crease in the order HBPT > HEPT > HMPT for hexaalkylphosphoric triamides and TDPT > TCyPT for trialkylphosphoric triamides. Also the nature of the ligand plays a role, probably in connection with its coordinating ability; thus, pyridine *N*-oxides appear to be more effective than phosphoric amides.

As anticipated above, the acidity of the aqueous phase is another important parameter to be considered. In fact, an increase of the H_2SO_4: catalyst ratio produces a remarkable increase of the overall yields, likely as a result of neutralization of anionic peroxo complexes in the aqueous phase making the extraction by the ligand more effective. At the same time, however, the selectivities in epoxide tend to drop, owing to the acid-catalyzed hydrolytic cleavage of the oxirane ring to diol.[12] This is particularly severe for cyclohexene oxide, whereas *trans*-2-octene oxide appears to be more resistant to ring-opening reactions.

Conclusions

The data reported in the preceding section clearly demonstrate the synthetic value of the two-phase system. In fact, a viable procedure has been established which may be employed for many other oxidative transformations. Moreover, in such a simple system, where the nature of the oxidizing species is fairly well understood, it should be possible to improve the efficiency by acting on the characteristics of the extracting agents. Indeed, a relevant point worthy of further studies is connected with the relative importance of the two salient features of the ligands employed, i.e., their lipophilicity and their coordinating ability, respectively, in determining the most effective oxidizing conditions.

Finally, from a mechanistic point of view, it is evident that the success of monodentate ligands in carrying out these oxidations gives further support to the suggestions of other authors and ourselves for an "external"[2b,3a,9] oxygen transfer from the peroxo metal species rather than an "internal" oxidation of the coordinated nucleophile via preliminary displacement of the originally bound ligand.[13]

Experimental Section

Materials. *p*-Chlorophenyl methyl sulfide was prepared by methylation of the commercially available thiol. Cyclohexene and *trans*-2-octene were purified by distillation. 1,2-Dichloroethane was obtained by standard procedures from highly pure commercial samples.

Hexaalkylphosphoric triamides were synthesized according to literature methods;[14] the products were purified by low pressure (4–5 atm) liquid chromatography on silica gel (>0.063 mm). Trialkylphosphoric triamides were obtained by condensation of the corresponding amines with $Cl_3P(O)$ and the products purified by chromatography. The pyridine *N*-oxide derivatives were synthesized by oxidation of the corresponding pyridines with *m*-chloroperbenzoic acid.

All other chemicals were used as received.

Procedures. In a typical run 1 mL of an aqueous solution of $Na_2MoO_4 \cdot 2H_2O$ (0.5 mmol) and H_2SO_4 (0.3 mmol) was added to a dichloroethane solution (25 mL) containing cyclohexene (100 mmol) and the ligand (1.0 mmol) in a glass reactor mantained at 50 °C. Then 1 mL of H_2O_2 70% w/v (20.5 mmol) was added under vigorous stirring.

After 5 h the two phases were separated and the amount of unreacted H_2O_2 determined by iodometric titration. In all cases comparison of the products in the organic phase with authentic samples confirmed their identity.

The yields were obtained by GLC analysis (internal standard) on an OV-101 3% on Chromosorb WAW-DMCS (1.5 m) column with a Varian 3700 instrument equipped with a Varian CDS 401 or a Perkin-Elmer Sigma 10 integrator.

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Registry No. DBTP, 132-65-0; HMPT, 680-31-9; HBPT, 22421-85-8; HEPT, 2622-07-3; TCyPT, 31160-09-5; TDPT, 7261-34-9; *p*-ClC_6H_4SMe, 123-09-1; *trans*-$CH_3CH{=}CH(CH_2)_4CH_3$, 13389-42-9; *p*-$ClC_6H_4S(O)Me$, 934-73-6; $Na_2Mo(VI)O_4$, 7631-95-0; $Na_2W(VI)O_4$, 13472-45-2; *p*-Cl-C_6H_4-$S(O)_2Me$, 98-57-7; $CH_3(CH_2)_4(CH(OH))_2CH_3$, 20653-90-1; cyclohexene, 110-83-8; dibenzothiophenoxide, 1013-23-6; cyclohexene oxide, 286-20-4; 2,3-epoxyoctane, 3234-26-2; 4-(3-phenylpropyl)pyridine *N*-oxide, 84824-92-0; 4-nonylpyridine *N*-oxide, 96689-75-7; dibenzothiophene dioxide, 1016-05-3; 1,2-cyclohexanediol, 931-17-9.

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Effect of Different Dialkylamino Groups on the Regioselectivity of Lithiation of O-Protected 3-(Dialkylamino)phenols

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The lithiation of 3-(dialkylamino)phenols (dialkylamino = 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, and dimethylamino) O-protected by a methyl, a methoxymethyl, or a carbamoyl group (X) has been studied. The results demonstrate that the site of lithiation depends on the relative ortho-directing capacities of both the dominant OX and the dialkylamino groups. With the moderate ortho-directing methoxy group the lithiation occurs exclusively (**1b** and **1c**) or predominantly (**1a**) ortho to both substituents. The site of lithiation of the *N*,*N*-dialkyl-3-(methoxymethoxy)anilines **4a–c** depends on the solvent used and on the type of dialkylamino group. With a strong ortho-directing group such as carbamoyloxy (**9a,b,d**) the lithiation takes place at the least hindered ortho position. In the absence of an electrophile the lithiated carbamates **9a,d** and **10a,d** rearrange stereospecifically to the corresponding benzamides **13a,d** and **14a,d**, respectively.

Heteroatom-facilitated lithiation of aromatic compounds is a convenient route to polysubstituted aromatics. Because of the high selectivity and the wide range of further transformations the process is often used in organic syn-

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thesis.[1-3] In addition to studies on the ortho-directing capacities of different heteroatom-bearing substituents, the regioselectivity of the metalation of nonequivalent ortho positions has been investigated.[4,5]

Two principally different mechanisms have been postulated for the ortho lithiation of aromatics, namely the coordination and the acid–base mechanisms.[6] According to the coordination mechanism the first step of the reaction comprises the formation of a complex between the heteroatom of a substituent of the aromatic ring and the organolithium reagent. In the acid–base mechanism that was postulated as the predominant mechanism for the lithiation of aromatics with electron-withdrawing substituents, a protophilic attack of the carbanionic part of a lithium reagent takes place at a sufficiently acidic ortho hydrogen atom. The latter mechanism is often postulated when an organolithium–*N,N,N',N'*-tetramethylethylenediamine (TMEDA) complex is used as the lithiating agent. Because of the non-Lewis-acid character of the organolithium–TMEDA complex lithiation occurs preferentially at the most acidic proton of the substrate.[4,6]

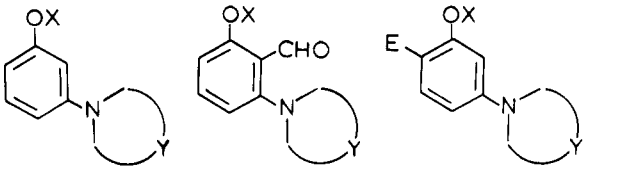
In the course of our work on the synthesis of analogues of the antitumor antibiotic mitomycin C[7] we have studied ortho lithiation and subsequent carbon–carbon bond formation at the position ortho to both a masked hydroxyl group and different dialkylamino groups of 3-(dialkylamino)phenols.

In the lithiation of phenols, methyl,[1] THP (tetrahydropyran),[1] and methoxymethyl[1,5,8-12] groups are widely used for O-protection. More recently, the use of the *O*-carbamoyl group ($CONEt_2$) has been reported.[13] In the literature only two examples of the lithiation of O-protected 3-(dialkylamino)phenols have been reported. Slocum and Jennings[4] have found that the lithiation of 3-*methoxy-N,N*-dimethylaniline by *n*-butyllithium (*n*-BuLi) in diethyl ether occurs exclusively ortho to both the dimethylamino and the methoxy groups. Addition of 1 equiv of TMEDA to the reaction mixture only slightly influenced the regioselectivity of the reaction, predominantly leading to lithiation ortho to both the dimethylamino and the methoxy groups.[4] However, recently Ronald and Winkle[5,12] have stated that the site of lithiation of 3-(*methoxymethoxy*)-*N,N*-dimethylaniline depends on the solvent used and the type of lithium reagent. With sterically hindered metalating agents such as *t*-BuLi and in electron-donating solvents such as diethyl ether, lithiation at the least hindered ortho position relative to the methoxymethoxy group is favored. However, with *n*-BuLi in *n*-hexane 3-(methoxymethoxy)-*N,N*-dimethylaniline is lithiated almost exclusively ortho to both substituents.

To our knowledge the effect of *other dialkylamino groups* on the lithiation of O-substituted 3-(dialkylamino)phenols has never been investigated. In this paper we report a systematic study on the rate and regioselectivity of lithiation of 3-(dialkylamino)phenols O-protected by a methyl, methoxymethyl, or carbamoyl group. The relative ortho-directing abilities of dialkylamino groups will also be discussed.

Results

As model compounds we have selected 3-(1-pyrrolidinyl)-, 3-(1-piperidinyl)-, 3-(4-morpholinyl)-, and 3-(dimethylamino)phenols O-protected by methyl, methoxymethyl, and diethylcarbamoyl groups. In most reactions *N,N*-dimethylformamide (DMF) was used as an electrophile because of the simple method of identification of the reaction products by ^1H NMR spectroscopy and a simple separation procedure of the isomers. Besides, the reaction of an organolithium species with DMF is relatively fast and clean and can be carried out with a large excess of the electrophile. The assignments of the structures of isomeric products are based on the analysis of the aromatic protons in the ^1H NMR spectra. All compounds obtained as the result of lithiation at the 2-position, ortho to both substituents, show a characteristic triplet corresponding to the H-5 proton.[14] The products of lithiation ortho to the OX and para to the dialkylamino group exhibit a doublet for the H-5 proton.[14]



1, X=CH_3
4, X=CH_2OCH_3
9, X=$CONEt_2$

2, X=CH_3
5, X=CH_2OCH_3

3, X=CH_3, E=CHO
6, X=CH_2OCH_3, E=CHO
7, X=CH_2OCH_3, E=CH_3
10, X=$CONEt_2$, E=Me_3Si
11, X=$CONEt_2$, E=CHO
12, X=H, E=CHO

a: Y=$(CH_2)_2$; **b**: Y=$(CH_2)_3$; **c**: Y=CH_2OCH_2 ; **d**: Y=H,H

Lithiation of *N,N*-Dialkyl-3-methoxyanilines. We found that the lithiation of *N,N*-dialkyl-3-methoxyanilines **1a–c** required long reaction times (20 h), the use of diethyl ether as a solvent, and elevated reaction temperatures to achieve moderate yields of products (50–67%) (Table I).

Lithiation of 1-(3-methoxyphenyl)pyrrolidine (**1a**) and subsequent reaction with DMF gave a crude reaction product in which two aldehydes were present in a ratio of about 1:2. The two aldehydes were isolated after chromatography as two crystalline products (**2a** and **3a**). The ^1H NMR spectrum of the major product **2a** showed besides a singlet at δ 10.44 (CHO, 1 H) a characteristic triplet at δ 7.27 of the H-5 proton.[14] In the ^1H NMR spectrum of the minor product **3a** a singlet at δ 10.13 (CHO) and a doublet at δ 7.70 of the H-5 proton[14] were observed. On the basis of these and other spectral data we concluded that the major reaction product is 2-methoxy-6-(1-pyrrolidinyl)benzaldehyde (**2a**) and the minor product is 2-methoxy-4-(1-pyrrolidinyl)benzaldehyde (**3a**). This means that the lithiation of **1a** using *n*-BuLi in diethyl ether occurs at both positions ortho to the methoxy group, although the lithiation ortho to both the methoxy and the 1-pyrrolidinyl group prevails.

The lithiation of the other *N,N*-dialkyl-3-methoxyanilines, viz., 1-(3-methoxyphenyl)piperidine (**1b**) and 4-(3-methoxyphenyl)morpholine (**1c**), was carried out under the same conditions. In the ^1H NMR spectrum of the crude reaction products obtained after the lithiation of **1b**

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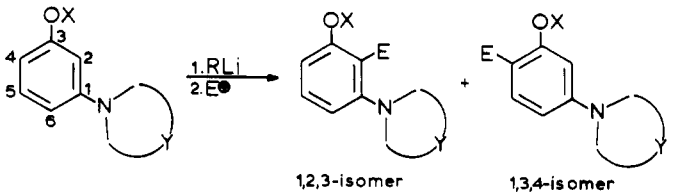
(14) The term "the H-5 proton" used refers to the 5-position of the aromatic ring of the starting anilines and to the meta position to both the OX and the dialkylamino groups in the obtained products.

Table I. Metalation Data for Masked 3-(Dialkylamino)phenols



substrate	X	Y	conditions[a]	electrophile (E)	% yield (compd) 1,2,3-isomer	1,3,4-isomer
1a	Me	$(CH_2)_2$	*n*-BuLi, Et_2O, reflux, 20 h	DMF (CHO)	35 (**2a**)	15 (**3a**)
1b	Me	$(CH_2)_3$	*n*-BuLi, Et_2O, reflux, 20 h	DMF (CHO)	60 (**2b**)	
1c	Me	CH_2OCH_2	*n*-BuLi, Et_2O, reflux, 20 h	DMF (CHO)	67 (**2c**)	
4a	CH_3OCH_2	$(CH_2)_2$	*n*-BuLi, *n*-hexane, 24 h, rt	DMF (CHO)	3 (**5a**)	24 (**6a**)
			n-BuLi, Et_2O, reflux, 2 h	DMF (CHO)		60 (**6a**)
			n-BuLi–TMEDA, *n*-hexane, 2 h, rt	DMF (CHO)	28 (**5a**)	38 (**6a**)
			n-BuLi, Et_2O, 3 h, reflux	MeI (Me)		78 (**7a**)
4b	CH_3OCH_2	$(CH_2)_3$	*n*-BuLi, *n*-hexane, 24 h, rt	DMF (CHO)	72 (**5b**)	
			n-BuLi, Et_2O, 2 h, rt	DMF (CHO)	33 (**5b**)	55 (**6b**)
4c	CH_3OCH_2	CH_2OCH_2	*n*-BuLi, *n*-hexane, 2 h, rt	DMF (CHO)	38 (**5c**)	26 (**6c**)
			n-BuLi, Et_2O, 2 h, rt	DMF (CHO)	18 (**5c**)	58 (**6c**)
9a	$CONEt_2$	$(CH_2)_2$	*sec*-BuLi–TMEDA, THF, −78 °C, 1 h	Me_3SiCl (Me_3Si)		96 (**10a**)
				DMF (CHO)		30[b] (**11a**)
9b	$CONEt_2$	$(CH_2)_3$	*sec*-BuLi–TMEDA, THF, −78 °C, 1 h	DMF (CHO)		17[c] (**11b**)
9d	$CONEt_2$	H,H	*sec*-BuLi–TMEDA, THF, −78 °C, 1 h	Me_3SiCl (Me_3Si)		93 (**10d**)
				DMF (CHO)		30[d] (**11d**)

[a] Room temperature denoted by rt. [b] In addition **12a** was isolated in a yield of 52%. [c] In addition **12b** was isolated in a yield of 39%. [d] In addition **12d** was isolated in a yield of 48%.

and **1c** and the reaction with DMF, only one absorption was observed at δ 10.27 and 10.38, respectively. The crystalline compounds **2b** and **2c** showed in their ^1H NMR spectrum a triplet of the H-5 proton[14] at δ 7.39 and 7.44, respectively. This confirmed the formation of 2-methoxy-6-(1-piperidinyl)benzaldehyde (**2b**) and 2-methoxy-6-(4-morpholinyl)benzaldehyde (**2c**).

Lithiation of *N,N*-Dialkyl-3-(methoxymethoxy)anilines. 1-[3-(Methoxymethoxy)phenyl]pyrrolidine (**4a**), 1-[3-(methoxymethoxy)phenyl]piperidine (**4b**), and 4-[3-(methoxymethoxy)phenyl]morpholine (**4c**) were lithiated in diethyl ether or *n*-hexane with *n*-BuLi (Table I). As expected the methoxymethoxy group, being a stronger activating and ortho-directing group compared with the methoxy group, accelerated the lithiation in diethyl ether considerably.

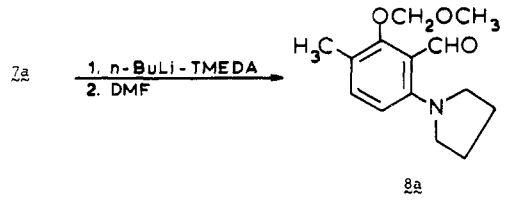
Compound **4b** was selectively lithiated ortho to both substituents when the reaction was carried out in *n*-hexane. The ^1H NMR spectrum of the crystalline product obtained after the lithiation of **4b** in *n*-hexane and reaction with DMF showed a singlet at δ 10.30 and a triplet at δ 7.37 of the H-5 proton.[14] This confirmed the formation of 2-(methoxymethoxy)-6-(1-piperidinyl)benzaldehyde (**5b**), which was isolated in a yield of 72%. When the lithiation of **4b** was carried out in diethyl ether the ^1H NMR spectrum of the crude reaction mixture showed two singlets at δ 10.20 and 10.30 (~3:2 ratio), suggesting the formation of two benzaldehydes. After column chromatography **5b** and the isomeric 2-(methoxymethoxy)-4-(1-piperidinyl)-benzaldehyde (**6b**) were obtained. Although the yield of **6b** prevailed over **5b**, the relative ratio of **6b** to **5b** was smaller than reported for the lithiation of 3-(methoxymethoxy)-*N,N*-dimethylaniline using *n*-BuLi in diethyl ether.[5,12]

Surprisingly different from the results of lithiation of **4b** and also from those reported by Ronald and Winkle[5,12] for 3-(methoxymethoxy)-*N,N*-dimethylaniline were the results obtained for the lithiation of the pyrrolidine derivative **4a**. The reaction was slow so that even in diethyl ether the lithiation of **4a** required reflux temperature. The ^1H NMR spectrum of the isolated product after the lithiation of **4a** in diethyl ether and the reaction with DMF exhibited a singlet at δ 10.19 of an aldehyde and a doublet at δ 7.73. The spectrum showed a similar pattern of the aromatic protons as the ^1H NMR spectrum of **6b**. Therefore we concluded that the lithiation of **4a** in diethyl ether occurs exclusively at the least hindered ortho position relative to the methoxymethoxy group. This conclusion was confirmed by the lithiation of **4a** in diethyl ether followed by reaction with methyl iodide. 1-[3-(Methoxymethoxy)-4-methylphenyl]pyrrolidine (**7a**) was obtained in a yield of 78%. The ^1H NMR spectrum of **7a** also showed a doublet of the H-5 proton at δ 6.96.

When the lithiation of **4a** was carried out in *n*-hexane, followed by reaction with DMF, a mixture of both isomeric benzaldehydes (8:1 ratio) was obtained in a total yield of 27%. The major product was shown to be 2-(methoxymethoxy)-4-(1-pyrrolidinyl)benzaldehyde (**6a**). The ^1H NMR spectrum of the minor product showed the characteristic absorption at δ 10.48 and a triplet at δ 7.26, which confirmed the structure of 2-(methoxymethoxy)-6-(1-pyrrolidinyl)benzaldehyde (**5a**). Therefore even in a noncoordinating solvent the lithiation of **4a** with *n*-BuLi occurs preferentially at the least hindered 4-position.

The use of the *n*-BuLi–TMEDA complex for the lithiation of **4a** in *n*-hexane increased the rate of the reaction and improved the relative **5a**:**6a** ratio. The reaction of **4a** with *n*-BuLi–TMEDA for 2 h followed by addition of DMF yielded a mixture of the benzaldehydes **5a** and **6a** (2:3 ratio) in a total yield of 66%.

In order to investigate the relative reactivity of both positions ortho to the methoxymethoxy group in **4a**, the 4-position was blocked by a methyl group. Attempts to lithiate **7a** with *n*-BuLi in diethyl ether or *n*-hexane were unsuccessful. However, after lithiation of **7a** in tetrahydrofuran for 1 h at room temperature and the reaction with DMF, 2-(methoxymethoxy)-3-methyl-6-(1-pyrrolidinyl)benzaldehyde (**8a**) was obtained in a yield of 15%. Higher yields of **8a** were obtained with the *n*-BuLi–TMEDA complex in *n*-hexane. Even under these conditions the lithiation was relatively slow. In addition to 30–44% of **8a** a substantial amount of 2-methyl-5-(1-



8a

pyrrolidinyl)phenol was obtained (30–15%) as a result of the competing cleavage of the phenyl methoxymethyl ether by the organolithium reagent.

Reaction of the morpholine derivative **4c** with *n*-BuLi in either diethyl ether or *n*-hexane led to a mixture of isomeric benzaldehydes (**5c** and **6c**). Compared with the lithiation of **4a** or **4b** by *n*-BuLi in *n*-hexane, the reaction of **4c** is very fast. The fast and nonselective course of the lithiation of **4c** in *n*-hexane might be due to the presence of the oxygen atom of the morpholinyl group, which can coordinate with the lithium reagent, leading, during the metalation, to a mixture of lithium species.

Lithiation of *N,N*-Dialkyl-3-[(diethylcarbamoyl)oxy]anilines. *N,N*-Dialkyl-3-[(diethylcarbamoyl)oxy]anilines **9a**, **9b**, and **9d** with 1-pyrrolidinyl, 1-piperidinyl, and dimethylamino groups were obtained in yields of 75%, 82%, and 72%, respectively, by reaction of the corresponding phenols with sodium hydride, followed by reaction with diethylcarbamoyl chloride.

Lithiation of these *N,N*-dialkyl-3-[(diethylcarbamoyl)oxy]anilines **9a**, **9b**, and **9d** was carried out under conditions applied by Sibi and Snieckus[13] (*sec*-BuLi, TMEDA, THF, −78 °C). Subsequently the lithium compounds were reacted with chlorotrimethylsilane (Me_3SiCl) or with DMF. The results are shown in Table I.

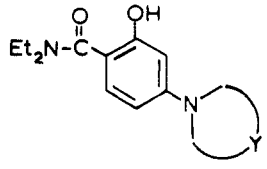
The lithiation of 3-(1-pyrrolidinyl)phenyl diethylcarbamate (**9a**), carried out during 1 h, followed by reaction with Me_3SiCl, yielded a crystalline product. The ^1H NMR spectrum of the crude product showed characteristic absorptions at δ 0.0 (s, 9 H) of the Me_3Si group and at δ 7.03, 6.17, and 5.99 of the aromatic protons. In particular the presence of the doublet at δ 7.03 for the absorption of the H-5 proton[14] confirmed the formation of 5-(1-pyrrolidinyl)-2-(trimethylsilyl)phenyl diethylcarbamate (**10a**). An analogous reaction of **9d** gave 5-(dimethylamino)-2-(trimethylsilyl)phenyl diethylcarbamate (**10d**) in a yield of 93%.

Compounds **9a**, **9b**, and **9d**, after 1 h of lithiation under standard conditions, were also reacted with DMF. Two different types of aldehydes were isolated in each of the reactions. The ^1H NMR spectra of the benzaldehydes in which the *O*-carbamoyl group was still present showed the typical doublet of the H-5 proton[14] at $\delta \sim 7.7$ as expected for the 5-(dialkylamino)-2-formylphenyl diethylcarbamates **11**. The other products isolated were identified as 4-(dialkylamino)-2-hydroxybenzaldehydes **12**. Such a hydrolysis of 2-formylphenyl carbamates to salicylaldehydes was also reported by Sibi and Snieckus.[13]

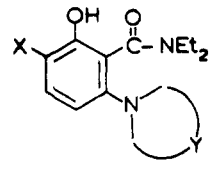
On the basis of the above results we have concluded that the lithiation of compounds **9** using the *sec*-BuLi–TMEDA complex in tetrahydrofuran at −78 °C occurs exclusively at the least-hindered ortho position to the *O*-carbamoyl group.

It was previously reported by Sibi and Snieckus[13] that in the absence of electrophiles lithiated aryl carbamates thermally rearrange to 2-hydroxybenzamides. The reaction probably occurs as an ortho anion-induced O → C 1,3-migration of the carbamoyl group and is an anionic equivalent of the Fries rearrangement.[13]

We applied the Snieckus[13] procedure to prepare *N,N*-diethyl-2-hydroxybenzamides substituted with a dialkylamino group. Thus after 1 h of lithiation of **9a** and **9d**, the lithium compound formed was allowed to warm to room temperature during 3 h. The isolated products were identified as the 4-(dialkylamino)-*N,N*-diethyl-2-hydroxybenzamides (**13a** and **13d**).



13



14, X=Me3Si
15, X=H

a: Y=$(CH_2)_2$; d: Y=H,H

In order to ascertain the relative reactivity of both ortho hydrogens to the *O*-carbamoyl group of the 3-(dialkylamino)phenyl diethylcarbamates, the lithiation of **10a** and **10d**, in which the position para to the dialkylamino group was blocked by Me_3Si, was carried out with the *sec*-BuLi–TMEDA complex under standard conditions.

Reaction of **10a** for 3 h at −78 °C, followed by 3 h at room temperature, and subsequent hydrolysis gave a white crystalline product. The ^1H NMR spectrum showed a singlet at δ 7.62, an AB quartet at δ 7.18 and 6.26, and a singlet of the Me_3Si group. The crude product underwent partial desilylation during column chromatography, but 57% of the product was isolated as *N,N*-diethyl-2-hydroxy-6-(1-pyrrolidinyl)-3-(trimethylsilyl)benzamide (**14a**). The desilylated product (34%) was recovered from the column by elution with methanol. On the basis of the spectral data the formation of *N,N*-diethyl-2-hydroxy-6-(1-pyrrolidinyl)benzamide (**15a**) was proven.

The analogous reaction of **10d** (1 h of lithiation) yielded after purification 89% of *N,N*-diethyl-6-(dimethylamino)-2-hydroxy-3-(trimethylsilyl)benzamide (**14d**). Desilylation of **14d** on silica gel was not observed.

Discussion

It is dangerous to draw conclusions about the relative directing effects of the various dialkylamino substituents because the lithiation reactions of compounds **1**, **4**, and **9** have been carried out at temperatures varying from −78 to +37 °C. Therefore it is possible that some products may have been formed under conditions of thermodynamic control and others under conditions of kinetic control. Although it is unlikely that at −78 °C equilibration between lithiated species occurs,[2] this is very well possible at higher temperatures.[15] A study of the effect of the temperature on the regioselectivity was hardly possible because of either the low reactivity (**1** and **4**) or the side reaction, even at −78 °C, of compounds **9**. Nevertheless some general remarks can be made on the directing effects of substituents at a given temperature.

The OX substituents (OCH_3, OCH_2OCH_3, and $OCONEt_2$) that we have used as protecting groups for the phenol function differ strongly in their ortho-directing capacities, as the result of different electron-withdrawing and coordinating abilities. On the basis of results published in the literature the methoxy group may be regarded as a moderate, the methoxymethoxy group as a moderately strong, and the *O*-carbamoyl group as a strongly activating and ortho-directing group. This behavior determines the

(15) Ziegler, F. F.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.

conditions of the lithiation, such as reaction temperature and reaction time, to achieve selectivity and high yields. Consequently the lithiation of *N,N*-dialkyl-3-*methoxy*anilines (**1a–c**) requires prolonged reaction times and reflux temperature. Lithiation of *N,N*-dialkyl-3-(*methoxymethoxy*)anilines (**4a–c**) occurs at lower temperature and is much faster. The carbamoyloxy group reduces the time of lithiation to 1 h and allows lowering the reaction temperature to −78 °C.

The OX substituent of the (substituted) *N,N*-dialkylhydroxyanilines is the dominant ortho-directing group in the lithiation; the directing capacities of the dialkylamino groups are much smaller. The presence of a dialkylamino group in the meta position relative to the OX group renders the two positions ortho to the OX group nonequivalent toward lithiation and also influences the regioselectivity of the reaction. Our results show that the degree of regioselectivity depends mainly on the relative ortho-directing capacities of both the dominant OX group and the dialkylamino group. In the *N,N*-dialkyl-3-*methoxy*anilines (**1a–c**) lithiation occurs exclusively (**1b** and **1c**) or preferentially (**1a**) ortho to both substituents, which means that both groups are involved in the stabilization of the intermediate lithium compound. This is in line with the results obtained by Slocum and Jennings[4] for 3-methoxy-*N,N*-dimethylaniline. On the other hand, in combination with a strongly directing substituent such as the *O*-carbamoyl group, the ortho-directing ability of dialkylamino groups is negligible. Sibi and Snieckus[13] found that the carbamoyloxy group, in contrast to the methoxy and the methoxymethoxy groups, shows a lower regioselectivity in metalation reactions of nonequivalent ortho sites. The lithiation of 3-methoxyphenyl diethylcarbamate for instance occurs preferentially ortho to both substituents, but in addition the product arising from lithiation at the other ortho position was isolated.[13] A dialkylamino group is both more bulky and weaker ortho-directing than the methoxy group. Consequently the lithiation of *3-(dialkylamino)phenyl diethylcarbamates* (**9a,b,d**) ortho to both substituents is even less favorable, and all the carbamates are lithiated exclusively at the least hindered position ortho to the carbamoyloxy group. Our results obtained with **10a** and **10d**, in which the less hindered ortho position is blocked, under the same reaction conditions, show, however, that both ortho positions are reactive so that we may conclude that steric hindrance does not prevent metalation of the "internal" position.

In the lithiation of *N,N*-dialkyl-(3-*methoxymethoxy*)anilines (**4a–c**) the solvent and the type of dialkylamino group have a large effect on the rate of the reaction and on the regioselectivity.

The different selectivities obtained in the lithiation of **4a** and **4b** in both diethyl ether and *n*-hexane can be attributed to the much stronger resonance interaction between the π-system of the phenyl ring and the nitrogen lone pair of the pyrrolidinyl group than in other dialkylamino groups. As shown by Effenberger et al.[16] the electron-donating abilities of the dialkylamino group decrease in the series pyrrolidine > dimethylamine > piperidine > morpholine. Therefore the pyrrolidinyl group will destabilize the negative charge in the carbanionic species in the lithiation of **4a** compared with **4b**. This might explain the higher reaction temperature needed for the lithiation of **4a** than for **4b**.

As a result of a stronger interaction of the pyrrolidinyl group with the aromatic π-system, the basicity of 1-phenylpyrrolidine (pK_a = 3.45) is lower than that of *N,N*-dimethylaniline (pK_a = 4.39) or 1-phenylpiperidine (pK_a = 5.22).[17] As a consequence the coordination ability of the pyrrolidinyl nitrogen atom toward lithium reagents should be reduced compared with other dialkylamino groups. This effect may be the reason that the lithiation of **4a** occurs even in a noncoordinating solvent such as *n*-hexane predominantly at the least hindered ortho position to the methoxymethoxy group. The formation of comparable amounts of both isomeric benzaldehydes **5a** and **6a** in the lithiation of **4a** when the *n*-BuLi–TMEDA complex is used, for which the "acid–base" mechanism has been postulated, suggests that the acidities of both positions ortho to the methoxymethoxy group are similar.

The present study shows that the relative differences in ortho-directing abilities of OX and dialkylamino groups in 1,3-disubstituted benzenes influence the regioselectivity of the lithiation. A greater difference in ortho-directing abilities of both groups corresponds to a more selective lithiation at the least hindered ortho position relative to the OX group.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded with a Bruker WP-80 spectrometer, and ^{13}C NMR spectra were recorded with a Nicolet MT 200 spectrometer (Me_4Si as an internal standard). Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer.

n-BuLi in *n*-hexane (Metallgeseltschaft) and *sec*-BuLi in cyclohexane (Merck) were titrated with 2-butanol in the presence of 1,10-phenanthroline to determine their concentrations.[18] Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium benzophenone ketyl before use. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA, Aldrich) and *n*-hexane were distilled from CaH and stored over 4-Å molecular sieves. Most other compounds used were commercially available unless stated otherwise. All reactions were carried out under a nitrogen atmosphere.

Preparation of *N,N*-Dialkyl-3-methoxyanilines 1a–c. 1-(3-Methoxyphenyl)pyrrolidine (**1a**), 1-(3-methoxyphenyl)-piperidine (**1b**), and 4-(3-methoxyphenyl)morpholine (**1c**) were prepared in yields of 80–92% by treatment of 3-methoxybenzenamine with 1,4-dibromobutane, 1,5-dibromopentane, and 1,1′-oxybis[2-bromoethane],[19] respectively, in refluxing toluene in the presence of diisopropylethylamine.[20] All compounds showed spectral (IR, NMR, and MS) data consistent with their assigned structures and boiling points as previously reported.[21,22]

Lithiation of *N,N*-Dialkyl-3-methoxyanilines 1a–c. General Procedure. To a solution of **1a–c** (4 mmol) in 10 mL of diethyl ether a solution of *n*-BuLi in *n*-hexane (4.4 mmol) was added at room temperature. The mixture was stirred under reflux for 20 h. Subsequently, a solution of DMF (0.64 g, 8.8 mmol) in 2 mL of diethyl ether was added at room temperature and allowed to react for 2 h. After hydrolysis with water and extraction with diethyl ether (3 × 25 mL) the organic layer was washed twice with water and dried over $MgSO_4$. After evaporation of the solvents the resulting red-brown oil was separated by column chromatography [silica gel; ethyl acetate/petroleum ether (bp 40–60 °C), 15:85].

Lithiation of 1-(3-Methoxyphenyl)pyrrolidine (1a). After chromatography, besides 42% of unreacted **1a**, 2-methoxy-6-(1-pyrrolidinyl)benzaldehyde (**2a**) was isolated in a yield of 35% as

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a yellow oil, which crystallized from petroleum ether (bp 60–80 °C). 2-Methoxy-4-(1-pyrrolidinyl)benzaldehyde (**3a**) was obtained as a yellowish solid in a yield of 15% by further elution of the column with chloroform.

2a: mp 54.5–55.5 °C [petroleum ether (bp 60–80 °C)]; ^{1}H NMR δ 10.44 (s, 1 H, CHO), 7.27 (t, 1 H, J_{ortho} = 8.1 Hz, H-4), 6.5–6.2 (m, 2 H, H-3 and H-5), 3.86 (s, 3 H, OCH_3), 3.3–3.1 (m, 4 H, NCH_2), 2.1–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 188.9 (d, CHO), 163.9 and 150.3 (s, C-2 and C-6), 134.2 (d, C-4), 112.4 (s, C-1), 107.3 and 98.0 (d, C-3 and C-5), 55.8 (q, OCH_3), 52.4 (t, NCH_2), 25.9 (t, NCH_2CH_2); IR (KBr) 1660 (CO) cm^{-1}; mass spectrum, *m/e* 205.112 (M^+; calcd, 205.110).

Anal. Calcd for $C_{12}H_{15}NO_2$ (M_r = 205.256): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.28; H, 7.63; N, 6.75.

3a: mp 113–114 °C (diisopropyl ether); ^{1}H NMR δ 10.13 (s, 1 H, CHO), 7.70 (d, 1 H, J_{ortho} = 8.8 Hz, H-6), 6.25–5.85 (m, 2 H, H-3 and H-5), 3.88 (s, 3 H, OCH_3), 3.55–3.25 (m, 4 H, NCH_2), 2.2–1.9 (m, 4 H, CH_2); ^{13}C NMR δ 187.3 (d, CHO), 130.7, 104.8, and 92.8 (d, Ar C), 55.2 (q, OCH_3), 47.7 (t, NCH_2), 25.4 (t, NCH_2CH_2); IR (KBr) 1650 (CO) cm^{-1}; mass spectrum, *m/e* 205.110 (M^+; calcd, 205.110).

Anal. Calcd for $C_{12}H_{15}NO_2$ (M_r = 205.256): C, 70.22; H, 7.37; N, 6.82. Found: C, 69.87; H, 7.40; N, 6.98.

Lithiation of 1-(3-Methoxyphenyl)piperidine (1b). After chromatography, besides 22% of the starting material **1b**, 2-methoxy-6-(1-piperidinyl)benzaldehyde (**2b**) was isolated as a yellow solid: yield 60%; mp 62–63 °C [petroleum ether (bp 60–80 °C)]; ^{1}H NMR δ 10.27 (s, 1 H, CHO), 7.39 (t, 1 H, J_{ortho} = 8.3 Hz, H-4), 6.75–6.5 (m, 2 H, H-3 and H-5), 3.88 (s, 3 H, OCH_3), 3.2–2.9 (m, 4 H, NCH_2), 1.9–1.5 (m, 6 H, CH_2); ^{13}C NMR δ 188.8 (d, CHO), 161.5 and 157.4 (s, C-2 and C-6), 135.0 (d, C-4), 107.4 (s, C-1), 110.9 and 104.2 (d, C-3 and C-5), 56.0 (q, OCH_3), 55.1 (t, NCH_2), 26.2 (t, NCH_2CH_2), 24.2 (t, $NCH_2CH_2CH_2$); IR (KBr) 1670 (CO) cm^{-1}; mass spectrum, *m/e* 219.126 (M^+; calcd, 219.126).

Anal. Calcd for $C_{13}H_{17}NO_2$ (M_r = 219.283): C, 71.20; H, 7.82; N, 6.39. Found: C, 71.24; H, 8.21; N, 6.48.

Lithiation of 4-(3-Methoxyphenyl)morpholine (1c). In this case no chromatography was necessary. The crude yellow solid was crystallized from diisopropyl ether, affording pure 2-methoxy-6-(4-morpholinyl)benzaldehyde (**2c**): yield 67%; mp 117–118 °C (diisopropyl ether); ^{1}H NMR δ 10.38 (s, 1 H, CHO), 7.44 (t, 1 H, J_{ortho} = 8.3 Hz, H-4), 6.7–6.5 (m, 2 H, H-3 and H-5), 3.90 (s, 3 H, OCH_3), 4.0–3.8 (m, 4 H, CH_2O), 3.2–3.0 (m, 4 H, NCH_2); ^{13}C NMR δ 188.9 (d, CHO), 162.7 and 155.3 (s, C-2 and C-6), 135.6 (d, C-4), 117.2 (s, C-1), 110.5 and 104.9 (d, C-3 and C-5), 67.0 (t, OCH_2), 56.0 (q, OCH_3), 53.6 (t, NCH_2); IR (KBr) 1665 (CO) cm^{-1}; mass spectrum, *m/e* 221.105 (M^+; calcd, 221.105).

Anal. Calcd for $C_{12}H_{15}NO_3$ (M_r = 221.255): C, 65.14; H, 6.83; N, 6.33. Found: C, 64.81; H, 7.04; N, 6.28.

1-[3-(Methoxymethoxy)phenyl]pyrrolidine (4a) and 1-[3-(Methoxymethoxy)phenyl]piperidine (4b). 3-(1-Pyrrolidinyl)phenol and 3-(1-piperidinyl)phenol were obtained by demethylation of **1a** and **1b**, respectively, using BBr_3 (molar ratio of the methyl phenyl ether to BBr_3 1:2). The demethylation was carried out during 24 h in dichloromethane. After hydrolysis the reaction mixture was neutralized with $NaHCO_3$ until evolution of CO_2 stopped (pH ≃7), extracted 3 times with diethyl ether, washed with water, and dried over $MgSO_4$. After evaporation of the solvents, 3-(1-pyrrolidinyl)phenol (yield 92%; mp 128–129 °C, lit.[23] mp 125–128 °C) and 3-(1-piperidinyl)phenol (yield 90%; mp 118–119 °C, lit.[23] mp 119–120 °C) were used without further purification to prepare **4a** and **4b** according to Christensen.[8]

Compound **4a** was prepared starting from 3-(1-pyrrolidinyl)-phenol (11.4 g, 0.07 mol). Distillation of the crude product yielded **4a** as a colorless oil: yield 67%; bp 102–103 °C (6 × 10^{-2} mbar); ^{1}H NMR δ 7.2–6.9 (m, 1 H, H-5), 6.5–6.1 (m, 3 H, Ar H), 5.13 (s, 2 H, OCH_2), 3.45 (s, 3 H, OCH_3), 3.35–3.1 (m, 4 H, NCH_2), 2.1–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 158.4 and 149.2 (s, C-1 and C-3), 129.8, 105.9, 102.9, and 99.9 (d, Ar C), 94.4 (t, OCH_2O), 55.9 (q, OCH_3), 47.6 (t, NCH_2), 25.4 (t, NCH_2CH_2); mass spectrum, *m/e* 207.125 (M^+; calcd for $C_{12}H_{17}NO_2$, 207.126).[24]

Compound **4b** was obtained starting from 3-(1-piperidinyl)-phenol (3.54 g, 0.02 mol) as a colorless oil: yield 80%; bp 101–102 °C (9 × 10^{-2} mbar); ^{1}H NMR δ 7.25–7.0 (m, 1 H, Ar H), 6.7–6.4 (m, 3 H, Ar H), 5.14 (s, 2 H, OCH_2), 3.47 (s, 3 H, OCH_3), 3.3–3.0 (m, 4 H, NCH_2), 1.8–1.5 (m, 6 H); ^{13}C NMR δ 158.3 and 153.5 (s, C-1 and C-3), 129.6, 110.2, 106.5, and 104.7 (d, Ar C), 94.5 (t, OCH_2O), 55.9 (q, OCH_3), 50.4 (t, NCH_2), 25.8 (t, NCH_2CH_2), 24.4 (t, $NCH_2CH_2CH_2$); mass spectrum, *m/e* 221.141 (M^+; calcd, 221.142).

Anal. Calcd for $C_{13}H_{19}NO_2$ (M_r = 221.299): C, 70.56; H, 8.65; N, 6.33. Found: C, 70.18; H, 8.93; N, 6.02.

4-[3-(Methoxymethoxy)phenyl]morpholine (4c). To a suspension of NaH (2.4 g, 0.1 mol) in 25 mL of DMF a solution of 3-aminophenol (10.9 g, 0.1 mol) in 35 mL of DMF was added dropwise at 50 °C, and the mixture was stirred for about 0.5 h. After that a solution of $ClCH_2OCH_3$ (8.05 g, 0.1 mol) in 15 mL of DMF was added, and the mixture was stirred for 2 h. Subsequently, 60 mL of toluene was added and the resulting solution hydrolyzed with 120 mL of water. After separation of the layers the water layer was extracted with toluene (2 × 30 mL). The combined toluene extracts were washed twice with a 5% solution of NaOH and water and dried over Na_2SO_4. After removal of the solvents the colorless oil was distilled to give 3-(methoxymethoxy)aniline: yield 55%; bp 89–91 °C (0.3 mbar); ^{1}H NMR δ 5.2 (s, 2 H, OCH_2), 3.4 (s, 3 H, OCH_3).

A solution of 3-(methoxymethoxy)aniline (8.40 g, 0.055 mol), 1,1′-oxybis[2-bromoethane] (12.8 g, 0.055 mol), and diisopropylethylamine (14.2 g, 0.11 mol) in 60 mL of toluene was stirred under reflux for 24 h. Upon cooling, the salts were filtered off, and the filtrate was washed with water and a 5% solution of NaOH (2 × 50 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure the residue was distilled to afford **4c**: yield 50%; bp 109–110 °C (8 × 10^{-2} mbar); ^{1}H NMR δ 7.3–7.0 (m, 1 H, Ar H), 6.7–6.5 (m, 3 H, Ar H), 5.16 (s, 2 H, OCH_2O), 4.0–3.7 (m, 4 H, OCH_2), 3.48 (s, 3 H, OCH_3), 3.3–3.0 (m, 4 H, NCH_2); ^{13}C NMR δ 158.3 and 152.6 (s, C-1 and C-3), 129.8, 109.2, 107.3, and 104.0 (d, Ar C), 94.4 (t, OCH_2O), 66.8 (t, OCH_2), 55.9 (q, OCH_3), 49.1 (t, NCH_2); mass spectrum, *m/e* 223.121 (M^+; calcd, 223.121).

Anal. Calcd for $C_{12}H_{17}NO_3$ (M_r = 223.275): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.39; H, 7.73; N, 5.91.

Lithiation of *N*,*N*-Dialkyl-3-(methoxymethoxy)anilines 4a–c. General Procedure. To a solution of **4a–c** (2 mmol) in 15 mL of diethyl ether or *n*-hexane a solution of *n*-BuLi (2.2 mmol) in *n*-hexane was added dropwise at room temperature. The reaction was carried out for the time shown in Table I. Subsequently, a solution of DMF (0.32 g, 4.4 mmol) in 2 mL of diethyl ether was added at room temperature whereupon the reaction mixture was stirred for 2 h. After hydrolysis the mixture was extracted with diethyl ether (3 × 25 mL), washed with water (2 × 20 mL), and dried over Na_2SO_4. After evaporation of the solvents the crude products were purified by column chromatography [alumina (neutral, II–III); ethyl acetate/petroleum ether (bp 40–60 °C), 1:4 or 1:9]. The yields are summarized in Table I.

2-(Methoxymethoxy)-6-(1-pyrrolidinyl)benzaldehyde (5a): light yellow crystals; mp 41–42 °C [petroleum ether (bp 60–80 °C)]; ^{1}H NMR δ 10.48 (s, 1 H, CHO), 7.26 (t, 1 H, J_{ortho} = 8.8 Hz, H-4), 6.6–6.4 (m, 2 H, Ar H), 5.24 (s, 2 H, OCH_2), 3.51 (s, 3 H, OCH_3), 3.3–3.1 (m, 4 H, NCH_2), 2.1–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 188.9 (d, CHO), 161.5 and 150.1 (s, C-2 and C-6), 134.2 (d, Ar C), 113.0 (s, C-1), 108.2 and 101.2 (d, Ar C), 94.9 (t, OCH_2O), 56.6 (q, OCH_3), 52.4 (t, NCH_2), 25.9 (t, NCH_2CH_2); IR (KBr) 1665 (CO) cm^{-1}; mass spectrum, *m/e* 235.120 (M^+; calcd, 235.121).

Anal. Calcd for $C_{13}H_{17}NO_3$ (M_r = 235.282): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.68; H, 7.46; N, 6.05.

2-(Methoxymethoxy)-4-(1-pyrrolidinyl)benzaldehyde (6a): yellow crystals; mp 88–89 °C (diisopropyl ether); ^{1}H NMR δ 10.19 (s, 1 H, CHO), 7.73 (d, 1 H, J_{ortho} = 9.0 Hz, H-6), 6.3–6.1 (m, 2 H, Ar H), 5.27 (s, 2 H, OCH_2), 3.52 (s, 3 H, OCH_3), 3.45–3.2 (m, 4 H, NCH_2), 2.2–1.9 (m, 4 H, CH_2); ^{13}C NMR δ 187.2 (d, CHO), 161.8 and 153.4 (s, C-2 and C-4), 130.2 (d, C-6), 114.9 (s, C-1), 106.1 and 96.2 (d, C-3 and C-5), 94.6 (t, OCH_2), 56.4 (q, OCH_3), 47.8 (t, NCH_2), 25.4 (t, NCH_2CH_2); IR (KBr) 1650 (CO) cm^{-1}; mass spectrum, *m/e* 235.119 (M^+; calcd, 235.121).

Anal. Calcd for $C_{13}H_{17}NO_3$ (M_r = 235.282): C, 66.36; H, 7.28; N, 5.95. Found: C, 65.97; H, 7.30; N, 6.09.

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(24) A satisfactory elemental analysis could not be obtained because of decomposition at room temperature.

2-(Methoxymethoxy)-6-(1-piperidinyl)benzaldehyde (5b): yellow needles; mp 65.5–66.5 °C [petroleum ether (bp 60–80 °C)]; ^{1}H NMR δ 10.30 (s, 1 H, CHO), 7.37 (t, 1 H, J_{ortho} = 8.3 Hz, H-4), 6.85–6.65 (m, 2 H, H-3 and H-5), 5.24 (s, 2 H, OCH_2), 3.50 (s, 3 H, OCH_3), 3.2–2.9 (m, 4 H, NCH_2), 1.9–1.5 (m, 6 H, CH_2); ^{13}C NMR δ 189.5 (d, CHO), 159.1 and 157.1 (s, C-2 and C-6), 134.9 (d, C-4), 118.5 (s, C-1), 112.1 and 108.1 (d, C-3 and C-5), 95.0 (t, OCH_2), 56.4 (q, OCH_3), 55.0 (t, NCH_2), 26.1 (t, NCH_2CH_2), 24.1 (t, $NCH_2CH_2CH_2$); IR (KBr) 1670 (CO) cm^{-1}; mass spectrum, *m/e* 249.138 (M$^+$; calcd, 249.136).

Anal. Calcd for $C_{14}H_{19}NO_3$ (M_r = 249.309): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.05; H, 7.76; N, 5.70.

2-(Methoxymethoxy)-4-(1-piperidinyl)benzaldehyde (6b): white crystals; mp 65–66 °C (diisopropyl ether); ^{1}H NMR δ 10.20 (s, 1 H, CHO), 7.72 (d, 1 H, J_{ortho} = 9.3 Hz, H-6), 6.6–6.4 (m, 2 H, H-3 and H-5), 5.26 (s, 2 H, OCH_2), 3.52 (s, 3 H, OCH_3), 3.5–3.2 (m, 4 H, NCH_2), 1.8–1.5 (m, 6 H, CH_2); ^{13}C NMR δ 187.3 (d, CHO), 161.9 and 156.6 (s, C-2 and C-4), 130.0 (d, C-6), 116.0 (s, C-1), 107.8 and 98.6 (d, C-3 and C-5), 94.7 (t, OCH_2), 56.4 (q, OCH_3), 48.5 (t, NCH_2), 25.4 (t, NCH_2CH_2), 24.3 (t, $NCH_2CH_2CH_2$); IR (KBr) 1650 (CO) cm^{-1}; mass spectrum, *m/e* 249.135 (M$^+$; calcd, 249.136).

Anal. Calcd for $C_{14}H_{19}NO_3$ (M_r = 249.309): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.05; H, 8.08; N, 5.48.

2-(Methoxymethoxy)-6-(4-morpholinyl)benzaldehyde (5c): yellow plates; mp 63–64 °C [petroleum ether (bp 60–80 °C)]; ^{1}H NMR δ 10.40 (s, 1 H, CHO), 7.42 (t, 1 H, J_{ortho} = 8.3 Hz, H-4), 6.9–6.6 (m, 2 H, H-3 and H-5), 5.25 (s, 2 H, OCH_2O), 4.0–3.8 (m, 4 H, OCH_2), 3.51 (s, 3 H, OCH_3), 3.2–3.0 (m, 4 H, NCH_2); ^{13}C NMR δ 188.8 (d, CHO), 160.5 and 155.0 (s, C-2 and C-6), 135.4 (d, C-4), 118.1 (s, C-1), 111.6 and 108.6 (d, C-3 and C-5), 94.9 (t, OCH_2O), 67.0 (t, OCH_2), 56.5 (q, OCH_3), 53.6 (t, NCH_2); IR (KBr) 1670 (CO) cm^{-1}; mass spectrum, *m/e* 251.117 (M$^+$; calcd, 251.116).

Anal. Calcd for $C_{13}H_{17}NO_4$ (M_r = 251.282): C, 62.14; H, 6.82; N, 5.57. Found: C, 61.92; H, 7.07; N, 5.53.

2-(Methoxymethoxy)-4-(4-morpholinyl)benzaldehyde (6c): colorless needles; mp 63–64 °C (diisopropyl ether); ^{1}H NMR δ 10.24 (s, 1 H, CHO), 7.75 (d, 1 H, J_{ortho} = 9.5 Hz, H-6), 6.7–6.4 (m, 2 H, H-3 and H-5), 5.27 (s, 2 H, OCH_2O), 4.0–3.7 (m, 4 H, OCH_2), 3.52 (s, 3 H, OCH_3), 3.5–3.2 (m, 4 H, NCH_2); ^{13}C NMR δ 187.7 (d, CHO), 161.7 and 156.6 (s, C-2 and C-4), 130.0 (d, C-6), 117.3 (s, C-1), 107.6 and 99.0 (d, C-3 and C-5), 94.7 (t, OCH_2O), 66.5 (t, OCH_2), 56.4 (q, OCH_3), 47.3 (t, NCH_2); IR (KBr) 1670 (CO) cm^{-1}; mass spectrum, *m/e* 251.117 (M$^+$; calcd, 251.116).

Anal. Calcd for $C_{13}H_{17}NO_4$ (M_r = 251.282): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.23; H, 6.93; N, 5.66.

1-[3-(Methoxymethoxy)-4-methylphenyl]pyrrolidine (7a). The lithiation of **4a** (9.5 g, 46 mmol) in diethyl ether (60 mL) by *n*-BuLi (60 mmol) was carried out as described above. Subsequently, a solution of methyl iodide (13 g, 92 mmol) in 20 mL of diethyl ether was added at room temperature whereupon the mixture was stirred for 70 h (negative Gilman test). After the typical workup, distillation of the crude reaction mixture afforded pure **7a**: yield 78%; bp 118–120 °C (8 × 10^{-2} mbar); ^{1}H NMR δ 6.96 (d, 1 H, J_{ortho} = 7.8 Hz, H-5), 6.35–6.05 (m, 2 H, H-2 and H-6), 5.18 (s, 2 H, OCH_2), 3.49 (s, 3 H, OCH_3), 3.4–3.1 (m, 4 H, NCH_2), 2.14 (s, 3 H, CH_3), 2.1–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 156.2 and 141.6 (s, C-1 and C-3), 130.9 (d, C-5), 114.0 (s, C-4), 105.2 and 98.8 (d, C-2 and C-6), 94.7 (t, OCH_2O), 55.9 (q, OCH_3), 47.9 (t, NCH_2), 25.4 (t, NCH_2CH_2), 15.3 (q, CH_3); mass spectrum, *m/e* 221.142 (M$^+$; calcd for $C_{13}H_{19}NO_2$, 221.142).[24]

2-(Methoxymethoxy)-3-methyl-6-(1-pyrrolidinyl)benzaldehyde (8a). To a solution of *n*-BuLi (2.2 mmol) in *n*-hexane (3 mL) was added TMEDA (0.26 g, 2.2 mmol) at −40 °C. The mixture was warmed to room temperature whereupon a solution of **7a** (0.50 g, 2 mmol) in 3 mL of *n*-hexane was added dropwise. After 2.5 h of lithiation a solution of DMF (0.32 g, 4.4 mmol) in 1 mL of *n*-hexane was added whereupon the reaction mixture was stirred for 2 h at room temperature. After the typical workup the mixture was separated by column chromatography [alumina, neutral (II–III); ethyl acetate/petroleum ether (bp 60–80 °C), 1:9] to give, besides **7a** (24%), **8a** in a yield of 44%. Further elution with chloroform afforded 2-methyl-5-(1-pyrrolidinyl)phenol (mp 159–160 °C, lit.[25] mp 160–161 °C) in a yield of 18%.[26]

(25) Lida, H.; Yuasa, Y.; Kibayashi, Ch. *Synthesis* **1982**, 47.

8a: orange oil; ^{1}H NMR δ 10.26 (s, 1 H, CHO), 7.19 (d, 1 H, J_{ortho} = 8.8 Hz, H-4), 6.58 (d, 1 H, J_{ortho} = 8.8 Hz, H-5), 5.13 (s, 2 H, OCH_2), 3.59 (s, 3 H, OCH_3), 3.4–3.1 (m, 4 H, NCH_2), 2.22 (s, 3 H, CH_3), 2.1–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 189.0 (d, CHO), 159.1 and 149.9 (s, C-2 and C-6), 136.5 (d, C-4), 118.2 and 116.8 (s, C-1 and C-3), 110.5 (d, C-5), 101.4 (t, OCH_2O), 57.8 (q, OCH_3), 52.7 (t, NCH_2), 25.8 (t, NCH_2CH_2), 15.5 (q, CH_3); IR (neat) 1665 (CO) cm^{-1}; mass spectrum, *m/e* 249.136 (M$^+$; calcd, 249.137).

Anal. Calcd for $C_{14}H_{19}NO_3$ (M_r = 249.309): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.30; H, 7.88; N, 5.63.

Preparation of 3-(Dialkylamino)phenyl Diethylcarbamates 9a,b,d. General Procedure. To a suspension of sodium hydride (0.66 g, 27.5 mmol) in 10 mL of DMF and 40 mL of diethyl ether a solution of 3-(dialkylamino)phenol (25 mmol) in 30 mL of diethyl ether was added dropwise at room temperature. The mixture was stirred until evolution of hydrogen ceased (about 15 min). Subsequently, a solution of diethylcarbamoyl chloride (4.07 g, 30 mmol) in 10 mL of diethyl ether was added. After the reaction mixture was stirred for 1.5 h at room temperature, water (50 mL) was added to it. After separation of the layers the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined extracts were washed with water and a 10% NaOH solution and subsequently dried with $MgSO_4$. After removal of the solvent the crude product was distilled under reduced pressure.

3-(1-Pyrrolidinyl)phenyl Diethylcarbamate (9a): yield 75%; bp 158–160 °C (9 × 10^{-2} mbar); ^{1}H NMR δ 7.16 (t, 1 H, J_{ortho} = 7.8 Hz, H-5), 6.5–6.25 (m, 3 H, Ar H), 3.5–3.2 (m, 8 H, NCH_2), 2.1–1.85 (m, 4 H, CH_2), 1.22 (t, 6 H, *J* = 7 Hz, CH_3); ^{13}C NMR δ 154.4, 152.6, and 149.9 (s, CO, C-1, and C-3), 129.4, 108.6, 108.4, and 104.9 (d, Ar C), 47.6 (t, NCH_2), 41.9 (br t, NCH_2CH_3), 25.4 (t, NCH_2CH_2), 14.2 and 13.5 (q, NCH_2CH_3); IR (neat) 1720 (CO) cm^{-1}; mass spectrum, *m/e* 262.167 (M$^+$; calcd for $C_{15}H_{22}N_2O_2$, 262.168).[24]

3-(1-Piperidinyl)phenyl Diethylcarbamate (9b): yield 82%; bp 158–161 °C (9 × 10^{-2} mbar); ^{1}H NMR δ 7.3–7.0 (m, 1 H, H-5), 6.8–6.4 (m, 3 H, Ar H), 3.5–3.0 (m, 8 H, NCH_2), 1.8–1.4 (m, 6 H, CH_2), 1.21 (t, 6 H, *J* = 7 Hz, CH_3); ^{13}C NMR δ 154.3, 153.2, and 152.4 (s, CO, C-1, and C-3), 129.2, 113.1, 112.0, and 109.6 (d, Ar C), 50.4 (t, NCH_2), 42.1 and 41.9 (t, NCH_2CH_3), 25.8 (t, NCH_2CH_2), 24.3 (t, $NCH_2CH_2CH_2$), 14.2 and 13.4 (q, NCH_2CH_3); IR (neat) 1720 (CO) cm^{-1}; mass spectrum, *m/e* 276.182 (M$^+$; calcd for $C_{16}H_{24}N_2O_2$, 276.184).

3-(Dimethylamino)phenyl Diethylcarbamate (9d):[27] yield 72%; bp 135–136 °C (9 × 10^{-2} mbar).

Lithiation of 3-(Dialkylamino)phenyl Diethylcarbamates 9a,b,d. General Procedure. To a stirred solution of *sec*-BuLi in cyclohexane (1.1 equiv) cooled to −78 °C THF (3 mL/mmol of *sec*-BuLi) and subsequently TMEDA (1.1 equiv) were added dropwise. Thereupon a THF solution of **9a,b,d**, (1 equiv, 1 mmol/0.5 mL of THF) was added and the resulting mixture was stirred at −78 °C for 1 h. Subsequently, a solution of an electrophile in THF (2 equiv, 1 mmol/0.5 mL of THF) was added at −78 °C. After 4 h of stirring at that temperature the reaction mixture was allowed to warm to room temperature during 2 h and kept for 0.5 h at that temperature. After hydrolysis by a saturated solution of NH_4Cl, the water layer was extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with water and dried over Na_2SO_4. After evaporation of the solvents the products were separated by crystallization or column chromatography.

5-(1-Pyrrolidinyl)-2-(trimethylsilyl)phenyl Diethylcarbamate (10a). This compound was obtained by lithiation of **9a** (10 mmol), followed by reaction with chlorotrimethylsilane. Crystallization gave pure **10a**: yield 96%; mp 70.5–71.5 °C [cold petroleum ether (bp 60–80 °C)]; ^{1}H NMR δ 7.03 (d, 1 H, J_{ortho} = 8.1 Hz, H-3), 6.17 (dd, 1 H, J_{ortho} = 8.1 Hz and J_{meta} = 2.2 Hz, H-4), 5.99 (d, 1 H, J_{meta} = 2.2 Hz, H-6), 3.4–2.9 (m, 8 H, NCH_2), 1.9–1.6 (m, 4 H, NCH_2CH_2), 1.2–0.9 (m, 6 H, NCH_2CH_3), 0.0 (s, 9 H, CH_3Si); ^{13}C NMR δ 157.5, 154.4, and 149.9 (s, CO, C-1, and C-5), 135.3 (d, C-3), 115.5 (s, C-2), 108.9 and 105.5 (d, C-4 and

(26) In the lithiations of **7d** carried out at 0 °C the relative ratios of **8a** to 2-methyl-5-(1-pyrrolidinyl)phenol were not improved.

(27) Ward, H. E., Jr.; Freeman, J. J.; Sovell, J. W.; Kosh, J. W. *J. Pharm. Sci.* **1981**, *70*, 433.

C-6), 47.5 (t, NCH_2CH_2), 41.7 and 41.4 (t, NCH_2CH_3), 25.4 (t, NCH_2CH_2), 14.2 and 13.4 (q, NCH_2CH_3), –0.5 (q, CH_3Si); IR (KBr) 1700 (CO) cm^{-1}; mass spectrum, m/e 334.207 (M^+; calcd, 334.208).

Anal. Calcd for $C_{18}H_{30}N_2O_2Si$ (M_r = 334.533): C, 64.63; H, 9.04; N, 8.37. Found: C, 64.76; H, 9.12; N, 8.36.

5-(Dimethylamino)-2-(trimethylsilyl)phenyl Diethylcarbamate (10d). This compound was obtained by lithiation of **9d** (10 mmol), followed by reaction with chlorotrimethylsilane. Crystallization gave pure **10d**: yield 93%; mp 56–56.5 °C [cold petroleum ether (bp 60–80 °C)]; ^1H NMR δ 7.21 (d, 1 H, J_{ortho} = 8.0 Hz, H-3), 6.48 (dd, 1 H, J_{ortho} = 8.0 Hz and J_{meta} = 2.4 Hz, H-4), 6.29 (d, 1 H, J_{meta} = 2.4 Hz, H-6), 3.6–3.2 (m, 4 H, NCH_2), 2.86 (s, 6 H, NCH_3), 1.3–1.0 (m, 6 H, NCH_2CH_3), 0.19 (s, 9 H, CH_3Si); ^{13}C NMR δ 157.5, 154.4, and 152.5 (s, CO, C-1, and C-5), 135.3 (d, C-3), 116.7 (s, C-2), 109.4 and 106.2 (d, C-4 and C-6), 41.7 and 41.4 (t, NCH_2), 40.3 (q, NCH_3), 14.2 and 13.3 (q, NCH_2CH_3), –0.6 (q, CH_3Si); IR (KBr) 1700 (CO) cm^{-1}; mass spectrum, m/e 308.191 (M^+; calcd, 308.192).

Anal. Calcd for $C_{16}H_{28}N_2O_2Si$ (M_r = 308.495): C, 62.29; H, 9.15; N, 9.08. Found: C, 62.17; H, 9.52; N, 9.04.

Lithiation of 9a,b,d Followed by Reaction with DMF. Lithiation of **9a,b,d** (2 mmol) followed by reaction with DMF gave in each case after hydrolysis a mixture of **11a,b,d** and **12a,b,d**, respectively. The products were separated by column chromatography [silica gel; ethyl acetate/petroleum ether (bp 40–60 °C)]. The yields of **11** and **12** are shown in Table I.

2-Formyl-5-(1-pyrrolidinyl)phenyl Diethylcarbamate (11a): oil; ^1H NMR δ 9.89 (s, 1 H, CHO), 7.71 (d, 1 H, J_{ortho} = 8.5 Hz, H-3), 6.41 (dd, 1 H, J_{ortho} = 8.5 Hz and J_{meta} = 2.2 Hz, H-4), 6.26 (d, 1 H, J_{meta} = 2.2 Hz, H-6), 3.6–3.2 (m, 8 H, NCH_2), 2.2–1.9 (m, 4 H, NCH_2CH_2), 1.25 (br t, 6 H, J = 7 Hz, NCH_2CH_3); ^{13}C NMR δ 186.6 (d, CHO), 155.1, 153.8, and 152.7 (s, CO, C-1, and C-5), 131.6 (d, C-3), 117.4 (s, C-2), 108.9 and 104.9 (d, C-4 and C-6), 47.8 (t, NCH_2), 42.3 and 42.0 (t, NCH_2CH_3), 25.4 (t, NCH_2CH_2), 14.3 and 13.3 (q, NCH_2CH_3); IR (neat) 1720 (CO), 1675 (CO) cm^{-1}; mass spectrum, m/e 290.160 (M^+; calcd for $C_{16}H_{22}N_2O_3$, 290.163).

2-Hydroxy-4-(1-pyrrolidinyl)benzaldehyde (12a): white crystals; mp 121.5–122.5 °C (diisopropyl ether); ^1H NMR δ 11.65 (s, 1 H, CHO), 9.50 (s, 1 H, OH), 7.27 (d, 1 H, J_{ortho} = 8.8 Hz, H-6), 6.25–5.9 (m, 2 H, Ar H), 3.6–3.2 (m, 4 H, NCH_2), 2.2–1.9 (m, 4 H, CH_2); ^{13}C NMR δ 192.1 (d, CHO), 164.1 and 153.6 (s, C-2 and C-4), 135.2 (d, C-6), 105.1 (d, Ar C), 100.1 (s, C-1), 97.2 (d, Ar C), 47.7 (t, NCH_2), 25.3 (t, NCH_2CH_2); IR (KBr) 1640 (CO) cm^{-1}.

Anal. Calcd for $C_{11}H_{13}NO_2$ (M_r = 205.256): C, 69.09; H, 6.85; N, 7.32. Found: C, 68.85; H, 6.68; N, 7.13.

2-Formyl-5-(1-piperidinyl)phenyl Diethylcarbamate (11b): oil; ^1H NMR δ 9.88 (s, 1 H, CHO), 7.68 (d, 1 H, J_{ortho} = 8.8 Hz, H-3), 6.69 (dd, 1 H, J_{ortho} = 8.8 Hz and J_{meta} = 2.6 Hz, H-4), 6.53 (d, 1 H, J_{meta} = 2.6 Hz, H-6), 3.6–3.2 (m, 8 H, NCH_2), 1.8–1.4 (m, 6 H, $NCH_2CH_2CH_2$), 1.23 (br t, 6 H, J = 7 Hz, NCH_2CH_3); ^{13}C NMR δ 186.6 (d, CHO), 155.8, 153.7, and 151.1 (s, CO, C-1, and C-5), 131.5 (d, C-3), 118.3 (s, C-2), 110.5 and 107.0 (d, C-4 and C-6), 48.3 (t, NCH_2), 42.3 and 42.0 (t, NCH_2CH_3), 25.3 (t, NCH_2CH_2), 24.3 (t, $NCH_2CH_2CH_2$), 14.3 and 13.3 (q, NCH_2CH_3); IR (neat) 1720 (CO), 1675 (CO) cm^{-1}; mass spectrum, m/e 304.178 (M^+; calcd for $C_{17}H_{24}N_2O_3$, 304.179).

2-Hydroxy-4-(1-piperidinyl)benzaldehyde (12b): mp 72–73 °C (diisopropyl ether); ^1H NMR δ 11.51 (s, 1 H, CHO), 9.53 (s, 1 H, OH), 7.28 (d, 1 H, J_{ortho} = 8.8 Hz, H-6), 6.43 (dd, 1 H, J_{ortho} = 8.8 Hz and J_{meta} = 2.2 Hz, H-5), 6.24 (d, 1 H, J_{meta} = 2.2 Hz, H-3), 3.6–3.3 (m, 4 H, NCH_2), 1.8–1.5 (m, 6 H, CH_2); ^{13}C NMR δ 192.2 (d, CHO), 164.1 and 156.3 (s, C-2 and C-4), 135.1 (d, C-6), 112.1 (s, C-1), 106.0 and 98.9 (d, C-3 and C-5), 48.2 (t, NCH_2), 25.3 (t, NCH_2CH_2), 24.4 (t, $NCH_2CH_2CH_2$): IR (KBr) 3400 (OH), 1640 (CO) cm^{-1}; mass spectrum, m/e 205.108 (M^+; calcd for $C_{12}H_{15}NO_2$, 205.110).[24]

5-(Dimethylamino)-2-formylphenyl Diethylcarbamate (11d): oil; ^1H NMR δ 9.90 (s, 1 H, CHO), 7.71 (d, 1 H, J_{ortho} = 8.8 Hz, H-3), 6.53 (dd, 1 H, J_{ortho} = 8.8 Hz and J_{meta} = 2.4 Hz, H-4), 6.37 (d, 1 H, J_{meta} = 2.4 Hz, H-6), 3.6–3.2 (m, 4 H, NCH_2), 3.05 (s, 6 H, NCH_3), 1.4–1.1 (m, 6 H, NCH_2CH_3); ^{13}C NMR δ 186.7 (d, CHO), 155.1, 155.0, and 153.7 (s, CO, C-1, and C-5), 131.5 (d, C-3), 117.5 (s, C-2), 108.6 and 104.9 (d, C-4 and C-6), 42.3 and 42.0 (t, NCH_2), 40.1 (q, NCH_3), 14.3 and 13.3 (q, NCH_2CH_3); IR (neat) 1720 (CO), 1675 (CO) cm^{-1}; mass spectrum, m/e 264.148 (M^+; calcd for $C_{14}H_{20}N_2O_3$, 264.147).

4-(Dimethylamino)-2-hydroxybenzaldehyde (12d): mp 77–78 °C (diisopropyl ether), lit.[28] mp 78–79 °C.

Preparation of 4-(Dialkylamino)-*N*,*N*-diethyl-2-hydroxybenzamides 13a,d and 6-(Dialkylamino)-*N*,*N*-diethyl-2-hydroxy-3-(trimethylsilyl)benzamides 14a,d. The lithiation of **9a,d** and **10a,d** (2 mmol) was carried out as described above; subsequently, the reaction mixture was warmed to room temperature during 3 h. After typical workup the crude product was purified by column chromatography [silica gel; ethyl acetate/petroleum ether (bp 40–60 °C), 1:4], to afford pure **13a,d** and **14a,d**, respectively.

***N*,*N*-Diethyl-2-hydroxy-4-(1-pyrrolidinyl)benzamide (13a)**: yield 69%; yellow crystals; mp 84.5–85.5 °C (diisopropyl ether); ^1H NMR δ 11.06 (s, 1 H, OH), 7.17 (d, 1 H, J_{ortho} = 8.3 Hz, H-6), 6.1–5.9 (m, 2 H, Ar H), 3.51 (q, 4 H, J = 7.1 Hz, NCH_2CH_3), 3.5–3.2 (m, 4 H, NCH_2), 2.1–1.9 (m, 4 H, NCH_2CH_2), 1.27 (t, 6 H, J = 7.1 Hz, CH_3); ^{13}C NMR δ 172.8 (s, CO), 162.0 and 150.9 (s, C-2 and C-4), 129.0 (d, C-6), 104.6 (s, C-1), 102.5 and 99.0 (d, C-3 and C-5), 47.4 and 42.3 (t, NCH_2), 25.4 (t, NCH_2CH_2), 13.5 (q, NCH_2CH_3); IR (KBr) 3200 (br, OH), 1630 (CO) cm^{-1}; mass spectrum, m/e 262.170 (M^+; calcd for $C_{15}H_{22}N_2O_2$, 262.168).[24]

***N*,*N*-Diethyl-4-(dimethylamino)-2-hydroxybenzamide (13d)**: yield 79%; yellow crystals; mp 104–105 °C (diisopropyl ether); ^1H NMR δ ~11.0 (br s, 1 H, OH), 7.18 (d, 1 H, J_{ortho} = 8.7 Hz, H-6), 6.3–6.1 (m, 2 H, Ar H), 3.52 (q, 4 H, J = 7.0 Hz, NCH_2), 2.98 (s, 6 H, NCH_3), 1.27 (t, 6 H, J = 7.0 Hz, NCH_2CH_3); ^{13}C NMR δ 172.5, (s, CO), 161.8 and 153.4 (s, C-2 and C-4), 128.8 (d, C-6), 105.2 (s, C-1), 102.5 and 99.5 (d, C-3 and C-5), 42.3 (t, NCH_2), 39.5 (q, NCH_3), 13.5 (q, NCH_2CH_3); IR (KBr) 3150 (br, OH), 1620 (CO) cm^{-1}; mass spectrum, m/e 236.150 (M^+; calcd for $C_{13}H_{20}N_2O_2$, 236.152).[24]

***N*,*N*-Diethyl-2-hydroxy-6-(1-pyrrolidinyl)-3-(trimethylsilyl)benzamide (14a).** During chromatography partial desilylation occurred. Further elution of the column with methanol gave *N*,*N*-diethyl-2-hydroxy-6-(1-pyrrolidinyl)benzamide (**15a**) as a white solid.

14a: yield 57%; mp 101–103 °C dec [cold petroleum ether (bp 60–80 °C)]; ^1H NMR δ 7.62 (s, 1 H, OH), 7.18 (d, 1 H, J_{ortho} = 8.3 Hz, H-4), 6.26 (d, 1 H, J_{ortho} = 8.3 Hz, H-5), 3.8–3.0 (m, 8 H, NCH_2), 2.1–1.8 (m, 4 H, NCH_2CH_2), 1.4–0.9 (m, 6 H, NCH_2CH_3), 0.25 (s, 9 H, CH_3Si); IR (KBr) 3200 (OH), 1600 (CO) cm^{-1}; mass spectrum, m/e 334.206 (M^+; calcd, 334.208).

Anal. Calcd for $C_{18}H_{30}N_2O_2Si$ (M_r = 334.533): C, 64.63; H, 9.04; N, 8.37. Found: C, 64.41; H, 9.39; N, 8.13.[29]

15a: yield 34%; mp 131–132 °C (diisopropyl ether); ^1H NMR δ 7.54 (s, 1 H, OH), 7.09 (t, 1 H, J_{ortho} = 8.1 Hz, H-4), 6.32 (m, 2 H, Ar H), 3.8–2.9 (m, 8 H, NCH_2), 2.0–1.6 (m, 4 H, NCH_2CH_2), 1.4–0.9 (m, 6 H, CH_3); ^{13}C NMR δ 170.8 (s, CO), 156.1 and 147.2 (s, C-2 and C-6), 130.6 (d, C-4), 109.3 (s, C-1), 105.6 and 105.2 (d, C-3 and C-5), 50.3 (t, NCH_2CH_2), 43.0 and 39.9 (t, NCH_2), 25.8 (t, NCH_2CH_2), 13.4 and 13.0 (q, NCH_2CH_3); IR (KBr) 3200 (br, OH), 1610 (CO) cm^{-1}; mass spectrum, m/e 262.170 (M^+; calcd, 262.168).

Anal. Calcd for $C_{15}H_{22}N_2O_2$ (M_r = 262.351): C, 68.67; H, 8.45; N, 10.68. Found: C, 68.55; H, 9.02; N, 10.45.

***N*,*N*-Diethyl-6-(dimethylamino)-2-hydroxy-3-(trimethylsilyl)benzamide (14d)**: yield 89%; white crystals; mp 87–88 °C [cold petroleum ether (bp 60–80 °C)]; ^1H NMR δ 7.57 (s, 1 H, OH), 6.98 (d, 1 H, J_{ortho} = 8.1 Hz, H-4), 6.15 (d, 1 H, J_{ortho} = 8.1 Hz, H-5), 3.2–2.8 (m, 4 H, NCH_2), 2.51 (s, 6 H, NCH_3), 1.1–0.6 (m, 6 H, NCH_2CH_3), 0.0 (s, 9 H, CH_3Si); ^{13}C NMR δ 170.7 (s, CO), 161.3 and 151.7 (s, C-2 and C-6), 136.3 (d, C-4), 117.4 and 111.9 (s, C-1 and C-3), 107.5 (d, C-5), 43.2 (q, NCH_3), 43.5 and 39.4 (t, NCH_2), 13.6 and 13.0 (q, NCH_2CH_3), –0.94 (q, CH_3Si); IR (KBr) 3200 (br, OH), 1600 (CO) cm^{-1}; mass spectrum, m/e 308.190 (M^+; calcd, 308.192).

Anal. Calcd for $C_{16}H_{28}N_2O_2Si$ (M_r = 308.495): C, 62.29; H, 9.15; N, 9.08. Found: C, 62.53; H, 9.29; N, 9.06.

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(29) A ^{13}C NMR spectrum was not recorded because of decomposition of **14a** in deuteriochloroform.

and to T. W. Stevens for recording the mass spectra.

Registry No. **1a**, 32040-07-6; **1a** (X = H), 25912-16-7; **1b**, 32040-06-5; **1b** (X = H), 27292-50-8; **1c**, 32040-09-8; **1c** (X = H), 27292-49-5; **2a**, 96648-99-6; **2b**, 96649-01-3; **2c**, 96649-02-4; **3a**, 96649-00-2; **4a**, 96649-03-5; **4b**, 96649-04-6; **4c**, 96649-06-8; **5a**, 96649-07-9; **5b**, 96649-09-1; **5c**, 96649-11-5; **6a**, 96649-08-0; **6b**, 96649-10-4; **6c**, 96649-12-6; **7a**, 96649-13-7; **7a** (X = H), 82961-68-0; **8a**, 96649-14-8; **9a**, 96649-15-9; **9a** (6-lithio deriv), 96665-97-3; **9b**, 96649-16-0; **9d**, 63907-38-0; **9d** (6-lithio deriv), 96665-98-4; **10a**, 96649-17-1; **10a** (6-lithio deriv), 96688-67-4; **10d**, 96649-18-2; **10d** (6-lithio deriv), 96688-68-5; **11a**, 96649-19-3; **11b**, 96649-20-6; **11d**, 96649-22-8; **12a**, 74427-40-0; **12b**, 96649-21-7; **12d**, 41602-56-6; **13a**, 96649-23-9; **13d**, 96649-24-0; **14a**, 96649-25-1; **14d**, 96649-26-2; **15a**, 96649-27-3; 3-$CH_3OC_6H_4NH_2$, 536-90-3; $Br(CH_2)_4Br$, 110-52-1; $Br(CH_2)_5Br$, 111-24-0; $(Br(CH_2)_2)_2O$, 5414-19-7; 3-$HOC_6H_4NH_2$, 591-27-5; $ClCH_2OCH_3$, 107-30-2; 3-$CH_3OCH_2OC_6H_4NH_2$, 96649-05-7; $ClCONEt_2$, 88-10-8; Me_3SiCl, 75-77-4.

Photochemical Transformations. 39. Effects of Ring Substituents and Leaving Groups on Photo-Wagner-Meerwein Rearrangements and Their Ground-State Analogues

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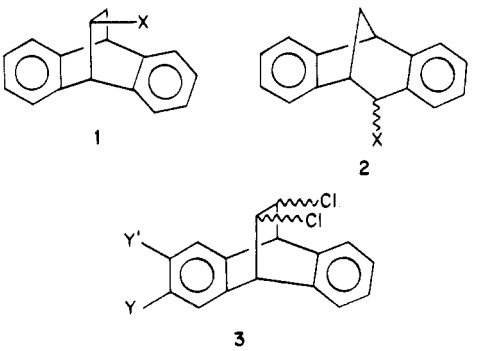
A variety of diarobicyclo[2.2.2]octa-2,5-dienes, substituted on the saturated bridge at C-7 or disubstituted at C-7 and C-8, have been subjected to direct irradiation in acetic acid, as well as to ground-state solvolysis. The ground-state reactions proceed as anticipated, occurring with preferred loss of the nucleofuge anti to the better participating ring, or with loss of the better nucleofuge, and with clean anti Wagner–Meerwein rearrangement to the diarobicyclo[3.2.1]octadienyl system, with one exception. The photoreactions proceed with reaction at the more readily reduced carbon–nucleofuge bond (chloride loss rather than methanesulfonate) with the dibenzo system. The (methylsulfonyl)oxy group is photoinert with both benzo rings unsubstituted but is photoactive with the better electron-donating veratrolo ring. The photo-Wagner–Meerwein rearrangements and photosolvolyses all proceed with preponderant or stereospecific syn migration, in contrast to the ground-state reactions. The photoreactivities are consistent with the requirement that electron transfer of an excited π^* electron to the σ^* orbital of the carbon–nucleofuge bond must occur faster than electron-demotion processes occur. The stereochemical results are accommodated by the assumption that the resulting zwitterionic biradical has two possible competing fates leading to products. One involves loss of nucleofuge concerted with a syn 1,2-migration, and the other is a nonconcerted process in which loss of nucleofuge results in formation of a biradical cation, which is nonstereospecific in its ultimate rearrangement.

The photoreactions of benzo- and diarobicyclo[2.2.2]-octadienes containing an aromatic light-absorbing ring and a remote reactive center have been studied extensively in this laboratory.[1-7] Irradiation excites the aromatic chromophore, which then, under favorable conditions, transfers excitation to the reactive center (generally a β-carbon–nucleofuge bond).

This results ultimately in a photo-Wagner–Meerwein rearrangement and/or a rearrangement with solvolysis; e.g., 1-Cl gives 2-Cl and 2-OAc (in acetic acid).[8] Results on isomeric dichlorides 3 with different Y and Y′ substituents[5,7] were consistent with the idea that the excitation transfer leading to fragmentation to chloride ion and an excited carbocation is an electron transfer from the π^* orbital of the photoexcited ring to the σ^* orbital of the carbon–chlorine bond. In particular, comparison of calculations from the Weller equation[9] (eq 1) (where ΔG is



$$\Delta G = E_{oxid}(D/D^+) - E_{red}(A/A^-) - E_{0-0}(D) - Ne^2/\epsilon r \quad (1)$$

the energy of electron transfer of the π^* electron to the carbon–nucleofuge bond, $E_{oxid}(D/D^+)$ is the oxidation potential of the aromatic ring, $E_{red}(A/A^-)$ is the reduction potential of the carbon–nucleofuge bond, E_{0-0} (D) is the excitation energy (0–0 band) of the aromatic ring, N is Avogadro's number, e is the charge on the electron, ϵ is the dielectric constant, and r is the charge separation) with

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