it follows that the "push" provided by 2,4-$(NO_2)_2C_6H_3S$ to expel a given amine from $T^{\pm}$ is not only greater than that exerted by an isobasic ArO in an analogue intermediate, but also greater than the "push" provided by 2,4-$(NO_2)_2C_6H_3O$ in a similar species. The latter conclusion can be explained by the small ΔpK_a (=0.6) between 2,4-dinitrophenol and its sulfur analogue.

Acknowledgment. This research was financially supported by "Dirección de Investigación de Universidad Católica de Chile" (DIUC), to which we are indebted.

Registry No. PTA, 934-87-2; NPTA, 15119-62-7; 1-formylpiperazine, 7755-92-2; piperidine, 110-89-4; piperazine, 110-85-0; 1-(β-hydroxyethyl)piperazine, 103-76-4; morpholine, 110-91-8; piperazinium ion, 22044-09-3.

Regiospecific Lithiation of Phenoxazine Ortho to the Oxygen Atom. Synthesis of 4-Mono- and 4,6-Disubstituted Phenoxazine Derivatives[1,2]

Yulia Antonio, Patricia Barrera, Olga Contreras, Fidencio Franco, Edvige Galeazzi, Josefina Garcia, Robert Greenhouse, Angel Guzmán, and Esperanza Velarde

Syntex, S.A., División de Investigación Apartado Postal 10-820, 11000 México, D.F., México

Joseph M. Muchowski*

Syntex Research, Institute of Organic Chemistry, 3401 Hillview Avenue, Palo Alto, California 94304

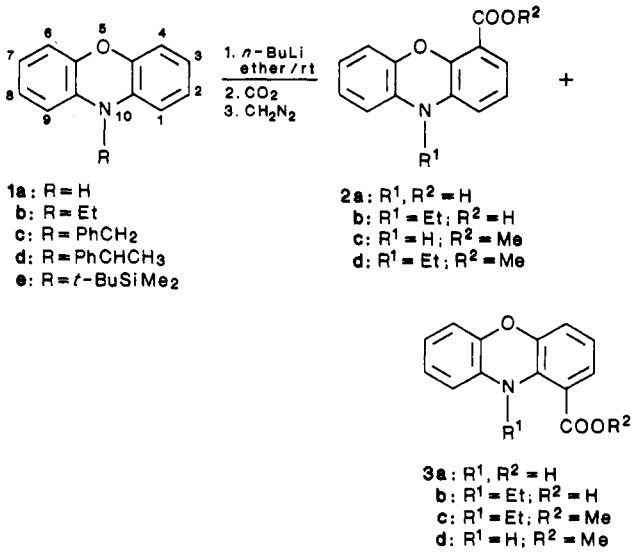
Received January 13, 1988

Under appropriate conditions, phenoxazine bearing a sterically demanding, bulky N-substituent (e.g., α-methylbenzyl or *tert*-butyldimethylsilyl) undergoes lithiation at C-4 or at C-4 and C-6 with *n*-butyllithium in THF solution. The lithiated species react with a variety of electrophilic reagents and upon subsequent N-deprotection provide access to 4-mono- or 4,6-disubstituted phenoxazines. This process is of particular synthetic utility (36–54% yields) when the N-substituent is *tert*-butyldimethylsilyl.

Nearly three decades ago, Gilman and Moore[3] reported that lithiation of phenoxazine (**1a**) and 10-ethylphenoxazine (**1b**) with *n*-butyllithium in ether followed by carbonation gave phenoxazine-4-carboxylic acid (**2a**) and the corresponding 10-ethyl derivative **2b** (Scheme I). Ten years later, Blank and Baxter[4] proved, by an unequivocal synthesis, that the carboxylic acid obtained by Gilman and Moore actually was phenoxazine-1-carboxylic acid (**3a**). The structure of the supposed 10-ethylphenoxazine-4-carboxylic acid was, however, apparently never questioned (see below).

In connection with one of our medicinal chemical programs, various 4-mono- and 4,6-disubstituted phenoxazine derivatives were required as synthetic intermediates. It was reasoned that lithiation of phenoxazine bearing a sterically demanding (and removable) nitrogen substituent should occur preferentially ortho to the oxygen atom and thus provide access to the required monosubstituted and/or disubstituted compounds. Support for this supposition was derived from a repetition of the Gilman and Moore lithiation–carbonation experiment on 10-ethylphenoxazine. Esterification of the crude product with diazomethane and preparative thin-layer chromatographic separation of the mixture, followed by saponification of the individual esters, provided two carboxylic acids in 13% and 22% yields. The more abundant product had a melting point (163–164 °C) that closely matched (mp 163.5–165 °C) that reported[3] for **2b**, while the less abundant acid (mp 149 °C), presumed to be **3b**, had previously not been reported. The structures of both carboxylic acids

Scheme I



were confirmed in the manner described in the latter part of this paper (see below).

The benzyl and trialkylsilyl moieties were selected for examination as substituents that might direct lithiation to C-4 (and C-6) of the phenoxazine nucleus. Lithiation of 10-benzylphenoxazine (**1c**) with 1 equiv of *n*-butyllithium in THF–hexane (0 °C, 15 min) followed by quenching with deuterium oxide, gave monodeuterated **1c** (52% d_1) with >99% of the label in the methylene carbon atom of the benzyl group.[6] The lithiation of 10-(α-methylbenzyl)phenoxazine (**1d**) and 10-(*tert*-butyldimethylsilyl)phenoxazine (**1e**)[7] was then examined since

(1) Contribution No. 753 from the Syntex Institute of Organic Chemistry.
(2) Presented in part at the 69th Canadian Chemical Conference, Saskatoon, Sask., Canada, June 1–4, 1986.
(3) Gilman, H.; Moore, L. O. *J. Am. Chem. Soc.* **1958**, *80*, 2195. A very similar ratio of the 1- and 4-carboxylic acids has been observed in the lithiation–carboxylation of 10-methylphenothiazine: Gschwend, H. W.; Rodriquez, H. R. *Org. React.* **1979**, *26*, 1; see especially p 47.
(4) Blank, B.; Baxter, L. L. *J. Med. Chem.* **1968**, *11*, 807.
(5) Gilman, H.; Moore, L. O. *J. Am. Chem. Soc.* **1957**, *79*, 3485.
(6) This experiment was performed in duplicate, and the deuterium incorporations reported are the arithmetic means.
(7) The trimethylsilyl analogue of **1e** was prepared in the same manner but it was too hydrolytically sensitive to be of use in the lithiation reactions.

0022-3263/89/1954-2159$01.50/0

Table I. Lithiation–Deuteration of 10-(α-Methylbenzyl)phenoxazine (1d)

run	n-BuLi, equiv	temp, °C	rctn time, h	deuterium distribution,[a] % total d_0	d_1	d_2	d_3	side chain d_0	d_1	total deuterium incorporation side chain	ring	total
1	1	0	1	24.4 (3.4)	64.2 (2.8)	11.3 (0.6)	–	61.8 (1.0)	38.2 (1.0)	0.38	0.49	0.87
2	2	0	3	2.5 (0.2)	44.3 (1.8)	5292 (2.0)	1.1 (0.1)	55.9 (0.6)	44.1 (0.7)	0.44	1.08	1.52
3	3	−20	3	9.6 (0.7)	70.9 (2.7)	18.2 (1.7)	1.0 (0.0)	57.0 (0.4)	43.0 (0.4)	0.43	0.67	1.11
4	3	0	1	2.0[b]	55.5	42.4	–	58.6	41.4	0.42	0.99	1.41
5	3	0	3	1.3 (0.2)	28.9 (0.2)	66.8 (0.0)	3.0 (0.1)	58.2 (0.1)	41.9 (0.2)	0.42	1.30	1.72

[a] Duplicate experiments unless otherwise specified. Results are the average with the mean deviation in parentheses. [b] Single experiment.

Table II. Lithiation–Deuteration of 10-(*tert*-Butyldimethylsilyl)phenoxazine (1e)

run	n-BuLi, equiv	TMEDA, equiv	temp, °C	rctn time, h	deuterium distribution,[a] % d_0	d_1	d_2	d_3	total deuterium incorporation
1	1	–	0	1	25.4[b]	64.4	9.7	–	0.84
2	1	1	0	3	22.9 (1.0)	62.7 (1.6)	11.7 (0.6)	1.8 (0.1)	0.92[c]
3	2	–	0	3	2.8[b]	67.4	29.7	–	1.27
4	2	2	0	3	11.4 (0.1)	64.8 (0.1)	21.9 (0.3)	1.6 (0.1)	1.16[d]
5	3	–	−20	3	32.1 (2.5)	61.5 (2.3)	4.7 (0.2)	1.7 (0.0)	0.76
6	3	–	0	3	2.4 (0.1)	61.5 (2.4)	34.6 (2.6)	1.5 (0.1)	1.36

[a] Duplicate experiments unless specified otherwise. Results are the average with the mean deviation in parenthreses. [b] Single experiments. [c] 5.8 (0.8)% recovered phenoxazine. Deuterium content not measured. [d] 6.8 (0.2)% recovered phenoxazine. Deuterium content not measured.

Table III. Lithiation–Dimethyl Disulfide Trapping of N-Protected Phenoxazines 1d and 1e

run	substrate	n-BuLi, equiv	Me_2S_2, equiv	temp, °C lithiation[b]	quenching	products,[a] % mono-MeS	di-MeS	starting material	phenoxazine	material balance, %
1	**1d**	2	2	0	0	9.6 (**4b**)	49 (**5b**)	5.6	32	96.2
2	**1d**	1.2	1.2	0	0[c]	21 (**4b**)	19 (**5b**)	15	35	90
3	**1d**	2	2	0	−78[c]	27 (**4b**)	24 (**5b**)	20	15	86
4	**1d**	1.5	1.6	0	−78	43 (**4b**)	6 (**5b**)	40	6	95
5	**1e**	1	1.2	0	−78	65 (**6b**)	7 (**7b**)	23	4	99

[a] Average of two experiments. Variation <2%. [b] All lithiations effected for 3 h. [c] Single experiments.

side-chain metalation was expected to be more difficult in the former and exceedingly unlikely in the latter. Compounds **1d** and **1e** were easily prepared, in good yields, by the sodium hydride induced alkylation of phenoxazine with α-methylbenzyl chloride and *tert*-butyldimethylchlorosilane, respectively. Whereas metalation of **1d** did not take place at all at −40 °C, even with *tert*-butyllithium (2 h), appreciable ring lithiation did occur in both **1d** and **1e** at 0 °C with *n*-butyllithium (1 h), as deduced from the NMR spectra of the crude products after quenching with D_2O. As a consequence, a detailed study was undertaken to determine the optimum conditions for mono- and dilithation of **1d** and **1e** with use of mass spectral analysis (see Experimental Section) to accurately assess deuterium incorporation.

The data in Table I show that the lithiation of 10-(α-methylbenzyl)phenoxazine (**1d**) occurred more rapidly at 0 °C than at −20 °C. Side-chain metalation could not be avoided, in spite of the presence of the methyl group, but monolithiation of this site remained constant at ca. 40%, irrespective of the number of equivalents of *n*-butyllithium used. Apparent monolithiation (and ca. 8% dilithiation) of the phenoxazine ring took place with 2 equiv of *n*-butyllithium at 0 °C (3 h, run 2) while dilithiation did not exceed 30% even when 3 equiv of *n*-butyllithium was used (run 5).

The results of the lithiation of the silylated phenoxazine **1e** were similar to those obtained for **1d** except that side-chain metalation was not a complicating factor (Table II). Lithiation with 1 equiv of *n*-butyllithium was effective for the introduction of one lithium atom (run 1), and this was not greatly improved when the lithiation was effected in the presence of tetramethylethylenediamine (TMEDA, run 2). As for **1d**, complete nuclear dilithiation of **1c** could not be accomplished with 3 equiv of *n*-butyllithium, even in the presence of TMEDA.

On the logical basis that the above deuteration studies would be predictive of the conditions required for the preferential generation of 4-mono- or 4,6-disubstituted phenoxazine derivatives, the putative monolithio derivative of **1d**, generated as in run 2, Table I (2 equiv of *n*-butyllithium, 0 °C, 3 h) was reacted with dimethyl disulfide at 0 °C. It was most surprising to find that under these conditions, a mixture of the 4-mono- and 4,6-bis(methylthio) compounds **4b** and **5b** (Scheme II) was formed in which the latter predominated by a factor of 5 (Table III, run 1). The **4b**:**5b** ratio improved to ca. 1 when 1.2 equiv of *n*-butyllithium was used (Table III, run 2) but this observation was not consistent with the deuteration studies either (of Table I, run 1). These results suggest that, at 0 °C, further lithiation of **4b** must occur at a rate quite comparable to the formation of **4b** itself. Indeed, if the putative monolithio species, generated with 1.5 equiv of *n*-butyllithium at 0 °C, was quenched with dimethyl disulfide at −78 °C, a temperature at which metalation of **1d** was expected to be very slow (see above), the **4b**:**5b** ratio rose to ca. 7 (Table III, run 4)! When analogous conditions were utilized with the silylated phenoxazine **1e**, the ratio of mono- to disubstitution (i.e., **6b**:**7b** exceeded 9 (Table III, run 5)).

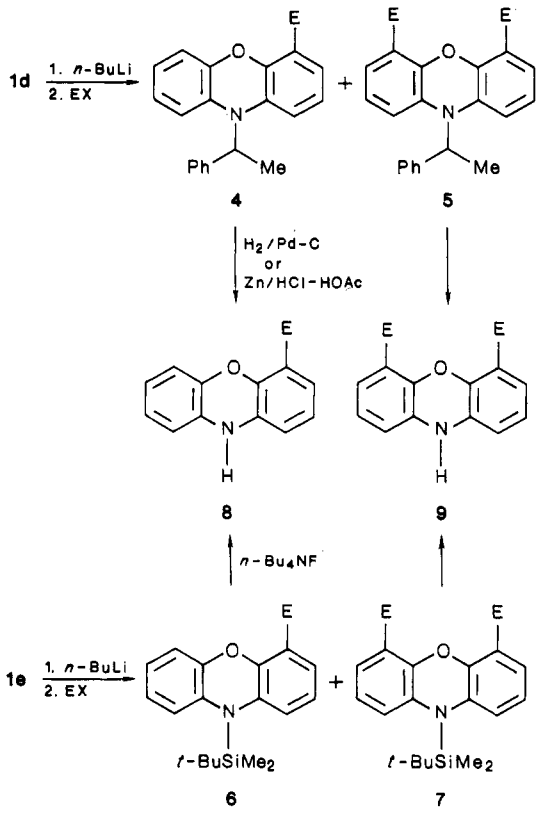
The following standard procedures for the selective preparation of mono- or disubstituted phenoxazine derivatives were adopted based on the data presented in Table III. All lithiation experiments were conducted at

Table IV. Synthesis of N-Protected 4-Mono- and 4,6-Disubstituted Phenoxazines

substrate	*n*-BuLi, equiv	electrophile (equiv)	E in product	products,[a] % mono	di	starting material	phenoxazine	material balance, %
1d	1.5	MeI (1.6)	Me	**4a** (40)	**5a** (5.5)	40	2	87.5
1d	3.3	MeI (3.8)	Me	–	**5a** (76)	18	2	96
1d	1.5	MeSSMe (1.6)	MeS	**4b** (43)	**5b** (6)	40	6	95
1d	3.3	MeSSMe (3.8)	MeS	–	**5b** (55)	–	3[b]	73
1d	1.5	Me_2NCHO (1.6)	CHO	**4c** (31)	**5c** (6)	51	3	90
1d	3.3	Me_2NCHO (3.8)	CHO	**4c** (12)	**5c** (61)	20	5	98
1d	1.5	Me_3SiCl (1.6)	Me_3Si	**4d** (55)	–	25	2	82
1d	3.3	Me_3SiCl (3.8)	Me_3Si	**4d** (2)	**5d** (63)	13	18	96
1d	1.5	CO_2 (excess)	CO_2Me	**4e** (38)[c]	**5e** (3)[c]	15	2[d]	82
1d	3.3	CO_2 (excess)	CO_2Me	**4e** (8)[c]	**5e** (50)[c]	6	28	92
1e	1	MeI (1.2)	Me	**6a** (61)	–	10	13	84
1e	1	MeSSMe (1.2)	MeS	**6b** (65)	**7b** (7)	23	4	99
1e	1	Me_2NCHO (1.2)	CHO	**6c** (75)	–	18	5	98
1e	3.3	Me_2NCHO (3.8)	CHO	**6c** (16)	**7c** (55)	2	4	77
1e	1	Me_3SiCl (1.2)	Me_3Si	**6d** (53)	–	4	6	63
1e	3.3	Me_3SiCl (3.8)	Me_3Si	–	**7d** (91)	4	3	98
1e	1	CO_2 (excess)	CO_2Me	**6e** (65)[c]	**7e** (9)[c]	13	3[e]	99
1e	3.3	CO_2 (excess)	CO_2Me	**6e** (6)[c]	**7e** (56)[c]	15	5[e]	91
1e	3.3	C_2Cl_6 (3.8)	Cl	**6f** (22)[f]	**7f** (69)[f]	–	8[g]	97

[a] All experiments were run in duplicate. The results are the mean and the deviation therefrom was ca. ±2%. [b] 4-(Methylthio)phenoxazine (**8b**) and 4,6-bis(methylthio)phenoxaine (**9b**) were also isolated in 13% and 2% yields, respectively. [c] Yields of methyl esters after esterification with diazomethane. [d] Methyl phenoxazine-4-carboxylate (**2c**) was also isolated in 24% yield. [e] Methyl phenoxazine-4-carboxylate (**2c**) was also isolated in 9% yield. [f] These yields are a minimum; the crude silyl compounds **6f** and **6f** isolated after column chromatography were desilylated directly to **8f** and **9g**. [g] Yield of phenoxazine obtained after desilylation of product mixture.

Scheme II



0 °C for 3 h with 1–1.5 and 3.3 equiv of *n*-butyllithium to generate the putative mono- and dilithio species, respectively. Mono- or disubstituted products were then produced preferentially by reaction with electrophilic reagents at −78 °C or −10 to 0 °C, respectively. The results of these experiments are compiled in Table IV. In general, where comparisons were made, the 4-mono- and 4,6-disubstituted phenoxazines **6** and **7**, derived from 10-(*tert*-butyldimethylsilyl)phenoxazine were produced in considerably better yields and with less recovery of starting materials (**1a** and **1e**) than were the corresponding phenoxazine congeners **4** and **5** (Table IV) derived from **1d**.

Table V. Synthesis of 4-Mono- and 4,6-Disubstituted Phenoxazines by Deprotection of the Corresponding N-Substituted Compounds

starting material	deprotection method	E in product	product (%)
4a	A[a]	Me	**8a** (63)
4b	B	MeS	**8b** (78)
4c	A	CH_2OH	**8e** (85)
4e	B	COOMe	**2c** (57)
5a	A	Me	**9a** (72)
5b	B	MeS	**9b** (70)
5c	A	CH_2OH	**9e** (72)
5f	A	COOH	**9f** (69)
6a	C	Me	**8a** (95)
6c	C	CHO	**8c** (96)
6d	C	Me_3Si	**8d** (90)
6e	C	COOMe	**2c** (92)
6f	C	Cl	**8f** (95)[b]
7c	C	CHO	**9c** (98)
7d	C	Me_3Si	**9d** (54)
7e	C	COOMe	**9h** (86)
7f	C	Cl	**9q** (95)[b]

[a] A = H_2/Pd–C; B = Zn/HCl; C = n-Bu_4NF. [b] The overall yields of **8f** and **9g** from **1e** were 22% and 69%, respectively.

The removal of the α-methylbenzyl group from **4** and **5** could be accomplished either by hydrogenolysis, at atmospheric pressure, over palladium on charcoal catalyst, or by reduction with zinc dust and hydrochloric acid in acetic acid solution. The mono- or disubstituted phenoxazines **8** or **9** were generally obtained in satisfactory yields by these processes (Table V), but the aldehydes **4c** and **5c** were overreduced to the benzylic alcohols **8e** and **9e**. In contrast, no limitations were encountered for the cleavage of the silyl group in **6** and **7** with tetra-*n*-butylammonium fluoride in THF solution.[8] Thus, the aldehydes **8c** and **9c** were isolated in very high yields and the chloro compounds **8f** and **9g**, the synthesis of which might have presented difficulties using the α-methylbenzyl pro-

(8) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. Corey, E. J.; Venkateswarlu, A. *Ibid.* **1972**, *94*, 6190.

Table VI. Purification Processes, Physical Constants, Etc. for 4-Mono- and 4,6-Disubstituted Phenoxazines

compd no.	purification conditions: method	purification conditions: solvent system	mp, °C	crystallization solvent
2c	CC[a]	EtOAc–hex (1:9)[b]	113–115.5	ether
4a	TLC	hex	oil	
4b	TLC	EtOAc–hex (2:98)	oil	
4c	CC	EtOAc–hex (1:9)	142–143	EtOAc
4d	CC	EtOAc–hex (2:98)	oil	
4e	TLC	EtOAc–hex (1:9)	oil	
5a	CC	hex	89–91	hex
5b	CC	hex	130	CH_2Cl_2–hex
5c	CC	EtOAc–hex (2:98)	181–182	CH_2Cl_2–hex
5d	CC	hex	130	CH_2Cl_2–hex
5e	CC	EtOAc–hex (1:9)	105–106	EtOAc–hex
6a	CC	hex	oil	
6b	TLC	EtOAc–hex (3:97)	oil	
6c	CC	EtOAc–hex (3:97)	61–62	pentane
6d	CC	hex	oil	
6e	TLC	EtOAc–hex (1:9)	oil	
7b	TLC	EtOAc–hex (3:97)	105–107	CH_2Cl_2–hex
7c	CC	EtOAc–hex (1:9)	161–162	CH_2Cl_2–hex
7d	CC	hex	77–78	CH_2Cl_2–pentane
7e	TLC	EtOAc–hex (1:9)	118–120	hex
8a	CC	EtOAc–hex (1:4)	91	pentane
8b	CC	EtOAc–hex (1:4)	115	ether–hex
8c	CC	CH_2Cl_2	182–183	EtOAc–hex
8d	CC	EtOAc–hex (2:98)	81.5	pentane
8e	CC	EtOAc–hex (35:65)	149–150	EtOAc–hex
8f	CC	EtOAc–hex (1:9)	82–83	CH_2Cl_2–pentane
9a	CC	CH_2Cl_2–hex (1:4)	150–151	CH_2Cl_2–hex
9b	CC	CH_2Cl_2–hex (1:4)	140–141	EtOAc–hex
9c	CRYST		266–267	EtOAc–hex
9d	CC	EtOAc–hex (5:95)	157–158	CH_2Cl_2–hex
9e	CC	EtOAc–hex (2:3)	183–184	EtOAc–hex
9f	CRYST		346 dec	EtOAc
9g	CC	EtOAc–hex (1:9)	175–176	CH_2Cl_2–pentane
9h	TLC	EtOAc–hex (1:4)	146–147	ether–hex

[a] TLC = thin layer chromatography on silica gel; CC = column chromatography on silica gel; CRYST = crystallization. [b] EtOAc = ethyl acetate; hex = hexane.

tecting group, were easily prepared via the silylated intermediates **6f** and **7f**. It is therefore apparent that the silylated phenoxazine **1e** is the preferred progenitor of 4-mono- and 4,6-disubstituted phenoxazines, both in terms of the efficacy in the introduction of the substituents and in the ease of removal of the N-protecting group.

The structures of the mono- and disubstituted phenoxazine derivatives **8** and **9** are supported by their elemental analyses (Table VII) and the full range of spectroscopic data. Much more definitive evidence for the

Table VII. Elemental Analyses of 4-Mono- and 4,6-Dusubstituted Phenoxazines

compd no.	mol formula	calcd C	calcd H	calcd N	found C	found H	found N
2b	$C_{15}H_{13}NO_3$	70.53	5.12	5.48	70.53	5.15	5.40
2c	$C_{14}H_{11}NO_3$	69.70	4.59	5.80	69.75	4.64	5.78
3c	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	71.38	5.64	5.13
4a	$C_{21}H_{19}NO$	83.78	6.35		83.57	6.46	
4b	$C_{21}H_{19}NOS$	75.75	5.74		75.83	5.59	
4c	$C_{21}H_{17}NO_2$	79.98	5.43		80.13	5.48	
4d	$C_{23}H_{25}NOSi$[a]						
4e	$C_{22}H_{19}NO_3$[b]						
5a	$C_{22}H_{21}NO$[c]						
5b	$C_{22}H_{21}NOS_2$[d]						
5c	$C_{22}H_{19}NO_3$	76.94	4.99	4.07	77.03	4.99	4.03
5d	$C_{26}H_{33}NOSi_2$	72.33	7.70	3.24	72.52	7.76	3.23
5e	$C_{24}H_{21}NO_5$	71.45	5.25		71.48	5.28	
6a	$C_{19}H_{25}NOSi$[e]						
6b	$C_{19}H_{25}NOSSi$[f]						
6c	$C_{19}H_{23}NO_2Si$	70.11	7.12		69.95	7.30	
6d	$C_{21}H_{31}NOSi_2$	68.22	8.45		68.01	8.38	
6e	$C_{20}H_{25}NO_3Si$[g]						
7b	$C_{20}H_{27}NOS_2Si$[h]						
7c	$C_{20}H_{23}NO_3Si$	67.95	6.55	3.96	68.16	6.47	3.88
7d	$C_{24}H_{39}NOSi_3$	65.24	8.90	3.17	65.39	8.99	
7e	$C_{22}H_{27}NO_5Si$[i]						
8a	$C_{13}H_{11}NO$	79.16	5.62		78.88	5.73	
8b	$C_{13}H_{11}NOS$	68.11	4.83	6.11	68.12	4.69	6.01
8c	$C_{13}H_9NO_2$	73.92	4.29	6.63	73.94	4.24	6.63
8d	$C_{15}H_{17}NOSi$	70.54	6.71		70.72	6.78	
8e	$C_{13}H_{11}NO_2$	73.22	5.20	6.56	73.02	5.19	6.54
8f	$C_{12}H_8ClNO$	66.21	3.70	6.43[j]	66.05	3.81	6.37
9a	$C_{14}H_{13}NO$[k]	79.59	6.20	6.63	79.67	6.17	6.64
9b	$C_{14}H_{13}NOS_2$	61.09	4.76	5.09[l]	61.31	4.71	4.96
9c	$C_{14}H_9NO_3$	70.29	3.79	5.86	70.04	3.94	5.64
9d	$C_{18}H_{25}NOSi_2$	65.99	7.69	4.27	66.17	7.87	4.32
9e	$C_{14}H_{13}NO_3$	69.12	5.38	5.75	69.17	5.36	5.58
9f	$C_{14}H_9NO_5$	61.99	3.34	5.16	62.11	3.28	5.02
9g	$C_{12}H_7Cl_2NO$	57.16	2.79	5.50	57.08	2.73	5.45
9h	$C_{16}H_{13}NO_5$	64.21	4.37	4.68	64.34	4.36	4.74

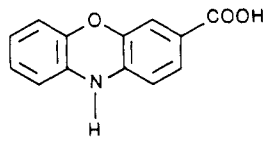
[a] Exact mass (high-resolution mass spectrum) calcd for $C_{23}H_{25}NOSi$ 359.1705, found 359.1698. [b] Exact mass (high-resolution mass spectrum) calcd for $C_{22}H_{19}NO_3$ 345.1365, found 345.1356. [c] Exact mass (high-resolution mass spectrum) calcd for $C_{22}H_{21}NO$ 315.1623, found 315.1622. [d] Exact mass (high-resolution mass spectrum) calcd for $C_{22}H_{21}NOS_2$ 379.1065, found 379.1054. [e] Exact mass (high-resolution mass spectrum) calcd for $C_{19}H_{25}NOSi$ 311.1705, found 311.1699. [f] Exact mass (high-resolution mass spectrum) calcd for $C_{19}H_{25}NOSSi$ 343.1426, found 343.1431. [g] Exact mass (high-resolution mass spectrum) calcd for $C_{20}H_{25}NO_3Si$ 355.1604, found 355.1607. [h] Exact mass (high-resolution mass spectrum) calcd for $C_{20}H_{27}NOS_2Si$ 389.1303, found 389.1309. [i] Exact mass (high-resolution mass spectrum) calcd for $C_{22}H_{27}NO_5Si$ 413.1659, found 413.1655. [j] Anal. Calcd for $C_{12}H_8ClNO$: Cl, 16.28. Found: Cl, 16.10. [k] Exact mass (high-resolution mass spectrum) calcd for $C_{14}H_{13}NO$ 211.0997, found 211.0998. [l] Anal. Calcd for $C_{14}H_{13}NOS_2$: S, 23.28. Found: S, 23.58.

structures of the monosubstituted compounds stems from that of phenoxazine-4-carboxylic acid (**2a**), which was conclusively established as follows. Firstly, this substance was different from both the 1-carboxylic acid **3a** and the 2-carboxylic acid[9] **10**. Secondly, 10-ethylphenoxazine-4-carboxylic acid (**2b**), synthesized from **4e**, was identical with that prepared according to Gilman and Moore[3,10] but

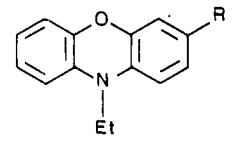
(9) Vanderhaege, H. *J. Org. Chem.* **1960**, *25*, 747.

(10) Careful repetition of the lithiation–carboxylation reaction reported by Gilman and Moore[3] for phenoxazine gave a mixture of mono- and dicarboxylic acids, which was esterified with diazomethane and separated by column chromatography on silica gel. This gave (order of increasing polarity) **3d** (34–39%), a diester (mp 109–110 °C, 8–9%) that appears to be dimethyl phenoxazine-1,4-dicarboxylate, an unknown diester (mp 190–194 °C, 19%), and a small amount of **2c** (0–4%).[11] When the metalation was effected with *tert*-butyllithium in ether (3 equiv, room temperature, 48 h), **2c** and **3d** were each formed in ca. 27% yield, while the two diesters were each isolated in ca. 1% yield.[12]

different from 10-ethylphenoxazine-3-carboxylic acid (**11a**) prepared by these authors from the 3-bromo compound **11b**.



10



11a: R = COOH
b: R = Br

In summary, a process has been devised that provides access to 4-mono- and 4,6-disubstituted phenoxazines **8** and **9** in three steps from phenoxazine. The overall yields of these compounds are quite acceptable, especially when **1e** is the precursor thereof. The method also has the distinct advantages of brevity and of commencing with a readily available starting material.[13]

Experimental Section

The melting points were determined in a Mel-Temp apparatus and are not corrected. The infrared spectra were measured with a Perkin-Elmer Model 237 grating spectrophotometer in chloroform solution unless otherwise specified. The NMR spectra were recorded with a Varian EM-390 or a Bruker WM-300 NMR spectrometer, and the chemical shifts were recorded as ppm (δ) from internal tetramethylsilane. The mass spectra were obtained with a MAT CH-7 or a MAT 1125 mass spectrometer. The high-resolution mass spectra were obtained with a MAT 311A mass spectrometer on samples that were at least of 95% purity by TLC and NMR spectroscopy.

The mass spectra of the deuterated derivatives of **1d** and **1e** were recorded on a MAT 311A mass spectrometer. The data was acquired with MAT SSX (rev. 6.0) acquisition software, and the results of 5–10 individual scans were averaged for each sample. The total deuterium content was calculated by using standard procedures[14] for the molecular ion. The deuterium content of the α-methylbenzyl substituent was calculated from the relative integrated intensities of the fragment ions of m/e 105–107. Control experiments using undeuterated standards showed that hydrogen rearrangement reactions did not significantly contribute to the relative intensities of these ions.

The high-resolution mass spectral data and the elemental analyses that are not found in the Experimental Section are found in Table VII.

The *n*-butyllithium in hexane solution was standardized by the method of Kofron and Baclawski.[15] All lithiation experiments were conducted under an atmosphere of dry nitrogen.

The term "dried" signifies dried over anhydrous sodium sulfate or anhydrous magnesium sulfate throughout the Experimental Section.

10-(α-Methylbenzyl)phenoxazine (1d). A solution of phenoxazine (76 g, 0.417 mol) in dry DMF (120 mL) was added dropwise to a stirred suspension of sodium hydride (50% suspended in mineral oil; 22 g, 0.458 mol) in dry DMF (500 mL) at room temperature. After the mixture was stirred for 1 h, α-methylbenzyl chloride (59 g, 0.43 mol) was added dropwise, and when the addition was completed, stirring was continued for a further 0.5 h. The solution was poured into water, the product was extracted with ethyl acetate, and the extract was washed with water, dried, and evaporated in vacuo. The residue, after crystallization from ether–hexane, gave a solid (98 g, 82% yield) with mp 100 °C: NMR ($CDCl_3$) δ 1.84 (d, 3 H, J = 7 Hz, Me), 5.19 (q, 1 H, J = 7 Hz, CH), 6.40 (m, 2 H, phenox) 6.72 (m, 6 H, phenox), 7.35 (m, 5 H, C_6H_5). Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.77; H, 6.11; N, 4.80.

10-(*tert*-Butyldimethylsilyl)phenoxazine (1e). Sodium hydride suspended in mineral oil (50%, 1.63 g, 34.2 mmol) was added to a solution of phenoxazine (5.0 g, 27.3 mmol) in anhydrous THF (100 mL), maintained in a nitrogen atmosphere, at room temperature. The mixture was heated at reflux temperature for 0.5 h, and then *tert*-butyldimethylchlorosilane (6.17 g, 41 mmol), dissolved in a DMF–THF mixture (1:4, 10 mL), was added thereto, and heating at reflux was continued for 5 min. The reaction mixture was poured into water, the product was extracted into ethyl acetate, and the extract was dried and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (250 g) with hexane–ethyl acetate (95:5) to elute the product (6.09 g, 75%), which after crystallization from hexane had mp 57 °C: NMR ($CDCl_3$) δ 0.29 (s, 6 H, Me_2Si), 1.00 (s, 9 H, *t*-BuSi), 6.93 (s, 8 H, phenox). Anal. Calcd for $C_{18}H_{23}NOSi$: C, 72.77; H, 7.79; N, 4.70. Found: C, 72.90; H, 7.86; N, 4.61.

Lithiation–Deuterium Quenching of 1d and 1e. The appropriate number of equivalents of *n*-butyllithium in hexane solution (2.43 M) was added to a stirred solution of the phenoxazine (2.00 g) in anhydrous tetrahydrofuran (70 mL) at the temperature indicated in Table I or II. After lithiation for the selected time period, deuterium oxide (at least 15 equiv) was added, and the reaction mixture was removed from the cooling bath and stirred at room temperature for 1 h. The reaction mixture was diluted with water (100 mL), the product was extracted into ethyl acetate, and the extract was dried and evaporated in vacuo. The residue was purified by passage through a short column of Florisil (40 g) with hexane–ether (9:1) for **1d** and hexane for **1e**. The phenoxazines were recovered in ≥95% yields in all cases except for the runs with TMEDA (Table II) where the recovery was ≥90%.

General Procedure for Selective Preparation of 4-Substituted Phenoxazine Derivatives 4 and 6. *n*-Butyllithium in hexane solution (2.43 M; 1.5 equiv for **1d**, 1 equiv for **1e**) was added to a stirred solution of the phenoxazine derivative (2.00 g) at 0 °C in anhydrous tetrahydrofuran (70 mL). After 3 h at 0 °C, the solution was cooled to −78 °C and the electrophilic reagent (1.6 equiv for **1d**, 1.2 equiv for **1e**) was added. The reaction mixture was stirred at −78 °C for 15 min and then it was poured into water. The product was extracted into ethyl acetate, and the extract was dried and evaporated in vacuo. The crude product was then purified by the method indicated in Table VI. The yields of purified products are found in Table IV, the melting points, solvents of crystallization, etc. are found in Table VI, and the elemental analysis and high resolution mass spectra are reported in Table VII. Typical NMR spectral data are given below.

4-(Methylthio)-10-(α-methylbenzyl)phenoxazine (4b): NMR ($CDCl_3$) δ 1.85 (d, 3 H, J = 7.0 Hz, Me), 2.43 (s, 3 H, SMe), 5.18 (q, 1 H, J = 7.0 Hz, CH), 6.32 (m, 2 H, phenox), 6.73 (m, 5 H, phenox), 7.34 (m, 5 H, C_6H_5).

4-Formyl-10-(*tert*-butyldimethylsilyl)phenoxazine (6c): NMR ($CDCl_3$) δ 0.34 (s, 6 H, Me_2Si), 1.06 (s, 9 H, *t*-BuSi), 7.00–7.60 (m, 7 H, phenox).

Lithiation and Carboxylation of 1d. Synthesis of Monoesters 4e and 2c and Diester 5e. The lithiation of **1d** was effected as described above. The reaction mixture was cooled to −78 °C, and a stream of dry gaseous carbon dioxide was then passed into the solution for 15 min. The reaction mixture was left to reach room temperature; it was poured into water, brought to pH 9 with dilute sodium hydroxide solution, and extracted with ethyl acetate. The extract was dried and evaporated in vacuo to give a mixture of **1d** (15%) and phenoxazine (2%). The aqueous alkaline phase was made acidic with 20% aqueous hydrochloric acid, and the products were extracted into ethyl acetate. The extract was washed with water, dried, and evaporated in vacuo. The crude product was dissolved in dichloromethane, and excess ethereal diazomethane was added. The solvent was removed in vacuo, and the residue was subjected to column chromatography on silica gel (150 g for a 28 mmol reaction) with ethyl acetate–hexane (1:9) as the eluting solvent. The monoester **4e** (38%) was obtained as an oil: NMR ($CDCl_3$) δ 1.87 (d, 3 H, J = 6.5 Hz, Me), 3.95 (s, 3 H, OMe), 5.18 (q, 1 H, J = 6.5 Hz, CH), 6.45–6.90 (m, 4 H, phenox), 7.10–7.25 (m, 3 H, phenox), 7.40 (s, 5 H, C_6H_5). The

(11) Barrera, P.; Velarde, E. Unpublished observations.
(12) Antonio, Y.; Galeazzi, E. Unpublished observations.
(13) Phenoxazine is sold by the Aldrich Chemical Co. It is very easily prepared on a large scale, albeit only in ca. 20% yield, from *o*-aminophenol. De Antoni, J. *Bull. Soc. Chim. Fr.* **1963**, 2871.
(14) Biemann, K., *Mass Spectrometry-Organic Chemical Applications*; McGraw-Hill: New York, 1962; p 204.
(15) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

diester **5e** (3%) had mp 105–106 °C after crystallization from ethyl acetate–hexane. The monoester **2c** (24%) had mp 113–114.5 °C after crystallization from ether and was identical to specimens obtained by deprotection of **4e** and **6e**.

Lithiation and Carboxylation of 1e. Synthesis of Monoesters 6e and 2c and Diester 7e. This reaction was carried out in the same manner as described above for the carboxylation of **1d**. The ethyl acetate extract of the alkaline solution gave **1e** (13%) and phenoxazine (3%). The aqueous alkaline solution was cooled to 0 °C and brought to pH 2 with dilute hydrochloric acid. The products were extracted into ethyl acetate, the extract was dried and evaporated in vacuo, and the residue was esterified with diazomethane as described above for the carboxylation of **1d**. The mixture of esters was spearated by preparative TLC on silica gel with hexane–ethyl acetate (9:1) as the developing solvent. The monoester **6e** was obtained as an oil (65%) and the diester **7e** as a solid (9%), mp 118–120 °C, after crystallization from hexane. A small amount (9%) of methyl phenoxazine-4-carboxylate (**2c**) was also isolated.

General Procedure for Selective Preparation of 4,6-Disubstituted Phenoxazine Derivatives 5 and 7. A 2.43 M solution of *n*-butyllithium in hexane (9.5 mL, 23 mmol) was added to a stirred solution of **1d** or **1e** (6.9 mmol) in anhydrous THF (70 mL) at 0 °C. The reaction mixture was stirred for 3 h, and then it was cooled to −10 °C. The electrophilic reagent (26.4 mmol) was added, the reaction temperature was raised to 0 °C, and after 1 h the mixture was poured into water. The reaction mixture was worked up as described for the preparation of the monosubstituted phenoxazines. The yields of purified products are found in Table IV, the purification methods, melting points, etc. are given in Table VI, and the elemental analyses and high resolution mass spectral data for these compounds are recorded in Table VII. Typical NMR spectra are given below.

4,6-Bis(trimethylsilyl)-10-(α-methylbenzyl)phenoxazine (5d): NMR ($CDCl_3$) δ 0.33 (s, 18 H, Me_3Si), 1.7 (d, 3 H, J = 6.5 Hz, Me), 5.08 (q, 1 H, J = 6.5 Hz, CH), 6.45 (dd, 2 H, J_o = 8 Hz, J_m = 1 Hz, H-1,9), 6.80 (m, 4 H, H-2,3,7,8), 7.36 (s, 5 H, C_6H_5).

4,6-Diformyl-10-(*tert*-butyldimethylsilyl)phenoxazine (7c): NMR ($CDCl_3$) δ 0.23 (s, 6 H, Me_2Si), 1.00 (s, 9 H, *t*-BuSi), 7.00–7.66 (m, 6 H, phenox), 10.56 (s, 2 H, CHO).

Synthesis of Dimethyl 10-(α-Methylbenzyl)phenoxazine-4,6-dicarboxylate (5e) and 10-(α-Methylbenzyl)-phenoxazine-4,6-dicarboxylic Acid (5f). Compound **1d** was reacted with 3.3 equiv of *n*-butyllithium as described above, and this solution was reacted with carbon dioxide and worked up as described for the synthesis of **4e**. The neutral fraction consisted of a mixture of the starting material (6%) and phenoxazine (28%). Acidification of the alkaline phase with dilute hydrochloric acid, extraction of the products into ethyl acetate, drying, and evaporation in vacuo gave a mixture of carboxylic acids. Direct crystallization of this mixture from hot ethyl acetate gave the dicarboxylic acid **5f** (ca. 40% yield), mp 350 °C dec. Anal. Calcd for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.57; N, 3.73. Found: C, 70.21; H, 4.61; N, 3.64.

If the crude carboxylic acid mixture was esterified with diazomethane and then subjected to column chromatographic separation on silica gel with hexane–ethyl acetate (9:1) as the eluting solvent, the dimethyl ester **5e** (50%) and a small amount (8%) of the monoester **4e** were isolated. The dimethyl ester **5e** had mp 105–106 °C after crystallization from ethyl acetate–hexane: NMR ($CDCl_3$) δ 1.86 (d, 3 H, J = 7.2 Hz, Me), 3.93 (s, 6 H, OMe), 5.20 (q, 1 H, J = 7.2 Hz, CH), 6.52 (dd, 2 H, J_o = 8.0 Hz, J_m = 1.8 Hz, H-1,9), 6.76 (t, 2 H, J_o = 8.0 Hz, H-2,8), 7.16 (dd, 2 H, J_o = 8.0 Hz, J_m = 1.8 Hz, H-3,7), 7.38 (s, 5 H, C_6H_5). Anal. Calcd for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.24. Found: C, 71.48; H, 5.28.

Synthesis of Dimethyl 10-(*tert*-Butyldimethylsilyl)-phenoxazine-4,6-dicarboxylate (7e). Compound **1e** was reacted with 3.3 equiv of *n*-butyllithium and then carboxylated as described for the sysnthesis of **5e**. The starting material (15%) and phenoxazine (5%) were isolated from the neutral fraction. Careful acidification of the alkaline phase to pH 2 at 0 °C, isolation of the product mixture, and esterification with diazomethane, as described for the synthesis of **6e**, gave a mixture of **2c**, **6e**, and **7e**. This mixture was separated by the method indicated in Table VI. Compound **7e** had mp 118–120 °C after crystallization from hexane.

Deprotection of 10-(α-Methylbenzyl)phenoxazine Derivatives 4 and 5. (a) By Catalytic Hydrogenolysis. A solution of the phenoxazine derivative in ethanol (**4c**, 200 mL/g) or ethanol (25–100 mL/g) and ethyl acetate (10–100 mL/g) containing suspended 10% palladium on carbon catalyst (50–100% by weight of phenoxazine taken) was hydrogenated at room temperature and atmospheric pressure until the theoretical amount of hydrogen was absorbed (3–21 h). The catalyst was removed by filtration through Celite, the filtrate was evaporated in vacuo, and the residue was purified by the method indicated in Table VI. The product yields are found in Table V.

(b) By Zinc and Hydrochloric Acid Reduction. Concentrated hydrochloric acid (0.5–1 mL/mmol phenoxazine derivative) was added dropwise with stirring to a solution of the N-substituted phenoxazine in glacial acetic acid (20–35 mL/g phenoxazine taken) containing suspended zinc dust (0.4–0.7 g/g phenoxazine derivative). After the addition was completed, the reaction mixture was stirred for 5–15 min and then poured into water. The product was extracted into ethyl acetate; the extract was washed with water, dried, and evaporated in vacuo. The residue was purified by the method indicated in Table VI, and the product yields are given in Table V.

Deprotection of the Silylated Phenoxazine Derivatives 6 and 7. Tetrabutylammonium fluoride (1–1.5 mol) was added to a stirred solution of the silylated phenoxazine (1 mol) in anhydrous tetrahydrofuran (1–100 mL/g phenoxazine) at room temperature. After being stirred for 5–15 min, the solution was poured into water, and the product was collected by filtration (**9c**) or extracted into ethyl acetate or dichloromethane (**8f**, **9g**). The extract was dried and evaporated in vacuo, and the residue was purified by the method indicated in Table VI and the product yields are compiled in Table V. Typical NMR spectra are given below.

Methyl Phenoxazine-4-carboxylate (2c): NMR ($CDCl_3$) δ 3.90 (s, 3 H, MeO), 5.43 (s, 1 H, NH), 6.30–6.89 (m, 6 H, phenox), 7.12 (dd, 1 H, J_o = 8.0 Hz, J_m = 1.7 Hz, H-3).

4-(Hydroxymethyl)phenoxazine (8e): NMR ($CDCl_3$) δ 3.93 (b s, 1 H, OH), 4.53 (d, 2 H, J = 5 Hz, CH_2), 6.23–6.80 (m, 7 H, phenox), 6.93 (s, 1 H, NH).

4,6-Diformylphenoxazine (9c): NMR ($CDCl_3$) δ 6.60–7.16 (m, 6 H, phenox), 8.43 (s, 1 H, NH), 10.36 (s, 2 H, CHO).

Synthesis of Phenoxazine-4-carboxylic Acid (2a) by Saponification of the Methyl Ester 2c. A solution of the ester **2c** (0.241 g, 1 mmol) in methanol (25 mL) and water (5 mL), containing potassium hydroxide (0.560 g), was heated at reflux temperature for 1 h. The solvent was removed in vacuo, 5% hydrochloric acid was added to the residue, and the product was extracted into ethyl acetate. The extract was washed with water, dried, and evaporated in vacuo. The residue (0.200 g), after crystallization from benzene–ether, had mp 181–182 °C and was identical in all respects with that obtained from the lithiation–carboxylation of **1e**. Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.31. Found: C, 68.59: H, 3.96; N, 6.13. This acid was, however, different from phenoxazine-1-carboxylic acid (**3a**), mp 244 °C, mmp with **2a** 215–221 °C, obtained according to Gilman and Moore,[3] as well as by the recently described procedure of Katritzky, et. al.[16]

Lithiation of 10-Ethylphenoxazine (1b). Synthesis of Methyl 10-Ethylphenoxazine-4-carboxylate (2d) and Methyl 10-Ethylphenoxazine-1-carboxylate (3c). The lithiation of 10-ethylphenoxazine (1.80 g, 9 mmol) was carried out in the same manner as described by Gilman and Moore,[3] but the carboxylation was effected with gaseous, not solid, carbon dioxide. The reaction mixture was diluted with water; the ether phase was separated and extracted with 10% aqueous sodium hydroxide. The aqueous phases were combined and made acidic with 20% hydrochloric acid, and the products were extracted into ethyl acetate. The extract was dried and evaporated in vacuo, and the residue was dissolved in ether and reacted with excess ethereal diazomethane. The ether was removed in vacuo, and the residue was subjected to preparative TLC with hexane–ethyl acetate (9:1) as the developing solvent. Three principal products (order of increasing

(16) Katritzky, A. R.; Vasquez de Miguel, L. M.; Rewcastle, G. W. *Heterocycles* **1987**, *26*, 3135.

polarity) were obtained: recovered 10-ethylphenoxazine (0.18 g, 10%), the ester **3c** [0.30 g, 13%; mp 91 °C after crystallization from hexane; NMR ($CDCl_3$) δ 1.16 (t, 3 H, J = 7.0 Hz, Me), 3.56 (q, 2 H, J = 7.0 Hz, CH_2), 3.89 (s, 3 H, OMe), 6.82–6.98 (m, 6 H, phenox), 7.34 (dd, 1 H, J_o = 7.6 Hz, J_m = 2.6 Hz, H-2], and the ester **2d** (0.50 g, 22%), an oil identical with that synthesized in the manner described below.

10-Ethylphenoxazine-1-carboxylic Acid (3b). A solution of **3c** (0.30 g) in methanol (10 mL) and 5% aqueous sodium hydroxide (5 mL) was heated at reflux temperature for 0.5 h. The reaction mixture was worked up in the manner described above for **2a**. Crystallization of the crude product from dichloromethane–hexane gave **3b** (0.227 g, 80%), mp 149 °C. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.72; H, 5.15; N, 5.49. This material was identical with a specimen synthesized from phenoxazine-1-carboxylic acid as follows. Phenoxazine-1-carboxylic acid (1.14 g, 5 mmol) was added portionwise to a suspension of sodium hydride (0.528 g, 11 mmol, 50% suspension in mineral oil) in dry DMF (10 mL) at 0 °C. The mixture was then stirred for 2 h at room temperature and cooled to 0 °C, and ethyl iodide (1.72 g, 0.88 mL, 11 mmol) was added thereto. After 18 h at room temperature, the reaction mixture was diluted with water, the product was extracted into ethyl acetate, and the extract was washed with saturated salt solution, dried, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (120 g) with hexane–ethyl acetate (4:1) to elute the oily ethyl ester of **3b** (1.10 g, 78%). Saponification of this material in the same manner as described above and crystallization of the product from dichloromethane–hexane gave 10-ethylphenoxazine-1-carboxylic acid (82% yield), identical with that described above.

10-Ethylphenoxazine-4-carboxylic Acid (2b). Saponification of **2d** in the manner described above and crystallization of the product from dichloromethane–hexane gave **2b** (85% yield), mp 163–164 °C (lit.[3] mp 163.5–165 °C).

Methyl 10-Ethylphenoxazine-4-carboxylate (2d). Sodium hydride (0.58 g, 1.2 mmol, 50% in mineral oil) was added to a stirred solution of methyl phenoxazine-4-carboxylate (**2c**, 0.241 g, 1 mmol) in dry DMF (5 mL, nitrogen atmosphere). After 0.5 h, ethyl iodide (0.129 g, 1.2 mmol) was added, and after stirring for 10 min the reaction mixture was poured into water. The ester was extracted into ethyl acetate; the extract was washed with water, dried, and evaporated in vacuo. The residue was passed through a short column of silica gel (15 g) with hexane–ethyl acetate (98:2) as the eluting solvent. The ester **2d** (0.255 g, 95% yield), identical with that obtained as described above, was obtained as an oil: IR ($CHCl_3$) 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.5 Hz, CH_3) 3.56 (q, 2 H, J = 7.5 Hz, CH_2), 3.89 (s, 3 H, OMe), 6.40–6.85 (m, 6 H, phenox), 7.07 (dd, 1 H, J_o = 8.0 Hz, J_m = 2.6 Hz, H-3); high-resolution MS calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1056.

Acknowledgment. We wish to thank Janice Nelson and Dr. Ken Straub, of the Syntex Analytical Department, for their extra effort on our behalf in obtaining the NMR and mass spectral measurements of the deuterated phenoxazine derivatives.

A New Preparation of 5-(Alkylthio)-1,2-dithiole-3-thiones and a Highly Functionalized 1,3-Dithiole-2-thione

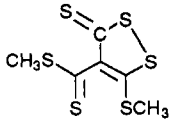
F. L. Lu, M. Keshavarz-K., G. Srdanov, R. H. Jacobson, and F. Wudl*

Institute for Polymers and Organic Solids, Department of Physics, University of California, Santa Barbara, California 93106

Received July 25, 1988

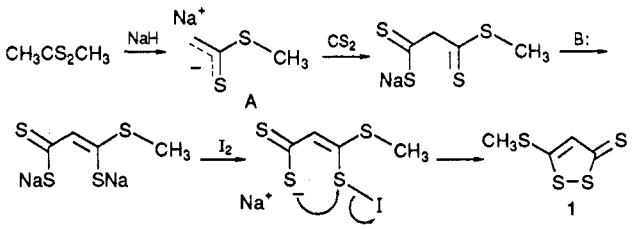
A "one-pot" preparation of the title 1,2-dithiole-3-thiones as well as the preparation and characterization of methyl 5-(methylthio)-2-thioxo-1,3-dithiole-4-dithiocarboxylate (**3**) are described. The X-ray structure determination of an iodine complex of the dithiolodithiole **5** is described in detail. The structure shows that this is a molecular solid with unusual three-dimensional intermolecular sulfur–sulfur "bonding".

The preparation of methyl dithioacetate via methylmagnesium bromide is well known,[1] and its use for the preparation of 1,2-dithiole-3-thione **1** according to Scheme I was reported recently.[2] We, independently, studied this sequence of reactions but with a different base and slightly different conditions. In Scheme I, B: is either sodium methyl dithioacetate or an excess of sodium hydride. If the chemical transformations depicted in Scheme I for methyl dithioacetate could be applied to dimethyl tetrathiomalonate, then heterocycle **2** would be formed.



2

Scheme I



Implicit in Scheme I was the gross, counterintuitive assumption that the ambident anion intermediate (A, Scheme I or B, Scheme II) *was more nucleophilic at its carbon than at its sulfur terminus.* In this publication we show that Scheme I is not only a viable method for the preparation of heterocycle **1**[2] but also for the synthesis of its 5-ethylthio and 5-benzylthio derivatives and that attempts to dithiocarboxylate dimethyl tetrathiomalonate at carbon, followed by iodine oxidation afforded a *1,3-dithiole* (**3**) rather than the expected 1,2-dithiole **2**. We proved the structure of **3** by a reductive alkylation of dithiolo dithiole **5** made by a pyrolytic route and by a pub-

(1) Meijer, J.; Vermeer, P.; Brandsma, L. *Recl, Trav. Chim. Pay-Bas* **1973**, *92*, 601.

(2) Hartke, K.; Hoffmann, R. *Liebigs Ann. Chem.* **1980**, 483. A "thio Claisen condensation" of methyl dithioacetate was also reported: Scheithauer, S.; Mayer, R. *Chem. Ber.* **1967**, *100*, 1413.

0022-3263/89/1954-2165$01.50/0