tion. We thank Dr. C. K. Shaw for providing some of the compounds needed for this study, Professor Emil White for helpful suggestions, and the Chemistry Department of the University of North Carolina at Chapel Hill for its hospitality to T.C. while he was on leave there during the writing of much of this paper.

Registry No. 3, 23015-31-8; **4**, 23018-02-2; *trans,cis*-2-aminodecalin, 23017-71-2; ethyl chloroformate, 541-41-3; *trans,trans*-2-aminodecalin, 936-35-6; *trans,cis*-2-decalol, 2529-06-8; *trans,trans*-2-decalol, 5779-35-1; *trans,cis*-2-decalyl acetate, 66964-88-3; *trans,trans*-2-decalyl acetate, 66964-89-4; *trans*-1-octalin, 2001-49-2; *trans*-2-octalin, 2001-50-5; ethyl *trans,cis*-2-decalylcarbonate, 73688-49-0; ethyl *N*-acetyl-*N*-(*trans,cis*-2-decalyl)carbamate, 73688-50-3; ethyl *N*-(*trans,cis*-2-decalyl)carbamate, 73688-51-4; ethyl *N*-acetyl-*N*-(*trans,trans*-2-decalyl)carbamate, 73688-52-5; ethyl *N*-(*trans,trans*-2-decalyl)carbamate, 73688-53-6.

The Hantzsch 1,4-Dihydropyridine Synthesis as a Route to Bridged Pyridine and Dihydropyridine Crown Ethers[1]

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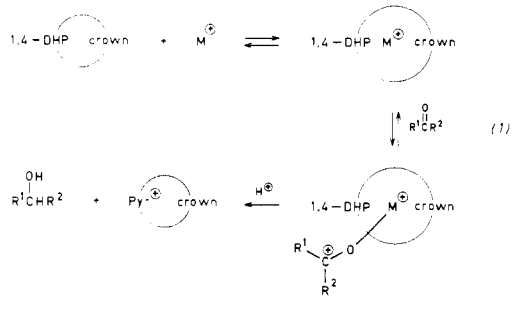
Received December 28, 1979 (Revised Manuscript Received March 31, 1980)

Mono-, di-, tri-, and tetraethylene glycols were transesterified with ethyl acetoacetate to give the bis(acetoacetate esters) **1a–d**. On treatment of **1c,d** with formaldehyde and excess $(NH_4)_2CO_3$ in H_2O a crude mixture of 1,4-dihydropyridines was obtained from which, after dehydrogenation to the pyridine form, the 3,5-bridged 2,6-dimethylpyridines **2c,d** were isolated along with dimers **7c,d**. Similar reaction of **1a** gave only dimer **7a**. The bridged pyridine **2d** was methylated to give pyridinium salt **3d**, which was reduced with $Na_2S_2O_4$ to give 1,4-dihydropyridine **4d**. Stable sodium salts of **4d** and **6d** were isolated. Bridged pyridines **10a–c** substituted with, respectively, methyl, phenyl, and 2-furyl at the γ position of the pyridine ring have also been prepared, using **1d**, $(NH_4)_2CO_3$, and acetaldehyde, benzaldehyde, and 2-furfuraldehyde and Hantzsch condensation followed by dehydrogenation and chromatographic separation. Protection of the 1,3-dicarbonyl system of ethyl 4-bromo-3-oxobutanoate as its Na chelate followed by nucleophilic substitution with the bisalkoxides from tetra-, penta-, and hexaethylene glycols gave 4-substituted bis(acetoacetate esters) **16a–c**. These on Hantzsch condensation yielded in low yield 2,6-bridged Hantzsch 1,4-dihydropyridines (**17a–c**). Treatment of **17a,b** with alkali metal hydrides gave insoluble materials thought to be the internally solvated alkali metal salts of the (vinylogous) amide nitrogen of the 1,4-dihydropyridine.

Introduction

Metal ions catalyze the reductions by 1,4-dihydropyridines (1,4-DHP) of many carbonyl compounds.[4] This is true both in enzymic reactions and in the reactions of simpler 1,4-DHP's. We are interested in the design of synthetic 1,4-DHP-containing systems wherein the efficiency of this catalytic aspect is high. One appealing approach to such an objective is to incorporate the 1,4-DHP into a poly(ethylene glycol) chain having sufficient "crown ether" character to complex a metal ion. If the position of the metal ion relative to the 1,4-DHP can be arranged properly, one can imagine the operation of the reaction sequence shown in eq 1.[5] The 1,4-DHP on (formal) loss of hydride is converted to a pyridine (Pyr) if the nitrogen atom bears a hydrogen and to a pyridinium salt (Pyr^+) if the nitrogen atom is alkylated.



We have reported on the success of this strategy.[1,6] For reasons of design that will be discussed in subsequent publications, the (dihydro)pyridine has been incorporated as an integral section of the macrocyclic system[7] rather than as an appendage to an already formed crown ether.[8] We describe here the results of our initial attempts to secure such systems using an approach based on a modified Hantzsch dihydropyridine synthesis.[9]

Results and Discussion

The best known version of the Hantzsch condensation is the reaction of an acetoacetate derivative with a carbonyl compound, usually but not always an aldehyde, and ammonia (eq 2). Considerable variation in structure can be

(1) Previous publication in this series: van Bergen, T. J.; Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1979**, *44*, 4953. Also de Vries, J. G.; Kellogg, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 2759.
(2) Department of Public Health, Rijswijk, The Netherlands.
(3) Undergraduate exchange student from Hope College, Holland, MI.
(4) For a compilation of references on this subject, see ref 1.
(5) Prior to our efforts in this direction, the synthesis of dihydropyridines or pyridinium salts bridged with poly(methylene) chains has been described: (a) Overman, L. E. *J. Org. Chem.* **1972**, *37*, 4214. (b) Dittmer, D. C.; Blidner, B. B. *Ibid.* **1973**, *38*, 1973. For a recent review of reductions by 1,4-DHP's, see: Kill, R. J.; Widdowson, D. A. *Bioorg. Chem.* *4*, 239–275.
(6) van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 3882.
(7) See, for example: Behr, J. P.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1978**, 143.
(8) Many pyridine-containing macrocycles incorporating poly(ethylene glycol), poly(methylene), or other chains have been prepared. A review complete through 1976 is given: Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513. For recent examples and citations of very recent literature see also: Newkome, G. R.; Kawato, T. *J. Org. Chem.* **1979**, *44*, 2693. Newkome, G. R.; Kawato, T.; Nayak, A. *Ibid.* **1979**, *44*, 2697. Heimann, U.; Vögtle, F. *Angew. Chem.* **1978**, *90*, 211.
(9) Review: Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.

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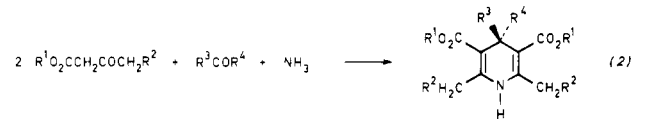


(2)

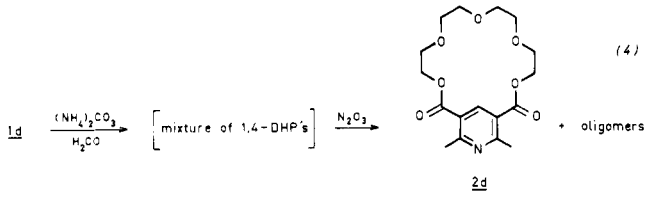
tolerated in the acetoacetate derivative and in the carbonyl component. The requirement for ammonia or ammonium ion appears to be nearly absolute, however; substituted amines do not react in reasonable yield in the Hantzsch condensation.

Two acetoacetates were linked by a poly(ethylene glycol) chain, as shown in eq 3, to adapt the Hantzsch conden-

$$2CH_3COCH_2CO_2C_2H_5 + HOCH_2(CH_2OCH_2)_n\text{-}CH_2OH \xrightarrow{\Delta} CH_3COCH_2CO_2CH_2(CH_2OCH_2)_n\text{-}CH_2O_2CCH_2COCH_3 + 2C_2H_5OH \quad (3)$$

1a, $n = 0$
b, $n = 1$
c, $n = 2$
d, $n = 3$

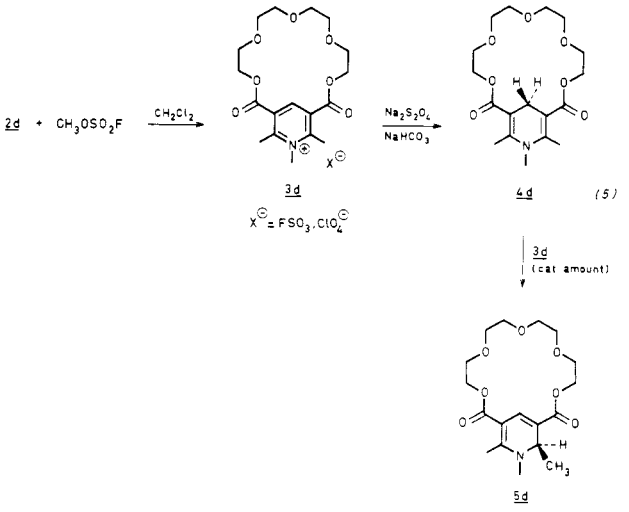
sation to crown ether synthesis. The condensation was then carried out with carbonyl component and a large excess of $(NH_4)_2CO_3$, which is intended to serve as ammonia source and buffer,[10] as well as template[11] for ring formation. On simultaneous and slow addition of a solution of **1d** and a solution of formaldehyde to a large excess of $(NH_4)_2CO_3$ in H_2O at room temperature, the yellow color and fluorescence characteristic of a 1,4-DHP appeared. The crude reaction mixture was extracted and without further attempt at purification N_2O_3 was passed through the solution to dehydrogenate the 1,4-DHP's.[9,12] Subsequent column chromatography allowed isolation of the bridged pyridine **2d** in 20–30% yield (eq 4). The structure of **2d** was established from analytical and spectral data.[13]



(4)

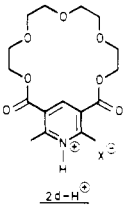
It was found that halving the amount of $(NH_4)_2CO_3$ and using either Na_2CO_3 or $MgCl_2 \cdot 6H_2O$ in place thereof led to no noteworthy change in yield. The effect of other metal ions on the condensation has not been examined.

For our purposes N-alkylated dihydropyridines were required; these were obtained from **2d** by means of the reactions shown in eq 5. Methylation of Hantzsch pyridines, despite the steric hindrance of the 2,6-methyl groups, usually proceeds well with dimethyl sulfate under mild conditions. However, with **2d**, and other Hantzsch pyridine crown ethers, we routinely experienced difficulties in alkylating nitrogen. The problem arises from the formation of unusually stable conjugate acids of the pyridines,



(5)

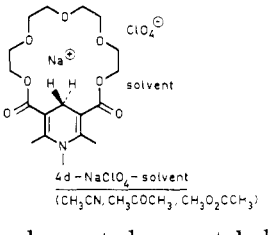
for example **2d**-H^+, which resist further alkylation. This



complication is not encountered with non-crown Hantzsch pyridines. After a number of unsuccessful experiments, it was found that methylation under as dry as possible conditions with CH_3OSO_2F, workup, and remethylation, this procedure being repeated several times, led to respectable yields of **3d**. **3d** was obtained in 80% yield in a single alkylation step, using highly purified **2d**, obtained by another route (see below).

The 1,4-DHP **4d** was obtained by reduction of **3d** (FSO_3^- is sometimes exchanged for ClO_4^-) with $Na_2S_2O_4$.[9] Reduction is best carried out at room temperature in only mildly basic solution to avoid rupture of the ester linkages. The yield of **4d** is nearly quantitative. The 1,2-dihydro isomer **5d** is obtained by isomerization of **4d** by pyridinium salt **3d**. This isomerization is a catalytic reaction in which the pyridinium salt acts as hydride acceptor. Transfer to the γ position is "blind" and reversible whereas transfer to the α positions of **3d** is irreversible.[14]

When treated with a saturated solution of $NaClO_4$ in acetone, acetonitrile, or methyl acetate, **4d** precipitates as a salt containing 1 equiv of $NaClO_4$ and one solvent molecule. The crystal structure of **4d**–$NaClO_4$–CH_3COCH_3



has been solved and reported separately.[15] We have thus far not obtained stable salts from the corresponding pyridine (**2d**) or pyridinium salt (**3d**) derivatives. This point will be reexamined, however, in view of the impressive successes particularly of Vögtle and co-workers in obtaining stable salts of somewhat related systems.[16]

(10) The choice of $(NH_4)_2CO_3$ was made primarily on the basis of the pioneering work of C.A.C. Haley and P. Maitland (*J. Chem. Soc.* **1951**, 3155), who demonstrated that optimal yields for the Hantzsch reaction, as well as various other condensation reactions carried out in aqueous solution, are obtained in weakly basic solutions. See also: Brody, F.; Ruby, P. R. In "Pyridine and Its Derivatives", Part I; Klingsberg, E., Ed.; Interscience: New York, 1960; p 500.

(11) (a) Busch, D. H. *Rec. Chem. Prog.* **1964**, *25*, 107. (b) Eschenmosher, A. *Pure Appl. Chem.* **1969**, *20*, 1.

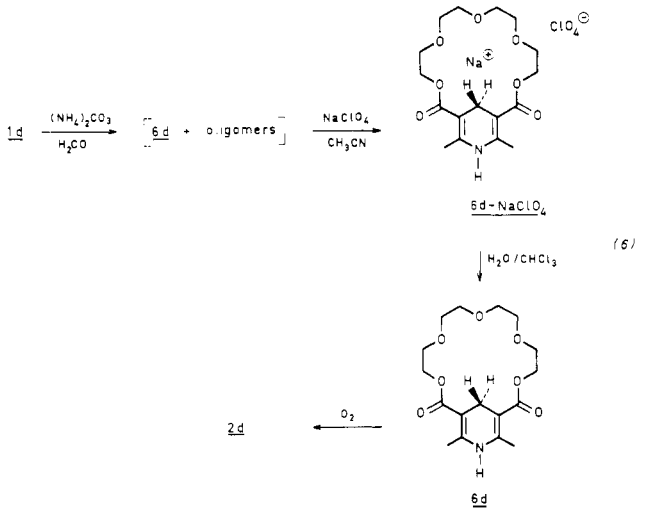
(12) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.

(13) A portion of these results has been published as a preliminary communication: van Bergen, T. J.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1976**, 964.

(14) van Bergen, T. J.; Mulder, T.; van der Veen, R. A.; Kellogg, R. M. *Tetrahedron* **1978**, *34*, 2377.

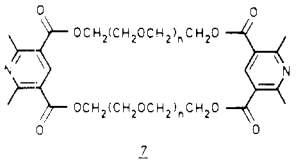
(15) van der Veen, R. H.; Kellogg, R. M.; Vos, A.; van Bergen, T. J. *J. Chem. Soc., Chem. Commun.* **1978**, 923.

The ease of formation of the $NaClO_4$ salt of **4d** suggested that the N–H derivative **6d** formed initially from the Hantzsch condensation, and which had been directly dehydrogenated in previous experiments rather than being isolated (several attempts at isolation had failed), might also form a stable salt permitting its isolation.[17] On treatment of the crude reaction product (eq 4) from the Hantzsch condensation with a saturated solution of $NaClO_4$ in CH_3CN, a powdery precipitate separated which was isolated by filtration and freed of residual starting materials by washing. This proved to be the exceptionally stable $NaClO_4$ salt of **6d** (no solvent incorporated) isolated in ca. 15% yield (eq 6). Pure **6d** is liberated by treatment



with H_2O; this material, in contrast to **6d**–$NaClO_4$, is very sensitive to air oxidation. The route described above is by far the simplest to **2d** and provides, moreover, very pure material.

The reactions of **1a–c** were also investigated.[18] With **1a** after oxidative workup only the dimer **7a** was isolated.

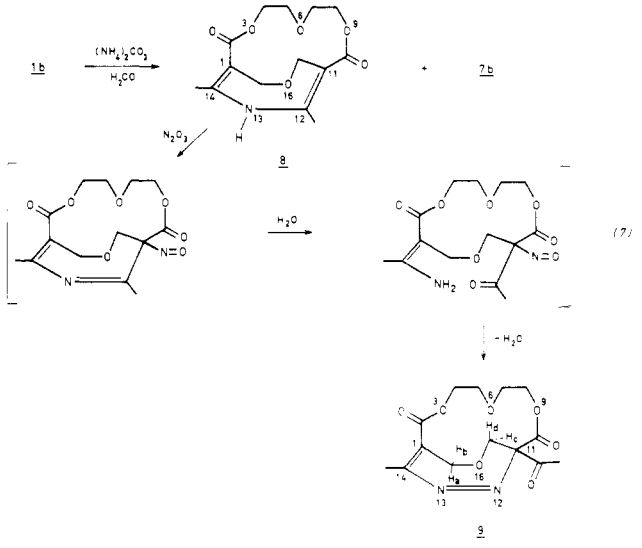


7

a) n = 1, b) n = 2, c) n = 3, d) n = 4

Although only a low yield of pure material was obtained, inspection of the spectra of the crude reaction mixture indicated that **7a** is formed in 40–60% crude yield. Isolation and purification are, however, difficult. Dimers **7b–d** were also isolated from the reaction products (after oxidative workup) of **1b–d**, respectively. These compounds were not obtained entirely pure. They show temperature-dependent ^1H NMR spectra (Experimental Section), but we refrain from any rationalization thereof owing to the presence of difficult to remove impurities.

In the reaction of **2b** there was also obtained after oxidative workup with N_2O_3 a crystalline compound eventually assigned structure **9**. This is probably derived from **8**, an aberrant Hantzsch product incorporating an extra equivalent of formaldehyde. A compound assigned structure **8** was isolated in very low yield from a mixture not subjected to oxidative workup. The transformation probably involves the mechanism shown in eq 7.



The structure of **9** was established by analysis of the spectral data. From the ^1H NMR spectrum it was apparent that the diethylene glycol bridge was still intact and that one methyl group appeared as a sharp singlet shifted upfield to δ 2.32, whereas the other methyl appears at δ 2.88, which is the normal chemical shift for 2,6-methyl groups on Hantzsch pyridines (for example, the 2,6-methyl groups of **2d** resonate at δ 2.88). The presence of a 1730-cm^{-1} carbonyl absorption (in addition to 1750- and 1720-cm^{-1} absorptions for nonconjugated and conjugated esters, respectively) substantiates the presence of an acetyl group. An extended spin–spin coupling involving the C-14 methyl, the C-15 methylene, and the C-17 methylene groups is also seen. The presence of a conjugated system is indicated by 236- and 294-nm absorptions in the UV spectrum and an IR absorption at 1630 cm^{-1}. Analysis of the spin–spin coupling system already mentioned revealed that H_{15a} is coupled to the C-14 methyl protons, J = 1 Hz, and that in addition to the $H_{15a-15b}$ and $H_{17c-17d}$ geminal couplings, J = 15 Hz, there is a 15-H_b to 17-H_c coupling, J = 3 Hz. This spin–spin coupling system, as well as the other spectral data, is in accord with structure **9** with the eight-membered ring fixed in the twisted conformation shown. The six required quaternary carbons are also found in the ^{13}C NMR spectrum at δ 70.5 (C-11), 109.0 and 148.2 (C-1 and C-14) and the carbonyl carbons at δ 166.7, 168.8, and 206.5.

By careful chromatography of a crude reaction mixture (eq 7) a small amount of a not entirely stable crystalline material assigned structure **8** was isolated. Initial inspection of the ^1H and ^{13}C NMR spectra indicated the absence of the symmetry plane seemingly demanded by structure **8**. However, a 14-CH_3, 15-$H_{a,b}$, 17-$H_{c,d}$ coupling system strongly reminiscent of that observed with **9** was found (see Experimental Section). This coupling system was completely analyzed and simulated. We believe that structure **8**, *locked* in the indicated conformation not possessing a symmetry plane, is best in accord with both the spectral data and the expected chemistry. Too little material was available to establish that it rearranges to **9** on treatment with N_2O_3 followed by hydrolytic workup.

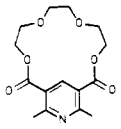
In the reaction of **1c**, the monomeric pyridine (**2c**) bridged with a 15-membered ring was also obtained in 25%

(16) See, for example: Weber, E.; Müller, W. M.; Vögtle, F. *Tetrahedron Lett.* **1979**, 2335, and accompanying references. We are grateful to Professor Vögtle for information on this point.

(17) The crude reaction mixture is not stable to air, consistent with the properties later established for **6d**. Various efforts to separate the product mixture by chromatography led, in our hands, only to isolation in low yield of **2d**.

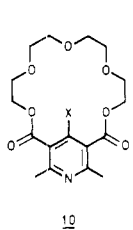
(18) Several attempts to obtain 3,5-bridged pyridines with chains longer than that of tetraethylene glycol failed, although this succeeds for 2,6-bridged (see further) systems. This problem has subsequently been solved by another synthetic approach: Piepers, O.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 383.

yield. This appears to be the lower limit for ring size in the Hantzsch approach to these types of bridged pyridines.



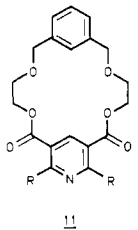
2c

Because of the encouraging results obtained with **1a**, formed from tetraethylene glycol, which forms 18-membered rings on Hantzsch condensation, exploratory studies were carried out on the possibility of preparing other 18-membered rings by this approach. Compounds **10a–c** were



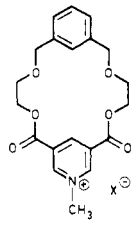
10

a) X = C_6H_5
b) X = CH_3
c) X =

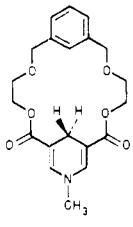


11

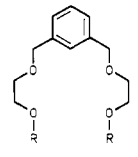
a) R = CH_3
b) R = H



12

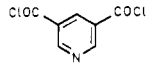


13



14

a) R = H
b) R = $-COCH_2COCH_3$

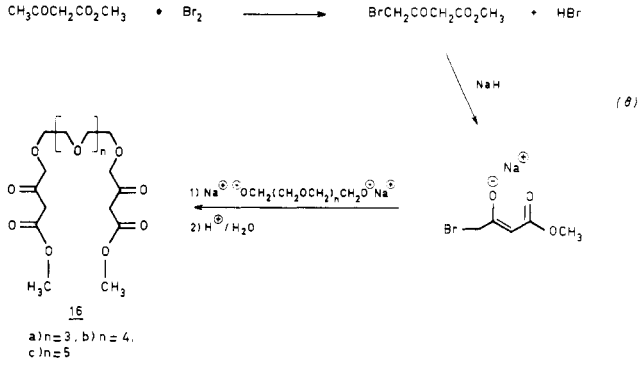


15

obtained after oxidative workup using, respectively, acetaldehyde, benzaldehyde, and 2-furfuraldehyde as carbonyl components in the Hantzsch condensation. Both **10b** and **10c** show complex ^1H NMR spectra for the poly(ethylene glycol) portions of the rings, consonant with the anticipated shielding effects of the aromatic ring at the pyridine γ position. The effect of temperature on the ^1H NMR spectra was not examined.

Compound **11a** is obtained from **14b**, assembled from 1,3-bis(bromomethyl)benzene by treatment with ethylene glycol under basic conditions to give **14a**, which is then transesterified with ethyl acetoacetate. Because of severe difficulties encountered on alkylating **11a**, the synthesis of **11b**, not having methyl groups at the α positions of the pyridine ring, was investigated. Condensation of **14a** with **15**[19] in the presence of $(C_2H_5)_3N$ gave **11b**.[20] Subsequent methylation and reduction with $Na_2S_2O_4$ gave in excellent yields **12** and **13**, respectively.

The utility of the Hantzsch condensation for the synthesis of 2,6-bridged pyridine systems was also investigated. This required the preparation of acetoacetates with the poly(ethylene glycol) chain attached not as an ester but to the 4-position of the acetoacetate. An obvious route to such compounds is through 4-bromoacetoacetates prepared by bromination of acetoacetate esters under conditions in which HBr isomerizes the initially formed 2-bromo derivative to the more stable 4-bromo isomer.[21] Nucleophilic substitution of bromide for alkoxy in 4-bromoacetoacetates fails under normal conditions, however, owing to the fact that the strong base, alkoxide, that must be used for nucleophilic substitution deprotonates more rapidly the acidic 2-methylene group of the acetoacetate. After some experimentation, a solution to this problem was found by protecting the acidic β-dicarbonyl portion of the acetoacetate as its sodium chelate (eq 8).



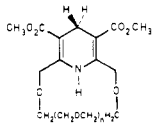
16

a) n = 3, b) n = 4, c) n = 5

(8)

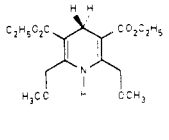
Nucleophilic substitution can then be carried out smoothly. This technique can also be used to introduce sulfur, nitrogen, and carbon substituents into the 4-position of the acetoacetate.[22]

Hantzsch condensation of **16a–c** under the conditions used for the preparation of other macrocyclic systems afforded **17a–c** in low yield. These compounds were isolated in their 1,4-DHP form by preparative high-pressure liquid chromatography. For comparison purposes **18**, obtained from methyl 4-methoxy-3-oxobutanoate, was also prepared.



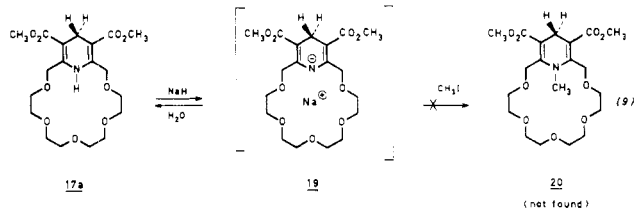
17

a) n = 3, b) n = 4, c) n = 5



18

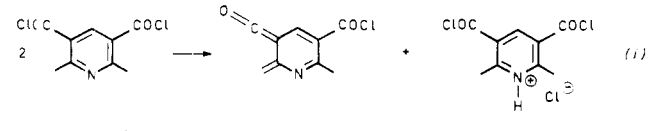
An attempt was made to prepare the "self-solvated" dipolar ion **19** (eq 9)[23] by using **17a**, which was present in greatest supply. On treatment of **17a** in diethyl ether with



17a 19 20 (not found)

(9)

(19) To the best of our knowledge the bis(acid chloride) from 2,6-dimethylpyridine-3,5-dicarboxylic acid (lutidinecarboxylic acid) has not been described in the literature as a pure compound. F. Zetzsche, C. Flütsch, F. Enderlin, and A. Loosli (*Helv. Chim. Acta*, **1926**, *9*, 182) describe a product of ambiguous composition obtained from lutidinecarboxylic acid and PCl_5. The acid chloride has been implied as a component in a polymerization process but experimental details are lacking: Hashimoto, S.; Nagasuna, Y. *Kobunshi Kagatus* **1967**, *24*, 215; *Chem. Abstr.* **1967**, *67*, 44150*m*. We have not been able to obtain this compound. It may be that it undergoes self-catalyzed elimination as shown in eq i followed by polymerization.



(i)

(20) For direct precedent for this route, see: (a) Frensch, K.; Vögtle, F. *Tetrahedron Lett.* **1977**, 2573. (b) Bradshaw, J. S.; Asay, R. E.; Maas, G. E.; Izatt, R. M.; Christensen, J. J. *J. Heterocycl. Chem.* **1978**, *15*, 825.

(21) Burger, A.; Ullyot, G. E. *J. Org. Chem.* **1947**, *12*, 342.

(22) Troostwijk, C. B.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1977**, 922.

(23) Attempts to prepare systems like **19** have been reported by Newkome (ref 8). Examples of self-solvated amide bases have been described by G. W. Gokel and B. J. Garcia (*Tetrahedron Lett.* **1977**, 317) and R. A. Bartsch and D. K. Roberts (*Ibid.* **1977**, 321).

sodium hydride, gas was evolved and a dark precipitate formed. The precipitate dissolved in methylene chloride to give a reddish solution, which, if treated quickly, could be neutralized with water or deuterium oxide back to **17a** (partially deuterated in the latter case). However, repeated attempts to alkylate **19** with methyl iodide led only to intractable materials and no identifiable quantities of **20**. Apparently **19** decomposes too quickly in methylene chloride to be alkylated.

Experimental Section

General. Melting points were recorded on a Mettler automatic FP-2 apparatus. UV spectra were taken with a Zeiss PMQ II apparatus. ^1H NMR spectra (Me_4Si internal standard) were recorded on 60-MHz Varian and JEOL instruments or on a Varian XL-100; ^{13}C NMR spectra (Me_4Si internal standard) were also recorded on the latter instrument. Mass spectra were measured on an MS-9 instrument. Waters high-pressure LC units were used for analytical and preparative separations. Elemental analyses were performed by the analytical division of these laboratories.

Compounds cited without reference were either in stock or were prepared by standard laboratory procedures.

Preparation of Acetoacetate Diesters of Poly(ethylene Glycols). The general procedure used for the preparation of ethylene glycol bis(acetoacetate)[24,25] (**1a**) is described; this procedure was also used for the synthesis of **1b–d**. A mixture of ethyl acetoacetate (260 g, 2.0 mol) and ethylene glycol (41 g, 0.66 mol) was stirred and heated slowly over a 3-h period to 180 °C at atmospheric pressure. During this period, 68 mL of ethanol was collected. Once ethanol ceased to distill off, distillation was continued at 20 mm, leading to the collection of excess ethyl acetoacetate [bp 80 °C (20 mm), 98 g]. The oily residue in the distillation pot was nearly pure **1a** (135 g, 0.59 mol, 89% yield) containing 6% of the enol form: IR (neat) 3500 (OH), 1740 and 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.88 (s, 6, CH_3), 3.50 (s, 4, CH_2), 4.60 (s, 4, OCH_2), and the enol at δ 1.97 (s, 6, CH_3) and 5.02 (s, 2, vinyl H); exact mass, m/e 230.082, calcd for $C_{10}H_{14}O_6$ 230.079.

There was also found 6% of the enol form in **1b**: IR (neat) 3500 (OH), 1740 and 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.33 (s, 6, CH_3), 3.62 (s, 4, CH_2), 3.80 (m, 4, CH_2O), 4.40 (m, 4, ester, CH_2O), and the enol at δ 2.02 (s, 6, CH_3) and 5.18 (s, 2, vinyl H); exact mass, m/e 274.103, calcd for $C_{12}H_{18}O_7$ 274.104.

For **1c** there was found 16% of the enol form: IR (neat) 3400 (OH), 1750 and 1720 (C=O), 1660 cm^{-1} (enol, C=O); ^1H NMR ($CDCl_3$) δ 2.20 (s, 6, CH_3), 3.35 (s, 4, CH_2), 3.53 (s, 4, OCH_2), 3.60 (m, 4, OCH_2), 4.20 (m, 4, ester OCH_2), and the enol at δ 1.93 (s, 6, CH_3) and 4.92 (s, 2, vinyl H). Neither an acceptable elemental analysis nor an exact mass-spectral molecular-weight determination was possible owing to decomposition of **1c** at elevated temperatures.

Compound **1d** (7% enol form) has: IR (neat) 3400 (OH), 1745 and 1720 (C=O), and 1655 cm^{-1} (enol C=O); ^1H NMR ($CDCl_3$) δ 2.25 (s, 6, CH_3), 3.42 (s, 4, CH_2), 3.59 (s, 8, OCH_2), 3.64 (m, 4, OCH_2), 4.24 (m, 4, ester OCH_2), and the enol at δ 4.93 (s, 2, vinyl H) and 1.93 (s, 6, CH_3). Because of decomposition of **1d** at elevated temperatures, neither an acceptable elemental analysis nor exact mass-spectral molecular-weight determination was possible.

2d[26] was prepared by adding a 35% formaldehyde solution (5.2 g, 0.06 mol of formaldehyde) dissolved in 500 mL of H_2O to a well-stirred solution of **1d** (21.7 g, 0.06 mol) in 4 L of H_2O containing $(NH_4)_2CO_3$ (180 g, 1.88 mol) dropwise over a 12-h period. The solution became turbid and yellow and exhibited fluorescence characteristic of 1,4-dihydropyridines. The reaction mixture was extracted with 300 mL of CH_2Cl_2, then saturated with NaCl, and again extracted with three 200-mL portions of CH_2Cl_2. The organic layer was dried over Na_2SO_4. After the solution was dried and filtered, the crude reduction product was dehydrogenated by bubbling N_2O_3 through the solution until a constant amount of brown gas was evolved (ca. 30 min with fairly vigorous passage of N_2O_3). The reaction mixture was washed first with 200 mL of aqueous $NaHCO_3$ (separation of layers can be difficult) and subsequently with five 100-mL portions of H_2O. After the solution was dried over Na_2SO_4 and filtered and the solvent was evaporated, 21.1 g (100% yield) of crude pyridines was obtained; the ratio of monomer **2d** to oligomers as determined by ^1H NMR is 29:71.

Isolation of **2d** was accomplished by dissolving the crude reaction mixture in 30 mL of CH_2Cl_2 and pouring it into 250 mL of rapidly stirred diethyl ether. After the solution had settled, the supernatant was decanted from the precipitated oligomers. There was obtained 12.0 g of material that was subjected to column chromatography [silica gel, eluted with diethyl ether/CH_2Cl_2 (1:1)], which gave **2d** (4.5 g, 0.012 mol, 20% yield): mp 90–92 °C (recrystallized from diethyl ether); IR (KBr) 1730 (C=O), 1120 cm^{-1} (CO); UV (CH_3CN) 236 nm (ϵ 10 500), 274 (3300), 282 (2600); ^1H NMR ($CDCl_3$) δ 2.88 (s, 6, CH_3), 3.75 (s, 8, OCH_2), 3.84 (m, 4, OCH_2), 4.55 (m, 4, ester OCH_2), 9.00 (s, 1, aryl H); mass spectrum, m/e (parent) calcd m/e 353 for $C_{17}H_{23}NO_7$.

Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.77; H, 6.45; N, 3.97.

The preparation of 6d–$NaClO_4$ was carried out as described above with 22 g (0.06 mol) of **1d**. The crude reaction mixture was extracted with four 125-mL portions of CH_2Cl_2. After being dried (Na_2SO_4), the solvent was removed to leave 18 g of oil containing ca. 30% monomeric dehydropyridine (**6**) as ascertained from the ^1H NMR spectrum. To this oil was added 50 mL of CH_3CN saturated with $NaClO_4$ (not dried prior to use). The mixture was shaken to dissolve the oil completely, and the mixture was allowed to stand overnight. The yellow precipitate was isolated by suction filtration and washed on the filter with $CHCl_3$. There was obtained **6d**–$NaClO_4$ (5.0 g, 10.4 mmol, 17% yield): mp (from CH_3CN) 262–265 °C dec; IR (KBr) 3400, 2900, 1710, 1660, 1630, 1510 cm^{-1}.

Anal. Calcd for $C_{17}H_{25}ClNaNO_{11}$: C, 41.88; H, 5.27; N, 2.93; Cl, 7.42. Found: C, 42.45; H, 5.18; N, 2.97; Cl, 7.59.

After 1 month of storage at room temperature, only a trace of pyridine formed by oxidation could be detected.

The noncomplexed form of **6d** was isolated by first washing the complex with $CHCl_3$ on a sintered-glass filter to remove any free pyridine. (It is not clear whether this pyridine itself is complexed to $NaClO_4$. If so, the complex is weak and also soluble in $CHCl_3$.) The complex **6d**–$NaClO_4$ (5 g, 10.4 mmol) was shaken in a separatory funnel with 75 mL of $CHCl_3$ and 75 mL of H_2O until the solid had dissolved completely. After separation of the layers, the H_2O layer was extracted with 50 mL of $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to give crude **6** (ca. 3.5 g, 10 mmol, ca. 100% yield) as a yellow oil that became solid on standing. Great care must be taken to avoid rapid air oxidation to pyridine **2d** at this stage. Recrystallization from 10 mL of hot CH_3COCH_3 containing 5–10 drops of H_2O gave on cooling pure **6**–H_2O: mp 114–117 °C; IR (KBr) 3590, 3290, 3100, 2890, 1690, 1630, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 6, CH_3), 3.40 (br s, 2, 21-CH_2), 3.59 (m, 12, OCH_2), 4.30 (br t, J = 7 Hz, 4, $COOCH_2$), 5.88 (br s, 1, NH), and a H_2O peak (2 protons) corresponding to the water of crystallization that could not be removed without decomposition of **6**.

Anal. Calcd for $C_{17}H_{25}NO_7 \cdot H_2O$: C, 54.66; H, 7.29; N, 3.76. Found: C, 54.71; H, 7.34; N, 3.85.

3d was prepared by reaction of **2d** (1.54 g, 4.36 mmol) in 8 mL of pure dry CH_2Cl_2 under stirring and a nitrogen atmosphere with methyl fluorosulfonate (0.8 mL, 10.0 mmol) for 20 h. **Caution**: Methyl fluorosulfonate should be handled with great care with gloves in an adequate hood. The solvent was removed along with excess methyl fluorosulfonate and the residue was dissolved in 15 mL of H_2O, filtered, and then treated with saturated aqueous $NaClO_4$ solution. The precipitated perchlorate was collected by filtration and was contaminated with 10–20% protonated **2d**–H^+. Recrystallization from CH_3OH gave pure **3d** (867 mg, 1.85 mmol, 43% yield): mp 190–193 °C; IR (KBr) 1730 (C=O), 1080 cm^{-1} (CO); UV (CH_3CN) 228 nm (ϵ 8800), 280 (6500), 288 (6300), 310 (900); ^1H NMR (CD_3COCD_3) δ 3.15 (s, 6, 2, 6-CH_3), 3.60 (s, 8, 2

(24) General procedure of A. R. Bader, L. O. Cummings, and H. A. Vogel (*J. Am. Chem. Soc.* **1951**, *73*, 4195).

(25) Described by Touey, G. P.; McConnell, W. V., Eastman Kodak Co. French Patent 1 401 130, Appl. 1964; *Chem. Abstr.* **1966**, *64*, 11435g.

(26) I.U.P.A.C. name: 18,20-dimethyl-3,6,9,12,15-pentaoxa-19-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,10-dione; for brevity other I.U.P.A.C. names are not given.

C_2H_4), 2.71 (m, 4, OCH_2), 4.38 (s, 3, NCH_3), 4.50 (m, 4, ester OCH_2), 9.08 (s, 1, aryl H).

Anal. Calcd for $C_{18}H_{26}NClO_{11}$: C, 46.21; H, 5.60; N, 2.99; Cl, 7.58. Found: C, 45.82; H, 5.64; N, 2.99; Cl, 7.41.

The compound exploded during analysis.

4d was prepared by treatment of the perchlorate **3d** (500 mg, 1.07 mmol) in 5 mL of aqueous $NaHCO_3$ solution with $Na_2S_2O_4$ (520 mg, 3.00 mmol) added portionwise. After the mixture was stirred for 2 h, the yellow precipitate was collected by filtration resulting in **4d** (340 mg, 0.92 mmol, 86% yield): mp 110–113 °C (from CH_3OH); IR (KBr) 1680 (C=O), 1630 and 1575 cm^{-1} (enamine); UV (CH_3OH) 232 nm (ϵ 14 300), 264 (9200), 360 (6100); ^1H NMR ($CDCl_3$) δ 2.35 (s, 6, 2, 6-CH_3), 3.10 (s, 3, NCH_3), 3.23 (br s, 2, 4-CH_2), 3.66 (s, 8, 2 C_2H_4), 3.67 (m, 4, OCH_2), 4.23 (m, 4, ester OCH_2).

Anal. Calcd for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37; N, 3.79. Found: C, 58.50; H, 7.34; N, 3.84.

5d was prepared by allowing **4d** (117 mg, 0.32 mmol) and **3d** (10 mg, 0.04 mmol) to react for 2 days at room temperature in CH_3CN. The reaction mixture was separated on silica gel with ether as eluant to give **5d** (48 mg, 0.13 mmol, 41% yield), mp 131.5–133 °C (from CH_3OH). A considerable amount of **4d** remained; the degree of conversion can be increased by raising the temperature or increasing the reaction time (done only on ^1H NMR scale). **5d**: UV (CH_3OH) 222 nm (ϵ 12 500), 289 (16 800), 380 (7000); ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 7 Hz, 3, 18-CH_3), 2.38 (s, 3, 20-CH_3), 3.00 (s, 3, NCH_3), 3.53 (s, 8, OCH_2), 3.50 (m, 4, OCH_2), 4.10 (m, 4, OCH_2CO), 4.30 (q, J = 7 Hz, 1, 18-H), 7.50 (s, 1, 21-H); exact mass, m/e 369.176, calcd for $C_{18}H_{27}NO_7$ 369.176.

Anal. Calcd for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37; N, 3.79. Found: C, 58.05; H, 7.33; N, 3.78.

Preparation of Salts 4d–$NaClO_4$–CH_3COCH_3, –CH_3CN, and –$CH_3O_2CCH_3$. **4d** (160 mg, 0.433 mol) was dissolved in 1 mL of CH_3CN containing dissolved $NaClO_4$ (100 mg, 0.82 mmol). After the material was dissolved, the solution was allowed to stand whereupon salt began to precipitate. In this fashion there was obtained **4d**–$NaClO_4$–CH_3CN (200 mg, 0.407 mmol, 94% yield), mp 176–180 °C (from CH_3CN).

Anal. Calcd for $C_{20}H_{30}NaN_2ClO_{11}$: C, 45.07; H, 5.67; N, 5.26. Found: C, 44.84; H, 5.66; N, 5.28.

2d (75 mg, 0.205 mmol) was dissolved in 1 mL of CH_3COCH_3 to which 0.5 mL of CH_3COCH_3 containing $NaClO_4$ (30 mg, 0.25 mmol) was added. After the mixture was allowed to stand in the refrigerator, the complex was collected by filtration to give **4d**–$NaClO_4$–CH_3COCH_3 (44 mg, 0.08 mmol), 39% yield, mp 172.5–175 °C.

Anal. Calcd for $C_{21}H_{33}NaNClO_{12}$: C, 45.86; H, 6.05; N, 2.55; Cl, 6.44; Na, 4.18. Found: C, 45.73; H, 6.05; N, 2.48; Cl, 6.50; Na, 4.22.

2d (74 mg, 0.20 mmol) was dissolved in 0.7 mL of $CH_3O_2CCH_3$ to which 0.3 mL of $CH_3O_2CCH_3$ containing dissolved $NaClO_4$ (30 mg, 0.25 mmol) was added. After the solutions were mixed, the complex began to separate. By filtration there was obtained **4d**–$NaClO_4$–$CH_3O_2CCH_3$ (70 mg, 0.124 mmol, 62% yield), mp 169.5–171.5 °C (from $CH_3O_2CCH_3$).

Anal. Calcd for $C_{21}H_{33}NaNClO_{13}$: C, 44.57; H, 5.88; N, 2.48; Na, 4.06. Found: C, 44.53; H, 5.78; N, 2.35; Na, 3.90.

2c was prepared by adding a 35% aqueous CH_2O solution (2.6 g, 0.03 mol) dissolved in 250 mL of H_2O to a well-stirred solution of triethylene glycol bis(acetoacetate) (**1c**) (9.6 g, 0.03 mmol) in 2 L of H_2O containing $(NH_4)_2CO_3$ (90 g, 0.94 mol). Stirring was continued for 16 h. The reaction mixture was worked up as described for **2d** to give a crude mixture (5.6 g) of pyridines containing **2c**. Column chromatography over silica gel with ether/CH_2Cl_2 (1:1) gave **2c** (2.3 g, 7.45 mmol, 25% yield): mp 167–169 °C (from C_3H_6O); IR (KBr) 1725 (CO), 1270 and 1120 cm^{-1} (CO); UV (CH_3CN) λ_{max} 236 nm (ϵ 12 400), 273 (3700), 280 (3000); ^1H NMR ($CDCl_3$) δ 2.09 (s, 6, CH_3), 3.80 (s, 4, OCH_2), 2.85 and 4.45 (each m, 4, OCH_2), 9.67 (s, 1, aryl H); mass spectrum, m/e (parent) 309.

Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53. Found: C, 58.14; H, 6.19; N, 4.65.

Attempted Preparation of 2b. To diethylene glycol bis(acetoacetate) (**1b**) (8.22 g, 0.03 mol) dissolved in 2 L of H_2O containing $(NH_4)_2CO_3$ (90 g, 0.94 mol) was added an aqueous 35% CH_2O solution (3.40 g, 0.04 mol) dissolved in H_2O. Stirring was continued for 48 h. The reaction mixture was worked up as described for **2d**. An oil (5.5 g) was obtained that contained no pyridines as established by ^1H NMR analysis (monitoring of aryl proton). Column chromatography over silica gel with CH_2Cl_2/ether (1:1) yielded **9** (900 mg, 2.75 mmol, 9% yield): mp 124–126 °C (from ether/acetone); IR (KBr) 1750, 1730, 1720 (CO), 1630 cm^{-1} (C=CCO); UV (CH_3CN) λ_{max} 236 nm (ϵ 4200), 294 (11 300); ^1H NMR ($CDCl_3$) δ 2.32 (s, 3, $COCH_3$), 2.88 (d, $J_{CH_3-H_{15a}}$ = 2 Hz, 3, 14-CH_3), 2.38 (d of d, $J_{CH_3-H_{15a}}$ = 2, $J_{H_{15a}-H_{15b}}$ = 15 Hz, 1, H_{15a}), 3.63 (d of d, $J_{H_{15a}-15b}$ = 15, $J_{H_{15b}-17c}$ = 3 Hz, 1, H_{15b}), 4.53 (d of d, $J_{15b-17c}$ = 3, $J_{15c-15d}$ = 15 Hz, 1, H_{17c}), 3.38 (d, $J_{17c-17d}$ = 15 Hz, 1, H_{17d}), 3.65–4.00 (m, 5, CH_2O), 4.22–4.75 (m, 3, CH_2O); ^{13}C NMR δ 16.4 and 26.9 (CH_3, J_{13C-H} = 135 Hz), 28.9, 47.8, 59.3 and 70.2 (OCH_2, J_{13C-H} = 150 Hz), 63.1 and 65.7 (CH_2, J_{13C-H} = 150 Hz), 70.5, 109.0, 148.2, 166.7, 168.8, and 206.5 (quaternary C); mass spectrum, m/e (parent) 326.

Anal. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.67; H, 5.50; N, 8.65.

In another experiment carried out on the same scale, the oxidation step in the workup procedure was omitted. The crude oily residue obtained by extraction with CH_2Cl_2 was subjected directly to column chromatography (silica gel with 1:1 ether/CH_2Cl_2); a compound assigned structure **8** (450 mg, 1.5 mmol, 5% yield) was obtained: mp 141–145 °C (from CH_3OH); IR (KBr) 3300 (NH), 1720 and 1660 cm^{-1} (C=O); UV (CH_3CN) λ_{max} 282 nm (ϵ 15 300); ^1H NMR ($CDCl_3$) δ 2.32 (s, 3, CH_3 and m, 3), 2.80 (s, 1, NH), 3.30 (d, J = 13 Hz, 1), 3.60–4.20 (m, 8, OCH_2), 4.38–5.20 (m, 3, OCH_2) (proton decoupling of the lower-field resonances led to collapse of the methyl absorption at δ 2.32); ^{13}C NMR (C_3D_6O) δ 20.77 (12,14-CH_3), 46.41, 59.17, 61.91, 65.63, 71.14, and 71.89 (OCH_2), 156.40, 167.93, and 170.414 (quaternary C) (the two methyl groups apparently have the same ^{13}C NMR chemical shift and the 6 quaternary carbons fall into three groups of two); mass spectrum, m/e (parent) 297, calcd for $C_{14}H_{19}NO_6$ 297.

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.60; H, 6.40; N, 4.76.

7a was formed when the bis(acetoacetate ester) of ethylene glycol (**1a**) (6.90 g, 0.03 mol) dissolved in 2 mL of H_2O containing $(NH_4)_2CO_3$ (90 g, 0.94 mol) was allowed to react with aqueous 35% H_2CO solution (3.4 g, 0.04 mol) dissolved in H_2O. Oxidative workup as described previously led to the isolation of an oil (2.17 g) consisting chiefly of **7a** in 32% yield. The oil was dissolved in 20 mL of CH_2Cl_2 and poured rapidly into 150 mL of C_6H_6. The supernatant was decanted, extracted with five 25-mL portions H_2O, dried over $Na_2S_2O_4$, filtered, and evaporated to leave 0.87 g of material that was triturated with CH_3COCH_3 to give **7a** (127 mg, 0.288 mmol, 1% yield in pure form): mp 196–198 °C (from CH_2Cl_2); IR (KBr) 1730 (C=O), 1260 and 1080 cm^{-1} (CO); UV (CH_3CN) λ_{max} 234 nm (ϵ 13 200), 273 (4400), 282 (3500); ^1H NMR ($CDCl_3$) δ 3.00 (s, 12, α-CH_3's), 4.82 (s, 8, OCH_2), 9.82 (s, 2, aryl H); exact mass, m/e (parent) 442.142, calcd for $C_{22}H_{22}O_8N_2$ 442.138.

Anal. Calcd for $C_{22}H_{22}O_8N_2$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.08; H, 5.11; N, 6.37.

7b was prepared from the bis(acetoacetate) of diethylene glycol (8.22 g, 0.03 mol) and 35% aqueous formaldehyde (3.40 g, 0.04 mol) which were dissolved in 2 L of water containing $(NH_4)_2CO_3$ (90 g, 0.94 mol). After 2 days of being stirred, the reaction mixture was subjected to oxidative workup. Drying over sodium sulfate, filtration, and evaporation gave 4.6 g of a residue which did not exhibit any monomeric pyridine in the ^1H NMR. Separation of the azo compound **9** was achieved by dissolving the residue in 25 mL of CH_2Cl_2 and pouring it into 150 mL of ether in which **9** is soluble. After decantation the procedure was repeated twice with the oily precipitate. Finally the ether fraction gave, upon column chromatography (see above), **9** in 6% yield. From the viscous precipitates the dimer **7b** could be obtained by pouring its solution in 15 mL of methylene chloride into 150 mL of benzene. The decanted supernatant was extracted three times with 25 mL of water. Then, drying over sodium sulfate, filtration, and evaporation gave 1.0 g (1.85 mmol 12%) of oily **7b** which seemed to consist of several conformers at room temperature: IR 1730 (C=O), 1280, 1230, and 1100 cm^{-1} (CO); UV (CH_3CN) λ_{max} 234 nm (14 600), 274 (6700), 282 (6200); ^1H NMR (Me_2SO-d_6 at 145 °C) δ 2.65 (d, J = 2.5 Hz, 12 H, α-CH_3), 3.75 and 4.40 (both m, 8 H, OCH_2), 8.40 (br s, 2 H, 4 aryl H) (the absorption for the

α-CH_3's coalesces at 137 °C splitting into a group of four peaks at lower temperature); mass spectrum, *m/e* 530, calcd for $C_{26}H_{30}N_2O_{10}$ 530.

7c was prepared from the bis(acetoacetate ester) of triethylene glycol (9.60 g, 0.03 mol) and 35% formaldehyde (3.40 g, 0.04 mol) as described for **7b**. After oxidative workup, 5.9 g (63%) of an oily mixture of pyridines was obtained. Column chromatography of this material (silica gel and ether/methylene chloride 1:1) gave, respectively, 1.8 g (2.9 mmol, 19%) of dimer **7c** and 1.0 g (3.37 mmol, 11%) of monomer **2c**. On changing the solvent to dimethoxyethane a third fraction of 2.02 g, consisting of dimer **7c** and material of higher molecular weight, eluted from the column. The first fraction of **7c** was dissolved in 30 mL of benzene and washed with five 10-mL portions of water to remove contaminants. Drying over anhydrous sodium sulfate, filtration, and evaporation gave **7c** as a viscous oil which decomposed above 180 °C: IR 1720 (C=O), 1280, 1225, 1100 cm^{-1} (CO); UV (acetonitrile) λ_{max} 233 nm (ε 12100), 274 (4600), 282 (3900); ^1H NMR (Me_2SO-d_6 at 124 °C) δ 2.60 (s, 12 H, CH_3), 3.30–3.80 (m, 16 H, OCH_2), 4.10–4.40 (m, 8 H, OCH_2), 8.12 (s, 2 H, 4-aryl H) (the absorptions for the α-CH_3's coalesce at 87 °C); mass spectrum, *m/e* (parent) 618, calcd for $C_{30}H_{38}N_2O_{12}$ 618.

7d was formed by working on a 0.06-mol scale as described for previous dimers and following the same oxidative workup procedure. There was obtained 16.6 g (78% yield) of an oily mixture of monomeric and other pyridines in a 1:4 ratio. These were separated by pouring the solution in 30 mL of CH_2Cl_2 into 750 mL of ether. When the solution had settled, the supernatant was decanted and evaporated, leaving a residue (4.9 g), which on column chromatography (see above) gave 2.0 g (5.7 mmol, 10%) of monomeric **2d**, mp 90–92 °C. The oil (12.2 g), which precipitated in ether, was separated into two fractions in the following way. Its solution in 50 mL of CH_2Cl_2 was poured into 200 mL of stirring ether, and after some time the supernatant was decanted. The precipitated oil was subjected to this treatment three more times, which after evaporation of the ether resulted in 4.7 g (6.7 mmol, 22%) of oily dimeric pyridine. In order to remove impurities this material was dissolved in 200 mL of benzene and washed repeatedly with 50-mL portions of water. Subsequent drying, filtration, and evaporation gave **7d**: IR 1720 (C=O), 1280, 1225, and 1100 cm^{-1} (CO); UV (acetonitrile) λ_{max} 232 nm (ε 14400), 274 (6100), 282 (5500); ^1H NMR (Me_2SO-d_6 at 101 °C) δ 2.63 (d, *J* = 1.0 Hz, 12 H, CH_3), 3.30–3.80 (m, 24 H, OCH_2), 4.00–4.45 (m, 8 H, OCH_2), 8.23 (s, 2 H, 4-aryl H) (α-CH_3's coalesce at −10 °C); mass spectrum, *m/e* (parent) 706 (weak), calcd for $C_{34}H_{46}N_2O_{14}$ 706.

1,3-Bis(bromomethyl)benzene was prepared by allowing *m*-xylene (750 g, 7.07 mol) to react with Br_2 (1630 g, 10.2 mol) over a period of 24 h.[27] The Br_2 was dried (in portions) by shaking with concentrated H_2SO_4. The reaction temperature was kept between 130 and 160 °C. The HBr generated during the reaction was trapped in aqueous NaOH solution. The crude reaction mixture was distilled without further purification. Fractions bp 140–150 °C (15 mm) and bp 150–165 °C (15 mm) were collected that became partly or wholly crystalline. The crystalline fractions were redistilled to give 1,3-bis(bromomethyl)benzene (306 g, 1.16 mol, 16% yield) that became solid: ^1H NMR (CCl_4) δ 4.41 (s, 4, CH_2), 7.31 (m, 4, aryl H). **Caution**: All of the brominated products formed are strong lacrymators.

1,3-Bis((2-hydroxyethoxy)methyl)benzene (14a). An emulsion of NaH (52 g, 55–60%, ca. 1.2 mol) in mineral oil was washed thoroughly with dry pentane. The washed NaH was added *very carefully* with vigorous stirring and cooling in an ice bath to ethylene glycol (250 mL). Excessive frothing occurs on adding the NaH too quickly. Once all the NaH had been added 1,3-bis(bromomethyl)benzene (142.2 g, 0.54 mol) was added in one portion. Over 2 h the reaction temperature was raised to 70 °C. (The ethylene glycol and xylene dibromide are immisible; the progress of the reaction is followed by the rate of disappearance of the layers.) After being stirred for 12 h, the reaction mixture was poured into H_2O and extracted three times with CH_2Cl_2. After the mixture was dried over $MgSO_4$ and CH_2Cl_2 was removed, the reaction mixture was distilled (distillation pot <225 °C to prevent polymerization) to give **14a** (72 g, 0.32 mol, 59% yield): bp 169–170 °C (0.04 mm); IR (neat) 3400 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (s, 2, OH, exchangeable with D_2O), 3.71 (m, 8, CH_2CH_2), 4.59 (s, 4, Ar CH_2); mass spectrum, *m/e* (parent) 226, calcd for $C_{12}H_{18}O_4$ 226.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.44; H, 7.96.

Bis(3-oxobutanoate Ester) of 1,3-Bis(2-hydroxyethoxy)benzene (14b). A mixture of **14a** (13.7 g, 0.06 mol) and ethyl 3-oxobutanoate (26 g, 0.2 mol) was stirred and heated to 190 °C for 4 h during which time 6.5 mL of C_2H_5OH were collected by distillation. The excess ethyl 3-oxobutanoate was distilled off under reduced pressure, leaving the desired **14b** (approximately 25 g, quantitative) consisting of 13% enol form: IR (neat) 3550 (OH), 1730 and 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.27 (s, 6, CH_3), 3.50 (s, 4, $COCH_2CO$), 3.72 (br t, *J* = 7 Hz, 4, $CO_2CH_2CH_2O$), 4.37 (br t, *J* = 7 Hz, 4, $CO_2CH_2CH_2O$), 4.61 (s, 4, Ar CH_2), 7.36 (br s, 4, aryl H); (enol) 1.97 (s, 6, CH_3) and 5.08 (br s, vinyl H).

Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.65. Found: C, 60.36; H, 6.50.

Preparation of 11a. To a well-stirred mixture of **14b** (11.83 g, 0.03 mol) and $(NH_4)_2CO_3$ (90 g, 0.94 mol) in 5 L of H_2O was added over 24 h a 35% aqueous H_2CO solution (2.6 g, 0.03 mol) diluted with 0.5 L of H_2O. After addition was complete, stirring was continued for another 24 h. The reaction mixture was saturated with NaCl and extracted with CH_2Cl_2. After being dried, the crude reaction mixture in CH_2Cl_2 was treated with N_2O_3 until brown gas was constantly evolved. After being washed with saturated aqueous $NaHCO_3$ and H_2O, the CH_2Cl_2 layer was dried over $MgSO_4$. After removal of the CH_2Cl_2, the dark brown reaction mixture was dissolved in 50 mL of CH_2Cl_2 and poured into 500 mL of $(C_2H_5)_2O$. The viscous residue was separated and the organic layer was evaporated to leave a heavy oil that was subjected to column chromatography on silica gel (eluant CH_2Cl_2/$(C_2H_5)_2O$ 1:1). The first band to elute consisted of a compound that became solid. After recrystallization from C_6H_6/petroleum ether (bp 40–60 °C) **11a** (1.73 g, 4.5 mmol, 15% yield) was obtained: mp 158.5–160 °C; IR ($CHCl_3$) 3000, 2900, 1730, 1600, 1570, 1470, 1370, 1310, 1030, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (s, 6, CH_3), 3.63 (s, 4, Ar CH_2), 3.82 (br t, *J* = 7 Hz, 4, $CO_2CH_2CH_2O$), 4.53 (br t, *J* = 7 Hz, 4, $CO_2CH_2CH_2O$), 7.20–7.80 (m, 4, aryl H), 8.86 (s, 1, pyr H).

Anal. Calcd for $C_{21}H_{23}O_6$: C, 65.45; H, 6.01; N, 3.63. Found: C, 65.38; H, 6.02; N, 3.63.

In an alternate procedure, to the bis(acetoacetate ester) (5.95 g, 15 mmol), $(NH_4)_2CO_3$ (7.0 g, 70 mmol) and NH_4ClO_4 (7 g, 60 mmol) in 1.5 L of CH_3CN was added over 24 h 35% aqueous H_2CO solution (1.3 g, 30 mmol) dissolved in 100 mL of CH_3CN. Without further workup the CH_3CN solution was treated with N_2O_3. The CH_3CN was removed and the residue worked up and chromatographed as described above to give **11a** (1.16 g, 3 mmol, 15% yield).

Preparation of 11b. By means of two separate syringe pumps a mixture of **14a** (2.0 g, 8.85 mmol) and $(C_2H_5)_3N$ (1 g, 10 mmol) in 25 mL of dry THF was added via one syringe and 3,5-bis(chlorocarbonyl)pyridine[28] (**15**, 1.8 g, 8.85 mmol) in 25 mL of dry THF was added via the other syringe over 24 h to a well-stirred solution of 100 mL of dry THF. After addition was complete the reaction mixture was stirred at 40 °C for 24 h. The ammonium salt was removed by filtration and the solvent was evaporated. The residue was recrystallized repeatedly from 1:1 C_6H_6/petroleum ether (bp 60–80 °C) to give **11b** (800 mg, 2.24 mmol, 25% yield): mp 127–128 °C; ^1H NMR ($CDCl_3$) δ 3.84 (br t, *J* = 7 Hz, 4, $CO_2CH_2CH_2O$), 4.55 (br t, *J* = 7 Hz, 4, $CO_2CH_2CH_2O$), 4.64 (s, 4, Ar CH_2), 7.25 (m, 3, aryl H), 8.95 (t, *J* = 2 Hz, 1, pyr 4-H), 9.40 (d, *J* = 2 Hz, 2, pyr 2,6-H).

Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.96; H, 5.62; N, 3.89.

The same compound was also obtained in 20% yield by treating the bis(ethylene glycol ester) of pyridine-3,5-dicarboxylic acid with

(27) (a) Atkinson, E. F. J.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1907**, *91*, 1687. (b) Ruggli, P.; Bussemaker, B. B.; Müller, W. *Helv. Chim. Acta* **1935**, *18*, 613. (c) An improved preparation has been described by W. Wieder, R. Nätscher, and F. Vögtle (*Justus Liebig Ann. Chem.* **1975**, 924).

(28) Meyer, H.; Tropsch, H. *Monatsh. Chem.* **1914**, *35*, 781, modified as described in ref 5b.

2 equiv of NaH and thereafter with α,α'-xylene dibromide.

Preparation of 12. **12** was prepared by dissolving **11b** (500 mg, 1.4 mmol) in 10 mL of dry CH_2Cl_2 to which methyl fluorosulfonate (0.4 mL, 5 mmol) was added at room temperature. Removal of the solvent and recrystallization from CH_3OH gave **12** (350 mg, 0.74 mmol, 53% yield): mp 213–214 °C; ^1H NMR (CD_3SOCD_3) δ 3.70 (m, 4, $CO_2CH_2CH_2O$), 4.30 (m, 4, $CO_2CH_2CH_2O$), 4.30 (s, 3, CH_3N^+), 4.50 (s, 4, aryl H), 7.1 (br complex, 4, aryl H), 9.0 (s, 1, pyr 4-H), 9.7 (s, 2, pyr 2,6-H).

No attempt was made to obtain an elemental analysis owing to scarcity of material.

13 was prepared by treating a solution of **12** (297 mg, 0.63 mmol) in 10 mL of an aqueous pH 7 phosphate buffer solution with solid $Na_2S_2O_4$ (1.5 g, 8.6 mmol). The reaction mixture is stirred for 15 min at room temperature and then 30 min in an ice bath. The 1,4-dihydropyridine **13** precipitate is removed by filtration and washed with cold H_2O. After being dried the solid is recrystallized from 2-propanol to give **13** (200 mg, 0.54 mmol, 86% yield): mp 134–136 °C; ^1H NMR (CD_3CN) δ 3.09 (s, 3, NCH_3), 3.35 (s, 2, pyr 4-CH_2), 3.70 (m, 4, $CO_2CH_2CH_2O$), 4.30 (m, 4, $CO_2CH_2CH_2O$), 4.60 (s, 4, Ar CH_2), 7.05 (br s, 2, pyr 2,6-H), 7.50 (br complex, 4, aryl H).

Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.22; O, 25.71. Found: C, 64.27; H, 6.08; O, 25.74.

Preparation of 10a. Benzaldehyde (3.15 g, 0.03 mol) was dissolved in 100 mL of H_2O and this solution was added over 10 h to **1d** dissolved in 2 L of H_2O containing $(NH_4)_2CO_3$ (90 g, 0.94 mol). After the solution was stirred for an additional 60 h and oxidative workup using N_2O_3, a brown oil (9.4 g) was obtained that also contained some unreacted benzaldehyde. After chromatography over silica gel (1:1 CH_2Cl_2/ether) **10a** (3.2 g, 7.47 mmol, 25% yield) is obtained: mp (from ether) 179–181 °C; ^1H NMR ($CDCl_3$) δ 2.59 (s, 6, CH_3), 3.60–4.60 (very complex m, 16, poly(ethylene glycol) H), 7.38 (m, 5, C_6H_5).

Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.40; H, 6.34; N, 3.26. Found: C, 63.74; H, 6.31; N, 3.19.

10b was prepared as described above by using acetaldehyde (1.32 g, 0.03 mol) as the carbonyl component. After oxidative workup, 9.2 g of an orange yellow solid was obtained. After chromatography over silica gel (1:1 CH_2Cl_2/ether) **10b** (2.8 g, 7.63 mmol, 25% yield) was obtained: mp 186.5–187.5 °C; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3, 21-CH_3), 2.53 (s, 6, 18,20-CH_3), 3.62 (br s, 8, OCH_2), 3.74 (m, 4, OCH_2), 4.51 (m, 4, $COOCH_2$).

Anal. Calcd for $C_{18}H_{25}NO_7$: C, 58.91; H, 6.87; N, 3.82. Found: C, 58.79; H, 6.84; N, 3.72.

10c was obtained by following the procedure described above with furfuraldehyde (2.8 g, 0.03 mol) as the carbonyl component. After oxidative workup, 9.9 g of brown yellow solid was obtained that consisted chiefly of **10c**. Instead of chromatography, recrystallization using charcoal was attempted. This led to unnecessary loss of material that could have been avoided by using a chromatographic purification procedure. The reaction has not been rerun. There was obtained ca. 500 mg of pure **10c**: mp 179–180 °C (from toluene/hexane); ^1H NMR ($CDCl_3$) δ 2.60 (s, 6, CH_3), 3.54 (m, 12, OCH_2), 4.06, 4.20, 4.45, and 4.60 (complex m, 4, $COOCH_2$), 6.50 (m, 1, furyl H), 7.32 (d, J = 4 Hz, 1, furyl H), 7.54 (m, 1, furyl H).

Anal. Calcd for $C_{21}H_{25}NO_8$: C, 60.20; H, 6.01; N, 3.34. Found: C, 60.03; H, 5.90; N, 3.34.

Synthesis of 16a–c. NaH (4 g, 0.17 mol), washed three times under N_2 with pentane, was suspended in 500 mL of freshly distilled dimethoxyethane (DME). After the solution was cooled to −30 °C, methyl 4-bromo-3-oxobutanoate[21] (30 g, 0.15 mol) in DME (100 mL) was added dropwise, and stirring was continued for 20 min, after which time the sodium chelate had apparently been formed completely. A solution of the bisalkoxide of the required poly(ethylene glycol) made by treatment of the glycol (0.078 mol) with NaH (4 g, 0.17 mol), washed as described above, in 500 mL of DME was added dropwise and with stirring to the solution of the chelate, keeping the temperature below 0 °C. After addition was complete, the solution was then refluxed for 15 h. Workup with dilute HCl, extraction with CH_2Cl_2, and drying over $MgSO_4$ followed by removal of solvent left the desired products (**16a**, 87% yield; **16b**, 84% yield; **16c**, 75% yield) as high-boiling liquids that were characterized by their ^1H NMR spectra but not further.[29] **16a**: ^1H NMR ($CDCl_3$) δ 3.55 (s, 4, OCH_2CO), 3.62 (br s, 8, OCH_2CH_2O), 3.67 (br s, 8, OCH_2CH_2O), 3.75 (s, 6, OCH_3), 4.20 (s, 4, $COCH_2CO$). **16b**: ^1H NMR ($CDCl_3$) δ 3.52 (s, 4, OCH_2CO), 3.55 (br s, 12, OCH_2CH_2O), 3.65 (br s, 8, OCH_2CH_2O), 3.68 (s, 6, OCH_3), 4.15 (s, 6, $COCH_2CO$). **16c**: ^1H NMR ($CDCl_3$) δ 3.52 (s, 4, OCH_2CO), 3.60 (complex, 24, OCH_2CH_2O), 3.70 (s, 6, OCH_3), 4.18 (s, 4, $COCH_2CO$). Small amounts of the enols were present, but no attempt was made to record these spectra independently.

Synthesis of 17a. To a stirred mixture of **16a** (28.1 g, 0.067 mol) and $(NH_4)_2CO_3$ (200 g, 2.21 mol) in 3 L of H_2O was added dropwise over 24 h a 35% aqueous solution of H_2CO (5.77 g, 0.067 mol). After being stirred for 48 h, the solution was extracted with CH_2Cl_2 and the organic layers were dried over $MgSO_4$. After removal of the solvent, the residual oil was extracted several times with diethyl ether. The ether-soluble material was subjected to high-pressure LC separation using a silica gel column and CH_2Cl_2/CH_3OH (99:1) as eluant. **17a** (3 g, 7.23 mmol, 11% yield) was isolated after recrystallization from diethyl ether: mp 115.5–116.5 °C; ^1H NMR ($CDCl_3$) δ 3.30 (br s, 2, 1,4-DHP CH_2), 3.65 (br s, 16, OCH_2CH_2O), 3.67 (s, 6, OCH_3), 4.60 (s, 4, OCH_2pyr), 8.00 (s, 1, NH).

Anal. Calcd for $C_{19}H_{29}O_8N$: C, 54.92; H, 7.04; N, 3.38. Found: C, 54.97; H, 7.09; N, 3.40.

Synthesis of 17b. The synthesis was carried out as described for **17a** but on a 42-mmol scale. After high-pressure LC separation and recrystallization from ether **17b** (1.9 g, 4.2 mmol, 10% yield) was obtained: mp 92.5–93.5 °C; ^1H NMR ($CDCl_3$) δ 3.36 (br s, 2, 1,4-DHP CH_2), 3.60 (br s, 20, OCH_2CH_2O), 3.65 (s, 6, OCH_3), 4.60 (s, 4, pyr CH_2), 8.0 (br s, 1, NH).

Anal. Calcd for $C_{21}H_{33}O_{10}N$: C, 54.90; H, 7.23; N, 3.05. Found: C, 54.72; H, 7.28; N, 3.29.

The synthesis of 17c was carried out as described for **17a** on a 30-mmol scale. After high-pressure LC separation **17c** (250 mg, 0.5 mmol, 1.7% yield) was obtained: ^1H NMR ($CDCl_3$) δ 3.30 (br s, 2, 1,4-DHP CH_2), 3.60 (br s, 24, OCH_2CH_2), 3.65 (s, 6, OCH_3), 4.60 (s, 4, pyr CH_2), 8.0 (br s, 1, NH). A satisfactory elemental analysis was not obtained.

Synthesis of 3,5-Bis(ethoxycarbonyl)-2,6-bis(methoxymethyl)-1,4-dihydropyridine (18). The synthesis was carried out as described for **17a** with ethyl 4-methoxy-3-oxobutanoate[22] (10.8 g, 0.075 mol). **18** (7 g, 22.6 mmol, 60% yield) was obtained: mp 87.5–88.5 °C; ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 6, CH_3), 3.35 (br s, 2, 1,4-DHP CH_2), 3.45 (s, 6, OCH_3), 4.20 (q, J = 7 Hz, 4, OCH_2CH_3), 4.60 (br s, 4, pyr CH_2), 7.80 (s, 1, NH).

Anal. Calcd for $C_{15}H_{23}O_6N$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.09; H, 7.28; N, 4.55.

Reaction of 17a with NaH. To a suspension of NaH (10 mg, 0.417 mmol, suspension in oil washed three times with pentane in diethyl ether) was added **17a** (50 mg, 0.12 mmol) dissolved in diethyl ether. A small amount of gas was evolved and a dark solid precipitated. This precipitate, after removal of the ether, was dissolved in CH_2Cl_2, and the solution was filtered rapidly taking care to avoid moisture. The clear solution was treated with excess H_2O and, after workup, **17a** was obtained in nearly quantitative yield, identical in all respects with starting material. Repetition of the same procedure but using a D_2O quench gave **17a** that was partially deuterated (^1H NMR and mass spectra).

Registry No. **1a**, 5459-04-1; **1b**, 24871-74-7; **1c**, 7139-67-5; **1d**, 7097-93-0; **2c**, 62921-54-4; **2d**, 62955-24-2; **3d**, 62921-62-4; **4d**, 62921-63-5; **4d** $NaClO_4$, 64189-56-6; **5d**, 62921-59-9; **6d**, 73636-32-5; **6d** $NaClO_4$, 73636-53-0; **7a**, 62921-55-5; **7b**, 62921-57-7; **7c**, 62921-58-8; **7d**, 73636-33-6; **8**, 73636-34-7; **9**, 62921-06-6; **10a**, 73636-35-8; **10b**, 73636-36-9; **10c**, 73651-40-8; **11a**, 73651-41-9; **11b**, 73636-37-0; **12**, 73636-39-2; **13**, 73636-40-5; **14a**, 73636-41-6; **14b**, 73636-42-7; **15**, 15074-61-0; **16a**, 73636-43-8; **16b**, 73636-44-9; **16c**, 73636-45-0; **17a**, 73636-46-1; **17b**, 73636-47-2; **17c**, 73636-48-3; **18**, 66762-72-9; ethyl acetoacetate, 141-97-9; ethylene glycol, 107-21-1; 1,3-bis(bromomethyl)benzene, 626-15-3; bis(ethylene glycol) pyridine-3,5-dicarboxylate, 73636-49-4; benzaldehyde, 100-52-7; acetaldehyde, 75-07-0; furfuraldehyde, 98-01-1; methyl 4-bromo-3-oxobutanoate, 17790-81-7; ethyl 4-methoxy-3-oxobutanoate, 66762-68-3.

(29) Other derivatives have been characterized fully.[22]