torial OH group is only 3.0 Å, making a correlation possible. No information regarding the helicity of the triene can be obtained, based upon the interatomic distances derived from molecular mechanics calculations.[4]

Summary. The presented two-dimensional NOE experiments establish the first direct experimental evidence for the existence of two groups of conformations of P_3 in solution, i.e., *tZc* and *cZc*. This is in contrast to earlier interpretations based on UV and CD data[5] but is in agreement with molecular mechanics calculations.[4] Therefore, the chemistry of P_3 is determined by a complicated conformational equilibrium, which can be important with regard to the explanations for the observed wavelength effect in the photochemistry of P_3.[2]

Acknowledgment. This research was supported by Grant No. DK00709, National Institute of Diabetes and Digestive and Kidney Research. We express our appreciation to Molecular Design Ltd. for the generous donation of computer software and to J. Ralph of the U.C. Berkeley NMR facility for many discussions and helpful suggestions.

Registry No. Previtamin D_3, 1173-13-3.

Synthesis and Some Properties of 11,12-Diaminodibenzo[*b*,*g*][1,8]naphthyridine

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In a recent series of papers a number of "proton sponges" have been studied with particular emphasis on their kinetic versus thermodynamic acidities.[1] In this paper we present the synthesis and pK_a determination of a novel heterocycle containing the elements of a "proton sponge". With this research, we wanted to ascertain the effect of electron-withdrawing functional groups (C=N) and steric crowding (two peri hydrogens) on the proton chelating moiety consisting of two 1,5 coplanar and rigidly disposed amino groups. Whereas we did not succeed in the preparation of a tetramethylated, exact equivalent to the 1,8-diaminonaphthalene archetype, we did prepare a desmethyl heterocycle, which is the subject of this report. We also report on the preparation of *p*-phenylenediaminobis(cyanoacrylonitrile) by a double barrel Curtius-type rearrangement.

Syntheses and Discussion

The title compound was prepared in an economical four-step sequence from readily available starting materials as shown in Scheme I. In the scheme, five steps are shown, but in fact steps c and d are carried out in a one-pot procedure without purification of the vinyl azide. The first two steps are based on work of Moore[2] but with improvement in yield. The Curtius-type rearrangement was published on a similar system[3] and in our hands proceeded efficiently, affording the aniline-trapped product in ~70% yield. Finally, the acid-catalyzed ring closure occurred smoothly at room temperature.

To test if our synthetic scheme was a general method to build up aza analogues of the acenes, we set out to prepare a tetraazaheptacene as shown in Scheme II.

The preparation of compound **3** was described by Moore and Robello[2] and, in our hands, the yields were found to vary over a wide range.[4]

We were able to show through the usual analytical techniques that molecule **5** had formed (even though mass spectroscopy was in perfect agreement with the proposed structure, elemental analysis results were slightly lower than calculated values for C and N, probably due to the hygroscopic nature of **5**), i.e., the Curtius rearrangement had taken place as expected. Unfortunately we have not been able to find conditions to afford the desired azaheptacene in isolable form. Changes in acid, solvent, and temperature did not yield material devoid of nitrile stretching mode absorption (2190 cm^{-1}) in the infrared. From this result we concluded that a polymer based on reaction of intermediate compound **4** with *p*-phenylenediamine was not going to be convertible to a polymer analogous to the Moore–Robello system.[5]

The title compound was isolated in the form of a yellow, microcrystalline powder containing one molecule of water. Double sublimation produced a yellow powder that still contained 0.4 molecules of water per formula unit, as determined by elemental analysis. The water of hydration is not detectable by mass spectroscopy. The compound is soluble in most polar organic solvents and THF (tetrahydrofuran) and essentially insoluble in nonpolar solvents. The pK_a was determined (spectrophotometrically)[6] to be 3.3 ± 0.2 in 80% (v/v) DMSO (dimethyl sulfoxide)/water. This compares with a pK_a value of 3.3 ± 0.2 for 9-aminoacridine (4.52 for 9-aminoacridine in water[7]), 2.2 ± 0.2 for 1,8-diaminonaphthalene (4.61 for 1,8-diaminonaphthalene in water[1]), and 12.34 for *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene in water.[1] As can be seen, the title compound is actually a relatively weak base with a pK_a identical with that of 9-aminoacridine. This result could imply that the protonation site of the title compound and 9-aminoacridine is actually the heterocyclic nitrogen. It is possible that the tetramethyl derivative will be a stronger base.[8] So far all attempts to methylate [CH_3I, $(CH_3O)_2SO_2$] compound **1** have failed. Either no methylation was observed or, under more vigorous conditions, only noncharacterization reaction mixtures were obtained.

It has not escapted our notice that the structural features of the title compound could have important implications in regard to (a) internucleotide intercalation into

(1) (a) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. *J. Chem. Soc., Chem. Commun.* **1968**, 723. (b) Alder, R. W.; Goode, N. C.; Miller, N. *J. Chem. Soc., Chem. Commun.* **1978**, 89. (c) Staab, H. A.; Saupe, T.; Krieger, C. *Angew. Chem. Int., Ed. Engl.* **1986**, *25*, 451. Staab, H. A.; Saupe, T.; Krieger, C. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 731. (d) Zirnstein, M. A.; Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 460.

(2) Moore, J. A.; Robello, D. R. *Macromolecules* **1986**, *19*, 2667. (a) We thank Professor Moore for a copy of the relevant experimental section from Dr. Robello's dissertation.

(3) Friedrich, K. *Angew. Chem., Int. Ed. Engl.* **1967**, 6, 959.

(4) Professor Moore's group apparently also had some difficulty in reproducibly obtaining good yields of C but have improved the method and will report their results in a forthcoming full paper; private communication from J. A. Moore (see ref 2, above).

(5) Shi and Wudl (Shi, S.; Wudl, F.) have observed that a polymeric diaminodicyanoethylene, analogous to **5** was obtained from **4** and *p*-phenylenediamine; unpublished, manuscript in preparation.

(6) Hibbert, F.; Hunte, K. P. P. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1995.

(7) Albert, A.; Ritchie, B. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 53 (note 9).

(8) Dr. Anthony W. Czarnik (Ohio State University) suggested to us that "the tetramethyl compound is not likely to be basic at the heterocyclic nitrogen, as the dimethylamino group will likely be orthogonal to the aromatic ring...; however, it may be unusually basic at the exocyclic amine site in much the same way that tetramethyl orthophenylenediamine is". Dr. Czarnik's statement is based on findings of his group that 9,10-diaminoanthracene is a considerably better electron donor than its *N*,*N*,*N*′,*N*′-tetramethyl derivative (Chung, Y.-S.; Duerr, B. F.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.*, in press. We thank Dr. Czarnik for a prepint copy forwarded to us).

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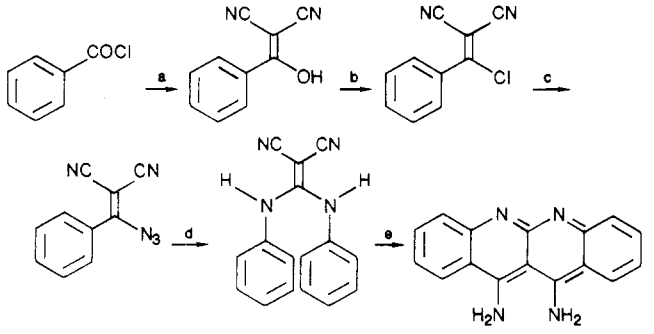
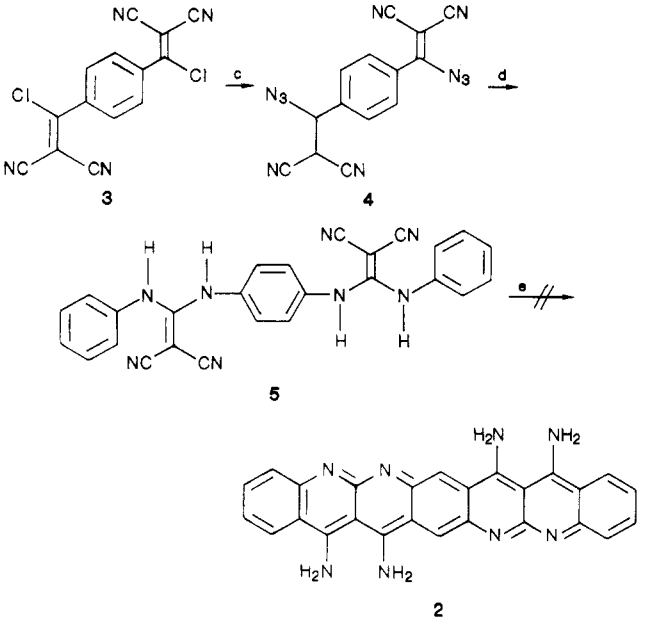
Scheme I[a]



[a] (a) $CH_2(CN)_2$, $BzEt_3N^+Cl^-/OH^-$, CH_2Cl_2; (b) PCl_5/CH_2Cl_2; (c) NaN_3/OMe; (d) $C_6H_5NH_2/\Delta$; (e) CF_3SO_3H/CH_2Cl_2, room temperature.

Scheme II[a]



[a] (c)–(e) as in Scheme I.

nucleic acids and (b) transition-metal chelation that could be pH-controlled via the remote heterocyclic nitrogens. Preliminary results indicate that transition-metal ions such as Ni and copper form insoluble complexes with **1**.

Experimental Section

α-Cyano-β-hydroxycinnamonitrile. Benzoyl chloride (18 g, 130 mmol) and malononitrile (8.46 g, 130 mmol) were dissolved in 200 mL of methylene chloride to which 3.0 g of benzyl triethylammonium chloride in 30 mL of 10 N sodium hydroxide was added dropwise under stirring at 0–5 °C. The mixture was allowed to stir for 1 h. A yellow solid was collected by filtration. The solid, upon washing several times with methylene chloride, was dissolved in 100 mL of water and the resulting solution was washed with 50 mL of ether twice and acidified to pH 2 with 5% aqueous hydrochloric acid. The solid that formed was taken up in dichloromethane, the solution was dried with $MgSO_4$, and the solvent was removed at reduced pressure to give white crystals; yield 57.6%. IR and NMR spectra were found to be the same as in the literature.[2a]

α-Cyano-β-chlorocinnamonitrile. Into a 250-mL two-necked flask equipped with a reflux condenser, a dropping funnel, and a magnetic stirring bar was charged a slurry of 4.0 g (21.3 mmol) of α-cyano-β-hydroxycinnamonitrile and 20 mL of dry dichloromethane. The condenser outlet was connected through a drying tube to a sodium hydroxide trap. The dropping funnel was charged with a solution of 9.0 g (43.2 mmol) of phosphorus pentachloride in 200 mL of dichloromethane. The phosphorus pentachloride solution was added dropwise to the stirred slurry at room temperature and the mixture was heated at reflux for 16 h. The methylene chloride was evaporated under vacuum and phosphorus oxychloride was distilled under reduced pressure. The tan residue was dissolved in a minimum of methylene chloride and passed through at 16 × 25 cm silica gel column using dichloromethane as eluent. Evaporation of the solve at reduced pressure afforded a yellow solid, which was further purified by recrystallization from chloroform/hexanes; yield 65.5%. IR (KBr ν, cm^{-1}): 3070 w (Ar H), 2325 (CN), 1594, 1581, 1550 S, 1485, 1443, 1252 s, 1187, 955, 9315, 773 s, 696 s, 652. ^1H NMR ($CDCl_3$ ∂ rel to TMS): 7.4–8.1 s (Ar CH). Anal. Calcd for $C_{10}H_5ClN_2$: C, 63.60; H, 2.65; N, 14.85. Found: C, 63.61; H, 2.79; N, 14.72.

2-Cyano-3,3-bis(phenylamino)acrylonitrile.[3] To 5 g of α-cyano-β-chlorocinnamonitrile (26.5 mmol) in 25 mL of acetone was added 3 g of sodium azide (46.2 mmol) in 13 mL of water with stirring. The mixture was stirred at 0 °C for 1 h and then 40 mL of cold water was added. A white precipitate was collected by filtration,[9] dissolved in 50 mL of dimethoxyethane, and dried with $MgSO_4$ at 0 °C for 2 h. After filtration, 4.0 g of aniline was added. The mixture was heated to 60–70 °C while being stirred for 90 min. The solvent was then evaporated under vacuum and the resulting solid was washed with cold benzene and dried to give 3.57 g of white solid; yield, 71.5%. IR (KBr ν, cm^{-1}: 3220 s (NH), 3060 w (Ar H), 2220 w, 2190 s (CN), 1630 s, 1600, 1520, 1440, 1380, 1250, 750 s, 700; ^1H NMR (DMF-d_7, ∂ rel to TMS): 10.0 (NH, 2 H), 7.3 (Ar H, 10 H). MS (EI, rel intensity): 260 (M^+, 3.9), 195 (14.7), 194 (100.0), 91 (22.2), 77 (51.7), 66 (31.0), 65 (14.1), 64 (11.1), 51 (37.9), 50 (10.3) m/e. Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.85; H, 4.62; N, 21.54. Found: C, 73.48; H, 4.63; N, 21.37.

11,12-Diaminodibenzo[*b*,*g*][1,8]naphthyridine (1). The above product (2-cyano-3,3-bis(phenylamino)acrylonitrile, 3.52 g) was suspended in 80 mL of methylene chloride. To it, 10 mL of trifluromethanesulfonic acid was added. The mixture was stirred for 40 h at room temperature and then neutralized with 2 N sodium hydroxide solution. The solid that formed was dissolved in 200 mL of methanol and 5 g of sodium hydroxide was added. The mixture was refluxed for 16 h and concentrated to 50 mL. Water, 100 mL, was added to precipitate the products. The solids were taken up in 100-mL portions of methylene chloride and dried with potassium carbonate. After evaporation, 2.38 g of crude product was recovered. The crude product was dissolved in acetone and passed through a 16 × 2.5 cm silica gel column to give 1.12 g of a yellow solid; yield, 31.8%; mp 314–316 °C. IR (KBr ν, cm^{-1}): 3400 s (NH_2), 3060 (Ar H), 1620 s, 1590 s, 1480 s, 1420, 1380, 1350, 1290, 1260, 915 w, 850 w, 750 s; ^1H NMR (DMSO-d_6, ∂ rel to TMS): 8.17 (d, 1 H), 7.51 (t, 1 H), 7.38 (d, 1 H), 7.14 (t, 1 H). ^{13}C NMR (DMF-d_7, ∂ rel to TMS): 161.1 (93), 151.7 (284), 144.8 (80), 131.9 (768), 124.0 (749), 122.1 (100), 121.2 (804), 117.6 (498), 96.4 (211). MS (EI, rel intensity): 261 (M^+ + 1, 63), 260 (M^+, 100) m/e. Anal. Calcd for $C_{16}H_{12}N_4 \cdot H_2O$: C, 69.06; H, 5.03; N, 20.14. Found: C, 69.01; H, 4.62; N, 19.83. (After two sublimations: Anal. Calcd for $C_{16}H_{12}N_4 \cdot (H_2O)_{0.4}$: C, 71.86; H, 4.79; N, 20.96. Found: C, 71.86; H, 4.82; N, 20.98.)

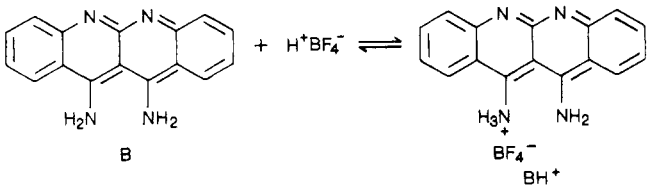
***p*-Phenylenediamino-3,3′-bis(2-cyanoacrylonitrile) (5). Method 1.** An acetone solution (20 mL) of α-cyano-β-chlorocinnamonitrile, 1.518 g (8.05 mmol) was mixed with 800 mg of sodium azide (12.70 mmol) in 10 mL of water at 0 °C with stirring. The solution was stirred at 0 °C for 1 h and then 40 mL of cold water was added. A white solid was collected by filtration.[9] The solid was dissolved in 25 mL of dimethoxyethane and dried with $MgSO_4$ for 2 h at 0 °C. After filtration, the solution was added to a solution of 435 mg of *p*-phenylenediamine (4.03 mmol) in 25 mL of dimethoxyethane. The resulting solution was heated to 60–70 °C for 1 h with stirring. The solvent was removed under vacuum. The residue was washed with benzene and methanol to give 2.56 g of a white-grey product (yield, 72%); mp 318 °C. IR (KBr ν, cm^{-1}): 3240 s (NH), 2205 s, 2190 s (CN), 1605 s, 1550 s, 1510 s, 1450 w, 1420 w, 1365 s, 1250 s, 1090 w, 830 w, 750, 690. ^1H NMR (DMF-d_7, ∂ rel to TMS): 10 (NH, 4 H), 7.2 (Ar H, 14

(9) Organic azides are notorious for their shock sensitivity and tend to explode. We therefore *never allowed the filter cake to dry*. Instead, as soon as the filtrate was removed (by suction), the solid residue was dissolved in DME and dried while in solution.

H). MS (EI, rel intensity): 443 ($M^+ + 1$, 4.5), 442 (M^+, 4.7), 377 (12.3), 376 (24.9), 276 (14.7), 275 (32.4), 261 (34.2), 260 (57.1), 259 (11.2), 209 (11.5), 195 (22.6), 194 (100.0), 119 (35.9), 108 (12.7) *m/e*. Anal. Calcd for $C_{26}H_{18}N_8$: C, 70.58; H, 4.07; N, 25.34. Found: C, 69.70; H, 4.14; N, 24.84.

Method 2. To 150 mg of **3** (0.5 mmol) in 5 mL of acetone was added 100 mg of sodium azide (1.54 mmol) in 2.5 mL of water at 0 °C while stirring. The resulting mixture was stirred at 0 °C for 1 h. Then 10 mL of cold water was added and a white solid was collected by filtration.[9] The solid was dissolved in 10 mL of dimethoxyethane and dried with $MgSO_4$. After filtration, 150 mg of aniline was added to the solution and the mixture was heated to 60–70 °C for 1 h. The solvent was then removed under vacuum and the residue was washed with benzene and methanol to afford 152 mg (yield 69%) of a white-grey product, identical by ^1H NMR and IR with the product obtained by method 1.

Measurements of pK_a.[5] Observation of the equilibrium protonation was made spectrophotometrically at 411.0 nm where 1 (or B below) absorbs strongly. Upon titrating with tetrafluoroboric acid, the absorbance decreased. In 80% (v/v) DMSO–H_2O at 20 °C with 10^{-4} mol/L B, the absorbance at 411.0 nm was measured in the presence of various concentrations of tetrafluoroboric acid in the range 2×10^{-5} to 7×10^{-5} mol/L. The equilibrium constants for the above reaction can be expressed as and can thus be obtained from the measured absorbance at



$$K_b = [BH^+]/[B][H^+]$$
$$K_a = [B][H^+]/[BH^+]$$

each hydrogen ion concentration. The average pK_a value is 3.3 ± 0.2. Since the difference in λ_{max} of the conjugate acid and base forms of 9-aminoacridine and 1,8-diaminonaphthalene were too small to give an accurate value for their pK_a's by direct titration, we used *p*-nitrophenol as an indicator in a spectrophotometric titration. Thus, *p*-nitrophenol (1×10^{-4} M) was titrated with 2 $\times 10^{-4}$ M 9-aminoacridine while monitoring the strong 321-nm absorption of the nitrophenol was monitored. The equilibrium constant was

$$K = \frac{[B_1^-][B_2H^+]}{[B_1H][B_2]} = \frac{K_{B_2}}{K_{B_1}}$$

where K_{B_1} is the dissociation constant of *p*-nitrophenol (determined previously) and K_{B_2} is the dissociation constant of the conjugate acid of the base whose K_a is unknown; finally,

$$pK_a = -\log K_{B_2}$$

Acknowledgment. We are indebted to the National Science Foundation for support of this work; Grant DMR 86-01206.

(*R,R*)-1,3-Dibenzylisoindoline: A New C_2-Symmetric Secondary Amine, by Stereoselective and Regioselective α,α'-Dialkylation of Isoindoline, and an Improved Procedure for the Preparation of Isoindoline

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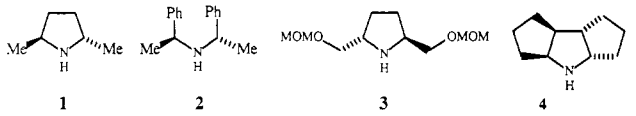
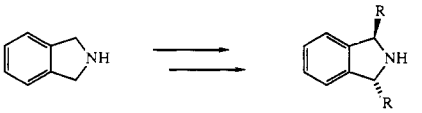
Received August 3, 1988

The advantages inherent in C_2 symmetry for asymmetric processes were first enunciated by Kagan in 1972, in the context of chiral phosphine design for asymmetric hydrogenation.[1] In 1977, Whitesell published the resolution of *trans*-2,5-dimethylpyrrolidine, **1**,[2] a C_2-symmetric amine which has seen some use in asymmetric processes[2,3] and has also been synthesized from alanine.[4] An amine with similar symmetry, **2**, was prepared much earlier by Overberger[5] and has been used as an enantioselective deprotonating agent[3a,6] and proton source.[7] Katsuki has used a MOM-protected *trans*-2,5-bis(hydroxymethyl)-pyrrolidine, **3**, as chiral auxiliary in a number of asymmetric processes.[8] In the accompanying paper, Whitesell reports the synthesis and resolution of a new C_2-symmetric pyrrolidine, **4**, which appears comparable to **1** in its effectiveness as a chiral auxiliary.[9]



1 2 3 4

Compounds **1–4** are prepared either by resolution or from a natural product, but structural analogues are unavailable. We now report the synthesis of the first member of a new class of secondary amines, prepared by sequential asymmetric alkylation[10] of isoindoline.[11] This alkylation sequence offers the potential advantage of structural variation in the electrophile, and either enantiomer is available, depending on the configuration of the chiral auxiliary.



In 1986, we reported a method for the asymmetric α-alkylation of heterocycles using an oxazoline chiral auxiliary.[10] The successful α,α'-dimethylation of piperidine[10] suggested the possible use of the method in the design of C_2-symmetric homochiral secondary amines. However, significant problems were encountered in extending the alkylation to other electrophiles in the piperidine system,[12] and so we chose to first apply the concept to a better behaved benzylic system.[13,14]

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(13) For a detailed study of the asymmetric alkylation of benzylic and allylic systems, see: Rein, K. R.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.*, submitted.

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