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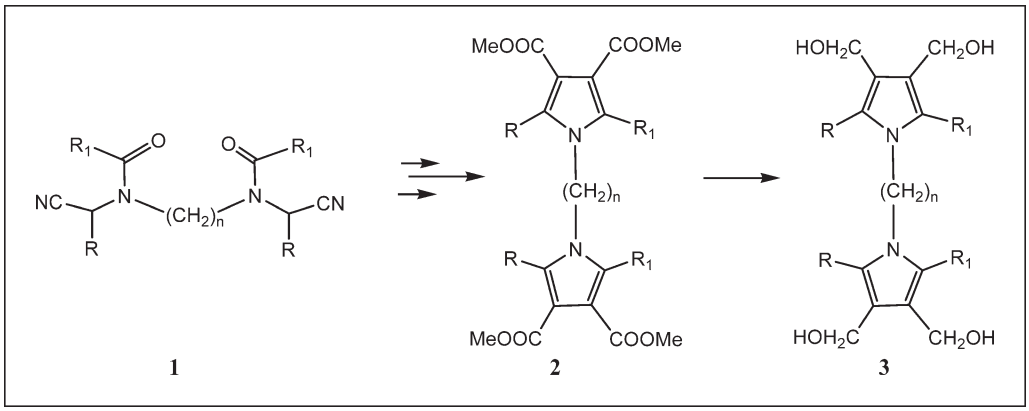

Open-chain bis-Reissert compounds **1** were converted to the corresponding bis-oxazolium intermediates *via* acid-catalyzed intramolecular cyclization. These oxazolium compounds exist in a variety of tautomeric structures in which the meso-ionic form can be intercepted by reaction with dipolarophiles in a 1,3-dipolar-cycloaddition reaction to produce a variety of highly functionalized bis-pyrrole esters **2**. In turn, the bis-pyrrole esters could be converted to the corresponding bis-pyrrole tetrols **3** in high yields.

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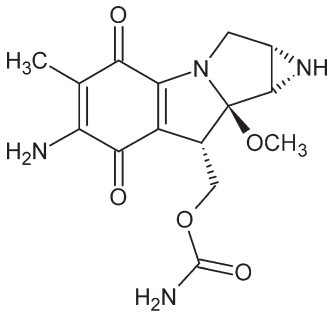
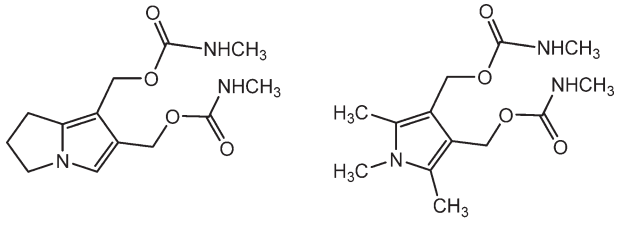
INTRODUCTION

Plant-derived natural products with their unique and complex architecture have often been the basis of new chemical entities for drug discovery in which the structural scaffold is used as a template pharmacophore in the derivation of simpler structural analogs. As part of a research program to prepare polyfunctional compounds for antitumor evaluation, we carried out the synthesis and evaluation of bis-pyrrole tetra esters and bis-pyrrole tetrols modeled upon the anticancer agent mitomycin.



Mitomycin C

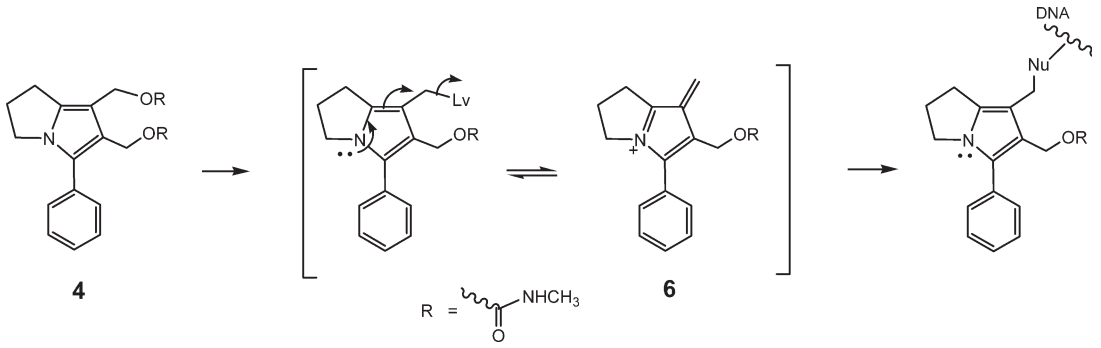
Extensive studies by Anderson *et al.* [4–7] have shown that functionalized pyrrole and pyrrolizine derivatives [*e.g.*, 1,2,5-trisubstituted 3,4-bis(hydroxymethyl pyrrole-*N*-methyl carbamate)] **4** and **5** possess potent antitumor activity *in vivo* analogous to that of the anticancer mitomycins and pyrrolizidine alkaloids.



4 **5**

These compounds have been designed with the expectation that the ring-nitrogen-assisted *O*-alkyl cleavage *in vivo* would generate highly reactive electrophilic vinylimine intermediates (*e.g.*, **6** from **4** in Scheme 1) that alkylate nucleic acids in cancer cells thereby inhibiting tumor growth. Furthermore, the stability and reactivity of the intermediate vinylimines could be modulated by varying the substituents (*e.g.*, electron donating

Scheme 1. Proposed mechanism of DNA alkylation by substituted pyrroles.

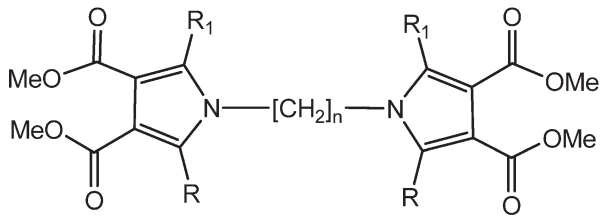


or electron withdrawing groups) on the heteroaromatic nucleus. Thus, an optimally functionalized molecule with stability *in vitro* and reactivity *in vivo* can be designed as a synthetic mimic of the anticancer alkaloids [4–7]. Indeed, the biological evaluation of a number of such derivatives has revealed compounds with potent antitumor activity *in vitro* and *in vivo* [8].

We considered an extension of this strategy where in multiple electrophilic centers can be generated for the alkylation of nucleic acids that would facilitate their interstrand and or intrastrand cross-linking. Bis-pyrrole tetrol derivatives **3** (*vide infra*), as the corresponding acetate or carbamates, where in the two pyrrole rings are linked by a flexible linker seemed appropriate to explore this concept. Conceptually, these compounds could act as highly efficient tetrafunctional alkylating agents, in which the intermediate electrophile could bind to multiple sites on the same or different DNA strands, thereby resulting in strand instability and strand scission (Scheme 2).

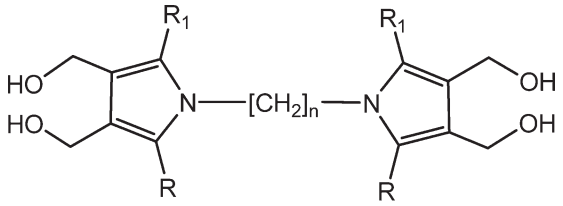
Alternatively, and in addition, the pyrrole units could also intercalate between base pairs on either or both strands and impair DNA replication. Consequently, potent anticancer activity was expected with these compounds if they could be selectively targeted to reach cancer cells.

The general structure of the target bis-pyrrole tetra esters **2** and alcohols **3** is represented below.



R = alkyl; R_1 = aryl; n = 2, 3

2



R = alkyl; R_1 = aryl; n = 2, 3

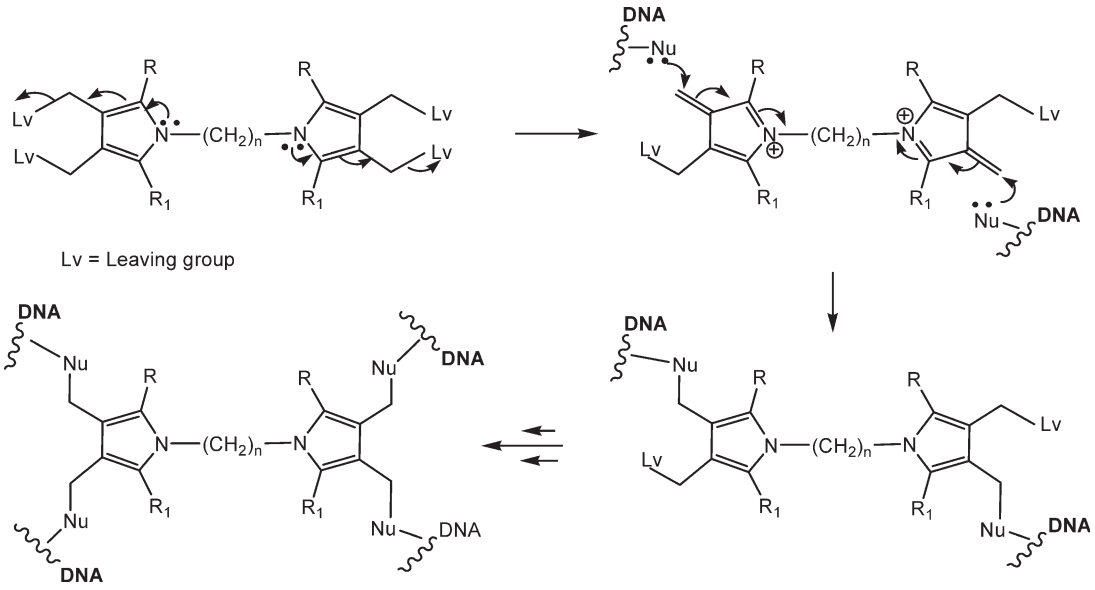
3

An important feature of such tetrafunctional bis-pyrroles (**2** and **3**) is that the distance between the two electrophilic sites that interact with DNA could be altered by varying the number of carbon atoms in the alkyl chain between the two pyrrole rings (Scheme 2). In addition, the bridging alkyl chain could also provide flexibility in juxtapositioning the electrophilic sites in the bis-pyrrole system to interact with nucleophilic sites on the target DNA strand(s). Furthermore, the substituents in the pyrrole nucleus (*e.g.*, R, R_1 = alkyl, aryl) could be used to modulate the electrophilic character of the intermediate vinylimines. Thus, multiple structural variations at different sites on the structure could be used to generate a rationally designed focused library of polyfunctionalized bis-pyrrole derivatives. Clearly, following Anderson's design strategy, the tetrols **3** could be further functionalized as the acetate, or carbamate derivatives that would then generate electrophilic intermediates for DNA alkylations. We present here our results in the synthesis of several target compounds of the general formula **2** and **3**.

CHEMISTRY

Functionalized pyrroles have been prepared by 1,3-dipolar cyclo-addition of azomethine and oxazolium

Scheme 2. Proposed mechanism of DNA alkylation and cross-linking by functionalized bis-pyrroles.



ylides with acetylenic compounds [9], as well as, benzotriazolyl derivatives with activated olefins [10]. For example, Anderson *et al*. [11] synthesized pyrrole carboxymethyl esters by initial 1,3-dipolar cycloaddition of the mesoionic form of the oxazolones, generated by the cyclization of α-amido acids [12], with dimethyl acetylene dicarboxylate (DMAD). Substituted pyrroles have also been synthesized from aminonitriles, the precursors of amino acids, *via* the corresponding Reissert compounds [13] as shown by extensive studies by McEwen *et al*. Thus, for example, the acid-catalyzed conversion of the Reissert compounds to the corresponding tetrafluoroborate [14] perchlorate [15,16], trifluoromethane sulfonate [17], and trifluoroacetate salts [18] is well known. These salts exist in a variety of tautomeric structures including diene- and meso-ionic forms that react with alkenes and alkynes to yield highly functionalized heterocyclic compounds.

However, these methodologies could not be directly used for the synthesis of our target tetra esters and tetra alcohols because the requisite bis-amino acids, as well as, the bis-aminonitriles were not readily available. Therefore, we established a general methodology for the preparation of these compounds from basic starting materials (Scheme 3).

Thus, the double Strecker reaction of an aldehyde, potassium cyanide, and diamine followed by the Schotten–Baumann acylation of the resultant bis-aminonitriles **7** gave the corresponding open-chain bis-Reissert compounds **1** [15]. Treatment of bis-Reissert compounds with acid generated the corresponding bis-oxazolium salts **8**. The 1,3-dipolar cycloaddition reactions were performed either on the isolated bis-oxazolium salts **8** or most preferably on *in situ* generated bis-oxazolium intermediates to provide the bis-pyrrole esters **2**, which on reduction gave the tetrols **3**.

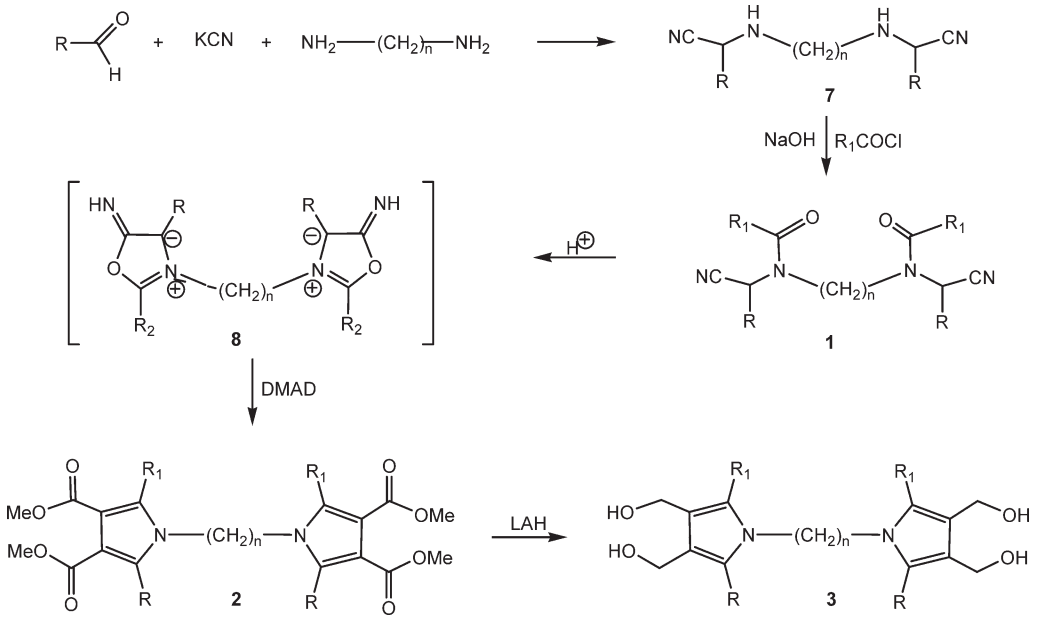
RESULTS AND DISCUSSION

The chemistry of Reissert compounds has been extensively investigated during the past several decades [13]. Of particular interest has been the synthesis of aldehydes from acid chlorides via the Reissert compounds. However, upon acid-catalyzed hydrolysis, open-chain Reissert compounds give only the corresponding carboxylic acids (*vide infra*) and not the aldehydes. Subsequently, McEwen *et al*. carried out extensive studies on the chemistry open-chain Reissert analogs [13,14]. Our synthesis of bis-pyrrole compounds of general structures **2** and **3** was modeled after McEwen's work.

Bis-aminonitriles. As mentioned before, the synthesis of the bis-aminonitriles of general structure **7** was accomplished by the double Strecker reaction using the corresponding aldehydes, amines, and KCN as per reported procedures [19]. The reaction conditions for the synthesis of the various aminonitriles and their spectral characteristics are given in the Experimental Section. Notably, in the IR spectrum, the characteristic νCN band at 2230–2240 cm^{-1} was observed for each of the compounds.

Open-chain bis-Reissert compounds. The aminonitriles **7a–d** was converted to a variety of open-chain bis-Reissert analogs **1a–n** by the Schotten–Baumann acylation reaction using the corresponding acyl chlorides in 75–80% yields. All compounds were isolated as crystalline solids. The physical properties, as well as, IR and NMR spectral characteristics of the Reissert compounds **1a–n** are given in Table 1. Notably in the IR spectrum,

Scheme 3. General strategy for the synthesis of bis-pyrrole tetrols.



the characteristic νCN band was observed between 2210 and 2300 cm^{-1}, depending on the structure. In the ^1H NMR spectra the —CHCN appeared at δ 4.7–4.8 ppm when attached to the ethyl group and at δ 6.3–6.7 ppm when attached to aryl substituents [13e].

Preparation of open-chain bis-Reissert salt analogs (8). Several open-chain Reissert analogs have been reported by McEwen *et al*. [13]. However, the corresponding oxazolium tetrafluoroborate salts could be isolated only in very few cases. The isolated salts were used in 1,3-dipolar cycloaddition reactions with DMAD to produce the corresponding 1,2,5-aryl substituted pyrroles. In other reports, the oxazolium tetrafluoroborate salts were used in (3 + 2) cycloaddition reaction with ethyl acrylate to obtain aryl-substituted pyridones [20].

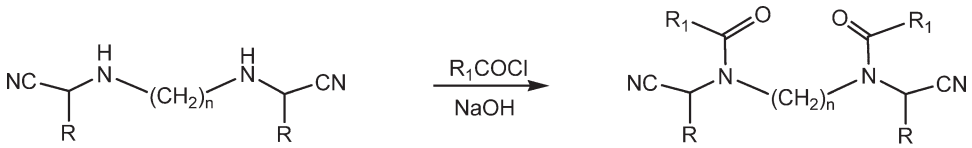
Our initial attempt to isolate the bis-oxazolium tetrafluoroborate salts, by the addition of 32% fluoroboric acid to a solution of **1a (**a representative analog of **1**) in acetic acid, failed to yield any isolable salts. Attempted preparation of the bis-oxazolium trifluoromethane sulfonate salts by the reaction of the bis-Reissert analogs **1** with trifluoromethane sulfonic acid was also not successful. However, the treatment of **1a** with 70% perchloric acid resulted in the successful isolation of the corresponding bis-oxazolium perchlorate salts. Typically, the reaction of **1a** with perchloric acid at low temperature yielded a yellow precipitate, which was isolated and subsequently crystallized from acetonitrile-ether. Thus, a few representative bis-oxazolium perchlorate salts **8a, 8b** prepared in this manner from the corresponding bis-Reissert analogs were fully characterized (see Experimental Section).

The mechanistic pathway for the formation of the bis-oxazolium salts involves the initial acid-catalyzed protonation of the nitrilic nitrogen of the Reissert analog (general structure **1**) followed by the intramolecular nucleophilic attack of the carbonyl oxygen on the nitrile carbon to give the bis-oxazolium salts (Scheme 4). The bis-oxazolium salt exists as different tautomeric forms **I–III**, which could interconvert in solution. We previously reported the ^{13}C NMR study of the representative bis-oxazolium perchlorate salts and confirmed that the amino form **II** is the most predominant tautomer in solution [21]. Our results are in agreement with that of Cook *et al*. [22]. The salt was found to revert back to the Reissert compound over a period of time in the presence of DMSO [21]. The open-chain bis-Reissert compounds were also converted to the corresponding bis-amino acid in the presence of 36% HCl presumably via the formation of the bis-oxazolium salt intermediate and subsequent hydrolysis [19]. That acid-catalyzed reaction of open-chain Reissert compounds results in the formation of carboxylic acids instead of aldehydes was first reported by Elliot [23]. However, the mechanistic pathway for the conversion bis-oxazolium salts to the corresponding bis-amino acid remains to be fully elucidated. Nevertheless, our results are consistent with structural studies on other classes of Reissert compounds [21–23].

Dipolar cycloaddition reactions of open-chain bis-Reissert compounds—The *in situ* approach. The bis-Reissert perchlorate salts **8** prepared as above could be successfully converted to the target bis-pyrrole tetra esters of general structure **2** by reaction with DMAD presumably via the meso-ionic species **9** (munchnone

Table 1

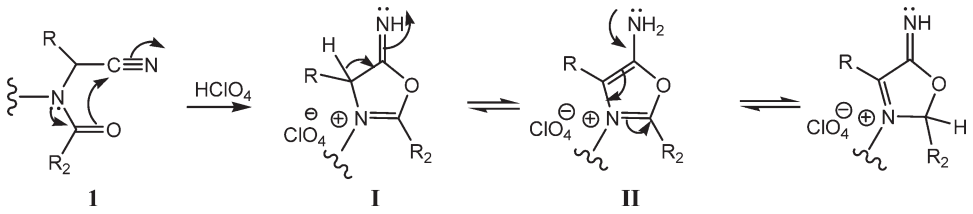
Synthesis and characterization of open-chain bis-Reissert analogs **1**.



7a-d **1a-n**

Compound	R	R_1	*n*	Yield (%)	Mp (°C)	Spectral data (IR, ν cm^{-1} and ^1H NMR, $CDCl_3$, 25°C δ ppm, *J* in Hertz)
1a	C_2H_5	C_6H_5	2	80	167–9	IR: 2950, 2246, 1646, 1452. ^1H NMR: 0.9 (t, 6H, *J* = 7 Hz, CH_2CH_3,) 1.4–2.2 (m, 4H, *J* = 7 Hz, CH_2CH_3), 3.7 (s, 4H, CH_2N), 4.8 (bt, 2H, CHCN), 7.5 (s, 10H, ArH)
1b	C_2H_5	*p*-Cl=C_6H_4	2	78	178–9	IR: 2950, 2255, 1705, 1650, 1410, 1300, 1100. ^1H NMR: 1.0 (t, 6H, *J* = 7 Hz, CH_2CH_3), 1.6–2.2 (m, 4H, CH_2CH_3), 3.7 (s, 4H, CH_2N), 4.7 (t, 2H, CHCN), 7.4 (s, 8H, ArH)
1c	C_2H_5	*p*-CH_3—C_6H_4	2	39	192	IR: 2980, 2240, 1640, 1400, 1300, 1060. ^1H NMR: 0.9 (t, 6H, *J* = 7 Hz, CH_2CH_3), 1.7 (m, 4H, CH_2CH_3), 2.4 (s, 6H, $ArCH_3$), 3.6 (bs, 4H, CH_2N), 4.8 (t, 2H, *J* = 6 Hz, CHCN), 7.3 (s, 8H, ArH).
1d	C_2H_5	*p*-OCH_3—C_6H_4	2	71	157	IR: 2950, 2230, 1640, 1620, 1400, 1300. ^1H NMR: 1.0 (t, 6H, *J* = 6 Hz, CH_2CH_3), 1.87 (m, 4H, *J* = 6 Hz, CH_2CH_3), 3.67 (s, 4H, CH_2N), 3.83 (s, 6H, OCH_3), 4.8 (t, 2H, *J* = 8 Hz, CHCN), 6.7–7.4 (q, 8H, ArH).
1e	C_2H_5	*p*-NO_2—C_6H_4	2	60	235–7	IR: 2980, 2245, 2100, 1610, 1400, 1300. ^1H NMR: 1.13 (t, *J* = 7 Hz, CH_2CH_3), 2.03 (q, 4H, *J* = 7 Hz CH_2CH_3), 3.93 (s, 4H, CH_2N), 5.0 (t, 2H, *J* = 7 Hz, CHCN), 7.56 (d, 4H, *J* = 6 Hz, ArH), 8.4 (d, 4H, *J* = 6 Hz, ArH).
1f	C_6H_5	C_6H_5	2	80	211	IR: 2210, 1970, 1900, 1640, 1290. ^1H NMR: 3.4 (m, 4H, CH_2N), 6.3 (bs, 2H, CHCN), 7.3–7.5 (m, 20H, ArH)
1g	C_6H_5	*p*-Cl—C_6H_4	2	75	222	IR: 2525, 1630, 1450, 1250, 830. ^1H NMR: 3–4 (m, 4H, CH_2N), 6.6–7.06 (m, 12H, CHCN and ArH), 7.1–7.57 (q, 8H, ArH)
1h	C_6H_5	*p*-CH_3—C_6H_4	2	45	216	IR: 2230, 1680, 1600, 1460, 1340, 1240, 805. ^1H NMR: 2.47 (s, 6H), 3.0–4.0 (m, 4H, CH_2N,) 6.33 (s, 2H, CHCN), 7.0–7.73 (m, 18H ArH)
1i	C_6H_5	*p*-OCH_3—C_6H_4	2	87	205–6	IR: 2990, 2215, 1620, 1420, 1310, 1260, 845. ^1H NMR: 2.9–3.5 (m, 4H, CH_2N) 3.8 (s, 6H,OCH_3) 6.3 (bs, 2H, CHCN) 6.8–7.5 (m, 18H, ArH)
1j	C_6H_5	*p*-NO_2—C_6H_4	2	53	185	IR: 2270, 1670, 1500, 1340, 830, 700. ^1H NMR: 3.33–4.33 (m, 4H, CH_2N), 7.06 (d, 2H CHCN), 7.33 (s, 10H, Aromatic), 7.9 (d, 4H, *J* = 6 Hz, ArH), 8.5 (d, 4H, *J* = 6 Hz, ArH)
1k	C_2H_5	C_6H_5	3	55	–	IR: 2950, 2300, 1680, 1400, 1060. ^1H NMR: 0.9 (t, 6H, *J* = 6 Hz, CH_2CH_3), 1.8 (m, 6H, CH_2CH_3, $CH_2CH_2CH_2$), 3.3 (t, 4H, *J* = 7 Hz, CH_2N), 4.7 (t, 2H, *J* = 8 Hz, CHCN), 7.3 (s, 10H, ArH)
1l	C_2H_5	*p*-Cl—C_6H_4	3	61	–	IR: 2250, 1640, 1400, 1290, 1070. ^1H NMR: 0.9 (t, 6H, *J* = 7 Hz, CH_2CH_3), 1.6–2.23 (m, 6H, CH_2CH_3, $CH_2CH_2CH_2$), 3.23 (t, 4H, *J* = 10 Hz, CH_2N), 4.73 (t, 2H, *J* = 10 Hz, CHCN) 7.03–7.4 (m, 8H, ArH)
1m	C_6H_5	C_6H_5	3	60	139	IR: 2215, 1650, 1460, 1380. ^1H NMR: 1.9 (m, 2H, $CH_2CH_2CH_2$), 3.2 (m, 4H, CH_2N), 6.6 (s, 2H, CHCN), 7.2–7.6 (bs, 20H, ArH)
1n	C_6H_5	*p*-OCH_3—C_6H_4	3	58	152	IR: 2325, 1620, 1460, 1100, 820. ^1H NMR: 1.67 (m, 2H, $CH_2CH_2CH_2$), 2.93 (m, 4H, CH_2N), 3.73 (s, 6H, $ArOCH_3$), 6.4 (s, 2H, CHCN), 6.7–7.46 (m, 18H, ArH)

Scheme 4. Formation of bis-oxazolium perchlorate salt from open-chain bis-Reissert compounds **1**.



imines) [12a,24] in a 1,3-dipolar cycloaddition reaction as shown in the general reaction sequence in Scheme 5. Presumably, the 1,3-dipolar cycloaddition reaction results in the initial formation of a bicyclic cycloadduct **10** that undergoes cycloreversion by retro-Diels–Alder reaction to give the pyrrole esters *via* elimination of the isocyanic acid. However, in general, the cycloaddition reactions resulted in considerable amount of decomposed products and the overall yield of the tetra ester **2** from the Reissert analog **1** was very low (17–25%, *vide infra* Experimental section). Furthermore, given the potentially explosive nature of these perchlorate salts, the isolation and subsequent reactions of additional analogs with dipolarophiles were not attempted further. Thus, an alternative strategy of a more general nature was needed for the synthesis of the target compounds.

We therefore considered the *in situ* generation of the oxazolium salts in the presence of acid and subsequent reaction of the salts with dipolarophiles to provide the desired target compounds. Mechanistically, it was anticipated that avoiding the presence of moisture in the reaction mixture was the key to ensuring the structural integrity of the oxazolium salts and their reaction with dipolarophiles. Hence, trifluoroacetic and 98% sulfuric acids appeared suitable for the *in situ* generation of the oxazolium salts from the corresponding open-chain Reissert Compounds. Indeed, heating the representative open-chain Reissert analogs **1a–c** with trifluoroacetic acid (TFA) and DMAD at 80–90°C for a prolonged period (nearly 22 days!) yielded the corresponding pyrrole tetra esters **2a–c** in 20–25% in isolable yields. Unlike the reaction with perchlorate salts, this reaction, however, yielded fewer amounts of decomposed products. Yet, the conversion of the Reissert analog to the ester was only 30–40% and the separation of the unreacted starting material from the product was quite tedious. Clearly, the method was not suitable for routine use. However, the treatment of the bis-Reissert analogs **1a–c** with sulfuric acid (98%) and DMAD at 90–95°C for 72–120 h yielded the tetra ester **1a–c** in modest yields of 30–45% in many cases. In the case of both TFA and sulfuric acids, the reaction was done neat in the absence of solvents. All attempts to use other solvents in the procedure failed to yield the desired product. Nevertheless, without exception, all the bis-Reissert analogs **1a–o**, could be successfully converted to the corresponding bis-pyrrole derivatives **2a–o** thereby establishing the generality of the reaction (Table 2). All the bis-pyrrole tetra esters **2a–o** showed characteristic carbonyl and aromatic stretching frequencies in the IR spectrum. It is noteworthy that in the NMR spectrum of all bis-pyrrole esters, with the exception of the symmetrically substituted **2f** and **2m** analogs, two sets of the carbmethoxy (COOMe) protons corresponding to each ester group was observed indicative of different electronic environments imposed by the neighboring alkyl and phenyl substituents.

Reduction of the tetra esters 2 to the tetra alcohols 3. Our initial attempts, analogous to the reported methods adopted for the pyrrole diesters [4,5,25], to reduce the tetra ester with lithium aluminum hydride (LAH) in ether or tetrahydrofuran resulted in a low yield of the desired tetra alcohol. The reaction mixture contained a variety of products, presumably owing to incomplete reduction. In fact, in a few cases, the partially reduced derivative (mixed ester alcohol compound) could be isolated and characterized by spectral methods (data not shown). In a modification of the reaction, it was observed that portion-wise addition of the ester into a suspension of LAH in tetrahydrofuran or dioxane also

Scheme 5. Formation of bis-pyrrole tetra esters **2** by 1,3 dipolar cycloaddition reaction of **8**.

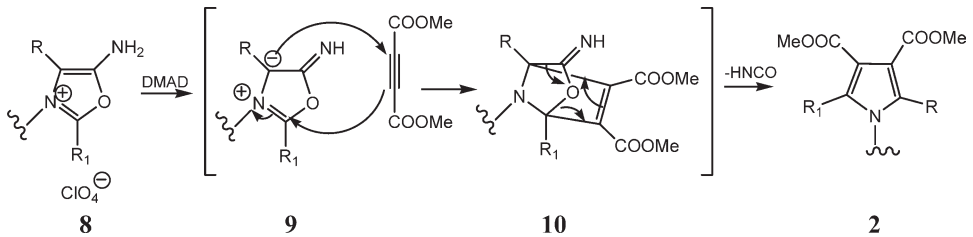
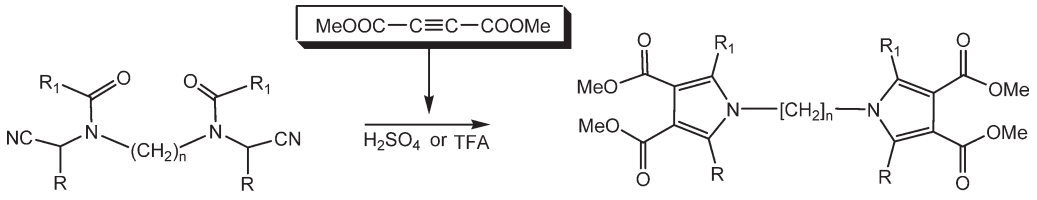


Table 2

Synthesis and characterization of bispyrrole tetra esters **2**.



Compound	R	R_1	*n*	Yield%	mp (°C)	Spectral data (IR, ν cm^{-1} and ^1H NMR, $CDCl_3$, 25°C δ ppm, *J* in Hertz)
2a	C_2H_5	C_6H_5	2	31	268	IR: 2970, 1720, 1710, 1610. ^1H NMR: 0.9 (t, 6H, *J* = 7 Hz, CH_2CH_3), 2.0 (q, 4H, *J* = 7 Hz, CH_2CH_3), 3.5 (s, 6H, $COOCH_3$), 3.7 (s, 4H, CH_2N), 3.8 (s, 6H, $COOCH_3$), 7.1–7.6 (m, 10H, ArH)
2b	C_2H_5	*p*-Cl—C_6H_4	2	36	249	IR: 2950, 1710, 1580, 1420, 1210. ^1H NMR: 0.9 (t, 6H, *J* = 7 Hz, CH_2CH_3), 2.1 (q, 4H, *J* = 7 Hz, CH_2CH_3), 3.6 (s, 6H, $COOCH_3$), 3.7 (s, 4H, CH_2N), 3.8 (s, 6H, $COOCH_3$), 7.3 (q, 8H, ArH).
2c	C_2H_5	*p*-CH_3—C_6H_4	2	18	240	IR: 2900, 1750, 1460, 1200. ^1H NMR: 0.8 (t, 6H, *J* = 7 Hz, CH_2CH_3), 1.9 (q, 4H, *J* = 7 Hz, CH_2CH_3), 2.4 (s, 6H, $ArCH_3$), 3.5 (s, 6H, $COOCH_3$), 3.6 (s, 4H, CH_2N), 3.7 (s, 6H, $COOCH_3$), 7.2 (s, 8H, ArH).
2d	C_2H_5	*p*-OCH_3—C_6H_4	2	48	244	IR: 2950, 1715, 1680, 1600, 1420. ^1H NMR: 0.9 (t, 6H, *J* = 7 Hz, CH_2CH_3), 2.0 (q, 4H, *J* = 7 Hz, CH_2CH_3), 3.5 (s, 6H, $COOCH_3$), 3.6 (s, 4H, CH_2N), 3.7 (s, 6H, $COOCH_3$), 3.8 (s, 6H, $ArOCH_3$), 6.7–7.2 (q, 8H, ArH).
2e	C_2H_5	*p*-NO_2—C_6H_4	2	33	260	IR: 2970, 1720, 1700, 1600. ^1H NMR: 1.0 (t, 6H, *J* = 6 Hz, CH_3), 2.2 (q, 4H, *J* = 6 Hz, CH_2CH_3), 3.6 (s, 6H, $COOCH_3$), 3.8 (s, 6H, $COOCH_3$), 3.9 (s, 4H, CH_2N), 7.1–8.2 (q, 8H, ArH)
2f	C_6H_5	C_6H_5	2	21	233–35	IR: 1750, 1450, 1200. ^1H NMR: 3.6 (bs, 16H, CH_2N, $COOCH_3$), 6.8–7.2 (m, 20H, ArH)
2g	C_6H_5	*p*-Cl—C_6H_4	2	35	244	IR: 3000, 1700, 1440, 1140. ^1H NMR: 3.6 (s, 16H, CH_2N, $COOCH_3$), 6.6–6.8 (m, 8H, ArH), 7.1–7.4 (m,10H, ArH)
2h	C_6H_5	*p*-CH_3—C_6H_4	2	29	232	IR: 2990, 1720, 1440, 1200. ^1H NMR: 2.5 (s, 6H, $ArCH_3$), 3.5 (s, 4H, CH_2N), 3.6 (s, 12H, $COOCH_3$), 6.5–7.5 (m, 18H, ArH).
2i	C_6H_5	*p*-OCH_3—C_6H_4	2	40	231–32	IR: 1740, 1270, 1120. ^1H NMR: 3.5 (s, 4H, CH_2N), 3.6 (s, 12H, $COOCH_3$), 3.8 (s, 6H, $ArOCH_3$), 6.8–7.3 (m, 18H, ArH)
2j	C_6H_5	*p*-NO_2—C_6H_4	2	27	250	IR: 3000, 1700, 1600, 1520, 1345, 1160. ^1H NMR: 1.6 (s, 4H, CH_2N) 3.6 (s, 12H, $COOCH_3$) 6.6–7.5 (m, 14H, ArH) 8.0–8.2 (d, 4H, ArH).
2k	C_2H_5	C_6H_5	3	40	196	IR: 3010, 1740, 1480, 1420, 1320, 1010. ^1H NMR: 1.1 (t, 6H, *J* = 7 Hz, CH_2CH_3), 1.6 (m, 2H, $CH_2CH_2CH_2$), 2.7 (q, 4H, *J* = 7 Hz, CH_2CH_3), 3.6 (t, 4H, CH_2N), 3.7 (s, 6H, $COOCH_3$), 3.8 (s, 6H, $COOCH_3$), 7.2–7.4 (m, 10H, ArH).
2l	C_2H_5	*p*-Cl—C_6H_4	3	32	204	IR: 1710, 1450, 1200. ^1H NMR: 1.2 (t, 6H, *J* = 7 Hz, CH_2CH_3), 1.6 (m, 2H, $CH_2CH_2CH_2$) 2.7 (q, 4H, *J* = 7 Hz, CH_2CH_3), 3.6 (t, 4H, *J* = 7 Hz, CH_2N), 3.7 (s, 6H, $COOCH_3$), 3.8 (s, 6H, $COOCH_3$), 7.3 (q, 8H, ArH).
2m	C_6H_5	C_6H_5	3	30	231	IR: 1710, 1480, 1440, 1320, 1220. ^1H NMR: 1.3 (m, 2H, $CH_2CH_2CH_2$), 3.2 (t, 4H, CH_2N), 3.6 (s, 12H, $COOCH_3$), 6.9–7.5 (m, 20H, ArH).
2n	C_6H_5	*p*-CH_3—C_6H_4	3	28	225	IR: 1730, 1700, 1480, 1320, 1200. ^1H NMR: 1.1 (m, 2H, $CH_2CH_2CH_2$), 3.2 (t, 4H, *J* = 8 Hz, CH_2N), 3.6 (s, 12H, $COOCH_3$), 3.8 (s, 6H, OCH_3), 6.8–7.4 (m, 18H, ArH).
2o	C_6H_5	*p*-NO_2—C_6H_4	3	18	130	IR: 1740, 1440, 1330, 1200. ^1H NMR: 1.0 (m, 2H, $CH_2CH_2CH_2$), 3.1 (t, 4H, CH_2N), 3.5 (s, 12H, $COOCH_3$), 6.8–7.3 (m, 14H, ArH), 8.0 (d, 4H, ArH)

gave only mixture of products representing fully reduced and partially reduced products. Isolation of this product mixture and subjecting it to further reduction again failed to complete the reduction and in fact more decomposition of the mixture resulted. However, when the tetra ester was dissolved in boiling dioxane followed by the addition of LAH in one lot, the reduction could be completed within 5 min. The tetra alcohols were obtained in high yields and no partially reduced product was observed (as ascertained by TLC). In the event, change of solvent from THF to dioxane not only allowed higher reflux temperatures to be used in the reaction but also apparently changed the solubility pattern of the LAH-product complex that facilitated for more efficient reduction of the ester to the alcohol. The good yield obtained in the ''inverse'' addition procedure at a high temperature must also be indicative of a thermodynamic control of the reaction leading to the formation of the stable tetra alcohol exclusively. The physical characteristics of the tetra alcohols are given in Table 3. It is noteworthy that in the ^{1}H NMR of most bis-pyrrole alcohols, two sets of methylene protons attached to the hydroxyl groups were observed, and might be reflective of the different electronic environments caused by the neighboring substituents.

In conclusion, we report here the synthesis of highly functionalized bis-pyrrole tetra esters and tetra alcohols through the use of the corresponding open-chain bis-Reissert compounds. A key feature of the synthetic strategy is the *in situ* generation of bis-Reissert oxazolium intermediates and the 1,3-dipolar cyclo-addition reactions with the transiently generated munchnone imines. The strategies and experimental protocols described here can be applied to other reactions of amino nitriles and amino acids to aid the synthesis of other substituted pyrroles, as well as, pyridones. The conversion of the tetra alcohols to various derivatives and their evaluation, as antitumor agents will be reported in due course.

EXPERIMENTAL

General. All chemicals and reagents were procured from reputed manufacturers and were used as such. The solvents were dried by standard procedures and stored under anhydrous condition. Benzene and toluene were dried over anhydrous calcium chloride, distilled and stored over sodium wire. Methylene chloride was dried by distilling over phosphorus pentoxide. Methanol and ethanol were dried over activated calcium oxide and distilled over magnesium turnings and stored over 4 Å molecular sieves. Reagent grade THF and dioxane were dried over sodium wire and distilled before use.

Melting points were determined on a Tempo melting point apparatus and are uncorrected. The proton NMR spectra were recorded at 25°C in deuteriochloroform or d_6-dimethyl sulfoxide (Aldrich Chemical Company, Milwaukee, WI) using a Varian-EM 360L NMR Spectrophotometer. All IR spectra were recorded on a Perkin Elmer Model 397 Double Beam Spectrophotometer. C, H, N analysis was performed at Alchemie Research Centre, Thane, Mumbai.

General procedure for the preparation of alkyl and aryl aminonitriles (7). An aqueous solution of potassium cyanide was added to a cooled solution of the diamine dihydrochloride in water with stirring. The aldehyde was added, either as such or as a solution in methylene chloride, dropwise over a period of 20 min. The stirring was continued for 4 h. When the aminonitrile separated out in the aqueous medium as a solid, it was filtered and washed with cold water to free from cyanide ions. The product was dried at the pump, stored in a desiccator, and refrigerated.

Whenever methylene chloride was used as the solvent, the organic layer was washed with ice-cold water, dried over sodium sulfate, and the solvent was removed under vacuum below 40°C. The product was stored in a desiccator and kept at 4°C until ready to use.

Typical examples

2,2′-(1,2-Ethanediyl-dimino)bis-butane nitrile (7a). The bis-aminonitrile (**7a**) was obtained from the reaction of propionaldehyde (29 g, 0.5 mol) potassium cyanide (32.5 g, 0.5 mol) and ethylene diamine dihydrochloride (36 g, 0.27 mol) in an aqueous medium at 0–5°C. Yield = 30.5 g (63%); mp 59°C; IR: 3280, 2230, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25°C): δ 1.1 (t, 6H, J = 7 Hz, $\underline{CH_3}CH_2$), 1.3–2.1 (m, 6H, 2H exchangeable with D_2O, $\underline{CH_2}CH_3$, NH), 2.4–3.2 (m, 4H, CH_2N), 3.4 (t, 2H, J = 7 Hz, $\underline{CH}CN$).

2,2′-(1,2-Ethanediyl-dimino)bis-benzenemethane nitrile (7b). The bis-aminonitrile **(7b)** could be obtained from benzaldehyde (37 g, 0.35 mol), potassium cyanide (23 g, 0.354 mol) and ethylene diamine dihydrochloride (25 g, 0.188 mol) in a 1:1 mixture of methylene chloride and water (250 mL) at 0–5°C. Yield = 33g (65%); mp 115°C; IR: 3300, 2950, 2240, 1460, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25°C): δ 1.8 (bs, 2H exchangeable with D_2O, NH), 2.8 (s, 4H, CH_2N), 4.75 (s, 2H, CHCN), 7.17 (m, 10H, ArH).

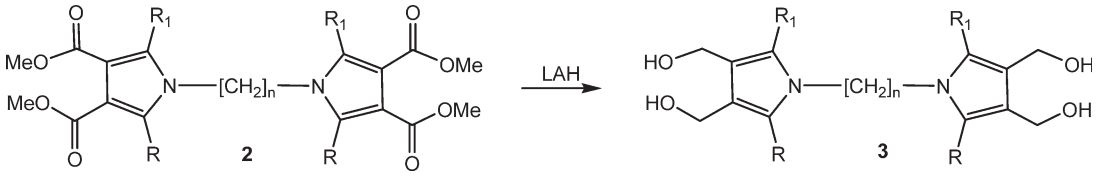
2,2′-(1,3-Propanediyl-dimino)bis-butane nitrile (7c). The reaction of propionaldehyde (29 g, 0.5 mol), potassium cyanide (32.5 g, 0.5 mol), and propylene diamine dihydrochloride (40 g, 0.27 mol) in water at 0–5°C yielded 31 g (59%) of **7c** as a colorless viscous liquid. IR: 3300, 2250, 1120; 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.05 (t, 6H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.3–2.4 (m, 8H, 2H exchangeable with D_2O, $\underline{CH_2}CH_3$, NH and $CH_2\underline{CH_2}CH_2$), 2.4–3.2 (bt, 4H, $\underline{CH_2}CH_2N$), 3.4 (t, 2H, J = 7 Hz, $\underline{CH}$—CN).

2,2′-(1,3-Propanediyl-dimino)bis-benzenemethane nitrile (7d). The bis-aminonitrile **(7d)** was afforded from benzaldehyde (35 g, 0.33 mol), potassium cyanide (21.5 g, 0.33 mol), and propylene diamine dihydrochloride (27 g, 0.184 mol) in a 1:1 mixture of methylene chloride and water (250 mL) at 0–5°C. Yield = 35 g (70%). mp 85°C; IR: 3350, 2950, 2240, 1500, 1460, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.8 (m, 4H, 2H D_2O exchangeable,CH_2—$\underline{CH_2}$—CH_2, NH), 2.9 (t, 4H, NCH_2), 4.8 (s, 2H, CHCN), 7.3–7.6 (m, 10H, ArH).

General procedure for the preparation of open chain bis-Reissert analogs (1). The bis-aminonitrile (**6**), benzene, and 30% aqueous sodium hydroxide solution were cooled to 0–5°C. The acid chloride was added to the mixture and the

Table 3

Synthesis and characterization of bispyrrole tetra alcohols **3**.



Compound	R	R_1	*n*	Yield %	mp (°C)	Spectral data (IR, ν cm^{-1} and ^1H NMR, $CDCl_3$, 25°C δ ppm, *J* in Hertz)
3a	C_2H_5	C_6H_5	2	86	210–15 (dec)	IR: 3325, 2950, 1440, 1220, 960. ^1H NMR: 0.7 (t, 6H, $J = 7$ Hz, $CH_2\underline{CH_3}$), 1.67 (q, 4H, $J = 7$ Hz, $\underline{CH_2}CH_3$), 2.93 (s, 4H, D_2O exchangeable, OH), 3.5 (s, 4H, $\underline{CH_2}N$), 4.17 (s, 4H, $\underline{CH_2}OH$) 4.27 (s, 4H, $\underline{CH_2}OH$), 7.0–7.4(m, 10H ArH)
3b	C_2H_5	*p*-Cl—C_6H_4	2	83	255 (dec)	IR: 3350, 2950, 1460, 1220, 980. ^1H NMR: 0.8 (t, 6H, $J = 7$ Hz, $CH_2\underline{CH_3}$), 1.8 (q, 4H, $J = 7$ Hz, $\underline{CH_2}CH_3$,), 3.3 (s, 4H, D_2O exchangeable, OH), 3.50 (s, 4H, $\underline{CH_2}N$), 4.1 (s, 4H, CH_2OH), 4.3 (s, 4H, CH_2OH), 7.0 (q, 8H, ArH)
3c	C_2H_5	*p*-CH_3—C_6H_4	2	85	178 (dec)	IR: 3350, 1420, 1360, 1240, 980. ^1H NMR: 0.7 (t, 6H, $J = 7$ Hz, $CH_2\underline{CH_3}$), 1.6 (q, 4H, $J = 7$ Hz, $\underline{CH_2}CH_3$), 2.33 (s, 6H, $Ar\underline{CH_3}$), 3.5 (s, 4H, CH_2N), 3.63 (bs, 4H, D_2O exchangeable, OH), 4.13 (s, 4H, CH_2OH), 4.33 (s, 4H, CH_2OH), 7.03 (bs, 8H, ArH).
3d	C_6H_5	C_6H_5	2	92	202 (dec)	IR: 3300, 2950, 1480, 1340, 1020. ^1H NMR: 2.47 (bs, 4H, D_2O exchangeable, OH), 3.47 (s, 4H, CH_2N), 4.10 (s, 8H, CH_2OH), 6.4–6.7 (m, 8H, ArH), 6.93–7.3 (m, 12H, ArH)
3e	C_6H_5	*p*-CH_3—C_6H_4	2	82	180–3 (dec)	IR: 3250, 1460, 1320, 1000. ^1H NMR: 2.3 (s, 6H, $Ar\underline{CH_3}$), 2.5 (bs, 4H, D_2O exchangeable, OH), 3.47 (s, 4H, CH_2N), 4.17 (s, 8H, $\underline{CH_2}OH$), 6.13–7.3 (m, 18H, ArH)
3f	C_6H_5	*p*-OCH_3—C_6H_4	2	87	209–10 (dec)	IR: 3300, 2950, 1600, 1450, 1340, 1240, 1000. ^1H NMR: 3.0 (bs, 4H, D_2O exchangeable, OH), 3.73 (s, 4H, NCH_2), 3.96 (s, 6H, $ArOCH_3$), 4.40 (s, 8H, $C\underline{H_2}OH$), 6.71–7.56 (m, 18H, ArH)
3g	C_2H_5	C_6H_5	3	83	188 (dec)	IR: 3375, 2920, 1610, 1350, 1260. ^1H NMR: 1.00 (t, 6H, $J =$ 7 Hz, $CH_2\underline{CH_3}$), 1.6 (m, 2H, $\underline{CH_2}CH_2N$), 2.47 (q, $J = 7$ Hz, 4H, $\underline{CH_2}CH_3$), 2.73 (s, 4H, D_2O exchangeable, OH), 3.40 (t, 4H, $J = 10$ Hz, $CH_2CH_2\underline{CH_2}N$), 4.30 (s, 4H, $\underline{CH_2}OH$), 4.5 (s, 4H, CH_2OH), 7.0–7.3 (m, 10H, ArH)
3h	C_2H_5	*p*-Cl—C_6H_4	3	91	150–55 (dec)	IR: 3300, 2950, 1680, 1480, 1020. ^1H NMR: 1.07 (t, 6H, $J =$ 7 Hz, $CH_2\underline{CH_3}$), 1.5 (m, 2H, $CH_2\underline{CH_2}CH_2$), 2.47 (q, 4H, J = 7 Hz $\underline{CH_2}CH_3$), 2.80 (bs, 4H, D_2O exchangeable, OH), 3.5 (t, $J = 10$ Hz, 4H, $NCH_2\underline{CH_2}CH_2N$), 4.23 (s, 4H, $\underline{CH_2}OH$) 4.47 (s, 4H, $\underline{CH_2}OH$), 7.16 (q, 8H, ArH)
3i	C_6H_5	C_6H_5	3	89	190–2 (dec)	IR: 3275, 2920, 1480, 1340, 970. ^1H NMR: 0.93 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.27 (t, 4H, NCH_2), 4.33 (bs, 12H, 4H D_2O exchangeable, $\underline{CH_2}OH$), 7.1–7.4 (m, 20H, ArH)
3j	C_6H_5	*p*-OCH_3—C_6H_4	3	80	192 (dec)	IR: 3325, 2950, 1580, 1440, 1000. ^1H NMR: 1.0 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.28 (t, 4H, $NCH_2CH_2\underline{CH_2}N$), 3.83 (s, 6H, OCH_3), 4.40 (bs, 12H, 4H D_2O exchangeable, $\underline{CH_2}OH$), 7.0–7.5 (m, 18H, ArH)

stoppered flask was vigorously shaken for 30 min. Whenever a solid was obtained, it was filtered, washed extensively with water to free it from alkali, and finally with small amount of cold methanol. In those cases, where the product reaction mixture was a sticky mass, it was triturated till it was solidified. Washing with water followed by cold methanol yielded solid product. In certain cases the reaction mixture was extracted with benzene. The benzene layer was washed with water, dried over sodium sulfate, and the solvent was removed *in vacuo*. These compounds were purified by column chromatography on silica gel.

Typical Examples

2,2′-[1,2-Ethanediyl-(N,N′-dibenzoyl)]bis-butane nitrile (1a). The aminonitrile **7a** (9.5 g, 0.05 mol), benzoyl chloride (15.5 g, 0.11 mol), and aqueous sodium hydroxide solution (30%, 20 mL) were mixed at 0–5°C in a stoppered flask and shaken vigorously for 30 min. The separated solid was filtered, washed to free from alkali, and dried to yield 16 g (80%) of a

white solid. A sample of the product **1a** was recrystallized from aqueous methanol. mp 167–169°C; IR: 2950, 2246, 1646, 1452 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.9 (t, 6H, J = 7 Hz, CH_3CH_2), 1.4–2.2 (m, 4H, CH_3CH_2), 3.7 (s, 4H, NCH_2), 4.8 (bt, 2H, CHCN), 7.5 (s, 10H, ArH). *Anal*. Calcd for $C_{24}H_{26}N_4O_2$ (402.5): C, 71.62; H, 6.51; N, 13.92. Found: C, 71.58; H 6.46; N 13.98.

2,2′-[1,2-Ethanediyl-{N,N′-(4,4′-dichloro-dibenzoyl}]bis-butane nitrile (1b). The compound **1b** was obtained in 78% yield from **7a** (9.5 g, 0.05 mol) *p*-chlorobenzoyl chloride (15 g, 0.11 mol) and aqueous sodium hydroxide (30%, 20 mL) as a white solid. mp 178–179°C; IR: 2950, 2255, 1705, 1650, 1410, 1300, 1100; ^1H NMR ($CDCl_3$): δ 1.0 (t, 6H, J = 7 Hz, CH_2CH_3), 1.6-2.2 (m, 4H, CH_2CH_3), 3.7 (s, 4H, CH_2N) 4.7 (t, 2H, CHCN), 7.4 (s, 8H, ArH). *Anal*. Calcd. for $C_{24}H_{24}N_4O_2Cl_2$ (471.38): C, 61.15; H, 5.13; N, 11.89. Found: C, 61.35; H, 5.02; N, 11.71.

2,2′-[1,2-Ethanediyl-{N,N′-(4,4′-dimethyl)-dibenzoyl}]bis-butane nitrile (1c). The compound was obtained in 39% yield from **7a** (9.5g, 0.05 mol) *p*-tolyl chloride (17 g, 0.11 mol) and aqueous sodium hydroxide (30%, 20 mL) as a white solid. mp 162°C; IR: 2980, 2240, 1640, 1400, 1300, 1060 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.9 (t, 6H, J = 7 Hz, CH_2CH_3), 1.7 (m, 4H, CH_2CH_3), 2.4 (s, 6H, $ArCH_3$), 3.6 (bs, 4H, CH_2N), 4.8 (t, 2H, J = 6 Hz, CHCN), 7.3 (s, 8H, ArH). *Anal*. Calcd for $C_{26}H_{30}N_4O_2$ (430.56): C, 72.53; H, 7.02; N, 13.01. Found: C, 72.67; H, 7.14; N, 13.23.

2,2′-[1,2-Ethanediyl-(N,N′-dibenzoyl)]bis-benzene methane nitrile (1f). The compound was obtained in 80% yield from the reaction of **7b** (14.5, 0.05 mol), benzoyl chloride (15.5 g; 0.11 mol), and aqueous sodium hydroxide (30%, 20 mL). mp 211°C; IR: 2210, 1970, 1900, 1640, 1290 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.4 (m, 4H, CH_2N), 6.3 (bs, 2H, CHCN), 7.3–7.5 (m, 20H, ArH). *Anal*. Calcd for $C_{32}H_{26}N_4O_2$ (498.59): C, 77.08; H, 5.25; N, 11.23. Found: C, 77.12; H, 5.01; N, 11.19.

2,2′-[1,2-Ethanediyl-{N,N′-(4,4′dimethoxy)-dibenzoyl}]bis-benzene methane nitrile (1i). The compound was obtained in 87% yield from the reaction of **7b** (5.8 g, 0.02 mol) *p*-methoxy benzoyl chloride (7 g, 0.041 mol), aqueous sodium hydroxide (30%, 15 mL) mp 205–6°C; IR: 2990, 2215, 1620, 1420, 1310, 1260, 845 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.9–3.5 (m, 4H, CH_2N) 3.8 (s, 6H, OCH_3) 6.3 (bs, 2H, CHCN) 6.8–7.5 (m, 18H, ArH); *Anal*. Calcd for $C_{34}H_{30}N_4O_4$ (558.63): C, 73.10; H, 5.41; N, 10.02. Found: C, 73.02; H, 5.38; N, 10.13.

2,2′-[1,3-Propanediyl-{N,N′-(4,4′-dichloro)-dibenzoyl}]bis-butane nitrile (1l). The analog could be obtained in 61% yield from the reaction of **7c** (2 g, 0.01 mol) *p*-chloro benzoyl chloride (3.7 g, 0.02 mol) and an aqueous sodium hydroxide solution (30%, 8 mL) as a viscous liquid. IR: 2250, 1640, 1400, 1290, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 (t, 6H, J = 7 Hz, CH_2CH_3), 1.6–2.23 (m, 6H, CH_2CH_3, $CH_2CH_2CH_2$), 3.23 (t, 4H, J = 10 Hz, CH_2N), 4.73 (t, 2H, J = 10 Hz, CHCN) 7.03–7.4 (m, 8H, ArH). *Anal*. Calcd for $C_{25}H_{26}N_4O_2Cl_2$ (485.42): C, 61.85; H, 5.39; N, 11.54. Found: C, 61.73; H, 5.27; N, 11.63.

2,2′-[1,3-Propanediyl-{N,N′-dibenzoyl}]bis-benzenemethane nitrile (1m). The compound was obtained in 78% yield from the reaction of **7d** (3 g, 0.01 mol) benzoyl chloride (3.7 g, 0.02 mol) and an aqueous sodium hydroxide solution (30%, 8 mL) as a white solid. mp 139°C; IR: 2215, 1650, 1460, 1380 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.9 (m, 2H, $CH_2CH_2CH_2$), 3.2 (m, 4H, CH_2N), 6.6 (s, 2H, CHCN), 7.2–7.6 (bs, 20H, ArH). *Anal*. Calcd. for $C_{33}H_{28}N_4O_2$ (512.61); C, 77.32; H, 5.50; N, 10.93. Found: C, 77.27; H, 5.37; N, 10.87.

2,2′-[1,3-Propanediyl-{N,N′-(4,4′-dimethoxy)-dibenzoyl}]bis-benzenemethane nitrile (1n). The compound was obtained in 59% yield from the reaction of **7d** (3 g, 0.01 mol) *p*-methoxy benzoyl chloride (3.6 g, 0.021 mol) and an aqueous sodium hydroxide solution (30%; 8 mL) as a white solid mp 152°C IR: 2325, 1620, 1460, 1100, 820 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.67 (m, 2H, $CH_2CH_2CH_2$), 2.93 (m, 4H, CH_2N), 3.73 (s, 6H, $ArOCH_3$), 6.4 (s, 2H, CHCN), 6.7–7.46 (m, 18H, ArH). *Anal*. Calcd. for $C_{35}H_{32}N_4O_4$ (572.67): C, 73.40; H, 5.63; N, 9.78. Found: C, 73.28; H, 5.57; N, 9.63.

Preparation of selected bis-oxazolium salts

3,3′-Ethylene-bis(2-phenyl 4-ethyl-5-aminooxazolium perchlorate) (8a). To the bis-Reissert analog **1a** (1.6 g, 4 mmol) was added 8 mL of perchloric acid (70%) slowly and with cooling to 10°C. The reaction mixture was stirred vigorously for 15 min and the resulting yellow precipitate was filtered and washed with dry ether. The crude salt was crystallized from acetonitrile-dry ether to get 1.25 g (50%) of the salt **8a**. mp 196–198°C (dec.); IR: 3400, 3300, 3200, 1680, 1620, 1570, 1420, 1070, 765 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.0 (t, 6H, J = 7 Hz, CH_3CH_2), 2.1–2.7 (m, 4H, CH_3CH_2), 4.6 (s, 4H, CH_2N), 6.8 (bs, 4H, D_2O exchangeable, NH_2), 7.8 (s, 10H, ArH). *Anal*. Calcd. for $C_{24}H_{28}N_4O_{10}Cl_2$ (603.4): C, 47.80; H, 4.70; N, 9.30. Found: C, 48.20; H, 4.60; N, 9.40.

3,3′-Ethylene-bis[2-(4-chlorophenyl)-4-ethyl-5-aminooxazolium perchlorate] (8b). This salt was obtained from **1b** (2 g, 4.25 mmol) and 70% perchloric acid (8 mL) in a similar procedure described for **8a** yielded 1.65 g (60 %) yield. mp 213°C (dec); IR: 3450, 2990, 1700, 1500, 1100 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.07 (t, 6H, J = 7 Hz, CH_3CH_2), 2.49 (q, 4H, J = 7 Hz, CH_3CH_2), 4.6 (s, 4H, CH_2N), 6.6–7.3 (bs, 4H, D_2O exchangeable, NH_2), 7.7 (s, 8H, ArH). *Anal*. Calcd. for $C_{24}H_{26}N_4O_{10}Cl_4$ (672.3): C, 42.88; H, 3.89; N, 8.33; Found: C, 43.19; H, 3.92; N, 8.34.

Reaction of oxazolium salt 8a with DMAD

1,1′-(1,2-Ethanediyl)-bis[dimethyl 2-ethyl, 5-phenyl pyrrole-3,4-dicarboxylate] (2a). The perchlorate salt **8a** (605 mg, 1 mmol) was heated with DMAD (0.5 mL, 4 mmol) at 80–85°C for 72 h. The reaction mixture turned brown and became a homogeneous hard mass. Chloroform was added to the cooled reaction mixture and warmed to 45°C and was filtered to separate the solid, presumably a polymer of isocyanuric acid. The chloroform solution was washed with saturated sodium bicarbonate solution followed by water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and 5 mL methanol was added to the mixture, stirred for 15 min and filtered. The crystals, after washing with cold methanol and drying, afforded 170 mg (28%) of **2a.** mp 268°C; IR (KBr): 2970, 1720, 1710, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.9 (t, 6H, J = 7 Hz, CH_2CH_3), 2.0 (q, 4H, J = 7 Hz, CH_2CH_3), 3.5 (s, 6H, $COOCH_3$), 3.7 (s, 4H, CH_2N), 3.8 (s, 6H, $COOCH_3$), 7.1–7.6 (m, 10H, ArH). *Anal*. Calcd. for $C_{34}H_{36}N_2O_8$ (600.6): C, 67.98; H, 6.04; N, 4.66. Found: C, 68.13; H, 5.93; N, 4.98.

Conversion of bis-Reissert analog 1 to bis-pyrrole tetra esters 2—The *in situ* procedure

General procedure using TFA. The bis-Reissert analog **1** (3 mmol), DMAD (7.5 mmol) and TFA (15 mmol) were added to dry dichloromethane (20 mL) and refluxed for 3 days and kept

at room temperature. After 22 days, the mixture was filtered and the solvent was removed *in vacuo*. The product crystallized out on addition of 4 mL of methanol. The white crystals were filtered and washed with cold methanol and was recrystallized thrice from chloroform-methanol to yield the pure ester.

Esters **2a–c** and **2f** were prepared with this method in 17–25% yield. The spectral properties of these esters are given in Table 2.

Typical example

1,1′-(1,2-Ethanediyl)-bis[dimethyl 2 ethyl, 5-(4-chlorophenyl)-pyrrole 3,4-dicarboxylate] (2b). **1b** (500 mg, 1.06 mmol) DMAD (462 mg, 3.2 mmol) and TFA (597 mg, 5.23 mmol) when reacted in dry dichloromethane for 25 days yielded 120 mg (17%) of **2b**.

General procedure using sulfuric acid. The bis-Reissert analog **1** (25 mmol) was mixed with DMAD (75 mmol) and sulfuric acid (98%, 50 mmol) was added to it. The color of the mixture turned light yellow to dark red. This mixture was heated to 85–95°C for 72–120 h. The reaction mixture was cooled and saturated sodium bicarbonate solution was added carefully. Chloroform was added to the mixture and warmed on a water bath and the mixture was filtered. The organic layer was washed with water and dried over anhydrous sodium sulfate and the removal of chloroform *in vacuo* yielded a viscous mass. Crystalline product appeared on addition of methanol. Whenever necessary a recrystallization was done from methanol or chloroform-methanol mixture. The physical properties and spectral data of the tetra esters **2** prepared by this procedure are given in Table 2.

Typical examples

1,1′-(1,2-Ethanediyl)-bis[dimethyl 2-ethyl-5-(4 chlorophenyl)-pyrrole 3,4-dicarboxylate] (2b). The open-chain bis-Reissert analog **1b** (3 g, 6.4 mol) was mixed with DMAD (2.8 g, 19.7 mmol) and sulfuric acid (98%) (1.3 g, 13.34 mmol) and heated at 90–95°C for 72 h. The work up of the mixture as described in the general procedure and subsequent crystallization from a mixture of chloroform and methanol (1:1) yielded 1.5 g (36 %) of **2b**. mp 249–50°C; IR: 2950, 1710, 1580, 1420, 1210 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.9 (t, 6H, J = 7 Hz, $CH_2\underline{CH_3}$), 2.1 (q, 4H, J = 7 Hz, $\underline{CH_2}CH_3$), 3.6 (s, 6H, $COO\underline{CH_3}$), 3.7 (s, 4H, CH_2N), 3.8 (s, 6H, $\underline{C}OOCH_3$), 7.3 (q, 8H, ArH). *Anal*. Calcd: for $C_{34}H_{34}N_2O_8Cl_2$ (669.55); C, 60.99; H, 5.11; N, 4.18. Found; C, 60.73; H, 5.07; N, 4.22.

1,1′-(1,2-Ethanediyl)-bis[dimethyl-2-ethyl-5-(4-methyl phenyl) pyrrole 3,4 dicarboxylate)] (2c). **1c** (3.7 g, 8.6 mmol) DMAD (3 g, 21.5 mmol) and H_2SO_4 (2 g, 20 mmol) when heated at 90–100°C for 48 h afforded 1.0 g (18%) of **2c.** mp 240°C; IR: 2900, 1750, 1460, 1200 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.8 (t, 6H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.9 (q, 4H, J = 7 Hz, $\underline{CH_2}CH_3$), 2.4 (s, 6H, $ArCH_3$), 3.5 (s, 6H, $COOCH_3$), 3.6 (s, 4H, CH_2N), 3.7 (s, 6H, $COOCH_3$), 7.2 (s, 8H, ArH). *Anal*. Calcd. for $C_{36}H_{40}N_2O_8$(628.7); C, 68.77; H, 6.41; N, 4.45. Found: C, 68.53; H, 6.52; N, 4.39.

1,1′-(1,2-Ethanediyl)-bis[dimethyl-2,5-diphenyl pyrrole 3,4-dicarboxylate] (2f). **1f** (10 g, 20.1 mmol) DMAD (5.6 g, 40 mmol) and H_2SO_4 (1.96 g, 20.1 mmol) at 105–10°C for 120 h yielded 3 g (21%) of **2f.** mp 233–35°C; IR: 1750, 1450, 1200 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.6 (bs, 16H, CH_2N, $COOCH_3$), 6.8–7.2 (m, 20H, ArH). *Anal*. Calcd. for $C_{42}H_{36}N_2O_8$ (696.75): C, 72.40; H, 5.20; N, 4.02; Found: C, 72.58; H, 5.36; N, 4.00.

1,1′-(1,3-Propanediyl)-bis[dimethyl 2-ethyl-5-(4-chlorophenyl) pyrrole 3,4-dicarboxylate] (2l). **1l** (5 g, 10 mmol), DMAD (4.3 g, 30 mmol) and H_2SO_4 (1.96 g, 20 mmol) when heated at 80–85°C for 72 h yielded 2.25 g (32%) of **2l**. mp 204°C; IR: 1710, 1450, 1200; ^1H NMR ($CDCl_3$): δ 1.2 (t, 6H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.6 (m, 2H, $CH_2\underline{CH_2}CH_2$) 2.7 (q, 4H, J = 7 Hz, $\underline{CH_2}CH_3$), 3.6 (t, 4H, J = 7 Hz, CH_2N), 3.7 (s, 6H, $COOCH_3$), 3.8 (s, 6H, $COOCH_3$), 7.3 (q, 8H, ArH). *Anal*. Calcd. for $C_{35}H_{36}N_2O_8Cl_2$ (683.58): C, 61.49; H, 5.30; N, 4.09. Found: C, 61.52; H, 5.60; N, 3.86.

1,1′-(1,3-Propanediyl)-bis[dimethyl 2,5-diphenyl pyrrole 3,4-dicarboxylate] (2m). **1m** (4.76 g, 9.25 mmol) DMAD (4.3 g, 30 mmol) and H_2SO_4 (1.96 g, 20 mmol) when heated at 80–85°C for 72 h yielded 2 g (30%) of **2m.** mp 231°C; IR: 1710, 1480, 1440, 1320, 1220. ^1H NMR ($CDCl_3$): δ 1.3 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.2 (t, 4H, CH_2N), 3.6 (s, 12H, $COOCH_3$), 6.9–7.5 (m, 20H, ArH). *Anal*. Calcd. for $C_{43}H_{38}N_2O_8$ (710.77): C, 72.60; H, 5.38; N, 3.94. Found: C, 72.50; H, 5.50; N, 3.65.

Reduction of bis-pyrrole tetra esters with lithium aluminum hydride: General procedure. The bis-pyrrole tetra ester **2** (0.5 mmol) was dissolved in 15 mL of refluxing dioxane. To the stirred refluxing solution, lithium aluminum hydride (3 mmol) was added in one portion and the stirring was continued. A vigorous reaction commenced after 5 min as evident from the brisk effervescence that lasted for 10–15 sec. When the frothing subsided, the mixture was allowed to cool to room temperature and a few drops of triethanolamine were added and stirred for 10 min. Water was added drop wise and stirring was continued for half an hour. The solid was filtered and dried at the pump. The solid was refluxed with 15 mL methanol for 15 min and filtered. The extraction with methanol was repeated twice more. The combined extract was concentrated to commence crystallization upon cooling. The crystals were filtered and dried. The physical properties and spectral data of the tetra alcohols **3** prepared by this procedure are given in Table 3.

Typical examples

1,1′-[(1,2-Ethanediyl)-bis [2-ethyl-5-phenyl pyrrole-3,4-dimethanol] (3a). Tetra ester **2a** (300 mg, 0.5 mmol) was reduced with LAH (150 mg, 3.94 mmol) in 10 mL of dioxane to yield 210 mg (86%) of **3a.** mp 210–15°C (dec); IR: 3325, 2950, 1440, 1220, 960; ^1H NMR ($CDCl_3$): δ 0.7 (t, 6H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.67 (q, 4H, J = 7 Hz, $\underline{CH_2}CH_3$), 2.93 (s, 4H, D_2O exchangeable, OH), 3.5 (s, 4H, $\underline{CH_2}N$), 4.17 (s, 4H, $\underline{CH_2}OH$) 4.27 (s, 4H, $\underline{CH_2}OH$), 7.0–7.4 (m, 10H, ArH). *Anal*. Calcd for $C_{30}H_{36}N_2O_4$ (488.63): C, 73.74; H, 7.42; N, 5.73. Found: C, 73.58; H, 7.63; N, 5.97.

1,1′-[(1,2-Propanediyl)bis[2-ethyl-5-phenyl pyrrole-3,4-dimethanol] (3i). Reduction of **2m** (355 mg, 0.5 mmol) with 175 mg (4.6 mmol) of LAH in 10 mL dioxane afforded 260 mg (89%) of **3i**; mp 190–92°C; IR: 3275, 2920, 1480, 1340, 970; ^1H NMR ($CDCl_3$): δ 0.93 (m, 2H, $CH_2\underline{CH_2}CH_2$), 3.27 (t, 4H, J = 7 Hz, CH_2N), 4.33 (bs, 12H, 4H $D_2\underline{O}$ exchangeable, $\underline{CH_2}OH$), 7.1–7.4 (m, 20H, ArH). *Anal*. Calcd for $C_{39}H_{38}N_2O_4$ (598.74): C, 78.23; H, 6.39; N, 4.67. Found: C, 78.37; H, 6.43; N, 4.39.

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