Preparation and Reactions of Mono-Reissert Compounds and Analogs at the 3,4-Position of Quinazoline [1]

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Quinazoline, acid chlorides, and trimethylsilyl cyanide have been converted to mono-Reissert compounds at the 3,4-position of the quinazoline system. Various reactions of these quinazoline Reissert compounds are reported.

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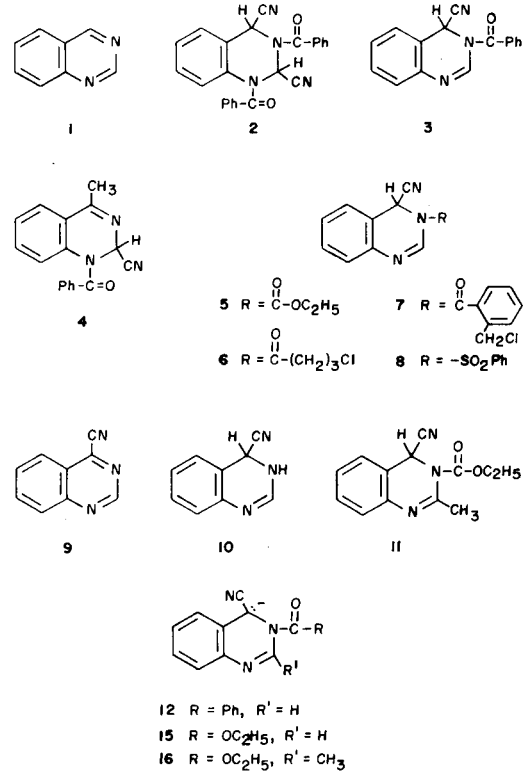
Although the chemistry of Reissert compounds [2] from isoquinolines, quinolines, phthalazine, and a number of other aza-aromatic heterocyclic systems has been well studied, relatively little has appeared on the Reissert compound chemistry of quinazoline (**1**). Such compounds would appear to be potentially useful synthetic intermediates for the exploitation of the chemistry of the quinazoline system.

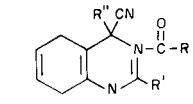
Attempted Reissert compound formation from **1** with benzoyl chloride and potassium cyanide using the methylene chloride-water solvent system led to ring opening and the isolation of 2-formylbenzanilide [3,4]. The reaction of **1** with an excess of trimethylsilyl cyanide and benzoyl chloride led to the di-Reissert compound **2** [5]. Recently Higashino and co-workers [6] reported the preparation of 3-benzyl-3,4-dihydro-4-quinazolinecarbonitrile (**3**), one of the two quinazoline mono-Reissert compounds, by an indirect method. Addition of hydrogen cyanide to **1** gave 3,4-dihydro-4-quinazolinecarbonitrile which was then benzoylated with benzoyl chloride in pyridine to give **3** [6]. We have reported the preparation of **3** from **1** by a convenient one-step procedure using equimolar amounts of trimethylsilyl cyanide and benzoyl chloride [7]. At the same time the other quinazoline mono-Reissert compound (**4**) was prepared from 4-methylquinazoline [7]. We now report on the preparation and some of the chemistry of the quinozoline mono-Reissert compound **3** and some of its analogs.

Reissert compound **3** was obtained in 67% yield, when quinazoline in dry methylene chloride was stirred for 48 hours at room temperature with equimolar amounts of trimethylsilyl cyanide and freshly distilled benzoyl chloride in the presence of a catalytic amount of aluminium chloride. In a similar manner Reissert analog **5** and Reissert compounds **6** and **7** were prepared when benzoyl chloride was replaced with ethyl chloroformate, 4-chlorobutyryl chloride, and *o*-chloromethylbenzoyl chloride, respectively. Reaction of the quinazoline with benzene sulfonyl chloride and trimethylsilyl cyanide did not give the Reissert analog **8**, in contrast to in isoquinoline, but instead

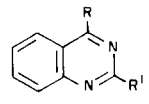


gave 4-cyanoquinazoline (**9**) and 4-cyano-3,4-dihydroquinazoline (**10**). Hydrogen cyanide is known to add across the 3,4 bond to give (**10**) [8], but when quinazoline was treated with trimethylsilyl cyanide in the presence of a catalytic amount of aluminium chloride in dry methylene chloride, quinazoline was recovered unchanged. This supports the fact that **9** and **10** arise from the intermediate **8**. A similar behavior is also observed in the phthalazine [2], quinoline [2], and thieno[2,3-*c*]pyridine [9] series.

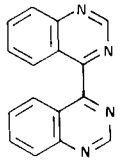
When 2-methylquinazoline was treated with trimethyl cyanide and ethyl chloroformate in the presence of a catalytic amount of aluminium chloride the Reissert analog **11** was obtained. The mono-Reissert compounds **3** was converted in moderate yield to the di-Reissert compounds **2**.



13 R = Ph, R' = H, R'' = CH_3
17 R = OC_2H_5, R' = H
R'' = CH_3, C_2H_5, CH_2Ph
18 R = OC_2H_5, R' = R'' = CH_3



14 R = CH_3, R' = H
19 R = C_2H_5, R' = H
20 R = CH_2Ph, R' = H
21 R = R' = CH_3



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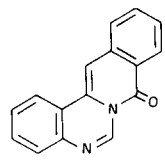

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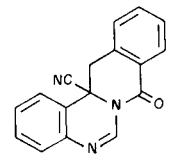

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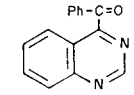

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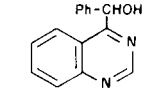

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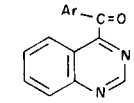
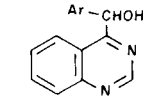
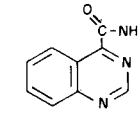


27 Ar = $-C_6H_4OCH_3$-o
28 Ar = $-C_6H_4Cl$-m



29 Ar = $-C_6H_4OCH_3$-o
30 Ar = $-C_6H_4Cl$-m



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Treatment of **3** with sodium hydride in the dimethylformamide gave the conjugate base **12** which was alkylated with methyl iodide to give **13**, which was hydrolyzed by potassium hydroxide to give 4-methylquinazoline (**14**) in 52% yield. Higashino has also reported [10] examples of the alkylation of **3**. The Reissert analogs **5** and **11** were readily converted to their conjugate bases **15** and **16**. Treatment of **15** and **16** with alkyl halides gave **17** and **16**, which were hydrolyzed by potassium hydroxide to give various 4-alkylquinazolines **14, 19, 20** and 2,4-dimethylquinazoline (**21**).

The Reissert compounds **6** on similar conversion to its conjugate base, gave 4,4'-biquinazoline (**22**), together with a small amount of quinazoline, instead of the intramolecular cyclised product. The structure of the compound **22** was deduced from its nmr spectrum and elemental analysis. The compound exhibited a singlet at δ 9.54 ppm, responsible for 2 protons, *viz.* the 2- and 2'-hydrogen atoms, and confirms that the molecule is symmetrical. There are no other signals except for the eight "aromatic" protons of the benzene ring between δ 8.20-7.55 ppm. Further conformation of the structure was had by oxidising **22** to 4-hydroxyquinazoline using 30% hydrogen peroxide. Quinazoline in the presence of aqueous cyanide is known to form 4,4'-biquinazoline. A benzoin type of reaction is postulated in the formation [11]. It appears that in presence of sodium hydride in dimethylformamide Reissert analog **6** hydrolyses to give quinazoline which *in situ* reacts with the cyanide to give **2**.

Reissert compound **7** underwent intramolecular alkylation when treated with sodium hydride in anhydrous dimethylformamide at 0-5°, to afford the 5-azaberbine derivative **23**. Compound **23** arises from the dehydrocyanation of the initially formed cyano derivative **24**. Such a dehydrocyanation may reasonably be expected to be facile as it leads to the totally aromatic product. This has been observed in other reactions of *o*-chloromethylbenzoyl Reissert compounds.

Benzaldehyde was condensed with **15** to give, after chromatography, 4-benzoylquinazoline (**25**) and α-phenyl-4-quinazolinemethanol (**26**). Both the structures were established by their independent synthesis and by their nmr spectrum. The compound **26** which is a yellow oil, exhibited singlets at δ 9.20 and δ 6.32 responsible for protons at carbon-2 of the quinazoline ring and for the proton alpha to the hydroxy group. A broad singlet is observed at δ 5.20, which is exchangeable with deuterium oxide and multiplet at δ 8.25-7.00, responsible for nine aromatic protons. A broad peak around 3180 cm^{-1} is recognized in its ir spectrum. The compound **25** exhibits a singlet at δ 9.40, responsible for one proton and multiplet at δ 8.30-7.00, responsible for nine aromatic protons. A strong carbonyl band at 1680 cm^{-1} is observed in its infrared spectrum. Compound **26** was easily oxidised to **25** by chromium trioxide pyridine at room temperature. The compound obtained was identical to the compound **25** in all respects. Similarly reduction of the ketone **25** with sodium borohydride gave the carbinol **26**. When benzaldehyde was replaced with other aldehyde such as *o*-anisaldehyde and *m*-chlorobenzaldehyde, a series of ketones **27** and **28** and carbinols **29** and **30** were obtained. The presence of ketones is not unusual, as such apparent oxidation during the work-up has also been observed in the isoquinoline [12] and phthalazine [13] series.

Acid hydrolysis of **3** in the presence of 2,4-dinitrophenylhydrazine gave a low yield of benzaldehyde-2,4-dinitrophenylhydrazone. This is in contrast to the acid hydrolysis of isoquinoline and quinoline Reissert compounds which give high yields of benzaldehyde [2]. Hydrolysis of **3** with hydrobromic and acetic acid gave a low yield of quinazoline-4-carboxamide (**31**). This contrasts with the acid hydrolysis, under different conditions, of Higashino and coworkers [6].

Thus quinazoline can, through mono-Reissert com-

pound formations at the 3,4-position, be converted into a variety of derivatives. Similar studies are being carried out with the mono-Reissert compound at the 1,2-position [7] and the quinazoline di-Reissert compound [5].

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710B spectrometer. Proton magnetic resonance spectra were determined with a Hitachi Perkin Elmer R-24 B instrument using tetramethylsilane as an internal standard. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan. Silica gel 60-200 mesh (J. T. Baker) was used for all column chromatographic separations unless otherwise noted. Thin layer chromatographic comparisons were determined on Eastman-Kodak silica gel chromatograms with fluorescent indicator (NO-13181).

Preparation of 3-Benzoyl-4-cyano-3,4-dihydroquinazoline (**3**).

To a well stirred solution of 1.25 g (9.6 mmoles) of quinazoline, 0.96 g (9.6 mmoles) of trimethylsilyl cyanide in 30 ml of anhydrous methylene chloride was added 1.34 g (9.6 mmoles) of benzoyl chloride (freshly distilled) in methylene chloride over a period of 60 minutes. The reaction mixture was stirred for 48 hours at room temperature and the solution was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide, and water. The methylene chloride solution was dried (magnesium sulfate), evaporated and the residue crystallized from 95% ethanol to give 1.67 g (67%) of **3**, mp 170-171.5°; ir (potassium bromide): 1690 (C=O), 1620 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 7.70 (s, 1H, C-2), 7.60-7.20 (m, 9H, aromatic), 6.20 (s, 1H, C-4).

Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.55; H, 4.24; N, 16.13.

This compound was identical with a sample prepared by the two-step sequence [6,10,14].

Other Reissert Compounds and Analogs.

Using the procedure described above for the preparation of **3** the compounds, **5-7** were prepared.

Compound **5** was obtained in 57% yield, mp 107-108°; ir (potassium bromide): 1715 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.89 (s, 1H), 7.40-7.08 (m, 4H), 6.03 (s, 1H), 4.37 (q, 2H, J = 7.0 Hz), 1.38 (t, 3H, J = 7.0 Hz).

Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 62.87; H, 4.83; N, 18.33. Found: C, 62.84; H, 4.80; N, 18.29.

Compound **6** was obtained in 49% yield, mp 126.5-127°; ir (potassium bromide): 1690 and 1620 cm^{-1} (C=O), (C=N); nmr (deuteriochloroform): δ 7.75 (s, 1H), 7.53-7.25 (m, 4H), 6.25 (s, 1H), 3.64 (t, 2H, J = 6.87 Hz), 3.10-2.82 (m, 2H), 2.20 (t, 2H, J = 6.67 Hz).

Anal. Calcd. for $C_{13}H_{12}ClN_3O$: C, 59.65; H, 4.62; N, 16.05. Found: C, 59.41; H, 4.62; N, 15.89.

Compound **7** was obtained in 59% yield, mp 153.5-154.5°; ir (potassium bromide): 1690 and 1620 cm^{-1} (C=O), (C=N); nmr (deuteriochloroform): δ 7.55-7.12 (m, 9H), 6.30 (s, 1H), 5.05, 4.13 (dd, 2H, J = 12 Hz).

Anal. Calcd. for $C_{17}H_{12}ClN_3O$: C, 65.91; H, 3.90; N, 13.56. Found: C, 65.88; H, 4.03; N, 13.73.

Attempted Preparation of **8**.

To a soluiton of 1.0 g (7.5 mmoles) of quinazoline (**1**) in 25 ml of anhydrous methylene chloride was added 0.75 g (7.5 mmoles) of trimethylsilyl cyanide. After ten minutes, 1.32 g (7.5 mmoles) of benzenesulfonyl chloride was added and the mixture was stirred at room temperature for 48 hours. The yellow solution obtained was poured into a column of silica gel and eluted with methylene chloride. By evaporation of the eluent, was obtained 0.5 g (43%) of 4-cyanoquinazoline, mp 118-119.5° (reported [15] mp 118-119°); ir (potassium bromide): 2240 cm^{-1} (CN).

Further elution with the methanol-methylene chloride (2:8) gave 0.25 g (17%) of the hydrochloride **10**, mp 211-213° (reported [16] mp 211-213°); ir (potassium bromide): 3250-2380 (s, broad), 1665, 1605, 1575, 1480, 1340 cm^{-1}; nmr (deuteriochloroform): δ 13.8-9.15 (broad exchangeable with deuterium oxide, 2H), 8.62 (s, 1H), 7.42 (broad s, 4-ArH), 6.68 (s, 1H). Compound **10** hydrochloride was stirred overnight with equal volume of 20% sodium hydroxide solution and chloroform. Concentration of the washed and dried chloroform layer gave 4-cyanoquinazoline, mp 114-116° (reported [16] mp 114-116°).

Preparation of 3-Benzoyl-4-cyano-2-methyl-3,4-dihydroquinazoline (**11**).

Reaction of 1.3 g (9.0 mmoles) of 2-methylquinazoline and 1.07 g (10.8 mmoles) of trimethylsilyl cyanide in anhydrous methylene chloride, with 1.26 g (10.8 mmoles) of ethyl chloroformate, after usual work up as described above, gave 0.51 g (23%) of **11** [17], mp 153-154° (from 95% ethanol). The ir and the nmr spectra were consistent with the assigned structure.

Anal. Calcd. for $C_{13}H_{13}N_3O_2 \cdot H_2O$: C, 59.77; H, 5.75; N, 16.09. Found: C, 60.36; H, 5.96; N, 15.72.

Conversion of **3** to **2**.

To a well stirred solution of 0.3 g (1.10 mmoles) of **2** and 0.13 g (1.30 mmoles) of trimethylsilyl cyanide in 15 ml of dry methylene chloride, was added 0.18 g (1.30 mmoles) of benzoyl chloride (freshly distilled) in methylene chloride (2 ml), over a period of 30 minutes. The reaction mixture was stirred for 48 hours at room temperature and the solution was washed with water, 5%, hydrochloric acid, water, 5% sodium hydroxide, and water. The methylene chloride solution was dried (magnesium sulfate), evaporated and the residue crystallized from 95% ethanol to give 0.06 g (15%) of **3**, mp 188-189.5° (reported [5] mp 189-191°); ir (potassium bromide): 3070, 2972, 1665, 1600, 1490 cm^{-1}; nmr (deuteriochloroform): δ 7.50-7.15 (m, 14H), 6.65-6.60 (m, 1H), 5.95 (s, 1H).

Preparation of 4-Alkylquinazolines.

To a stirred solution of 0.5 g (2.0 mmoles) of **5** and an alkyl halide (2.5 mmoles) in 15 ml of anhydrous dimethylformamide was added 2.5 mmoles of 50% sodium hydride in oil dispersion. The mixture was stirred under a nitrogen atmosphere for 3 hours and poured into 100 g of crushed ice. The solid or oil obtained was subjected to hydrolysis, without further characterization, by refluxing it with 40% potassium hydroxide in a 1:1 ethanol-water system. The product was isolated by removing ethanol and extracting the aqueous layer with chloroform (2 × 20 ml). The combined extract was washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give the product, which was recrystallized by an appropriate solvent system. The method gave **14** (42% from ether) mp 36-37°, picrate 183-186° (reported [18] mp 36-37°, picrate 183-185°); **19** (35%) mp 169-171° as picrate (reported [18] mp 170-171°); and **20** (21%) mp 152-154° as picrate (reported [18] mp 154°).

Similarly **11** gave 15% of 2,4-dimethylquinazoline (**21**) identified as its picrate, mp 169-172° (reported [19] 170°).

Using this same procedure **3** gave a 52% yield of **14**.

Attempted Cyclization of 4-Cyano-3-(4-chlorobutyryl)-3,4-dihydroquinazoline (**6**).

To a well stirred solution of 0.5 g (1.0 mmole) of **6** in 15 ml of anhydrous dimethylformamide at room temperature under nitrogen atmosphere was added 0.07 g (1.5 mmoles) of 50% sodium hydride in oil. After stirring for two hours, the mixture was poured onto ice and the product filtered and recrystallized from benzene-hexane to give 0.15 g (60%) of **22**, mp 249-250° (reported [11] mp 245° and [20] mp 246-247°). A trace of quinazoline was also obtained; ir (potassium bromide): 1635, 1580, 1550, 1505, 1485, 1360, 1320, 1150, 1085, 960, 775 cm^{-1}; nmr (deuteriochloroform): δ 9.54 (s, 2H), 8.20-7.50 (m, 8H).

Anal. Calcd. for $C_{16}H_{10}N_4$: C, 74.44; H, 3.91; N, 21.69. Found: C, 74.14; H, 4.12; N, 21.66.

Oxidation of 4,4'-Biquinazoline.

A solution of 30 mg of **22** in 3 ml of glacial acetic acid and 0.5 ml of 30% hydrogen peroxide was stirred together at room temperature for 3 days. The solution was evaporated to dryness, the residue was dissolved in water and the *p*H of the solution was adjusted to 4. The solution was evaporated to dryness again. The residue obtained, was extracted with boiling ethanol (30 ml), and the extract treated with charcoal, filtered, and evaporated again. The residue was extracted with benzene and filter-

ed and the filtrate concentrated to 10 ml, diluted with pet ether and on cooling, gave 1.6 mg (50%) of 4-hydroxyquinazoline as white cotton like crystals. The compound had ir, nmr, and mp identical with those of an authentic sample obtained from Aldrich Chemical Company.

Cyclization of 4-Cyano-3-(2-chloromethylbenzoyl)-3,4-dihydroquinazoline (**7**).

To a well stirred solution of 1.0 g (3.2 mmoles) of **7** in 15 ml of anhydrous dimethylformamide at 0° under an argon atmosphere was added 3.2 mmoles of sodium hydride (50% in oil dispersion). After stirring for one hour at 0° and an additional two hours at room temperature, the mixture was poured into ice and the product filtered. The bright yellow solid was washed with water and recrystallized from 95% ethanol to give 0.46 g (58%) of **23**, mp 240-242°; ir (potassium bromide): 3050, 1655, 1520, 1590, 1545, 1490, 1460, 1395, 1345, 1325, 1295, 1245, 1180, 890 cm^{-1}.

Anal. Calcd. for $C_{16}H_{10}N_2O \cdot 0.3H_2O$: C, 76.35; H, 4.00; N, 11.13. Found: C, 76.18; H, 4.18; N, 11.19.

Reaction of **5** with Aldehydes.

To a mixture of 0.25 g (1.0 mmole) of **5** and 0.16 g (1.5 mmoles) of benzaldehyde in 10 ml of anhydrous dimethylformamide was added 0.07 g (1.5 mmoles) of 50% sodium hydride in oil. The mixture was stirred under a nitrogen atmosphere at room temperature for 3 hours and poured into ice-water. Extraction with chloroform (2 × 25 ml) gave, after washing with water, drying and concentration, an oil, which was chromatographed on silica using chloroform-hexane (1:4) to give two pure fractions. One fraction solidified after two days and on crystallization with ethyl acetate/hexane, gave 4-benzoylquinazoline (15%), mp 96-97.5° (reported [18] 97-98°); ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 9.40 (s, 1H), 8.30-7.00 (m, 9H). The second fraction, obtained as a yellow oil was α-phenyl-4-quinazolinemethanol (12%); ir (neat): 3180 cm^{-1} (OH); nmr (deuteriochloroform): δ 9.20 (s, 1H), 8.25-7.00 (m, 9H, aromatic), 6.32 (s, 1H), 5.20 (broad singlet, 1H, exchangeable with deuterium oxide). The spectra was consistent with the reported values [21].

Similarly *o*-anisaldehyde, gave 15% of α-(2-anisyl)-4-quinazolinemethanol (**29**), mp 150-152° (reported [11] 151-153°) (white prisms); ir (potassium bromide): 3160 cm^{-1} (broad); nmr (deuteriochloroform): δ 9.18 (s, 1H), 8.30-6.95 (m, 8H), 6.82 (s, 1H), 5.32 (broad singlet, 1H), 3.87 (s, 3H). Also obtained was 2-anisyl-4-quinazolinyl ketone **27** (10%), mp 98-99° (reported [11] 100-101°); ir (potassium bromide): 1685 cm^{-1}; nmr (deuteriochloroform): δ 9.25 (s, 1H), 8.35-6.55 (m, 8H), 3.35 (s, 3H).

m-Chlorobenzaldehyde gave 25% of α-(*m*-chlorophenyl)-4-quinazolinemethanol (**30**), mp 159-160.5° (reported [11] mp 160-161°); ir (potassium bromide): 3120 cm^{-1} (OH); nmr (deuteriochloroform): δ 9.19 (s, 1H), 8.30-6.85 (m, 8H), 6.32 (s, 1H), 5.22 (broad singlet, 1H). Also obtained was 5% of *m*-chlorophenyl-4-phenylquinazolinyl ketone (**28**), mp 116-117° (reported [11] mp 116-117°); ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 9.30 (s, 1H), 8.25-7.10 (m, 8H).

Reduction of **25** to **26**.

A suspension of 0.20 g (0.2 mmole) of the ketone **25** in 5 ml of methanol, was cooled to 0-5° and 0.25 g of sodium borohydride was added in small portions. The mixture was stirred in the cold until a clear solution was obtained and was stirred for additional 30 minutes at room temperature. A 5% hydrochloric acid solution was added to neutralize the solution. Methanol was removed *in vacuo*, and to the residue 15 ml of water was added. The solution was extracted with chlroforom (10 × 2). Drying (sodium sulfate) removal of chloroform gave 0.15 g (75%) of **26**, identical in all respects with the compound reported above.

Oxidation of **26** to **25**.

A mixture of 0.10 g (0.1 mmole) of the alcohol **26**, 70 mg of chromium trioxide, and 3 ml of pyridine was stirred overnight at room temperature and poured into 20 ml of cold water. The mixture was extracted with ether solution and the ether was washed with 10% sodium carbonate solution and with water, and dried over anhydrous magnesium sulfate. Removal of the ether gave an oil, which solidified after 5 days to give **25** in 25% yield, mp 95-97°, identical in all respects with the compound reported above from **5**.

Acid Hydrolysis of **3**. a).

Concentrated hydrochloric acid (5 ml/0.25 g of Reissert compound) was added to an equimolar mixture of Reissert compound and 2,4-dinitrophenylhydrazine, and the mixture was heated for 30 minutes. After the mixture had been allowed to stand at room temperature for 2 days, 20 mg of benzaldehyde 2,4-dinitrophenylhydrazone, was obtained, mp 239-241° (reported [22] mp 239°).

b).

A mixture of 0.15 g (1.0 mmole) of **3**, 10 ml of glacial acetic acid and 10 ml of hydrobromic acid (40%) was heated on the steam bath for 3 hours. The solution was cooled and 15 ml of acetone was added. After few days, 50 mg of solid was obtained. The solid was dissolved in water and treated with aqueous ammonia. The aqueous layer was extracted with methylene chloride (2 × 10 ml). Removal of the methylene chloride gave 20 mg (11%) of quinazoline-4-carboxamide (**31**), mp 171-173° (reported [23] mp 171-172°). The ir and nmr spectra were consistent with the structure.

Acknowledgement.

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