Quinazolines. X. Direct Formation of Aminoquinazolines from Hydroxyquinazolines and Phenyl Phosphorodiamidate (1)

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Treatment of several types of hydroxyquinazoline ring systems with phenyl phosphorodiamidate resulted in *direct* formation of the corresponding aminoquinazolines. The reaction can be conducted either by fusion in the absence of solvent or with diphenyl ether added as a diluent. The main advantage of the method is that it obviates the usual requirement for chlorination or thiation prior to amination.

Conversion of a 2-hydroxypyrimidine or 4-hydroxypyrimidine into the corresponding amino derivative is customarily effected in two stages: (1) introduction of a labile leaving group, *e.g.* by chlorination with phosphorus oxychloride or thiation with phosphorus pentasulfide, and (2) treatment of the resultant chloro or mercapto compound with ammonia at elevated temperature and pressure. Although this classic two-step route has enjoyed wide use for many years (2,3), the literature abounds with reports of unexpected difficulties and outright failures. Sometimes these can be traced to competing side reactions or to the incompatibility of the first-step reagent with functional groups already present in the molecule. In other instances problems are encountered in the amination step, especially when the use of autoclave equipment under stringently anhydrous conditions is required.

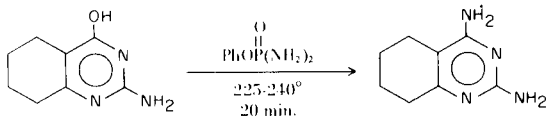
In view of these considerations a chemical reagent capable of converting hydroxypyrimidines into aminopyrimidines *directly* would possess obvious synthetic value. An intriguing approach to the design of such a reagent suggested itself following the appearance of two reports proposing adenosine-5′-phosphoramidate as a possible "active ammonia" species in certain enzymatic transaminations involving amino acids (4,5). It was conceivable that simple phosphoramidate analogs of adenosine-5′-phosphoramidate (AMP-NH_2) might participate in a transamination process of the type depicted in Scheme I (with a hydroxypyrimidine as the substrate), provided that the free energy gain accompanying the formation of a new P-O bond and rupture of a P-N bond were high enough to drive the reaction to completion.

Experimental validation of this concept has been provided recently with the successful conversion of 6-methyluracil and 6-methylisocytosine into 2,4-diamino-6-methylpyrimidine on heating with phenyl phosphorodiamidate for 0.5-1.0 hour at 215-230° in the absence of solvent (6). A variety of *N*-substituted and *N,N*-disubstituted phenyl phosphorodiamidates were also used (7), and the reaction was extended to purines (8) and N^1-alkyluracils (9). In the present paper we should like to call further attention to this novel amination reaction, and to extend its scope by providing several examples from our own work on condensed pyrimidines.

Phenyl phosphorodiamidate can be prepared from phosphorus oxychloride, phenol and ammonia (10) or from phenyl phosphorodichloridate and ammonia (11), the latter method being selected in this work. In a typical amination the hydroxypyrimidine and phenyl phosphorodiamidate were heated in an open flask for 20-60 minutes at temperatures (internal) ranging from 205° to 250° (see Experimental). Partial to complete melting was observed, with considerable evolution of ammonia and phenol. Reactions were carried out with an equimolar amount or an excess of phenyl phosphorodiamidate, and with diphenyl ether as an inert diluent in some instances. Because the crude product always appeared to consist in part of phosphorylated material, further treatment was necessary in order to obtain the desired aminopyrimidines. Accordingly, the cooled fusion mixture was usually subjected to one of several alkaline or acid work-up procedures. A useful method in some instances was digestion with hot *n*-butylamine, which led to the desired dephosphorylation (probably by transamidation) and at the same time provided a good crystallization solvent for the dephosphorylated product. Identification of the amination products was achieved by comparison with authentic specimens obtained previously in our laboratory

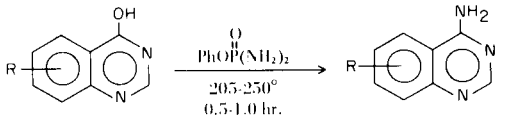
by alternate routes and, in those instances where new compounds were formed, by microanalysis.

Amination of 2-amino-5,6,7,8-tetrahydro-4-hydroxyquinazoline (**1**) proceeded in 38% yield to give 2,4-diamino-5,6,7,8-tetrahydroquinazoline (**2**). Previous routes to this compound were from **1** by chlorination and amination and from cyclohexanone and cyanoguanidine by direct fusion (12).



1 2, 38%

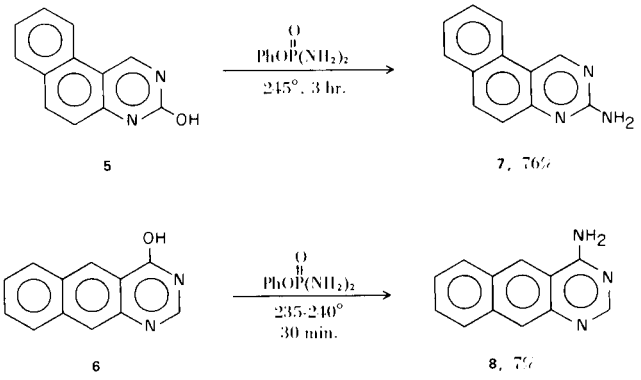
The reaction of 4-hydroxyquinazoline (**3a**) and its 6-chloro and 7-chloro derivatives **3b** and **3c** led to the corresponding 4-aminoquinazolines **4a-4c** in yields of 15% to 47% depending on conditions. In the reaction of **3b** the use of a two-fold excess of phenyl phosphorodiamidate did not seem to affect the yield significantly, whereas the addition of diphenyl ether to the fusion mixture as a diluent caused a marked decrease. The choice of work-up was also an important factor. With **3c** for example, digestion with dilute hydrochloric acid was superior to boiling with *n*-butylamine. Addition of a catalytic amount of ammonium chloride to the fusion mixture resulted in some yield improvement, in accord with earlier reports (7). The presence of halogen atoms on the quinazoline did not appear to be detrimental.



3a, R H 4a, R H, 47%
b, R 7-Cl b, R 7-Cl, 30%
c, R 6-Cl c, R 6-Cl, 45%

Amination was also achieved in two tricyclic ring systems. Reaction of phenyl phosphorodiamidate with 3-hydroxybenzo[*f*]quinazoline (**5**) and 4-hydroxybenzo-[*g*]quinazoline (**6**) afforded the amino derivatives **7** and **8**, respectively. Previous routes to these compounds have been *via* chlorination and amination (13,14) or from the corresponding thiols on treatment with sodium amide (15). The marked difference in yield of **7** and **8** is noteworthy. In the latter instance we believe the low yield to be due mainly to the fact that **6** is extremely high-melting and that a truly homogeneous melt was not obtained.

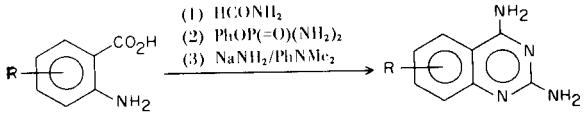
In summary, the ability of phenyl phosphorodiamidate to effect *direct* transformation of hydroxy groups into amino groups in the several ring systems reported here



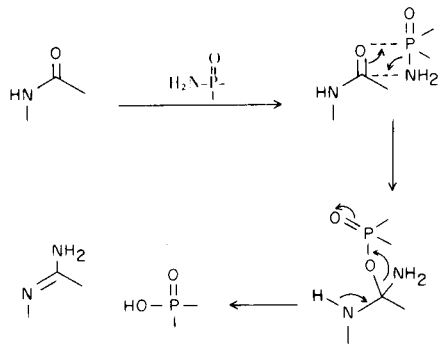
5 7, 76%

6 8, 7%

constitutes a novel and potentially useful functionalization method in condensed pyrimidine chemistry. As an example, coupling of this reaction with our previously described (15) sodium amide amination procedure provides a new approach to the synthesis of 2,4-diaminoquinazolines of biological interest (16) from readily available anthranilic acid starting materials.



SCHEME I



EXPERIMENTAL (17)

2,4-Diamino-5,6,7,8-tetrahydroquinazoline (**2**).

A mixture of **1** (1.65 g., 0.01 mole) (12) and phenyl phosphorodiamidate (1.9 g., 0.011 mole) (11) was heated in an open pear-shaped flask until a clear amber-colored melt was obtained (230°) and a strong odor of ammonia and phenol was detected. After 20 minutes at 235-240° (internal) the mixture was cooled and the solid was pulverized in a mortar and digested with 10% sodium hydroxide at 90°. Filtration, washing with small portions of saturated ammonium chloride (50 ml. total), and recrystallization from acetone (charcoal) gave 0.62 g. (38% yield) of **2** which was indistinguishable from the authentic reference sample (12).

4-Aminoquinazoline (**4a**).

A mixture of 4-hydroxyquinazoline (3.0 g., 0.021 mole) (18) and phenyl phosphorodiamidate (3.9 g., 0.023 mole) (11) in an open pear-shaped flask was immersed into an oil bath pre-heated to 160°. The temperature was raised to 230-235° (internal) and maintained for 30 minutes. After cooling, the fused melt was digested with boiling *n*-butylamine (200 ml.) and the insoluble residue was filtered off. Treatment of the filtrate with decolorizing carbon and concentration to a small volume gave 1.4 g. (47% yield) of small pale-yellow needles, m.p. 269-272° and 275-280° (double m.p.) (lit. (19) m.p. 266-268°).

Anal. Calcd. for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.41; H, 4.69; N, 29.02.

4-Amino-7-chloroquinazoline (**4b**).

A mixture of 7-chloro-4-hydroxyquinazoline (30 g., 0.17 mole) (20) and phenyl phosphorodiamidate (32 g., 0.18 mole) in diphenyl ether (250 ml.) was heated with stirring at 230-235° (internal) for 45 minutes, cooled partially and filtered. The filter cake was washed with dichloromethane to remove most of the diphenyl ether and then digested with 1% hydrochloric acid (1500 ml.). After removal of a small amount of insoluble residue the digest was basified and filtered; yield 9 g. (30%). The analytical sample was prepared by recrystallization from *n*-butylamine; colorless needles, m.p. 305-310° sublimes.

Anal. Calcd. for $C_8H_6ClN_3$: C, 53.50; H, 3.37; Cl, 19.74; N, 23.40. Found: C, 53.31; H, 3.43; Cl, 19.99; N, 23.36.

4-Amino-6-chloroquinazoline (**4c**).

A mixture of 6-chloro-4-hydroxyquinazoline (1.0 g., 0.0055 mole) (20), phenyl phosphorodiamidate (1.0 g., 0.0058 mole), ammonium chloride (50 mg.), and diphenyl ether (20 ml.) was heated at 245-250° for 1 hour and worked up as in the preceding experiment; yield 0.45 g. (45%), m.p. 340-345° dec. (*n*-$BuNH_2$).

Anal. Calcd. for $C_8H_6ClN_3$: C, 53.50; H, 3.37; Cl, 19.74; N, 23.40. Found: C, 53.19; H, 3.18; Cl, 19.60; N, 23.20.

3-Aminobenzo[*f*]quinazoline (**7**).

A mixture of 3-hydroxybenzo[*f*]quinazoline (1.0 g., 0.0051 mole) (13), phenyl phosphorodiamidate (2.0 g., 0.012 mole), and diphenyl ether (100 ml.) was heated for 3 hours at 245° (internal). After cooling to room temperature the mixture was filtered. Dilution of the filtrate with dichloromethane (100 ml.) and passage of dry hydrogen chloride gas through the solution caused precipitation of **7**·HCl as a pale yellow solid (0.9 g., 76%). Treatment of this material with sodium hydroxide liberated the free base **7**, which was indistinguishable from the authentic reference sample (13).

4-Aminobenzo[*g*]quinazoline (**8**).

A mixture of 4-hydroxybenzo[*g*]quinazoline (10 g., 0.056 mole) (14), phenyl phosphorodiamidate (15 g., 0.087 mole), and diphenyl ether (150 ml.) was heated for 1 hour at 240-245° (internal) and worked up as in the synthesis of **4b**; yield 0.7 g. (7%). The identity of **8** was confirmed by comparison with a reference specimen (14).

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(17) Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in potassium chloride disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Analytical samples were dried at 70-100° (0.05 mm.). Melting points were taken in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Massachusetts) at a heating rate of 2°/min. and are uncorrected. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tennessee and by Werby Laboratories, Boston, Massachusetts.

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