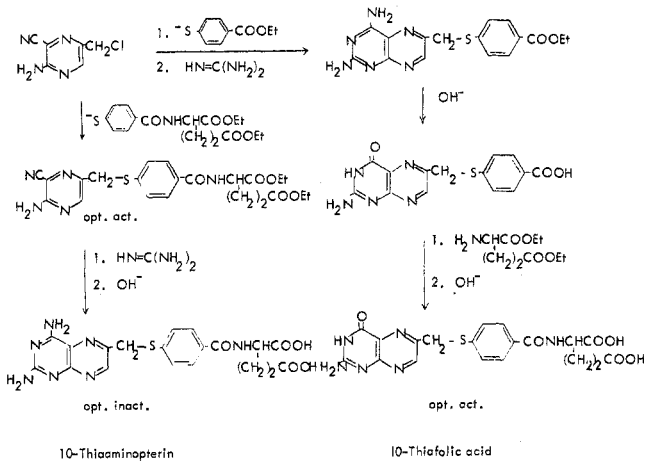

Figure 1.

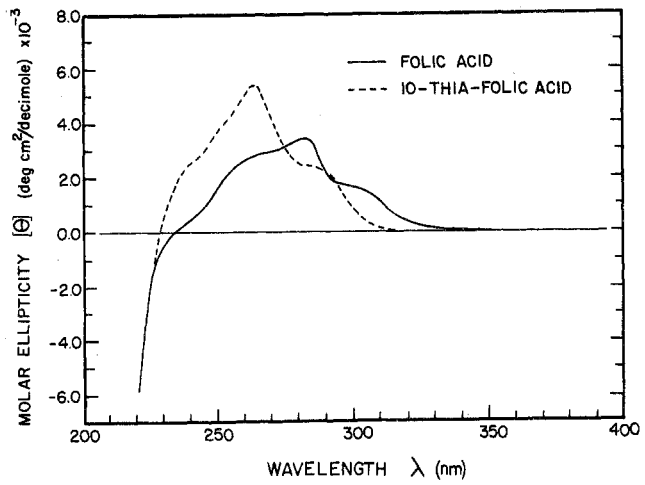

Figure 2. CD spectrum (0.01 *N* NaOH) of 10-thiafolic acid compared with that of folic acid.

In comparing the CD spectra of folic acid and of its 10-thia analog, it was noted that while the shapes of the absorption curves were similar, a considerable hypsochromic shift is seen in the 10-thia as compared to the 10-amino compound (Figure 2). Presumably, resonance involving the interaction of the heteroatom with the benzene ring is favored to a greater extent in the aminophenyl than in the thiophenyl compound. It should be noted that, while the CD spectra of methylenetetrahydrofolates have been measured,[12] the CD spectrum of folic acid has not been reported previously.

In contrast to the compounds discussed above, 10-thiaaminopterin proved to be optically inactive. This indicated that the *p*-aminobenzoyl-L-glutamyl side chain had racemized during the very basic conditions of the guanidine cyclization. An attempt was made to minimize racemization during the guanidine cyclization by heating the reaction mixture for 3.5 hr at 80° instead of refluxing it overnight. Analysis using TLC showed that cyclization was less than half complete, while the product has racemized totally, indicating that racemization is faster than cyclization.

Aminopterin synthesized by the addition of *p*-aminobenzoyl-L-glutamic acid to 2-amino-3-cyano-5-chloromethylpyrazine, followed by guanidine cyclization, also proved to be racemic. Both in the synthesis of aminopterin and the synthesis of 10-thiaaminopterin the intermediate 5-substituted 2-amino-3-cyanopyrazines retained full optical activity.

The problem of side-chain racemization during the guanidine cyclization cannot be ignored since it affects the biological interactions of the products. In the analog of methotrexate carrying a D-glutamic acid rather than an L-glutamic acid residue, ability to inhibit the growth of L-1210 leukemia cells is lowered considerably.[13] In addition, it was noted, using NMR spectroscopy, that the orientation of the aromatic rings of *p*-aminobenzoyl-L-glutamate and *p*-aminobenzoyl-D-glutamate on being bound to dihydrofolic acid reductase is quite different.[14]

The racemization problem in synthesizing folic acid analogs by the use of the Taylor synthesis can be avoided by carrying out the cyclization at the pteroic acid level and then forming the amide carrying the optically active substituent. No racemization takes place during the relatively mild conditions used to hydrolize esters of folic or related compounds.

Experimental Section

Materials. 2-Amino-3-cyano-5-chloromethylpyrazine was synthesized by the procedure of Taylor and Kobayashi.[6] 10-Thia-10-deazafolic acid and 10-thia-10-deaza-4-amino-4-deoxyfolic acid were prepared by a synthesis described elsewhere.[10]

CD Spectra. The spectra shown in Figure 2 were obtained with a Jasco J-20 automatic recording spectropolarimeter.

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Registry No.—Folic acid, 59-30-3; 10-thiafolic acid, 54931-98-5.

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Reaction of *n*-Butyllithium and 2,2,6,6-Tetramethylpiperidine Nitroxyl[1]

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Stable nitroxyl radicals[2-4] are widely used as radical scavengers[4] and as probes for certain types of molecular motion.[5] In the course of other problems that utilized ni-

Table I
Products from Reaction of *n*-Butyllithium and 2,2,6,6-Tetramethylpiperidine Nitroxyl (TEMPO)

Product	Yield, %[a] Based on BuLi	Based on TEMPO
Butane	13	
Butene	4	
Octane	1	
Di-*n*-butyl ether	2	
n-Butyl alcohol	14	
TEMPOBu	65	46
TEMP		11
TEMPOH[b]		11
$TEMPOCH_3$[c]		33
Total	99	101

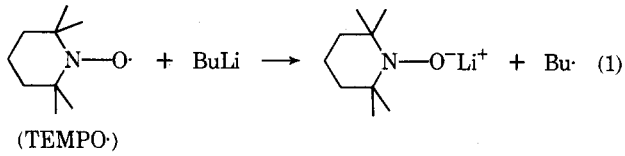
[a] The reaction for which these products are reported consumed 1.27 mmol of *n*-butyllithium and 1.80 mmol of TEMPO. [b] TEMPOH was detected by GLC as the quantitative conversion of TEMPOH to TEMPO in the injection port of the GLC was demonstrated using authentic TEMPOH. [c] $TEMPOCH_3$ is formed from $TEMPOLi^+$ by alkylation with dimethyl sulfate.

troxyl radicals in these applications, we required a procedure for destroying these radicals rapidly and quantitatively at low temperature in hydrocarbon solution. Here we report that the reaction of *n*-butyllithium with nitroxyl radicals is an effective method for accomplishing this objective, and describe the products of a representative reaction.

Results and Discussion

Addition of *n*-butyllithium (1.6 mmol, an excess) to a solution of 1.8 mmol of 2,2,6,6-tetramethylpiperidine nitroxyl[2,3,6] in *n*-hexane solution at −70° resulted in rapid disappearance (<1 min) of the characteristic red color of the stable radical. The resulting mixture was treated with 1,2-dibromoethane in order to convert excess *n*-butyllithium to *n*-butyl bromide. An aliquot of this reaction mixture was hydrolyzed and analyzed by GLC. A second aliquot was first treated with dimethyl sulfate to O-methylate lithium 2,2,6,6-tetramethylpiperidine nitroxide and facilitate its analysis by GLC, then hydrolyzed and analyzed. Table I summarizes the observed yields of products. These yields are corrected for the quantities of butane and butenes present in the starting *n*-butyllithium solution, and for the presence of 0.33 mmol of *n*-butyl bromide—representing unreacted *n*-butyllithium—among the products. They therefore represent the products of a reaction that consumed 1.27 mmol of *n*-butyllithium and 1.80 mmol of the nitroxyl radical. For convenience, the starting nitroxyl radical and the products derived from it are abbreviated as derivatives of tetramethylpiperidine (TEMP): thus, the nitroxyl radical is abbreviated TEMPO·, *N*-*n*-butoxytetramethylpiperidine is abbreviated TEMPOBu, and similar abbreviations are used for related compounds.

A detailed examination of the mechanisms leading to those products has not been carried out. A plausible sequence leading to the major products starts with one-electron oxidation of *n*-butyllithium by TEMPO·,[7,8] followed by coupling of a second equivalent of TEMPO· with the resulting *n*-butyl radical (eq 1 and 2). The extent of aggregation of the *n*-butyllithium may play a role in this reaction,[9] but has not been explored. It is ignored in this formulation.



(1)

(TEMPO·)

$$Bu\cdot + TEMPO\cdot \longrightarrow TEMPOBu \quad (2)$$

The variety of other products formed in the reaction clarifies the deviation of the stoichiometry of the reaction from the 2TEMPO:1BuLi expected on the basis of these two equations. Most of these products can be rationalized using straightforward reactions (eq 3–6).

$$Bu\cdot + Et_2O \longrightarrow BuH + CH_3\dot{C}HOEt \quad (3)$$

$$Bu\cdot + RH \longrightarrow BuH + R\cdot \quad (4)$$

$$BuLi + TEMPOBu \longrightarrow BuOBu + TEMP^-Li^+ \quad (5)$$

$$BuLi + TEMPO^-Li^+ \longrightarrow TEMP^-Li^+ + BuOLi \quad (6)$$

Reactions 5 and 6 are similar to the well-established cleavage of the oxygen–oxygen bond of dialkyl peroxides and lithium hydroperoxides by organolithium reagents.[9-11] Since these reactions appear to involve intermediate free alkyl radicals,[11] they may also contribute to other products formed. The observation among the products of a small quantity of a substance not alkylated by dimethyl sulfate and listed in Table I as TEMPOH is difficult to explain, and is probably an artifact. Independent experiments established that the conversion of authentic $TEMPO^-Li^+$ to $TEMPOCH_3$ by dimethyl sulfate was quantitative under the conditions employed in this assay. The presence of a derivative of TEMPO· that was not alkylated by dimethyl sulfate is compatible with its formulation as TEMPOH, but incompatible with the presence of a species having an acidic OH group in a solution containing butyllithium. It seems possible that $TEMPO^-Li^+$ present in this reaction mixture is less reactive than that in a solution containing only $TEMPO^-Li^+$ by virtue of its complexation with other species present in the mixture. In this event, the quantity of $TEMPO^-Li^+$ actually produced in the reaction should be considered to be the sum of the entries in Table I for TEMPOH and $TEMPOCH_3$.

The small quantities of butene and octane formed do not merit discussion, other than to note that the bimolecular reaction of butyl radicals would be expected to yield butene (by disproportionation) and octane (by coupling) in a ratio of approximately 1:7.[12] Thus, most of the butene and butane are formed by reactions other than bimolecular radical–radical disproportionation of *n*-butyl radicals. The coupling of TEMPO· and *n*-butyl radical generates little butane or butene (<5%).[8] Hence the majority of the butane formed in the reaction of butyllithium and TEMPO· probably results from hydrogen abstraction from some other component of the reaction system, probably by *n*-butyl radicals. The major hydrogen donor has not been identified.

Attempts to reduce the importance of reaction 2, and thereby to increase the probability of reaction between butyllithium and butyl radicals, by adding TEMPO· very slowly to an excess of butyllithium were only partially successful. The yield of TEMPOBu was decreased from 46 to 25% under the best conditions examined, and the relative yield of butane was significantly increased. The product balance in these experiments was not, however, sufficiently high to justify development of this system as a method of generating alkyl radicals in the presence of alkyllithium reagents.

In summary, the reaction of butyllithium with TEMPO· (and with other nitroxyl radicals examined) provides a rapid method of converting the radical to diamagnetic products.[14] The reaction mechanism has not been established in any detail, but the reaction products are compatible with initial one-electron oxidation of the organolithium reagent by the nitroxyl radical.

Experimental Section

Organometallic reagents were manipulated using standard procedures.[15] GLC analyses were carried out using an F & M Model 810 instrument and flame ionization detection, by unexceptional internal standard techniques. Butane and butene analyses utilized a 3-ft 3% Apiezon on alumina column; other analyses utilized an 8-ft 20% UC-W98 silicone rubber on Chromosorb P column. *n*-Hexane was purified by distillation under nitrogen from a suspension of sodium benzophenone ketyl. THF was distilled from $LiAlH_4$, and DME from disodium benzophenone dianion. TEMPO· was prepared by oxidation of TEMP with hydrogen peroxide catalyzed by sodium phosphotungstate;[6] it had mp 34–35° (lit.[6] mp 39°). Reagent dimethyl sulfate was purified by washing with cold saturated sodium bicarbonate solution and drying over potassium carbonate.[16] The dry solution was transferred to a Schlenk tube and traces of methanol were removed by a vacuum of 0.05 Torr. The dimethyl sulfate was stored in the Schlenk tube under prepurified nitrogen. It was reevacuated before use. Organolithium reagents were supplied by Foote Mineral Co., and were analyzed by the Gilman double titration method.[17]

***N*-Methoxy-2,2,6,6-tetramethylpiperidine (TEMPOCH$_3$).** DME (50 ml), 0.147 g (6.4 mg-atoms) of sodium metal, and 0.885 g (5.67 mmol) of freshly sublimed 2,2,6,6-tetramethylpiperidine nitroxyl were added to a flame-dried round-bottomed flask equipped with a condenser and a magnetic stirring bar and stoppered with a serum cap. The mixture was stirred under nitrogen at ambient temperature for 8 hr. Iodomethane (0.805 g, 5.67 mmol) was added to the resulting pale yellow solution of TEMPO$^-$Na$^+$, and the solution was stirred for an additional 4 hr under nitrogen. The reaction solution was saturated with sodium chloride, extracted with 50 ml of ether, and washed with distilled water and saturated sodium chloride solution. The ether was dried ($MgSO_4$) and concentrated to give a crude oil which was purified by column chromatography. The product was eluted from 6 g of silica gel G with 40 ml of cyclohexane followed by 40 ml of benzene, to give 0.4 g (41%) of *N*-methoxy-2,2,6,6-tetramethylpiperidine, having ir (CCl_4) 2980, 2930, 2810, 1475, 1385, 1355, 1060 cm^{-1}; NMR (CCl_4) δ 3.6 (s, 3 H, OCH_3), 1.0–1.5, multiplet (18 H); mass spectrum (70 eV) *m/e* (rel intensity) 171 (10.5), 156 (100), 88 (17), 69 (16), 55 (15), 41 (17).

***N*-Butoxy-2,2,6,6-tetramethylpiperidine (TEMPOBu).** The procedure for synthesizing TEMPOCH$_3$ was repeated using 1-iodobutane instead of 1-iodomethane, yielding 0.196 g (19%) of *N*-butoxy-2,2,6,6-tetramethylpiperidine, a colorless liquid, having ir (CCl_4) 2990, 2980, 2970, 2810, 1450, 1380, 1365, 1260, 1250, 1210, 1190, 1140, 1070, 1050 cm^{-1}. This ir spectrum was indistinguishable from that of TEMPOBu collected by GLC from a typical reaction of 2,2,6,6-tetramethylpiperidine and *n*-butyllithium. TEMPOBu had NMR (CCl_4) δ 3.6 (t, 2 H, J = 7 Hz, OCH_2–), 1.0–1.8 (m, 25 H).

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.20; H, 12.74; N, 6.57. Found: C, 73.06; H, 12.62; N, 6.44.

Lithium 2,2,6,6-Tetramethylpiperidine Nitroxide. A solution of 0.03 g (0.192 mmol) of TEMPO· in 3 ml of DME was titrated to a colorless end point with 0.47 *M* lithium naphthalenide in DME, giving lithium 2,2,6,6-tetramethylpiperidine nitroxide and naphthalene. Hydrolysis of this solution afforded *N*-hydroxy-2,2,6,6-tetramethylpiperidine. Treatment with dimethyl sulfate yielded TEMPOCH$_3$ in quantitative yield.

Reaction between *n*-Butyllithium and 2,2,6,6-Tetramethylpiperidine Nitroxyl. Typical Procedure. Freshly sublimed TEMPO· (0.278 g, 1.8 mmol) and ca. 10 ml of *n*-hexane were added under nitrogen to a dry, stoppered, 40-ml centrifuge tube. *n*-Dodecane (104 mg) and *n*-pentane (28 mg) were added as internal GLC standards, and the solution was cooled to −78° in a Dry Ice–isopropyl alcohol bath. One milliliter of 1.60 *M* *n*-butyllithium was added to the mixture by syringe. When the reaction was complete, excess *n*-butyllithium was quenched with ca. 100 mg (0.535 mmol, 0.05 ml) of 1,2-dibromoethane. Five milliliters of the resulting solution was transferred to another dry centrifuge tube and hydrolyzed with 0.5 ml of distilled water. The remaining solution was treated with 0.2 ml (excess) of dimethyl sulfate, and shaken vigorously for 1 min. The products were analyzed by GLC. The hydrolyzed sample was used for butane, butene, and 2,2,6,6-tetramethylpiperidine analyses, the alkylated sample for all others. The results of this and similar reactions are summarized in Table I.

Registry No.—TEMPOCH$_3$, 34672-84-9; 2,2,6,6-tetramethylpiperidine nitroxyl (TEMPO), 2564-83-2; iodomethane, 74-88-4; TEMPOBu, 56514-19-3; 1-iodobutane, 542-69-8; *n*-butyllithium, 109-72-8.

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A Mild Oxidation of Alkyl Halides to Aldehyde Derivatives

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There have been several reports of the oxidation of alkyl halides to ketones or aldehydes.[1] None of these methods offer the direct conversion of an alkyl halide to a protected aldehyde (ketone). This type of transformation has synthetic utility especially in the case of labile aldehydes.

Hydrazones have not been widely used for protection of aldehydes or ketones,[2] probably owing to the widespread belief that they are difficult to cleave. Recently, however, several methods of mild hydrolytic cleavage for hydrazones and substituted hydrazones have been developed,[2,3] making the use of this group a viable means of carbonyl protection.

In this communication we wish to report a high-yield synthesis of acyl hydrazones from alkyl halides. This reac-