washed with water. Recrystallization from methanol was accompanied with considerable loss of product and no improvement of the melting point: 0.18 g (90%); mp 167–70 °C; IR 3020, 2920, 1585, 1500, 1470, 1438, 1420, 1270, 1230, 1160, 1120, 1070, 850, 750, 740, 730, 690 cm^{-1}; H^1 NMR δ 4.17 (s, 3 H), 7.62 (m, 14 H), 8.35 (s, 2 H). Anal. Calcd for $C_{25}H_{19}N$: C, 90.05; H, 5.74; N, 4.20. Found: C, 89.21, H, 5.79; N, 4.20.

Pyrrole **15** (100 mg, 0.3 mmol) in benzene reacted immediately with *N*-phenylmaleimide (52 mg, 0.3 mmol) at room temperature. Evaporation of benzene and recrystallization of the product from methanol gave white needles of adduct **16**: 100 mg (76%); mp 203–5 °C; IR 3050, 3020, 2960, 1760 (sh), 1700, 1490, 1440, 1380, 1325, 1190, 1160, 1150, 985, 860, 750, 710, 690, 680 cm^{-1}.

1,3-Diphenylnaphtho[2,3-*c*]thiophene (17a). A mixture of **13** (0.2 g, 0.6 mmol) and phosphorus pentasulfide (0.26 g, 1.2 mmol) in pyridine (7 mL) was heated under nitrogen for 15 min. The cold reaction mixture furnished thiophene **17a** as deep red needles: 0.19 g (95%); mp 194–5 °C (lit.[10] mp 198–202 °C); IR 3040, 1590, 1500, 1445, 1120, 1030, 870, 765, 750, 740, 690 cm^{-1}. As reported,[10] thiophene **17a** did not add *N*-phenylmaleimide easily even on heating.

1,3-Diphenylnaphtho[2,3-*c*]furan (17b) and Adduct 18. A methanolic solution of **13** (1 g, 3 mmol in 15 mL) was heated to boiling on a steam bath. Sodium borohydride (0.1 g, 30 mmol) was added to the hot solution, and the reaction mixture was allowed to stand at room temperature for 20 min. Water was added and the resulting solid was collected and dried. TLC showed the presence of unreacted **13** in the mixture; nevertheless, the mixture (0.3 g) was treated with hot acetic acid and furan **17b** crystallized out as deep reddish-brown glistening plates. The product was collected and washed with acetic acid: 0.15 g (50% based on complete reduction of one carbonyl group); mp 140–3 °C (lit.[10] mp 148–51 °C); IR 1595, 1470, 1190, 910, 855, 770, 740, 690 cm^{-1}.

As reported by Cava and VanMeter,[10] furan **17b** is unstable in organic solvents and added *N*-phenylmaleimide instantaneously at room temperature to give adduct **18** (85%): mp 284–6 °C (lit.[10] mp 287–90 °C); IR 3060, 3000, 1775 (sh), 1700, 1600, 1500, 1450, 1380, 1345, 1315, 1285, 1200, 1055, 1000, 960, 920, 890, 790, 770, 750, 730, 713, 650 cm^{-1}. Adduct **18** (100 mg, 0.2 mmol) was dissolved in acetic acid–concentrated sulfuric acid (3:1 mL) and heated on a steam bath. The yellow imide **19** precipitated out in quantitative yield (95 mg): mp 378–80 °C; IR 1750, 1700, 1430, 1360, 1160, 1120, 885, 750, 685 cm^{-1}.

Acknowledgment. The authors are thankful to Professors M. Z. Nazer and S. Sabri, University of Jordan, for the NMR spectra.

Registry No.—**1a,** 5435-97-2; **1b,** 7510-34-1; **1c,** 33315-71-8; **1d,** 53476-29-2; **1e,** 53476-31-6; **2a,** 6307-20-6; **2b,** 1056-77-5; **2c,** 68630-10-4; **2d,** 68630-11-5; **2e,** 68630-12-6; **3,** 643-79-8; *exo*-**4a,** 68681-89-0; *endo*-**4a,** 68681-90-3; **5a,** 21815-18-9; **5b,** 716-39-2; **8,** 573-57-9; **9,** 7149-49-7; **10,** 68630-13-7; **12,** 68630-14-8; **13,** 18929-62-9; **14,** 36724-38-6; **15,** 68682-85-9; **16,** 68630-15-9; **17a,** 18929-58-3; **17b,** 18929-57-2; **18,** 18944-83-7; **19,** 68630-16-0; *N*-phenylmaleimide, 941-69-5; maleic anhydride, 108-31-6; *trans*-dibenzoylethylene, 959-28-4; hydrazine, 302-01-2; methylamine, 74-89-5.

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Nickel Peroxide Dehydrogenation of Oxygen-, Sulfur-, and Nitrogen-Containing Heterocycles

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Twenty-seven partially reduced O-, S-, and N-containing heterocycles have been oxidized by the use of nickel peroxide. Of particular interest were the conversions of several oxazolines to the corresponding oxazoles, a conversion apparently without precedent in the chemical literature, and the efficient oxidation of thiazolines to thiazoles. Since NiO_2 can effect thiazoline dehydrogenations in the presence of other functionalities, as may be judged by the successful oxidation of phleomycin A_2 to bleomycin A_2, the oxidant should be of utility for the preparation of natural products containing thiazoles.

Although the potential of nickel peroxide as an oxidant in organic synthesis has been recognized for a number of years,[5] and a remarkable variety of transformations have been recorded,[6] there have been few reported examples of the use of this reagent for heterocyclic dehydrogenations.[7] We have recently utilized nickel peroxide for the oxidation of several Δ^2-thiazolines to the corresponding thiazoles;[8] in most cases, especially those involving thiazoline moieties that were part of relatively complex molecules, this oxidant was clearly the reagent of choice. Since the oxidation of partially reduced heterocycles is a topic of continuing interest and investigation,[9] we have studied the potential utility of NiO_2 for other types of heterocyclic dehydrogenations. Of special concern in these studies was the oxidation of oxazolines to the corresponding 1,3-oxazoles, a conversion apparently without precedent in the chemical literature.

Results and Discussion

A series of eight substituted 4,5-dihydro-1,3-oxazoles were prepared as described[10] and utilized in efforts to effect oxidation to the corresponding oxazoles. Although Barco et al.[9a] have recently described the dehydrogenation of several isox-

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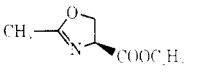
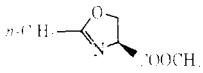
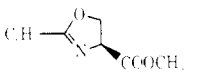
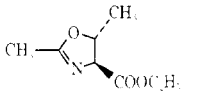
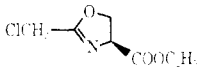
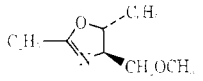
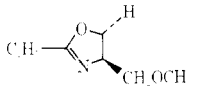
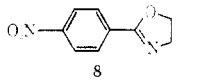
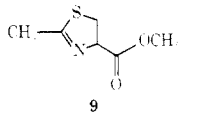
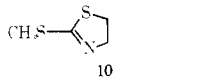
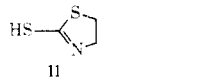
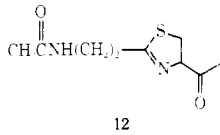
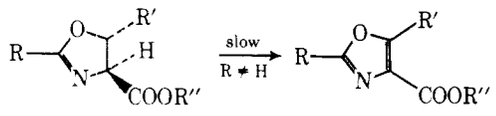
Table I. Nickel Peroxide Oxidations of Oxazolines and Thiazolines

heterocycle	registry no.	NiO_2 (equiv of O_2/ equiv of substrate)	solvent	conditions	starting material recovered, %	registry no.	product formed, %[a]
 1	68683-04-5	1.5	hexane	16 h, reflux	0	10200-43-8	53[b]
		1.5	hexane	11 h, reflux	0		50[b]
 2	68683-05-6	3.8[c]	C_6H_6	40 h, reflux	0	68683-08-0	58
 3	55044-06-9	1.5	cyclohexane	6 h, reflux	0	59171-72-1	69[d]
 4	68683-06-7	6.0[e]	cyclohexane	5 days, reflux	5	23000-15-9	19[f]
		4.0[c]	methylcyclo-hexane	3 days, reflux	32		22[f]
 5	68683-07-8	3.8[c]	cyclohexane	4 days, reflux	0	68683-09-0	19[g]
 6	64313-05-9	1.5	hexane	5 days, reflux	90		0
		1.5	methylcyclo-hexane	5 days, reflux	78	68683-10-3	2[f]
 7	64228-20-2	3.0[c]	hexane	4 days, reflux	19	68683-11-4	35[f]
		3.0[c]	methylcyclo-hexane	4 days, reflux	13		23[f]
 8	7465-63-6	5.0	C_6H_6	7 h, reflux	0	62882-08-0	28[h]
 9	6436-58-4	2.0	$CHCl_3$	3 days, 25 °C	0	6436-60-8	81[i]
 10	19975-56-5	2.4	CH_2Cl_2	1 day, 25 °C	32	5053-24-7	43[f]
		3.7	C_6H_6	4 h, reflux	0		60[g]
 11	96-53-7	1.0	$CHCl_3$	12 h, 25 °C	0	5685-05-2	88[j]
 12	66386-15-0	2.6	C_6H_6	3.5 h, reflux	0	64949-84-4	56
		MnO_2, 2.5	C_6H_6	4.5 h, reflux	23		69
		2.4	$CHCl_3$	3 days, 25 °C	0		93
13	66386-12-7	3.1	CH_2Cl_2	4.5 days, 25 °C	0	66386-13-8	75

[a] Isolated yields, unless otherwise indicated. [b] Bp 106–110 °C (12 mm).[13a] [c] Oxidant was added in two equal portions during the course of the reaction. [d] Mp 85–7 °C.[13b] [e] Oxidant was added in four equal portions during the course of the reaction. [f] A mixture of starting material and product resulted from NiO_2 treatment; percentage of the latter was determined from the integrated intensity of the signals corresponding to 5-H of the oxazoles (ca. δ 8.2) or 4-H and 5-H of the thiazole (δ 7.18, 7.62) derived from **10**. [g] The isolated product was 90% pure, as judged by NMR spectrometry. [h] Mp 160–1 °C.[13c] [i] Mp 52–5 °C.[12] [j] The product was 2,2′-bis(2-thiazoline) disulfide.[13]

azolines to the respective 1,2-oxazoles using MnO_2, this reagent gave disappointing results when used for the oxidations of the oxazolines considered herein, as did quinones such as DDQ and phenanthrenequinone. Better results were obtained when the same compounds were treated with nickel peroxide that had been prepared by the method of Nakagawa et al.[5] As shown in Table I, for simple 2-alkyl- and 2-aryl-substituted 4-carboalkoxy-1,3-oxazolines (**1–3**) reasonably good yields of the corresponding oxazoles were obtained by treatment with NiO_2.[11] However, the presence at the 4-position of a methoxymethyl substituent afforded species (**6** and **7**) that could not be oxidized efficiently with nickel peroxide. In the absence of a 4-substituent (compound **8**) oxazole formation still proceeded, but only in 28% yield, presumably indicating the facilitating effect of the 4-carboalkoxy group but possibly also reflecting the effect of the 2-nitrophenyl substituent. The presence of additional substitution at C-5 hindered oxazoline → oxazole conversion (compare **6** and **7**), even when an acti-

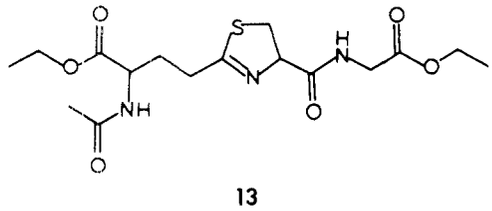
vating substituent was present at C-4 (**1** and **4**). Presumably, approach of the oxidant to the C-4 hydrogen atom is restricted by the larger cisoid substituents on C-5. The low yield of oxazole derived from **5** may possibly be due to activation of the



imine to nucleophilic addition of water[14] (associated with nickel peroxide), resulting in degradation and adsorption[6] to the oxidant.

Unlike oxazolines, several reagents have been reported to effect the dehydrogenation of thiazolines.[8] However, while these reagents have been shown to oxidize efficiently thiazolines of relatively simple structure, only MnO_2 was found to have utility for the preparation of thiazoles of more complex structure (e.g., those derived from cysteinyl peptides).[8] Nickel peroxide has now been found to be substantially more efficient for most thiazoline → thiazole conversions, as reflected in the results obtained with thiazoline **12** (Table I). In analogy with results obtained in the oxazoline series (and consistent with the observed facility of oxidation of simple thiazolines by several oxidants[8]) thiazoline **9** was converted to methyl 2-methylthiazole-4-carboxylate in 81% yield. Not surprisingly, dehydrogenation of 2-methylthio-2-thiazoline (**10**)[15] did not proceed as readily as that of **9**, but a 60% yield of isolated 2-methylthiothiazole was obtained by treatment of **10** with NiO_2. Less vigorous treatment of the structurally related 2-thio-2-thiazoline afforded a yellow, crystalline material of low melting point in 88% yield, but this was found to be 2,2'-bis(2-thiazoline) disulfide[14] rather than the desired thiazole. Analogous coupling of 3-pyrroline was also observed to occur more rapidly than conversion to pyrrole and additional transformations of this type have been noted.[6]

As the search for a more effective oxidant for heterocyclic dehydrogenations was occasioned by the need to effect the thiazoline → thiazole transformation in a molecule of moderate complexity, it was of interest to determine the utility of the reagent for the dehydrogenation of even more densely functionalized species. Thiazoline **13** was obtained by dehy-



13

drative cyclization of *N,S*-diacetylglutathione diethyl ester in 5% ethanolic chloroform[8b] and treated with 3 equiv of NiO_2 in methylene chloride; the desired thiazole was obtained in 75% yield. Also of interest was the oxidative conversion of phleomycin A_2[16] to bleomycin A_2 which was accomplished (83% conversion) by the use of NiO_2.[8]

In addition to oxazolines and thiazolines, several other types of O- and N-containing heterocycles have been treated with NiO_2 in an effort to effect dehydrogenation (Table II). For example, treatment of 2,3-dihydrobenzofuran (**14**)[22] with NiO_2 gave benzofuran in yields up to 52%. As noted for certain oxazolines, however, the substituted analogue 2-methyl-2,3-dihydrobenzofuran (**15**)[23] was oxidized somewhat less efficiently, while the structurally related species 1,4-benzodioxan (**16**)[24] could not be oxidized to the known[25] 1,4-benzodioxin. Also treated with the oxidant was 2,3-dihydro-2-phenylchromone (**17**)[26] which was converted to the expected 2-phenylchromone[17] in 71% isolated yield.

While attempted conversion of 3-pyrroline to pyrrole resulted instead in oxidative coupling, both *N*-acyl and *N*-alkyl-3-pyrrolines (**20**[27] and **21**, respectively) could be converted to the corresponding pyrroles via the agency of NiO_2. As shown in Table II, the oxidations of 5-acetyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (**18**)[28] and 1-benzoyl-2,3-dihydroindole (**19**)[29] were also carried out successfully in reasonable yields. The ability of nickel peroxide to introduce more than one unit of unsaturation into a heterocyclic species was studied in terms of the conversion of *cis*-*N*-methyl-1,2,3,6-tetrahydrophthalimide (**22**)[30] to *N*-methylphthalimide; as indicated in Table II, the conversion proceeded smoothly over a period of 7 h to give the desired product in 62% yield. Also attempted was the oxidation of 5,6-dihydrouridine (**23**)[31] to uridine. Although a substantial molar excess of NiO_2 was required to produce uridine in modest yield, the extent of transformation must be viewed in the context of the known[19a,31,32] instability of the starting material in aqueous solution and the absence of any other reported chemical method for carrying out the same conversion. In parallel with the enzymatic oxidation of dihydrouracil by dihydrouracil dehydrogenase,[33] NiO_2 was also found to mediate the same conversion, although in low yield (10%; data not shown).

The efficient dehydrogenation of **25** and two other pyrazolines by NiO_2[7a] prompted the use of the oxidant for additional transformations of the same general type. Thus 4,5-dihydro-1-phenyl-1,2,3-triazole-4-carboxamide (**24**)[34] was treated with 1.7 equiv of NiO_2 in benzene at reflux. After 4 h, workup afforded the expected triazole in 41% yield. Also treated under identical conditions was 5,6-dihydro-2,3-diphenylpyrazine (**26**);[35] the isolated yield of 2,3-diphenylpyrazine[21] was 92%.

Experimental Section

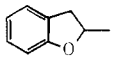
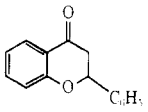
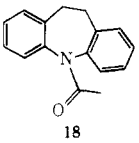
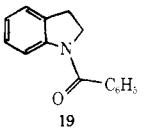
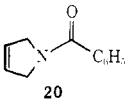
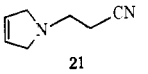
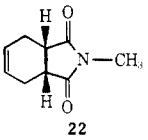
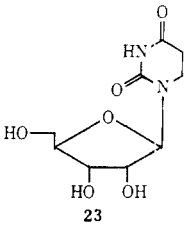
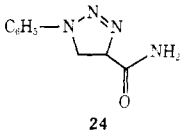
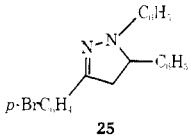
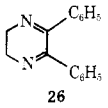
Compounds **1–8**,[10] **9**,[13] **10**,[15] **12**,[8] **18**,[28] **19**,[29] **20**,[27] **24**,[34] and **26**[35] were prepared as described. Compounds **11**, **14–17**, and **23** were obtained from commercial sources, as were authentic samples corresponding to the oxidized products expected from many of the dehydrogenations.

Methyl 2-*n*-Propyloxazole-4-carboxylate. The dehydrogenation of methyl 2-*n*-propyloxazoline with NiO_2 is representative of the oxidations of oxazolines **1–8**. A solution of 0.5 g (3.0 mmol) of 2-*n*-propyloxazoline-4-carboxylate in 30 mL of cyclohexane was treated with 3 g of NiO_2 (in two portions) while the reaction mixture was heated at reflux for 40 h. The cooled reaction mixture was filtered and the filtrate was concentrated under diminished pressure. The crude oil that remained was purified by preparative thin-layer chromatography on silica gel (developed twice with 10% acetone in hexane). This procedure afforded the desired oxazole as a pale yellow oil: yield 0.29 g (58%); IR (film) 2960, 2870, 1750, 1655, 1585, 1460, 1435, 1320, 1200, 1140, 1105, 995, 940, 800, and 760 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.02 (t, 3, J = 8 Hz), 1.58–2.32 (m, 2), 2.84 (t, 2, J = 8 Hz), 3.95 (s, 3), and 8.20 (s, 1). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.91; H, 6.77; N, 8.10.

Methyl 2-Methylthiazole-4-carboxylate. The dehydrogenation of methyl 2-methylthiazoline-4-carboxylate is typical of the oxidations of thiazolines **9–12**. A solution of freshly distilled (40 °C (0.05 torr)) methyl 2-methylthiazoline-4-carboxylate (**9**) (152 mg; 0.95 mmol) in 25 mL of reagent grade chloroform was shaken with 520 mg (1.92 mmol "O_2", as determined by titration of I_2 released from I^-) of NiO_2 for 3 days at room temperature. Filtration through Celite and concentration of the filtrate afforded yellow crystals of the desired thiazole: yield 121 mg (81%); mp 52–5 °C (lit.[16] mp 58 °C); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.76 (s, 3), 3.91 (s, 3), and 8.04 (s, 1).

2-(3-Acetamido-3-ethoxycarbonyl)propyl-Δ^2-thiazoline-4-(*N*-ethoxycarbonylmethyl)carboxamide (13). *N,S*-Diacetylglutathione diethyl ester[8b] (200 mg, 0.4 mmol) was dissolved in 5% ethanolic chloroform (25 mL) and treated with dry hydrogen chloride at room temperature for 13 h. Thin-layer chromatography (silica gel; development with 9:1 benzene–ethanol; visualization with sodium nitroprusside and UV light) indicated the disappearance of starting material (R_f 0.38) and appearance of a new compound (**13**) with R_f 0.49, as well as a smaller amount of the corresponding free sulfhydryl species (R_f 0.33). The acidic chloroform solution was washed with saturated sodium carbonate solution and dried over sodium sulfate. Concentration gave an oily residue which was triturated with dry benzene. Evaporation of the benzene afforded 122 mg (70%) of thia-

Table II. Nickel Peroxide Oxidations of Some N- and O-Containing Heterocycles

heterocycle	registry no.	NiO_2 (equiv of O_2/ equiv of substrate)	solvent	conditions	starting material recovered, %	registry no.	product formed, %[a]
 14	496-16-2	1.4	C_6H_6	6.5 h, reflux	40	271-89-6	32[b]
		2.2	C_6H_6	11 h, reflux	0		52
		2.4[c]	C_6H_6	13 h, reflux	0		30
 15	1746-11-8	1.9	C_6H_6	6 h, reflux	44	4265-25-2	19[b]
 16	493-09-4	0.8	C_6H_6	24 h, reflux	94		0
 17	487-26-3	1.6	C_6H_6	4 h, reflux	0	525-82-6	71[d]
 18	13080-75-6	1.7	C_6H_6	4 h, reflux	0	19209-60-0	73
 19	61589-14-8	1.3	C_6H_6	18 h, reflux	0	1496-76-0	37
		4.4	C_6H_6	24 h, reflux	0		54
 20	15431-85-3	3.4	C_6H_6	3.5 h, reflux	0	5145-65-3	59
 21	37632-57-8	5.0	C_6H_6	7 h, reflux	0	43036-06-2	26
 22	62950-21-4	2.2	C_6H_6	1.5 h, reflux	0	68683-12-5	30[e,f]
		2.3	C_6H_6	7 h, reflux	0		62[e,f]
 23	5627-05-4	50	H_2O	44 h, 25 °C	0	58-96-8	24[g]
 24	17843-16-2	1.7	benzene	4 h, reflux	0	2055-53-0	41[h]
 25	19429-34-6	2.5	benzene	5.5 h, reflux	0	16901-34-1	95[i]
 26	1489-06-1	1.7	benzene	4 h, reflux	0	1588-89-2	92[j]

[a] Isolated yields unless otherwise indicated. The products were characterized by physical properties, as noted below, and also by TLC, mass spectrometry, and, where appropriate, by IR and UV spectroscopy. [b] A mixture of starting material and product resulted from NiO_2 treatment; percentage of the latter was determined by NMR. [c] Oxidant was added in three equal portions during the course of the reaction. [d] Mp 93–4 °C.[17] [e] Mp 132.5 °C.[18] [f] The product was *N*-methylphthalimide. [g] Identified by its characteristic ultraviolet spectrum[19] and chromatographic properties. [h] Mp 232.5–3.5 °C.[20] [i] Reference 7a. [j] Mp 112–5 °C.[21]

zoline 13 as a white solid, homogeneous on TLC (R_f 0.49): $C_{16}H_{25}N_3O_6S$ (M^+ calcd 387.1470; found 387.146); λ_{max} (C_2H_5OH) 229 nm (ϵ 3300) and 244 (2800, sh); λ_{max} (1:1 C_2H_5OH–HCl) 267 nm (5400); $[\alpha]^{25}_D$ +40° (c 2.0, $CHCl_3$); mass spectrum m/e 387.146, 342.113 ($C_{14}H_{20}N_3O_5S$), and 314.118 ($C_{13}H_{20}N_3O_4S$); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.28 (t, 6, J = 8 Hz), 2.02 (s, 3), 2.22 (m, 2), 2.57 (m, 2), 3.61 (d, 2, J = 9.5 Hz), 3.9–4.4 (m, 6), 4.70 (bd of d, 1, J = 6, 14 Hz), 5.07 (t, 1, J = 9.5 Hz), 6.62 (bd, 1, J = 8.5 Hz), and 7.65 (bt, 1, J = 6 Hz).

2-(3-Acetamido-3-ethoxycarbonyl)propylthiazole-4-(*N*-ethoxycarbonylmethyl)carboxamide. Thiazoline 13 (110 mg, 0.28 mmol) was dissolved in dry methylene chloride (10 mL) and shaken vigorously with freshly prepared nickel peroxide (400 mg, activity 2.2 mequiv O_2/g by liberated iodine titration) for 4.5 days. Filtration and concentration of the filtrate in vacuo afforded the desired thiazole as a clear gum: yield 82 mg (75%); λ_{max} (C_2H_5OH) 232 nm; mass spectrum m/e 385, 340, 312, 270, and 241; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.28 (2 t, 6), 2.05 (s, 3), 2.27 (bm, 2), 3.07 (t, 2, J = 7.5 Hz), 4.0–4.5 (m, 6), 4.77 (bdd, 1, J = 7.5, 14 Hz), 6.55 (bd, 1, J = 7.5 Hz), 7.90 (bs, 1), and 8.00 (s, 1). In an effort to obtain a crystalline derivative via transesterification, a sample of the thiazole was dissolved in dry methanol and treated with dry hydrogen chloride at 0 °C (1 h) and then at room temperature (3 h). After standing overnight at room temperature, the reaction mixture was poured into saturated aqueous sodium carbonate and extracted with portions of chloroform. The combined chloroform extract was dried (sodium sulfate), concentrated, and purified by chromatography on a silica gel column (elution with 24:1 methylene chloride–ethanol). The product was obtained as a clear glass, homogeneous on silica gel TLC (R_f 0.34; development with ethyl acetate; UV visualization): λ_{max} (C_2H_5OH) 232 nm (ϵ 8200); mass spectrum m/e 357 (observed at low resolution), 326.080 ($C_{13}H_{16}N_3O_5S$; $M^+ - OCH_3$), 298.087 ($C_{12}H_{15}N_3O_4S$); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.05 (s, 3), 2.27 (bm, 2), 3.08 (t, 2, J = 7.5 Hz), 3.73 (s, 3), 3.77 (s, 3), 4.23 (d, 2, J = 6 Hz), 4.73 (bdd, 1, J = 7.5, 14 Hz), 7.27 (d, 1, J = 7.5 Hz), 7.98 (s, 1), and 8.07 (t, 1, J = 6 Hz).

General Procedure for Oxidation of the Heterocycles in Table II. Nickel peroxide was prepared as described[5] and available oxygen was determined either by titration of iodine liberated from potassium iodide solution or by oxidation of benzyl alcohol to benzaldehyde. The heterocycles in Table II were dissolved in the indicated solvents at concentrations of 0.04–0.1 M and treated with nickel peroxide as described. After the indicated reaction period, workup involved filtration of the oxidant through Celite, concentration of the filtrate, and purification where necessary by crystallization or (for *N*-benzoylpyrrole) by chromatography on silica gel.

1-(2-Cyanoethyl)pyrrole. A solution of 0.29 g (4.2 mmol) of 3-pyrroline and 0.22 g (4.1 mmol) of acrylonitrile in 5 mL of ether was heated at reflux for 24 h. The solution was concentrated to give 0.46 g (90%) of a light yellow oil having R_f 0.18 on silica gel TLC (development with benzene): NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.3–3.1 (m, 4), 3.53 (bs, 4), and 5.77 (bs, 2).

The synthesized 1-(2-cyanoethyl)-Δ^3-pyrroline (21) (0.108 g; 0.88 mmol) was dissolved in 10 mL of benzene and treated with 2.0 g of NiO_2 (4.4 mmol of active O_2). The mixture was heated at reflux for 7 h, then filtered through Celite. The filtrate was concentrated under diminished pressure to give 28 mg (26%) of 1-(2-cyanoethyl)pyrrole,[36] R_f 0.45 on silica gel TLC (development with benzene): NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.70 (t, 2, J = 6.5 Hz), 4.13 (t, 2, J = 6.5 Hz), 6.20 (bs, 2), and 6.68 (bs, 2).

***cis*-*N*-Methyl-1,2,3,6-tetrahydrophthalimide (22).** To a solution of 5.93 g (39 mmol) of tetrahydrophthalimide in 115 mL of ethanol was added, in one portion, a solution containing 2.64 g (40 mmol) of potassium hydroxide in 10 mL of 75% aqueous ethanol. The combined solution was concentrated under diminished pressure to afford a yellow oil which was dissolved in 10 mL of methanol and treated with 20.0 g (140 mmol) of methyl iodide. An exothermic reaction became apparent after a few minutes and the reaction mixture was cooled in an ice bath. The reaction mixture was then maintained overnight at room temperature and the precipitated potassium iodide was filtered. The filtrate was concentrated under diminished pressure and the oily residue was partitioned between ether (25 mL) and water (25 mL); the aqueous layer was extracted with two additional portions of ether and the combined ether extract was dried ($MgSO_4$) and concentrated. Recrystallization of the solid residue from benzene–hexane gave 5.77 g (89%) of tetrahydrophthalimide 22 as colorless crystals: mp 60–62 °C (lit.[30] mp 72.5–73 °C); NMR ($CDCl_3$ $(CH_3)_4Si$)) δ 2.2–2.6 (m, 4), 2.98 (s, 3), 3.0–3.2 (m, 2), and 5.8–6.0 (m, 2). Compound 22 was treated with NiO_2 according to the general procedure described above and in Table II.

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Registry No.—Nickel peroxide, 12035-36-8; *N,S*-diacetylglutathione diethyl ester, 66386-11-6; tetrahydrophthalimide, 27813-21-4; 3-pyrroline, 109-96-6; acrylonitrile, 107-13-1.

References and Notes

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