Synthesis of 1-(*o*-Substituted-phenyl)-3,4-dimethylenepyrrolidines by the Thermal Elimination of Sulfur Dioxide

Raphael M. Ottenbrite* [1a], Henry Chin [1a], and Peter V. Alston [1b]

Department of Chemistry, Virginia Commonwealth University,
Richmond, Virginia 23284

and

E. I. du Pont de Nemours and Company, Textile Fibers Department,
Kinston, North Carolina 28501

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Precursors of 1-(*o*-substituted-phenyl)-3,4-dimethylenepyrrolidines, 5-(*o*-substituted-phenyl)-1,3,4,6-tetrahydrothieno[3,4-c]pyrrole 2,2- dioxides **2**, were synthesized by reacting *o*-substituted anilines with 3,4-bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide. A disubstitution product along with the desired **2** was obtained when excess amine was used to neutralize the amine salts that were formed from nucleophilic substitution. A 1,4-HBr elimination product was obtained in three out of four cases when sodium carbonate was used to neutralize the amine salts. The 1,4-HBr elimination product resulted from a competing base attack on the acidic sulfolene protons. The 3,4-dimethylenepyrrolidines were obtained by thermal elimination of sulfur dioxide from **2**.

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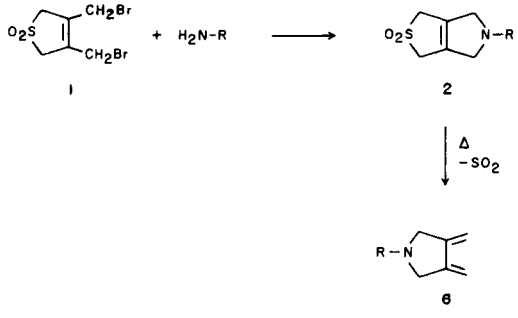
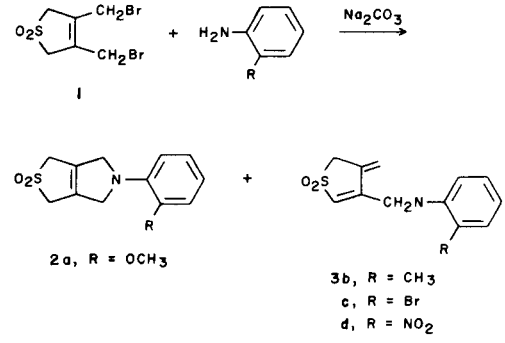
The 3,4-dimethylenepyrrolidines are of specific interest as reactants in the Diels-Alder reaction [2,3] and monomers in polymerization reactions [4] as well as for their photoreactivity [3] and medicinal application [5]. The synthesis of 3,4-dimethylenepyrrolidines by the reaction of 3,4-bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide (**1**) with primary amines to produce 1,3,4,6-tetrahydrothieno-[3,4-*c*]pyrrole 2,2-dioxides **2** and the subsequent thermal elimination of sulfur dioxide from these bicyclic compounds has been reported [6,7].



In this paper we report the extension of this synthetic scheme to the preparation of 1-(*o*-substituted-phenyl)-3,4-dimethylenepyrrolidines **6**. Steric effects exhibited by the *ortho* substituents of the anilines caused reaction conditions, yields, and reaction products to differ from their *para* and *meta* substituted counterparts.

Results and Discussion.

The reaction of 3,4-bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide (**1**) with *ortho*-substituted anilines was initially carried out under the reaction conditions that were previously employed with the *meta*- and *para*-substituted anilines [6a]. A 1:1 molar ratio of **1** and the aniline was reacted in methanol and sodium carbonate was used to neutralize the amine salts that were formed. Under these reaction conditions, the bicyclic product **2** was obtained only with *o*-anisidine and a 1,4-HBr elimination product **3** was obtained with *o*-toluidine, *o*-bromoaniline, and *o*-nitroaniline (Table I). The 1,4-HBr elimination product has been previously observed in the reactions of the



more basic alkylamines with **1**, but was not observed with the less basic *meta*- and *para*-substituted anilines [6]. The lower reactivity of the *ortho*-substituted anilines because of steric hindrance from the *ortho* substituent apparently allowed the elimination reaction to compete successfully with the substitution reaction.

The sodium carbonate which was used to neutralize the amine salts formed during the substitution reaction is apparently a strong enough base to cause the elimination reaction. When equivalent moles of sodium carbonate and **1** were stirred for 12 hours in methanol without any amine, nmr analysis of the crude products showed that **1** had completely undergone 1,4-HBr elimination. Compound **1**

Table I

Reaction Products of Substituted Anilines with 3,4-Bis(bromomethyl)-2,5-dihydrothiophene (**1**)

Substituted Aniline	Solvent	Ratio Amine to **1**	Sodium Carbonate	Products, % Bicyclic **2**	Elimination **3**	Disubstituted **4**
o-Nitroaniline	CH_3OH	1:1	+	0	2.8	0
	CH_3OH	3:1	0	0	0	0
	CH_3CN	3:1	0	0	0	0
o-Bromoaniline	CH_3OH	1:1	+	0	24	0
	CH_3OH	3:1	0	23	0	21
	CH_3CN	3:1	0	13	0	29
o-Toluidine	CH_3OH	1:1	+	0	54	0
	CH_3OH	3:1	0	34	0	0
	CH_3CN	3:1	0	39	0	2
o-Anisidine	CH_3OH	1:1	+	54	0	0
	CH_3OH	3:1	0	21	0	21
	CH_3CN	3:1	0	24	0	10
Aniline	CH_3OH [a]	1:1	+	74	0	0
	CH_3CN	3:1	0	76	0	0
	Aniline [b]	—	0	20	0	65
p-Toluidine	CH_3OH [a]	1:1	+	71	0	0
	CH_3CN	3:1	0	60	0	0
p-chloroaniline	CH_3OH [a]	1:1	+	70	0	0
	CH_3CN	3:1	0	30	0	0

[a] Reference [6a]. [b] Reference [8].

Table II

NMR Spectra of 1-(Substituted-phenyl)-3,4-dimethylenepyrrolidines

	NMR Spectra, δ [a,b]				
R	Endo vinyl Hydrogens	Exo vinyl Hydrogens	Methylene Hydrogens	Aromatic Hydrogens	R
o-OCH_3	5.20 (m)	4.77 (m)	3.87 (m)	6.67-6.37 (m)	3.67 (s)
m-OCH_3	5.57 (m)	5.08 (m)	4.10 (m)	7.38-6.09 (m)	3.82 (s)
p-OCH_3	5.53 (m)	5.07 (m)	4.03 (m)	6.90-6.56 (m)	3.77 (s)
o-CH_3	5.43 (m)	4.98 (m)	3.88 (m)	7.23-6.79 (m)	2.33 (s)
m-CH_3	5.55 (m)	5.07 (m)	4.10 (m)	7.33-6.29 (m)	2.34 (s)
p-CH_3	5.55 (m)	5.07 (m)	4.06 (m)	7.10-6.54 (m)	2.27 (s)
o-Br	5.47 (m)	5.02 (m)	4.07 (m)	7.56-6.57 (m)	—
H	5.55 (m)	5.07 (m)	4.09 (m)	7.45-6.48 (m)	—

[a] The nmr solvent was deuteriochloroform. [b] The nmr spectra *meta, para,* and unsubstituted dienes were published previously in reference [6a].

alone under identical conditions did not undergo the elimination reaction. Apparently, the elimination reaction is being promoted by base attack at the acidic sulfolene proton.

To minimize the competing elimination reaction **1** was reacted with the *ortho*-substituted anilines in a less basic environment. The ratio of aniline to **1** was increased to 3:1 and the sodium carbonate was not used. Under these con-

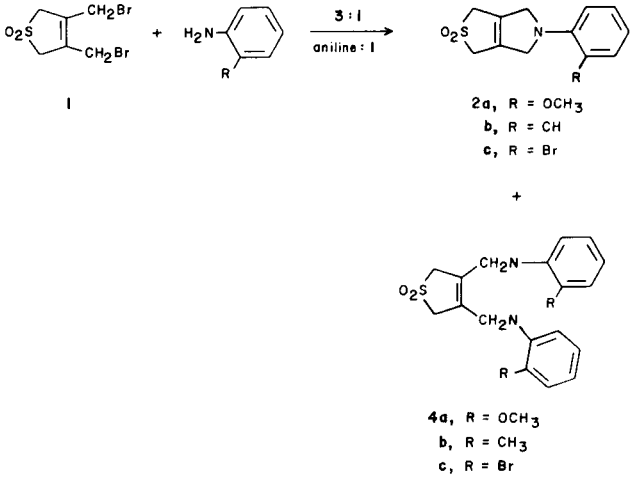
Table III

Physical Constants of 5-(*o*-Substituted-phenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxides **2**, 4-(*N*-*o*-Substituted-phenylaminomethyl)-2-hydro-3-methylenethiophene 1,1-Dioxides **3**, 3,4-Bis(*N*-*o*-substituted-phenylaminomethyl)-2,5-dihydrothiophene 1,1-Dioxides **4**, and 5-(*o*-Substituted-phenyl)-1,3-dihydrothieno[3,4-*c*]pyrrole 2,2-Dioxides **5**

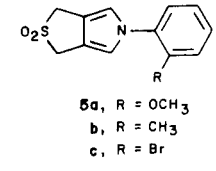
No.	Substituent	MP °C	NMR Spectra, [a]	IR Spectra (KBr) cm^{-1}
2a	OCH_3	140 dec	7.06 (s, 4H), 4.53 (m, 4H), 4.00 (m, 4H), 3.97 (s, 3H)	3068, 1598, 1229, 1117, 1196, 736
2b	CH_3	136.5 dec	7.00-6.40 (m, 4H), 4.07 (s, 4H), 3.72 (s, 4H), 2.27 (s, 3H)	3021, 1492, 1308, 1106, 1179, 763
2c	Br	149 dec	7.29-6.46 (m, 4H), 4.19 (s, 4H), 3.59 (s, 4H)	3074, 1594, 1298, 1120, 1197, 741
3b	CH_3	182-185	7.27-6.33 (m, 5H), 5.58 (m, 1H), 5.40 (m, 1H), 4.22 (m, 2H), 4.05 (m, 2H), 3.67-3.17 (broad s, 1H), 2.17 (s, 3H)	3437, 3088, 1607, 1303, 1124, 1219, 748
3c	Br	149-150.5	7.57-6.40 (m, 5H), 5.60-5.43 (fused m, 2H), 5.30-4.43 (broad s, 1H), 4.23 (m, 2H), 4.07 (m, 2H)	3398, 3072, 1589, 1288, 1101, 1325, 743
3d	NO_2	155 dec	8.40-6.60 (m, 5H), 5.67-5.53 (fused m, 2H), 4.43 (m, 2H), 4.13 (m, 2H), 4.03-4.48 (broad s, 1H)	3382, 3090, 1620, 1228, 1173, 1249, 775
4a	OCH_3	138 dec	6.63-6.13 (m, 8H), 3.87 (s, 4H), 3.73 (s, 4H), 3.67 (s, 6H)	3408, 3065, 1604, 1385, 1132, 1221, 719
4b	CH_3	136-138	7.17-6.40 (m, 8H), 4.08 (s, 4H), 3.89 (s, 2H), 3.45 (s, 2H), 2.15 (s, 6H)	3446, 3016, 1607, 1293, 1109, 1251, 747
4c	Br	149.5-150.5	7.57-6.55 (m, 8H), 4.33-3.73 (broad s, 2H), 4.13 (s, 4H), 3.91 (s, 4H)	3416, 3064, 1599, 1300, 1120, 1245, 741
5a	OCH_3	163-164	7.06-6.57 (m, 6H), 4.03 (s, 4H), 3.67 (s, 3H)	3023, 1506, 1308, 1128, 765
5b	CH_3	164-166	6.97 (m, 4H), 6.40 (s, 2H), 4.07 (s, 4H), 2.10 (s, 3H)	3027, 1499, 1303, 1112, 769
5c	Br	160-162	7.83-7.23 (m, 4H), 6.77 (s, 2H), 4.23 (s, 4H)	3058, 1493, 1323, 1128, 758

[a] The nmr solvent was deuteriochloroform.

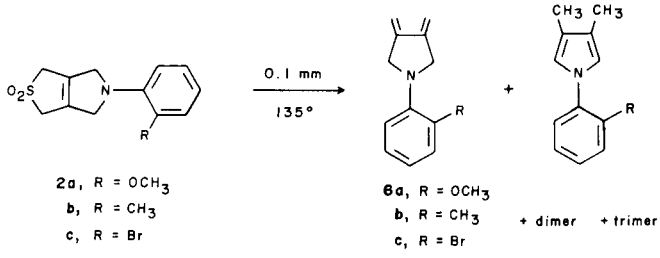
ditions, the bicyclic compound **2** and a disubstituted product **4** were obtained with *o*-anisidine, *o*-toluidine, and *o*-bromoaniline (Table I). No reaction products were observed with *o*-nitroaniline which has very weak nucleophilic and basic character; only starting materials were obtained. Steric hindrance by the *ortho* substituent which decreases the propensity for nucleophilic cyclization is the apparent cause of the appearance of **4** as a reaction product. When **1** was reacted with aniline or with *p*-substituted anilines under identical conditions, no disubstituted products were detected. The disubstituted product was obtained with aniline when the reaction was carried out in a large excess of aniline without solvent [8].



The reaction solutions of *o*-toluidine and *o*-anisidine with **1** were found to develop a purple color under atmospheric conditions. This color change was attributed to the oxidation of the bicyclic compound **2**. When the reactions were carried out in a nitrogen atmosphere, the purple color was not observed. Furthermore, the bicyclic compounds could be converted quantitatively into their oxidized counterparts **5** by stirring in acetonitrile under atmospheric conditions for 24 hours.



The thermal decomposition of the 5-(*o*-substituted-phenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-dioxides at 135° and under reduced pressure (0.1 mm) resulted in the elimination of sulfur dioxide and the formation of the corresponding exocyclic dienes **6**. The decompositions were carried out in a sublimator and the exocyclic dienes were recovered from the cold finger. The dienes contained a trace amount of rearranged product, 1-substituted-3,4-dimethylpyrrole (identified by nmr). All of the dienes were oils at room temperature and under these conditions, they readily polymerized on standing. At temperatures below their freezing point, the dienes can be stored for months. The residue that remained in the bottom of the sublimator has been previously identified to contain dimeric and trimeric Diels-Alder adducts of the exocyclic dienes [6].



The liquid state of the 1-(*o*-substituted-phenyl)-3,4-dimethylenepyrrolidines at ambient conditions was unexpected since their *para* and *meta* substituted counterparts are solids under these conditions. A possible explanation for this difference is that the planarity and the conjugation between the phenyl and nitrogen moities is reduced because of steric hindrance between the *ortho* substituents and the methylene protons of the pyrrolidine ring. The chemical shifts of the vinyl and methylene protons of the *ortho*-substituted dienes which are upfield from their *meta/para* counterparts support this hypothesis (Table II). The nonplanarity is expected to increase electron-donation into the diene moiety *via* the nitrogen lone pair and cause an upfield chemical shift. The vinyl and methylene protons of 1-alkyl-3,4-dimethylenepyrrolidines which have no delocalization of the nitrogen lone pair also exhibited this upfield chemical shift [6b].

In conclusion, *ortho*-substituted anilines react with 3,4-bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide (**1**) to give 1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-dioxide (**2**) in lower yield (13-54%) than their *meta/para* substituted counterparts (63-83%) because, 1,4-HBr elimination and disubstitution reactions compete more successfully with nucleophilic cyclization. The corresponding 3,4-dimethylenepyrrolidines were produced in good yields (~60%); however, they are liquids at ambient conditions and polymerize readily.

Table IV

Combustion Analytical Data

No.	Molecular Formula	Elemental Analysis Calculated C	H	N	Found C	H	N
2a	$C_{13}H_{15}NO_3S$	58.85	5.70	5.28	58.76	5.72	5.28
2b	$C_{13}H_{15}NO_2S$	62.62	6.06	5.62	62.56	6.02	5.63
2c	$C_{12}H_{12}BrNO_2S$	45.87	3.85	4.46	45.95	3.87	4.55
3b	$C_{13}H_{15}NO_2S$	62.62	6.06	5.62	62.34	6.06	5.57
3c	$C_{12}H_{12}BrNO_2S$	45.87	3.85	4.46	45.90	3.92	4.60
3d	$C_{12}H_{12}N_2O_4S$	51.42	4.32	9.99	51.36	4.27	9.90
4a	$C_{20}H_{24}N_2O_4S$	61.83	6.23	7.21	61.55	6.23	7.16
4b	$C_{20}H_{24}N_2O_2S$	67.38	6.79	7.86	67.12	6.70	7.81
4c	$C_{18}H_{18}BrN_2O_2S$	44.46	3.73	5.76	44.51	3.76	5.96
5a	$C_{13}H_{13}NO_3S$	59.29	4.98	5.32	58.92	5.02	5.42
5b	$C_{13}H_{13}NO_2S$	63.13	5.30	5.66	62.97	5.36	5.62
5c	$C_{12}H_9BrNO_2S$	46.16	3.23	4.49	46.02	3.24	4.59

EXPERIMENTAL

All melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The nuclear magnetic resonance (NMR) spectra were obtained from a Varian T-60 spectrometer. Chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) and the NMR signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The ir spectra were obtained in potassium bromide on a Perkin-Elmer Model 283 infrared spectrometer. The elemental analysis were provided by A. H. Robins Research Laboratories, Richmond, Virginia.

The bicyclic compounds **2** and their disubstituted products **4** that are characterized in Tables III-IV were prepared by the procedures given for the preparation of 5-(*o*-methoxyphenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]-pyrrole 2,2-dioxide. The elimination products **3** were prepared by the procedure given for 4-(*N*-*o*-methylphenylaminomethyl)-2-hydro-3-methylenethiophene 1,1-dioxide. The oxidation products **5** that are also characterized in Table III and IV were prepared by the procedure given for 5-(*o*-methylphenyl)-1,3-dihydrothieno[3,4-*c*]pyrrole 2,2-dioxide. The 1-substituted-3,4-dimethylenepyrrolidines **6** were prepared by the procedure given for 1-(*o*-bromophenyl)-3,4-dimethylenepyrrolidine.

5-(*o*-Methoxyphenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide (**2a**).

a) Procedure Using Acetonitrile as the Solvent and an Amine to **1** Ratio of 3:1.

Dibromosulfone (**1**) (1.00 g, 3.3 mmoles) and *o*-methoxyaniline (1.23 g, 10 mmoles) were dissolved in 70 ml of acetonitrile. This solution was placed in a 100 ml round-bottom flask and sealed under a nitrogen atmosphere in order to minimize oxidation. The reaction was allowed to stir for 12 hours. The amine salt which precipitated from the solution was filtered and the solvent was removed under reduced pressure. The addition of methanol caused a white solid (0.35 g) to precipitate. The nmr

analysis indicated that the solid was a mixture of bicyclic and disubstituted products. The composition of this mixture was determined by nmr to be 30% disubstituted and 71% bicyclic products. The compounds were separated by their different solubilities in methanol. The bicyclic product was preferentially precipitated from a methanol solution by allowing the solution to stand overnight in a freezer. Then the disubstituted product was precipitated by concentration of the methanol solution. The overall yields were 10% disubstituted and 24% bicyclic.

b) Procedure Using Methanol as the Solvent and an Amine to **1** Ratio of 3:1.

Dibromosulfone (1.00 g, 3.3 mmoles) and *o*-methoxyaniline (1.23 g, 10 mmoles) were dissolved in 50 ml of boiling methanol. The reaction was allowed to stir 12 hours under nitrogen atmosphere at room temperature. The solid precipitate (0.45 g) was removed by filtration and washed with 20 ml of methanol. The nmr spectrum of the precipitate indicated a 50-50 mixture of bicyclic and disubstituted products. The overall yields were 21% bicyclic and 21% disubstituted products. The separation of the mixture was accomplished using the same procedure given in the preceding preparation.

c) Procedure Using Methanol as the Solvent and an Amine to **1** Ratio of 1:1.

The dibromosulfone **1** (1.00 g, 3.3 mmoles) was dissolved in 50 ml of refluxing methanol. Sodium carbonate (0.36 g, 3.3 mmoles) and *o*-methoxyaniline (0.41 g, 3.3 mmoles) were added to the hot methanol solution. The reaction mixture was allowed to stir for 12 hours at room temperature under a nitrogen atmosphere. During this time all of the sodium carbonate was consumed and most of the bicyclic product precipitated out of solution. The reaction solution was allowed to stand in a freezer overnight and some additional bicyclic product was recovered. Total yield was 54%. No additional compounds could be isolated from the reaction solution.

4-(*N*-*o*-methylphenylaminomethyl)-2-hydro-3-methylenethiophene 1,2-Dioxide (**3b**).

The dibromosulfone (1.00 g, 3.3 mmoles) was dissolved in 50 ml of refluxing methanol. Sodium carbonate (0.36 g, 3.3 mmoles) and *o*-toluidine (0.37 g, 3.3 mmoles) were added to this hot solution. The reaction mixture was allowed to stir for 12 hours at room temperature under a nitrogen atmosphere. The methanol was removed under reduced pressure and the resultant solid residue was stirred in 40 ml of chloroform. The undissolved salts were removed by filtration. Evaporation of the chloroform yielded an oil. The addition of a few ml of methanol caused the oil to solidify, yielding 0.39 g of the 1,4-elimination product. An additional 0.05 g of the product was isolated on concentration of the methanol solution. Total yield was 0.44 g (54%).

5-(*o*-Methylphenyl)-1,3-dihydrothieno[3,4-*c*]pyrrole 2,3-Dioxide (**5b**).

Compound **2b** (0.10 g) was dissolved in 25 ml of acetonitrile and allowed to stir for 24 hours in the presence of air. The solvent was removed under reduced pressure. The nmr of the residue indicated a complete conversion to the oxidized analog, **5b**, mp 164-166°.

1-(*o*-Bromophenyl)-3,4-dimethylenepyrrolidine (**6c**).

5-(*o*-Bromophenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-dioxide (0.25 g) was placed in a No. 50 Kontes sublimator and decomposed at 135° under reduced pressure (0.1 mm). The exocyclic diene was collected on the cold finger of the sublimator which was cooled with crushed dry ice. The product was scraped off the cold finger as a solid which turned into a viscous liquid on warming to room temperature and readily polymerized. The diene could be stored in a freezer for months, yield 60%.

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