Heterocycles from *N*-Ethoxycarbonylthioamides and Dinucleophilic Reagents. 1. Dihydro-1,2,4-triazolones and 1,2,4-Oxadiazolones

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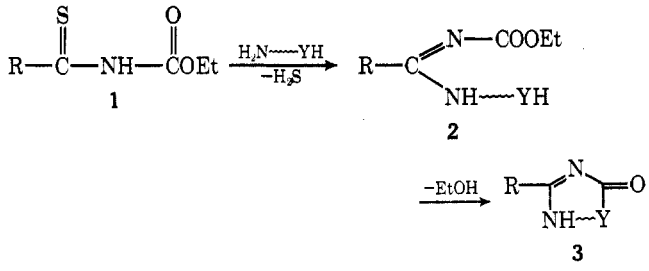
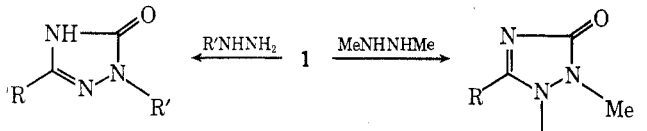
N-Ethoxycarbonylthioamides react with hydrazine or monosubstituted hydrazines to form 2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**4–7**), and with 1,2-dimethylhydrazine to form 1,2-dimethyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones (**8**). Analogous reactions with hydroxylamine or *N*-methylhydroxylamine yield 1,2,4-oxadiazol-5(4*H*)-ones (**9**) or 2-methyl-1,2,4-oxadiazol-5(2*H*)-ones (**10**), respectively.

Through their condensation–cyclization reactions, alkoxycarbonyl isothiocyanates have proved valuable synthetic tools in heterocyclic chemistry.[1] The carbamates resulting from addition of alcohols or amines to ethoxycarbonyl isothiocyanate[2] and their *S*-methyl derivatives[3] have been found to undergo cyclization reactions with difunctional nucleophilic reagents. However, analogous reactions of the somewhat less easily accessible *N*-ethoxycarbonylthioamides (**1**) have not attracted attention. Treatment of **1** with primary or secondary amines results in elimination of H_2S and formation of *N'*-ethoxycarbonylamidines (**2**).[4] These compounds may be expected to undergo cyclization with loss of EtOH, if the amine used as reagent contains a suitably located, second nucleophilic group YH. The present paper describes such reactions of **1** leading to heterocycles **3** with 1,2,4-triazole and 1,2,4-oxadiazole ring systems.



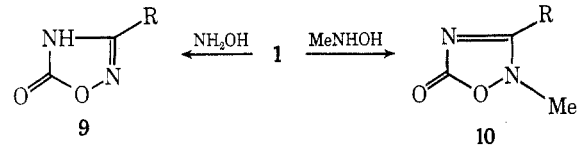
Treatment of an *N*-ethoxycarbonylthioamide (**1**) with hydrazine or a monosubstituted hydrazine causes evolution of H_2S and formation of a 2,4-dihydro-3*H*-1,2,4-triazol-3-one (**4–7**) in good to excellent yield (Tables I–IV). An analogous reaction with 1,2-dimethylhydrazine yields 1,2-dimethyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones (**8**) in moderate to good yields (Table V). Aqueous sodium hydroxide hydrolyzes carbamoyl derivatives **7** readily to the corresponding **4**.



4, R′ = H
5, R′ = Me
6, R′ = Ph
7, R′ = NH_2CO

There is considerable confusion in the literature concerning the location of the double bond in the dihydrotriazolone ring of compounds **4–6**. Some authors place it between positions 1 and 5, others between positions 4 and 5.[5] Structure **4** for the dihydro-1,2,4-triazolones obtained in this study is supported by appearance of the carbonyl band in their ir spectra at a considerably higher wavenumber (1700–1760 cm^{-1}) than for dimethyl derivatives **8** (1655–1660 cm^{-1}), in which the carbonyl group has to be conjugated with the double bond. With regard to monomethyl derivatives **5**, no firm conclusion can be drawn on the basis of the carbonyl band (1670–1690 cm^{-1}). However, the proposed structure is consistent with the close similarity between the uv spectra of **4** (maximum at 265–270 nm) and **5** (maximum at 270–275 nm) and their significant difference from those of the corresponding **8** (maximum at 235–260, shoulder at 275–280 nm). The possibility that derivatives **5** are 1-methyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones may be excluded, since compounds of such structure are known to exist in the enol form as 3-hydroxy-1,2,4-triazoles. Furthermore, the melting point (216.5–218.5 °C) of the product of the reaction of *N*-ethoxycarbonylthiobenzamide with methylhydrazine agrees well with that of 2-methyl-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (218–219 °C)[6] but differs considerably from that of 3-hydroxy-1-methyl-5-phenyl-1,2,4-triazole (195–196 °C)[5], both of which have been prepared by unambiguous routes. In the case of compounds **6** and **7**, the wavenumber of the carbonyl band (1685–1715 and 1700–1760 cm^{-1}, respectively) is again compatible with a structure containing an unconjugated carbonyl. These conclusions concerning the position of the C,N double bond in compounds **4–7** are in complete agreement with the findings of a recent, systematic study of the structure of 5-phenyldihydro-1,2,4-triazol-3-ones.[5]

N-Ethoxycarbonylthioamides (**1**) react similarly with hydroxylamine and *N*-methylhydroxylamine to form 1,2,4-oxadiazol-5(4*H*)-ones (**9**), in excellent yield, and 2-methyl-



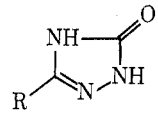
1,2,4-oxadiazol-5(2*H*)-ones (**10**), in moderate yield, respectively (Tables VI, VII). Comparison of the ir spectra of **9** with those of the corresponding **10**, in which there is conjugation between carbonyl and C,N double bond, shows that the carbonyl bands of the former appear at a higher wavenumber than those of the latter. Although the difference (10–45 cm^{-1}) is not always large, it is nonetheless consistent with lack of conjugation in **9**. There are no characteristic differences between the uv spectra of **9** and **10**.

The NMR spectra of the compounds prepared in this study are consistent with the proposed structures and exhibit signals in the ranges of δ 10–13 and 3–4 for NH and NCH_3 protons, respectively.

In all cases, the progress of the reaction is followed easily by testing for evolution of H_2S with lead acetate paper. Because of their simplicity, good yield, and straightforward product isolation, the investigated reactions provide a method of preparation of compounds **4–10** which compares favorably with other approaches to these heterocycles.[7]

With regard to the reaction pathway, it undoubtedly involves initial interaction of the thiocarbonyl of **1** with an amino group of the reagent similar to the earlier mentioned reactions

Table I.[a] 5-R-2,4-Dihydro-3*H*-1,2,4-triazol-3-ones



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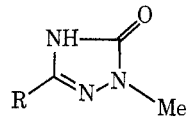
Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
939-07-1	C_6H_5	87	323–324 (dec)[c,d]	1750
3214-02-6	4-MeC_6H_4	97	384–386 (dec)[c,e]	1730
59812-14-5	4-EtC_6H_4	94	357–359 (dec)[c]	1700
59812-15-6	4-*i*-PrC_6H_4	98	367–369 (dec)[c]	1700
59812-16-7	4-*t*-BuC_6H_4	99	397–399 (dec)[c]	1700
33199-43-8	4-$MeOC_6H_4$	96	334–335 (dec)[c,f]	1740
59812-17-8	4-$EtOC_6H_4$	91	371–373 (dec)[c]	1720
33199-40-5	4-ClC_6H_4	93	>400[c,g]	1760, 1730
59812-18-9	2-Pyrrolyl	90	333–335 (dec)[h]	1720
27050-49-3	2-Thienyl	95	336–337 (dec)[c,i]	1730
59812-19-0	3-Indolyl	87	375–385 (dec)[c]	1740
931-37-3	Et	97	206–208 (dec)[j,k]	1740

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from *n*-BuOH. [d] Lit. mp 321–322 °C: G. Young and E. Witham, *J. Chem. Soc.*, 224 (1900). [e] Lit. mp 372 °C: B.-G. Baccar and F. Mathis, *C. R. Acad. Sci.*, **261**, 174 (1965). [f] Lit. mp 334 °C: ref 7a. [g] Lit. mp 410–412 °C: ref 7c. [h] Recrystallized from water. [i] Lit. mp 337 °C (dec): H. Gehlen, P. Demin, and K. H. Uteg, *Arch. Pharm. (Weinheim Ger.)*, **303**, 310 (1970). [j] Sublimed. [k] Lit. mp 204 °C (dec): C.-F. Kröger, L. Hummel, M. Mutscher, and H. Beyer, *Chem. Ber.*, **98**, 3025 (1965).

Table II.[a] 5-R-2-Methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones

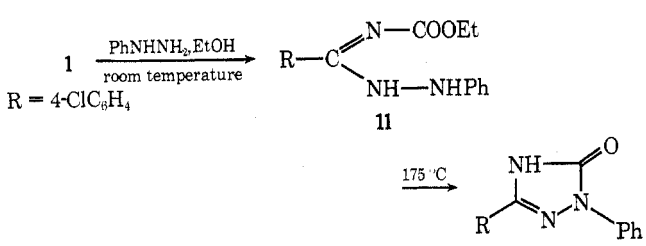


5

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
54034-38-7	C_6H_5	71	216.5–218.5[c,d]	1675
59812-20-3	4-MeC_6H_4	74	251–252.5[e]	1680
59812-21-4	4-EtC_6H_4	70	196–197[c]	1680
59812-22-5	4-*i*-PrC_6H_4	69	204–206[f]	1680
59812-23-6	4-*t*-BuC_6H_4	77	244–246[f]	1690
59812-24-7	4-$MeOC_6H_4$	63	218–219.5[c]	1680
59812-25-8	4-$EtOC_6H_4$	69	217–219[e]	1680
59812-26-9	2-Pyrrolyl	63	263–264[e]	1670
59812-27-0	2-Thienyl	60	251–252[e]	1675
4114-22-1	Et	86	108–109[e,g]	1690

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 3–10 °C. [c] Recrystallized from EtOAc. [d] Lit. mp 218–219 °C: ref 6. [e] Recrystallized from EtOH. [f] Recrystallized from EtOH–H_2O. [g] Lit. mp 108–109 °C: C.-F Kröger, L. Hummel, M. Mutscher, and H. Beyer, *Chem. Ber.*, **98**, 3025 (1965).

of 1 with simple amines.[4] This is supported by isolation of the expected intermediate **11** from the reaction of *N*-ethoxycarbonyl-4-chlorothiobenzamide with phenylhydrazine when an ethanolic solution of the reagents is allowed to stand at room temperature. The presence of the carbonyl band at 1670 cm^{-1} in the ir spectrum of **11** is indicative of an α,β-unsaturated carbonyl group. When this compound is heated at its melting point, ethanol is eliminated to form the corresponding dihydro-1,2,4-triazolone (**6**, R = 4-chlorophenyl).



Experimental Section[8]

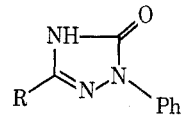
***N*-Ethoxycarbonylthioamides (1). A. Aromatic.** They were prepared by $AlCl_3$-catalyzed thioacylation of aromatic compounds with ethoxycarbonyl isothiocyanate.[9]

B. Heteroaromatic. The 2-pyrrolyl and 2-thienyl derivatives are known compounds.[4] ***N*-Ethoxycarbonyl-3-indolylthioamide.**[10] A mixture of 11.7 g (0.10 mol) of indole and 13.1 g (0.10 mol) of ethoxycarbonyl isothiocyanate was allowed to stand at room temperature for 48 h. The resulting dark-colored solid was crushed into a powder and washed with ice-cold ethyl acetate to give 14.3 g (59%) of crude product, mp 162–163 °C. Recrystallization from ethyl acetate gave the pure compound in the form of yellow crystals: mp 163–164 °C; ir 3250 (NH), 1720 cm^{-1} (C=O); NMR δ 1.3 (t, 3), 4.2 (q, 2), 7.1–7.7 (m, 3), 8.2–8.3 (m, 1), 8.4–8.7 (m, 1), 11.1 (s, 1), 12.1 (s, 1).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.10; H, 4.91; N, 11.36.

C. Aliphatic. *N*-Ethoxycarbonylthiopropanamide. A solution of ethylmagnesium bromide was prepared under nitrogen by slow addition (1 h) of 24.0 g (0.22 mol) of ethyl bromide dissolved in 100 ml of ethyl ether to 4.80 g (0.20 mol) of magnesium turnings covered by 50 ml of ethyl ether.

Table III.[a] 5-R-2-Phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones

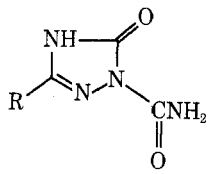


6

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
3346-44-9	C_6H_5	94	232.5–233.5[c,d]	1700
3214-05-9	4-MeC_6H_4	88	267–268[c,e]	1715
59812-28-1	4-EtC_6H_4	98	249–250[c]	1705
59812-29-2	4-*i*-PrC_6H_4	97	236.5–238[c]	1700
59812-30-5	4-*t*-BuC_6H_4	93	287–288[c]	1685
59812-31-6	4-$MeOC_6H_4$	96	235–237[c]	1700
59812-32-7	4-$EtOC_6H_4$	93	239–240.5[c]	1705
27423-54-7	4-ClC_6H_4	73	283–284[c]	1700
59812-33-8	2-Pyrrolyl	91	237–238[f]	1700
19382-16-2	2-Thienyl	96	260–261	1680
59811-92-6	3-Indolyl	86	349–350 (dec)[g]	1710
28669-27-4	Et	60	121–122[f,h]	1700

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from EtOH. [d] Lit. mp 229 °C: R. Fusco and C. Musante, *Gazz. Chim. Ital.*, **68**, 147 (1938). [e] Lit. mp 264 °C: C. Gastaldi and E. Principalle, *ibid.*, **56**, 557 (1926). [f] Recrystallized from EtOH–H_2O. [g] Recrystallized from *n*-BuOH. [h] Lit. mp 122–123 °C: ref 7b.

Table IV.[a] 5-R-2-Carbamoyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones

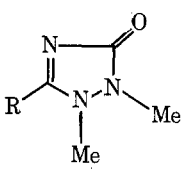


7

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
59811-93-7	4-MeC_6H_4	98	329–330 (dec)[c]	1740 1700
59811-94-8	2-Pyrrolyl	95	325–327 (dec)[d]	1760, 1730, 1715

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for the compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from EtOH–H_2O. [d] Recrystallized from H_2O.

Table V.[a] 5-R-1,2-Dimethyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones



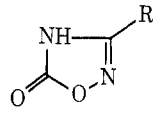
8

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
50369-46-5	C_6H_5	42	241–243[c,d]	1660
59811-95-9	4-MeC_6H_4	60	214–215.5[c]	1660
59811-96-0	4-EtC_6H_4	65	226–227[c]	1660
59811-97-1	4-*i*-PrC_6H_4	61	225–227[c]	1660
59811-98-2	4-*t*-BuC_6H_4	57	213–214[e]	1660
59811-99-3	4-$MeOC_6H_4$	64	235–236.5[c]	1655
59812-00-9	4-$EtOC_6H_4$	60	210.5–212.5[c]	1655

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from EtOH. [d] Lit. mp 255–256 °C: ref 5. [e] Recrystallized from EtOAc.

After the stirred solution had been cooled to −35 to −45 °C (dry ice–$CHCl_3$ bath), 23.6 g (0.18 mol) of ethoxycarbonyl isothiocyanate in 200 ml of ethyl ether was added slowly (1 h) while the temperature was kept at −35 to −45 °C. The reaction mixture was stirred for an additional 3 h at the same low temperature and then was allowed to warm up to room temperature. The precipitated salt was collected by filtration and washed with four 50-ml portions of ethyl ether. It was then mixed with 200 ml of ether and hydrolyzed with 200 ml of saturated aqueous ammonium chloride. Following separation of layers, the aqueous layer was extracted with two 50-ml portions of

Table VI.[a] 3-R-1,2,4-Oxadiazol-5(4*H*)-ones

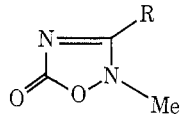


9

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
1456-22-0	C_6H_5	96	202–203[c,d]	1755
31827-28-8	4-MeC_6H_4	98	221–222.5[c,e]	1760
59812-01-0	4-EtC_6H_4	85	190.5–192[c]	1770, 1730
59812-02-1	4-*i*-PrC_6H_4	98	197–198[c]	1775, 1735
59812-03-2	4-*t*-BuC_6H_4	98	234–236[c]	1775, 1735
59812-04-3	4-$MeOC_6H_4$	97	211–212[f]	1795 1730
59812-05-4	4-$EtOC_6H_4$	93	222.5–224[f]	1745
59812-06-5	2-Pyrrolyl	89	215–217 (dec)[g]	1760
35637-09-3	2-Thienyl	83	202–205.5[g]	1790 1725
59812-07-6	3-Indolyl	90	233–234 (dec)[h]	1800 1720
57689-63-1	Et	50	69–70.5[i,j]	1770

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from EtOH. [d] Lit. mp 198 °C: C. Musante, *Gazz. Chim. Ital.*, **68**, 331 (1938). [e] Lit. mp 220 °C: L. H. Schubart, *Ber.*, **22**, 2433 (1889). [f] Recrystallized from EtOH–H_2O. [g] Recrystallized from H_2O. [h] Recrystallized from *n*-BuOH. [i] Following removal of EtOH from the reaction mixture, the residue was extracted with Et_2O and the dried ($MgSO_4$) extract was evaporated to a new residue which was distilled under reduced pressure (bp 154–156 °C, 3 Torr). [j] Recrystallized from benzene–petroleum ether (bp 30–60 °C).

Table VII.[a] 3-R-2-Methyl-1,2,4-oxadiazol-5(2*H*)-ones



10

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
59812-08-7	4-MeC_6H_4	34[c,d]	121.5–122.5[e]	1750
59812-09-8	4-$MeOC_6H_4$	50[d]	146–148[e]	1750
52531-61-0	4-ClC_6H_4	51[d]	168–170[f,g]	1750
59812-10-1	2-Pyrrolyl	50[c]	214–215[e]	1745

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] NaOAc used to free MeNHOH from its salt. [d] NaOMe used to free MeNHOH from its salt. [e] Recrystallized from H_2O. [f] Recrystallized from *i*-PrOH. [g] Lit. mp 168.5–170 °C: ref 7d.

ethyl ether and the combined ethereal solutions were dried over anhydrous magnesium sulfate. After removal of ether, the product was distilled at 3 Torr and the fraction boiling between 82 and 85 °C was collected. There was obtained 15.4 g (54%) of product as a yellow oil: ir 3400, 3300, 3200 (NH), 1760 cm^{-1} (C=O); NMR δ 1.0–1.4 (m, 6), 2.9 (q, 2), 4.1 (q, 2), 11.4 (s, 1).

Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.88; N, 8.69. Found: C, 44.54; H, 7.11; N, 8.64.

***N*-Ethoxycarbonylphenylthioacetamide.** This was obtained in 50% yield following the procedure used for preparation of the previous compound. Thus, benzylmagnesium chloride from 6.30 g (0.050 mol) of benzyl chloride and 1.20 g (0.050 mol) of magnesium was allowed to react with 5.90 g (0.045 mol) of ethoxycarbonyl isothiocyanate in a total of 100 ml of ether at −45 to −35 °C. The crude product (5.0 g, mp 39–42 °C) was recrystallized from petroleum ether (bp 35–60 °C) to give the pure compound as yellow crystals: mp 45–47 °C; ir 3400, 3300, 3180 (NH), 1760 cm^{-1} (C=O); NMR δ 1.2 (t, 3), 4.1 (q, 2), 4.2 (s, 2), 7.1 (s, 5), 11.8 (s, 1).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.32; H, 5.82; N, 6.32.

5-Substituted 2,4-Dihydro-3*H*-1,2,4-triazol-3-ones (4). To a solution of 0.010 mol of *N*-ethoxycarbonylthioamide in 20 ml of ethanol was added 0.020 mol of 95% hydrazine in 5 ml of ethanol. The reaction mixture was heated on a steam bath until evolution of hydrogen sulfide had ceased (10–30 min), then it was cooled and filtered to yield the product.

5-Substituted 2-Methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (5). Methylhydrazine (1.0 ml) was added to 0.0050 mol of *N*-ethoxycarbonylthioamide dissolved in 5 ml of tetrahydrofuran and the solution was refluxed for 15 min, then cooled and poured into icewater. The resulting mixture was neutralized with acetic acid and the precipitated solid was collected by filtration. (In the case of the 5-ethyl derivative, which is water soluble, equimolar amounts of reagents were used and the product was isolated by evaporation to dryness.)

5-Substituted 2-Phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (6). To 0.010 mol of *N*-ethoxycarbonylthioamide dissolved in 20 ml of ethanol was added 0.020 mol of phenylhydrazine in 5 ml of ethanol and the solution was refluxed until evolution of hydrogen sulfide had ceased (2–6 h). After the mixture had been cooled, any solid product was collected by filtration. The filtrate was concentrated to a small volume and chilled or mixed with ice to yield a new precipitate which was combined with the first one.

***N'*-Ethoxycarbonyl-*N*-phenylamino-4-chlorobenzamidine (11).** A mixture of 1.1 g (0.0050 mol) of *N*-ethoxycarbonyl-4-chlorothiobenzamide, 25 ml of 95% ethanol, and 1.1 g (0.010 mol) of phenylhydrazine was let stand at room temperature for 12 h. The precipitated material was collected by filtration and washed with ice-cold ethanol to yield 1.0 g (63%) of pure 11 as white crystals: mp 171 °C (partial melting followed by solidification and further melting at 283–284 °C; recrystallization from ethanol did not change the melting behavior); ir 3340, 3280 (NH), 1670 cm^{-1} (C=O); NMR δ 1.2 (t, 3), 4.0 (q, 2), 6.5–7.5 (m, 9), 8.8 (s, 1), 9.4 (s, 1).

Anal. Calcd for $C_{16}H_{16}N_3O_2Cl$: C, 60.47; H, 5.08; N, 13.22. Found: C, 60.67; H, 5.15; N, 13.22.

Conversion of 11 into 2-Phenyl-5-(4-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one. Compound 11 (0.20 g) was heated in an oil bath at 170–180 °C for 5 min. After it had been cooled and recrystallized from ethanol, the product was identified as 2-phenyl-5-(4-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one on the basis of its melting point, as well as its ir and NMR spectra.

5-Substituted 2-Carbamoyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (7). To 0.010 mol of *N*-ethoxycarbonylthioamide dissolved in 15 ml of ethanol was added a solution of 0.020 mol of semicarbazide hydrochloride and 0.020 mol of sodium acetate in 10 ml of aqueous ethanol and the resulting mixture was stirred magnetically until completion of hydrogen sulfide evolution (15–24 h). The precipitated product was collected by filtration and combined with a new precipitate formed when the filtrate had been concentrated to a small volume and mixed with ice.

Hydrolysis of 7 into 4. A mixture of 0.40 g of 7 and 10 ml of 10% aqueous sodium hydroxide was boiled for 10 min and the resulting solution was neutralized with dilute hydrochloric acid to yield a precipitate which was collected by filtration and washed with cold water. The products, obtained in 75% yield, were identified by their melting points, as well as their ir and NMR spectra.

5-Substituted 1,2-Dimethyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones (8). A mixture of 0.0050 mol of 1,2-dimethylhydrazine dihydrochloride, 0.010 mol of sodium methoxide, 0.0050 mol of *N*-ethoxycarbonylthioamide, and 5 ml of methanol was refluxed for 1 h. The resulting mixture was cooled and treated with a slight excess of 10% aqueous sodium hydroxide to yield a solid product which was collected by filtration and washed with a little ice-cold water.

3-Substituted 1,2,4-Oxadiazol-5(4*H*)-ones (9). A mixture of 0.010 mol of *N*-ethoxycarbonylthioamide, 0.020 mol of hydroxylamine hydrochloride, 0.020 mol of sodium acetate trihydrate, and 20 ml of aqueous ethanol was refluxed until evolution of hydrogen sulfide had ceased (2–3 h). The resulting solution was concentrated to a small volume and mixed with ice to form a precipitate which was collected by filtration.

3-Substituted 2-Methyl-1,2,4-oxadiazol-5(2*H*)-ones (10). To a solution of 0.010 mol of *N*-ethoxycarbonylthioamide in 10 ml of ethanol was added 0.010 mol of *N*-methylhydroxylamine hydro-

chloride and 0.010 mol of sodium acetate dissolved in aqueous ethanol. The resulting solution was refluxed until evolution of hydrogen sulfide had ceased (1–2 h). In some cases (indicated in Table VII), sodium methoxide was used instead of sodium acetate. Then the reaction was carried out in 10 ml of methanol and the mixture was stirred magnetically (22–24 h).

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Registry No.—**1** (R = 3-indolyl), 59812-11-2; **1** (R = Et), 59812-12-3; **1** (r , ph), 5499-31-0; **11** (R = 4-ClC_6H_4), 59812-13-4; indole, 120-72-9; ethoxycarbonyl isothiocyanate, 16182-04-0; ethyl bromide, 74-96-4; benzyl chloride, 100-44-7; methylhydrazine, 60-34-4; phenylhydrazine, 100-63-0; *N*-ethoxycarbonyl-4-chlorothiobenzamide, 57774-74-0; semicarbazide HCl, 563-41-7; 1,2-dimethylhydrazine 2HCl, 306-37-6; hydroxylamine HCl, 7803-49-8; *N*-methylhydroxylamine HCl, 4229-44-1.

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Nitrones and Nitroxides Derived from Oxazolines and Dihydrooxazines[1]

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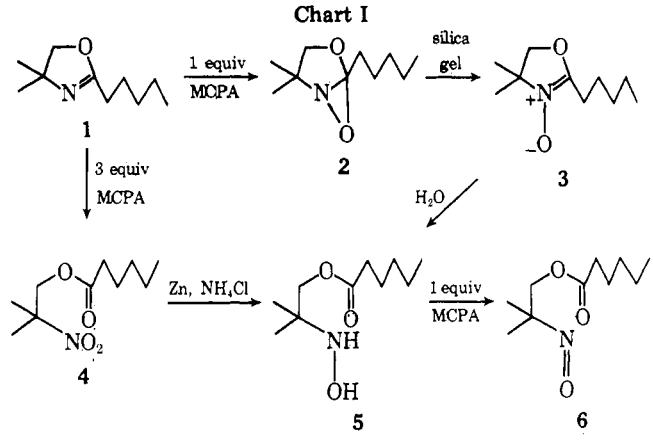
A new synthetic route to several doxyl nitroxides **14** and two tetrahydro-1,3-oxazine nitroxides **26** and **27** is described. Oxidation of the representative oxazoline **1** with 1 equiv of MCPA gave oxaziridine **2**. Excess MCPA led to nitro ester **4** and nitroso ester **6**. Isomerization of **2** on silica gel afforded nitrone **3**, reaction of which with moisture produced ester **5**. Analogous reactions applied to dihydrooxazine **7** led to oxaziridine **8**, nitroso ester **10**, nitro ester **11**, nitrone **9**, and ester **12**. Treatment of **3** with a series of organometallic reagents followed by Cu^{2+}-catalyzed air oxidation of the intermediate **13** led to doxyl nitroxides. In contrast, reaction of **3** with vinylmagnesium bromide or vinyllithium at 25 °C gave dienes **19** and **21**. With excess 1-lithio-1-hexyne at −15 °C, nitrone **3** gave open-chain nitrone **22**. Allylmagnesium bromide and **3** at 25 °C followed by oxidation gave nitroxide **23**. Analogous reactions at 25 °C of nitrone **9** with methyllithium and butyllithium afforded the nitroxides **26** and **27**.

Doxyl (4,4-dimethyloxazolidine-*N*-oxyl) nitroxide spin labels[3] have played an important role in studies of biological systems using the spin labeling technique.[4] Alternative, flexible synthetic entries to new stable nitroxides are central to continued progress in the spin labeling field. We recently communicated a new procedure for assembling doxyl nitroxides which bypasses the usual ketone precursors and which permits the synthesis of doxyl nitroxides having unsaturation in the doxyl chains (**1** → **3** → **14**).[1] This procedure takes advantage of the wide variety of oxazolines made available through the elegant work of Meyers.[5,6,7] We now present experimental details relating to our new doxyl synthesis, starting with the representative oxazoline **1**. We also describe for the first time analogous reactions of dihydrooxazine **7** and its conversion into a second series of stable nitroxide free radicals.[17]

Results and Discussion

The addition of an organometallic reagent to the requisite nitrone constitutes the key step in the new doxyl synthesis.[8] Since the nitrones are derived from the corresponding oxazoline or dihydrooxazine, we have investigated the oxidation of these latter substances in some detail.[9] Thus, oxidation of oxazoline **1** with 1 equiv of *m*-chloroperoxybenzoic acid (MCPA) in ether at −10 °C produced oxaziridine **2** (~95%) (Chart I). Small amounts of blue nitroso ester **6** could be observed visually and by NMR in samples of crude **2**, although

Chart I



reaction of **1** with 2 equiv of MCPA still gave mostly **2** with minor amounts of **6** and nitro ester **4**. Prolonged reaction of **1** with 3 equiv of MCPA gave a good yield of nitro ester **4**. In order to confirm the identity of compounds **4** and **6**, nitro ester **4** was synthesized by acylation of the corresponding alcohol with hexanoic acid and then reduced with zinc and NH_4Cl to *N*-hydroxy ester **5**. Reaction of **5** with 1 equiv of MCPA gave blue nitroso ester **6** in good yield. Structure assignments throughout this paper are based on the highly characteristic NMR spectra together with other analytical data found in the Experimental Section.