Synthesis of 22. A mixture of compound **19** (0.81 g, 2.7 mmol) and hydriodic acid (8 mL) was refluxed for 11 h. After being cooled to room temperature, the reaction mixture was extracted with Et_2O. The aqueous layer was saturated with NaCl and extracted again with Et_2O. The Et_2O extracts were combined and washed with a saturated solution of aqueous sodium thiosulfate. The Et_2O extract was then dried over anhydrous $MgSO_4$. Removal of Et_2O gave a sticky residue which on treatment with CH_2Cl_2–hexane yielded an almost colorless solid. Recrystallization was done from Et_2O–hexane to give the product (0.34 g, 44%) as an isomeric mixture (ratio 2:3): mp 87–91 °C; MS (EI), *m/e* 219 ($M^+ - CF_3$), 201 [$M^+ - (CF_3 + H_2O)$]; IR (KBr) 3500–3000 (br, hydrogen-bonded OH), 1400–1100 cm^{-1} (CF); ^1H NMR ($CDCl_3$) δ 2.0–2.5 (br, OH), 7.64 (m, Ar H); ^{19}F NMR ($CDCl_3$) δ −83.26 (s, CF_3), −84.12 (s, CF_3). Anal. Calcd for $C_{10}H_6F_6O_3$: C, 41.67; H, 2.08. Found: C, 41.22; H, 2.23.

Preparation of Ortho Diketone 23. The phthalanol **19** (8.00 g) was heated at 280 °C (bath) with a few drops of trifluoroacetic acid under an atmosphere of nitrogen. The compound was analyzed periodically on GC to check conversion to free ketone. The conversion to free ketone was essentially complete in 5–6 h. It was then distilled under reduced pressure to give the free ketone **23** as a colorless liquid (5.8 g, 81%), bp 74 °C (2.8 mm). After several days of standing under an inert atmosphere at room temperature, the ketone solidified to large colorless crystals which were extremely hygroscopic and low melting. No attempt was made to obtain a melting point. MS (EI), *m/e* 201 ($M^+ - CF_3$), 151 (201 − CF_2), 123 (151 − CO); IR (neat) 3080 (Ar CH), 1755, 1725 (C=O), 1400–1100 cm^{-1} (CF). Anal. Calcd for $C_{10}H_4F_6O_2$: C, 44.44; H, 1.48. Found: C, 44.65; H, 1.27. The free ketone **23** on exposure to the atmosphere readily absorbs moisture to give a colorless solid, mp 87–92 °C. GC, TLC, MS, and NMR (including isomer ratio) of this solid compare with that of compound **22**. Similarly, the free ketone **23** adds dry methanol to give a colorless crystalline solid whose GC, TLC, MS, and NMR (including isomer ratio) are similar to that of compound **19**.

Preparation of 26. This reaction was carried out at −78 °C. *o*-Dibromotetrafluorobenzene (36.96 g, 120 mmol) was dissolved in freshly distilled dry Et_2O (500 mL). A solution of *n*-BuLi (131 mL of 2.2 M solution in hexane, 288 mmol) was added dropwise at such a rate that the reaction temperature did not rise above −75 °C. After the addition of *n*-BuLi was over, the reaction mixture was stirred for 1/2 h. A solution of methyl trifluoroacetate (41.5 g, 324 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred overnight (16 h) during which the temperature rose to −32 °C. The reaction mixture was acidified with 3 M aqueous HCl. The layers were separated, and the aqueous layer was saturated with NaCl and extracted with Et_2O. This extract was combined with the original Et_2O layer. After drying over $MgSO_4$ and removing solvent, a viscous liquid residue was obtained. This was distilled under reduced pressure by using a Vigreux column (100 × 15 cm). The distillation was repeated on the major fraction of the distillate to yield a colorless viscous liquid (20.6 g, 46%), bp 68–73 °C (1.4 mm); two isomers in the ratio 1:1, MS (EI), *m/e* 357 (M^+ − OH), 343 (M^+ − OMe), 305 ($M^+ - CF_3$); IR (neat) 3580 (free OH), 3440 (bonded OH), 2850 (CH), 1640, 1510 (Ar), 1400–1050 cm^{-1} (CF); ^1H NMR (CD_3COCD_3) δ 3.37 (s, OMe), 3.44 (s, OMe) 8.25 (b, OH); ^{19}F NMR (CD_3COCD_3) δ −81.0 (m, CF_3), −138.0 (m, Ar CF), −148.0 (m, Ar CF); ^{13}C NMR (CD_3COCD_3) δ 52.68 (s, OMe), 53.05 (s, OMe), 104.7 (q, *J* = 35.0 Hz, CCF_3), 109.3 (q, *J* = 35.8 Hz, d, *J* = 8.5 Hz, CCF_3), 118.1 (d, *J* = 15.6 Hz), 122.0 (m), 142.0–147.0 (series d, Ar carbons), 123.0 (q, *J* = 285 Hz, CF_3). Anal. Calcd for $C_{11}H_4O_3F_{10}$: C, 35.29; H, 1.07. Found: C, 35.00; H, 1.13.

Collection of the X-ray Data and Solution of the Structure for Compound 8. Crystals were grown by evaporation of a dichloromethane–petroleum ether solution: $C_9H_5O_3F_3$ space group $P2_12_12-D^4$; *a* = 6.942 (19) Å; *b* = 8.047 (2) Å; *c* = 16.196 (56) Å; *Z* = 4. The crystal volume was 0.0028 mm^3. Lattice constants and intensity data were measured by using Nb-filtered Mo Kα radiation on a Picher FACS I diffractometer. A total of 1244 reflections were measured by using the θ–2θ scan method with a scan speed of 2°/min to 2θ − 55°. Upon irradiation, the crystal suffered an 80% decrease in intensity over a period of 48 h, presumably due to a degradation in the lattice. The structure was solved by MULTAN80 and refined to final *R* value of 0.164. The rather high *R* value reflects the poor quality of the crystal data.

Acknowledgment. We thank Dr. Wallace S. Brey, Jr., of University of Florida for NMR data, Dr. Costandy Saba of University of Dayton Research Institute for mass spectral analyses, and Dr. Albert Fratini of the University of Dayton for the X-ray analysis.

Registry No. **3**, 583-53-9; **6**, 90719-12-3; **8**, 76284-63-4; *cis*-**17**, 90719-13-4; *trans*-**17**, 90719-14-5; **18**, 90740-87-7; *trans*-**19**, 90719-15-6; *cis*-**19**, 90719-16-7; *cis*-**21**, 90719-17-8; *trans*-**21**, 90719-18-9; *cis*-**22**, 90719-19-0; *trans*-**22**, 90719-20-3; **23**, 90719-21-4; **24**, 827-08-7; *cis*-**26**, 90719-22-5; *trans*-**26**, 90719-23-6; MeO_2CCF_3, 431-47-0; $MeSiCl_3$, 75-79-6.

Tests of a Piperidino Mask for the Protection of Functionalized Carbon Sites in Multistep Syntheses

R. A. Olofson* and Duain E. Abbott

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received January 13, 1984

Primary alkyl chlorides (R–Cl) are easily isolated in excellent yield after treatment of the appropriate *N*-alkylpiperidines (R–NC_5H_{10}) with α-chloroethyl chloroformate. The method is exemplified by the conversion of a variety of alkylpiperidines, including systems with other sensitive functionalities, to the respective chlorides in yields varying from 90 to 97%. The potential significance of this process in drug congener preparation and in total synthesis is outlined. Similar fragmentations of *N-sec*-alkylpiperidines are described.

α-(chloroethyl chloroformate (ACE–Cl) recently has been introduced[1] as a clean and economical[2] reagent for the selective N-dealkylation of tertiary amines. High yield applications to the preparation of the prescription pharmaceuticals, nalbuphine and naltrexone, have been described.[1] Dealkylation is effected by heating the tertiary amine with ACE–Cl in 1,2-dichloroethane to give the intermediate **2** which is de*ACE*ylated just by warming in methanol. Ordinarily, the yields of **3** are nearly quanti-

$$R_3N \xrightarrow{\text{ACE-Cl}} \underset{\mathbf{1}}{[R_3\overset{+}{N}\text{–ACE Cl}^-]} \rightarrow \underset{\mathbf{2}}{R_2NC(=O)OCHClCH_3} + RCl$$

$$\mathbf{2} + MeOH \xrightarrow{\text{warm}} \underset{\mathbf{3}}{R_2NH\cdot HCl} + CO_2 + CH_3CH(OMe)_2$$

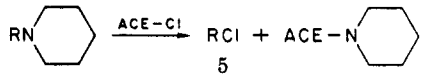
(1) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

(2) Reaction of a 1:1.1 neat mixture of MeCHO and $COCl_2$ in the presence of a reusable $PhCH_2N^+(n\text{-}Bu)_3\ Cl^-$ catalyst affords ACE–Cl in 96% vacuum distilled yield. See footnote 4 in ref 1.

0022-3263/84/1949-2795$01.50/0

tative, even when a variety of functionalities are present in the R groups.[1] With ACE–Cl, N-dealkylation selectivities parallel the data for an earlier, related reagent, vinyl chloroformate,[3,4] and are in accord with the occurrence of competing $S_{N}1$ (E_1) and $S_{N}2$ cleavages of the intermediate quaternary salt **1**. The empirical results of this competition can be summarized as follows: $ArCH_2$, allyl, and *tert*-alkyl[5] >> *sec*-alkyl > methyl[6] > primary alkyl >> piperidine ring opening.[1,3,7]

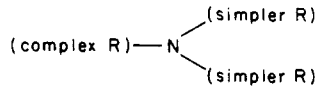
The immense discrimination against scission of a piperidine ring, even when the third nitrogen substituent is another primary alkyl moiety,[8] provided the foundation for the work described here. Tertiary, secondary, and primary alkylpiperidines (**4**) should react with ACE–Cl to



4 5 6

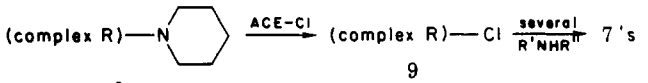
afford high yields of the alkyl chlorides[9] **5** even when the R unit in **4** is burdened by several functionalities. In effect, one would only be changing the focus of the original dealkylation process to make **5** instead of **3** the product of interest. Because methanolysis of **6** yields volatile products and salts, the facile isolation–purification of a neutral, nonpolar **5** was foreseen.

Several uses for the postulated new scheme can be imagined. For example, tertiary amines of type **7** are common



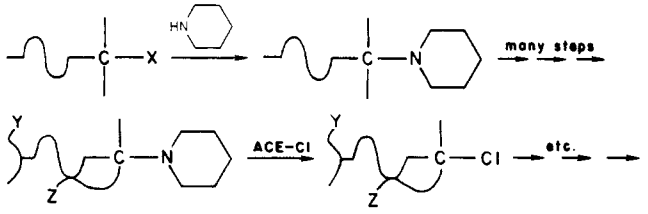
7

medicinal agents. When a new pharmaceutical lead compound of type **7** is found, several analogues are normally made in which the "simpler R" groups are varied to optimize activity and minimize side effects. For the efficient preparation of this analogue series, the second compound made and tested should be **8**, which then could serve as a single source for all of the compound variations **7** via the chloride **9** or its iodide substitution product.



8 9

Second, the new scheme could make the piperidino unit a useful multistep masking agent for the early introduction–protection and much later elaboration of functionality at a particular carbon site in complex total syntheses:



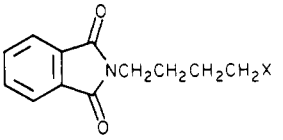
Note the availability of convenient methodology for the attachment of the piperidino unit by alkylation with an alkyl halide or by one of the newer palladium-catalyzed additions to alkenes or polyenes.[10] To take advantage of the enolization–activation of the α-carbon position, introduction of the piperidine as its amide might be preferred. Then the group could be kept in this oxidation state for several steps until convenient to reduce it to the amine with BH_3 or $LiAlH_4$. Similarly the group could be attached as an enamine and one or more of the many transformations based on enamine-type activation could be performed before reducing the modified enamine to the alkylpiperidine.

N-Alkylpiperidines also fulfill another prerequisite of a multistep masking agent. They are stable under most of the conditions required for the variety of transformations ordinarily utilized in complex syntheses. As their protonated salts, they even are deactivated toward reaction with electrophilic and radical reagents including oxidants in these categories. Note, that the facile interconversion between *N*-alkylpiperidines and their protonated salts, in effect, simultaneously provides two complementary masking moieties for a single potential reaction site. Other readily cleaved blocking groups, if stable to acids and electrophiles are not stable to bases and nucleophiles or vice versa; if stable to reduction, they are not stable to oxidation. A piperidine–piperidinium double mask efficiently resolves this dichotomy.

Another pair of advantages can be envisioned in schemes using this mask for multistep protection. First, acid–base extraction methods are readily adapted for the isolation of process intermediates. Second, the formation of readily crystallized amine salts can further facilitate the purification of these intermediates.

In choosing appropriate model reactions, it is evident from the dealkylation selectivity data above that the most stringent and useful tests should involve systems in which the attachment of "complex R" to the piperidine nitrogen is via an unactivated primary carbon. Cleavage of *N*-methylpiperidines would be purposeless and tests of benzyl, allyl, and *tert*-alkyl could be viewed as "straw man" experiments. Moreover, other methodology already exists for the late insertion of functionality at the latter three sites in total synthesis. Because of an added complication, some tests of *sec*-alkylpiperidines also could prove significant.

In the first experimental studies to be discussed, the (piperidinobutyl)phthalimide (**10**[11]) served as the model.



10, X = 1-piperidinyl
11, X = Cl

This was treated with ACE–Cl (2-fold excess) in 1,2-dichloroethane, first at 0 °C and then at reflux for 30 min. Some 1,8-bis(dimethylamino)naphthalene (**12**, stable to

(3) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.
(4) Olofson, R. A.; Schnur, R. C. *Tetrahedron Lett.* **1977**, 1571. Olofson, R. A.; Pepe, J. P. *Ibid.* **1977**, 1575. Olofson, R. A.; Yamamoto, Y. S.; Wancowicz, D. J. *Ibid.* **1977**, 1563.
(5) No comparison between these three groups is available.
(6) Except in very nonhindered systems where methyl can approach *sec*-alkyl in reactivity: Cy_2NMe gives 100% cyclohexyl loss, *i*-Pr_2NMe gives 100% isopropyl loss, $CyNMe_2$ gives 9:1 Cy:Me loss, and *i*-$PrNMe_2$ gives ca. 1:1 *i*-Pr:Me loss.[7]
(7) Schnur, R. C. Ph.D. Thesis, The Pennsylvania State University, 1973.
(8) *N*-Ethylpiperidine is converted to piperidine·HCl in 99% yield.[1]
(9) Or the generally equivalent alkenes (vide infra).
(10) Bender, D. D.; Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1982**, *47*, 1278 and references therein.
(11) Donahoe, H. B.; Seiwald, R. J.; Neuman, M. M. C.; Kazuo, K. K. *J. Org. Chem.* **1957**, *22*, 68.

ACE–Cl under the reaction conditions) was included in the reaction medium to guarantee that any acid from trace moisture or impurities in the reagent would be scavenged and not tie up the more weakly basic **10**. After the reflux period, the mixture was concentrated, then diluted with methanol, and heated again. A normal extraction workup followed by filtration through a silica plug afforded pure *N*-(4-chlorobutyl)phthalimide (**11**, mp 73–75 °C (lit.[12] mp 73–75 °C)) in 94% overall yield. In other tests, $PhCH_2N^+(n\text{-}Bu)_3\ Cl^-$ (**13**) (with and without **12**) was included in the N-dealkylation medium in the hope that the presence of added "naked chloride" would accelerate S_N2 displacement in the intermediate **1**. Yields of **11** varied from 94–97% (without **12** or **13**, the yield of **11** was 91%). Overall, the effect of added **12** and **13** seemed positive but small (with the demonstration of any advantage least certain for **13**). Yield reductions accompanied other experimental variations including changes in temperature, solvent, workup, addition sequence, and omission of methanolysis.

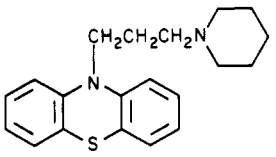
Under the standard conditions, 1-phenethylpiperidine (**14**) was converted to its chloride (**15**) in 90% distilled yield

$PhCH_2CH_2X$ $PhOCH_2CH_2CH_2CH_2X$

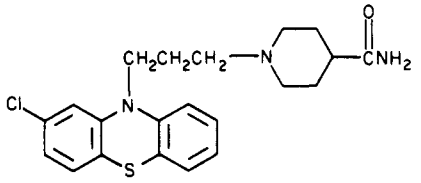
14, X = 1-piperidinyl **16**, X = 1-piperidinyl
15, X = Cl **17**, X = Cl

(84% without **12** and **13** present, 90% with KCl/18-crown-6 in place of **13**) and the (phenoxybutyl)piperidine (**16**) similarly afforded its chloride **17** in 91% distilled yield (no **13**, 80% with no **12** or **13**) (small distillation scale, actual yields higher). The scission, **14** → **15**, also was performed with vinyl chloroformate using an HCl treatment followed by methanolysis to destroy the ((vinyloxy)carbonyl)piperidine.[3] Then the yield of **15** was 81% (no **12** or **13** present).

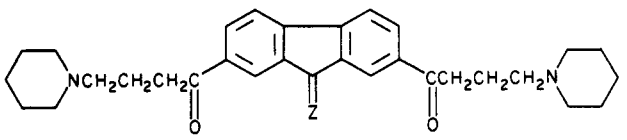
As part of a series of reactions more pertinent in drug congener synthesis, the (piperidinopropyl)phenothiazine (**18**), pipamazine (**19**, an antiemetic), and the tilorone[13]



18



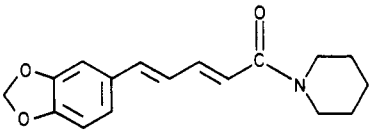
19



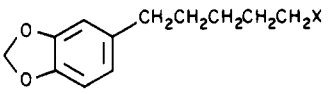
20, Z = H_2
21, Z = O

analogues (**20** and **21**) were treated with ACE–Cl. The chloropropyl compound from **18** was isolated in 95% recrystallized yield (**12** but no **13** present, 90% with no **12**). The formation of the chloro compound from **19** in 90% yield has extra significance because it exemplifies the equivalence between piperidine and a 3- or 4-substituted piperidine as a leaving group in the "double mask" concept. Thus, if a C-substituted piperidine is a new pharmaceutical lead, it can serve as the source of the series of analogues to be prepared even if the secondary amine portion of the molecule is not recovered intact after the N-dealkylation (the primary amide in **19** should react with ACE–Cl in the presence of a proton scavenger[7]). The double N-dealkylation of the fluorene **20** and the fluorenone **21** afforded the bis(chlorobutyryl) derivatives in 95% and 90% pure yields, respectively. Note that the measured yields are the products of the yields for two independent N-dealkylation steps.

In a final experiment involving a primary alkylpiperidine, **23** was cleaved to the corresponding chloride **24** in 95% yield. The reaction is meant to symbolize an extension to piperidides as already outlined. Here, **23** was made from commercial piperine **22** by hydrogenation followed by $LiAlH_4$ treatment.

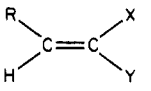


22 (piperine)



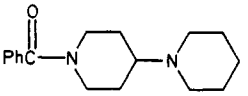
23, X = 1-piperidinyl
24, X = Cl

Attempts to extend the concept to *N-sec*-alkylpiperidines were limited to two preliminary investigations. Here the problem is not the facility or selectivity of the scission but rather the nature of the product. Either the alkyl halide or the alkene (E_1) could be obtained. Chemically these often are easily interconvertible. The main problems arise when the alkyl halide is desired and the actual product is the alkene (**25**) in which X and Y together comprise one H and one alkyl group so there is potentially little discrimination between the two ends of the C=C bond. Both tests involve such systems.

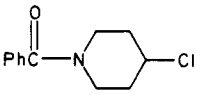


25

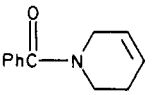
In the first experimental series, the *N*-benzoyl-4-piperidinopiperidine (**26**) was treated with ACE–Cl. A



26



27



28

full equivalent of **12** was included in the reaction medium to scavenge any HCl generated by an elimination cleavage. Methanolysis followed by normal workup afforded an oil identified as an 81:19 mixture of the chloride **27** and the alkene **28** in a total yield of 93%. The experimental conditions were varied in several ways in efforts to change the ratio, **27**:**28**. When the amount of **12** was reduced to 0.25 equiv, the ratio was 74:26 (total yield 90%), and with 0.1 equiv of **12** and 0.1 equiv of **13** present, the ratio decreased to 65:35 (92% yield). When the reaction mixture with 0.25

(12) Servigne, M.; Szarriasi, E.; Neuvy, L. *C. R. Hebd. Seances Acad. Sci.* **1954**, *238*, 2169.
(13) A broad spectrum orally active antiviral agent; orally active inducer of interferon production.

equiv of 12 was heated at 50 °C overnight (instead of at reflux for 45 min), the ratio was 72:28 (93% yield), and when a mixture of the same composition was heated very rapidly to reflux (continued for 45 min), a 75:25 product ratio was obtained (85% yield). The ratio changes are too small to explain meaningfully but large enough to encourage further experimentation. If the alkene **28** had been desired, this should be readily available by an E_2 elimination from **27**. If the chloride **27** had been the goal, the absolute yield was satisfactory.

With ACE–Cl, *N-sec*-alkylmorpholines should cleave between the *sec*-alkyl and N.[1] Since morpholine enamines are more easily made than their piperidino analogues, cyclododecanone was converted to its morpholine enamine which then was hydrogenated to *N*-cyclododecylmorpholine (**29**). Reaction of **29** with ACE–Cl in the presence of excess **12** gave cyclododecene in 80% yield. The cycloalkene yield was <50% when only a trace of **12** was included in the reaction medium. Chlorocyclododecane was not found in either experiment.

The reasons for the big differences in the ratio of elimination to substitution in the N-dealkylations of **26** and **29** are not understood. More work needs to be done before enough is known to predict the product in new systems—or to predictably change the product ratio.

From the cleavage yields obtained, it is evident that the "piperidine double mask" has passed its first model tests with high grades (average 93% per bond broken).

Experimental Section[14,15]

The 1,2-dichloroethane was distilled from P_2O_5 and stored over Linde 4-Å molecular sieves. Chromatography columns were packed with 70–230 mesh silica gel 60 (Merck). ACE–Cl was obtained from SNPE and purified by reduced pressure distillation, bp 77 °C (180 mm). Commercial **12** and **13** were dried by recommended procedures. Dealkylations were performed in oven-dried glassware by using a system designed to maintain a small positive pressure of dried N_2.

Reaction of *N*-(4-Piperidinobutyl)phthalimide (10) with ACE–Cl. ACE–Cl (0.68 g, 4.8 mmol) was added (5 min) to a rapidly stirred solution of **10**[11] (1.06 g, 2.3 mmol) and **12** (0.3 g) in dichloroethane (20 mL) maintained at 0 °C. The light yellow mixture was allowed to warm to room temperature, then refluxed for 30 min, and reduced to a third in volume by simple distillation. Methanol (20 mL) was added slowly enough to permit a convenient rate of CO_2 evolution. During this time the color of the mixture lightened noticeably. The mixture was refluxed for 1.5 h and then evaporated in vacuo, and the solid residue partitioned between CH_2Cl_2 (20 mL) and 1 M HCl (10 mL). The layers were separated and the organic layer was extracted with water (2 × 20 mL), dried (Na_2SO_4), and eluted through a silica plug (2 × 20 cm) with 10% ether–CH_2Cl_2. **11** was isolated from the eluate as a white solid: 0.84 g (94% yield); mp 73–75 °C (lit.[12] mp 73–75 °C). When 0.2 equiv of **13** was included in the reaction mixture, the yield of **11** was 97%, mp 74–75 °C. For other variations, see text and ref 15.

Reaction of 1-Phenethylpiperidine (14) with ACE–Cl. Reaction of ACE–Cl (9.29 g, 65 mmol) with **14** (distilled, 9.44 g, 50 mmol) in the presence of **12** (0.98 g, 4.5 mmol) and **13** (4.7 g, 15 mmol) in dichloroethane (50 mL) followed by methanolysis and extraction as above afforded an organic layer from which (2-chloroethyl)benzene (**15**) was isolated as a colorless liquid by distillation: 6.32 g (90% yield, NMR pure); bp 89 °C (18 mm) [lit.[16] bp 68.5–69 °C (4 mm)].

Reaction of *N*-(4-Phenoxybutyl)piperidine (16) with ACE–Cl. Dealkylation of **16**[17] (7.01 g, 30 mmol) with ACE–Cl (6.20 g, 44 mmol) in dichloroethane (50 mL) in the presence of **12** (1 g) and **13** (4.3 g, 14 mmol) as outlined above afforded **17** in 91% yield (5.07 g, NMR pure), bp 79 °C (0.3 mm) [lit.[18] bp 135–138 °C (12 mm)].

Reaction of 10-(3-Piperidinopropyl)phenothiazine (18) with ACE–Cl. Standard treatment of **18**[19] (2.37 g, 7.3 mmol) with ACE–Cl (1.36 g, 9.2 mmol) in dichloroethane (30 mL) in the presence of **12** (1.1 g) gave 1.91 g (95% yield, NMR pure) of 10-(3-chloropropyl)phenothiazine after workup as for **11** (including silica chromatography), mp 68–69 °C (lit.[19] mp 67–69 °C).

Reaction of Pipamazine (19) with ACE–Cl. Treatment as above of pipamazine (Nausidol (G. D. Searle) mp 138–139 °C (lit.[20] mp 139 °C)) (0.70 g, 1.74 mmol) afforded 10-(3-chloropropyl)-2-chlorophenothiazine as a light yellow oil after chromatography: 0.49 g (90% yield); ^{1}H NMR ($CDCl_3$) δ 7.2–6.8 (m, 7 H), 4.00 (t, 2 H, J = 6 Hz), 3.62 (t, 2 H, J = 6 Hz), 2.18 (quintet, 2 H, J = 6 Hz); high-resolution mass spectrum, m/e (relative intensity) 313.0092 ($M[^{37}Cl_2]^+$, 7%, $C_{15}H_{13}{}^{37}Cl_2NS$ requires 313.0086), 311.0118 ($M[^{37}Cl^{35}Cl]^+$, 33%, $C_{15}H_{13}{}^{37}Cl^{35}ClNS$ requires 311.0016), 309.0141 ($M[^{35}Cl_2]^+$, 44%, $C_{15}H_{13}{}^{35}Cl_2NS$ requires 309.0146), 248 (19%), 246 (51%), 234 (32%), 232 (100%).

Reaction of 2,7-Bis(4-piperidinobutyryl)fluorene (20) with ACE–Cl. Dealkylation of **20**[21] (1.42 g, 3.1 mmol) with ACE–Cl (1.14 g, 8 mmol) (no **12** or **13**) followed by standard methanolysis and chromatography afforded 2,7-bis(4-chlorobutyryl)fluorene of mp 173–176 °C (lit.[21] mp 172–175 °C) (compared with authentic sample) in 95% yield (1.11 g).

Reaction of 2,7-Bis(4-piperidinobutyryl)-9*H*-fluoren-9-one (21) with ACE–Cl. Similar treatment of **21**[21] (0.76 g, 1.56 mmol) gave crystalline 2,7-bis(4-chlorobutyryl)fluoren-9-one in 90% yield (0.56 g): mp 148–150 °C; IR (CH_2Cl_2) μ 5.80 (s), 5.93 (s); ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 2 H), 8.25 (d, 2 H, J = 8 Hz), 7.73 (d, 2 H, J = 8 Hz), 3.60 (t, 4 H, J = 6 Hz), 3.22 (t, 4 H, J = 6 Hz), 2.28 (quintet, 4 H, J = 6 Hz); high-resolution mass spectrum, m/e (relative intensity) 390.0591 ($M[^{37}Cl^{35}Cl]^+$, 1%, $C_{21}H_{18}{}^{37}Cl^{35}ClO_3$ requires 390.0603), 388.0624 ($M[^{35}Cl_2]^+$, 3%, $C_{21}H_{18}{}^{35}Cl_2O_3$ requires 388.0633), 352 (11%), 317 (15%), 316 (67%), 313 (10%), 311 (22%), 275 (100%), 247 (18%), 206 (46%), 189 (29%).

4-(5-Piperidinopentyl)-1,2-(methylenedioxy)benzene (23). Hydrogenation of commercial piperine in MeOH (Pd on carbon) according to the procedure of Borsche[22] afforded tetrahydropiperine which was reduced from the amide to the amine (**23**) by a standard $LiAlH_4$ reduction (in ether): clear oil from elution through silica; ^{1}H NMR ($CDCl_3$) δ 6.63 (s, 3 H), 5.86 (s, 2 H), 2.7–2.1 (m, 8 H), 1.8–1.2 (m, 12 H); high-resolution mass spectrum, m/e (relative intensity) 275.1881 (M^+, 11%, $C_{17}H_{25}NO_2$ requires 275.1885), 98 (100%); HCl salt mp 138–140 °C.

Reaction of 23 with ACE–Cl. Standard treatment of **23** (1.26 g, 4.6 mmol) with ACE–Cl (0.85 g, 5.9 mmol) in the presence of 0.01 g **12** gave **24** as a pale yellow oil in 95% yield (0.99 g) after methanolysis, extraction, and chromatography: ^{1}H NMR ($CDCl_3$) δ 6.63 (s, 3 H), 5.86 (s, 2 H), 3.50 (t, 2 H, J = 6 Hz), 2.52 (t, 2 H, J = 6 Hz), 1.9–1.3 (m, 6 H); high-resolution mass spectrum, m/e (relative intensity) 228.0744 ($M[^{37}Cl]^+$, 8%, $C_{12}H_{15}{}^{37}ClO_2$ requires 228.0731), 226.0766 ($M[^{35}Cl]^+$, 27%, $C_{12}H_{15}{}^{35}ClO_2$ requires 226.0761), 136 (20%), 135 (100%).

***N*-Benzoyl-4-piperidinopiperidine (26).** Acylation of 4-piperidinopiperidine (Aldrich) with benzoyl chloride in ether gave **26**: mp 108–110 °C (crystallized from hexanes); IR (CH_2Cl_2) μ 6.18 (vs); ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 5 H), 4.7–4.6 (m, 2 H), 3.2–2.9 (m, 2 H), 2.6–2.3 (m, 5 H), 1.8–1.4 (m, 10 H); high-resolution mass spectrum, m/e (relative intensity) 272.1888 (M^+, 17%, $C_{17}H_{24}N_2O$ requires 272.1888), 189 (12%), 167 (17%), 124 (100%), 105 (45%), 98 (26%).

Reaction of 26 with ACE–Cl. Treatment of **26** (1.37 g, 5 mmol) with ACE–Cl (0.94 g, 6.5 mmol) in the presence of **12** (1.07 g, 5 mmol) followed by methanolysis, extraction, and chromato-

(14) For a list of apparatus used in physical and spectral measurements see: Olofson, R. A.; Cuomo, J. *J. Org. Chem.* **1980**, *45*, 2538.
(15) For a complete discussion of this work including experimental data on variations just summarized in the main text see: Abbott, D. E. M.S. Thesis, The Pennsylvania State University.
(16) Conant, J. B.; Dirner, W. R. *J. Am. Chem. Soc.* **1924**, *46*, 232.
(17) Angel, J. *C. R. Hebd. Seances Acad. Sci.* **1963**, *257(4)*, 920.
(18) Sayles, D. C.; Degering, E. F. *J. Am. Chem. Soc.* **1949**, *71*, 3161.
(19) Caldwell, A. G. British Patent 811643, April 8, 1959; *Chem. Abstr.* **1960**, *53*, P17154f.
(20) Searle, G. D. and Co. British Patent 830709, March 16, 1960; *Chem. Abstr.* **1961**, *55*, P3625b.
(21) Albrecht, W. L.; Fleming, R. W.; Horgan, S. W.; Kihm, J. C.; Mayer, G. D. *J. Med. Chem.* **1974**, *17*, 886.
(22) Borsche, W. *Chem. Ber.* **1911**, *44*, 2942.

graphic filtration afforded an oil identified as a mixture of **27** and **28**, ratio 81:19 (93% total yield). The two products were separated by GC (5 ft × $^1/_4$ in. 20% SE-30 on Gas Chrom Q). **27** (slower): IR (CH_2Cl_2) μ 6.18 (s); ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 4.3–4.2 (m, 1 H), 3.7–3.3 (m, 4 H), 2.0–1.8 (m, 4 H); high-resolution mass spectrum, m/e (relative intensity) 225.0716 ($M[^{37}Cl]^+$, 5%, $C_{12}H_{14}{}^{37}ClNO$ requires 225.0734), 224.0671 ($M[^{37}Cl - H]^+$, 18%, $C_{12}H_{13}{}^{37}ClNO$ requires 224.0656), 223.0753 ($M[^{35}Cl]^+$, 18%, $C_{12}H_{14}{}^{35}ClNO$ requires 223.0764), 222.0687 ($M[^{35}Cl - H]^+$, 57%, $C_{12}H_{13}{}^{35}ClNO$ requires 222.0685), 105 (100%), 77 (57%). **28** (faster): IR (CH_2Cl_2) μ 6.18 (s); ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 5.9–5.7 (m, 2 H), 4.2–3.4 (m, 4 H), 2.2–1.7 (m, 2 H); high-resolution mass spectrum, m/e (relative intensity) 187.0991 (M^+, 29%, $C_{12}H_{13}NO$ requires 187.0997), 186 (16%), 105 (100%), 77 (36%). For a summary of product ratio vs. reaction condition variations see discussion; for experimental details see ref 15.

***N*-Cyclododecylmorpholine (29).** Cyclododecanone was converted to its morpholine enamine as described by Wakselman.[23] This was hydrogenated over PtO_2 in methanol at 2 atm and **29** was obtained as an oil (NMR and TLC pure) after a standard acid extraction workup: ^1H NMR ($CDCl_3$) δ 3.6–3.4 (m, 4 H), 2.6–2.3 (m, 5 H), 1.45–1.35 (m, 22 H); high-resolution mass spectrum, m/e (relative intensity) 253.2409 (M^+, 16%, $C_{16}H_{33}NO$ requires 253.2405), 224 (9%), 210 (11%), 182 (6%), 126 (100%).

Reaction of 29 with ACE–Cl. N-Dealkylation of **29** as above using 2 equiv of ACE–Cl and 2 equiv of **12** gave cyclododecene in 80% yield. By GC, IR, and NMR the product was identical with a sample of commercial *trans*-cyclododecene. No chlorocyclododecane was found (GC, NMR). For details of other reaction variations, see ref 15.

(23) Wakselman, C. *Bull. Soc. Chim. Fr.* **1967**, *10*, 3763.

Acknowledgment. We are grateful to the National Institutes of Health for the Grant (GM 13980) which supported this research. We also thank Dr. John Carson, Dr. Serge Lecolier, and Dr. Jean-Pierre Senet for valuable discussions and David Morrison for experimental support.

Registry No. **10**, 6821-01-8; **11**, 42152-99-8; **12**, 20734-58-1; **13**, 23616-79-7; **14**, 332-14-9; **15**, 622-24-2; **16**, 74246-27-8; **17**, 2651-46-9; **18**, 3733-38-8; **19**, 84-04-8; **20**, 34927-63-4; **21**, 34924-25-9; **22**, 94-62-2; **23**, 90670-01-2; **24**, 90670-02-3; **26**, 90670-03-4; **27**, 90670-04-5; **28**, 71785-91-6; **29**, 58748-24-6; AEC-Cl, 50893-53-3; 10-(3-chloropropyl)phenothiazine, 5909-59-1; 10-(3-chloropropyl)-2-chlorophenothiazine, 2765-59-5; 2,7-bis(4-chlorobutyryl)fluorene, 34927-52-1; 2,7-bis(4-chlorobutyryl)fluoren-9-one, 90670-00-1; tetrahydropiperine, 23434-88-0; 4-piperidinopiperidine, 4897-50-1; cyclodecanone, 830-13-7; *N*-(cyclododec-1-enyl)-morpholine, 3725-39-1; *trans*-cyclododecene, 1486-75-5.

Photostimulated Reactions of *o*-Bis(phenylsulfonyl)benzene Derivatives with Sodium Arenethiolates in Me_2SO. Evidence for Competing Pathways Involving a Common Intermediate σ Radical

Marino Novi,* Giacomo Garbarino, and Carlo Dell'Erba

Istituto di Chimica Organica dell'Università, C.N.R. Centro di Studio sui Diariloidi e loro Applicazioni, Corso Europa, Palazzo delle Scienze, 16132 Genova, Italy

Received December 8, 1983

The effects of incremental additions of benzenethiol on the product distribution of the photostimulated reactions of 2,3-bis(phenylsulfonyl)-1,4-dimethyl- (**1a**) and 1,2-bis(phenylsulfonyl)-3,4,5,6-tetramethylbenzene (**1b**) with sodium benzenethiolate in Me_2SO have been studied. In agreement with the electron-transfer mechanism previously proposed, the benzenethiol, by acting as a hydrogen atom donor trapping agent on the σ radical intermediates **2a,b**, favors the formation of the reduction products **5a,b** to the detriment of the other possible reaction products (viz., **3a**, **4a**, and **4b**). Substantial evidence that the formation of **3a**, **4a**, and **5a** as well as of **4b** and **5b** occurs via competing pathways involving respectively **2a** and **2b** as common intermediates has been obtained by the observation that the **5a**/**3a**, **5a**/**4a**, and **5b**/**4b** molar ratios can be well linearly correlated with the concentration of the benzenethiol. Inhibition of the reaction rate by the thiol is observed even in the experiments where there is negligible or no formation at all of the substitution product via an $S_{RN}1$ chain process. This observation together with the fact that the raw quantum yield of the reaction of **1b** with benzenethiolate (where only cyclization and reduction products are formed) exceeds unity ($\phi = 4$) indicates that the intramolecular arylation leading to **4a,b** proceeds, at least in part, via a chain process. An hypothesis on such a chain mechanism is advanced in Scheme III.

In a previous paper[1] we showed that the reaction of 2,3-bis(phenylsulfonyl)-1,4-dimethylbenzene (**1a**) with sodium benzenethiolate in Me_2SO, when subjected to photostimulation by a sunlamp, yields a mixture of the substitution product **3a**, of the cyclization product **4a**, and of the reduction product **5a**.

To account for the experimental results, we proposed the mechanism depicted in Scheme I according to which the reaction initially proceeds through a single electron transfer from the arenethiolate anion to the substrate with formation of the radical anion $\mathbf{1a}^{-\cdot}$ which fragments into benzenesulfinate anion and the σ radical **2a**. The various reaction products then arise from **2a** through the three competing paths C, D, and E. In particular, path C is supposed to involve a $S_{RN}1$ process, path D a homolytic intramolecular arylation, and path E the abstraction of a hydrogen atom from the medium.

The results we obtained recently[2] from an electrochemical investigation on the cathodic reduction of **1a** were consistent with this mechanism and, in particular, they

(1) Novi, M.; Dell'Erba, C.; Garbarino, G.; Sancassan, F. *J. Org. Chem.* **1982**, *47*, 2292.

(2) Novi, M.; Dell'Erba, C.; Garbarino, G.; Scarponi, G.; Capodaglio, G. *J. Chem. Soc., Perkin Trans. 2* **1984**, 951.

0022-3263/84/1949-2799$01.50/0