

Stephen D. Pastor* [1] and Edward T. Hessel

Research and Development Laboratories, Plastics and Additives Division, CIBA-GEIGY Corporation, Ardsley, New York 10502

Received September 17, 1987

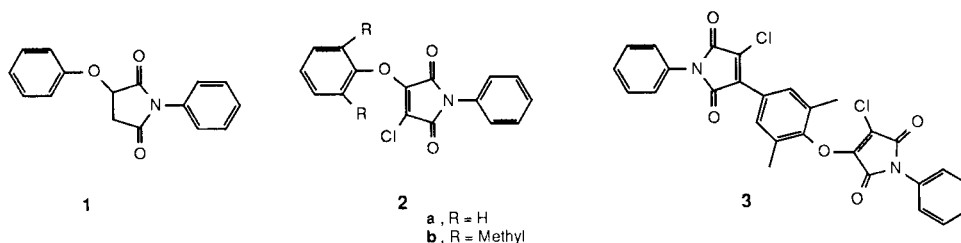
The reaction of *N*-phenylmaleimide, **4a**, with sodium 2,6-di-*t*-butylphenolate, **5a**, in dimethylsulfoxide (DMSO) resulted a complex oligomeric mixture. The dimer **8** was isolated from the reaction of the *N*-alkylmaleimide **4b** with **5a** in DMSO. The reaction of **4a** with **5a** in tetrahydrofuran (THF), which is an aprotic solvent that is known to promote ion pairing, resulted in the isolation of a low yield of **6a**. The reaction of **4a** with **5a** in the hydrogen-bonding solvent *t*-butyl alcohol gave **6a** in slightly higher yield. The *N*-alkylpyrrolidine-2,5-diones **6c-f** were obtained by the reaction of the maleimides **4c-e** with the corresponding sodium phenolate **5a-b** in *t*-butyl alcohol reaction medium. The isolated yield of product increased with the size of the *N*-alkyl substituent of the maleimide. Surprisingly, the reaction of the 2,6-dimethylphenolate **5c** with **4d** led to the isolation of the dimer **10** with the formation of a *quaternary* carbon atom. The yield of **6a** was observed to counterion dependent, increasing in the order $\text{Na}^+ < \text{Li}^+ < \text{MgBr}^+$ in *t*-butyl alcohol. The bis-maleimides **12** and **14** were obtained by the reaction of either **11** or **13** with **5d** in THF.

J. Heterocyclic Chem., **25**, 807 (1988).

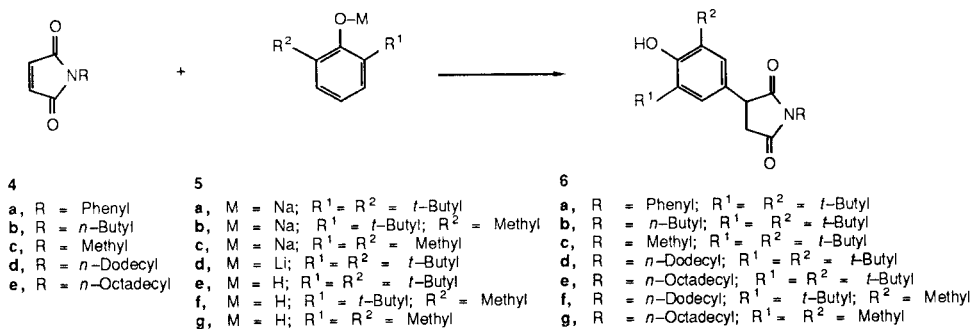
Since the initial pioneering studies of Kornblum and co-workers [2], the chemistry of ambident anions has been the focus of numerous mechanistic and synthetic studies [3]. The control of site reactivity of ambident anions provides the synthetic chemist with an important tool for the formation of carbon-carbon and carbon-heteroatom bonds.

Our study on the addition of sterically-hindered 4-hydroxybenzenethiols to 1*H*-pyrrole-2,5-diones [4], commonly known as maleimides, directed our interest to the study of the reaction of sterically-hindered phenolate

anions with both *N*-aryl- and *N*-alkylmaleimides. Renner *et al.* reported [5] that the reaction of *N*-arylmaleimides with phenol in the presence of triethylamine gave exclusively **1**, the product of 1,4-addition of the phenolic oxygen over the α,β -unsaturated double bond of the maleimide. Similarly, Relles and Schluenz reported that the reaction of *N*-phenyldichloromaleimide with phenol under basic conditions gave the phenoxy-adduct **2a** [6]. Relles and Schluenz noted, however, that the reaction of 2,6-dimethylphenol with *N*-phenylmaleimide in the presence of potas-



Scheme 1



sium carbonate using a dichloromethane reaction medium gave the expected phenoxy-derivative **2b** and the product of carbon alkylation **3**, which constitutes the only report in the literature of carbon alkylation of a phenolate anion by a maleimide. We report in this paper the reaction of sterically-hindered phenolate anions with maleimides leading to carbon alkylation of the phenolate anion.

Results and Discussion.

The reaction of the *N*-aryl-substituted maleimide **4a** with the sodium phenolate **5a** in dimethylsulfoxide (DMSO) did not give the expected Michael-addition product **6a**, but rather a complex mixture of products. The ¹H nmr spectrum of the reaction product exhibited broad peaks suggestive of an oligomeric species such as **7**. The base promoted polymerization of **4a** was reported by Bryce-Smith *et al.* [7] and Renner *et al.* [5]. Similarly, the reaction of the *N*-alkyl-substituted maleimide **4b** with **5a** gave a complex mixture of products from which the dimer **8** was isolated (4% recrystallized).

The structure of **8** rests on the following observations. In the ¹H nmr spectrum of **8**, distinct multiplets were observed for the nonequivalent methine protons of the 3,4-disubstituted pyrrolidine ring of **8**. An ABX coupling pattern was observed for the monosubstituted pyrrolidine ring. A molecular ion was observed in the mass spectrum of **8** at 512 mass units. The spectral and elemental analyses of **8** were fully in accord with the structure illustrated.

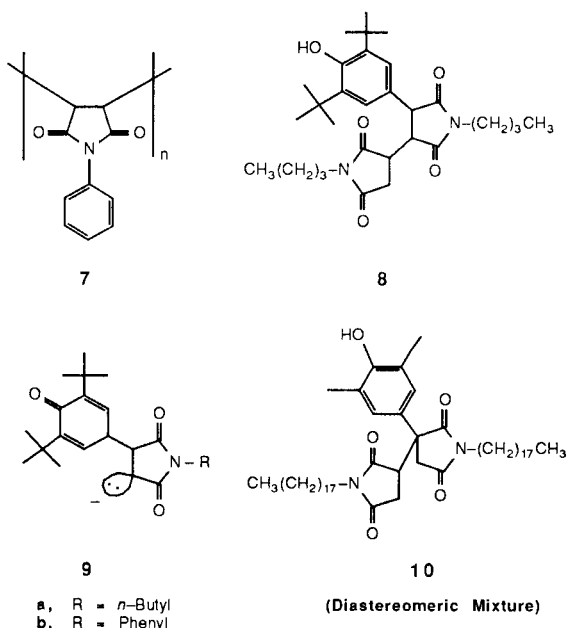
actions [9,10]. The observation of **8** suggests that in the dipolar aprotic solvent DMSO the initial adduct **9a**, which was formed by the reaction of **5a** with the maleimide **4b**, rapidly adds to another molecule of **4b** leading to the observed dimer **8**. A repetition of this process leads to oligomerization by an anionic process. A similar process with **9b** leads to the oligomerization observed in the case of the *N*-arylmaleimide.

The use of an aprotic solvent where the initial anion **9b** is less nucleophilic due to ion-pairing should enable the isolation of **6a**. Enolate [11] and phenolate [12,13] anions are known to exhibit ion-pairing and aggregation in tetrahydrofuran (THF). Indeed, **6a** was obtained by the reaction of **4a** with **5a** in THF, albeit in low yield (2% recrystallized).

It is well known that the nucleophilicity of anions can be significantly reduced by hydrogen-bonding solvents [14,15]. Similarly, the C/O ratio is known to increase in hydrogen-bonding solvents due to the shielding of the oxygen by the hydrogen-bonded solvent sphere. Reutov *et al.* warns, however, that the C/O ratio of the free ions, (C/O)_{ion}, and that of the ion pair, (C/O)_p, may be different [16]. In any case, the reaction of **4a** with **5a** in *t*-butyl alcohol solvent gave **6a** in slightly higher yield (8% recrystallized).

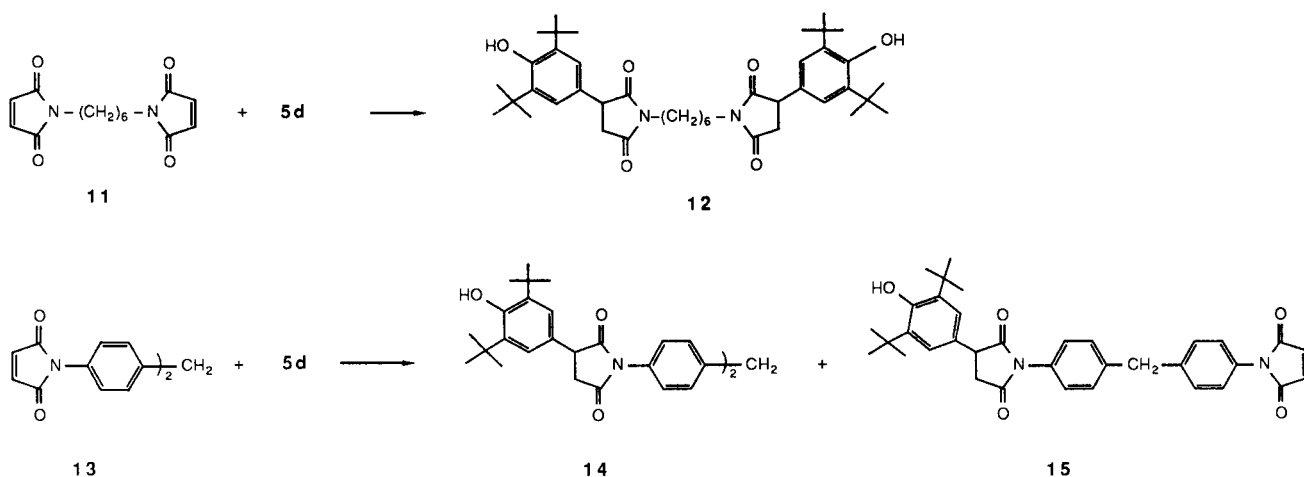
The reaction of **4b** with **5a** in *t*-butyl alcohol gave **6b** (12% recrystallized). In an analogous manner, the pyrrolidines **6c-e** were obtained by the reaction of **5a** with the corresponding maleimides **4c-e**. The isolated yield of pyrrolidine increased as the size of the *N*-alkyl substituent of the starting maleimide increased. The isolated yields ranged from 9% for **6c** (R = methyl) to 37% for **6e** (R = *n*-octadecyl). Although other explanations are possible, a decrease in the rate of oligomerization due to the increasing size of the *N*-alkyl substituent is a likely explanation.

The reaction of the *t*-butyl-methyl-substituted phenolate **5b** with **4d** in *t*-butyl alcohol proceeded in the expected manner to give **6f** (22% recrystallized). Surprisingly, the reaction of the dimethyl-substituted phenolate **5c** with **4e** did not give the expected Michael adduct **6g** but rather the diastereomeric mixture **10** with the formation of a *quaternary* carbon atom. The diastereomeric mixture could be readily separated on a preparative hplc, although the stereochemistry of the individual diastereomers was not investigated further. In any case, in the ¹H nmr spectrum of each diastereomer of **10**, two doublet resonances (AB quartet) were observed that were assigned to the nonequivalent protons in the disubstituted pyrrolidine ring. In both diastereomers the expected ABX pattern was observed for the nonequivalent protons in the monosubstituted pyrrolidine ring. The theoretical spectra calculated was consistent with the assignments made from the observed spectrum of either diastereomer of **10**. In the ¹³C nmr of the lower R_f diastereomer of **10**, a resonance was



Although ion-pairing effects have been demonstrated in dipolar aprotic solvents [8], the reactivity of anionic nucleophiles is generally enhanced in dipolar aprotic solvents due to the lack of hydrogen-bonding and ion-dipole inter-

Scheme II



observed at δ 47.1 that was assigned to the *quaternary* carbon atom in the disubstituted pyrrolidine ring. The assignments of the resonances in the ^{13}C nmr spectrum were substantiated by APT and DEPT experiments.

The question remains as to why dimerization with the formation of a *quaternary* carbon occurs in the reaction of the dimethylphenolate **5c** with **4e** but was not observed in the reactions of either **5a** or **5b**. Although it is tempting to suggest explanations based upon either steric, ion pairing, or basicity arguments of the dimethyl- or di-*t*-butyl phenolates, caution must be exercised in the interpretation of the above observations because in many of the reactions complex mixtures were obtained, for example, in the reaction of **4a** with **5a** in DMSO, and the formation of isomers similar to **10** in small quantities may have gone unnoticed. Further mechanistic studies of these reactions are warranted.

The literature [17] suggests that the yield of **6a** could be further increased by changing from the sodium to the harder lithium counterion (hard in the sense of Pearson's hard-soft acid-base theory [18]) in the phenolate. Consistent with expectations, the yield of **6a** obtained increased from 8% (recrystallized) to 36% (recrystallized) upon changing from the sodium to lithium counterion, respectively, in *t*-butyl alcohol solvent.

The increased yield of **6a** upon changing the counterion of the phenolate from sodium to the harder lithium counterion suggested that a further improvement in yield could be obtained by changing to the even harder divalent magnesium counterion. High C/O ratios have been reported in the alkylation of magnesium enolates [19]. Indeed, the use of the magnesium phenolate resulted in an increased yield, albeit small, of **6a** (41% recrystallized).

Unfortunately, the low solubility of the bismaleimides **11** and **13** precluded the use of *t*-butyl alcohol as a reaction medium. The reaction of either **11** or **13** with **5a** in THF lead to intractable mixtures. Trace yields of the desired products **12** and **14** were obtained using the lithium phenolate **5d** in THF. In the case of the reaction of **13** with **5d**, the monoaddition product **15** could be isolated by preparative hplc.

EXPERIMENTAL

All melting-points were obtained on a Thomas-Hoover melting-point apparatus and were uncorrected. The ir spectra (1% solution in sodium chloride cells) were recorded on a Perkin-Elmer Model 1300 spectrometer. The ^1H nmr spectra were recorded on a Varian Model CFT-20, XL-200, or Jeol Model FX-90Q spectrometer. The ^{13}C nmr were taken on a Varian Model XL-200 spectrometer with full proton decoupling. Theoretical spectra were calculated using the PMR simulation program [20]. The ^1H nmr and ^{13}C nmr spectra are reported in ppm relative to tetramethylsilane, where a positive sign is downfield from the standard. The ms were obtained on a Finnegan Model 8200 mass spectrometer. Preparative hplc were carried out on a Waters Prep 500A hplc.

Merck 9385 silica gel 60 (230-400 mesh) was used for flash chromatography [21]. Merck precoated (0.25 mm) silica gel 60 F-254 plates were used for tlc. Merck precoated (2.0 mm) silica gel 60 F-254 was used for preparative tlc. All solvents were dried prior to use. THF was distilled immediately prior to use from a deep-blue solution of sodium ketyl (sodium/benzophenone). The *t*-butyl alcohol was dried over 4 Å molecular sieves. Reagents were purchased from commercial laboratory supply houses. Reactions were carried out in flame-dried apparatus under a dry-nitrogen atmosphere. Elemental Analyses were performed by Analytical Research Services, CIBA-GEIGY Corporation.

3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)-1-phenylpyrrolidine-2,5-dione (**6a**).

Method A. Sodium phenolate in THF.

To a solution of **5a** prepared from 2.40 g (100 mmoles) of sodium hydride and 20.63 (100 mmoles) of **5e** in 150 ml of THF was added dropwise a solution of 17.32 g (100 mmoles) of **4a** in 50 ml of THF. The reac-

tion mixture was stirred at room temperature for 24 hours and then to the reaction mixture was added a solution of 10 ml of concentrated hydrochloric acid in 10 ml of THF. The reaction mixture was concentrated *in vacuo* and it was diluted with 150 ml of toluene. The resultant solution was extracted sequentially with 1 *M* aqueous sodium hydroxide (2 x 100 ml) and water (2 x 50 ml) and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was triturated with petroleum ether to give 0.78 g (2%) of white crystals, mp 204°; ir (chloroform): 3610 (OH), 1770, 1710 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.46 (s, (CH₃)₃C, 18 H), 2.96 (dd, 1 H), 3.39 (dd, 1 H), 4.08 (dd, 1 H), 5.21 (s, OH, 1 H), 7.08 (s, ArH, 2 H).

Anal. Calcd. for C₂₄H₂₉NO₃: C, 76.0; H, 7.7; N, 3.7. Found: C, 76.0; H, 7.8; N, 3.8.

Method B. Sodium phenolate in *t*-Butyl Alcohol.

To a solution of **5a** prepared from 2.40 g (100 mmoles) of sodium hydride and 20.63 g (100 mmoles) of **5e** in 230 ml of *t*-butyl alcohol was added portionwise 17.32 g (100 mmoles) of **4a**. The reaction mixture was stirred at room temperature for 24 hours and then to it was added a solution of 8 ml concentrated hydrochloric acid in 10 ml of *t*-butyl alcohol. The reaction mixture was diluted with 1 l of toluene and the resultant solution was extracted sequentially with aqueous 1 *M* sodium hydroxide (2 x 200 ml) and water (3 x 200 ml). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was triturated with petroleum ether and recrystallized from cyclohexane to give 3.3 g (8%) of a white solid, **6a**, identical in every respect to that prepared by method A above.

Method C. Lithium phenolate in *t*-Butyl Alcohol.

To a stirred suspension of 0.81 g (100 mmoles) of lithium hydride in 75 ml of *t*-butyl alcohol was added a solution of 20.63 g (100 mmoles) of **5e** in 100 ml of *t*-butyl alcohol. The reaction mixture was heated at 50° for 48 hours and to the resultant homogeneous reaction mixture at room temperature was added portionwise 17.32 g (100 mmoles) of **4a**. The reaction mixture was stirred at room temperature for 18 hours and then it was poured into a stirred mixture of 10 ml of concentrated hydrochloric acid and 300 ml of water. The resultant mixture was extracted with chloroform (2 x 250 ml) and the combined organic extracts were filtered through a short column of silica gel. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was recrystallized from toluene to give 13.6 (36%) of a white solid, **6a**, identical in every respect to that prepared by method A above.

Method D. Magnesium Phenolate in *t*-Butyl Alcohol.

To a stirred solution of 13.30 g (100 mmoles) ethylmagnesium bromide in 70 ml of anhydrous diethyl ether at room temperature was added dropwise a solution of 20.63 g (100 mmoles) of **5e** in 100 ml of diethyl ether. To the resulting reaction mixture was added 175 ml of *t*-butyl alcohol and then 156 ml of diethyl ether was removed by distillation. To reaction mixture at 25° was added portionwise 17.32 g (100 mmoles) of **4a**. The reaction mixture was stirred at room temperature for 24 hours and the reaction mixture was worked up as in method B above to give 15.5 g (41%) of a white solid, **6a**, identical in every respect to that prepared in method A above.

3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)-1-*n*-butylpyrrolidine-2,5-dione (**6b**).

To a solution of sodium *t*-butoxide prepared from 2.40 (100 mmoles) of sodium hydride and 135 ml of *t*-butyl alcohol was added dropwise a solution of 20.63 g (100 mmoles) of **5e** in 100 ml of *t*-butyl alcohol. The reaction mixture was stirred at room temperature for 150 minutes and to the resultant green solution was added dropwise over 120 minutes a solution of 15.31 g (100 mmoles) of **4b** in 50 ml of *t*-butyl alcohol. The reaction mixture was stirred overnight at room temperature and then to the resultant reaction mixture was 10 ml of glacial acetic acid. The reaction mixture was poured into 1.5 l of water and the mixture was extracted twice with chloroform. The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The

residue was purified by flash chromatography (3:1 heptane:toluene eluent) to give 4.25 g (12%) of a white solid, mp 109-112°; ir (carbon tetrachloride): 3600 (OH), 1770, 1690 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 0.91 (t, CH₃, 3 H), 1.41 (s, (CH₃)₃C, 18 H), 1.61 (m, 4 H), 2.75 (dd, ³J_{AX} = 6 Hz, ²J_{AB} = 20 Hz, 1 H), 3.15 (dd, ³J_{AX} = 10 Hz, ²J_{AB} = 20 Hz, 1 H), 3.59 (t, NCH₂, 2 H), 3.91 (dd, ³J_{AX} = 6 Hz, ²J_{BX} = 10 Hz, 1 H), 5.21 (s, OH, 1 H), 6.93 (s, ArH, 2 H).

Anal. Calcd. for C₂₂H₃₄NO₃: C, 73.3; H, 9.5; N, 3.9. Found: C, 73.5; H, 9.6; N, 3.8.

3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)-1-methylpyrrolidine-2,5-dione (**6c**).

By the procedure used to prepare **6b**, compound **6c** was prepared from 2.40 g (100 mmoles) of sodium hydride, 20.63 g (100 mmoles) of **5e**, and 11.11 g (100 mmoles) of **4c** in *t*-butyl alcohol solvent. The residue was recrystallized from petroleum ether to give 13.20 g of impure product. The crude product was purified by flash chromatography (1:1 heptane:ethyl acetate eluent) followed by trituration with a mixture of heptane and toluene to give 3.0 g (9%) of a white solid, mp 164-166°; ir (carbon tetrachloride): 3630 (OH), 1780, 1710 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.43 (s, (CH₃)₃C, 18 H), 2.80 (dd, ³J_{AX} = 5.5 Hz, ²J_{AB} = 19 Hz, 1 H), 3.11 (s, NCH₃, 3 H), 3.21 (dd, ³J_{BX} = 9.5 Hz, ²J_{AB} = 19 Hz, 1 H), 3.96 (dd, ³J_{AX} = 5.5 Hz, ³J_{BX} = 9.5 Hz, 1 H), 5.21 (s, OH, 1 H), 6.99 (s, ArH, 2 H).

Anal. Calcd. for C₁₉H₂₇NO₃: C, 71.7; H, 8.9; N, 4.4. Found: C, 71.6; H, 8.7; N, 4.7.

3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)-1-*n*-dodecylpyrrolidine-2,5-dione (**6d**).

By the procedure used to prepare **6b**, compound **6d** was prepared from 2.40 g (100 mmoles) of sodium hydride, 20.63 g (100 mmoles) of **5e**, and 26.54 g (100 mmoles) of **4d** in *t*-butyl alcohol solvent. The residue was purified by flash chromatography (8:2 heptane:ethyl acetate eluent) followed recrystallization from petroleum ether to give 8.15 g (17%) of a white solid, mp 66-70°; ir (methylene chloride): 3630 (OH), 1770, 1700 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 0.89 (t, CH₃, 3 H), 1.30 (s, (CH₃)₃C, 18 H), 1.43 (complex m, 20 H), 2.74 (dd, ³J_{AX} = 5 Hz, ²J_{AB} = 18 Hz, 1 H), 3.18 (dd, ³J_{BX} = 9 Hz, ²J_{AB} = 18 Hz, 1 H), 3.58 (t, NCH₂, 2 H), 3.93 (dd, ³J_{AX} = 5 Hz, ²J_{BX} = 9 Hz, 1 H), 5.21 (s, OH, 1 H), 6.96 (s, ArH, 2 H).

Anal. Calcd. for C₃₀H₄₉NO₃: C, 76.4; H, 10.5; N, 3.0. Found: C, 76.4; H, 10.1; N, 3.1.

3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)-1-*n*-octadecylpyrrolidine-2,5-dione (**6e**).

By the procedure used to prepare **6b**, compound **6e** was prepared from 2.40 g (100 mmoles) of sodium hydride, 20.63 g (100 mmoles) of **5e**, and 34.96 g (100 mmoles) of **4e** in *t*-butyl alcohol solvent. The residue was purified by dry-column chromatography (3:1 heptane:ethyl acetate eluent) followed by recrystallization from petroleum ether to give 20.5 g (37%) of a white solid, mp 65-73°; ir (carbon tetrachloride): 3650 (OH), 1780, 1710 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 0.89 (t, CH₃, 3 H), 1.27 (s, (CH₃)₃C, 18 H), 1.43 (complex m, 32 H), 2.77 (dd, ³J_{AX} = 5 Hz, ²J_{AB} = 18 Hz, 1 H), 3.21 (dd, ³J_{BX} = 8.5 Hz, ²J_{AB} = 18 Hz, 1 H), 3.58 (t, NCH₂, 2 H), 3.93 (dd, ³J_{AX} = 5 Hz, ²J_{BX} = 8.5 Hz, 1 H), 5.18 (s, OH, 1 H), 6.96 (s, ArH, 2 H).

Anal. Calcd. for C₃₆H₆₁NO₃: C, 77.8; H, 11.1; N, 2.5. Found: C, 78.0; H, 11.1; N, 2.7.

3-(3-*t*-butyl-4-hydroxy-5-methylphenyl)-1-*n*-dodecylpyrrolidine-2,5-dione (**6f**).

By the procedure used to prepare **6b**, compound **6f** was prepared from 1.20 g (50 mmoles) of sodium hydride, 8.21 g (50 mmoles) of **5f**, and 13.27 g (100 mmoles) of **4d** in *t*-butyl alcohol solvent. The residue was purified by preparative hplc (8:2 heptane:ethyl acetate eluent) to give 4.70 g (22%) of a light-yellow wax; ir (chloroform): 3590, 3450 (OH), 1775, 1700 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 0.89 (t, CH₃, 3 H), 1.27 (s, (CH₃)₃C, 9 H), 1.39 (complex m, 20 H), 2.21 (s, 3 H), 2.74 (dd, ³J_{AX} = 5 Hz, ²J_{AB} = 18 Hz, 1 H), 3.18 (dd, ³J_{BX} = 8.5 Hz, ²J_{AB} = 18 Hz, 1 H), 3.58 (t, NCH₂, 2 H), 3.88 (dd, ³J_{AX} = 5 Hz, ²J_{BX} = 8.5 Hz, 1 H), 4.91 (s, OH, 1 H),

6.77 (d, ArH, 1 H), 6.93 (d, ArH, 1 H).

Anal. Calcd. for $C_{27}H_{35}NO_3$: C, 75.5; H, 10.1; N, 3.3. Found: C, 75.4; H, 10.5; N, 3.5.

3-(3,5-Di-*t*-butyl-4-hydroxyphenyl)-4-(1-*n*-butyl-2,5-dioxopyrrolidin-3-yl)-1-*n*-butylpyrrolidine-2,5-dione (**8**).

By the procedure used to prepare **6b**, compound **8** was prepared from 2.40 g (100 mmoles) of sodium hydride, 20.63 g (100 mmoles) of **5e**, and 15.31 g (100 mmoles) of **4b** in dimethyl sulfoxide solvent. The residue was extracted with a mixture of 10 ml of toluene and 1 l of hot hexane. The hexane solution was concentrated to 150 ml and the resultant precipitated was collected by filtration. The crude product was recrystallized from cyclohexane to give 1.03 g (4%) of a white solid, mp 151-154°; ir (chloroform): 3630 (OH), 1770, 1710 (C=O) cm^{-1} ; 1H nmr (deuteriochloroform): δ 0.99 (t, CH_3 , 6 H), 1.35-1.55 (complex m, 26 H), 2.52 (dd, 1 H), 2.80 (dd, 1 H), 3.25-3.65 (complex m, 7 H), 5.21 (s, OH, 1 H) 7.21 (s, ArH, 2 H); ms m/z 512 (M^+).

Anal. Calcd. for $C_{30}H_{44}N_2O_5$: C, 70.3; H, 8.6; N, 5.5. Found: C, 70.4; H, 8.7; N, 5.4.

Diastereomers of 3-(3,5-dimethyl-4-hydroxyphenyl)-3-(1-*n*-octadecyl-2,5-dioxopyrrolidin-3-yl)-1-*n*-octadecylpyrrolidine-2,5-dione (**10**).

By the procedure used to prepare **6b**, the diastereomers of compound **10** were prepared from 2.40 g (100 mmoles) of sodium hydride, 12.22 g (100 mmoles) of **5g**, and 34.96 g (100 mmoles) of **4e** in *t*-butyl alcohol solvent. The residue was purified by preparative hplc (4:1 heptane:ethyl acetate eluent) to give two major components that were diastereomers.

The lower R_f diastereomer was isolated to give 2.90 g (7%) of a white solid; mp 84-86°; ir (methylene chloride): 3600 (OH), 1780, 1710 (C=O) cm^{-1} ; 1H nmr (deuteriochloroform): δ 0.88 (t, CH_3 , 6 H), 1.26 (complex m, 64 H), 2.22 (s, $ArCH_3$, 6 H), 2.41 (dd, $^3J_{AX} = 9.5$ Hz, $^2J_{AB} = 18$ Hz, 1 H), 2.91 (dd, $^3J_{BX} = 6$ Hz, $^2J_{AB} = 18$ Hz, 1 H), 3.03 (d, $^2J_{AB} = 17.5$, 1 H), 3.35 (dd, $^3J_{AX} = 9.5$ Hz, $^2J_{BX} = 6$ Hz, 1 H), 3.45 (t, NCH_2 , 2 H), 3.51 (t, NCH_2 , 2 H), 3.85 (d, $^2J_{AB} = 17.5$ Hz, 1 H), 4.38 (s, OH, 1 H), 7.02 (s, ArH, 2 H); ^{13}C nmr (deuteriochloroform): δ 17.5, 19.6, 22.2, 26.3, 27.2, 28.8, 28.9, 29.4, 31.5, 32.9, 38.7, 38.8, 41.1, 46.2, 47.1, 124.0, 126.3, 131.5, 151.9, 174.6, 175.1, 177.4, 178.8.

Anal. Calcd. for $C_{52}H_{88}N_2O_5$: C, 76.0; H, 10.8; N, 3.4. Found: C, 75.9; H, 10.8; N, 3.5.

The higher R_f diastereomer was isolated to give 2.30 g (6%) of a white solid, mp 90-94°; ir (methylene chloride): 3610 (OH), 1780, 1710 (C=O) cm^{-1} ; 1H nmr (deuteriochloroform): δ 0.88 (t, CH_3 , 6 H), 1.26 (complex m, 64 H), 2.22 (s, $ArCH_3$, 6 H), 2.55 (dd, $^3J_{AX} = 5.5$ Hz, $^2J_{AB} = 19$ Hz, 1 H), 2.77 (dd, $^3J_{BX} = 9$ Hz, $^2J_{AB} = 19$ Hz, 1 H), 3.10 (d, $^2J_{AB} = 18.5$, 1 H), 3.28 (d, $^2J_{AB} = 18.5$ Hz, 1 H), 3.42 (t, NCH_2 , 2 H), 3.54 (t, NCH_2 , 2 H), 3.62 (dd, $^3J_{AX} = 5.5$ Hz, $^2J_{BX} = 9$ Hz, 1 H), 4.78 (s, OH, 1 H), 7.02 (s, ArH, 2 H).

Anal. Calcd. for $C_{52}H_{88}N_2O_5$: C, 76.0; H, 10.8; N, 3.4. Found: C, 76.2; H, 11.2; N, 3.4.

1,6-Bis[3,5-di-*t*-butyl-4-hydroxyphenyl]-2,5-dioxopyrrolidin-1-yl]hexane (**12**).

To a solution of 14.95 g (72 mmoles) of **52** in 200 ml of THF at 5° was added dropwise 45 ml (72 mmoles) of a 1.6 *M* solution of *n*-butyllithium in hexane. After stirring for 15 minutes at room temperature, 10.0 g (36 mmoles) of **11** [22] was added slowly over a period of 4 hours using a powder-addition funnel. After the addition was complete a solution of 2.5 g of concentrated hydrochloric acid in 10 ml of THF was added to the reaction mixture. The reaction mixture was filtered to remove insolubles and the solvent was removed *in vacuo*. The residue was purified by preparative hplc (7:3 heptane:ethyl acetate eluent) to give 0.3 g (1%) of a light yellow solid; mp 190-193°; ir (methylene chloride): 3630 (OH), 1770, 1700 (C=O) cm^{-1} ; 1H nmr (deuteriochloroform): δ 1.46 (complex m, 44 H), 2.77 (dd, 2 H), 3.19 (dd, 2 H), 3.58 (t, NCH_2 , 4 H), 3.40 (dd, 2 H), 5.21 (s, OH, 2 H), 6.96 (s, ArH, 4 H); ms m/z 688 (M^+).

Anal. Calcd. for $C_{42}H_{60}N_2O_5$: C, 73.2; H, 8.4; N, 4.1. Found: C, 73.5; H, 8.4; N, 4.2.

Reaction of **5e** with **13**.

By the procedure used to prepare **6a** method A, the diadduct **14** and monoadduct **15** were prepared from 0.80 g (100 mmoles) of lithium hydride, 20.63 g (100 mmoles) of **5e**, and 17.90 g (50 mmoles) of **13** in THF. The residue was purified by preparative hplc (3:2 heptane:ethyl acetate) to give two major components.

The higher R_f component was isolated to give 1.00 g (3%) of a light yellow solid, **14**, mp 135-140° ir (methylene chloride): 3640 (OH), 1780, 1720 (C=O) cm^{-1} ; 1H nmr (deuteriochloroform): δ 1.49 (s, $(CH_3)_3C$, 36 H), 3.01 (dd, 2 H), 3.39 (dd, 2 H), 4.11 (s, $ArCH_2Ar$, 2 H), 4.13 (partially obscured dd, 2 H), 5.27 (s, OH, 2 H), 7.11 (s, ArH, 4 H), 7.33 (m, ArH, 8 H).

Anal. Calcd. for $C_{49}H_{58}N_2O_5$: C, 76.3; H, 7.6; N, 3.6. Found: C, 76.2; H, 7.8; N, 3.7.

The lower R_f component was isolated to give 1.50 g (5%) of a light yellow solid, **15**, mp 120-125°; ir (methylene chloride): 3640 (OH) cm^{-1} ; 1H nmr (deuteriochloroform): δ 1.47 (s, $(CH_3)_3C$, 18 H), 3.01 (dd, 2 H), 3.39 (dd, 1 H), 4.09 (s, $ArCH_2Ar$, 2 H), 4.11 (partially obscured dd, 1 H), 5.27 (s, OH, 1 H), 6.89 (s, vinyl-H, 2 H), 7.11 (s, ArH, 2 H), 7.33 (m, ArH, 8 H).

Anal. Calcd. for $C_{35}H_{36}N_2O_5$: C, 74.5; H, 6.4; N, 4.9. Found: C, 74.4; H, 6.5; N, 4.9.

Acknowledgment.

The authors wish to thank CIBA-GEIGY Corporation for support and permission to publish this work. S. D. P. wishes to thank Prof. Bruce Ganem for stimulating discussions and Carolyn F. Windus for the artwork.

REFERENCES AND NOTES

- [1] Author to whom all correspondence should be addressed.
- [2a] N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Ifland, *J. Am. Chem. Soc.*, **77**, 6269 (1955); [b] N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *J. Am. Chem. Soc.*, **78**, 1497 (1956); [c] N. Kornblum and R. Seltzer, *J. Am. Chem. Soc.*, **83**, 3668 (1961); [d] N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Am. Chem. Soc.*, **85**, 1141 (1963); [d] N. Kornblum, R. Seltzer, and P. Haberfield, *J. Am. Chem. Soc.*, **85**, 1148 (1963).
- [3] For a review see: [a] H. O. House, "Modern Synthetic Reactions", Benjamin, Menlo Park, 1972, pp 520-530; [b] F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry", Part B, 2nd Ed, Plenum, New York, 1983, pp 21-31; [c] O. A. Reutov, I. P. Beletskaya, and A. L. Kurts, "Ambident Anions", Consultants Bureau (Plenum), New York, 1983.
- [4] S. D. Pastor, E. T. Hessell, P. A. Odorisio, and J. D. Spivack, *J. Heterocyclic Chem.*, **22**, 1195 (1985).
- [5] A. Renner, I. Forgo, W. Hofmann, and K. Ramsteiner, *Helv. Chim. Acta*, **61**, 1443 (1978).
- [6] H. M. Relles and R. W. Schlunz, *J. Org. Chem.*, **37**, 3637 (1972).
- [7] D. Bryce-Smith, A. Gilbert, I. S. McColl, and P. Yianni, *J. Chem. Soc., Chem. Commun.*, 951 (1984).
- [8] H. E. Zaugg, J. F. Ratajczyk, J. E. Leonard, and A. D. Schaefer, *J. Org. Chem.*, **37**, 2249 (1972).
- [9] G. W. Klumpp, "Reactivity in Organic Chemistry", Wiley-Interscience, New York, 1982, p 187.
- [10] D. K. Bohme and L. B. Young, *J. Am. Chem. Soc.*, **92**, 7354 (1970).
- [11] L. M. Jackman and N. M. Szeverenyi, *J. Am. Chem. Soc.*, **99**, 4954 (1977).
- [12] W. T. Reichle, *J. Org. Chem.*, **37**, 4254 (1972).
- [13] S. D. Pastor and E. T. Hessell, *J. Organomet. Chem.*, **328**, 263 (1987).
- [14] A. L. Kurts, A. Masias, N. K. Genkina, I. P. Beletskaya, and O. A. Reutov, *Dokl. Akad. Nauk. SSSR (Engl. Transl.)*, **187**, 595 (1969); *Chem. Abstr.*, **71**, 112364 (1969).
- [15] F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry", Part A, 2nd Ed, Plenum, New York, 1983, p 268.
- [16] Ref [2c] pp 134-146 and references therein.
- [17] D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Am. Chem. Soc.*, **80**, 1391 (1958).

[18] For a discussion in regard to ambident anion chemistry, see: [a] Ref [2c] and references therein; [b] I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", John Wiley and Sons, New York, 1976.

[19] G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

[20] The pmr software program (The algorithm was written by M. Saunders, Yale University) is available from Serena Software, Bloomington, IN 47402-3076.

[21] C. W. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

[22] J. K. Stille and L. Plummer, *J. Org. Chem.*, **26**, 4026 (1961).