259–261 °C (N_2) (lit. mp 230–240 °C,[15] near 250 °C[16]). Preparation according to Krollpfeiffer and Schneider[16] gave a less pure product, which required chromatography on magnesium oxide with chloroform.

Anal. Calcd for $C_{19}H_{12}N_2O$: C, 80.3; H, 4.3; N, 9.8. Found: C, 80.8; H, 4.4; N, 9.4.

Perchlorate and Bromide Salts of Besthorn's Red. A saturated solution of Besthorn's Red in absolute EtOH with 72% aqueous perchloric acid in EtOH gave yellowish crystals, quickly washed with anhydrous ether and dried under vacuum over P_2O_5.

Anal. Calcd for $C_{19}H_{13}ClN_2O_5$: C, 59.3; H, 3.4; N, 7.3. Found: C, 59.0; H, 3.6; N, 7.2.

The IR spectrum (KBr) exhibited broad absorption at 2380 cm^{-1} (highly acidic O–H).

The bromide, prepared by treating Besthorn's Red with 48% hydrobromic acid, had a very similar IR spectrum, with a strong, very broad, O–H stretching mode at 2340 cm^{-1} and a strong O–H bending mode at 690 cm^{-1}.

14-Methoxyimidazo[1,2-*a*:3′,4′-*a*′]diquinolinium (13, X = OMe) Fluoborate. A solution of the methosulfate[15] (0.25 g, 0.61 mmol) of Besthorn's Red in 20 mL of water was extracted several times with $CHCl_3$ until the extracts were no longer red. The yellow aqueous layer was diluted to 50 mL with ethanol, and 1 mL of 50% fluoboric acid was added. Yellow-orange crystals (0.15 g, 65% yield) of 14-methoxyimidazo[1,2-*a*:3,4-*a*′]diquinolinium fluoborate precipitated: mp 222–226 °C, after crystallization from MeOH; UV (MeOH) (log ε) 406 (4.24), 385 (4.28), 368 (sh, 4.14), 349 (sh, 3.91), 313 (sh, 3.81), 297 (sh, 4.20), 292.5 (4.21), 261 (4.42), 256 (sh, 4.41), 246 (4.43), 230 (4.42).

Anal. Calcd for $C_{20}H_{15}BF_4N_2O$: C, 62.2; H, 3.9; N, 7.3. Found: C, 61.8; H, 4.1; N, 7.0.

1-(Methoxy-2-quinolylmethyl)carbostyril (14, X = OMe). A solution of 0.96 g (2.3 mmol) of the methosulfate[16] of Besthorn's Red in 200 mL of water treated with 4 mL of 50% potassium hydroxide solution according to Krollpfeiffer and Schneider[16] gave 300 mg of tan crystals, which after three recrystallizations from methanol (charcoal) gave 66 mg of white crystals: mp 210–212 °C (lit. mp 213.5–214.5 °C); UV (cyclohexane) (log ε) 353 (3.53), 347 (3.58), 335.5 (3.74), 331 (3.73), 318 (3.88), 311 (3.70), 305 (3.69), 297.5 (3.56), 290 (sh, 3.56), 281 (3.96), 271 (3.97), 264.5 (sh, 3.88), 231 (sh, 4.74), 227.5 (4.75) nm.

Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.9; H, 5.1; N, 8.9. Found: C, 75.7; H, 5.3; N, 8.8.

1-(2-Quinolylmethyl)carbostyril (14, X = H). Imidazo[1,2-*a*:3,4-*a*′]diquinolinium sulfate (13, X = H) (622 mg), hydrolyzed according to Brown and White,[6] gave 484 mg (86% yield) of 1-(2-quinolylmethyl)carbostyril (14, X = H): mp 108–109.5 °C [after fusion at 110 °C and recrystallization from pentane, mp 125–128 °C (lit.[6] mp 125 °C)]; UV (cyclohexane) (log ε) 355 (3.62), 348 (3.66), 337 (3.79), 332 (3.77), 323.5 (sh, 3.73), 317 (3.90), 310 (3.71), 304 (3.70), 296.5 (3.56), 290.5 (3.57), 279.5 (4.00), 270 (3.99), 262 (sh, 3.89), 235 (4.77), 226 (4.78) nm.

Registry No. 1, 98779-37-4; 2 (X^- = ClO_4^-), 98779-39-6; 2 (X^- = PF_6^-), 98779-38-5; 3 (X^- = BF_4^-), 98779-75-0; 3 (X^- = ClO_4^-), 98779-74-9; 3 (X^- = I^-), 98779-76-1; 3 (X^- = PF_6^-), 98779-73-8; 4 (X^- = CLO_4^-), 98779-43-2; 4 (X^- = I^-), 98779-40-9; 4 (X^- = PF_6^-), 98779-42-1; 5, 98779-44-3; 6, 98779-45-4; 7 (X^- = BF_4^-), 98779-47-6; 12 (R_2 = Et,R_1 = R_3 = R_4 = R_5 = H,X = S^-), 98779-48-7; 12 (R_4 = Me, R_1 = R_2 = R_3 = R_5 = H,X = S^-), 98779-52-3; 12 (R_2 = Et, R_4 = Me, R_1 = R_3 = R_5 = H, X = S^-), 98779-53-4; 12 (R_2 = Et, R_5 = Me, R_1 = R_3 = R_4 = H, X = S^-, 98779-54-5; 12 (R_2 = Et, R_1 = R3 = R_4 = R_5 = H, X = SMe)·ClO_4^-, 98779-51-2; 12 (R_2 = Et, R_1 = R_3 = R_4 = R_5 = H, X = SMe)·I^-, 98779-49-8; 12 (R_2 = Et, R_4 = Me, R_1 = R_3 = R_5 = H, X = SMe)·I^-, 98779-55-6; 13 (X = O^-), 98779-77-2; 13 (X = S^-), 98779-56-7; 13 (X = H)·Br^-, 98779-57-8; 13 (X = H)·ClO_4^-, 98779-59-0; 13 (X = H)·picrate$^-$, 98779-58-9; 13 (X = OH)·Br^-, 98779-66-9; 13 (X = OH)·ClO_4^-, 98779-65-8; 13 (X = OH)·$MeOSO_3^-$, 98779-67-0; 13 (X = OMe)·BF_4^-, 98779-69-2; 13 (X = SMe)·ClO_4^-, 98779-62-5; 13 (X = SMe)·I^-, 98779-60-3; 14 (X = H), 98779-71-6; 14 (X = OMe), 98779-70-5; 14 (X = SMe), 98779-63-6; benzoyl chloride, 98-88-4; chloroacetic acid, 79-11-8; 11,11′-dithiobis(3-ethyldipyrido[1,2-*a*:1′,2′-*c*]imidazolium bis(fluoroborate), 98800-53-4; 5-ethyl-2-methylpyridine, 104-90-5; 2-picoline, 109-06-8; 3-picoline, 108-99-6; pyridine, 110-86-1; pyridine sulfur trioxide complex, 26412-87-3; quinaldine, 91-63-4; quinoline, 91-22-5; sodium dithionite, 7775-14-6; sulfur dioxide, 7446-09-5.

Supplementary Material Available: Full IR data for all compounds, mass spectra for 1 and 12 (R_2 = Et; R_1 = R_3 = R_4 = R_5 = H; X = S^-), and UV data for most compounds (10 pages). Ordering information is given on any current masthead page.

Synthesis of Quinazoline-2,4,5,8(1*H*,3*H*)-tetrones and Their Amine Nucleophilic Addition Chemistry

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The amination of quinazoline-2,4,5,8(1*H*,3*H*)-tetrones was studied in conjunction with synthetic efforts toward the imidazo[4,5-*g*]quinazoline-4,6,8,9-tetrone system. Under the basic reaction conditions employed, the quinazolinetetrone system possesses a negative charge delocalized into both the pyrimidine and benzoquinone rings. Thus, unfavorable electrostatic effects preclude nucleophilic addition to this system by amines. Activation toward nucleophilic attack was realized by the placement of a 6-acetamido group (1). Even though this system is still anionic under the amination conditions, substitution products were observed under mild conditions. Thus, treatment of 1 with aniline/DMF resulted in the formation of the 8-phenylimino derivative (11) while treatment with methylamine (in water or DMF) resulted in formation of the 6-methylamino 8-methylimino derivative (3). The activating influence of the 6-acetamido group is proposed to involve the contribution of tautomeric species such as $\mathbf{1a}^-$. Nucleophilic attack at either the 8- or 6-position of $\mathbf{1a}^-$ is electrostatically favorable since the negative charge develops at the acetamido oxygen which is removed from the anionic quinazoline nucleus.

Only a few quinazoline-5,8-diones have been reported in the literature[1] whereas imidazo[4,5-*g*]quinazoline-4,9-diones are unknown. Since imidazo[4,5-*g*]quinazolines have been noted to mimic purines in enzymatic reactions,[2]

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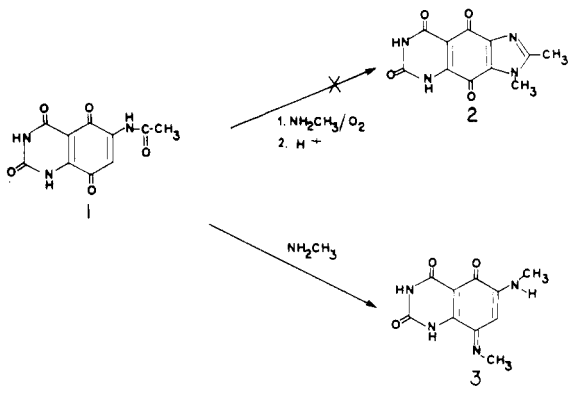
the 4,9-dione derivatives may represent purine mimics possessing some of the properties of benzoquinones. The proposed strategy for elaborating these derivatives was to annelate the imidazo ring to an appropriately functionalized quinazoline-5,8-dione. Thus, subjecting 6-acetamidoquinazoline-2,4,5,8-(1*H*,3*H*)-tetrone (1) to oxidative amination[3] and cyclization was to provide 2,3-dimethylimidazo[4,5-*g*]quinazoline-4,6,8,9-(3*H*,5*H*,7*H*)-tetrone (2) (eq 1). As indicated in eq 1, the only observed product



(1)

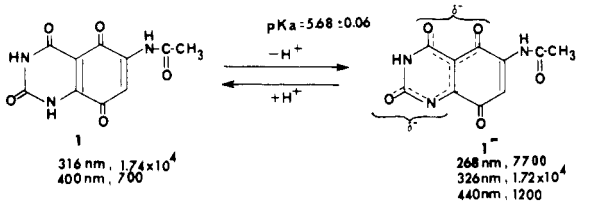
was 6-(methylamino)-8-(iminomethyl)quinazoline-2,4,5-(1*H*,3*H*)-trione (3). Typically, quinones react with amines to afford Michael addition products,[4] but carbonyl addition products are observed with sterically hindered benzoquinones.[5] Queries were thus posed concerning the factors that facilitate nucleophilic addition at the 8-carbonyl center of 1. In this report, the reactivity of 1 with amines is examined and these factors are discussed.

Results and Discussion

Synthesis of 1 was carried out as outlined in Scheme I. The methodology employed permitted the introduction of substituents at the 6-position of the quinazoline ring and the convenient elaboration of the fused benzoquinone ring.

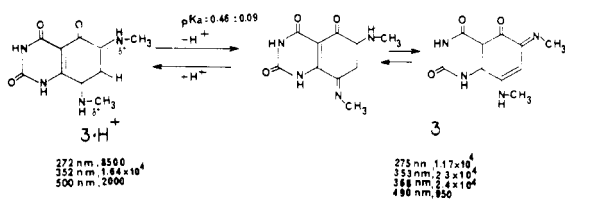
4 was prepared as previously reported[6] in three steps, starting with gentisic acid. Catalytic reduction of 4 to the amino carboxamide (5) was followed by annelation of the pyrimidine[7] ring to provide the quinazoline system 7. Nitration of 7 provided a single mononitrated product in quantitative yield. Assignment of the structure of this product as the 6-nitro derivative (8) is based on the electrophilic substitution chemistry of quinazolines cited in the literature. Theoretical considerations[8] of electrophilic substitution on the quinazoline ring predict that the order of reactivity is at positions 8 > 6 > 5 > 7. The electrophilic substitution chemistry[9] of quinazoline-2,4-(1*H*,3*H*)-diones indeed evidences this reactivity order with 8- and/or 6-substitution as the major feature. The lack of substitution chemistry at the 7-position was taken advantage of when elaborating the benzoquinone ring. After reduction of 8 and acetylation to provide 9, oxidative demethylation with fuming nitric acid afforded 1 in high yield. In as yet unreported work, analogues of 7 bearing 6-bromo or 6-trifluoroacetamido substitutents could be oxidized in a similar fashion. When 1 was treated with bromine in refluxing acetic acid, both substitution at the 7-position and deacetylation occurred to afford 10. Given the unreactivity of the 7-position toward electrophilic attack, particularly in the quinone derivative, a likely mechanism involves addition of Br_2 to the 6–7 double bond followed by elimination of HBr. The unreactivity of 10 with amines provided insights into the role of the 6-acetamido group in 8-carbonyl additions.

Amination Studies of 1 and 10. Spectrophotometric pK_a determinations[10] indicate that 1 and 10 are almost completely ionized under basic amination conditions. The pK_a value of 5.68 measured for 1 is attributed to dissociation of the N(1) proton (eq 2). This pK_a value is much



(2)

lower than the value of 10.6 measured for N(1) proton dissociation from 3-methylquinazoline-2,4-(1*H*,3*H*)-dione.[11] The large pK_a difference is attributed to delocalization of the anion into the electron-deficient benzoquinone ring, 1^- in eq 2. Likewise, N(1) proton dissociation from 10 possesses the low pK_a value of 5.62 (see the Experimental Section). In spite of the delocalized anion, 1^- was observed to react with amine nucleophiles. Thus, treatment of 1^- with refluxing aerobic 40% aqueous methylamine for 15 min afforded 3 in 56% yield. Alternately, treatment with anhydrous methylamine/DMF afforded 3 after 15 min at room temperature. TLCs of completed reactions on silica gel [butanol–acetic acid–H_2O (5:2:3)] indicated that only 3 was produced. Provided in eq 3 are UV–visible spectral properties of 3 and of its protonated form ($3\cdot H^+$). The



(3)

reaction of 1 with aniline required heating in DMF at reflux for 2 min. The 8-iminophenyl derivative of 1 (11) was isolated from this reaction in 20% yield. A TLC of the completed reaction on silical gel [butanol–acetic acid–H_2O (5:2:3)] indicated only the presence of 11. Provided in eq 4 are UV–visible spectral properties of 11

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(2) Leonard, N. J. *Acc. Chem. Res.* **1982**, *15*, 128.

(3) Oxidative amination is proposed to be a multistep process involving a Michael addition to the quinone followed by enolization to provide an aminated hydroquinone that then oxidizes under the aerobic reaction conditions. Finley, K. T. In "The Chemistry of the Quinonoid Compounds", Part II; Patai, S. ed.; Wiley Interscience: New York, 1974; p 877.

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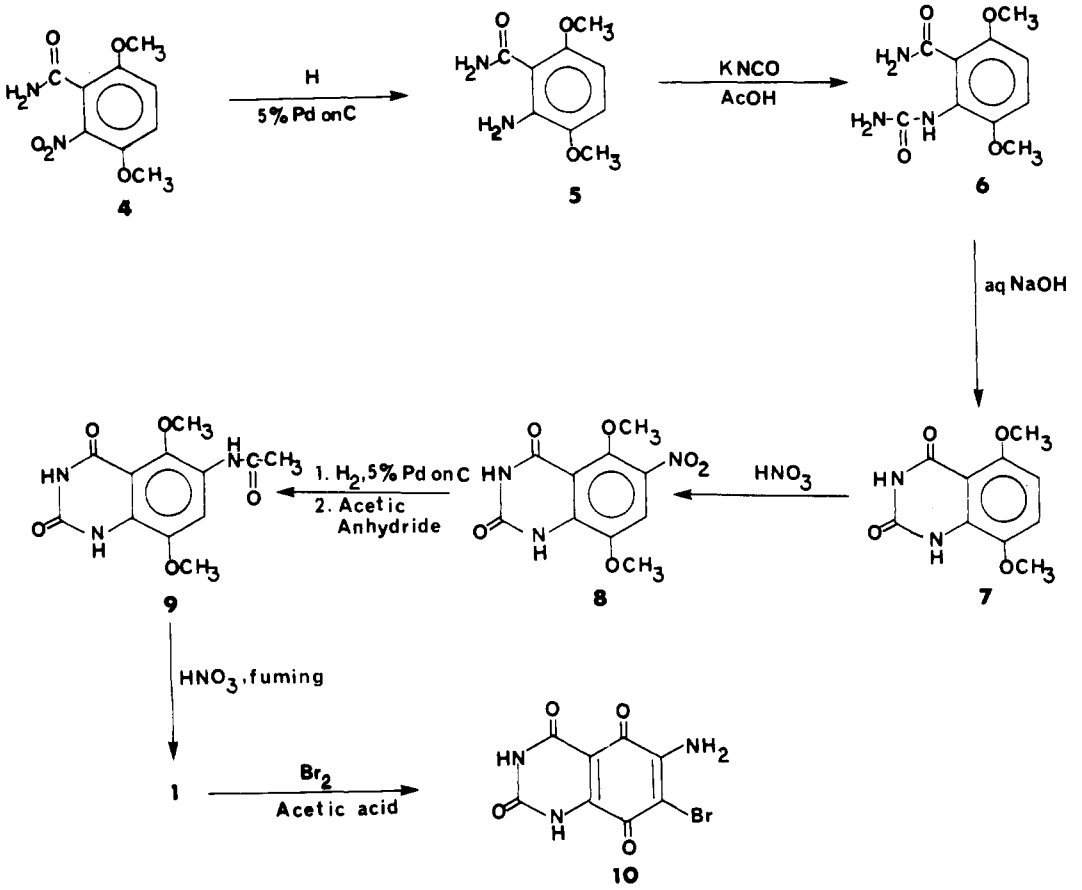
(8) Dewar, M. J. S.; Maitlis, P. M. *J. Chem. Soc.* **1957**, 2521.

(9) Armarego, W. L. F. In "Fused Pyrimidines, Part I, Quinazolines"; Brown, D. J.; Ed.; Interscience: New York, 1967; p 132.

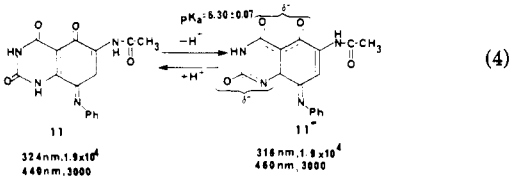
(10) Spectrophotometric pK_a values were determined in aqueous buffer (μ = 1.0, KCl) at 30 ± 0.2 °C.

(11) Gut, J.; Prystas, J.; Jonas, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1961**, *26*, 944.

Scheme I



and of its anionic form (11^-). When **10** was subjected to the amination conditions described above, no reaction was observed.



(4)

While elemental analyses, ^{1}H NMR, ^{13}C NMR, and mass measurements are consistent with the structural assignment for **3** and **11**, they do not exclude the 5-imino isomers as possibilities. However, nucleophilic attack at the 5-carbonyl center or the 7-position of 1^- seem unreasonable since a second anion will develop in the quinazoline ring during either process. The evidence for 8-carbonyl addition was obtained from cyclization attempts and the pK_a measurements provided above. If 5-imino derivatives are actually formed, it should be possible to cyclize these to imidazo[4,5-*f*]quinazolines. Reduction of **3** to its hydroquinone derivative and fusion with urea did not result in cyclization. Neither did reduction of **11** followed by treatment with refluxing 4 N HCl.[12] Inspection of the structure assigned to **3** reveals the presence of a potentially basic extended amidine system (eq 2). Indeed **3** is a weak base possessing an acid dissociation constant (pK_a) of 0.46. Extended amidine resonance may also explain the lack of observable acid-catalyzed imine hydrolysis. As noted in the Experimental Section, **3** is recrystallized from boiling 4 N HCl. Also, extended amidine resonance will permit rotation about the imine C–N bond; thus the ^{1}H NMR spectrum of **3** in trifluoroacetic acid-d_1 shows only two methyl group resonances. Reaction at the 5-carbonyl center of **1** to provide the 5-imino derivative should significantly increase the pK_a value for N(1) proton dissociation. This assessment is based on the presence of an anion in an extended amidine system and the high pK_a value for proton dissociation from a neutral amidine. The pK_a for N(1) proton dissociation from **11** (eq 4) is only slightly higher than that of **1**, further suggesting imine formation at the 8-carbonyl center.

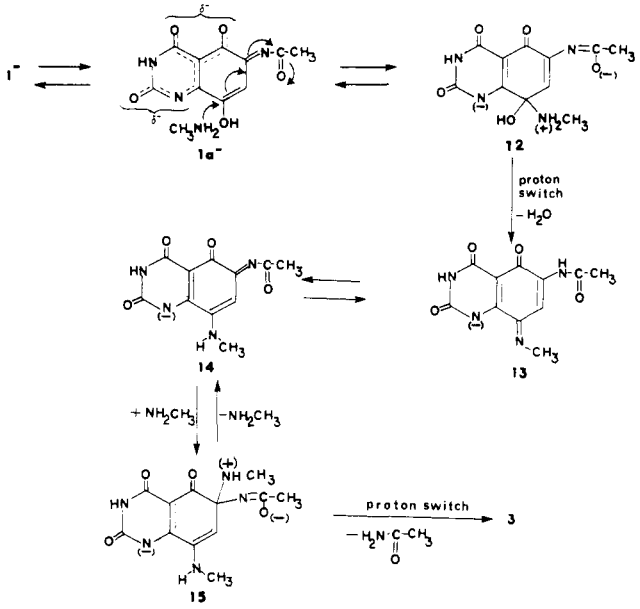
The mechanism of amination is discussed in conjunction with Scheme II. The results cited above indicate that the 6-acetamido group facilitates reactions at the 6- or 8-positions of 1^-. Thus, 1^- readily undergoes amination at these positions and 10^- does not. The role of the 6-acetamido group is best explained by considering the presence of the tautomeric forms $\mathbf{1a}^-$ and **14** (Scheme II). Analogous tautomers have been postulated as contributors to other acetamido-substituted benzoquinones.[13] Nucleophilic attack on $\mathbf{1a}^-$ and **14** affords the dipolar species **12** and **15**, respectively, wherein the negative charge is maximally separated from the ionized quinazoline ring. As with stepwise carbonyl additions,[14] these dipolar intermediates likely undergo a rapid proton switch followed by elimination of water or acetamide to provide the substitution products. Since nucleophilic attack on 10^- will result in an electrostatically unstable dipolar intermediate, amination products are not observed.

Another aspect of the mechanism deserving of comment in Scheme II is the sequence of 8-imino formation followed by displacement of acetamide. Isolation of **13** was not possible, but when aniline was employed as the nucleo-

(12) Conditions are those of the Phillips benzimidazole synthesis: Phillips, M. A. *J. Chem. Soc.* **1928**, 2393.

(13) Carroll, F. I.; Blackwell, J. T. *J. Heterocyl. Chem.* **1969**, *9*, 909.
(14) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705.

Scheme II



phile, only **11** was obtained. Since this weak nucleophile does not go on to displace the acetamido group, the 8-position must be more susceptible to attack. The unreactivity of 10^- also suggests this sequence; if substitution at the 6-position of 1^- occurred first, then 8-iminomethyl formation would not have followed. By invoking the unreactivity of 10^-, it may also be stated that the 6-acetamido group is eliminated as such and not hydrolyzed to the 6-amino derivative first.

It is concluded that the electrostatic effect of the anionic quinazoline ring, in conjunction with the tautomerized 6-acetamido group acting as an electron sink, promotes formation of 8-imino derivatives of **1**. Thus, electrostatic factors, as well as steric factors,[5] can promote imine formation in a benzoquinone derivative. This chemistry precluded the synthesis of **2**; the synthesis of this compound by a different strategy will be discussed in a later report.

Experimental Section

Elemental analyses were performed by MicAnal Laboratories, Tucson, AZ. Uncorrected melting points were determined with a Mel-Temp apparatus. TLCs were run with Merck silica gel 60 (F_{254}) plates. IR spectra were taken as a KBr pellet with a Nicolet MX-1 FT IR spectrophotometer. ^1H and ^{13}C NMR spectra were taken on a Bruker WH-90 and a Varian XL-100 spectrometer. UV and visible spectra were obtained with a Perkin-Elmer 559 UV–visible spectrophotometer. Mass measurements were carried out in the electron-impact mode with a Varian MAT 200 spectrometer. Measurements of pH were made with a Radiometer PHM84 pH meter equipped with a Radiometer GK2401C combination electrode.

All analytically pure compounds were dried over KOH pellets under high vacuum for 24 h. Some of these contained water of crystallization that was calculated from the elemental analyses found.

2-Carbamoyl-3,6-dimethoxyaniline (5). Reduction of **4** (9.4 g, 41.5 mmol), in 200 mL of 95% ethanol, was carried out in the presence of 0.9 g of 5% Pd on charcoal under 50 psi H_2 for 4 h. The reaction mixture was filtered through Celite and then concentrated to ca. 25 mL in vacuo. Crystallization of the product began when this volume was reached and was completed by chilling. The filtered and dried colorless needles were analytically pure: 6.3 g (77%); mp 115–117 °C; TLC [10% ethanol in chloroform] on silica gel, R_f 0.50; IR (KBr) 3404, 1634, 1614, 1554, 1401, 1226 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.13 and 6.78 (2 H, AB syst, J = 8.7 Hz, aromatic protons), 3.73 (6 H, s, dimethoxy), 7.61 and 7.35 (2 H, br s, amide), 6.17 (2 H, s, amine). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.27. Found: C, 54.71; H, 6.16; N, 14.38.

1-Ureido-2-carbamoyl-3,6-dimethoxybenzene (6). Dissolution of 4.4 g (22 mmol) of **5** in a solution consisting of 31 mL of glacial acetic acid and 15 mL of H_2O was followed by portionwise addition of 3.64 g (43 mmol) of potassium cyanate over a period of 1 h at room temperature with stirring. Stirring at room temperature was continued for 12 h, resulting in formation of a microcrystalline mass. Filtration, washing with ethanol, and drying provided a crude yield of 2.0 g (38%). Recrystallization for analysis was carried out from hot water: mp 160–161 °C; TLC [butanol–acetic acid–H_2O (5:2:3)] on silica gel, R_f 0.75; IR (KBr) 3405, 3210, 1666, 1590, 1519, 1480, 1255 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.93 and 6.84 (2 H, AB syst, J = 9.1 Hz, aromatic), 7.31 (3 H, br s, ureido protons), 5.84 (2 H, br s, amide), 3.70 (6 H, s, dimethoxy). Anal. Calcd for $C_{10}H_{13}N_3O_4 \cdot 0.75H_2O$: C, 47.52; H, 5.78; N, 16.63. Found: C, 47.54; H, 5.61; N, 16.35.

5,8-Dimethoxyquinazoline-2,4-(1*H*,3*H*)-dione (7). A solution of 3.47 g (14.5 mmol) of **6** and 11 g of NaOH in 77 mL of H_2O was refluxed for 2 h. Near the end of this time, the sodium salt of the product began to crystallize from the reaction mixture. After chilling for 12 h to complete crystallization, the solids were filtered off and the filtrate was discarded. Dissolution of the sodium salt in 100 mL of hot water was followed by acidification to pH 4 with acetic acid. Upon cooling, **7** crystallized from solution in an analytically pure form: yield 1.56 g (48%); mp dec pt >300 °C; TLC [20% methanol in chloroform] on silica gel, fluorescent blue spot with R_f 0.69; ^1H NMR (Me_2SO-d_6) δ 6.64 and 7.21 (AB syst, J = 9.2 Hz, 2 H, aromatic), 3.80 (3 H, s, methoxy), 3.76 (3 H, s, methoxy); IR (KBr pellet) 3569, 3476, 2941, 1710, 1517, 1405, 1266, 1107 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_2O_4 \cdot H_2O$: C, 49.99; H, 5.03; N, 11.65. Found: C, 49.65; H, 4.91; N, 11.57.

6-Nitro-5,8-dimethoxyquinazoline-2,4-(1*H*,3*H*)-dione (8). Dispersal of 1.0 g (4.5 mmol) of **7** in 16 mL of acetic acid, chilled by means of an ice bath, was followed by the addition of 4 mL of concentrated sulfuric acid. Rapid addition of 10 mL of concentrated nitric acid was then carried out with continued chilling. After it was allowed to stir for 5 min, the reaction was poured over ice, resulting in crystallization of the product as a light yellow solid. Filtration and drying afforded 1.2 g (~100%) of analytically pure **8**: mp dec pt >300 °C; TLC [butanol–acetic acid–H_2O (5:2:3)] on silica gel, R_f 0.72; ^1H NMR (Me_2SO-d_6) δ 7.73 (1 H, s, 7-H), 3.90 (3 H, s, methoxy), 3.95 (3 H, s, methoxy); IR (KBr) 3073, 1714, 1692, 1602, 1531, 1389, 1335, 1227, 1075 cm^{-1}. Anal. Calcd for $C_{10}H_9N_3O_6$: C, 44.95; H, 3.39; N, 15.72. Found: C, 44.87; H, 3.42; N, 15.78.

6-Acetamido-5,8-dimethoxyquinazoline-2,4-(1*H*,3*H*)-dione (9). Reduction of **8** (2.0 g, 7.48 mmol) in 100 mL of H_2O/10 g of KOH was carried out in the presence of 0.5 g of 5% Pd on charcoal under 50 psi H_2 for 30 min. The reduced reaction mixture was filtered through Celite and the filtrate adjusted to pH 6.0 with acetic acid. Addition of 10 mL of acetic anhydride to the filtrate was followed by stirring at room temperature for 2 h. During this time the reaction mixture warmed and a gray solid began to crystallize. Crystallization was completed upon chilling for 2 h in a refrigerator. The product obtained on filtering and drying was analytically pure: 1.41 g (65%); mp 285–290 °C dec; TLC [butanol–acetic acid–H_2O (5:2:3)] on silica gel, R_f 0.63; ^1H NMR (trifluoroacetic acid-d_1 with 1 drop of D_2O, against Me_4Si) δ 8.20 (1 H, s, 7-H), 4.09 (3 H, s, methoxy), 4.03 (3 H, s, methoxy), 2.50 (3 H, s, acetamido methyl); IR (KBr) 3421, 3186, 3068, 1726, 1676, 1543, 1393, 1240 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_3O_5 \cdot 0.75H_2O$: C, 49.40; H, 4.66; N, 14.39. Found: C, 49.68; H, 4.58; N, 14.45.

6-Acetamidoquinazoline-2,4,5,8-(1*H*,3*H*)-tetrone (1). Portionwise addition of 1.41 g (4.83 mmol) of **9** to 30 mL of fuming nitric acid was carried out over 10 min at ice temperature. After complete addition the reaction was stirred at ice temperature for 30 min and then poured over cracked ice. Crystallization of the product was complete in 2 h. Filtration and drying afforded 0.92 g (76%) of an orange solid. Recrystallization for analysis and spectral studies were carried out from DMF: mp dec pt >300 °C; TLC [butanol–acetic acid–H_2O (5:2:3)] on silica gel, R_f 0.54; ^1H NMR (Me_2SO-d_6) δ 7.95 (1 H, s, 7-H), 2.46 (3 H, s, acetamido methyl); MS (EI mode) m/e 249 (M^+); IR (KBr) 3262, 3094, 1738, 1716, 1704, 1663, 1600, 1490, 1402, 1199 cm^{-1}. Anal. Calcd for

$C_{10}H_7N_3O_5 \cdot 0.75H_2O$: C, 45.72; H, 3.26; N, 15.98. Found: C, 45.81; H, 3.04; N, 15.77.

6-(Methylamino)-8-(methylimino)quinazoline-2,4,5-(1*H*,3*H*)-trione (3). Addition of 0.19 g (0.76 mmol) of 1 to 5 mL of 40% aqueous monomethylamine was followed by heating at reflux for 15 min. After the reaction mixture was chilled for 1 h, the red product was filtered off and washed with water and then methanol. Recrystallization from 4 N HCl afforded fibrous red crystals: 0.10 g (56%); mp 220–250 °C with evolution of gas; TLC [butanol–acetic acid–H_2O (5:3:2)] on silica gel, R_f 0.22 as a red spot; ^1H NMR (trifluoroacetic acid-d_1 with 1 drop of D_2O against Me_4Si) δ 6.00 (1 H, s, 7-H), 3.44 and 3.37 (6 H, two s, aminomethyl and iminomethyl, no assignments made); ^{13}C NMR (trifluoroacetic acid-d_1 with 1 drop of D_2O, against Me_4Si) δ 158.8, 145.8, 138.0, 137.2, 136.6, 136.1, 90.2, 72.1 (no assignments made), 16.1 and 14.7 (methyl groups); MS (EI mode) m/e 234 (M^+), 203 ($M^+ - CO$), 190 ($M^+ - HN{=}C{=}O$), 178 ($M^+ - HC{\equiv}CNHCH_3$); IR (KBr) 3232, 1641, 1635, 1596, 1525, 1499, 1464, 1413 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_4O_3 \cdot 1.25H_2O$: C, 46.78; H, 4.90; N, 21.81. Found: C, 46.75; H, 4.44; N, 21.44.

8-(Phenylimino)-6-acetamidoquinazoline-2,4,5-(1*H*,3*H*)-trione (11). A mixture consisting of 200 mg (0.80 mmol) of 1, 2.0 g of aniline, and 10 mL of DMF was heated at reflux for 2 min. Upon cooling to room temperature, the volume of the reaction mixture was diluted to 50 mL with water. After chilling for 12 h, this mixture yielded red crystals that were filtered and recrystallized from ethanol: yield of copper-colored flakes 51.5 mg (20%); dec pt >250 °C; TLC [butanol–acetic acid–H_2O (5:2:3)] on silica gel, R_f 0.51; ^1H NMR (Me_2SO-d_6) δ 11.18 and 9.57 (3 H, two br s, N(1)-H, N(3)-H, and amide NH, no assignments made), 7.86 (1 H, s, 7-H), 7.56–6.95 (5 H, complex m, phenyl), 2.11 (3 H, s, methyl of 6-acetamido group); IR (KBr) 3445, 3312, 1733, 1696, 1493, 1396 cm^{-1}; MS (EI mode) m/e 324 (M^+), 282 ($M^+ - HN{=}C{=}O$). Anal. Calcd for $C_{16}H_{12}N_4O_4 \cdot 2.5H_2O$: C, 52.03; H, 4.64; N, 15.16. Found: C, 51.94; H, 3.19; N, 15.02. The percentage of hydrogen is seen to deviate widely.

6-Amino-7-bromoquinazoline-2,4,5,8-(1*H*,3*H*)-tetrone (10). A mixture of 0.107 g (0.43 mmol) of 1 and 1.0 mL of bromine in 20 mL of acetic acid was heated at reflux for 5 min. Upon cooling of the reaction to room temperature, the purple precipitate was filtered off and washed with diethyl ether: yield of **10** as an analytically pure purple microcrystalline solid 0.10 g (87%); mp dec pt >300 °C; TLC [butanol–acetic acid–H_2O (5:2:3)] on silica gel, R_f 0.51; IR (KBr) 3174, 1754, 1710, 1591, 1502, 1387 cm^{-1}; MS (EI mode) m/e 287 ($M^+ + 2$), 244 ($M^+ + 2 - O{=}C{=}NH$), 206 ($M^+ - HBr$). Anal. Calcd for $C_8H_4BrN_3O_4$: C, 33.58; H, 1.40; N, 14.67. Found: C, 33.50; H, 1.40; N, 14.57. pK_a for N(1) proton dissociation is 5.62 ± 0.08. UV data λ_{max}, nm (ϵ): (**10**) 286 (1×10^4), 326 (1.66×10^4), 508 (1200), (**10**$^-$) 274 (1.3×10^4), 350 (2.3×10^4), 480 (690).

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Proton-Ionizable Crown Compounds. 2. Synthesis, Complexation Properties, and Structural Studies of Macrocyclic Polyether–Diester Ligands Containing a 4-Hydroxypyridine Subcyclic Unit‖

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A series of macrocyclic polyether–diester ligands containing a proton-ionizable 4-hydroxypyridine subcyclic unit has been prepared. These new macrocyclic ligands form stable complexes with both alkylammonium perchlorate salts and with alkylamines. The crystal structure for one of these complexes with an alkylamine shows that the hydroxy proton has been donated to the amine with the resultant formation of a 4-pyridone unit. Chiral dimethyl- and diphenyl-substituted macrocycles containing the 4-hydroxypyridine subcyclic unit exhibit chiral recognition for the enantiomers of 2-(1-naphthyl)ethylamine and their hydrogen perchlorate salts.

We are interested in the design of host macrocycles which show selectivity toward guest molecules and ions, especially those with enantiomeric properties. An important aspect of such design is the creation of host molecules capable of exchanging protons on the host for the guest ions of interest at membrane interfaces. Such capability could lead to the design of selectivity into an appropriate membrane system making continuous proton-coupled ion transport possible. The feasibility of proton-coupled transport of alkali metal cations by calixarenes has been shown,[1] and selectivity for Cs^+ over other alkali cations in mixtures of these has been demonstrated.[2]

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