

Quinazolines. IX. Direct Amination *via* the Chichibabin Reaction (1)

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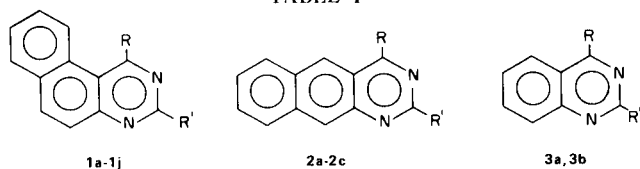
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Condensed 2-amino-, 4-amino-, and 2,4-diaminopyrimidines are prepared most commonly *via* one of several general routes. In one of these, the corresponding hydroxy compound is treated with phosphorus oxychloride and the resultant chloro derivative is allowed to react with ammonia (2). Alternatively, the hydroxypyrimidine can be thiated with phosphorus pentasulfide followed either by S-methylation with dimethyl sulfate and amination (3a) or by direct amination (3b). Unfortunately, chlorination and thiation reactions of condensed hydroxypyrimidines are not always successful, especially when one amino group is already present on the pyrimidine ring. Furthermore, amination often requires high temperature and pressure as well as stringent exclusion of moisture. A different strategy obviating these difficulties to some degree involves the use of pyrimidine precursors already containing potential amino groups in place. Examples of this approach include the condensation of anthranilaldehydes or anthranilonitriles with formamide,

cyanamide, or guanidine (2f,4) and the thermal cyclization of  $N^1,N^5$ -bis(2-naphthyl)biguanides to 1,3-diaminobenzo[*f*]quinazolines (5a,b). In the present paper we should like to call attention to the potential synthetic utility of still another approach, involving the use of the Chichibabin reaction to effect direct amination in condensed pyrimidine ring systems.

Although it has been used extensively with pyridines, quinolines, and isoquinolines (6,7) and has been the subject of spirited mechanistic controversy (8), the Chichibabin reaction has enjoyed scant recognition as a method of amination of monocyclic and polycyclic pyrimidines. Otiai and Karii (9a) reported in 1939 that treatment of 4-methylpyrimidine with sodium amide in decalin affords a mixture of 2-amino-4-methylpyrimidine and 2,4-diamino-6-methylpyrimidine, together with two other unidentified products. More recently the reaction of quinazoline has been claimed to give 4-aminoquinazoline (9b) or 2,4-diaminoquinazoline (9c), and an unusually

TABLE I



Starting Material	Conditions °C/hours	Product	% Yield
<b>1a</b> (R = OH, R' = H)	120/1.5	<b>1b</b> (R = OH, R' = NH <sub>2</sub> )	96 (a)
<b>1c</b> (R = H, R' = OH)	140/4	<b>1d</b> (R = NH <sub>2</sub> , R' = OH)	70
<b>1e</b> (R = NH <sub>2</sub> , R' = H)	115/4.5	<b>1f</b> (R = R' = NH <sub>2</sub> )	93 (a)
<b>1g</b> (R = H, R' = NH <sub>2</sub> )	130/4	<b>1f</b>	65
<b>1h</b> (R = SH, R' = H)	100/0.1	<b>1e</b>	65 (a)
<b>1h</b>	120/4	<b>1f</b>	51
<b>1i</b> (R = H, R' = SH)	145/4.5	<b>1f</b>	40
<b>1j</b> (R = NH <sub>2</sub> , R' = SH)	140/4	<b>1f</b>	76 (a)
<b>2a</b> (R = SH, R' = H)	112/3	<b>2b</b> (R = NH <sub>2</sub> , R' = H)	30
<b>2a</b>	120/4.5	<b>2c</b> (R = R' = NH <sub>2</sub> )	43
<b>3a</b> (R = SH, R' = H)	125/4.5	<b>3b</b> (R = R' = NH <sub>2</sub> )	71

(a) Aminations performed with commercial sodium amide; see reference (14).

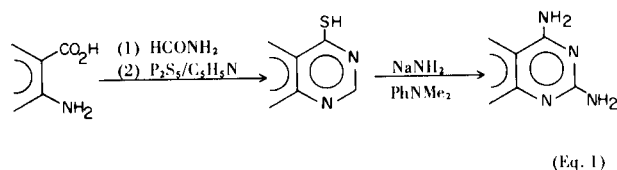
facile amination 1-alkyl-1*H*-benzo[*de*]quinazolines at the 2-position has been described (9d). Insofar as we know, however, no Chichibabin reactions have ever been reported with fully aromatic polycyclic pyrimidine ring systems of more than two rings. Moreover, Chichibabin reactions have not been investigated with quinazolines or other condensed pyrimidines containing a polar substituent such as amino, hydroxy, or mercapto at the 2-position.

The results of eleven Chichibabin reactions carried out in this study are summarized in Table I, and a general procedure is given in the Experimental section.

It is of interest to note that 1-hydroxybenzo[*f*]quinazoline (**1a**) and 1-aminobenzo[*f*]quinazoline (**1e**) were somewhat more reactive than the corresponding 3-isomers **1c** and **1g**. This may be due either to a steric effect or to variations in charge distribution on the pyrimidine ring as a function of the nature and point of attachment of the polar substituent.

Compounds containing a mercapto function on the pyrimidine moiety provided particularly noteworthy results, in that the difference in ease of replacement between hydrogen and a mercapto group permitted selective monoamination to be carried out under suitable experimental conditions. Thus, 1-mercaptobenzo[*f*]quinazoline (**1h**) could be transformed exclusively into **1e** after a few minutes at 100°, whereas heating at 120° for 4 hours led to 1,3-diaminobenzo[*f*]quinazoline (**1f**) as the sole product. Similarly, reaction of the linear isomer 4-mercaptobenzo[*g*]quinazoline (**2a**) afforded 4-aminobenzo[*g*]quinazoline (**2b**) after 3 hours at 112° but gave 2,4-diaminobenzo[*g*]quinazoline (**2c**) after 4.5 hours at 120°. Selective monoamination was more difficult to achieve in the benzo[*g*]quinazoline series than in the benzo[*f*]quinazoline series because the time and temperature differentials between monoamination and diamination were considerably greater in the latter instance. Variations in the ease of monoamination and diamination among the several examples of the three ring systems reported here are probably due in part to differences in electron density distribution. Similar arguments have been advanced recently in order to account for reactivity differences among monaza heterocycles in the Chichibabin reaction (10). However, although theoretical calculations of electron densities have been performed for quinazoline (11), comparable data for the benzo[*f*]quinazolines and benzo[*g*]quinazolines have not been reported to date.

The present finding that 2,4-diaminopyrimidine derivatives can be generated *directly* from 4-mercapto precursors in a single operation is of general preparative interest. Anthranilic acids are readily accessible starting materials, and 4-hydroxyquinazolines derived from them by reaction with formamide can usually be thiated in excellent yield. Thus, the three-step sequence summarized



below (Eq. 1) represents a potentially valuable new route to 2,4-diaminoquinazolines and other 2,4-diaminopyrimidine ring systems of biological interest (12).

#### EXPERIMENTAL (13)

##### General Procedure for Chichibabin Reactions.

A 0.5-liter three-neck flask equipped with a magnetic stirrer, gas inlet tube, and air condenser was cooled by means of a Dry Ice/acetone bath and charged with liquid ammonia (50 ml.). The top of the condenser was fitted with a one-way valve to permit venting. A few crystals of ferric nitrate were added, followed by metallic sodium (1 g.) cut into small pieces. When all the sodium had reacted, the ammonia was allowed to evaporate and *N,N*-dimethylaniline (50 ml., previously dried over Linde 4A molecular sieves) was added (14). The compound to be aminated (1 g.) was added to the well-stirred sodium amide suspension, the gas inlet tube was replaced with a thermometer, and the flask was heated for the requisite length of time (Table I). Heating was carried out in an electrically heated oil bath or by means of a thermostatically regulated mantle. At the end of the reaction the mixture was allowed to cool to room temperature and treated successively with solid ammonium chloride (0.5 g.) and, *dropwise* (15), with water (5-10 ml.). The temperature was not permitted to exceed 35° during this process. After 30 minutes of additional stirring the solid was filtered, washed with a little water, rinsed with benzene and dichloromethane, dried under reduced pressure, and recrystallized from a suitable solvent.

##### Source of Starting Materials and Identification of Products.

All the benzo[*f*]quinazolines reported here were available from previous work in this laboratory (2f) and were re-synthesized as necessary. 4-Mercaptobenzo[*g*]quinazoline (**2a**) was prepared by thiation of 4-hydroxybenzo[*g*]quinazoline which was obtained from 3-amino-2-naphthoic acid and formamide (2d, 16). 4-Aminobenzo[*g*]quinazoline (**2b**) and 2,4-diaminobenzo[*g*]quinazoline (**2c**) were identified on the basis of m.p., mixture m.p., and spectral (ir, uv) comparison with authentic samples kindly provided by Dr. S. K. Sengupta of these laboratories, who had prepared them earlier by amination of the corresponding chloro derivatives (16). 4-Mercaptoquinazoline (**3a**) was synthesized according to the literature route (17), and 2,4-diaminoquinazoline (**3b**) was identified by comparison with an authentic specimen obtained *via* dehydrogenation of 2,4-diamino-5,6,7,8-tetrahydroquinazoline (18) or condensation of anthranilonitrile and cyanamide in the presence of pyridine hydrochloride (4d).

#### REFERENCES

(1) This investigation was supported in part by Research Grant C6516 and Research Career Development Award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service. For Paper VIII of this series see reference (5b).

(2a) G. H. Hitchings, E. A. Falco, and K. W. Ledig, U.S. Patent

- 2,945,859 (July 19, 1960) [*Chem. Abstr.*, **54**, 24820 (1960)]; (b) V. Oakes, H. N. Rydon, and K. Undheim, *J. Chem. Soc.*, 4678 (1962); (c) J. K. Horner and D. W. Henry, *J. Med. Chem.*, **11**, 946 (1968); (d) A. Etienne and M. Legrand, *Compt. Rend.*, **231**, 232 (1950); (e) M. Legrand, *ibid.*, **231**, 1318 (1950); (f) A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **31**, 2607 (1966).
- (3a) H. Meerwein, P. Laasch, R. Mersh, and J. Nentwig, *Chem. Ber.*, **89**, 224 (1956); (b) E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 4466 (1951).
- (4a) L. F. Theiling and R. L. McKee, *ibid.*, **74**, 1834 (1952); (b) H. J. Rodda, *J. Chem. Soc.*, 3509 (1956); (c) K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, Y. Baba, and T. Miyadera, *Chem. Pharm. Bull.* (Tokyo), **10**, 865 (1962); (d) A. Rosowsky, J. L. Marini, M. E. Nadel, and E. J. Modest, *J. Med. Chem.*, **13**, 882 (1970).
- (5a) A. Rosowsky and E. J. Modest, *J. Heterocyclic Chem.*, **3**, 387 (1966); (b) A. Rosowsky, K. K. N. Chen, M. E. Nadel, N. Papathanasopoulos, and E. J. Modest, *ibid.*, **9**, 275 (1972) (Paper VIII of this series).
- (6) M. T. Leffler, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N.Y., 1942, pp. 91-104.
- (7) T. Kametani, K. Kigasawa, Y. Iwabuchi, and T. Hayasaka, *J. Heterocyclic Chem.*, **2**, 330 (1965); T. Kametani and H. Nemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1910 (1967); T. Kametani, H. Nemoto, and S. Takano, *ibid.*, **16**, 367 (1968); T. Kametani, H. Nemoto, and S. Takano, *Yakugaku Zasshi*, **88**, 453 (1968) [*Chem. Abstr.*, **69**, 9973 (1968)].
- (8) L. S. Levitt and B. W. Levitt, *Chem. Ind.* (London), 1621 (1963); G. C. Barrett and K. Schofield, *ibid.*, 1980 (1963); H. L. Jones and D. L. Beveridge, *Tetrahedron Letters*, 1577 (1964); R. A. Abramovitch, F. Helmer, and J. G. Saha, *Can. J. Chem.*, **43**, 725 (1965).
- (9a) E. Otiai and M. Karri, *J. Pharm. Soc. Japan*, **59**, 18 (1939) [*Chem. Abstr.*, **33**, 3791 (1939)]; (b) T. Higashino, *Yakugaku Zasshi*, **80**, 245 (1960) [*Chem. Abstr.*, **54**, 13125 (1960)]; (c) S. Skraup, German Patent 958,197 (February 14, 1957) [*Chem. Abstr.*, **53**, 8177 (1959)]; (d) A. F. Pozharskii, I. S. Kashparov, and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, **183** (1968) [*Chem. Abstr.*, **69**, 9996 (1968)].
- (10) W. Adam and A. Grimison, *Tetrahedron*, **21**, 3417 (1965).
- (11) W. L. F. Armarego, in "Fused Pyrimidines: Part I, Quinazolines," D. J. Brown, Ed., Interscience Publishers, New York, N.Y. 1967, p. 14.
- (12) For a review of our recent work in this area see A. Rosowsky and E. J. Modest, *Ann. N.Y. Acad. Sci.*, **186**, 258 (1971).
- (13) Melting points were determined in Pyrex capillary tubes in a modified Wagner-Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938)] or in an electrically heated metal block (Laboratory Devices, Inc., Cambridge, Massachusetts). Ultraviolet spectra were measured with a Cary Model 15 spectrophotometer. Infrared spectra were taken in potassium chloride disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer.
- (14) In four of the experiments reported here (Table I) commercial sodium amide was employed. Satisfactory results were achieved when freshly purchased, freshly opened bottles of sodamide were used. However, prolonged storage on the shelf or in an evacuated desiccator led to extensive deterioration and loss of aminating ability. Inasmuch as the activity of the sodium appears to be of critical importance, it is recommended that freshly prepared rather than commercially obtained material be used.
- (15) Rapid evaporation of excess ammonia occasionally results in splashing and deposition of a sodium mirror on the upper walls of the reaction flask. It is advisable to remove this mirror by manual swirling of the liquid ammonia prior to evaporation and addition of *N,N*-dimethylaniline (see W. R. Brasen and C. R. Hauser, in "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N.Y., 1963, page 587, footnote 7). Failure to remove residual sodium creates a fire hazard if water is employed to terminate the reaction.
- (16) S. K. Sengupta, S. Chatterjee, H. K. Protopapa, and E. J. Modest, *J. Org. Chem.*, **37**, 1323 (1972).
- (17) D. Libermann and A. Rouaix, *Bull. Soc. Chim. France*, 1793 (1959).
- (18) E. J. Modest, S. Chatterjee, and H. K. Protopapa, *J. Org. Chem.*, **30**, 1837 (1965).