process.[2a]

In the case of **1**, the reaction with sodium hydride in dimethylformamide (DMF) took a different route from that of **13**, resulting in the formation of 4-quinazolinecarbonitrile (**9**),[6] α-phenyl-4-quinazolinylmethyl benzoate (**10**), and *O*-benzoylbenzoin (**11**).[11]

The IR spectrum of **10** showed a carbonyl absorption peak (1705 cm^{-1}). The ^{1}H-NMR spectrum showed a singlet due to C^2–H (9.18 ppm) and a multiplet due to the aromatic and methine hydrogens (15H, 7.07—8.33 ppm). Alkaline hydrolysis of **10** and subsequent oxidation gave 4-benzoylquinazoline (**12**), which was synthesized by the reaction of **2** with **5** in the presence of cyanide ion.[12]

The formation of **9**, **10**, and **11** may be explained by the following three steps, as shown in Chart 5.

The first step is the generation of the anion of **1** (C) by the removal of the hydrogen at the 4-position with sodium hydride, followed by the expulsion of a benzaldehyde anion (D) to give **9**. The effect of the N^1-atom in the anion C as well as the N^3-carbonyl group may favor the expulsion of the anion D to yield the aromatic system rather than the formation of the corresponding aziridine intermediate.

The second step is the generation of the anion C and **5** by the reaction between the resulting anion D and **1**, followed by the addition of C to **5** to form an intermediate E. Then E gives the ester (**10**) with the expulsion of a cyanide ion by way of an intermediate (F), similar

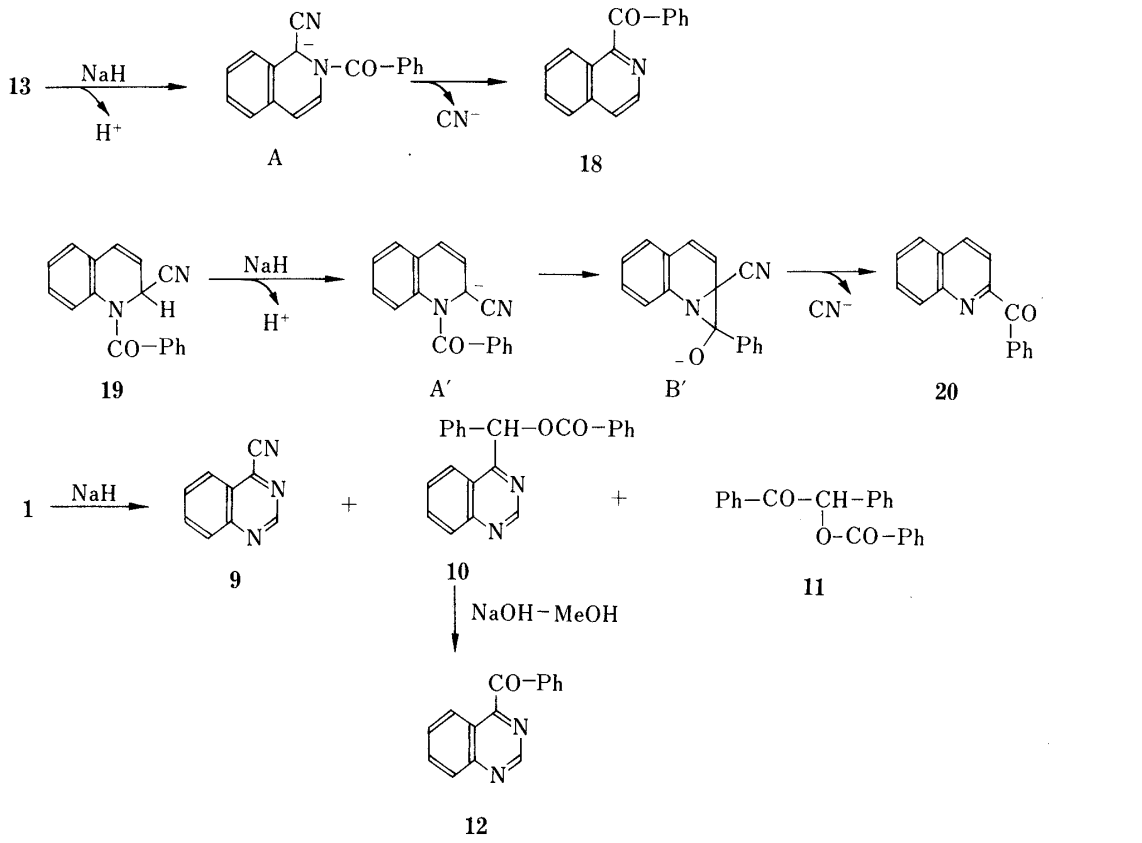


Chart 4

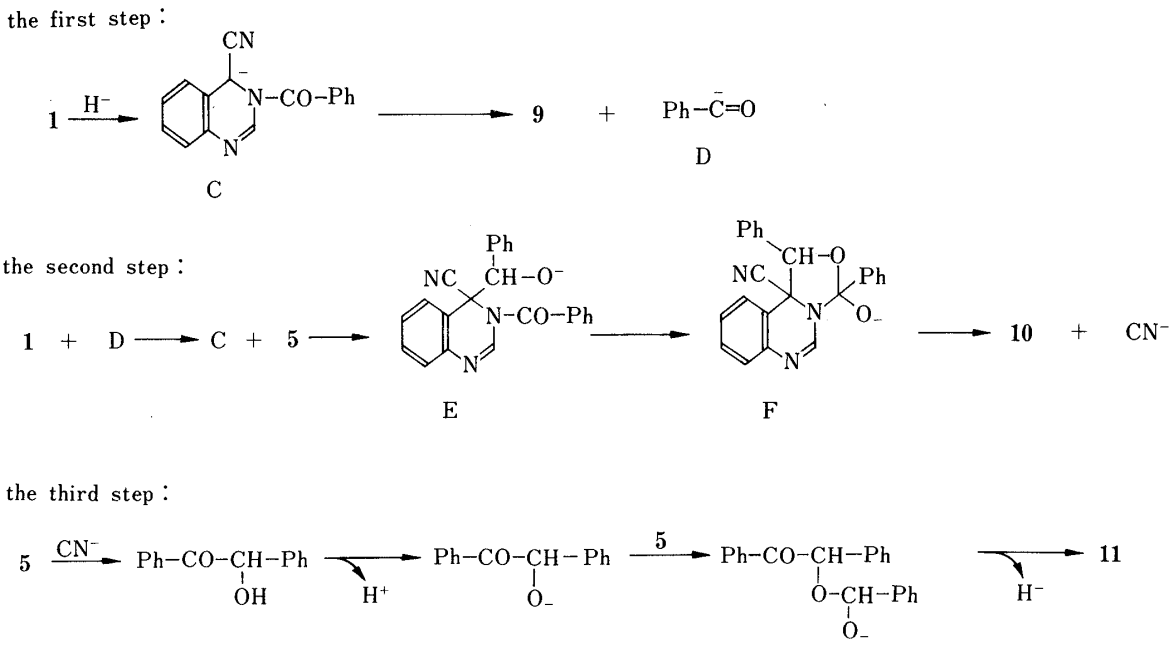


Chart 5

to the cyclic intermediate observed in the reaction of the anion A′ with aromatic aldehydes.[13)]

The third step is the benzoin condensation catalyzed by the resulting cyanide ion, followed by benzoylation, to lead to **11**.

Expetimental

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 MS spectrometer. The exact mass measurements were made on a JEOL JMS-01SG-2 MS spectrometer combined with a JEC spectrum computer.

Quinazoline Reissert Compound (1)——Benzoyl chloride (12 mmol, 1.69 g) was added to a solution of **3** (10 mmol, 1.57 g) in pyridine (20 ml) under ice cooling, and the mixture was heated at 50 °C for 5 min. After cooling, the reaction mixture was poured onto an excess of ice. The separated crystals were washed with 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 **1**, which was recrystallized from benzene–petr. ether to give colorless needles, mp 171—172 °C. Yield 2.14 g (82%). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 7.65 (1H, s, C^2–H), 7.14—7.64 (9H, m, aromatic H), 6.18 (1H, s, C^4–H). ^{13}C-NMR ($CDCl_3$): 42.53 (d), 115.75 (s), 117.99 (s), 126.44 (d), 126.75 (d), 128.35 (d), 128.83 (d), 129.30 (d), 130.78 (d), 130.95 (s), 132.77 (d), 138.79 (s), 141.39 (d), 168.79 (s). *Anal.* Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.82; H, 4.35; N, 16.08.

Alkaline Hydrolysis of 1——A mixture of **1** (1 mmol, 261 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 benzene. The benzene extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 using benzene as the eluent. The first and second fractions gave benzoic acid (**4**, 41%, 50 mg) and quinazoline (**2**, 62%, 80 mg), respectively.

Alkaline Hydrolysis of Isoquinoline Reissert Compound (13)——By the same procedure as described for the alkaline hydrolysis of **1**, **13** (1 mmol, 260 mg) gave **4** (29%, 35 mg), **14** (78%, 101 mg), and **15** (17%, 29 mg), obtained from the first, second, and their fractions.

Acid Hydrolysis of 1——A mixture of **1** (1 mmol, 261 mg) and 20% HCl (4 ml) was stirred for 20 h. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and then chromatographed on a column of SiO_2 using $CHCl_3$ as an eluent. The first fraction gave **4** (45%, 55 mg).

The HCl layer was neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 using $CHCl_3$ as the eluent. The first fraction gave **2** (trace), and the second fraction gave 2-benzamido-2-(2-aminophenyl)acetonitrile (**6**, 32%, 80 mg) which was recrystallized from benzene to give a colorless powder, mp 167—168 °C. IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O), 3260 (NH), 3350, 3430 (NH_2). ^{1}H-NMR ($SO(CD_3)_2$): 9.50 (1H, d, exchangeable with D_2O, J = 7.8 Hz, CH–NH), 6.18—7.97 (10H, m, aromatic H and CH–NH), 5.14 (2H, br s, exchangeable with D_2O, NH_2). MS *m/e* Calcd for $C_{15}H_{13}N_3O$: 251.1059 (M^+). Observed: 251.1059.

Acetylation of 6——A mixture of **6** (1 mmol, 251 mg) and Ac_2O (150 mg) was heated at 60 °C for 5 min. The reaction mixture was neutralized with 5% K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 using $CHCl_3$ as the eluent. The first fraction gave 2-benzamido-2-(2-acetamidophenyl)acetonitrile (**7**, 84%, 246 mg), which was recrystallized from benzene–petr. ether to give a colorless powder, mp 160—162 °C. IR ν_{max}^{KBr} cm^{-1}: 1640, 1660 (C=O). ^{1}H-NMR ($CDCl_3$): 8.77 (1H, br s, exchangeable with D_2O, –NH–Ac), 8.22 (1H, d, exchangeable with D_2O, J = 8.0 Hz, CH–NH), 7.00—7.96 (9H, m, aromatic H), 6.28 (1H, d, changeable into s with D_2O, J = 8.0 Hz, CH–NH). ^{13}C-NMR ($SO(CD_3)_2$): 21.35 (q), 39.17 (d), 116.16 (s), 124.02 (d), 124.94 (d), 125.86 (d), 126.35 (d), 126.57 (d), 126.73 (s), 127.54 (d), 130.03 (d), 131.95 (s), 133.94 (s), 164.38 (s), 167.25 (s). *Anal.* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.44; H, 5.08; N, 14.15.

Preparation of 3-Benzoyl-4-cyano-3,4-dihydroquinazolinium Chloride (8) and 1-Amino-3-phenyloxazolo[4,3-*a*]isoquinolinium Chloride (17)——Hydrogen chloride gas was introduced into a solution of **1** or **13** (1 mmol) in benzene (20 ml) for 5 min. The separated crystals were collected, and washed with benzene to give **8** or **17**.

8: mp 120 °C (dec.), colorless powder, yield 53% (165 mg). IR ν_{max}^{KBr} cm^{-1}: 3480 (NH), 1720 (C=O). ^{1}H-NMR ($SO(CD_3)_2$): 8.65 (1H, s, C^2–H), 7.24—8.17 (11.5H, m, aromatic H, NH, and 3/4·H_2O), 6.68 (1H, s, C^4–H). ^{13}C-NMR ($SO(CD_3)_2$): 41.88 (d), 114.05 (s), 116.87 (s), 118.01 (d), 127.59 (d), 128.14 (d), 128.46 (d), 129.22 (d), 129.87 (s), 130.97 (s), 131.01 (d), 132.69 (d), 149.64 (d), 167.25 (s). *Anal.* Calcd for $C_{16}H_{12}ClN_3O \cdot 3/4 \cdot H_2O$: C, 61.74; H, 4.37; N, 13.50. Found: C, 61.78; H, 3.97; N, 13.86. MS *m/e*: 261 ($M^+ - HCl$).

17: mp 167—170 °C, orange needles, yield 72% (236 mg). IR ν_{max}^{KBr} cm^{-1}: 3200 (NH_2). ^{1}H-NMR ($SO(CD_3)_2$): 7.21—8.33 (14.5H, m, aromatic H, NH_2, and 3/4·H_2O). ^{13}C-NMR ($SO(CD_3)_2$): 102.84 (s), 118.38 (d), 120.61 (s), 121.74 (d), 123.69 (d), 124.83 (d), 127.05 (d), 128.08 (d), 128.20 (s), 129.10 (s), 129.55 (d), 130.25 (d), 132.47 (d), 141.03 (s), 150.78 (s). *Anal.* Calcd for $C_{17}H_{13}ClN_2O \cdot 3/4 \cdot H_2O$: C, 65.81; H, 4.71; N, 9.03. Found: C, 65.75; H, 4.33; N, 8.76.

Hydrolysis of 8——A mixture of **8** (1 mmol, 311 mg) and H_2O (4 ml) was stirred for 4 h at room temperature. Work-up of the reaction mixture in the same manner as described for the acid hydrolysis of **1** gave **6** (20%, 50 mg), **4**

(33%, 40 mg), and **2** (trace).

Reaction of 1 with NaH——Fifty milligrams of 50% NaH (in oil) was added to a solution of **1** (1 mmol, 261 mg) in DMF (1 g) under ice cooling, and the mixture was stirred for 5 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 using $CHCl_3$ as the eluent. The first fraction gave *O*-benzoylbenzoin[11] (**11**, 28%, 88 mg), the second fraction gave 4-quinazolinecarbonitrile[6] (**9**, 26%, 40 mg), and the third fraction gave α-phenyl-4-quinazolinylmethyl benzoate (**10**, 24%, 82 mg). Compound **10** was recrystallized from MeOH to give colorless prisms, mp 149 °C IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O). ^{1}H-NMR ($CDCl_3$): 7.07—8.33 (15H, m, aromatic H and CH–O), 9.18 (1H, s, C^2–H). *Anal.* Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.84; H, 4.72; N, 8.00.

4-Benzoylquinazoline (12)——A solution of **10** (1 mmol, 340 mg) in methanolic NaOH (NaOH (420 mg) in MeOH (6 ml)) was refluxed for 30 min. The solvent was removed under reduced pressure, and the residue was poured onto an excess of ice. The reaction mixture 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 using $CHCl_3$ as an eluent. The first fraction gave **12** (88%, 206 mg), which was recrystallized from petr. ether to give colorless needles, mp 97—98 °C. The melting point of this compound **12** was undepressed on admixture with an authentic sample prepared by another route.[12]

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References

1) *a*) A. Reissert, *Chem. Ber.*, **38**, 3427 (1905); *b*) J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).
2) *a*) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955); *b*) F. D. Popp, "Advances in Heterocyclic Chemistry," Vol. 9, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, Inc., New York, 1968, p. 1; *c*) *Idem, ibid.*, Vol. 24, 1979, p. 187.
3) F. D. Popp, *Heterocycles*, **1**, 165 (1973).
4) *a*) B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1146; *b*) T. Higashino, H. Kokubo, A. Goto, M. Takemoto, and E. Hayashi, *Chem. Pharm. Bull.*, **32**, 3690 (1984).
5) D. Bhattacharjee and F. D. Popp, *J. Heterocycl. Chem.*, **17**, 1211 (1980).
6) T. Higashino, *Yakugaku Zasshi*, **80**, 245 (1960).
7) T. Higashino, Y. Matsushita, M. Takemoto, and E. Hayashi, *Chem. Pharm. Bull.*, **31**, 3951 (1983).
8) A. Reissert, *Chem. Ber.*, **38**, 1603 (1905).
9) M. J. Cook, A. R. Katritzky, and A. D. Page, *J. Am. Chem. Soc.*, **99**, 165 (1977).
10) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).
11) E. P. Kohler and J. L. E. Erickson, *J. Am. Chem. Soc.*, **53**, 2301 (1931).
12) T. Higashino, M. Goi, and E. Hayashi, *Chem. Pharm. Bull.*, **22**, 2493 (1974).
13) L. R. Walters, N. Thanukrishna, and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1177 (1958).