

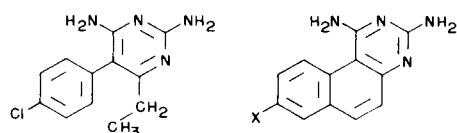
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## Quinazolines. IV. A Novel Synthesis of 1,3-Diamino-benzo[*f*]quinazolines from *N*<sup>1</sup>,*N*<sup>5</sup>-Bis(2-naphthyl)biguanides (1-3)

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Sir:

Many derivatives of 2,4-diaminopyrimidine possess versatile chemotherapeutic properties and can be considered as dihydrofolate reductase inhibitors (4). In a program of design and synthesis of structural analogs of pyrimethamine (I) as potential antifolate, antitumor, and antimalarial agents, we have recently reported the synthesis of 1,3-diaminobenzo-

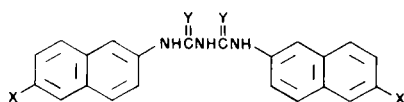


I

II (X = H)

III (X = Cl)

IV (X = Br)



V (X = H, Y = NH)

VI (X = Cl, Y = NH)

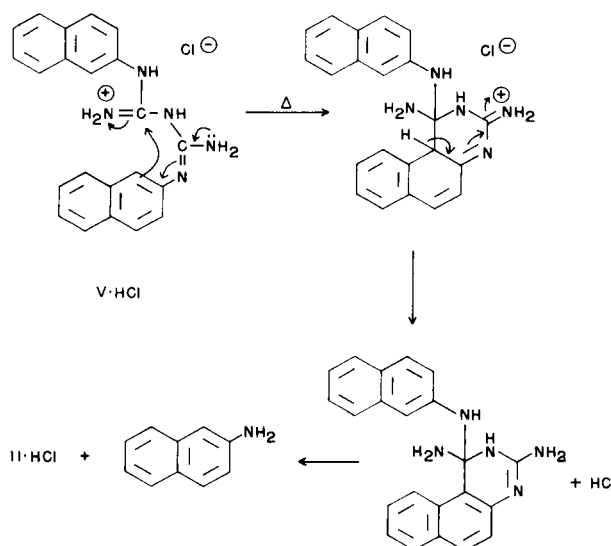
VII (X = Br, Y = NH)

VIII (X = H, Y = S)

[*f*]quinazoline (II) from 1-cyano-2-naphthylamine by several lengthy alternate routes (2,3).

We now wish to report a novel and more convenient synthesis of II and other substituted 1,3-diaminobenzo[*f*]quinazolines by thermal cyclization of bis(2-naphthyl)biguanide hydrochlorides. To our knowledge, this unique intramolecular reaction represents the first *direct* synthesis of a fully aromatic polycyclic 2,4-diaminopyrimidine ring system from a stable precursor already containing all of the necessary atoms in place. Furthermore, this

CHART I



route is a significant improvement over previous methods in terms of overall yield, number of steps, time required, and accessibility of starting materials.

The two-step synthesis of II involved first the reaction of 2-naphthylamine hydrochloride with sodium dicyanamide in refluxing 2-methoxyethanol, followed by brief heating of the resulting *N*<sup>1</sup>,*N*<sup>5</sup>-bis(2-naphthyl)biguanide hydrochloride (V hydrochloride) in diphenyl ether at 250°. 6-Chloro-2-naphthylamine (5) and 6-bromo-2-naphthylamine (6) were likewise converted, via bisarylbiguanide hydrochloride salts VI hydrochloride and VII hydrochloride, into the previously unreported 1,3-diamino-8-chlorobenzo[*f*]quinazoline (III) and 1,3-diamino-8-bromobenzo[*f*]quinazoline (IV), respectively (7).

After investigating several approaches for the preparation of bisarylbiguanide hydrochlorides (8,9), we found that V hydrochloride could be obtained most conveniently by reaction of 2 equivalents of 2-naphthylamine hydrochloride with 1 equivalent of

sodium dicyanamide in refluxing 2-methoxyethanol for 15 minutes. For the synthesis of VI hydrochloride and VII hydrochloride, it was found that 1-butanol, rather than 2-methoxyethanol, was the solvent of choice. Yields of 60-70% were consistently observed, and the products were readily isolated in a high state of purity.

For the preparation of II, a well-stirred suspension of V hydrochloride in diphenyl ether was heated until the appearance of a distinct yellow color was observed at about 240°. The internal temperature was maintained at 250° for 2 minutes (10). After cooling and dilution with 1:1 ethanol-ether, a crude yellow solid was isolated, washed with 1:1 ethanol-ether, and dissolved directly in hot water. Basification and a single crystallization of the precipitated solid from aqueous ethanol gave 25-40% of pure II, m.p. 200-202°. The physical properties of this material were indistinguishable from those of II obtained previously by other methods (2,3). In the same fashion, VI hydrochloride and VII hydrochloride were readily converted into III, m.p. 250-253°, and IV, m.p. 266-267°, respectively, the yields being of the same order as in the preparation of II.

Temperature and heating time appear to be critical factors for the success of this reaction. Thus, when V hydrochloride was heated for less than 2 minutes, or at temperatures below 245°, significant amounts of unchanged V hydrochloride were recovered; on the other hand, when heating was continued much beyond 2 minutes, extensive decomposition occurred and no worthwhile product could be isolated. When the cyclization was attempted with V instead of V hydrochloride, copious evolution of ammonia was observed above 190° and no identifiable product could be recovered.

A plausible mechanism for the conversion of V hydrochloride into II hydrochloride is shown in Chart I. Electrophilic attack at position 1 of the naphthalene ring is consistent with the known tendency of 2-naphthylamine to take part in other types of reactions involving ring closure at this position (11-14). Aromatization of the newly formed pyrimidine ring occurs via the elimination of 2-naphthylamine, which has been recovered from the reaction. The elimination of 2-naphthylamine in preference to ammonia in this case is in sharp contrast to a closely related reaction in which 3-mercapto-1-(2-naphthyl)aminobenzo[f]quinazoline is formed from *N*-(2-naphthyl)thiourea by dry fusion at 240° (14). In

the latter instance, the species actually undergoing cyclization is probably *N*<sup>1</sup>,*N*<sup>5</sup>-bis(2-naphthyl)dithio-biuret (VIII), and hydrogen sulfide elimination, rather than 2-naphthylamine elimination, is favored in the aromatization step.

The present synthesis of substituted 1,3-diaminobenzo[f]quinazolines via the corresponding bisarylbisguanide hydrochlorides offers several advantages over our previous methods (2,3). The reaction is rapid, produces clean material, and can be carried out readily on a large scale. Moreover, the need for preparing substituted 1-cyano-2-naphthylamines, which can be a troublesome task in itself, is conveniently avoided. Efforts are currently under way in our laboratory to prepare a number of additional 1,3-diaminobenzo[f]quinazolines for chemotherapeutic evaluation as inhibitors of folic acid metabolic enzymes.

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