PTERIDINES. PART XLII. SYNTHESIS OF SOME BENZO(g)PTERIDINES. A NOVEL AROMATIZATION REACTION[1,2a]

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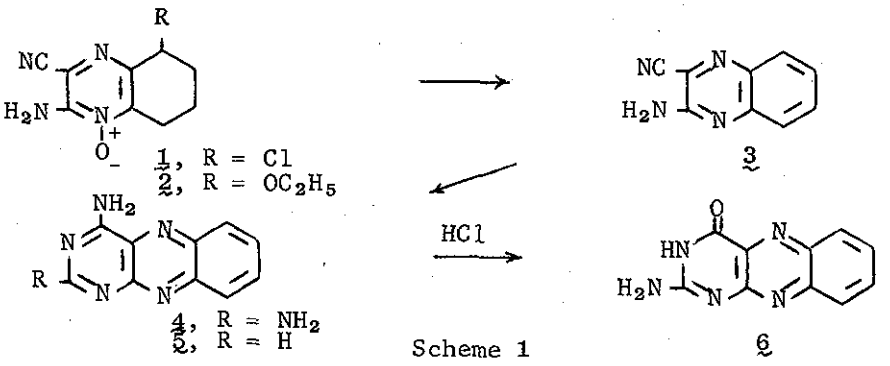
Condensation of 6-chloro-2-oximinocyclohexanone with aminomalononitrile gave 2-amino-3-cyano-5-chloro-5,6,7,8-tetrahydroquinoxaline 1-oxide (1), which upon heating in acetic acid underwent a novel aromatization reaction, with loss of HCl and H_2O, to give 2-amino-3-cyanoquinoxaline (3). An analogous aromatization reaction was observed with 3-amino-2-cyano-5,6-dihydrobenzo(h)quinoxaline 1-oxide (9), which gave 3-amino-2-cyano-benzo(h)quinoxaline (10) upon heating with a trace of HCl or H_2SO_4. These o-aminonitriles were then converted to variously substituted fused pteridine derivatives by conventional cyclization techniques.

In the course of our studies on the unequivocal synthesis of pteridines,[3], we became interested in developing an improved route to 2,4-diaminobenzo(g)pteridines, which have been found to possess interesting biological properties.[4] Benzo(g)pteridines have usually had to be prepared from precursors which already contained a benzene ring.[5] Although a method for dehydrogenation of tetrahydrobenzo(g)pteridines with sulfur has been reported, it has not been applied to substrates carrying amino substituents, and it requires drastic conditions which limit its potential usefulness.[6]

We have developed a new approach to the synthesis of benzo(g)pteridines which is applicable to the preparation of derivatives with almost any pattern of pyrimidine substitution.[7] It involves the intermediate formation of a tetrahydroquinoxaline (or, occasionally, a dihydroquinoxaline) which is aromatized by a novel procedure utilizing the N-oxide functionality, introduced as a concomitant of the initial ring closure reaction. Annelation of the pyrimidine ring then completes the synthesis.

Thus, aminomalononitrile was condensed with 6-chloro-2-oximinocyclohexanone to give 2-amino-3-cyano-5-chloro-5,6,7,8-tetrahydroquinoxaline 1-oxide (1), a reactive intermediate which should be useful for the preparation of derivatives substituted at position 5 through displacement reactions analogous to those which have been employed for 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide.[8] Indeed, the chloro substituent in 1 proved to be so reactive that attempted recrystallization from ethanol gave 2-amino-3-cyano-5-ethoxy-5,6,7,8-tetrahydroquinoxaline 1-oxide (2). Other alcohols reacted similarly but much more slowly because 1 does not dissolve in them as readily.

The reactivity of the 5-chloro substituent has been exploited in a novel aromatization of 1. Simply heating 1 in acetic acid results in loss of HCl and H_2O giving 2-amino-3-cyanoquinoxaline (3) directly. Cyclization of 3 with guanidine or with triethyl orthoformate followed by ammonia gave 2,4-diaminobenzo(g)pteridine (4) and 4-aminobenzo(g)pteridine (5) respectively; hydrolysis of 4 with dilute hydrochloric acid gave benzo(g)pterin (6). These reactions are summarized in Scheme 1.

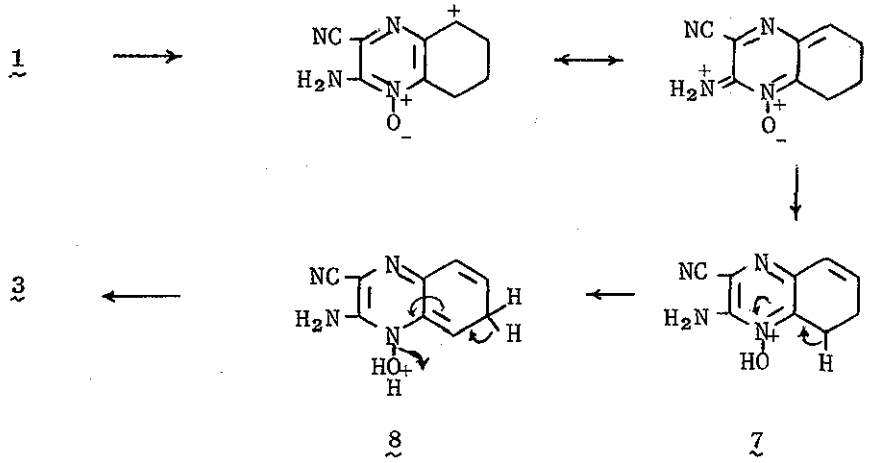


Scheme 1

The aromatization of 1 to 3 requires elevated temperatures; it has not been observed under any conditions at less than 100°. It proceeds upon attempted sublimation of 1 under conditions as mild as 130°/20 mm., although the yield is much better at 180°. Aromatization also proceeds, although more slowly and less cleanly, in refluxing o-dichlorobenzene (b.p. 180°).

Since these conditions are consistent with initial elimination of HCl from 1, followed by prototropic rearrangement and final dehydration, the aromatization reaction was attempted under basic conditions. However, since nucleophiles as weakly basic as ethanol cause displacement of the active chloro substituent in 1, non-nucleophilic bases were investigated. Compound 1 was heated in o-dichlorobenzene (the only solvent found which dissolves 1 without immediate reaction) in the presence of DBU or DABCO, but only traces of 3 and large amounts of intractable decomposition products were formed. Tlc examination of the reaction mixture indicated the probable initial formation of a 7,8-dihydroquinoxaline 1-oxide, suggesting that the first step (elimination of HCl) may have proceeded normally, but that the final dehydration step failed.

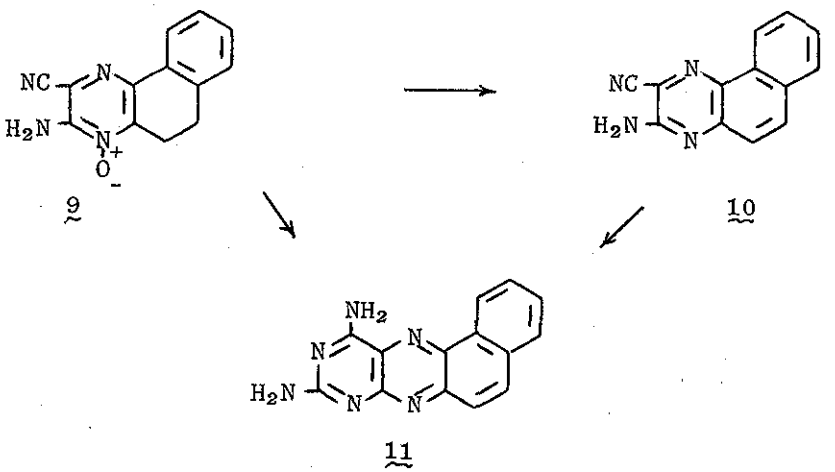
On the basis of these observations, we suggest that the aromatization of 1 to 3 probably proceeds as indicated in Scheme 2. The initial loss of chloride ion from 1 may be assisted by stabilization of the incipient benzylic-like carbonium ion at position 5 by the 2-amino group. In the absence of a nucleophile (e.g., ethanol), subsequent deprotonation would then give 7 and HCl, which undoubtedly promotes the prototropic rearrangement (7 to 8) which preceeds dehydration to 3.



Scheme 2

To gain further insight into the nature of this intriguing aromatization process, 3-amino-2-cyano-5,6-dihydrobenzo(h)quinoxaline 4-oxide (9), a dihydroquinoxaline analogous to the postulated intermediate 7, was prepared by the condensation of amino-malononitrile with 2-oximino-1-tetralone. Although it resisted aromatization under sublimation conditions, and when heated under reflux in acetic acid for 24 hours, addition of a trace of hydrogen chloride or sulfuric acid to the acetic acid solution resulted in immediate aromatization to

give 3-amino-2-cyanobenzo(h)quinoxaline (10). Cyclization with guanidine in the presence of sodium methoxide then gave 9,11-diaminonaphtho(1,2-g)pteridine (11), which could also be prepared directly from 9 under the same conditions.



9 10 11

EXPERIMENTAL

2-Amino-3-cyano-5-chloro-5,6,7,8-tetrahydroquinoxaline 1-Oxide (1): A suspension of 5.0 g (0.025 mol) of 6-chloro-2-oximinocyclohexanone hydrochloride and 6.25 g (0.025 mol) of aminomalononitrile tosylate in 30 ml of isopropanol was stirred for 18 hr at room temperature. Filtration then gave 2.55 g (46%) of a light grey powder, mp 155-158°. The compound decomposed upon attempted recrystallization, but it was sufficiently pure to be used directly in subsequent reactions.

Calcd for $C_9H_9N_4OCl$: 224.046484. Found (ms): 224.046596

2-Amino-3-cyano-5-ethoxy-5,6,7,8-tetrahydroquinoxaline 1-Oxide (2): A solution of 1.13 g (5.0 mmol) of 2-amino-3-cyano-5-chloro-5,6,7,8-tetrahydroquinoxaline 1-oxide in 30 ml of ethanol was heated under reflux for 15 min, filtered hot, and the filtrate cooled and filtered to give 0.81 g (69%) of light yellow flakes, mp 180-183°. The mp was raised to 184-186° by recrystallization from ethanol.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.38; H, 5.99; N, 23.70.

2-Amino-3-cyanoquinoxaline (3): A suspension of 1.97 g of crude 2-amino-3-cyano-5-chloro-5,6,7,8-tetrahydroquinoxaline 1-oxide in 5 ml of glacial acetic acid was heated under reflux for 3 hours. The suspension was cooled, 10 ml of water added, and the mixture filtered to give 0.98 g (65%) of a brown powder which was purified by chromatography on florisil (chloroform) (47%); mp 221-225°, with immediate resolidification and remelting at 400-402°.[9] The same product was obtained as a gold powder in 35% yield by sublimation of 1 at 180°/15 mm.

Anal. Calcd for $C_9H_6N_4$: C, 63.52; H, 3.55; N, 32.93. Found: C, 63.68; H, 3.68; N, 33.09.

2,4-Diaminobenzo(g)pteridine (4): Guanidine hydrochloride (0.14 g, 1.5 mmol) was added to a solution of 0.07 g (3.0 mmol) of sodium in 5 ml of anhydrous methanol, the precipitated sodium chloride was removed by filtration, and 0.17 g (1.0 mmol) of 2-amino-3-cyanoquinoxaline added. The mixture was heated under reflux for 18 hours and then filtered to give 0.16 g (75%) of a yellow microcrystalline powder, mp 365-370°. Recrystallization from trifluoroacetic acid gave the trifluoroacetic acid salt of 4 for analysis.

Anal. Calcd for $C_{12}H_9N_6O_2F_3$: C, 44.17; H, 2.78; N, 25.76. Found: C, 44.22; H, 2.82; N, 25.47.

Benzo(g)pterin (6): A solution of 0.42 g of 2,4-diaminobenzo(g)pteridine in 10 ml of 1 N hydrochloric acid was heated under reflux for 1 hour, cooled and filtered to give 0.40 g (95%) of a yellow-orange powder. The material was purified by recrystallization from DMSO followed by thorough drying at 140°/0.5 mm; mp 411-417°.

Anal. Calcd for $C_{10}H_7N_5O$: C, 56.33; H, 3.31; N, 32.85. Found: C, 56.01; H, 3.55; N, 32.46.

4-Aminobenzo(g)pteridine (5): A suspension of 0.51 g (3.0 mmol) of 2-amino-3-cyanoquinoxaline in 3 ml of triethyl orthoformate and 3 ml of acetic anhydride was heated under reflux for 4 hours, cooled and evaporated to dryness. The residue was stirred with excess methanolic ammonia for 2 hours and the resulting suspension filtered to give 0.32 g (54%) of a brown powder, mp 316-317°. Recrystallization from trifluoroacetic acid gave the ditrifluoroacetic acid salt of 5 for analysis.

Anal. Calcd for $C_{14}H_9N_5O_4F_6$: C, 39.54; H, 2.13; N, 16.51. Found: C, 39.28; H, 2.02; N, 16.44.

3-Amino-2-cyano-5,6-dihydrobenzo(h)quinoxaline 4-Oxide (9): A suspension of 8.75 g (50 mmol) of 2-oximino-1-tetralone[10]

and 12.15 g (50 mmol) of aminomalononitrile tosylate in 50 ml of isopropanol was stirred for 18 hours and the mixture filtered to give 7.01 g (59%) of a tan powder, mp 230-233°. Recrystallization from DMF followed by thorough drying then gave a yellow microcrystalline solid, mp 244-246°.

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.63; H, 4.23; N, 23.52. Found: C, 65.74; H, 4.22; N, 23.79.

3-Amino-2-cyanobenzo(h)quinoxaline (10): A suspension of 0.48 g (2.0 mmol) of 3-amino-2-cyano-5,6-dihydrobenzo(h)-quinoxaline 4-oxide and 0.1 g (1 mmol) of conc. sulfuric acid in 15 ml of acetic acid was heated under reflux for 16 hours. The hot solution was poured over 20 g of ice and the mixture stirred for 15 minutes and then filtered to give 0.32 g (73%) of a yellow solid, mp 239-241° (softens, then resolidifies).[9] The mp was raised to 253-255° by recrystallization from DMF.

Anal. Calcd for $C_{13}H_8N_4$: C, 70.89; H, 3.66; N, 25.44. Found: C, 70.56; H, 3.42; N, 25.63.

9,11-Diaminonaphtho(1,2-g)pteridine (11): Method A. Cyclization of 3-amino-2-cyanobenzo(h)quinoxaline (0.22 g, 1.0 mmol) with guanidine, as described above for the preparation of 4, gave 0.23 g (89%) of a brown powder, mp > 300°, which was purified by dissolution in hot DMSO, reprecipitation with water, and then extraction of the resulting solid first with boiling DMF, then with boiling water, and finally with hot methanol.

Anal. Calcd for $C_{14}H_{10}N_6$: C, 64.11; H, 3.84; N, 32.05. Found: C, 63.88; H, 3.69; N, 31.97.

Method B: Cyclization of 0.48 g (2.0 mmol) of 3-amino-2-cyano-5,6-dihydrobenzo(h)quinoxaline 4-oxide with guanidine, as described above for the preparation of 4, gave 0.24 g (46%) of 11, identical with the material prepared by Method A.

REFERENCES AND NOTES

1. For the previous paper in this series, see E. C. Taylor, J. V. Berrier, A. J. Cocuzza, R. Kobylecki and J. J. McCormack, J. Med. Chem., submitted

2. (a) This work was supported by a grant (#CA12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service; (b) National Science Foundation Fellow, 1967-1971.

3. For leading references, see ref. 1 and preceding papers in this series.

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