92901-91-2; 13, 92901-92-3; 14, 92901-93-4; $PhCH_2OH$, 100-51-6; $ClCH_2C(O)OEt$, 105-39-5; $PhCH_2OCH_2C(O)OEt$, 32122-09-1; $PhCH_2OCH_2CO_2H$, 30379-55-6; 2,5-dimethyloxazole-4-methanol, 92901-94-5; ethyl 2,5-dimethyloxazole-4-carboxylate, 23000-15-9.

A New Route to the Pyridine Nucleus Fused to Some Heterocycles

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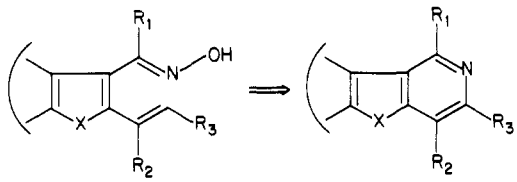
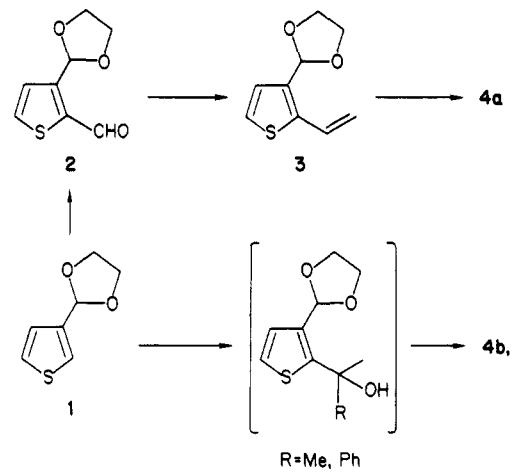
In a previous paper,[1] we reported a synthesis of 9-aza-6-thiaellipticine in connection with studies of the antitumor 6*H*-pyrido[4,3-*b*]carbazole ellipticine isostere. As a starting material we required the unsubstituted thieno[3,2-*c*]-pyridine. Although Barger and Easson[2] failed to produce thieno[3,2-*c*]pyridine by the Bischler–Napieralski reaction, this compound was prepared by Gronowitz and Sandberg[3] using the Pictet–Spengler reaction, which requires a difficult final oxidation step. Thieno[3,2-*c*]pyridines and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines prepared in a similar way have also been reported as the isoquinoline isosteres and have attracted much attention because of their biological activity.[4]

In seeking a more direct route to fused pyridine ring systems, we have found that 1-aza-1,3,5-hexatrienes based on the five-membered ring of thiophene or indole undergo a facile intramolecular thermal cyclization with loss of water to yield fused pyridine rings.[5] We here report on the use of this cyclization to prepare some thieno[3,2-*c*]-pyridines and some 5*H*-pyrido[4,3-*b*]indoles.



The carbonyl intermediates **4a–c** needed for the thieno[3,2-*c*]pyridines were prepared as shown in Scheme I and converted into oximes **5a–c** by reaction with hydroxylamine. The oximes were cyclized by heating in Decalin at 200–210 °C for 4–6 h to give **6a**,[3] **6b**,[6] and **6c** in yields of 67–80% (Table I).

Scheme I



The carbonyl intermediates **11a–c** of 5*H*-pyrido[4,3-*b*]indoles[7] were prepared as shown in Scheme II. The corresponding oximes **12a–c** cyclized at a lower temperature (119 °C) than **5a–c**, presumably because of electron donation by the indole nitrogen, giving 5*H*-pyrido[4,3-*b*]indoles **13a–c** (Table II). In the preparation of **13a,b**, the intermediate oximes were not isolated; the methanol used in the oxime synthesis was replaced by toluene and the resulting solution refluxed to effect cyclization. Although the yields of **13a,b** obtained by this route were modest, the conversions based on recovered **11a,b** that had not been converted into oxime were 72–86%.

Thus the thermal cyclization of the 1-aza-1,3,5-hexatriene system offers a direct route to fused pyridine ring systems that avoids the necessity for oxidation of an intermediate tetrahydropyridine.[4,7]

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on Varian T-60 and JEOL PMX-60Si instruments in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were measured on Hitachi RMU-7L and Shimazu GC-MS 6020 spectrometers. Satisfactory elemental analyses for all purified compounds have been submitted to the editor.

2,3-Thiophenedicarbaldehyde 3-(Ethylene acetal) (2). To an ice-cooled solution of thiophene-3-aldehyde ethylene acetal (1, 31 g, 0.2 mol) in anhydrous THF (150 mL) was added dropwise a solution of *n*-BuLi (330 mL of 1.5 M solution in *n*-hexane, 0.2 mol) with stirring. After 0.5 h, dry dimethylformamide (17.5 g, 0.24 mol) in anhydrous THF (20 mL) was added. The ice bath was removed, and stirring was continued for 3 h at room temperature. The solution was quenched with water and extracted with benzene. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The oily residue was distilled to give **2** (35.6 g, 97%): bp 161-165 °C (2 torr); mass spectrum, *m/e* 184 (M^+); ^1H NMR δ 6.15 (1 H, s, CH), 9.95 (1 H, s, CHO).

2-Vinylthiophene-3-carbaldehyde Ethylene Acetal (3). A solution of **2** (28 g, 0.15 mol) in anhydrous THF (100 mL) was added dropwise to an ice-cooled solution of methyl triphenylphosphonium bromide (64 g, 0.18 mol) and *n*-BuLi (270 mL of 1.5 M solution in *n*-hexane, 0.18 mol) in anhydrous THF (120 mL). The mixture was stirred at room temperature overnight, quenched with brine, and extracted with benzene. The benzene was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to

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(3) Gronowitz S.; Sandberg E. *Arkiv. Kemi* **1970**, *32*, 217.
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(5) Recently, thermal electrocyclic reaction of 2-aza-1,3-butadiene derivatives at high temperature have been reported: Govindan C. K.; Taylor, G. *J. Org. Chem.* **1983**, *48*, 5348 and related references cited therein.
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(8) Kano S.; Sugino E.; Shibuya S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 3856.

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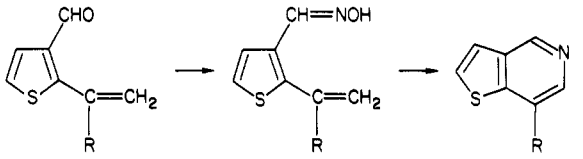
Table I.

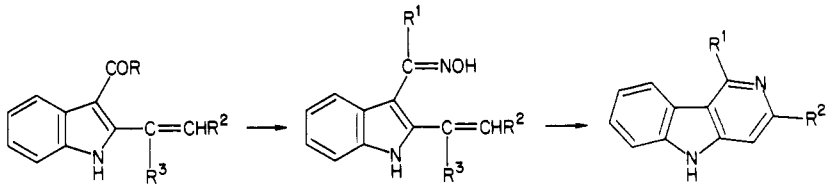


4 5 6

	R	yield, %	bp, °C/torr	^{1}H NMR, δ
4a	H	72		10.00 (1 H, s, CHO)
4b	Me	66	125–128/1	2.22 (3 H, bs, CH_3), 5.20 (1 H, bs, vinyl H), 5.40 (1 H, bs, vinyl H), 9.94 (1 H, s, CHO)
4c	Ph	72	167–170/1	5.49 (1 H, d, J = 1 Hz, vinyl H), 9.65 (1 H, s, CHO)
5a	H	65	mp 84–85	
5b	Me	93	mp 51	2.11 (3 H, bs, vinyl H)
5c	Ph	94		5.41 (1 H, d, J = 1 Hz, vinyl H), 5.75 (1 H, d, J = 1 Hz, vinyl H), 7.94 (1 H, s, CH=N)
6a	H	70	mp 42–43[a]	
6b	Me	67	61–62/1.5[b]	7.47 (1 H, d, J = 5 Hz, C_3-H), 7.63 (1 H, d, J = 5 Hz, C_2-H), 8.20 (1 H, s, C_6-H), 8.95 (1 H, s, C_4-H)
6c	Ph	80	185–186/1	8.54 (1 H, s, C_6-H), 9.12 (1 H, s, C_4-H)

[a] Lit.[3] mp 42–43 °C. [b] Lit.[8] bp 60–62 °C (1.5 torr).

Table II



11 12 13

	R^1	R^2	R^3	yield, %	mp, °C	^{1}H NMR, δ
11a	CO_2Me	H	Me	63	139–141	2.20 (3 H, bs, CH_3), 3.82 (3 H, s, CO_2CH_3), 5.25 (1 H, bs, vinyl H), 5.43 (1 H, bs, vinyl H)
11b	CO_2Me	Me	Ph	86	218–220	
11c	H	Me	Ph	(ref 8)		
12a	CO_2Me	H	Me	(not isolated)		
12b	CO_2Me	Me	Ph	(not isolated)		
12c	H	Me	Ph	91	219–221	1.87 (3 H, d, J = 7 Hz, CH_3), 6.07 (1 H, q, J = 7 Hz, vinyl H), 8.02 (1 H, s, CH=N)
13a	CO_2Me	H	Me	37[a]	188–190	2.53 (3 H, s, CH_3), 4.07 (3 H, s, CO_2CH_3), 8.40 (1 H, s, C_3-H)
13b	CO_2Me	Me	Ph	47[b]	256–257	2.51 (3 H, s, CH_3), 4.05 (3 H, s, CO_2CH_3)
13c	H	Me	Ph	93	258–259	2.53 (3 H, s, CH_3), 9.13 (1 H, s, C_1-H)

[a] Conversion 72% based on recovered starting material. [b] Conversion 86% based on recovered starting material.

dryness. The residue was purified by column chromatography (silica gel, 150 g) using benzene/*n*-hexane (1:1). The eluates were combined and concentrated under reduced pressure, and the residue was distilled to give **3** (20.9 g, 77%): bp 135–137 °C (2 torr); mass spectrum, *m/e* 182 (M^+).

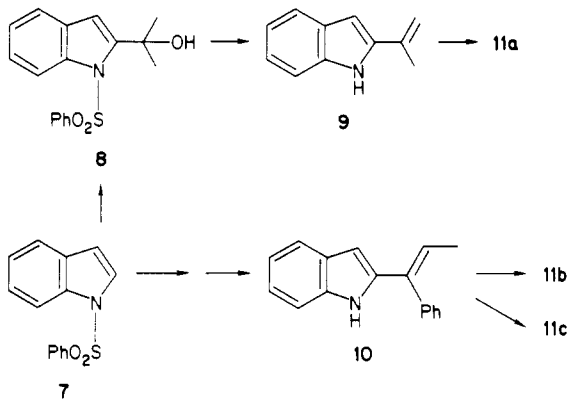
2-Vinylthiophene-3-carbaldehyde (4a). A mixture of **3** (18.2 g, 0.1 mol) and $KHSO_4$ (15 g, excess) in water (50 mL) and acetone (300 mL) was heated at 60 °C with stirring for 4.5 h. After removal of acetone and addition of water, the mixture was extracted with benzene, and the extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure below 60 °C to give **4** (9.9 g, 72%): ^{1}H NMR δ 10.00 (1 H, s, CHO). This almost pure material could not be distilled because it was too unstable at elevated temperature, and it was used directly for the preparation of **5a**.

2-Isopropenylthiophene-3-carbaldehyde (4b) and 2-(α-styryl)thiophene-3-carbaldehyde (4c) were prepared by the procedure used for **2**, quenching the mixture with acetone or acetophenone, respectively. The resulting tertiary alcohols were not purified and were hydrolyzed to **4b** and **4c** by the procedure used for **4a** (see Table I for yields and properties).

Oximes 5a–c and **12c** were prepared by treating **4a–c** or **11c** with 2 equiv of NH_2OH·HCl and 2 equiv of NaOAc in ethanol under reflux for 2 h with stirring (see Tables I and II).

Thieno[3,2-c]pyridines 6a–c were prepared by heating **5a–c** in Decalin at 200 °C for 4–6 h. The Decalin was removed under

Scheme II



reduced pressure, and the residue was distilled under reduced pressure (Table I).

α-[1-(Phenylsulfonyl)-2-indolyl]-α,α-dimethylmethanol (8). To a stirred solution of lithium diisopropylamide [prepared from 1.5 M *n*-hexane solution of *n*-BuLi (57.3 mL, 0.086 mol) and diisopropylamine (12.6 mL, 0.09 mol) in anhydrous THF (60 mL)] was added a solution of *N*-(phenylsulfonyl)indole (**7**) (20 g, 0.078 mol). After 0.5 h a solution of acetone (6.7 mL, excess) in anhydrous THF was added at −78 °C. The mixture was gradually warmed to room temperature and kept there for 4 h with stirring. It was poured into aqueous NH_4Cl solution and extracted with EtOAc. The extract was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, 300 g) using 1% EtOAc/*n*-hexane to give **8** (7.5 g, 30.5%) and recovered starting material (10.5 g). **8**: mp 71–73 °C; mass spectrum, *m/e* 315 (M^+), 300 ($M^+ - 15$), 258 (base); ^1H NMR δ 1.82 (6 H, s, CH_3).

2-Isopropenylindole (9). A stirred mixture of **8** (23.2 g, 0.074 mol), 10% NaOH solution (100 mL), and ethanol (200 mL) was refluxed for 2 h. The solvent was evaporated, and the residue was extracted with benzene, which was washed with brine and evaporated. Purification by column chromatography (silica gel, 300 g) using 0.5% EtOAc/*n*-hexane gave **9** (8.7 g, 75%): mp 116–118 °C; mass spectrum, *m/e* 157 (M^+); ^1H NMR δ 2.16 (3 H, bs, CH_3), 5.03 (1 H, bs, vinyl H), 5.25 (1 H, s, vinyl H); HRMS, calcd for $C_{11}H_{11}N$, 157.0890, found 157.0860.

Methyl 2-[2-(1-Methylvinyl)-3-indolyl]-2-oxoacetate (11a) and Methyl 2-[2-(1-Phenyl-1-propenyl)-3-indolyl]-2-oxoacetate (11b). **9** or **10** (0.025–0.03 mol) was treated with 1.5 equiv of oxalyl chloride and 2.2 equiv of triethylamine at 0 °C for 2 h with stirring. Excess methanol was added, and the mixture was stirred at room temperature overnight.

11a: The mixture was diluted with EtOAc, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 100 g) (Table II).

11b: The precipitate was collected, washed with ether, and recrystallized from benzene (see Table II).

1-(Methoxycarbonyl)-3-methyl-4-phenyl-5*H*-pyrido[4,3-b]indole (13b) and 1-(Methoxycarbonyl)-4-methyl-5*H*-pyrido[4,3-*b*]indole (13a). Keto ester **11a** or **11b** was treated with 1.5–2.0 equiv each of NH_2OH·HCl and NaOAc in MeOH under reflux overnight. The MeOH was replaced by toluene, and the mixture was refluxed for 6–14 h. Column chromatography over silica gel and elution with benzene/$CHCl_3$ gave recovered starting keto ester. The second eluate with 1% MeOH/$CHCl_3$ gave the pyridoindole (Table II).

3-Methyl-4-phenyl-5*H*-pyrido[4,3-*b*]indole (13c). Oxime **12c** was refluxed in toluene for 6 h. The toluene was evaporated and the residue was crystallized from ethanol to give **13c**.

Registry No. 1, 13250-82-3; **2**, 13250-83-4; **3**, 92642-98-3; **4a**, 41057-09-4; **4b**, 92642-99-4; **4c**, 92643-00-0; **5a**, 41056-88-6; **5b**, 92643-01-1; **5c**, 92643-02-2; **6a**, 272-14-0; **6b**, 39677-82-2; **6c**, 92643-03-3; **7**, 40899-71-6; **8**, 92643-04-4; **9**, 78133-83-2; **10**, 78329-46-1; **11a**, 92643-05-5; **11b**, 92643-06-6; **11c**, 77092-51-4; **12a**, 92643-07-7; **12b**, 92643-08-8; **12c**, 92669-35-7; **13a**, 92643-09-9; **13b**, 92643-10-2; **13c**, 92643-11-3; 2-(2-hydroxy-2-propanyl)-3-(1,3-dioxolan-2-yl)thiophene, 92643-12-4; 2-(1-hydroxy-1-phenylethyl)-3-(1,3-dioxolan-2-yl)thiophene, 92643-13-5; 2-(1-hydroxyphenylpropyl)-1-(phenylsulfonyl)indole, 77092-50-3; 3-(1,2-dioxo-2-chloroethyl)-2-isopropenylindole, 92643-14-6; 3-(1,2-dioxo-2-chloroethyl)-2-(1-phenyl-1-propenyl)indole, 92643-15-7.

Electrochemical Behavior of Nitroaromatic Podands: Contrast between Lariat Ethers and Their Open-Chained Analogues

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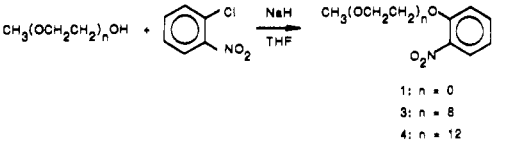
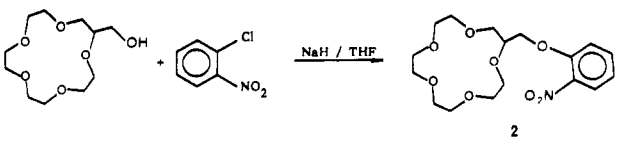
During recent years, there has been substantial interest in polyethylene glycols (PEGs) and polyethylene glycol ethers as complexing ligands for a variety of cations.[1] Podands[2] are more economically attractive than crown[3] or lariat ethers[4] in those cases where the podand is functionally equivalent to the cyclic material (the coronand).[2] Indeed, numerous examples of this functional equivalence have been noted,[5] and in recent work of our own, we have studied binding profiles for several PEGs and assessed their efficacy in phase-transfer reactions.[1] We now report that in contrast to many recent examples of podand–coronand equivalence, the electrochemical behavior of nitroarene-substituted PEGs is similar to that of 2-nitroanisole (**1**) but not to 2-[(2-nitrophenoxy)methyl]-15-crown-5 (**2**).[6]

Results and Discussion

Nitroarene-substituted podands **3** and **4** were prepared by treatment of 2-chloronitrobenzene in THF with the anion (NaH) of $CH_3(OCH_2CH_2)_nOH$ where *n* is 8 or 12.[6] The compounds were obtained in analogy to the previously reported[6] crown **2** in 68% and 61% yields, respectively, as shown in eq 1. Both compounds were obtained as yellow oils and each was pure after chromatography over alumina.





2

The cyclic voltammograms of 2-nitroanisole, 2-(1,4,7,10,13,16,19,22,25-nonaoxahexaeicosyl)nitrobenzene (also called 2-[methoxyocta(ethoxy)]nitrobenzene, **3**), and 2-[methoxydodeca(ethoxy)]nitrobenzene (**4**) as well as the corresponding crown **2** were determined as previously described[6,7] (see Experimental Section), and scans for **3**

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