parent ion was used to obtain the C_2H_6 ratio. The parent peak at 33 was used for trideuterioethane (Table III).

Acknowledgment. This research was supported by Grant CHE-78-24173 from the National Science Foundation under the US-USSR Chemical Catalysis Program. The NMR spectra were obtained at the Colorado State University Regional NMR Center, funded by the National Science Foundation, Grant CHE-78-18581.

Supplementary Material Available: Table IV, ^1H NMR chemical shifts, and coupling constants of dimethylpalladium and iodomethylpalladium complexes **2a**, **10a**, and **10b** in different solvents (1 page). Ordering information is given on any current masthead page.

Regioselective Carbonyl Amination Using Diisobutylaluminum Hydride

Hisashi Yamamoto*[1] and Keiji Maruoka[1]

Contribution from the Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822.
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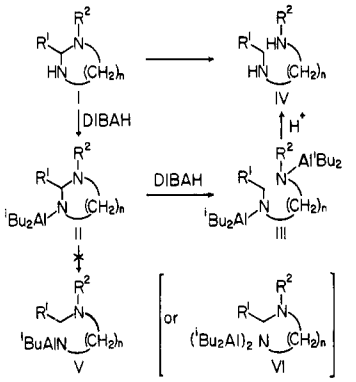
Abstract: A new, selective, and mild approach to N-alkylation of polyamines has been demonstrated, which involves the novel reductive cleavage of the C-N bond in cyclic amidines by diisobutylaluminum hydride. This method provides a new entry to a wide variety of N-alkylated polyamines and many interesting macrocyclic polyamines hitherto accessible only by lengthy or complicated synthesis.

The N-alkylation reaction of amines has long been recognized to be one of the most fundamental reactions for the formation of carbon-nitrogen bonds.[2] However, the alkylation of polyamines is often accompanied by di- or polyalkylations such that the separation of the desired monoalkylated polyamine from the reaction mixture is at best complicated. The hitherto available methodologies for monoalkylation are partially useful only when a large excess of polyamines is used. Therefore, a selective monoalkylation of polyamines has still been awaited with interest.[3]

During the course of an investigation into the chemistry of cyclic polyamines and their metal cation inclusion complexes, we devised a new, selective, and mild approach to monoalkylation of polyamines, which involves the novel reductive cleavage of aminals and amidines[4] by diisobutylaluminum hydride (DIBAH).[5]

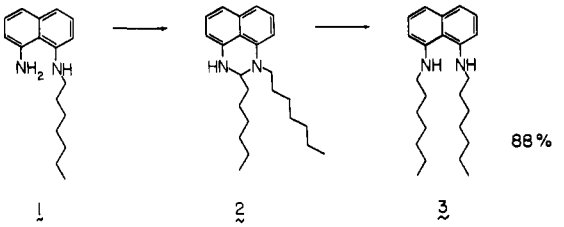
The general type of transformation which is described herein is summarized in Scheme I. DIBAH is an effective and selective reducing agent which cleanly converts the aluminum amide II[6] to the bis(aluminum amide) III,[7] leading to the monoalkylated

Scheme I



1,(n + 2)-diamine IV after hydrolysis.[8] The reaction should proceed regioselectively, since the formation of the aluminum imide V (or dialuminum amide VI) would be energetically much less favorable.[5,9]

Our process is typified by the conversion of *N*-heptyl-1,8-diaminonaphthalene (**1**) to *N*,*N*'-diheptyl-1,8-diaminonaphthalene (**3**). Treatment of **1** in benzene with heptaldehyde (1 equiv) gave



the 1-heptyl-2-hexyl-2,3-dihydroperimidine (**2**) in quantitative yield.[10] Reduction of **2** with DIBAH (6 equiv) in *n*-hexane afforded the diamine **3** as the major product, which was diluted

(1) Address correspondence to Department of Applied Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan.

(2) Recent N-alkylations of amines: (a) Baiker, A.; Richarz, W. *Tetrahedron Lett.* **1977**, 1937. (b) Botta, M.; DeAngelis, F.; Nicoletti, R. *Synthesis* **1977**, 722. (c) Baiker A.; Richarz, W. *Synth. Commun.* **1978**, *8*, 27. (d) Gribbe, G. W.; Jasinski, J. M.; Pellicone, J. T. *Synthesis* **1978**, 766. (e) Watanabe, Y.; Yamamoto, M.; Mitsudo, T.; Takegami, Y. *Tetrahedron Lett.* **197,**, 1289. (f) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898.

(3) Recent selective polyamine alkylations: (a) Humora, M. J.; Wuick, J. *J. Org. Chem.* **1979**, *44*, 1166. (b) Humora, M. J.; Seitz, D. E.; Quick, J. *Tetrahedron Lett.* **1980**, *21*, 3971. (c) Bergeron, R-J.; McGovern, K. A.; Channing, M. A.; Burton, P. S. *J. Org. Chem.* **1980**, *45*, 1589. (d) Chatrapromma, K.; McManis, J. S.; Ganem, B. *Tetrahedron Lett.* **1980**, *21*, 2475. (e) Chantrapromma, K.; McManis, J. S.; Ganem, B. *Ibid.* **1980**, *21*, 2605.

(4) (a) Benkovic, S. J.; Benkovic, P. A.; Chrzanowski, R. *J. Am. Chem. Soc.* **1970**, *92*, 523. (b) Barrows, T. H.; Farina, P. R.; Chrzanowski, R. L.; Benkovic, P. A.; Benkovic, S. J. *Ibid.* **1976**, *98*, 3678. (c) Moad, G.; Benkovic, S. J. *Ibid.* **1978**, *100*, 5495.

(5) For general reviews, see: (a) Mole, T.; Jeffery, E. A. "Organoaluminum Compounds"; Elsevier; Amsterdam, 1972; (b) bruno, G. "The Use of Aluminum Alkyls in Organic Synthesis"; Ethyl Corporation: Baton Rouge, LA, 1970 and 1973.

(6) The formation of II was supported by the treatment of the perimidine **2** with 1 equiv of DIBAH at 0 °C to evolve 1 equiv of hydrogen gas.

(7) Aminals are in rapid equilibrium with their imine forms. One may simply be seeing rapid transformation of II to the imine form, followed by the imine reduction here. However, treatment of **6** or **12**, which gives no imine form, with DIBAH under the comparable conditions afforded the corresponding C-N bond cleavage product. Therefore, we support the reducing ability of DIBAH toward the C-N bond.

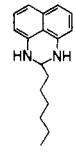
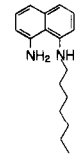
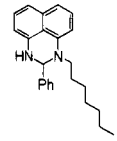
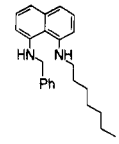
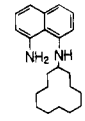
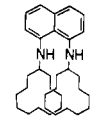
(8) Northop, R. C., Jr.; Russ, P. L. *J. Org. Chem.* **1975**, *40*, 558.

(9) In the presence of excess DIBAH, tertiary amine in II (R^2 = alkyl) should coordinate to another DIBAH, while another amide nitrogen would be stabilized by the adjacent aluminum. Therefore, cleavage of the C-N bond between the R^1 and R^2 groups would be favored. Furthermore, formation of an aluminum imide like V generally requires much higher energy compared to that of an aluminum amide (cf. ref 5a, pp 229-232).

(10) Vinot, N. *C. R. Hebd. Seances Acad. Sci.* **1961**, *252*, 899.

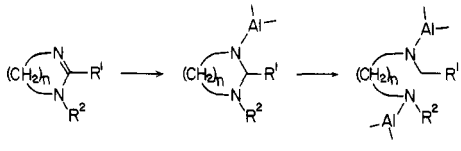
0002-7863/81/1503-4186$01.25/0

Table I. N-Alkylation of 1,8-Diaminonaphthalene Derivatives by Reductive Cleavage

entry	diamine	carbonyl compd	reacn condn[a]	dihydroperimidine	reduction with DIBAH[b]	product	overall % yield[c]
1	1,8-diaminonaphthalene	$CH_3(CH_2)_5CHO$	25 °C, 20 min		0 °C, 2 h		94
2	*N*-heptyl-1,8-diaminonaphthalene	PhCHO	25 °C, 10 h[d]		80 °C, 30 min		85
3	1,8-diaminonaphthalene	$(CH_2)_{11}C{=}O$	cat. *p*-TsOH, 80 °C, 3 h	*e*	25 °C, 45 min		98
4	*N*-cyclododecyl-1,8-diaminonaphthalene	$(CH_2)_{11}C{=}O$	cat. *p*-TsOH, 110 °C, 10 h	*e*	25 °C, 12 h		84

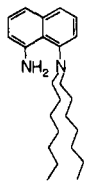
[a] The resulting water was removed azeotropically. [b] All reductions were carried out as described for 1-heptyl-2-hexyl-2,3-dihydroperimidine (2), using 6–7 equiv of DIBAH. The reaction mixture was worked up by successive treatment with water (3 molar equiv to DIBAH) and anhydrous magnesium sulfate (0.5 g/mmol of DIBAH), followed by filtration. [c] Yield from 1,8-diaminonaphthalene derivatives. [d] Water was evaporated with benzene. [e] Without isolation of the dihydroperimidines, the reaction mixture was directly treated with excess DIBAH at 0 or 25 °C.

Scheme II

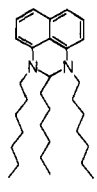


with benzene, treated successively with sodium fluoride (4 molar equiv to DIBAH)[11] and water (3 molar equiv to DIBAH), and stirred vigorously for 20 min. Filtration, washing of the white precipitates with benzene, and removal of the solvent gave the diamine **3** in 88% yield after purification. Without isolation of the intermediate **2**, diamine **3** was obtained in 88% yield by direct treatment of the crude **2** with DIBAH under similar reduction conditions described above.

The difficulty of distinguishing between the structure of **3** and its regioisomer **4** was encountered with the spectral data (^{1}H NMR, IR, and mass) of **3**, which might be identical with those of **4**. Therefore, the structure of **3** was established by treatment of **3** with heptaldehyde according to the procedure described above, followed by careful examination of the methine peak (N–CH–N, δ 4.00–4.33) in the ^{1}H NMR of the adduct **5**. It was further

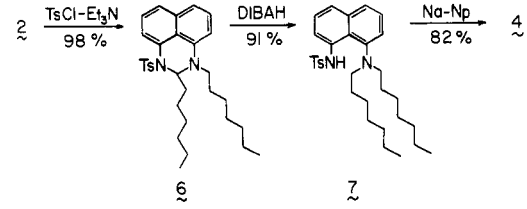


4



5

confirmed by regioselective synthesis of **4** according to the following reaction sequence. Tosylation of **2** with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane gave *p*-toluenesulfonamide **6** in 98% yield. DIBAH reduction in *n*-hexane afforded *N*,*N*-diheptyl-*N'*-(*p*-toluenesulfonyl)-1,8-diaminonaphthalene (**7**) (91% yield), regioselectively. Lastly, removal of the *p*-toluenesulfonyl group in **7** with sodium–naphthalene in tetrahydrofuran (THF)[12] generated *N*,*N*-diheptyl-1,8-diaminonaphthalene (**4**) in 82% yield.



6 **7**

Further examples are listed in Table I, which exemplifies the effectiveness of this method. Even bulky cyclododecyl groups can be cleanly introduced with complete regioselectively (entries 3, 4).

Some applications of this novel reductive cleavage were demonstrated by the selective synthesis of macropolycyclic polyamines. Although interesting "guest" compounds are plentiful,[13] the synthesis of the corresponding "host" structures[14] (e.g., macrocyclic polyethers and polyamines) is rendered by the limited utility of most of the existing methods. The invention of new synthetic methodology for host molecules is, therefore, one of the more crucial elements for the development of bioorganic as well as bioinorganic chemistry. Thus, reaction of 1,8-diaminonaphthalene

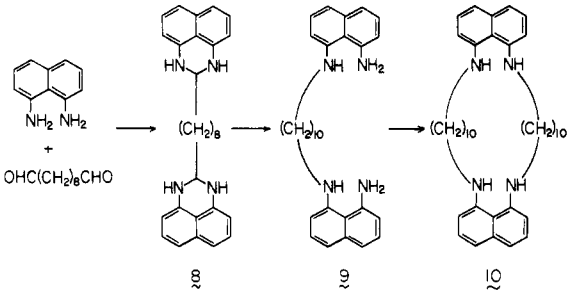
(11) The NaF–H_2O method is a general workup procedure for organoaluminum reactions. The resulting white slurry can be easily removed by filtration.

(12) The NaF–H_2O method is a general workup procedure for organoaluminum reactions. The resulting white slurry can be easily removed by filtration.
Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

(13) For a general review of host–guest chemistry, see, for example: (a) Cram, D. J. In "Applications of Biochemical Systems in Organic Chemistry, Part II"; Jones, J. B., Sih, C. J., Perlman, D., Eds.; John wiley and Sons: New York, 1976; (b) Gokel, G. W.; Durst, H. D. *Aldrichimica Acta*, **1976**, *9*, 3; (c) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8; (d) Lehn, J.-M. *Ibid.* **1978**, *11*, 49.

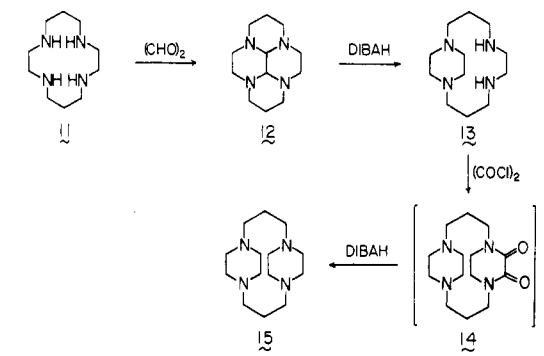
(14) For polyamino compounds as a useful host, see: (a) Högberg, S. A. G.; Cram, D. J. *J. Org. Che.* **1975**, *40*, 151; (b) Lehn, J.-M.; Pine, S. H.; Watanabe, E.; Willard, A. K. *J. Am. Chem. Soc.* **1977**, *99*, 6766; (c) Buhleier, E.; Wehner, W.; Vogtle, F. *Synthesis* **1978**, 155.

with 1,10-decanedial[15] (0.5 equiv) in benzene at 25 °C for 2 h afforded 1,8-bis(2-dihydroperimidyl)octane (**8**), which was directly treated with DIBAH in *n*-hexane (4 equiv) at 25 °C for 3 h to furnish *N,N'*-decamethylenebis(1,8-diaminonaphthalene) (**9**) in 85% yield after purification. Simultaneous and separate addition

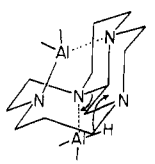


of **9** and 1,10-decanedial to refluxing benzene over 75 min led to the formation of the bis(2-dihydroperimidyl) derivative, which was reduced with DIBAH in *n*-hexane (10 equiv) at 25 °C for 15 h to give **10** in 40% yield.

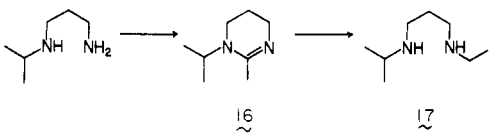
Another attractive approach to the synthesis of macropolycyclic polyamines was illustrated in the following sequence. Reaction of 1,4,8,11-tetraazacyclotetradecane (**11**) in methanol with aqueous glyoxal[16] at 0 °C for 30 min gave the tetracyclic adduct **12** quantitatively, which was converted by DIBAH in toluene under reflux for 4 days into 1,5,8,12-tetraazabicyclo[13.2.2]-hexadecane (**13**) in 96% yield. The structure of **13** followed from (a) spectral data (see Experimental Section), (b) transformation to the dimethyl derivative (aqueous CH_2O–$NaBH_3CN$–AcOH, 25 °C for 5 h)[17] and bis(*p*-toluenesulfonamide) (*p*-TsCl–NEt_3, 25 °C for 2 h) of **13**. The introduction of the ethylene bridge was performed by the reaction of **13** with oxalyl chloride at 0 °C for 1.5 h, and then the reduction of the resulting diamide **14** using DIBAH at 25 °C for 1 day to furnish 1,5,8,12-tetraazatricyclo-[10.2.2.2^{5,8}]octadecane (**15**). The selective cleavage of **12** by



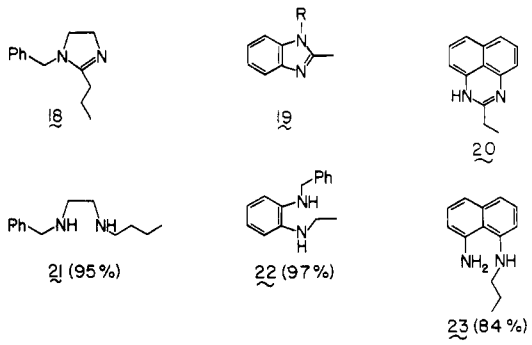
DIBAH can be explained by initial chelate formation of diisobutylaluminum amide, followed by the coordination of another nitrogen atom to DIBAH, and finally the C–N bond cleavage by DIBAH as shown below.



Since DIBAH is an effective reducing agent for conversion of imines to amino derivatives,[18] our new process can be extended to the reductive cleavage of the amidine system by DIBAH (Scheme II) to furnish the regiospecifically alkylated polyamines. Thus, reaction of *N*-isopropyl-1,3-diaminopropane with ethyl acetoacetate in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate[19] produced 1-isopropyl-2-methyltetrahydropyrimidine (**16**), which was converted by DIBAH in *n*-hexane to *N*-isopropyl-*N'*-ethyl-1,3-diaminopropane (**17**) in 97%

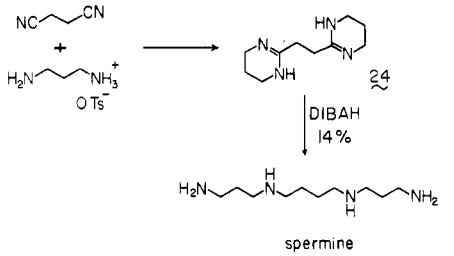


yield. Similarly, several cyclic amidines (**18**, **19** (R = $PhCH_2$), and **20**) were cleanly reduced by DIBAH in a regioselective manner to give the corresponding diamines **21**, **22** (R = $PhCH_2$), and **23**, respectively, in high yields as indicated. On the other



hand, reduction of 2-methylbenzimidazole (**19**, R = H) with DIBAH gave recovered starting material even under vigorous reaction conditions.[20]

The present method was employed in the facile synthesis of spermine which is widely distributed in the animal kingdom and in microorganisms and forms a basic skeleton of spermine plant alkaloids.[21] Thus, succinonitrile was treated with 1,3-diaminopropane mono-*p*-toluenesulfonate at 140 °C for 30 min to furnish 1,2-bis(2-tetrahydropyrimidyl)ethane (**24**) in 95% yield.[22] Al-



spermine

though the direct transformation of **24** into spermine (14% yield) did not proceed smoothly under vigorous reaction conditions, the difficulty was easily overcome by protection of the amino group with hexamethyldisilazane.[23] The trimethylsilyl group was favorable for our purpose for ease of both introduction and removal. Thus, the bis(tetrahydropyrimidine) **24** was converted in situ to the bis(trimethylsilylamide) **25** by treatment with hexamethyldisilazane in the presence of a catalytic amount of fuming sulfuric acid under reflux for 12 h. This bis(silylamide) **25**, after evaporation of excess hexamethyldisilazane, was directly subjected to the reductive cleavage by excess DIBAH (20 equiv) in xylene under reflux for 3 days to furnish spermine in 63% yield.

(15) 1,10-Decanedial was prepared in 80% yield by the oxidation of 1,10-decanediol with pyridinium dichromate (PDC) at 25 °C for 20 h. See: Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(16) Weisman, G. R.; Ho, S. C. H.; Johnson, V. *Tetrahedron Lett.* **1980**, *21*, 335.

(17) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *3m*, 1673.

(18) For reduction of imines by DIBAH see: (a) Newmann, W. P. *Justus Liebigs Ann. Chem.* **1958**, *318*, 80; (b) Van Amerongen, G. *Adv. Chem. Ser.* **1966**, *52*, 136; (c) Smith, G. H.; Perry, D. C. *J. Polymn. Sci., Part A-1* **1969**, *7*, 707.

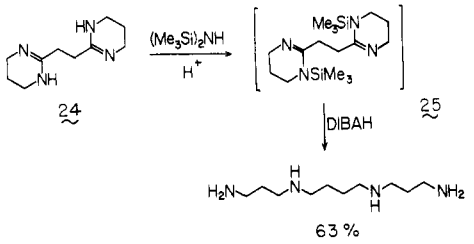
(19) Baganz, H.; Rabe, S. *Chem. Ber.* **1965**, *98*, 3652.

(20) It should be noted that N-alkylated cyclic amidines can be reduced by DIBAH much easier than the nonalkylated homologues.

(21) For general reviews, see: Badawi, M. M.; Bernauer, K.; Van Den Broek, P.; Groger, D.; Guggisberg, A.; Johne, S.; Kompis, I.; Schneider, F.; Veith, J.-J.; Hesse, H.; Schmid, H. *Pure Appl. Chem.* **1973**, *33*, 81.

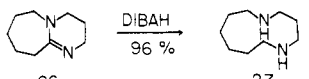
(22) Oxley, P.; Short, W. F. *J. Chem. Soc.* **1947**, 497.

(23) Duranti, E.; Balsamini, C. *J. Chem. Soc.* **1974**, 815.

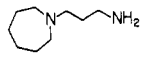


24 25

If R^1 and R^2 of Scheme II are members of another ring system, then the reaction results in an expansion of the ring by $n + 1$ members. This process provides a general, selective, and suitably mild approach to cyclic polyamines,[24] which is typified by the conversion of commercially available 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (**26**) to the 11-membered cyclic diamine **27** by



26 27



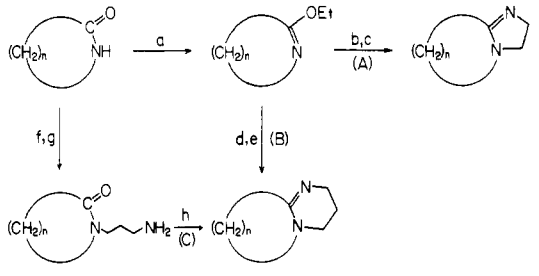
28

excess DIBAH in toluene under reflux for 7 h. The crude mixture was worked up with sodium fluoride–water and purified by preparative TLC to furnish 1,5-diazacycloundecane (**27**) in 96% yield. The structure of **27** was further established (a) by comparison with the isomeric diamine **28** made from the reduction of *N*-(3-aminopropyl)-ε-caprolactam with DIBAH (b) and by transformation to the corresponding *N,N'*-dimethyl derivative (aqueous CH_2O–$NaBH_3CN$–AcOH) or bis(*p*-toluenesulfonamide) (*p*-TsCl–NEt_3) of **27**.

The additional examples presented in Table III illustrate the wide generality and flexibility of the new approach. Macrocyclic amines of up to the 30-membered ring (entry 9) can be readily prepared. It can also be seen that even the highly strained nine-membered-ring structure (entry 1), which cannot be prepared by other methods, can be prepared efficiently. In addition, a simple route to optically active cyclic diamine (entry 10) is now possible based on the present procedure.

For the synthesis of cyclic polyamines, we found it necessary to develop efficient synthetic routes to the cyclic amidine system[25] in addition to those already in the literature.[26,27] Below we outlined the three general procedures we followed in preparing the amdines used in this study (Scheme III): (A) conversion of the lactam to the imino ether ($Et_3O^+BF_4^-$),[28] followed by treatment with aziridine, and subsequent rearrangement to the dihydroimidazole with iodine[26] or trimethylsilyl iodide; (B) conversion of the lactam to the imino ether ($Et_3O^+BF_4^-$), followed by stirring with 3-bromopropylamine hydrobromide, and subsequent neutralization with potassium carbonate to give the tetrahydropyrimidine; (C) cyanoethylation of the lactam with acrylonitrile,[27] followed by hydrogenation over PtO_2, and finally cyclization with titanium tetrachloride to produce the tetrahydropyrimidine.

Scheme III



[a] a, $Et_3O^+BF_4^-$; b, $(CH_2)_2NH$–NH_4Br; c, I_2–benzene or $(CH_3)_3SiI$; d, $Br(CH_2)_3NH_3^+Br^-$; e, K_2CO_3; f, CH_2=CHCN–EtONa; g, H_2, PtO_2; h, $TiCl_4$.

The synthetic method described herein provides a new entry to a wide variety of N-alkylated polyamines and many unusual macrocyclic ligands hitherto accessible only by lengthy or complicated synthesis. Work is continuing on these and related synthetic applications.

Experimental Section

General Methods. The infrared spectra were recorded on a Perkin-Elmer 710A spectrometer, the mass spectra on a Varian MAT high-resolution mass spectrometer, ^1H NMR spectra on a Varian EM-360 or HA-100 spectrometer, and Fourier transfer ^{13}C NMR spectra on a Varian XL-100 spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ 0). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Melting-point determinations were performed by using a Büchi-510 capillary melting point apparatus in open capillaries and are uncorrected. All experiments were carried out under an atmosphere of dry argon. For TLC analysis throughout this work, Merck precoated TLC plates (silica gel 60 F_{254}, 0.2 mm) were used. The products were purified by preparative TLC on silica gel plates (Merck), or preparative column chromatography on silica gel E. Merck Art. 9385, or silanized silica gel E. Merck Art. 7719.

In experiments requiring dry solvents, tetrahydrofuran was freshly distilled from sodium metal under an argon atmosphere, using benzophenone ketyl as indicator. Dichloromethane was distilled from phosphorus pentoxide and stored over 4-Å molecular sieves. Benzene and toluene were dried over sodium metal. Triethylamine was stored over potassium hydroxide pellets. Diisobutylaluminum hydride in *n*-hexane (1.0 M) was a commercial product. Other simple chemicals were purchased and used as such.

General Method for Preparation of Perimidines. Perimidines were prepared by the reaction of (*N*-alkyl-) 1,8-diaminonaphthalenes with aldehydes or ketones in benzene in the presence or absence of *p*-toluenesulfonic acid monohydrate. Synthesis of 1-heptyl-2-hexyl-2,3-dihydroperimidine (**2**) is illustrative.

The physical properties and analytical data for the perimidines and their reduced products are given in Table II.

1-Heptyl-2-hexyl-2,3-dihydroperimidine (2). Heptaldehyde (1.14 g, 10 mmol) was added dropwise to a solution of *N*-heptyl-1,8-diaminonaphthalene (2.56 g, 10 mmol) in benzene (50 mL) at 0 °C. Stirring was continued at 0 °C for 30 min. Then the solvent was evaporated and the crude product was directly subjected to column chromatography on silica gel (ether–hexane, 1:10 to 1:5) to afford **2** as a light orange oil: TLC R_f 0.49 (ether–hexane, 1:9, two developments); IR (liquid film) 3440, 1610, 1482, 1447, 1175, 813, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.23–7.39 (1 H, m, aryl CH), 4.08–4.60 (2 H, m, NH, NCHN), 2.68–3.73 (2 H, m, NCH_2); mass spectrum *m/e* 352.291 (calcd for $C_{24}H_{36}N_2$ 352.288).

***N,N'*-Diheptyl-1,8-diaminonaphthalene (3).** A solution of DIBAH in *n*-hexane (6 mL, 6 mmol) was added to **2** (352 mg, 1 mmol) at 0 °C. The resulting solution was stirred at 25 °C for 8 h and then under reflux for 1 h. The mixture was cooled to 0 °C, diluted with benzene (18 mL), treated successively with sodium fluoride (1 g, 24 mmol) and water (0.3 mL, 18 mmol) at 0 °C, and stirred vigorously for 20 min at 25 °C. Filtration, washing of the white precipitate with chloroform, and removal of solvents left the crude oil, which was purified by column chromatography on silica gel (ether–hexane, 1:30) to give **3** (319 mg, 88% yield) as white crystals: TLC R_f 0.37 (ether–hexane, 1:30); mp 37–39 °C (recrystallized from benzene–hexane); IR ($CHCl_3$) 3373, 1589, 1464, 1300, 1135, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.37–7.26 (6 H, m, aryl

(24) For recent synthesis of macrocyclic polyamines see: (a) Koyama, H.; Yoshino, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 481; (b) Tait, A. M.; Busch, D. H. *Inorg. Nucl. Chem. Lett.* **1972**, *8*, 491; (c) Dye, J. L.; Lok, M. T.; Tehan, F. J.; Ceraso, J. M.; Voorhees, K. J. *J. Org. Chem.* **1975**, *38*, 1773; (d) Richman, J. E.; Atkins, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268; (e) Hay, R. W.; Lawrance, G. A.; Curtis, N. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 591; (f) Barefield, E. K.; Wagner, F.; Hodges, K. D. *Inorg. Chem.* **1976**, *15*, 1370; (g) Kramer, U.; Guggisberg, A.; Hesse, M.; Schmid, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 861; *Ibid.* **1978**, *17*, 200; *Helv. Chim. Acta* **197**, *61*, 1342; (h) Kemp, D. S.; Punzar, R. V.; Chabala, J. C. *Tetrahedron Lett.* **1978**, 547; (i) Tundo, P. *Ibid.* **1978**, 4693; see also ref 8.

(25) The use of aqueous workup should be avoided, since the cyclic amidines, especially the tetrahydropyrimidines, are highly soluble in water. Attempted extraction of the amidines with ether from the aqueous sodium hydroxide solution was unsuccessful.

(26) Bormann, D. *Agnew, Chem., Int. Ed. Engl.* **1973**, *12*, 768.

(27) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591.

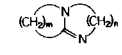
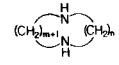
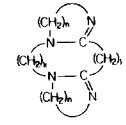
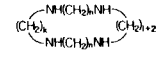
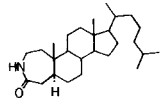
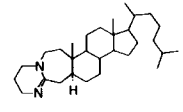
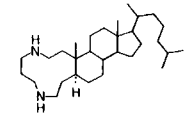
(28) Paquette, L. A.; Kakihara, R.; Hansen, J. F.; Philips, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 152.

Table II. Physical Properties and Analytical Data of Perimidines and Their Reduced Products

perimidine or its reduced products	TLC R_f (solvent)	IR, cm^{-1} [a]	^1H NMR, δ	spectrum, mass, *m/e*
2-hexyl-2,3-dihydroperimidine	0.4 (benzene, 2 developments)	3443, 1613, 1419, 1135, 1105	6.30–7.20 (6 H, m, aryl CH), 4.24 (1 H, t, J = 5.2 Hz, NCHN), 4.05 (2 H, s, NH)	254.185 (calcd for $C_{17}H_{22}N_2$ 254.178)
N-heptyl-1,8-diaminonaphthalene	0.5 (benzene)	3390, 1593, 1531, 1300, 800, 741	6.26–7.14 (6 H, m, aryl CH), 4.52 (3 H, s, NH), 2.92 (2 H, t, J = 6.0 Hz, NCH_2)	256.192 (calcd for $C_{17}H_{24}N_2$ 256.194)
N-cyclododecyl-1,8-diaminonaphthalene	0.5 (benzene)	3397, 1595, 1534, 1306, 1135, 1106	6.34–7.32 (6 H, m, aryl CH), 4.74 (3 H, br s, NH), 3.34–3.67 (1 H, m, NCH), 1.39 (22 H, br s, CCH_2C)	324.262 (calcd for $C_{22}H_{32}N_2$ 324.257)
N,N'-dicyclododecyl-1,8-diaminonaphthalene	0.47 (benzene–hexane, 1:2)	3376, 1591, 1473, 1446, 1112	6.44–7.28 (6 H, m, aryl CH), 5.18 (2 H, br s, NH), 3.46 (2 H, m, NCH)	490.435 (calcd for $C_{34}H_{54}N_2$ 490.429)
1-heptyl-2-phenyl-2,3-dihydroperimidine	0.38 (ether–hexane, 1:9, 2 developments)	3440, 1583, 1466, 1420, 1373, 1275, 1163, 1080, 805, 760	6.17–7.47 (6 H, m, aryl CH), 5.22 (1 H, s, NCHN), 4.40 (1 H, br s, NH), 2.58–3.35 (2 H, m, NCH_2)	344.224 (calcd for $C_{24}H_{28}N_2$ 344.225)
N-benzyl-*N'*-heptyl-1,8-diaminonaphthalene	0.39 (ether–hexane, 1:10)	3388, 1597, 1144, 1118	6.37–7.38 (6 H, m, aryl CH), 5.50 (2 H, br s, NH), 4.14 (2 H, s, $PhCH_2$), 2.88 (2 H, t, J = 6.2 Hz, CCH_2N)	346.248 (calcd for $C_{24}H_{30}N_2$ 346.241)

[a] IR spectra were taken as liquid films for *N*-heptyl-1,8-diaminonaphthalene and 1-heptyl-2-phenyl-2,3-dihydroperimidine and as the $CHCl_3$ solutions for the other compounds.

Table III. Synthesis of Cyclic Polyamines

entry	lactam	method[a]	% yield	amidine	reaction time,[b] h	% yield[c]	amine[d]
							
1	m = 4	A	60	n = 2	3	79	
2	m = 5			n = 3 (DBU)	7	96	
3	m = 7	A	62	n = 2	1.5	90	
4	m = 7	B	55	n = 3	4	74	
5	m = 11	A	78	n = 2	1.5	92	
6	m = 11	B	56	n = 3	1.5	83	
7	m = 11	C	77	n = 3			
							
8	k = 6, l = 8[e]	A	39[g]	n = 2	1.5	68	
9	k = 12, l = 8[e]	A	37[g,h]	n = 2	1.5	83	
10		C	97		12	86	

[a] Methods A–C refer to the three general methods in the Experimental Section. [b] All reductions were carried out as described for DBU (see Experimental Section), using 6–12 equiv of DIBAH. [c] Yields were determined by isolation involving chromatography on silica gel. [d] All compounds have been adequately characterized by spectral data (^1H and ^{13}C NMR, IR, and mass); see Table IV. [e] Stetter, H.; Marx, J. *Justers Liebigs Ann. Chem.* 1957, *607*, 59. [f] Oka, K.; Hara, S. *J. Org. Chem.* 1978, *43*, 3790. [g] In addition to the desired bis amidine, the monoamide-monoamidine was also obtained in ca. 20% yield. [h] The aziridine derivative was treated with 0.3 equiv of trimethylsilyl iodide in CH_2Cl_2 (0.3 M) at 25 °C for 2 h and then under reflux for 9 h.

CH), 5.40 (2 H, br s, NH), 3.00 (4 H, t, J = 6.0 Hz, NCH_2); mass spectrum m/e 354.304 (calcd for $C_{24}H_{38}H_2$ 354.304). The diamine **3** could be obtained in 88% yield by the direct treatment of the crude **2** with DIBAH in *n*-hexane under similar conditions described above.

The synthesis of other 1,8-diaminonaphthalene derivatives by reductive cleavage of perimidines with DIBAH was carried out as shown in Table I.

1,3-Diheptyl-2-hexyl-2,3-dihydroperimidine (5). A mixture of the diamine **3** (178 mg, 0.5 mmol) and heptaldehyde (68 mg, 0.6 mmol) in benzene (4 mL) was refluxed for 3 h. Evaporation of the solvent left the crude oil, which was directly subjected to column chromatography on silica gel (ether–hexane, 1:40) to give **5** (205 mg, 91% yield) as a colorless oil: TLC, R_f 0.48 (ether–hexane, 1:40); IR (liquid film) 1580, 1451, 1419, 1331, 1145, 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27–7.49 (6H, m, aryl CH), 4.00–4.33 (1 H, br t, NCHN), 2.65–3.85 (4 H, m, NCH_2); mass spectrum, m/e 450.397 (calcd for $C_{31}H_{50}N_2$ 450.397).

1-Heptyl-2-hexyl-3-(*p*-toluenesulfonyl)-2,3-dihydroperimidine (6). *p*-Toluenesulfonyl chloride (1.144 g, 6 mmol) was added portionwise to a stirred solution of **2** (1.036 g, 3 mmol) and triethylamine (2.51 mL, 18 mmol) in dichloromethane (6 mL) at 0 °C. The resulting mixture was allowed to warm to 25 °C and further stirring was continued at 25 °C for 2 days. Then the mixture was poured onto water and extracted with chloroform. The combined extracts were washed with water once, dried, and concentrated. Purification of the crude product by column chromatography on silica gel (benzene–hexane, 1:2, then only benzene) gave **6** (1.488 g, 98% yield) as a light brown oil: TLC R_f 0.58 (ether–hexane), 1:9, two developments); IR (liquid film) 1596, 1419, 1355, 1166, 1090, 805, 759 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.08–8.00 (10 H, m, aryl CH), 5.39 (1 H, br s, NCHN), 2.80–3.17 (2 H, m, NCH_2), 2.14 (3 H, s, aryl CH_3); mass spectrum, m/e 506.300 (calcd for $C_{31}H_{42}N_2O_2S$ 506.297).

***N,N*-Diheptyl-*N'*-(*p*-toluenesulfonyl)-1,8-diaminonaphthalene (7).** A solution of DIBAH in *n*-hexane (8.8 mL, 8.8 mmol) was added dropwise to **6** at 0 °C. The resulting solution was stirred at 25 °C for 30 min. The solution was then diluted with benzene (18 mL) and treated successively with sodium fluoride (1.478 g, 35.2 mmol) and water (0.48 mL, 26.4 mmol) at 0 °C. After being vigorously stirred at 25 °C for 20 min, the suspension was filtered and washed with chloroform. Evaporation of the solvents, followed by column chromatography on silica gel (ether–hexane, 1:8, then 1:5) gave **7** (407 mg, 91% yield) as a pink oil: TLC R_f 0.35 (ether–hexane, 1:5) IR (liquid film) 1592, 1473, 1419, 1352, 1307, 1164, 1093, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97–7.96 (10 H, m, aryl CH), 2.76–3.24 (4 H, m, NCH_2), 2.26 (3 H, s, aryl CH_3); mass spectrum, m/e 508.313 (calcd for $C_{31}H_{44}N_2O_2S$ 508.312).

***N,N*-Diheptyl-1,8-diaminonaphthalene (4).** Sodium naphthalene in dry THF (0.5 M) was prepared by treatment of naphthalene (1.018 g, 7.9 mmol) in THF (14.4 mL) with metallic sodium (166 mg, 7.2 mmol) at 25 °C for 1 h.[12] This solution (3.5 mL, 1.75 mmol) was added to a solution of **7** (180 mg, 0.35 mmol) in THF (1 mL) at 25 °C. The reaction was over immediately. Then a little water was added. The mixture was poured onto water and extracted with ether several times. The combined extracts were dried, concentrated, and purified by column chromatography on silica gel (ether–hexane, 1:50, then 1:10) to afford **4** (102 mg, 82%): TLC R_f 0.53 (ether–hexane, 1:9); IR (liquid film) 3490, 3299, 1595, 1472, 1305, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.31–7.63 (6 H, m, aryl CH), 6.06 (1 H, s, NH), 2.75–3.14 (4 H, m, NCH_2); mass spectrum, m/e 354.304 (calcd for $C_{24}H_{38}N_2$ 354.304).

***N,N'*-Decamethylenebis(1,8-diaminonaphthalene) (9).** 1,10-Decanedial (1.70 g, 10 mmol) in benzene (20 mL) was added dropwise to a solution of 1,8-diaminonaphthalene (3.16 g, 20 mmol) in benzene (80 mL) at 25 °C, and the resulting mixture was stirred at 25 °C for 2 h. The water was then removed azeotropically with 20 mL of benzene. The residual solution was treated with DIBAH in *n*-hexane (80 mmol) at 0 °C. Further stirring was continued at 25 °C for 3 h, and the mixture was worked up by the $NaF–H_2O$ method. Filtration, washing of the residue with chloroform, and purification of the concentrated filtrates by column chromatography on silica gel (CH_2Cl_2–hexane, 2:1, then 3:1) gave **9** (3.860 g, 85% yield) as pink crystals: TLC R_f 0.28 (CH_2Cl_2–benzene, 2:1); mp 104.5–105.5 °C (recrystallized from benzene–hexane); IR ($CHCl_3$) 3400, 1590, 1295, 1130, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.37–7.41 (12 H, m, aryl CH), 4.72 (6 H, br s, NH), 3.06 (4 H, t, NCH_2), 1.13–1.93 (16 H, br s, CCH_2C); mass spectrum, m/e 454.304 (calcd for $C_{30}H_{38}N_4$ 454.310).

Macrocyclic Tetramine 10. The tetramine **9** (454 mg, 1 mmol) in chloroform–benzene (40 mL, 1:3), and 1,10-decanedial (170 mg, 1 mmol) in benzene (40 mL) were added separately and simultaneously to refluxing benzene (40 mL) over 75 min. The resulting water was distilled off azeotropically with 10 mL of benzene. The residual solution was then cooled to 0 °C, and DIBAH in *n*-hexane was added at this temperature. Further stirring was carried out at 25 °C for 15 h. The reaction mixture was worked up by the $NaF–H_2O$ method. Filtration, washing of the residue with hot benzene, and purification of the concentrated filtrates by column chromatography on silica gel (hot benzene) gave **10** (237 mg, 40% yield) as white crystals: TLC R_f 0.41 (CH_2Cl_2–hexane, 1:1); mp 198–199 °C (recrystallized from benzene); IR (Nujol) 3333, 1580, 1292, 1150, 1086, 790, 742 cm^{-1}; ^1H NMR (benzene-d_6, at 50 °C) δ 6.48–7.46 (12 H, m, aryl CH), 2.90 (8 H, t, NCH_2), 1.18–1.66 (32 H, br, s. CCH_2C), 0.42 (4 H, br s, NH); mass spectrum, m/e 592.917 (calcd for $C_{40}H_{56}N_4$ 592.919).

Tetracyclic Tetramine 12. Aqueous 40% glyoxal (290 mg, 2 mmol) in methanol (2 mL) was added dropwise to 1,4,8,11-tetraazacyclotetradecane (400 mg, 2 mmol) in methanol (15 mL) at 0 °C. The reaction was over immediately. Further stirring was continuted at 0 °C for 30 min. Then the solvent was evaporated, and the residue was directly applied to column chromatography on silica gel (*i*-$PrNH_2$–$CHCl_3$, 1:30) to give **12** (426 mg, 97% yield) as light yellow crystals:[16] TLC R_f 0.35 (*i*-$PrNH_2$–$CHCl_3$, 1:19); IR (liquid film) 1460, 1440, 1356, 1340, 1295, 1143, 1100, 890, 820, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (2 H, s, NCHN), 1.73–3.87 (18 H, m), 0.91–1.50 (2 H, m); ^{13}C NMR ($CDCl_3$, Me_4Si) 77.15 (NCN), 44.91, 52.58, 54.51, 56.10 (NC), 19.73 (CCC) ppm; mass spectrum, m/e 222.183 (calcd for $C_{12}H_{22}N_4$ 222.184).

1,5,8,12-Tetraazabicyclo[10.2.2]hexadecane (13). DIBAH in *n*-hexane (150 mL, 150 mmol) was added dropwise to the tetramine **12** (1.11 g, 5 mmol) at 0 °C and the resulting solution was allowed to warm to 25 °C. Then *n*-hexane was replaced by toluene (70.7 mL). This solution was refluxed for 4 days. The reaction mixture was cooled to 0 °C, and worked up in the usual manner with benzene (300 mL), sodium fluoride (25.2 g), and water (8.1 mL). Filtration, washing of the residue with ethanol, and purification of the concentrated filtrates by column chromatography on silanized silica gel (*i*-$PrNH_2$–$CHCl_3$, 1:9) gave **13** (1.085 g, 96% yield) as a colorless oil: silanized TLC R_f 0.29 (*i*-$PrNH_2$–$CHCl_3$, 1:9); IR (liquid film) 3280 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 2.12–3.87 (22 H, m, NCH_2, NH), 1.44–1.93 (4 H, m, CCH_2C); ^{13}C NMR ($CDCl_3$, Me_4Si) 50.02, 51.69, 57.42 (NC), 25.98 (CCC) ppm; mass spectrum, m/e 226.212 (calcd for $C_{12}H_{26}N_4$ 226.216).

1,5,8,12-Tetraazatricyclo[10.2.2.$2^{5,8}$]octadecane (15). A solution of oxalyl chloride (140 mg, 1.1 mmol) in dichloromethane (2 mL) was added dropwise over 30 min at 0 °C to a stirred solution of the tetramine **13** (226 mg, 1 mmol). During this operation, a white precipitate appeared. Stirring was continued at 0 °C for 1 h. Then the solvent was evaporated and the residue was directly applied to column chromatography on silica gel (*i*-$PrNH_2$–$CHCl_3$, 1:20) to furnish the diamide **14** (117 mg, 42% yield); TLC R_f 0.56 (*i*-$PrNH_2$–$CHCl_3$, 1:9).

A solution of DIBAH in *n*-hexane (2 mL, 2 mmol) was added dropwise to the diamide **14** at 0 °C, and the resulting solution was stirred at 25 °C for 1 day. Then the reaction was quenched at 0 °C in the usual manner with benzene (6 mL), sodium fluoride (336 mg), and water (0.1 mL). Filtration, washing of the white precipitate with ethanol, and purification by column chromatography on silanized silica gel (*i*-$PrNH_2$–$CHCl_3$, 1:4) afforded **15** (35 mg, 80% yield): silanized TLC R_f 0.4 (*i*-$PrNH_2$–$CHCl_3$, 1:2); ^1H NMR ($CDCl_3$) δ 2.04–3.91 (24 H, m, NCH_2), 1.37–2.04 (4 H, m, CCH_2C); ^{13}C NMR ($CDCl_3$, Me_4Si) 49.58, 56.01 (NC), 23.87 (CCC) ppm; mass spectrum m/e 252.227 (calcd for $C_{14}H_{28}N_4$ 252.231).

***N,N'*-Dimethyl Derivative of 13.** Aqueous 37% formaldehyde (0.2 mL, 2.5 mmol) and sodium cyanoborohydride (50 mg, 0.8 mmol) were added successively to a stirred solution of the tetramine **13** (56 mg, 0.25 mmol) in acetonitrile (1.5 mL) at 25 °C. Stirring was continued for 5 h at 25 °C. During this period, the reaction mixture was kept neutral by the addition of acetic acid (8 drops). Evaporation of the solvent left a viscous oil, which was directly subjected to column chromatography on silica gel (*i*-$PrNH_2$–$CHCl_3$, 1:7) to furnish the title compound (62 mg, 98% yield) as a colorless oil: IR (liquid film) 1682, 1469, 1360, 1136, 1070, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21, 2.44 (6 H, s, NCH_3); ^{13}C NMR ($CDCl_3$, Me_4Si) 23.95, 42.01, 46.41, 51.61, 56.45, 56.89 ppm; mass spectrum, m/e 254.243 (calcd for $C_{14}H_{30}N_4$ 254.247).

Bis(*p*-toluenesulfonamide) of 13. *p*-Toluenesulfonyl chloride (210 mg, 1.1 mmol) was added portionwise to a solution of the tetramine **13** (113 mg, 0.5 mmol) and triethylamine (0.28 mL, 2 mmol) in dichloromethane (3 mL) at 0 °C. The ice bath was removed, and further stirring was continued at 25 °C for 2 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel (*i*-$PrNH_2$–$CHCl_3$, 1:30) furnished the title compound (191 mg, 72% yield) as white crystals: TLC R_f 0.39 (*i*-$PrNH_2$–$CHCl_3$, 1:19); IR (Nujol) 1505, 1607 cm^{-1} (C=C), 1166, 1348 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 7.07–7.85 (8 H, m, aryl CH), 2.21–3.52 (20 H, m, NCH_2), 2.44 (6 H, s, CH_3), 1.44–2.00 (4 H, m, CCH_2); ^{13}C NMR ($CDCl_3$, Me_4Si) 21.75, 28.09, 47.82, 48.17, 48.79, 53.28, 127.43, 129.81, 136.59, 143.37 ppm; mass spectrum m/e 378 (M^+ – TsH).

1-Isopropyl-2-methyltetrahydropyrimidine (16). A mixture of *N*-isopropyl-1,3-diaminopropane (11.6 g, 0.1 mol) and ethyl acetoacetate

(12.76 mL, 0.1 mol)[19] in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate (10 mg) was heated at 210 °C for 5 h. The resulting dark orange viscous oil was directly distilled under reduced pressure to give **16** (7.81 g, 56% yield) as a colorless oil: bp 104.5 °C (22 mmHg); IR (liquid film) 1635, 1443, 1320, 1220, 1145, 1025, 948 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97 (1 H, heptet J = 6.8 Hz, NCH), 2.93–3.47 (4 H, m, NCH_2), 1.99 (3 H, s, N=CCH_3), 1.53–2.13 (2 H, m, CCH_2C), 1.18 (6 H, d, J = 6.8 Hz, $C(CH_3)_2$); mass spectrum, m/e 140.142 (calcd for $C_8H_{16}N_2$ 140.131).

N-Ethyl-N'-isopropyl-1,3-diaminopropane (17). A solution of DIBAH in *n*-hexane (12 mL, 12 mmol) was added dropwise to **16** at 0 °C, and the resulting solution was stirred at 25 °C for 1 day and then under reflux for 30 min. The mixture was worked up in the usual way with benzene (12 mL), sodium fluoride (2 g), and water (0.65 mL). Purification of the crude diamine by column chromatography on silica gel (*i*-$PrNH_2$–$CHCl_3$, 1:7) gave **17** (278 mg, 97% yield) as a colorless oil: TLC R_f 0.33 (*i*-$PrNH_2$–$CHCl_3$, 1:5) bp 111–114 °C (29 mmHg, bath temperature); IR (liquid film) 3448, 1465, 1306, 1177, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10–3.73 (1 H, m, NCH), 2.43–3.00 (6 H, m, NCH_2), 2.30 (2 H, s, NH), 1.48–1.97 (2 H, m, CCH_2C), 1.09 (3 H, t, J = 7.0 Hz, CH_2CH_3), 1.07 (6 H, d, J = 7.0 Hz, $C(CH_3)_2$); mass spectrum, m/e 144.165 (calcd for $C_8H_{20}N_2$ 144.163).

1-Benzyl-2-propyl-4,5-dihydroimidazole (18). A mixture of *N*-benzylethylenediamine (7.5 g, 50 mmol) and ethyl butyroacetate (7.9 g, 50 mmol)[29] in the presence of *p*-toluenesulfonic acid monohydrate (5 mg) was heated at 210 °C for 5 h. The mixture was allowed to cool to 25 °C and then distilled under reduced pressure to give **18** (6.89 g, 68% yield) as a light yellow oil: TLC R_f 0.33 (*i*-$PrNH_2$–ether, 1:20); bp 124–126 °C (0.3 mmHg); IR (liquid film) 1668, 1620, 1452, 1425, 1213, 989, 728, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (5 H, s, aryl CH), 4.26 (2 H, s, $PhCH_2N$), 2.92–3.92 (4 H, m, NCH_2CH_2N), 2.05–2.47 (2 H, m, N=CCH_2), 1.38–1.95 (2 H, m, N=$CCCH_2$), 0.98 (3 H, t, J = 7.0 Hz, CH_3); mass spectrum, m/e 202.152 (calcd for $C_{13}H_{18}N_2$ 202.147).

N-Benzyl-N'-butylethylenediamine (21). The reduction of **18** (202 mg, 1 mmol) with DIBAH in *n*-hexane (6 mL, 6 mmol) was carried out at 25 °C for 1 h and then under reflux for 1 h. The reaction mixture was worked up in the usual manner with sodium fluoride and water. Purification of the crude diamine by column chromatography on silica gel (*i*-$PrNH_2$–ether, 1:30) gave **21** (196 mg, 95% yield) as a colorless oil: TLC R_f 0.44 (*i*-$PrNH_2$–ether, 1:20); bp 148–151 °C (0.45 mmHg, bath temperature); IR (liquid film) 3350, 1478, 1126, 738, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (5 H, s, aryl CH), 3.79 (2 H, s, $PhCH_2$), 2.75 (4 H, s, NCH_2CH_2N), 2.57 (2 H, t, J = 6.2 Hz, NCH_2), 1.77 (2 H, s, NH), 1.12–1.66 (4 H, m, CCH_2C), 0.72–1.12 (3 H, m, CH_3); mass spectrum, m/e 206.174 (calcd for $C_{18}H_{22}N_2$ 206.178).

1-Benzyl-2-methylbenzenzimidazole (19). Benzyl chloride (0.92 mL, 8 mmol) was added dropwise to a methanolic solution (5 mL) of 2-methylbenzimidazole (396 mg, 3 mmol) at 25 °C, and the resulting mixture was refluxed for 40 h. Then the solvent was evaporated. The residue was washed with saturated sodium bicarbonate and extracted with chloroform. Purification of the concentrated extracts by column chromatography on silica gel (ethyl acetate) gave **19** (176 mg, 26% yield) as a brown oil: TLC R_f 0.37 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 6.84–7.80 (9 H, m, aryl CH), 5.16 (2 H, s, NCH_2), 2.46 (3 H, s, CH_3); mass spectrum, m/e 222.290 (calcd for $C_{15}H_{14}N_2$ 222.292).

N-Benzyl-N'-ethyl-o-phenylenediamine (22). A solution of DIBAH in *n*-hexane (4.46 mL, 4.46 mmol) was added dropwise to **19** (164 mg, 0.74 mmol) at 0 °C. Stirring was continued at 25 °C for 16 h. Then the mixture was worked up by the sodium fluoride–water method. Column chromatography of the crude diamine on silica gel (ethyl acetate–hexane, 1:6, then 1:4) furnished **22** (162 mg, 97% yield) as a yellow oil: TLC R_f 0.70 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 6.45–7.46 (9 H, m, aryl CH), 4.18 (2 H, s, $PhCH_2N$), 3.23 (2 H, br s, NH), 3.04 (2 H, q, J = 7.2 Hz, NCH_2CH_3), 1.19 (3 H, t, J = 7.2 Hz, CH_3); mass spectrum, m/e 226.317 (calcd for $C_{15}H_{18}N_2$ 226.324).

N-Propyl-1,8-diaminonaphthalene (23). A solution of DIBAH in *n*-hexane (7 ml, 7 mmol) was added dropwise to a solution of 2-ethylperimidine[30] (196 mg, 1 mmol) in benzene (3.5 mL) at 0 °C, and the resulting mixture was refluxed for 15 h. Workup with NaF–H_2O, followed by the purification of the crude diamine by column chromatography on silica gel (benzene), gave **23** (167 mg, 84% yield) as a purple oil: TLC R_f 0.45 (benzene); IR (liquid film) 3340, 3300, 2925, 1588, 1510, 1408, 1132, 782, 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29–7.23 (6 H, m, aryl CH), 4.64 (3 H, br s, NH), 2.93 (2 H, t, J = 7.2 Hz, NCH_2), 1.60 (2 H, hextet, J = 7.2 Hz, $NCCH_2$), 0.92 (3 H, t, J = 7.2 Hz, CH_3); mass spectrum, m/e 200.289 (calcd for $C_{13}H_{16}N_2$ 200.286).

Reduction of 2-Methylbenzimidazole with DIBAH. A solution of DIBAH in *n*-hexane (7 mL, 7 mmol) was added dropwise to 2-methylbenzimidazole (132 mg, 1 mmol) at 0 °C. The resulting mixture was heated to reflux for 5 h. After removal of the solvent under reduced pressure, the mixture was further heated at 50 °C for 1 h and then at 140 °C for 4 h to give only recovered starting material.

1,2-Bis(2-tetrahydropyrimidyl)ethane (24). The bis(*p*-toluenesulfonate) of **24** was prepared from succinonitrile, 1,3-diaminopropane, and its bis(*p*-toluenesulfonate). Recrystallization from 95% ethanol gave the white needle crystals, mp 270–272 °C (lit.[22] mp 285 °C). The bis(*p*-toluenesulfonate) (5.38 g, 10 mmol) of **24**, thus obtained, was treated with sodium methoxide (1.188 g, 22 mmol) in methanol (20 mL) at 0 °C for 20 min. Evaporation of methanol, and addition, followed by evaporation of chloroform to remove a trace methanol, left the white solid, which was washed with hot benzene several times to afford **24** (1.876 g, 97% yield) as white crystals: mp 194–197 °C (recrystallized from benzene, lit.[22] mp 200 °C); ^1H NMR ($CDCl_3$) δ 7.31 (2 H, s, NH) 3.27 (8 H, t, J = 5.8 Hz, NCH_2), 2.42 (4 H, s, CH_2CH_2), 1.43–2.00 (4 H, m, CCH_2C); mass spectrum, m/e 194.154 (calcd for $C_{10}H_{18}N_4$ 194.153).

Spermine from 24. A solution of DIBAH in *n*-hexane (16 mL, 16 mmol) was added to bisamidine **24** (194 mg, 1 mmol) at 0 °C. The solvent was evaporated, and the residue was heated at 150 °C for 11 h. The reaction mixture was then cooled to 25 °C, diluted with benzene, and worked up by the NaF–H_2O method. Purification of the crude product by column chromatography on silica gel (aqueous $EtNH_2$–MeOH, 1:3) gave spermine (29 mg, 14% yield) as a colorless oil: bp 172–176 °C [40 mmHg, bath temperature (authentic sample, mp 150 °C (5 mmHg))]; IR (liquid film) 3997, 3307, 1620, 1487, 1382, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46–2.93 (12 H, m, NCH_2), 1.53 (6 H, s, NH), 1.33–1.88 (8 H, m, CCH_2C); mass spectrum, m/e 202.218 (calcd for $C_{10}H_{20}N_4$ 202.216). This product was dissolved in ethanol and treated with concentrated hydrochloric acid to give the ammonium salt as a white solid, which was recrystallized from 12% HCl–EtOH; mp 309–311 °C (lit.[31] mp 310–311 °C dec).

Sperimine from Bis(trimethylsilylamide) of 24. A mixture of bisamide **24** (388 mg, 2 mmol) and hexamethyldisilazane (6.5 mL, 30 mmol) was refluxed gently in the presence of fuming sulfuric acid (1 drop) for 12 h.[23] Then excess hexamethyldisilazane was evaporated under reduced pressure, and a solution of DIBAH in *n*-hexane (24 mL, 24 mmol) was added at 0 °C. The solvent was replaced by xylene (11 mL), and the resulting solution was refluxed for 3 days. Usual workup, followed by purification of the crude product as described above, afforded spermine (254 mg, 63% yield).

General Method for Preparation of Cyclic Polyamines. Cyclic polyamines were prepared by the reduction of cyclic amidines with DIBAH in toluene (1.0 M) under reflux. Synthesis of 1,5-diazacycloundecane (**27**) from DBU (**26**) is representative.

1,5-Diazacycloundecane (27). A solution of DIBAH in toluene (12 mL, 12 mmol) was added to DBU (304 mg, 2 mmol) at 0 °C. The resulting colorless solution was heated to reflux for 7 h. At this stage, analysis of the reaction mixture by TLC indicated complete or nearly complete consumption of the starting material. The solution was diluted with benzene (36 mL), treated successively with sodium fluoride (2.016 g, 48 mmol) and water (0.65 mL, 36 mmol) at 0 °C, and stirred vigorously at 25 °C for 20 min. Filtration, washing of the residue with hot chloroform, and removal of the solvent left the essentially pure **27**, which was further purified by preparative TLC (aqueous $EtNH_2$–MeOH, 1:4) to furnish the pure diamine **27** (300 mg, 96% yield) as a colorless oil: TLC R_f 0.31 (aqueous $EtNH_2$–MeOH, 1:4); IR (liquid film) 3339, 760 (NH), 1157 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 2.90 (2 H, s, NH), 2.80 (4 H, t, J = 4.8 Hz, NCH_2), 2.44–2.87 (4 H, m, NCH_2), 1.26–1.75 (10 H, br s, CCH_2C); ^{13}C NMR ($CDCl_3$, Me_4Si) 25.72, 25.89, 26.95, 28.71, 29.06, 48.61, 50.46, 53.37. 53.63 ppm; mass spectrum m/e 156.166 (calcd for $C_9H_{20}N_2$ 156.163).

The syntheses of other cyclic polyamines starting from the corresponding cyclic amidines were carried out in a similar manner as described above (Table III). The physical properties and analytical data of these cyclic polyamines are listed in Table IV.

N-(3-Aminopropyl)hexamethyleneimine (28). A solution of DIBAH in *n*-hexane (16 mL, 16 mmol) was added dropwise to *N*-(3-aminopropyl)caprolactam (332 mg, 2 mmol) at 0 °C. Stirring was continued at 25 °C for 10 h and then under reflux for 1 h. The solution was diluted and worked up with sodium fluoride (2.688 g, 64 mmol) and water (0.86 mL, 48 mmol). Filtration, washing of the residue with hot chloroform and purification of the concentrated filtrate by column chromatography on silica gel (aqueous NH_3–MeOH, 1:8) gave **28** (170 mg, 55% yield): TLC R_f 0.35 (aqueous NH_3–MeOH, 1:5); bp 144–148 °C (3.8 mmHg,

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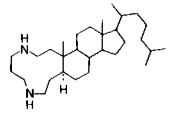
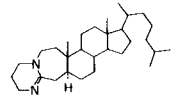
Table IV. Physical Properties and Analytical Data of Cyclic Polyamines

cyclic polyamine (*m,n*) or (*k,l,n*)	bp (mmHg) or mp (solvent), °C	IR, cm^{-1} [a]	^1H NMR, δ	^{13}C NMR, ppm from Me_4Si	mass spectrum, *m/e*
(4,2)	128–133 (24)[b]	3355 (NH), 1138 (CN)	2.59–3.00 (4 H, m, NCH_2), 2.74 (4 H, s, NCH_2CH_2N), 2.31 (2 H, s, NH), 1.41–1.83 (6 H, m, CCH_2C)		128.135 (calcd for $C_7H_{16}N_2$ 128.131)
(7,2)	132–135 (0.5)[b]	3424 (NH), 1133 (CN)	2.50–2.78 (4 H, m, NCH_2), 2.68 (4 H, s, NCH_2CH_2N), 1.77 (2 H, s, NH), 1.19–1.62 (12 H, br s, CCH_2C)	21.14, 24.57, 26.68, 45.27, 46.32	170.179 (calcd for $C_{10}H_{22}N_2$ 170.178)
(7,3)	159–162 (3.6)[b]	3303 (NH), 1136 (CN)	2.25–2.80 (10 H, m, NCH_2, NH), 1.13–1.79 (14 H, br s, CCH_2C)	24.40, 26.24, 27.65, 45.27, 46.32	184.200 (calcd for $C_{11}H_{24}N_2$ 184.194)
(11,2)	159–161 (0.6)[b]	3335 (NH),[c] 1164 (CN)	2.48–2.72 (4 H, m, NCH_2), 2.68 (4 H, s, NCH_2), 1.65 (2 H, s, NH), 1.17–1.68 (20 H, br s, CCH_2C)	25.54, 26.24, 26.95, 27.12, 29.06, 48.44, 48.88	226.247 (calcd for $C_{14}H_{30}N_2$ 226.241)
(11,3)	165–168 (0.9)[b]	3315 (NH), 1133 (CN)	2.45–2.88 (8 H, m, NCH_2), 1.85 (2 H, s, NH), 1.15–1.58 (22 H, br s, CCH_2C)	24.92, 25.54, 26.24, 26.60, 28.53, 48.52, 48.79	240.260 (calcd for $C_{15}H_{32}N_2$ 240.257)
(6,8,2)	47–49 (ether)	3318 (NH), 1136 (CN)	2.76 (8 H, s, NCH_2CH_2N), 2.57 (8 H, br t, J = 5.0 Hz, NCH_2), 1.56 (4 H, br s, NH), 1.08–1.73 (24 H, br s, CCH_2C)	27.04, 27.39, 29.50, 29.94, 30.29, 48.88, 49.49	339.955 (calcd for $C_{20}H_{44}N_4$ 340.357)
(12,8,2)	71–72 (ether)	3342 (NH), 1145 (CN)	2.68 (8 H, s, NCH_2CH_2N), 2.59 (8 H, t, J = 6.0 Hz, NCH_2), 1.94 and 1.72 (4 H, br, s, NH), 1.04–1.65 (36 H, br s, CCH_2C)	27.12, 29.41, 30.03, 48.96, 49.41	424.445 (calcd for $C_{26}H_{56}N_4$ 424.451)
	138.5–140 (*i*-$PrNH_2$)[e]	3297 (NH),[d] 1132 (CN)	2.30–3.10 (10 H, NCH_2, NH), 0.65, 0.73, 0.83, 0.92, (15 H, 4 s, CH_3)	12.15, 16.64, 18.93, 21.58, 22.81, 23.07, 24.04, 24.57, 28.62, 31.26, 32.14, 35.67, 36.02, 36.37, 39.72, 39.98, 40.33, 42.45, 42.71, 46.15, 47.38, 49.85, 56.45, 56.80	444.444 (calcd for $C_{30}H_{56}N_2$ 444.444)

[a] Unless otherwise specified, the IR spectra were taken as liquid films. [b] Bath temperature. [c] Nujol mull. [d] Chloroform solution. [e] [α] 15.3° (*c* 3, benzene).

Table V. Physical Properties and Analytical Data of Cyclic Amidines

amidine[a] (*m,n*)[b]	bp[c] (mmHg), °C	IR, cm^{-1}	^1H NMR, δ	mass spectrum, *m/e*
(4,2)	90–93 (1.55)	1641, 1291, 1010	2.77–3.99 (6 H, m, NCH_2), 2.16–2.62 (2 H, m, $N{=}CCH_2$), 1.47–2.08 (4 H, m, CCH_2C)	124.103 (calcd for $C_7H_{12}N_2$ 124.100)
(7,2)	159–161 (6.0)	1607, 1452, 1004	3.05–3.94 (6 H, m, NCH_2), 2.08–2.58 (2 H, m, $N{=}CCH_2$), 1.11–2.08 (10 H, m, CCH_2C)	166.143 (calcd for $C_{10}H_{18}N_2$ 166.147)
(7,3)	154–159 (0.7)	1615, 1454, 1374, 1320	2.91–3.53 (6 H, m, NCH_2), 2.08–2.60 (2 H, m, $N{=}CCH_2$), 1.10–2.08 (12 H, m, CCH_2C)	180.165 (calcd for $C_{11}H_{20}N_2$ 180.163)
(11,2)	188–192 (5.0)	1608, 14391, 1239	2.88–3.91 (6 H, m, NCH_2), 2.15–2.51 (2 H, m, $N{=}CCH_2$), 1.21–1.84 (18 H, m, CCH_2C)	222.213 (calcd for $C_{14}H_{26}N_2$ 222.210)
(11,3)	180–183 (0.6)	1627, 1451[d]	2.90–3.43 (6 H, m, NCH_2), 1.97–2.43 (2 H, m, $N{=}CCH_2$), 1.07–1.97 (20 H, m, CCH_2C)	236.229 (calcd for $C_{15}H_{28}N_2$ 236.225)
			3.06–3.43 (6 H, m, NCH_2), 0.66, 0.82, 0.89, 0.92 (15 H, 4 s, CH_3)	440.415 (calcd for $C_{30}H_{52}N_2$ 440.413)

[a] The bisamidines (entry 8 and 9 in Table III) were characterized by mass spectra. The bisamidine in entry 8: *m/e* 332.290 (calcd for $C_{20}H_{36}N_4$ 332.294). The bisamidine in entry 9: *m/e* 416.695 (calcd for $C_{26}H_{48}N_4$ 416.699). [b] For this abbreviation, see Table III. [c] Bath temperature. [d] Nujol. [e] ^{13}C NMR (Me_4Si) 12.24, 18.85, 21.66, 22.02, 22.99, 24.04, 24.39, 28.18, 31.00, 32.23, 34.96, 35.93, 36.37, 38.31, 39.01, 39.72, 40.16, 41.04, 42.45, 42.80, 45.88, 48.35, 48.61, 54.34, 56.45, 162.48 ppm.

bath temperature); ^{1}H NMR ($CDCl_3$) δ 2.39-2.85 (8 H, m, NCH_2), 1.41-1.79 (12 H, br s, CCH_2C and NH_2); ^{13}C NMR ($CDCl_3$, Me_4Si) 27.12, 28.27, 31.62, 41.04, 55.75, 56.26 ppm; mass spectrum m/e 156.164 (calcd for $C_9H_{20}N_2$ 156.163).

***N,N'*-Dimethyl-1,5-diazacycloundecane.** The diamine **27** (780 mg, 5 mmol) in acetonitrile (30 mL) was treated successively with aqueous 37% formaldehyde (4.05 mL, 50 mmol) and sodium cyanoborohydride (754 g, 12.5 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h. Then glacial acetic acid (25 drops) was added dropwise at 25 °C to neutralize the reaction mixture. Further stirring was continued at 25 °C for 2 h. Evaporation of the solvents, followed by purification of the residue by column chromatography on silica gel (*i*-$PrNH_2$-$CHCl_3$, 1:20), gave *N,N'*-dimethyl-1,5-diazacycloundecane 825 mg, 90% yield) as a colorless oil: TLC R_f 0.40 (*i*-$PrNH_2$-$CHCl_3$, 1:9; IR (liquid film) 1471, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.21-2.57 (5 H, m, NCH_2), 2.12 (6 H, s, NCH_3), 1.30-1.69 (10 H, br s, CCH_2O); ^{13}C NMR ($CDCl_3$, Me_4Si) 24.39, 25.80, 25.98, 42.01, 53.19, 57.24; mass spectrum m/e 184.200 (calcd for $C_{11}H_{24}N_2$ 184.194).

Bis(*p*-toluenesulfonamide) of 27. Treatment of the diamine **27** with *p*-toluenesulfonyl chloride (2.5 equiv) and triethylamine (5 equiv) in dichloromethane at 0 °C for 1 h and then at 25 °C for 2 h, followed by purification of the resulting crude product by column chromatography on silica gel (ether-hexane, 1:1), gave the bis(*p*-toluenesulfonamide) as white crystals: TLC R_f 0.29 (ether-hexane, 1:1); IR (Nujol) 1340, 1159 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ 7.10-7.77 (5 H, m, aryl CH), 2.76-3.26 (8 H, br t, NCH_2), 2.42 (6 H, s, CH_3), 1.41-2.01 (10 H, br s, CCH_2C); mass spectrum, m/e 309 (M^+ - TsH).

General Methods for Preparation of Cyclic Amidines. Method A. The lactam (10 mmol) was added to a solution of triethyloxonium tetrafluoroborate[32] (11 mmol) in dichloromethane (25 mL) at 25 °C, and the resulting mixture was stirred at 25 °C for 17 h. Then the mixture was poured onto 5% potassium hydroxide solution (50 mL). The organic layer was separated and washed with cold water (3 × 50 mL). Each aqueous layer was washed with dichloromethane. The combined extracts were concentrated to give the imino ether in quantitative yield. Without purification this was dissolved in aziridine[33] (0.8 mL)-dichloromethane (3.3 mL) and treated with ammonium bromide (0.2 mmol) at 25 °C. Further stirring was continued at 25 °C for 30 h to ensure the formation of amidine, which was rearranged by exposure to iodine (0.5 mL) in benzene (15 mL) at 25 °C for 4 h and then reflux for 1 h to furnish the dihydroimidazole after purification by column chromatography on silica gel.

Method B. The lactam (10 mmol) was converted as described above into the imino ether in quantitative yield, which was treated with 3-bromopropylamine hydrobromide (11 mmol) in absolute ethanol (15 mL) at 25 °C. Stirring was continued at 25 °C for 40 h. Then powdered potassium carbonate (22 mmol) was added at 0 °C and the whole mixture was stirred at 0 °C for 150 min. Dilution with chloroform (300 mL), filtration, and washing of the residue with chloroform gave the tetrahydropyrimidine after purification by preparative TLC.

Method C. Sodium ethoxide was prepared by dissolving metallic sodium (10 mmol) in absolute ethanol (5 mL), followed by evaporation of excess ethanol. Toluene (30 mL) and the lactam (10 mmol) were added at 25 °C, and the resulting suspension was heated gently until a clear yellow solution was produced. Then acrylonitrile (100 mmol) was added slowly over 4 h at 25 °C with vigorous stirring. Further stirring was carried out at 25 °C for 3 h. The mixture was diluted with ethyl acetate to separate the polymer as yellow precipitates. The filtrate was concentrated and directly subjected to column chromatography on silica gel to give the *N*-cyanoethyl lactam. The *N*-cyanoethyl lactam (6.6 mmol) was dissolved in absolute ethanol (165 mL)-chloroform (3.3 mL) and hydrogenated over platinum oxide (50 mg) at 25 °C for 9 h. Filtration, washing of the residue with chloroform, and purification of the concentrated filtrate by column chromatography on silica gel gave the *N*-(3-aminopropyl) lactam. Titanium tetrachloride (1.5 mmol) was added dropwise to a solution of *N*-(3-aminopropyl) lactam (1 mmol) in xylene (5 mL) at 25 °C and the resulting mixture was refluxed for 9.5 h. The mixture was then cooled to 25 °C and treated with a methanolic solution (5 mL) of sodium hydroxide (6 mmol). Filtration, washing of the residue with chloroform, and purification by column chromatography on silica gel gave the tetrahydropyrimidine.

Physical properties and analytical data of the cyclic amidines are given in Table V.

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Effect of Nucleophile Basicity on Intramolecular Nucleophilic Aminolysis Reactions of Carbonate Diesters

Thomas H. Fife* and J. E. C. Hutchins

Contribution from the Department of Biochemistry, University of Southern California, Los Angeles, California 90033. *Received October 6, 1980*

Abstract: The rates of phenol release from para-substituted phenyl 2-pyridylethyl carbonates have been measured in H_2O at 25 °C (μ 0.5 M). The pH-rate constant profiles are sigmoidal, showing participation by the pyridine neutral base species. The D_2O solvent isotope effect is nearly unity, indicating that participation is by a nucleophilic reaction. The Hammett ρ value for intramolecular pyridine assisted phenol release is +2.2, and the fit is better with σ^- than with σ, indicating considerable C-O bond breaking in the transition state. The effective molarity of the neighboring pyridine of *p*-nitrophenyl 2-pyridylethyl carbonate is 81 M in comparison with pyridine acting as a bimolecular catalyst in the hydrolysis of ethyl *p*-nitrophenyl carbonate. Intramolecular nucleophilic attack is 217 times more favorable when a five-membered ring is formed with phenyl 2-pyridylmethyl carbonate than in the case of phenyl 2-pyridylethyl carbonate where the reaction proceeds via a six-membered ring. The effective molarity of neighboring pyridine in the 2-pyridylmethyl series is 2×10^3 M. Sigmoidal pH-rate constant profiles were also obtained with neighboring imidazole, *N,N*-dimethylamino, and *N*-methylpiperidine nucleophiles. Values of the limiting rate constants (k_B) are similar in spite of pK_{app} values which vary from 3.9 to 10. The effective molarity of the dimethylamino group of *p*-nitrophenyl *N,N*-dimethylaminopropyl carbonate is only 32 M in comparison to reaction of trimethylamine with ethyl *p*-nitrophenyl carbonate. On the other hand, the effective molarity of the dimethylamino group of *p*-nitrophenyl *o*-(*N,N*-dimethylamino)phenyl carbonate (pK_{app} = 3.9) is >10^5 M. The most efficient intramolecular nucleophiles in reactions of *p*-nitrophenyl carbonate diesters are those of low pK_a. In contrast, with analogous carboxylate esters the converse is the case, even though the rate constants for bimolecular aminolysis of *p*-nitrophenyl acetate and ethyl *p*-nitrophenyl carbonate are closely similar. These results may indicate that C-N bond formation is not complete in the transition states of the intramolecular reactions.

Intramolecular nucleophilic attack on phenyl esters by amine bases has been extensively studied.[1-5] These reactions are considerably more efficient than corresponding bimolecular reactions proceeding by the same mechanism. The neighboring imidazole

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