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Ring Fission of Quinazolines by Means of the Reissert Reaction

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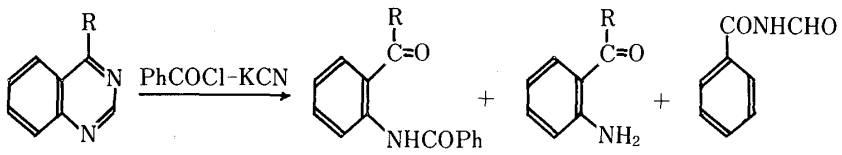
Under the Reissert reaction conditions, quinazoline (**1a**) afforded 2′-formylbenzanilide (**2a**), *o*-aminobenzaldehyde (**3a**), and *N*-formylbenzamide (**4**). Similarly, 4-methyl- (**1b**) and 4-ethoxyquinazoline (**1c**) gave the corresponding benzanilides **2b** and **2c**, respectively, *o*-aminoacetophenone (**3b**, from **1b**), and benzamide (**5**). It was confirmed that the same results were obtained in the absence of the cyanide ion. A substituent at the 2-position prevented the ring fission, and only the corresponding N^3-benzoyl pseudo-base (**14**) was obtained.

The generality of the ring fission was shown by the reactions of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**6**) and 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**8**), giving 5-amino-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**7**) and 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbaldehyde (**9**), respectively.

Keywords——4-substituted quinazoline; 1*H*-pyrazolo[3,4-*d*]pyrimidine; 3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine; 2′-acylbenzanilide; 2-aminophenyl alkyl ketone; *N*-formylbenzamide; ring fission

It has been reported by Uff *et al.*[1] that, under the conditions for Reissert compound formation[2] with benzoyl chloride and aqueous potassium cyanide, quinazoline (**1a**) gave neither a Reissert compound (3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile) nor an *N*-benzoyl pseudo-base, the only product being 2′-formylbenzanilide (**2a**). Since we were interested in the preparation of the hitherto unknown quinazoline Reissert compound, we reexamined the above reaction and observed an interesting ring fission in addition to the formation of **2a**.

When attempts were made to form the Reissert compound by a standard method[2] using benzoyl chloride and aqueous potassium cyanide, **1a** underwent ring fission to give **2a**,[3] *o*-aminobenzaldehyde (**3a**),[4] and *N*-formylbenzamide (**4**).[5] On repeating the above reaction using water alone, the same products were isolated. In the case of 4-methylquinazoline (**1b**)[6] a similar ring fission proceeded to give 2′-acetylbenzanilide (**2b**),[7] *o*-aminoacetophenone (**3b**)[8] and benzamide (**5**). However, 4-ethoxyquinazoline (**1c**)[9] did not form ethyl anthranilate (**3c**),[10] corresponding to **3a**, but gave 2′-(ethoxycarbonyl)benzanilide (**2c**)[11] and **5**.



1	R	2	3	4
1a	H	**2a**	**3a**	**4**
1b	Me	**2b**	**3b**	**5**[a]
1c	OEt	**2c**		**5**[a]

a) **5**: benzamide.

Chart 1

Uff *et al.*[1] suggested a mechanism for the formation of **2a** in which the ring fission at the 1,2-bond proceeds *via* the hydrated dibenzoylquinazolinium cation (A) and the dibenzoylquinazoline pseudo-base (B), to give the ring-opened product (C), as shown in Chart 2.

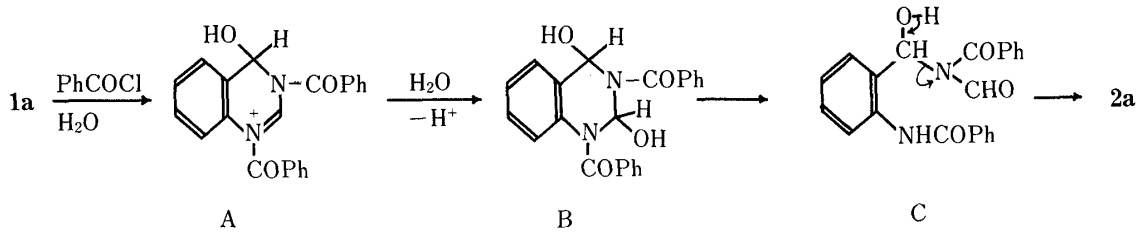


Chart 2

However, our mechanism, as shown in Chart 3, is different from that mentioned above, for the following reasons. It is well known that the quinazolinium cation in water undergoes covalent hydration to form the 3,4-dihydro-4-hydroxyquinazolinium cation,[12] and quinazoline 3-oxide in aqueous alkali metal hydroxide at ordinary temperature readily undergoes ring fission at the 2,3-bond to form 2′-(hydroxyiminomethyl)formanilide.[13a] It was also reported that *N*-oxidation of 4-alkylquinazoline with monoperphthalic acid results in the formation of the corresponding N^1- and N^3-monooxides.[13b] Even if a methyl group is present at the 4-position, methylmagnesium iodide adds across the 3,4-bond of **1b** to give 3,4-dihydro-4,4-dimethylquinazoline (**10**). Thus, the first step is undoubtedly the formation of N^3- (D) and N^1-benzoylquinazolinium cations (D′) which readily undergo covalent hydration to form the corresponding pseudo-bases E and E′. The subsequent ring fission at the 2,3-bond, followed by decomposition, leads to **3** and **4** (or **5**). The product **2** originates from E′ through the same process, as shown in Chart 3.

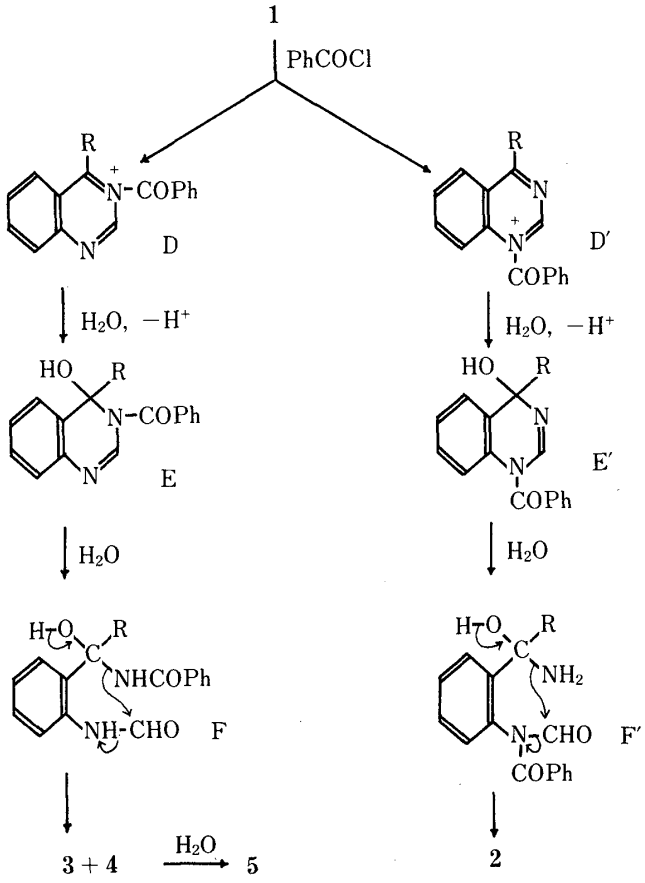


Chart 3

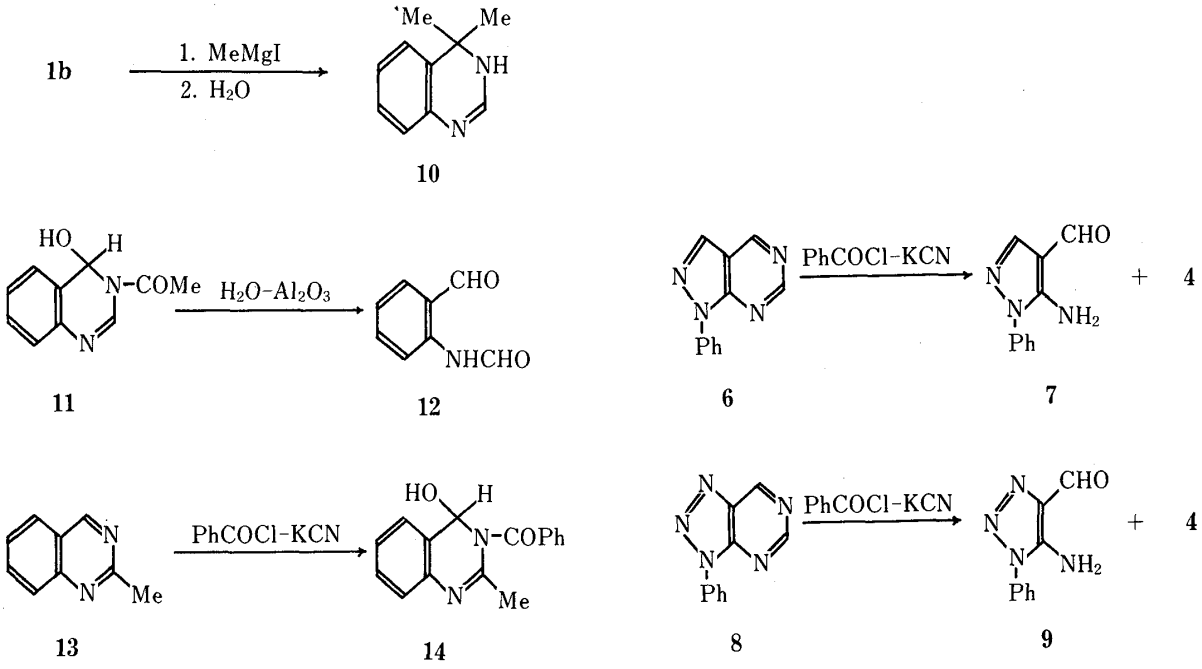


Chart 4 Chart 5

We found that the N^3-acetyl pseudo-base (**11**), which was isolated from the reaction of **1a** with acetic anhydride, gave 2′-formylformanilide (**12**) on reaction with alumina in the presence of water, confirming the ring fission at the 2,3-bond.[14] From our mechanism, it can be assumed that a substituent at the 2-position would prevent the ring fission. In fact, under the condition for Reissert compound formation, 2-methylquinazoline (**13**) gave neither a Reissert compound nor ring fission products, the only product being the N^3-benzoyl pseudo-base (**14**).

In terms of the principle of hard and soft acids and bases,[15] the effect of the N^1- and N^3-atoms in the *N*-benzoylquinazolinium cations D and D′ presumably enhances the hardness of the C^4-atom, thus favoring attack by the hard base water (or hydroxide ion) rather than by the soft base cyanide ion. This effect causes D and D′ to form the *N*-benzoyl pseudo-bases E and E′, which are the key intermediates for the ring fission.

In order to establish the generality of this ring fission, other fused pyrimidine ring systems were examined. Thus, both 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**6**)[16a] and 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**8**)[16c] underwent similar ring fission, resulting in the formation of 5-amino-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**7**)[16b] and 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbaldehyde (**9**),[16c] respectively, and **4**, as shown in Chart 5.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Jasco IRA-1 grating infrared spectrophotometer. The ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were measured at 90 Mc and at 23 °C on a JEOL JNM-FX90Q FTNMR spectrometer, and chemical shifts are given on the δ(ppm) scale with tetramethylsilane as an internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br s, broad singlet). Mass spectra (MS) were obtained on a JEOL JMS-01-SG-2 mass spectrometer combined a JEC-6 spectrum computer. Samples were vaporized in a direct system.

Reaction of Quinazolines (1) with Benzoyl Chloride in the Presence of KCN——Standard Method: A solution of KCN (6 mmol) in H_2O (3 ml) was added dropwise to a stirred solution of **1** (3 mmol) and benzoyl chloride (3 mmol) in $CHCl_3$ (3 ml), and the mixture was stirred for 30 min. The $CHCl_3$ layer was extracted with 1 N HCl to separate **3**, washed with 2 N, NaOH, dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2. The first fraction with benzene gave **2**, and the first fraction with $CHCl_3$ gave **4** (or **5**).

The HCl extract was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over

N_2SO_4 and chromatographed on a column of SiO_2. The first fraction with $CHCl_3$ gave **3**.

The reaction of qunazoline (**1a**) gave 2′-formylbenzanilide (**2a**, mp 73 °C, 15%), *o*-aminobenzaldehyde (**3a**, trace), and *N*-formylbenzamide (**4**, mp 112—114 °C, 18%). The above reaction in the absence of KCN gave **2a** (33%), **3a** (2%), and **4** (34%). Compound **2a**, the oxime of **3a** (mp 136—137 °C), and **4** showed undepressed melting points on admixture with the corresponding authentic samples.[3,5,17]

The reaction of 4-methylquinazoline (**1b**) gave 2′-acetylbenzanilide (**2b**, mp 83 °C, 15%), *o*-aminoacetophenone (**3b**, trace), and benzamide (**5**, 17%), while the reaction in the absence of KCN gave **2b** (14%), **3b** (trace), and **5** (11%). Compound **2b** showed undepressed melting point on admixture with an authentic sample,[7] and **3b** was easily converted into **2b** by benzoylation with benzoyl chloride.

The reaction of 4-ethoxyquinazoline (**1c**) gave 2′-(ethoxycarbonyl)benzanilide (**2c**, mp 99 °C, 10%) and **5** (52%). The reaction in the absence of KCN gave **2c** (15%) and **5** (46%). Compound **2c** showed undepressed melting point on admixture with an authentic sample.[11]

Reaction of 1b with MeMgI——A solution of MeMgI (prepared from MeI (852 mg, 6 mmol) and Mg (291 mg, 12 mmol)) in ether (10 ml) was added to a solution of **1b** (288 mg, 2 mmol) in ether (5 ml), and the mixture was refluxed for 7 h, then cooled. Aqueous NH_4Cl–NH_3 (NH_4Cl (2 g) and 28% NH_3 (1 ml) in H_2O (5 ml)) was added to the reaction mixture. The aqueous solution was extracted with benzene. The benzene solution was combined with the ether solution, and the combined solution was dried over Na_2SO_4, then concentrated to dryness. The residue was chromatographed on a column of SiO_2 using benzene as an eluent. The first fraction gave an oily material which was not purified, and the second fraction gave 3,4-dihydro-4,4-dimethylquinazoline (**10**, 41%, 131 mg). Compound **10** was recrystallized from benzene–petr. ether to give pale yellow scales, mp 114—115 °C. MS *m/e* Calcd. for $C_{10}H_{12}N_2$ (M^+): 160.1001. Observed: 160.1002. IR ν_{max}^{KBr} cm^{-1}: 2800—3200 (NH). ^{1}H-NMR (in $CDCl_3$) δ: 6.98—7.17 (5H, m, aromatic H and C^2–H), 5.88 (1H, br s, exchangeable with D_2O, NH), 1.50 (6H, s, $2\times CH_3$).

Preparation of 2-Methylquinazoline (13)——Pd catalyst prepared from 1% $PdCl_2$ (10 ml) and MgO (6.0 g) was added to a solution of 4-chloro-2-methylquinazoline[18] (8.0 g, 45 mmol) in MeOH (60 ml) and benzene (100 ml), and the mixture was shaken in an H_2 stream. After rapid absorption of H_2 (1010 ml, 45 mmol), the catalyst was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was decomposed by addition of a solution of NH_4Cl (10 g) in 28% NH_3 (15 ml), and the mixture was extracted with benzene. The benzene extract was dried over Na_2SO_4, and passed through a column of Al_2O_3 to remove impurities. Evaporation of the benzene gave **13**, mp 40 °C (bp 61 °C (20 mmHg)), in 62% yield (4.0 g). Compound **13** showed undepressed melting point on admixture with an authentic sample.[19]

3-Benzoyl-3,4-dihydro-4-hydroxy-2-methylquinazoline (14)——A solution of KCN (390 mg, 6 mmol) in H_2O (6 ml) was added to a solution of **13** (432 mg, 3 mmol) and benzoyl chloride (422 mg, 3 mmol) in $CHCl_3$ (3 ml), and the mixture was shaken for 1 h. The $CHCl_3$ layer was washed with aqueous K_2CO_3 and dried over Na_2SO_4. Evaporation of the $CHCl_3$ gave **14** in 21% yield (167 mg). Recrystallization from petr. ether–benzene gave colorless needles, mp 172 °C. *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.27; H, 5.26; N, 10.38. MS *m/e*: 266 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 3050 (OH). ^{1}H-NMR (in $SO(CD_3)_2$) δ: 7.10—7.65 (9H, m, aromatic H), 6.05 (1H, d, changed into br s with D_2O, J=5.4 Hz, C^4–H), 6.60 (1H, d, exchangeable with D_2O, J=5.4 Hz, C^4–OH), 2.18 (3H, s, C^2–CH_3). ^{13}C-NMR (in $SO(CD_3)_2$) δ: 24.76 (q), 74.66 (d), 124.24 (d), 126.03 (d), 126.51 (d), 128.52 (d), 128.63 (d), 129.17 (d), 129.44 (d), 132.20 (s), 138.80 (s), 139.51 (s), 150.84 (s), 170.61 (s).

The above reaction in the absence of KCN gave the same product **14** in 10% yield.

Reaction of 1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (6) with Benzoyl Chloride in the Presence of KCN——A solution of KCN (260 mg, 4 mmol) in H_2O (1 ml) was added to a stirred solution of **6** (392 mg, 2 mmol) and benzoyl chloride (281 mg, 2 mmol) in $CDCl_3$ (1 ml), and the mixture was shaken for 10 min. The $CHCl_3$ layer was dried over Na_2SO_4 and chromatographed on a column of SiO_2. The first fraction with $CHCl_3$ gave **4** in 32% yield (95 mg). The second fraction gave 5-amino-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**7**), mp 121 °C, in 35% yield (131 mg). Compound **7** showed undepressed melting point on admixture with an authentic sample.[16b]

The above reaction in the absence of KCN gave **4** and **7** in 27 and 29% yields, respectively.

Reaction of 3-Phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (8) with Benzoyl Chloride in the Presence of KCN——The same procedure as described for the reaction of **6**, using **8** (394 mg, 2 mmol), benzoyl chloride (281 mg, 2 mmol), and KCN (260 mg, 4 mmol), gave **4** and 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbaldehyde (**9**), mp 113 °C, in 30% (113 mg) and 19% yields (71 mg), respectively. Compound **9** showed undepressed melting point on admixture with an authentic sample.[16c]

The above reaction in the absence of KCN gave **4** and **9** in 34 and 16% yields, respectively.

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References and Notes

1) B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1146.

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) A. Bischler and M. Lang, *Chem. Ber.*, **28**, 287 (1895).
4) L. I. Smith and J. W. Opie, "Organic Synthesis," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 56.
5) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5914 (1951).
6) T. Higashino, *Yakugaku Zasshi*, **80**, 245 (1960).
7) G. W. Gribble and F. P. Bousquet, *Tetrahedron*, **27**, 3785 (1971).
8) L. A. Elson, C. S. Gibson, and J. D. A. Johnson, *J. Chem. Soc.*, **1930**, 1128.
9) M. T. Bogert and C. E. May, *J. Am. Chem. Soc.*, **31**, 509 (1909).
10) P. Karrer, C. Nägeli, and H. Weidmann, *Helv. Chim. Acta*, **2**, 242 (1919).
11) Mehner, *J. Prakt. Chem.* [2], **64**, 84 [*Beilstein*, **14**, 341].
12) W. L. F. Armarego, "Advances in Heterocyclic Chemistry," Vol. 1, ed. by A. R. Katritzky, Academic Press, Inc., New York, 1963, p. 253.
13) *a*) T. Higashino, *Chem. Pharm. Bull.*, **9**, 635 (1961); *b*) T. Higashino, T. Amano, Y. Tamura, N. Katsumata, Y. Washizu, T. Ono, and E. Hayashi, *ibid.*, **20**, 1874 (1972).
14) Unpublished data. The results will be reported in detail in a separated paper.
15) R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963).
16) *a*) T. Higashino, Y. Iwai, and E. Hayashi, *Yakugaku Zasshi*, **94**, 666 (1974); *b*) *Idem, Chem. Pharm. Bull.*, **24**, 3120 (1976); *c*) T. Higashino, T. Katori, and E. Hayashi, *ibid.*, **27**, 2431 (1979).
17) H. J. Roth and H. H. Lausen, *Arch. Pharm. Ber. Dtsh. Pharm. Ges.*, **306**, 775 (1973).
18) H. C. Scarborough, B. C. Lawes, T. L. Minulli, and J. L. Compton, *J. Org. Chem.*, **27**, 957 (1962).
19) M. T. Bogert and F. P. Nabenhauer, *J. Am. Chem. Soc.*, **46**, 1702 (1924).