48 hr at 80°. After cooling, the tube was opened and the solvent was removed on a rotary evaporator. The residue was mixed with concentrated aqueous NaCl solution and extracted three times with pentane. The pentane extract was dried over $CaCl_2$ and concentrated on a rotary evaporator. The remainder of the pentane phase was worked up by preparative gas chromatography, and each product was identified by combined GC and MS analysis.

The other solvolysis reactions were run in the same way, under the conditions reported in Table I.

Cyclopropyl *p*-tolyl ketone (23, X = CH_3):[20] NMR (CCl_4) δ 0.80–1.40 (m, 4 H), 2.25–2.85 (m, 1 H), 2.35 (s, 3 H), 7.15–7.95 (q, 4 H); MS M^+ *m/e* (rel intensity) 160 (57) and 119 (100); ir $\nu_{C=O}$ 1680 cm^{-1}.

1-*p*-Tolyl-3-buten-1-yne (22, X = CH_3): NMR (CCl_4) δ 2.40 (s, 3 H), 5.35–6.28 (m, 3 H), 7.0–7.90 (q, 4 H); MS M^+ *m/e* (rel intensity) 142 (100) and 116 (70); ir ν_{C-H} 915 and 970 cm^{-1}, $\nu_{C=C}$ 1600 and 1665 cm^{-1}, $\nu_{C\equiv C}$ 2200 cm^{-1}. The brominated derivative of **22** (X = CH_3) has been characterized by its mass spectra: M^+ *m/e* (rel intensity) 238 (8), 240 (8), and 119 (100) (p-$CH_3C_6H_4C{\equiv}O^+$) and by ir, $\nu_{C=O}$ 1710 cm^{-1}.

The trifluoroethanol ketal derivative of **23** (X = CH_3) was identified from spectroscopic data: MS M^+ *m/e* (rel intensity) 342 (4) and 243 (100); NMR (CCl_4) δ 1.25 (m, 4 H), 235 (s, 3 H), 2.30–2.50 (m, 1 H), 3.55–4.10 (q, 4 H), 7.0–7.5 (q, 4 H); ir ν[C $(OCH_2CF_3)_2$] 1160 and 1280 cm^{-1}.

Cyclopropyl *p*-anisyl ketone (23, X = OCH_3):[21] NMR (CCl_4) δ 0.75–1.40 (m, 4 H), 2.25–2.85 (m, 1 H), 3.85 (s, 3 H), 6.75–7.95 ppm (q, 4 H); MS M^+ *m/e* (rel intensity) 176 (36) and 135 (100); ir $\nu_{C=O}$ 1680 cm^{-1}.

1-*p*-Anisyl-3-buten-1-yne (22, X = OCH_3): NMR (CCl_4) δ 3.75 (s, 3 H), 5.20–5.95 (m, 3 H), 6.60–6.80 (m, 4 H); MS M^+ *m/e* (rel intensity) 158 (100) and 142 (80); ir ν_{C-H} 915 and 990 cm^{-1}, $\nu_{C=C}$ 1600 and 1635 cm^{-1}, $\nu_{C\equiv C}$ 2200 cm^{-1}. The brominated derivative of **22** (X = OCH_3) was characterized from its mass spectra, M^+ *m/e* (rel intensity) 254 (5), 256 (5), and 135 (100) (p-CH_3O-$C_6H_4C{\equiv}O^+$) and from ir, $\nu_{C=O}$ 1715 cm^{-1}.

The trifluoroethanol ketal derivative of **23** (X = OCH_3) has been identified from spectroscopic data: MS M^+ *m/e* (rel intensity) 358 (40) and 259 (100); NMR (CCl_4) δ 1.30 (m, 4 H), 2.35–2.60 (m, 1 H), 3.50–4.20 (m, 7 H), 6.60–7.70 (q, 4 H); ir ν_{C-O} 1170, 1250, and 1280 cm^{-1}.

D. Kinetic Procedures. The solutions used during the kinetic runs were prepared with absolute ethanol (Fluka) and with triply distilled water. The solvolysis rates were measured by means of a Combi titrator 3 D (Metrohm AG CH-9100, Herisau, Switzerland). The pH of the solution was adjusted to 6.88. About 30 ml of solvent was transferred to the reaction vessel, which was placed in a constant-temperature bath adjusted to the appropriate temperature within a range of ±0.01°. After the stirred solution had reached thermal equilibrium, 5 mg of reactant (**14** or **15**) were added to it. The solvolysis proceeded with continual stirring. The HBr liberated during the solvolysis was automatically neutralized with 0.015 *N* NaOH solution prepared with the same aqueous ethanol solvent used for the solvolysis mixture. The titer was registered automatically on a graph, and the data were gathered in such a way that the Guggenheim method[22] could be employed for calculation of the rate constants. The errors reported were determined by means of a least-squares computer program.

Acknowledgment. The authors gratefully acknowledge the financial support of the Centre National de la Recherche Scientifique of France (J.S.).

Registry No.—**10c,** 33745-37-8; **11,** 53968-63-1; **12,** 41893-65-6; **13,** 41886-92-4; **14,** 55088-78-3; **15,** 55088-79-4; **16,** 55088-80-7; **17,** 55088-81-8; **18,** 55088-82-9; **19,** 55088-83-0; **20,** 55088-84-1; **21,** 55088-85-2; **22** (X = H), 13633-26-6; **22** (X = CH_3), 30011-66-6; **22** (X = OCH_3), 55088-86-3; **23** (X = CH_3), 7143-76-2; **23** (X = CH_3) trifluoroethanol ketal derivative, 55088-87-4; **23** (X = OCH_3), 7152-03-6; **23** (X = H), 3481-02-5; **24** (X = CH_3), 55088-82-9; **24** (X = OCH_3), 55088-88-5; triphenylphosphine, 603-35-0; 1,3-dibromopropane, 109-64-8; cyclopropyltriphenylphosphonium bromide, 14114-05-7; *p*-methylbenzaldehyde, 104-87-0; K-*t*-BuO, 865-47-4; *p*-anisaldehyde, 123-11-5.

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Biological Spin Labels as Organic Reagents. Oxidation of Alcohols to Carbonyl Compounds Using Nitroxyls

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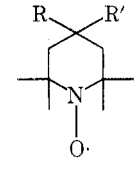
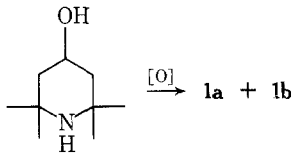
Stable nitroxyl radicals such as 4-oxotetramethylpiperidinooxy (**1,** TEMPO) are widely employed as spectroscopic probes for observing binding sites and molecular motion in macromolecules.[1,2] We report here that as a result of their remarkable redox properties, nitroxyl radicals in conjunction with an added oxidizing agent can conveniently convert a variety of alcohols to carbonyl compounds.



1a, R, R′ = =O
b, R = H; R′ = OH
c, R, R′ = H

Our interest in nitroxyls was first aroused by a report[3] that ketone **1a** was formed during the peracid oxidation of 4-hydroxy-2,2,6,6-tetramethylpiperidine (**2**) to the nitroxyl alcohol **1b.** No mechanism was proposed to account for this



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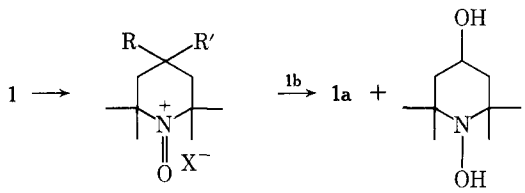
unexpected by-product. We reasoned that peracid might transform **1b** to the immonium oxide salt **3b**,[4] and that in-



3a, R, R′ = =O
b, R = H; R′ = OH
c, R, R′ = H

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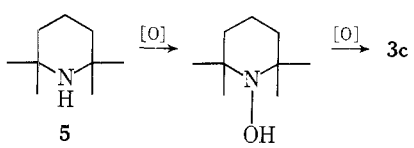
termolecular oxidation of **1b** by the reactive $^{+}N{=}O$ electrophile of **3b** would give rise to **1a.** The reported isolation by Russian workers[4c] of acetaldehyde as its 2,4-dinitrophenylhydrazone when **3b** (X = Br) is heated in ethanol supports this hypothesis. In fact, when 1 equiv each of 2,2,6,6-tetramethylpiperidinooxy[5] **1c** and *m*-chloroperoxybenzoic acid are stirred in CH_2Cl_2 at 0° and then treated with an equimolar amount of 4-*tert*-butylcyclohexanol and warmed to room temperature for 2 hr, a 70% yield of 4-*tert*-butylcyclohexanone is obtained. Since the nitroxyl component is itself derived from the corresponding amine, a much simpler and more convenient procedure employs commercially available 2,2,6,6-tetramethylpiperidine and 2 molar equiv of peracid.[6] Generation of the immonium oxide salt undoubtedly occurs by an overall four-electron oxidation, initially involving the hydroxylamine **6.** Table I summa-



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rizes the oxidation of representative alcohols by this modified technique. Yields, which are generally respectable, can be improved 5–10% by using the 1:1 nitroxyl–peracid reagent mentioned above. The method, however, is not adaptable to primary aliphatic alcohols since the aldehydes produced undergo further, as yet unelucidated, reactions in the oxidizing medium.

We can substantiate no one mechanism for this oxidation, but the results with 3-pentanol and 2-undecanol do provide a valuable clue. In these instances starting alcohol is consumed after 3.5 hr at room temperature, yet no pentanone or undecanone is formed, as is evident from infrared spectroscopic analysis in the OH and C=O regions. Refluxing the reaction mixtures eventually affords the desired ketones. One mechanism consistent with these observations may involve addition of the alcohol across the $^{+}N{=}O$ bond followed by Cope-like elimination of **7.** Unfortunately, any attempted purification of the reaction intermediate(s) also results in their rapid decomposition to ketone.

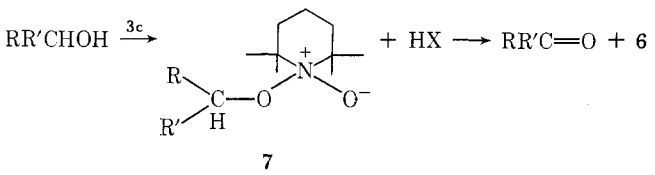

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Table I

Alcohol	Time, hr[a]	Product	Yield,[c] %
4-*tert*-Butylcyclohexanol	3	4-*tert*-Butylcyclohexanone[d]	70 (70% conversion)
Cyclooctanol	2	Cyclooctanone	69 (70% conversion)
Piperonyl alcohol	0.25	Piperonal	60
3-Pentanol	3.5[b]	3-Pentanone	45[e]
2-Undecanol	3.5[b]	2-Undecanone	50
3β-Cholestanol	10	Cholestanone	52

[a] Alcohol and oxidizing agent were mixed at 0°, then slowly warmed to room temperature over 15 min; reactions were continued at room temperature except as noted. [b] Reaction subsequently refluxed for 5 hr before work-up. [c] Yields are reported for chromatographed products, and are *not* optimized. [d] A small amount of 4-*tert*-butylcaprolactone was also formed. [e] This yield was determined by VPC.

We are currently exploring other aspects of nitroxyl-mediated oxidation, including remote control, site-specific oxidation, as well as the design of a catalytic process (perhaps electrochemical) based on the hydroxylamine–nitroxyl–immonium oxide redox cycle.

Experimental Section

Using Tetramethylpiperidine and *m*-Chloroperoxybenzoic Acid (1:2) for the Oxidation of Cyclooctanol. A mixture of *m*-chloroperoxybenzoic acid (Aldrich Chemical Co., 85% pure, 0.564 g, 2.8 mmol) in CH_2Cl_2 (8 ml) in a flask fitted with a $CaCl_2$ drying tube was cooled in an ice bath during the dropwise addition of tetramethylpiperidine (Aldrich, 1.4 mmol, 0.234 ml). After stirring for 30 min at room temperature the solution was recooled to 0° and cyclooctanol was added (0.178 g, 1.4 mmol) dissolved in CH_2Cl_2 (4 ml). The ice bath was removed and stirring was continued for 2 hr. Extraction with 5% aqueous $NaHCO_3$ then 5% HCl, drying of the organic layer ($MgSO_4$), and concentration afforded 0.363 g of red oil. Column chromatography over silica gel using 1:99 ether–hexane furnished 85 mg (0.68 mmol) of cyclooctanone having infrared and NMR spectra identical with those of an authentic sample. Continued elution afforded 54 mg (0.42 mmol) of starting alcohol.

Using Tetramethylpiperidinooxy and *m*-Chloroperoxybenzoic Acid (1:1) for the Oxidation of 4-*tert*-Butylcyclohexanol. To a 0° solution of the nitroxyl **1c** (0.206 g, 1.32 mmol) in CH_2Cl_2 (15 ml) was added solid *m*-chloroperoxybenzoic acid (Aldrich, 85% pure, 0.260 g, 1.32 mmol). The mixture was stirred under N_2 for 10 min, then treated with a solution of 4-*tert*-butylcyclohexanol (0.206 g, 1.32 mmol) in CH_2Cl_2 (4 ml). The orange color faded slightly and after 2 hr at room temperature, the crude product (0.404 g) was isolated as described above. Column chromatography over silica gel using hexane, then ether–hexane mixtures afforded 100 mg (0.65 mmol) of 4-*tert*-butylcyclohexanone which was identical with an authentic sample. Further elution yielded 60 mg (0.39 mmol) of 4-*tert*-butylcyclohexanol and a small amount (15 mg) of 4-*tert*-butylcaprolactone, as identified by its infrared spectrum.

Acknowledgment. The author acknowledges a particularly helpful discussion about this work with Professor Jerrold Meinwald. Thanks are due to the Research Corporation and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this research.

Registry No.—**1c**, 2564-83-2; tetramethylpiperidine, 768-66-1; *m*-chloroperoxybenzoic acid, 937-14-4; 4-*tert*-butylcyclohexanol, 98-52-2; cyclooctanol, 696-71-9; piperonyl alcohol, 495-76-1; 3-pentanol, 584-02-1; 2-undecanol, 1653-30-1; 3β-cholestanol, 17608-41-2.

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2-Amino-2-thiazoline. VIII.[1] A Nonregioselective Reaction of 2-Amino-2-thiazoline with Benzoyl Isothiocyanate to Give a Thermally Unstable Thiourea and a Thiazolotriazine

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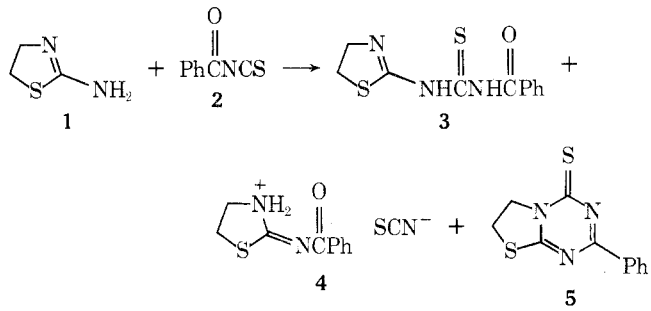
The reactions of 2-amino-2-thiazoline (**1**) with electrophiles giving products resulting from attack on either or both nitrogen atoms have been recently summarized.[2] Although the interaction of **1** with a given electrophile usually gives rise to a product resulting from a regioselective attack, behavior within a family of electrophiles cannot be predicted with certainty. The isothiocyanate family has provided a particularly perplexing series of examples in this regard. Yamamoto and Yoda,[3] for example, have reported that alkyl isothiocyanates react with **1** to give thiocarbamoyl derivatives resulting from nonregioselective attack on both nitrogen atoms. Phenyl isothiocyanate, on the other hand, exhibits regioselective attack on the exocyclic nitrogen atom of **1**,[4] whereas carbethoxy isothiocyanate undergoes the opposite mode of reaction and interacts with the ring nitrogen of **1**.[1] These examples demonstrate that reactions of **1** with isothiocyanates are characterized by lack of predictability as to regioselectivity.

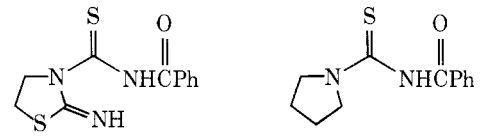
We report here the investigation of the reaction of **1** with another acyl isothiocyanate, namely, benzoyl isothiocyanate (**2**). If **2** were to behave as does carbethoxy isothiocyanate, regioselective attack of **2** on the ring nitrogen atom of **1** would produce a single derivative.

Results and Discussion

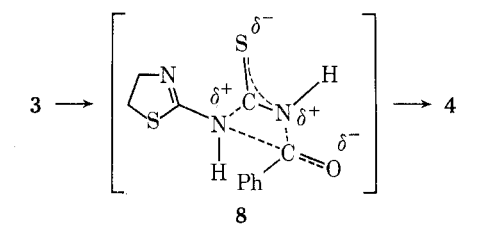
The reaction of 2-amino-2-thiazoline (**1**) with benzoyl isothiocyanate (**2**) was found to give three products: 1-benzoyl-3-(2-thiazolin-2-yl)-2-thiourea (**3**), 2-benzamido-2-thiazoline thiocyanic acid salt (**4**), and 6,7-dihydro-2-phenyl-4*H*-thiazolo[3,2-*a*]triazine-4-thione (**5**). The structural assignments of the products follow from their elemental analyses, chemical behavior, and spectral properties.



The ir spectrum of **3** shows diagnostic absorptions at 3280 and 1639 cm^{-1} in KBr and at 3440 and 1645 cm^{-1} in $CHCl_3$ solution, observations consistent with values reported for conjugated amides.[5] The alternate structure **6**, which would have resulted from attack of **2** on the ring nitrogen atom of **1**, may be ruled out on the following bases: the NMR spectrum of **3** shows NH signals at δ 10.12 and 11.35 (the imino NH of **6** would be expected to appear at much higher field[6]); the chemical behavior of **3** is also consistent with that of a disubstituted thiourea in that **3** gives a positive ammoniacal silver nitrate test, which **6** would not be expected to exhibit;[7] furthermore, the *S*-methyl derivative of **3**, generated in situ from **3** and iodomethane, proved to be stable to alkali at room temperature, but liberated methyl mercaptan after being heated at 100° for 30 sec. This latter test is diagnostic of 1,3-disubstituted thioureas.[7] A model compound, 1-(*N*-benzoylthiocarbamoyl)pyrrolidine (**7**), prepared from **2** and pyrrolidine, which would have been expected to behave similarly to **6**, gave negative results in both the ammoniacal silver nitrate and *S*-methyl tests mentioned above.



Compound **3** undergoes facile thermal conversion to **4** on being heated at the boiling point of common solvents for a short time. The phenomenon, first noted on attempted recrystallization of **3** from CH_3CN, probably proceeds through the transition state **8**. The alternate process, i.e., thermal retroreaction of **3** to give **1** and **2**, followed by benzoylation of **1** to give **4**, is untenable, since no **5** is produced. Qualitatively, the rate of thermolysis of **3** in boiling solvents to give **4** was shown to proceed as follows: very slowly in methylene chloride, slowly in chloroform or methanol, moderately rapidly in 1,2-dichloroethane, and very rapidly in dioxane. Also **3** undergoes rearrangement to **4** near its melting point as evidenced by the strong $FeCl_3$ test exhibited by the cooled melt of **3** as well as by its ir spectrum.



The structure of **4** was elucidated by its unequivocal synthesis as outlined in Scheme I. 1-Benzoyl-3-(2-hydroxyethyl)-2-thiourea (**9**) was prepared and cyclized to **10** as previously described.[8] The free base **10** was also prepared

Scheme I