Synthesis and Chemistry of N-Oxygenated Pyrroles: Crystal and Molecular Structure of a Highly Stable *N*-Hydroxypyrrole 18-Crown Ether Hydrate

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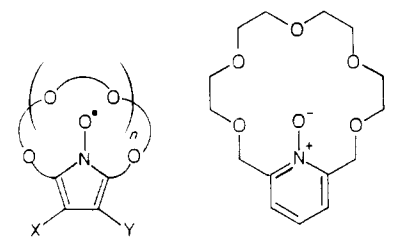
N-Oxygenated succinimides **5–8**, **13**, and **14**, *N*-oxydithiosuccinimides **10** and **11**, and N-oxygenated pyrroles **12**, **30a,e**, **38**, and **39** were synthesized as possible precursors of a pyrrole nitroxide crown ether. *N*-Methoxypyrrole dithiocrown ethers **21** and **23–27** were prepared by bis(S-cycloalkylation) of **11**. Whereas thermolysis of **29c** gave pyrrole **30c**, it was necessary to convert **29b** into isoxazoline **31b** before thermolysis. *N*-Hydroxypyrrole **30a** was the isolated product. Adduct **31d** was not stable at 25 °C and gave pyrrole **30d** upon generation. Dibromide **39** was converted into *N*-methoxypyrrole crown ether **40**. O-Demethylation gave *N*-hydroxypyrrole crown ether **41**, which was surprisingly resistant toward oxidation to give nitroxide **42**. Crystals of **41**·H_2O are monoclinic, space group $P2_1/a$ with eight formula units in a cell of dimensions a = 19.528 (4) Å, b = 17.177 (5) Å, c = 14.424 (3) Å, and β = 101.54 (2)°. The structure was solved by direct methods and refined by full-matrix least-squares calculations. R and R_w are 0.061 and 0.063, respectively, for 2094 observed reflections. The two independent molecules of the complex in the asymmetric unit have very similar conformations of the 18-crown ring. The water molecule is not a mere water of hydration but is tightly incorporated into each macrocycle cavity via strong N–O–H···O(water) bonds (mean O···O distance = 2.56 (1) Å) and weaker O–H···O hydrogen bonds between the water molecule and the ring oxygen atoms (mean O···O distance = 2.84 (1) Å).

Macrocyclic polyethers (crown ethers) are of current interest owing to their ability to undergo selective complexation with certain charged as well as neutral species.[1] Nitroxide-substituted crown ethers and cryptands in which the N–O• group is thrust into the cavity are of interest as possible indicators of alkali metal and alkaline earth metal ion concentrations through changes in their electron spin resonance (ESR) spectra upon complexation.[2] Such nitroxides may have application as magnetic resonance imaging (MRI) contrast-enhancing agents should they show improved resistance toward reduction.[3] Molecular models suggested that 2,5-disubstituted pyrrole nitroxide crown ethers of general structure **1** might show interesting



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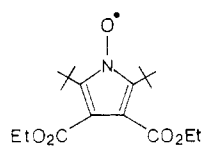

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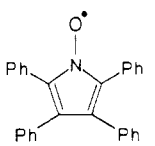

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properties in this regard, especially in view of the report[4] that the closely related pyridine crown ether **2** complexes K^+ strongly. Ramasseul and Rassat[5] have reported the only examples, **3** and **4**, of stable (toward isolation) pyrrole nitroxides together with several that are persistent, but unisolable. Herein we describe the synthesis and chemistry of a series of N-oxygenated pyrroles[6] designed as possible precursors to a pyrrole nitroxide crown ether. To our surprise, the penultimate intermediate *N*-hydroxypyrrole crown ether **41** proved to be unusually stable toward oxidation to the nitroxide. We conclude this report with an X-ray crystallographic structure determination on **41** that provides a possible explanation for its unusual stability.

No general methods are available for the oxidation of a pyrrole to an *N*-hydroxypyrrole, the envisaged precursor for the corresponding nitroxide. Intermediates were therefore utilized in which the crucial NO bond was already present. Certain N-substituted succinimides have been converted into the corresponding 2,5-bis[(trimethylsilyl)oxy]pyrroles by silylation on the carbonyl oxygen atom and concomitant enolization.[7,8] As our first approach, we therefore prepared *N*-oxysuccinimides **5–8**. However, we were unable to effect conversion into the corresponding pyrrole **9** under a variety of conditions, including, for example, lithium diisopropylamide (LDA) followed by MeI.

Next, **5–8** were treated with Lawesson's thiation reagent[9] with the aim of introducing the more nucleophilic sulfur atom at the sites of alkylation. While **7** and **8** gave dithioimides **10** and **11** cleanly (by NMR), only **11** was obtainable in pure form owing to decomposition of **10** during chromatography. Dithioimide **11** proved to be remarkably unreactive toward several alkylating agents. For example, **11** was recovered unchanged after a solution in neat MeI or benzyl bromide was refluxed or after treatment with excess triethyloxonium tetrafluoroborate in CH_2Cl_2.

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(1) For leading references, see: Grootenhuis, P. D. J.; Uiterwijk, J. W. H. M.; Reinhoudt, D. N.; van Staveren, C. J.; Sudhölter, E. J. R.; Bos, M.; van Eerden, J.; Klooster, W. T.; Kruise, L.; Harkema, S. *J. Am. Chem. Soc.* **1986**, *108*, 780.
(2) For leading references, see: Keana, J. F. W.; Cuomo, J.; Lex, L.; Seyedrezai, S. E. *J. Org. Chem.* **1983**, *48*, 2647.
(3) See: Keana, J. F. W.; Pou, S. *Physiol. Chem. Phys. Med. NMR* **1985**, *17*, 235 and references cited therein.
(4) Wagner, W. R.; Rastetter, W. H. *J. Org. Chem.* **1983**, *48*, 294.
(5) Ramasseul, R.; Rassat, A. *Bull. Soc. Chim. Fr.* **1970**, 4330.
(6) For examples of *N*-hydroxypyrroles, see: Blatt, A. H. *J. Am. Chem. Soc.* **1934**, *56*, 2774. Abramovitch, R. A.; Cue, B. W. *J. Am. Chem. Soc.* **1976**, *98*, 1478.
(7) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.
(8) Lozzi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1984**, *49*, 3408.
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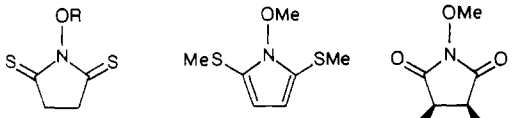
5, R = tetrahydropyranyl (THP)
6, R = (methoxyethoxy)methyl (MEM)
7, R = $SiMe_2$-*t*-Bu
8, R = Me



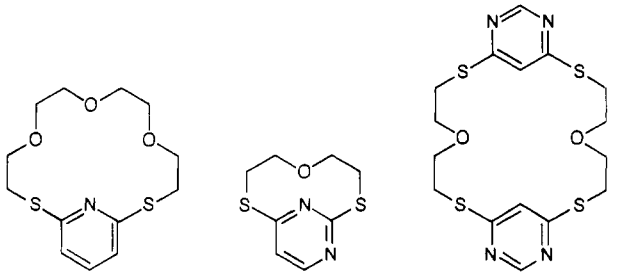
10, R = $SiMe_2$-*t*-Bu
11, R = Me

12

13, R = Ph
14, R = Me

However, deprotonation of **11** with LDA followed by reaction with MeI gave the somewhat unstable 2,5-bis(methylthio)pyrrole **12** in high yield. With the aim of incorporating a substituent at the 3- and 4-positions of the pyrrole ring by this series of reactions, *N*-methoxysuccinimides **13** and **14** were prepared from the corresponding meso anhydrides. Unfortunately, dithiation of **13** and **14** could not be effected cleanly.

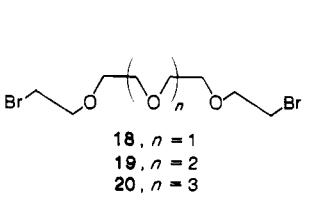
Several di- or tetrathio crown ethers, for example, **15**,[10] **16**,[11] and **17**,[12] in which the sulfur atoms are attached to



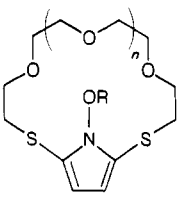
15 16 17

the α-positions of a pyridine or pyrimidine ring have been prepared in modest yields. With these models in mind, we next allowed **11** to react with LDA followed by dibromide **18**. Dithio crown ether **21** (17%) accompanied by some bis(crown ether) **25** (7%) was thus prepared. While the robust *N*-methoxy group was a necessary component of the crown ether synthesis up to this point, it also thwarted the penultimate step, namely, cleavage to *N*-hydroxypyrrole **22**. A variety of conditions were tried, including, for example, excess LiI[13] in refluxing pyridine or quinoline. We then prepared the next two higher homologues, **23** and **24** from **11** and dibromides **19** and **20**, respectively. The expectation was that the cavity in **23** and **24** would be larger than that of **21**, possibly allowing complexation of the LiI, thus facilitating the cleavage reaction (see below). In the event, LiI also proved to be unreactive toward **23** and **24** while trimethylsilyl iodide[14] or BBr_3 in CH_2Cl_2[15] led to decomposition.

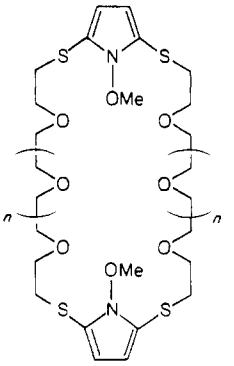
The methoxy group's resistance toward cleavage in this series dictated the development of an alternative approach. The readily available *N*-hydroxypyrrole **28a**[16] was con-



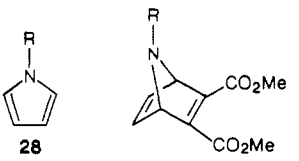
18, *n* = 1
19, *n* = 2
20, *n* = 3



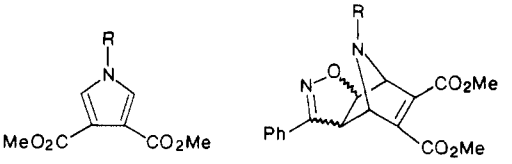
21, *n* = 1; R = Me
22, *n* = 1; R = H
23, *n* = 2; R = Me
24, *n* = 3; R = Me



25, *n* = 1
26, *n* = 2
27, *n* = 3



28 29



30 31

a, R = OH
b, R = $OSiMe_2$-*t*-Bu
c, R = CO_2Me
d, R = CO_2-*t*-Bu
e, R = OMe
f, R = CO_2Et

verted into the stable silyl ether **28b**. Noting that Rassat's[5] stable pyrrole nitroxides had either ester or phenyl groups in the 3- and 4-positions of the pyrrole ring, we sought to introduce ester groups into **28b** by adaptation of the known reaction[17] of certain N-substituted pyrroles with dimethyl acetylenedicarboxylate followed by thermolysis. Thus, **28b** was allowed to react with dimethyl acetylenedicarboxylate to form Diels–Alder adduct **29b**. Aspects of the chemistry of adduct **29b** were compared with those of adducts **29c** and **29d**, derived respectively from the known pyrroles **28c**[18] and **28d**.[19] Whereas heating adduct **29c** at 170 °C gave diester **30c** presumably accompanied by the elimination of acetylene, adduct **29b** did not undergo a clean thermolysis to give **30b** either when similarly heated neat or in solvents. Also, whereas 300-nm photolysis of adduct **29c** in ether led to azepine **32**,[17] under similar conditions adduct **29b** was recovered unchanged. The desired reaction could be effected through alteration of the nature of the unsaturated fragment expected from the thermolysis of adduct **29b**. Thus, **29b** was allowed to react with ben-

(10) Weber, E.; Vögtle, F. *Chem. Ber.* **1976**, *109*, 1803.
(11) Newkome, G. R.; Nayak, A.; Otemaa, J.; Van, D. A.; Benton, W. H. *J. Org. Chem.* **1978**, *43*, 3362.
(12) Newkome, G. R.; Nayak, A.; Sorci, M. G.; Benton, W. H. *J. Org. Chem.* **1979**, *44*, 3812.
(13) McMurry, J. *Org. React.* **1976**, *24*, 187.
(14) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.
(15) McOmie, J. F. W.; West, D. E. *Org. Synth.* **1973**, *Collect. Vol. V*, 412.
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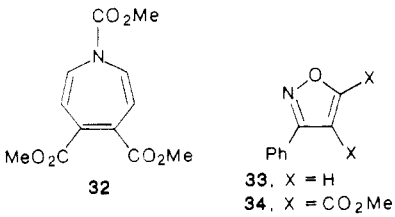
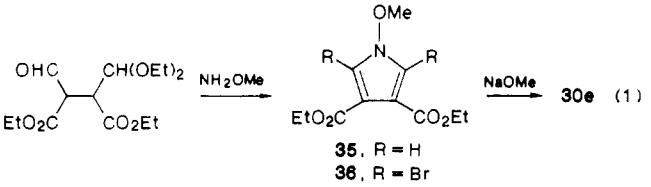


zonitrile oxide[20] to give an exo,endo mixture of cycloadducts **31b** from which one isomer was isolated in pure form. Thermolysis of this mixture at 135 °C followed by silica gel chromatography gave *N*-hydroxypyrrole **30a** in 64% yield. The expected "unsaturated" fragment, 3-phenylisoxazole (**33**), was isolated as a byproduct from the reaction.

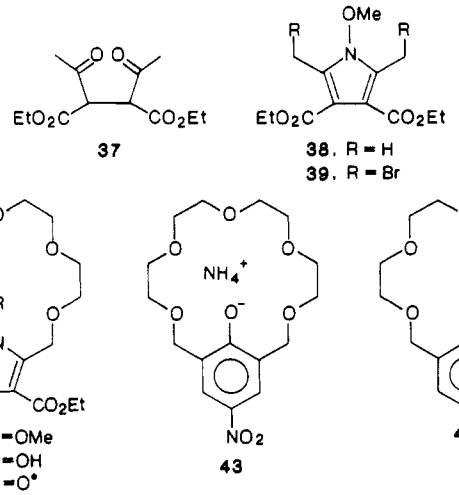
The structure of **30a** was confirmed as follows. Methylation (diazomethane) gave crystalline **30e**, identical with a sample that was prepared by methanolysis of **35**. Ester **35** was obtained by the alternative route[21] (eq 1).



Bromination of **35** with Br_2 in CCl_4 in the presence of Fe powder gave dibromide **36**, a substrate designed to accept substituents at the 2- and 5-positions via palladium-catalyzed mixed coupling reactions.[22]

The stability of cycloadducts **31b** toward isolation was unexpected in view of the report[19] that carbethoxy adduct **31f** readily undergoes a retro-Diels–Alder reaction at 20 °C. In order to assess whether the bulkiness of the group attached to the N atom of **31** was an important factor in this regard, we prepared (*tert*-butoxycarbonyl)pyrrole derivative **29d** and then allowed it to react with benzonitrile oxide. The product of this reaction was not adduct **31d**, but instead consisted of a mixture of diester **30d** (19%) and isoxazole **33** (17%), accompanied by pyrrole **28d** (56%) and isoxazole diester **34** (68%). Evidently adduct **31d** was formed together with some of the regioisomer resulting from cycloaddition at the other double bond of **29d**. However, in contrast to the behavior of adduct **31b**, both apparently underwent the "thermolysis" reaction under the reaction conditions or during the workup at 25 °C. We conclude that, with regard to the substituent on the bridging nitrogen atom in **31**, electronic factors are more important than steric factors in determining the stability of these adducts toward isolation.

The above approach was set aside when the pyrrole nitroxide crown ether precursor **41** was successfully prepared via a route similar to that of eq 1. Thus, diketone **37**[23] was allowed to react with methoxyamine hydrochloride to give pyrrole **38**.[24] Dibromination of **38** with NBS gave **39**, which was then allowed to react with tetraethylene glycol in the presence of NaH to produce crown ether **40** in 30% yield. The methoxy group was removed by reaction with LiI in pyridine to give *N*-hydroxypyrrole crown ether **41**, which crystallized from ethyl acetate–



hexanes as the monohydrate.

The oxidation of **41**·H_2O to nitroxide **42** proved to be surprisingly difficult. Extensive experimentation on **41**·H_2O using oxidants known[25] to oxidize certain *N*-hydroxy amines to the corresponding nitroxide free radicals (*m*-chloroperoxybenzoic acid, cupric acetate, lead dioxide, silver oxide, potassium superoxide, singlet oxygen, or potassium *tert*-butoxide–oxygen) failed to generate nitroxide **42**.

At this point an X-ray crystallographic analysis of **41** was undertaken in order to confirm its structure and to gain insight into its remarkable resistance toward oxidation. Our X-ray analysis of **41**·H_2O reveals that there are two discrete independent molecules of the complex in the crystal asymmetric unit, with only normal van der Waals distances between them. The molecules are only loosely bound in the crystal lattice, and although there is relatively large motion in the ester side chains, the macrocyclic ring conformations and hydrogen bonding are well defined. The two molecules, A and B, have very similar conformations for the macrocyclic ether rings and differ mainly in the conformations adopted by the CO_2Et moieties on the pyrrole rings. A view of molecule A is given in Figure 1 (see also Figure 1b in the Supplementary Material). The water molecule is not a mere "water of hydration" but is in fact tightly incorporated into each macrocycle cavity and is held by a short (strong) N–O–H···O(water) hydrogen bond (O···O = 2.548 (11) and 2.568 (10) Å) and by normal O–H···O hydrogen bonds between water and macrocycle ether oxygen atoms (O···O = 2.817, 2.819, 2.848, and 2.859 (11) Å). All hydrogens involved in hydrogen bonding were clearly resolved in difference maps computed near the conclusion of the refinement. In particular, in the short N–O–H···O(water) hydrogen bonds in both molecules, the hydrogen atom was adjacent to the pyrrole oxygen rather than the water oxygen, consistent with the complex being formulated as a hydrogen-bonded system N–O–H···OH_2, as opposed to a hydronium salt $N–O^-···H–O^+H_2$.

The conformation adopted by the crown ether rings in both A and B molecules is fairly similar to that found[26] in the ammonium salt of the *p*-nitro-18-crown-phenolate **43**, although the conformation for **41**·H_2O is more symmetrical (i.e., there is a mirror plane that contains atoms N1, O31, O(w), and O13 (Figure 1b, Supplementary Material)). As observed previously,[26] the torsion angle pattern in the macrocycle is close to gauche about the C–C bonds

(20) Brief mention of this method without details is made by: Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic: New York, 1977; p 257.
(21) This is an adaptation of: Kornfeld, E. C.; Jones, R. G. *J. Org. Chem.* **1954**, *19*, 1671.
(22) See, for example: Heck, R. F. *Org. React.* **1982**, *27*, 345.
(23) Fales, H. M.; Highet, R. J. *J. Org. Chem.* **1980**, *45*, 1699.
(24) The corresponding *N*-hydroxy derivative is known. See: Knorr, L. *Ann. Chem.* **1886**, *236*, 290.
(25) For a review, see: Keana, J. F. W. In *Spin Labeling in Pharmacology*; Holtzmann, J. L., Ed.; Academic: New York, 1984; Chapter 1.
(26) Browne, C. M.; Ferguson, G.; McKervey, M. A.; Mulholland, D. L.; O'Connor, T.; Parvez, M. *J. Am. Chem. Soc.* **1985**, *107*, 2703.

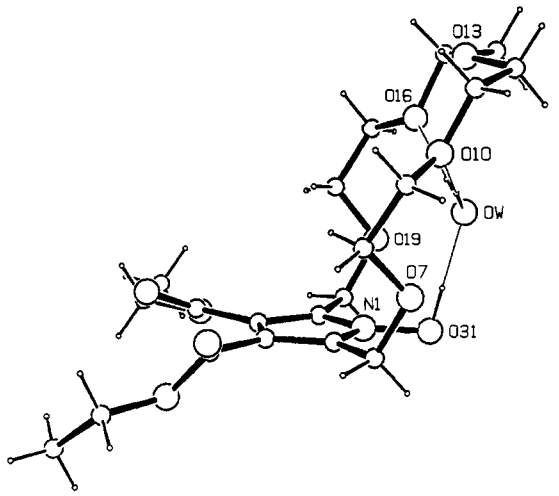


Figure 1. Side view of **41**·H_2O. For clarity the various atoms are shown as spheres of an arbitrary radius.

and close to anti about the C–O bonds except for those angles involving pyrrole atoms. The symmetrical conformation adopted by **41**·H_2O is undoubtedly a consequence of the incorporation of the water molecule into the cavity. Space for the water molecule is achieved by tilting the pyrrole ring plane out of the macrocycle plane (Figure 1), leading to dihedral angles between these planes of 72 and 78°, respectively, for A and B. In **43**[26] the corresponding dihedral angle was only 58° and in systems such as **44**, which has no intracavity water, the dihedral angle is reduced to 28°.[26] Bond lengths and angles in **41**·H_2O are comparable with those observed in related systems[26] containing 18-crown macrocycles, with mean macroring C–C and C–O bond lengths of 1.486 (18) and 1.413 (17) Å, respectively. The corresponding bond lengths in **43** are 1.489 and 1.417 Å. The mean N–OH bond length is 1.384 (10) Å. As anticipated, this value is significantly longer than that found in nitrone N–O bonds. For example, the N–O bond length in phenyl-*tert*-butylnitrone is 1.307 (8) Å.[27]

The remarkable stability of *N*-hydroxypyrrole **41** toward oxidation to nitroxide **42** likely stems from the presence of the strong intramolecular hydrogen bonds present in **41**·H_2O.[28]

Experimental Section[29]

***N*-(Tetrahydropyranyloxy)succinimide (5).** To a stirred solution of 1.2 g (10 mmol) of *N*-hydroxysuccinimide in 70 mL of dry CH_2Cl_2 were added 1.3 g (15 mmol) of dihydropyran and 250 mg of pyridinium *p*-toluenesulfonate. After 4 h the mixture was concentrated to dryness and the residue was taken up in $CHCl_3$. The solution was washed with aqueous NaCl, dried ($MgSO_4$), and concentrated to dryness, giving 1.7 g (85%) of crystalline **5**, mp 114–118 °C. Recrystallization from EtOAc–hexanes gave 1.5 g (75%) of **5** as white crystals: mp 122–123 °C; NMR δ 1.50–2.10 (m, 6), 2.72 (s, 4), 3.61 (m, 1), 4.40 (m, 1), 5.36 (s, 1). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.01; H, 6.46; N, 6.84.

***N*-((Methoxyethoxy)methoxy)succinimide (6).** To *N*-hydroxysuccinimide (263 mg, 2.3 mmol) in dry CH_2Cl_2 (15 mL) were added (methoxyethoxy)methyl chloride (424 mg, 3.4 mmol) and Et_3N (344 mg, 2.4 mmol). After 1.5 h at 25 °C, the solution was washed with water and dried, giving 353 mg (76%) of crude **6**: NMR δ 2.72 (s, 4), 3.38 (s, 3), 3.55 (t, 2), 4.02 (t, 2), 5.10 (s, 2).

***N*-((*tert*-Butyldimethylsilyl)oxy)succinimide (7).** To a solution of *N*-hydroxysuccinimide (2.055 g, 18 mmol) in 15 mL of dry THF at 0 °C was added *N*-methyl-*N*-(*tert*-butyldimethylsilyl)trifluoroacetamide (4.31 g, 18 mmol). After 5 h the volatiles were removed in vacuo, giving 4.0 g (97%) of crude **7**, which was purified by sublimation at 50 °C/2.5 mm and using ice water in the cooling trap. There was obtained 3.6 g (88%) of **7** as fine white needles: mp 66–67 °C; NMR δ 0.22 (s, 6), 1.02 (s, 9), 2.69 (s, 4).

***N*-Methoxydithiosuccinimide (11).** A mixture of dry *N*-methoxysuccinimide[30] (1.2 g, 9.3 mmol) and Lawesson's reagent[9] (9.4 g, 23 mmol) in dry toluene (50 mL) was refluxed for 12 h. The green mixture was cooled and filtered with the aid of a toluene rinse. The filtrate was concentrated to dryness, and the residue was dissolved in ether (10 mL) and chromatographed over silica gel (20 g). Elution of the greenish-yellow band with 7:3 hexanes–ether gave 2.25 g of crude **11**, which was flash chromatographed (elution with 9:1 hexanes–ether) twice over silica gel (10 g) to give a yellow solid, which was sublimed (50 °C/0.05 mm) to give **11** (0.831 g, 55%) as yellow prisms: mp 80–81 °C (dec); NMR δ 3.13 (s, 4), 4.05 (s, 3); IR ($CDCl_3$) 1340, 1250 cm^{-1}. Anal. Calcd for $C_5H_7NOS_2$: C, 37.27; H, 4.38; N, 8.70. Found: C, 37.29; H, 4.40; N, 8.66.

***N*-Methoxy-2,5-bis(methylthio)pyrrole (12).** To a solution of diisopropylamine (61 mg, 0.60 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (2.34 M in hexane, 0.26 mL, 0.6 mmol) over 5 min. After 1 h a solution of **11** (32 mg, 0.20 mmol) in 1 mL of THF was added. The color changed from yellow to yellow-green to deep brown. After 15 min (still at −78 °C) MeI (170 mg, 1.2 mmol) was added and the mixture was allowed to warm to 25 °C over 4 h. Saturated aqueous NH_4Cl (3 drops) was added and the mixture was evaporated to dryness. The residue was extracted with CH_2Cl_2, and the extract was washed with water and dried ($MgSO_4$). Removal of the solvent gave **12** (35 mg, 93%, pure by NMR) as a pale brown liquid that darkens further upon standing at 25 °C: NMR δ 2.37 (s, 6), 4.11 (s, 3), 6.09 (s, 2).

***N*-Methoxy-*meso*-2,3-diphenylsuccinimide (13).** A mixture of *meso*-2,3-diphenylsuccinic anhydride[31] (706 mg, 2.8 mmol) and methoxyamine hydrochloride (245 mg, 2.94 mmol) was placed in a bath at 120 °C and then the temperature was raised to 175 °C while water aspirator vacuum was applied to the container. After 1.5 h the mixture was cooled and the yellow-brown melt was extracted with $CHCl_3$. The extract was treated with charcoal, filtered, and concentrated to dryness to give crude **13** (580 mg, 74%). This was dissolved in CH_2Cl_2 and flash chromatographed over silica gel. Elution with CH_2Cl_2 gave 550 mg (70%) of pure **13**. An analytical sample was prepared by sublimation at 120 °C/0.05 mm as pale yellow needles: mp 122–123 °C; NMR δ 4.02 (s, 2), 4.08 (s, 3), 7.15–7.50 (m, 10). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.57; H, 5.38; N, 4.98. Found: C, 72.49; H, 5.36; N, 5.02.

***N*-Methoxy-*meso*-2,3-dimethylsuccinimide (14).** A stirred mixture of *meso*-2,3-dimethylsuccinic anhydride[32] (128 mg, 1.0 mmol, mp 39–39.5 °C, prepared from the meso diacid by treatment with acetyl chloride; Ac_2O treatment gives a 1:1 mixture of meso and *d,l* isomers) and methoxyamine hydrochloride (88 mg, 1.0 mmol) was placed in a bath at 55 °C and then the temperature was raised to 125 °C. After 1 h the mixture was cooled and extracted with CH_2Cl_2. The extract was washed with aqueous $NaHCO_3$ and water and then dried ($MgSO_4$). Removal of the solvent gave 90 mg (57%) of crude **14** as a colorless oil. This was flash chromatographed over silica gel using CH_2Cl_2 as the eluent to give 73 mg (47%) of **14** as a colorless oil that was pure by NMR: NMR δ 1.26 (dd, 6), 2.94 (m, 2), 3.94 (s, 3).

Bis[2-(2-bromoethoxy)ethyl] Ether (18). To a refluxing solution of tetraethylene glycol (freshly distilled, 19.42 g, 0.10 mol) and pyridine (18.19 g, 0.23 mol) was added thionyl bromide (47.81 g, 0.23 mol) over 3 h. After a 16-h reflux period the mixture was cooled and treated with 10 mL of 2% aqueous HCl followed by 50 mL of water. The mixture was extracted with benzene, giving

(27) Liu, J.; Wang, X.; Chen, B.; Xu, G. *Jiegou Huaxue* **1987**, *6*, 17.
(28) Attempted oxidation studies on the "anhydrous" form of **41** were hampered by the strongly hygroscopic nature of the vacuum-dried amorphous semisolid substrate.
(29) Footnote 36 of Keana et al. applies here (Keana, J. F. W.; Prabhu, V. S.; Ohmiya, S.; Klopfenstein, C. E. *J. Org. Chem.* **1986**, *51*, 3456).
(30) Bowie, J. H.; Hearn, M. T. W.; Ward, A. D. *Aust. J. Chem.* **1969**, *22*, 175.
(31) Buchan, R.; Watson, M. B. *J. Chem. Soc. C* **1968**, 2465.
(32) Cason, J.; Schmitz, F. J. *J. Org. Chem.* **1963**, *28*, 555.

23.9 g of crude **18** as a brownish-red oil. Two distillations (bp 110–117 °C/0.05 mm) gave 13.5 g (42%) of **18** as a pale yellow oil: NMR δ 3.48 (t, 4), 3.625–3.725 (m, 8), 3.82 (t, 4). Anal. Calcd for $C_8H_{16}Br_2O_3$: C, 30.01; H, 5.04. Found: C, 29.60; H, 5.13.

***N*-Methoxypyrrole Crown Ethers 21 and 25.** LDA was prepared at −78 °C in 30 mL of THF from 318 mg (3.13 mmol) of diisoopropylamine and 1.39 mL (3.13 mmol) of 2.25 M *n*-BuLi in hexane. To this solution at −78 °C was added a solution of **11** (200 mg, 1.25 mmol) in 3 mL of THF over 5 min. The color changed from yellow to deep brown. After 15 min a solution of dibromide **18** (500 mg, 1.56 mmol) in 5 mL of THF was added over a 3-h period. The solution was allowed to warm to 0 °C over 2 h and then to 25 °C, where it was stirred overnight. Several drops of saturated aqueous NH_4Cl was added and the solution was concentrated in vacuo and then extracted with CH_2Cl_2. The extract was washed with water and dried, giving 424 mg of a dark brown oil. This was flash chromatographed over silica gel. Elution with CH_2Cl_2 gave 125 mg of an oil, which was discarded. Continued elution with ether gave 167 mg of a mixture of **21** and **25** (by NMR), which was subjected to preparative TLC (ether elution). The bands at R_f 0.45 and 0.40 were discarded. The band at R_f 0.31 gave 64 mg (17%) of **21** as a pale brown oil: NMR δ 2.88 (t, 4), 3.45–3.75 (m, 12), 4.08 (s, 3), 6.15 (s, 2); MS *m/e* 319.0916 (calcd for $C_{13}H_{21}NO_4S_2$, 319.0907). Anal. Calcd for $C_{13}H_{21}NO_4S_2$: C, 48.89; H, 6.63; N, 4.39. Found: C, 48.52; H, 6.64; N, 4.09.

The band at R_f 0.18 gave 27 mg (7%) of **25** as a brown oil: NMR δ 2.89 (t, 8), 3.45–4.75 (m, 24), 4.08 (s, 6), 6.14 (s, 4); MS *m/e* 638.1849 (calcd for $C_{26}H_{42}N_2O_8S_4$, 638.1814). While the 300-MHz ^1H NMR spectra of **21** and **25** were virtually indistinguishable, a 1:1 mixture showed the S–CH_2 protons as two overlapping triplets.

1,2-Bis[2-(2-bromoethoxy)ethoxy]ethane (19). Dibromide **19** (17.60 g, 48%, pale yellow oil, bp 148 °C/0.05 mm) was prepared from 23.83 g of pentaethylene glycol in a manner similar to the preparation of **18**. NMR of **19**: δ 3.47 (t, 4), 3.60–3.74 (m, 12), 3.81 (t, 4). Anal. Calcd for $C_{10}H_{20}Br_2O_4$: C, 32.97; H, 5.54. Found: C, 32.45; H, 5.55.

***N*-Methoxypyrrole Crown Ethers 23 and 26.** These substances were prepared from dibromide **19** (569 mg) and **11** (200 mg) in a manner similar to the preparation of crown ethers **21** and **25**. The preparative TLC band at R_f 0.41 gave 78 mg (17%) of **23** as a pale brown oil: NMR δ 2.86 (t, 4), 3.40–3.65 (m, 16), 4.09 (s, 3), 6.18 (s, 2); MS *m/e* 363.1226 (calcd for $C_{15}H_{25}NO_5S_2$, 363.1168). Anal. Calcd for $C_{15}H_{25}NO_5S_2$: C, 49.57; H, 6.94; N, 3.86. Found: C 49.35; H, 7.01; N, 3.61.

The band at R_f 0.24 gave 114 mg (25%) of **26** as a pale brown oil: NMR δ 2.89 (t, 8), 3.45–3.75 (m, 32), 4.08 (s, 6), 6.15 (s, 4); MS *m/e* 726.2404 (calcd for $C_{30}H_{50}N_2O_{10}S_4$, 726.2336).

2,2′-Bis[2-(2-bromoethoxy)ethoxy]ethyl Ether (20). Dibromide **20** (10.75 g, 34%, pale yellow oil, bp 175 °C/0.1 mm) was prepared from 22.11 g of hexaethylene glycol in a manner similar to the preparation of **18**. NMR of **20**: δ 3.47 (t, 4), 3.60–3.73 (m, 16), 3.81 (t, 4). Anal. Calcd for $C_{12}H_{24}Br_2O_5$: C, 35.29; H, 5.93. Found: C, 34.99; H, 6.06.

***N*-Methoxypyrrole Crown Ethers 24 and 27.** These substances were prepared from dibromide **20** (637 mg) and **11** (200 mg) in a manner similar to the preparation of crown ethers **21** and **25**. Flash chromatography over silica gel and elution with CH_2Cl_2 gave first **24** (170 mg, 34%) as a pale brown oil: NMR δ 2.86 (t, 4), 3.40–3.73 (m, 20), 4.10 (s, 3), 6.19 (s, 2); MS *m/e* 407.1445 (calcd for $C_{17}H_{29}NO_6S_2$, 407.1429). Anal. Calcd for $C_{17}H_{29}NO_6S_2 \cdot 0.15H_2O$: C, 49.76; H, 7.20; N, 3.42. Found: C, 49.42; H, 7.27; N, 3.12.

Further elution with 10:1 CH_2Cl_2–ether gave 113 mg (22%) of **27** as a pale brown oil: NMR δ 2.89 (t, 8), 3.45–3.85 (m, 40), 4.09 (s, 6), 6.15 (s, 4); MS *m/e* 814.2879 (calcd for $C_{34}H_{58}N_2O_{12}S_4$, 814.2858).

***N*-((*tert*-Butyldimethylsilyl)oxy)pyrrole (28b).** To 1.66 g (20 mmol) of *N*-hydroxypyrrole[16] in 22 mL of dry THF was added slowly 5.0 g (21 mmol) of *N*-methyl-*N*-(*tert*-butyldimethylsilyl)trifluoroacetamide.[33] After a 1-h stir the solution was rotoevaporated to give a dark yellow oil, which was vacuum distilled to give 3.0 g of **28b** (bp 83–84 °C/9 mm) as a colorless oil: NMR δ 0.20 (s, 6), 1.00 (s, 9), 5.92–6.02 (m, 2), 6.56–6.68 (m, 2). Anal. Calcd for $C_{10}H_{19}NOSi$: C, 60.86; H, 9.70; N, 7.10. Found: C, 60.84; H, 9.58; N, 6.97. The dark distillation residue was dissolved in CH_2Cl_2 and chromatographed over silica gel. Elution with 1:1 ether–hexanes gave an additional 0.92 g of pure **28b** (combined yield, 99%).

Dimethyl *N*-((*tert*-Butyldimethylsilyl)oxy)-7-azabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (29b). A solution of 177 mg (0.90 mmol) of **28b** and 138 mg (0.98 mmol) of freshly distilled dimethyl acetylenedicarboxylate was heated at 75 °C for 5 min and then cooled to 25 °C, dissolved in $CHCl_3$, and chromatographed over silica gel. Elution with $CHCl_3$ gave 190 mg (62%) of **29b** as a colorless oil. In one experiment a sample crystallized upon standing, giving **29b** as white crystals: mp 56–58 °C; NMR δ 0.03 (s, 6), 0.83 (s, 9), 3.80 (s, 6), 4.56–4.64 (m, 2), 6.82–6.92 (m, 2). Anal. Calcd for $C_{16}H_{25}NO_5Si$: C, 56.61; H, 7.42; N, 4.13. Found: C, 56.79; H, 7.51; N, 4.09.

Adducts 31b from the Reaction of 29b and Benzonitrile Oxide. To a stirred solution of 91 mg (0.55 mmol) of benzhydroximic chloride[34] in 10 mL of ether at 0 °C was added a solution of 186 mg (0.55 mmol) of **29b** in 15 mL of ether. Then a solution of 0.1 mL of Et_3N in 5 mL of ether was slowly added over 7 min. After a 1-h stir at 0 °C 8 mL of water was added, and the organic layer was separated, dried ($MgSO_4$), and evaporated to dryness, giving a yellow oil, which was chromatographed over silica gel. Elution with ether gave 190 mg (75%) of **31b** as a light yellow semisolid that was a 1:1 mixture of endo and exo isomers. Anal. Calcd for $C_{23}H_{30}N_2O_6Si$: C, 60.24; H, 6.59; N, 6.11. Found: C, 59.91; H, 6.63; N, 6.34. Rechromatography separated the two isomers into the white crystalline endo isomer (mp 101–102 °C; NMR δ 0.10 (s, 6), 0.90 (s, 9), 3.24 (s, 3), 3.86 (s, 3), 4.28–4.48 (m, 1), 4.60–4.80 (m, 2), 5.30–5.48 (m, 1), 7.34–7.52 (m, 3), 7.60–7.78 (m, 2) (Found: C, 60.59; H, 6.55; N, 6.23)) and the exo isomer as a white semisolid (NMR δ −0.12 (s, 3), −0.06 (s, 3), 0.80 (s, 9), 3.90 (s, 3), 3.96 (s, 3), 4.09 (d, 1), 4.48 (m, 1), 4.66 (m, 1), 5.06 (d, 1), 7.36–7.56 (m, 3), 7.64–7.84 (m, 2)).

Dimethyl 1-Hydroxy-3,4-pyrroledicarboxylate (30a) and 3-Phenylisoxazole (33). A 153-mg sample of the adduct mixture **31b** was heated at 135 °C under 1 mm of pressure with stirring for 5 min. An NMR spectrum of the resulting pale brown-yellow oil indicated complete conversion to silyloxy pyrrole **30b** and 3-phenylisoxazole (**33**). The mixture was chromatographed over silica gel that was deactivated by shaking in 95% aqueous MeOH. Elution with ether gave **33** (28 mg, 58%): NMR δ 6.69 (d, 1), 7.40–7.60 (m, 3), 7.76–7.96 (m, 2), 8.47 (d, 1). Anal. Calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.40; H, 5.08; N, 9.74. Continued elution with the same solvent gave 42 mg (64%) of **30a** as a colorless oil: NMR δ 3.78 (s, 6), 7.19 (s, 2), 8.0 (br s, 1). Anal. Calcd for $C_8H_9NO_5$: C, 48.24; H, 4.56; N, 7.03. Found: C, 48.31; H, 4.34; N, 7.19.

Dimethyl 1-Methoxy-3,4-pyrroledicarboxylate (30e). A. From 30a. A stirred mixture of **30a** (42 mg), 20 mg of $NaHCO_3$, 1 g of dry silica gel, and 4 mL of ether at 0 °C was treated with 20 mL (large excess) of a diazomethane–ether solution. After 15 min the silica gel was removed by filtration and rinsed 3 times with 94:5:1 EtOAc–*i*-PrOH–Et_3N. The combined organic phases were evaporated, giving 44 mg (96%) of **30e** as a yellow oil. Crystallization from ether–hexanes gave the analytical specimen as white microcrystals: NMR δ 3.87 (s, 6), 4.10 (s, 3), 7.40 (s, 2). Anal. Calcd for $C_9H_{11}NO_5$: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.40; H, 4.78; N, 6.46.

B. From 35. To a solution of 241 mg (1.00 mmol) of **35** in 5 mL of MeOH was added 108 mg (2.00 mmol) of sodium methoxide. The solution was stirred at 20 °C for 20 h and then poured onto ice and extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$), and evaporated to give 183 mg (86%) of **30e** as a yellow oil.

Diethyl 1-Methoxy-3,4-pyrroledicarboxylate (35). To 4.50 g (14.8 mmol) of diethyl 2-formyl-3-(diethoxymethyl)succinate[20] in 15 mL of ether was added the filtrate from a mixture of 1.25 g (15 mmol) of methoxyamine hydrochloride and 1.0 g (15 mmol) of KOH in 40 mL of EtOH. The resulting solution was evaporated

(33) Mawhinney, T. P.; Madson, M. A. *J. Org. Chem.* **1982**, *47*, 3336.

(34) Perold, G. W.; Steyn, A. P.; von Reiche, F. V. K. *J. Am. Chem. Soc.* **1957**, *79*, 462.

in vacuo and then 9 mL of concentrated sulfuric acid was added at 0 °C with stirring. The solution was stirred at 45 °C for 5 min and then poured onto ice and extracted with $CHCl_3$. The extract was washed with water, saturated $NaHCO_3$, and water and dried ($MgSO_4$). Concentration to dryness left a red oil, which was chromatographed over silica gel. Elution of the second yellow band with 1:1 ether–hexanes followed by crystallization from the eluent gave 1.75 g (49%) of **35** as white microcrystals: mp 57–58 °C; NMR δ 1.34 (t, 6), 4.07 (s, 3), 4.30 (q, 4), 7.35 (s, 2). Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.75; H, 6.27; N, 5.81. Found: C, 54.92; H, 6.23; N, 5.79.

Dimethyl 7-(*tert*-Butyloxycarbonyl)-7-azabicyclo[2.2.1]-hepta-2,5-diene-2,3-dicarboxylate (29d). *N*-(*tert*-Butoxycarbonyl)pyrrole[18] (176 mg, 1.06 mmol) and 1.30 mL (10.6 mmol) of dimethyl acetylenedicarboxylate were heated together at 120 °C for 20 min. The volatiles were removed under vacuum and the remaining dark residue was chromatographed over silica gel. Elution with ether–hexanes gave 220 mg (67%) of **29d** as a light yellow oil. The analytical specimen was obtained by preparative TLC: NMR δ 1.40 (s, 9), 3.83 (s, 6), 5.43–5.56 (m, 2), 7.10–7.22 (m, 2). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53. Found: C, 58.33; H, 6.22; N, 4.51.

Dimethyl 1-(*tert*-Butyloxycarbonyl)-3,4-pyrroledicarboxylate (30d) and Dimethyl 3-Phenyl-4,5-isoxazoledicarboxylate (34). To a stirred solution of **29d** (195 mg, 0.631 mmol) and benzhydroximic chloride[29] (123 mg, 0.791 mmol) in 25 mL of ether at 0 °C was added slowly a solution of 0.12 mL (0.87 mmol) of Et_3N in 9 mL of ether. After a 1-h stir 10 mL of water was added. The ether layer was dried ($MgSO_4$) and evaporated to give a light yellow oil, which was chromatographed over silica gel. Elution with ether–hexanes gave 59 mg (56%) of **28d**, identified by NMR, followed by 16 mg (17%) of 3-phenylisoxazole (**33**). Continued elution gave 112 mg (68%) of **34** as a colorless oil: NMR δ 3.92 (s, 3), 4.02 (s, 3), 7.40–7.60 (m, 3), 7.60–7.88 (m, 2). Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.25; N, 5.36. Found: C, 59.61; H, 4.17; N, 5.33. This was followed by elution of 35 mg (19%) of **30d** as a colorless oil, which solidified on standing to a white solid: mp 69–70 °C; NMR δ 1.62 (s, 9), 3.86 (s, 6), 7.75 (s, 2). Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.01; N, 4.95. Found: C, 55.31; H, 5.98; N, 5.01.

Diethyl 1-Methoxy-2,5-dibromo-3,4-pyrroledicarboxylate (36). To a solution of 75 mg (0.31 mmol) of **35** in 4 mL of CCl_4 was added 20 mg (0.36 mmol) of Fe powder followed by 0.1 mL (2 mmol) of Br_2.[35] The mixture was refluxed for 2 h, cooled to 25 °C, treated with 2 mL of water, and then stirred for 10 min. The organic phase was dried ($MgSO_4$) and evaporated, giving 57 mg (50%) of essentially pure **36** as a yellow oil. The analytical specimen was obtained by preparative TLC (ether eluent): NMR δ 1.34 (t, 6), 4.10 (s, 3), 4.32 (q, 4). Anal. Calcd for $C_{11}H_{13}NO_5Br_2$: C, 33.11; H, 3.28; N, 3.51; Br, 40.05. Found: C, 33.35; H, 3.09; N, 3.70; Br, 39.91.

Diethyl 1-Methoxy-2,5-dimethyl-3,4-pyrroledicarboxylate (38). To a stirred solution of 2.54 g (9.85 mmol) of diketone **37**[22] in 15 mL of acetic acid was added a solution of 0.822 g (9.85 mmol) of methoxyamine hydrochloride and 1.34 g (9.85 mmol) of NaOAc·$3H_2O$ in 3 mL of water. After a 10-min reflux period the mixture was cooled, diluted with 30 mL of water, and extracted with $CHCl_3$. The extract was washed with 2 N KOH, dried ($MgSO_4$), and evaporated, giving 2.00 g (75%) of crude **38** as a colorless oil. The analytical specimen was obtained by preparative TLC (ether eluent): NMR δ 1.32 (t, 6), 2.42 (s, 6), 3.92 (s, 3), 4.28 (q, 4). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.18; N, 5.25.

Diethyl 1-Methoxy-2,5-bis(bromomethyl)-3,4-pyrroledicarboxylate (39). To a solution of 758 mg (2.82 mmol) of **38** in 25 mL of CCl_4 were added 1.00 g (5.64 mmol) of NBS and 20 mg of benzoyl peroxide. The mixture was refluxed for 5 h and filtered. The filtrate was washed with water and then was dried ($MgSO_4$) and evaporated, giving a reddish oil, which was chromatographed over silica gel. Elution with 1:1 ether–hexanes gave 877 mg (66%) of **39** as a pale yellow oil: NMR δ 1.36 (t, 6), 4.14 (q, 4), 4.16 (s, 3), 4.74 (s, 4). The oil slowly decomposed to a dark mass upon standing at 25 °C.

(35) Vogel, A. I. *A Textbook of Practical Organic Chemistry*, 3rd ed.; Longmans: London, 1973; p 533.

***N*-Methoxy Crown Ether 40.** To a refluxing stirred suspension of NaH (269 mg of a 60% NaH–mineral oil dispersion, 7.0 mmol of NaH) in 400 mL of dry THF was slowly added a solution of 1.000 g (2.34 mmol) of dibromide **39** and 454 mg (2.34 mmol) of tetraethyleneglycol in 40 mL of THF. After a 6-h reflux period the mixture was cooled and quenched by the slow addition of 30 mL of water. Most of the THF was removed by rotoevaporation and the resulting solution was neutralized at 0 °C by addition of concentrated HCl. The solution was extracted with $CHCl_3$, and the extract was dried ($MgSO_4$) and evaporated to give 1.223 g of a reddish oil, which was chromatographed over silica gel. Elution with 49:1 ether–MeOH gave 322 mg (30%) of **40** as a colorless oil. The analytical specimen was obtained by preparative TLC (9:1 ether–MeOH) as an oil, which solidified on standing to a white solid: mp 82–83 °C; NMR δ 1.30 (t, 6), 3.35–3.70 (m, 16), 4.25 (q, 4), 4.45 (s, 3), 4.72 (s, 4). Anal. Calcd for $C_{21}H_{33}NO_{10}$: C, 54.89; H, 7.24; N, 3.05. Found: C, 54.83; H, 7.36; N, 2.88.

***N*-Hydroxy Crown Ether Monohydrate (41·H_2O).** A stirred mixture of 31 mg (0.067 mmol) of **40**, 155 mg (1.16 mmol) of anhydrous LiI, and 2 mL of dry pyridine was refluxed for 24 h and then cooled, and the volatiles were removed under reduced pressure. The residue was treated with 2 mL of $CHCl_3$, 2 mL of water, and 10 drops of 6 N HCl and stirred for 5 min. The organic phase was dried and evaporated to give 25 mg of a yellow oil. This was purified by preparative TLC (9:1 ether–MeOH) to give 21 mg (70%) of **41** as a colorless oil, which solidified on standing overnight: mp 102–104 °C; NMR δ 1.33 (t, 6), 3.55–3.70 (m, 16), 4.06 (s, 4, water), 4.27 (q, 4), 4.77 (s, 4), 13.07 (s, 1). Anal. Calcd for $C_{20}H_{31}NO_{10}\cdot 0.9H_2O$: C, 52.03; H, 7.16; N, 3.03. Found: C, 52.29; H, 7.32; N, 2.77.

X-ray Structural Analysis of 41·H_2O. Crystals of **41** monohydrate were grown by slow diffusion of hexanes into a solution of **41** in ethyl acetate. Accurate cell dimensions and crystal orientation matrix were determined on a CAD-4 diffractometer by a least-squares treatment of the setting angles of 25 reflections in the range $6 < \theta < 15°$. Using a crystal of dimensions 0.10 × 0.30 × 0.40 mm intensities of reflections with $2 < 2\theta < 44°$ were measured using ω–2θ scans with an ω scan width of (0.60 + 0.35 tan θ) and graphite-monochromatized Mo Kα radiation. Intensities of three standard reflections measured every 4 h showed no evidence of crystal decay. A total of 6094 reflections were measured, of which 5795 were unique (R factor on averaging, 0.018). Only the 2094 reflections with $I > 3\sigma(I)$ were labeled "observed" and used in the subsequent calculations. Data were corrected for Lorentz and polarization factors but not for absorption, which was negligible.

Crystal Data. $C_{20}H_{31}NO_{10}\cdot H_2O$, M_r 463.5, monoclinic, $P2_1/a$, a = 19.528 (4) Å, b = 17.177 (5) Å, c = 14.424 (3) Å, β = 101.54 (2)°, V = 4740 (3) Å^3, Z = 8, D_c = 1.30 g cm^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 1.0 cm^{-1}, $F(000)$ = 1984, T = 294 K. The space group was determined uniquely from the systematic absences ($0k0$ absent if $k = 2n + 1$; $h0l$ absent if $h = 2n + 1$).

Structure Solution. The structure was solved with the aid of MULTAN-82,[36] which revealed all non-hydrogen atoms. Refinement was by full-matrix least-squares calculations, initially with isotropic and then with anisotropic thermal parameters. At an intermediate stage in the refinement, difference maps showed maxima in positions consistent with the expected locations of the hydrogen atoms. In the final round of refinement calculations, the hydrogen atoms were positioned on geometrical grounds (C–H, O–H, 0.95 Å) and included (as riding atoms) in the structure factor calculations with an overall B(iso) of 6.0 Å^2. That the O–H hydrogens were correctly positioned was checked by an appropriate difference map calculation before the last round of refinement. The final R and R_w values are 0.0611 and 0.0632, respectively, with a maximum shift/error ratio of 0.03 in the last refinement cycle. A final difference map showed no significant residual electron density. Scattering factors were from ref 37. All calculations were performed on a PDP11/73 using SDS-Plus.[38]

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Details of molecular geometry, atomic coordinates, calculated hydrogen coordinates, torsion angles, anisotropic thermal parameters, mean planes, and structure factors are available as Supplementary Material. Diagrams of molecule A (Figure 1,1b) were prepared with ORTEP.[39]

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Supplementary Material Available: Structure numbering (Figure 1b) and tables of molecular dimensions (bond lengths and angles), positional parameters, calculated hydrogen coordinates, torsion angles, anisotropic thermal parameters, and mean planes for $41 \cdot H_2O$ (16 pages); structure factors for $41 \cdot H_2O$ (21 pages). Ordering information is given on any current masthead page.

Synthesis of Vallesiachotamine[1]

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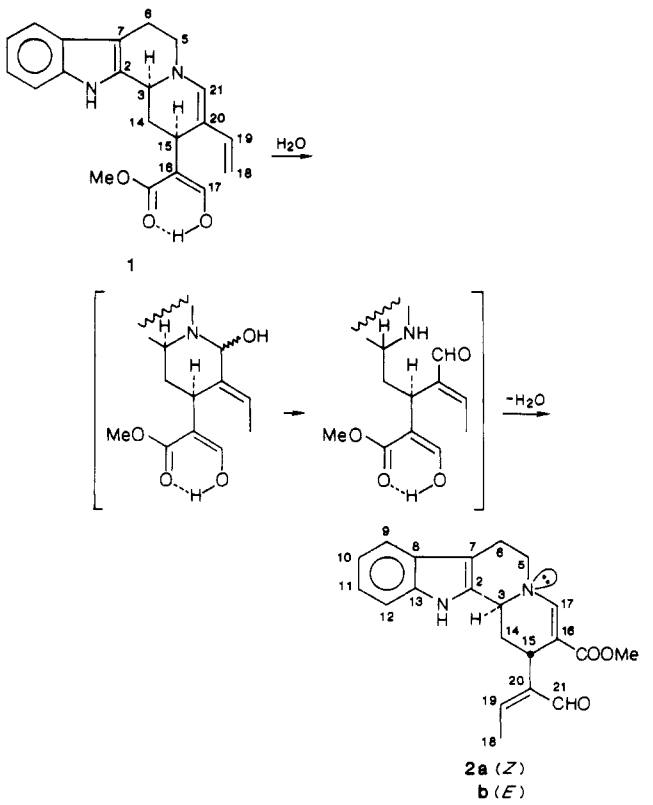
Interaction of methyl *N*-tryptophylnicotinate bromide with the lithium salt of ethyl α-(trimethylsilyl)acetate and acid-catalyzed cyclization has yielded a tetracyclic ester, whose condensation with acetaldehyde has produced ethyl vallesiachotamate. Reactions of lithiated, alkylthiolated esters with the nicotinate salt (followed by cyclization) have afforded related adducts. Ester-to-aldehyde group conversion has led to the alkaloid vallesiachotamine in the 19*Z* and 19*E* forms.

Vallesiachotamine (**2**), a minor constituent of the Peruvian plant *Vallesia dichotoma* Ruiz et Pav,[2a] of the Asian shrub *Rhazya orientalis*,[2b] and of the Cameroonian plant *Strychnos tricalysioides* Hutch. and M. B. Moss[2c] is an indole alkaloid of (at first glance) unusual structure but related by hydration, ring-chain tautomerization, and dehydration (Scheme I) to dehydrogeissoschizine (**1**), the vital, biosynthetic link connecting the large number of corynanthoid, heteroyohimboid, and yohimboid bases with those of the Strychnos family and others of like structural complexity.[3] The tetracyclic, urethane vinylogue structure of the alkaloid (**2**) with the trans H(3) -H(15) configuration was an ideal candidate for a short synthesis by way of the time-tested, two-step route of carbon nucleophile addition to 1-tryptophyl-3-acylpyridinium salts, followed by acid-induced ring closure (Scheme II).[4,5] Therefore a study of the alkaloid synthesis via this route was initiated.

The nicotinic ester derivative **3** (Y = OMe) was the starting pyridinium salt of choice. Whereas it already had been converted into tetracycle **4** (R = $CH(CO_2Me)_2$, Y = OMe) with malonic ester anion acting as the carbon nucleophile,[4b] alternative paths more readily introducing the crotonaldehyde side chain of vallesiachotamine were sought. For this reason the lithium salt of ethyl (trimethylsilyl)acetate was exposed to the methyl nicotinate

Scheme I



1

2a (*Z*)
b (*E*)

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