Synthesis of 1,3,4-Oxadiazol-2-ones with Aliphatic Groups at N-3

Jamin Huang*, Dean F. Bushey, Michael D. Graves†,
Brenda F. Johnson and Dianne D. Singleton

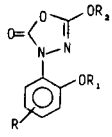
Union Carbide Agricultural Products Company, Inc, T. W. Alexander Drive, P. O. Box 12014,
Research Triangle Park, North Carolina 27709

Received June 9, 1986

A series of 3-substituted-5-methoxy-1,3,4-oxadiazol-2-ones were prepared from aldehydes, ketones, phenylacetic acids, and 1,2- and 1,3-diketones. Conditions for the formation of these oxadiazolones from the precursor *N*-carbamoyl chlorides depended on the structure, and varied from spontaneous ring closure to those requiring bases. Variation in the N-3 substituents sometimes produced mixtures of isomers which were separated and identified. These molecules were prepared in order to study the effect of the N-3 substituent variation on the biological properties of oxadiazolones.

J. Heterocyclic Chem., **24**, 1 (1987).

Several 3-alkyl- and 3-benzyl-5-alkoxy-1,3,4-oxadiazol-2-ones are known [1-5]. Recent interest [6-8] in 3-aryl-5-alkoxy-1,3,4-oxadiazolones of the type **1** as biologically active materials prompted us to synthesize a number of



1

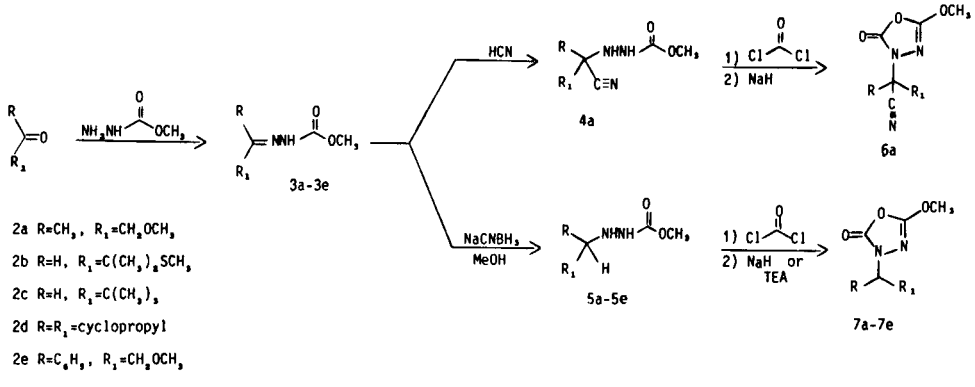
other novel oxadiazolones with aliphatic substituents on the 3-nitrogen. These compounds were derived from aldehydes, ketones, phenylacetic acids, 1,2-diketones or 1,3-diketones. The by-products of some of these reactions were also isolated. The effect of N-3 aliphatic substituents on the biological activity of oxadiazolones will be reported in a separate publication.

Starting with Aldehydes, Ketones or Phenylacetic Acids.

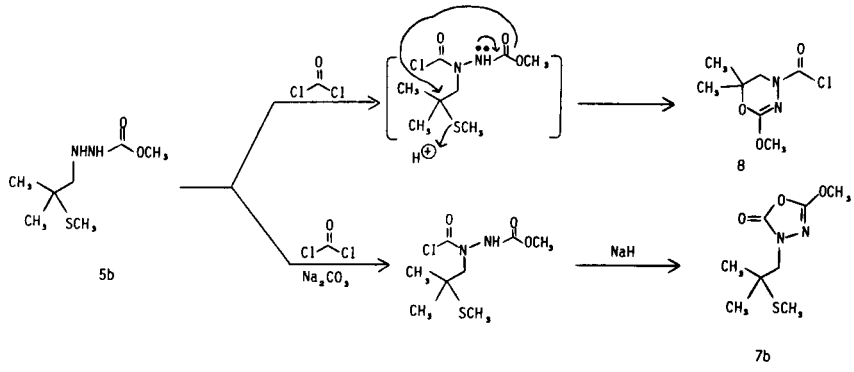
Oxadiazolones **6a** and **7a-7e** were prepared from the appropriate aldehydes or ketones as shown in Scheme I. Hydrocyanation of **3a** with hydrogen cyanide [9] produced carbazate **4a**. Oxadiazolones **6a** and **7a-7e** were obtained by treating the methyl 3-alkylcarbazates **4a** and **5a-5e** with phosgene to form the corresponding *N*-carbamoyl chlorides, followed by treatment with triethylamine or preferably sodium hydride to effect the cyclization similar to the procedures reported by others [1-4, 6-8].

However, during the preparation of **7b** from carbazate **5b**, the reaction of **5b** with phosgene led to the isolation of a six-membered cyclic product **8** [10]. The formation of **8** may be rationalized as depicted in Scheme II. The elimination of the acid-sensitive methylthio group was circumvented by conducting the reaction in the presence of excess sodium carbonate, which, on further treatment with sodium hydride, led to the desired product **7b**.

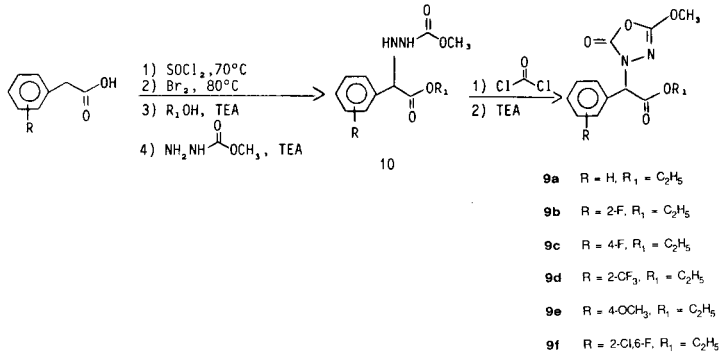
The synthesis of oxadiazolones substituted with α-phenylacetate moieties, **9a-9f**, was achieved according to Scheme III. α-Bromophenylacetic chlorides were obtained according to known procedures [11,12]. The carbazates of type **10** were isolated from the reaction of acid chlorides with appropriate alcohol followed by the nucleophilic



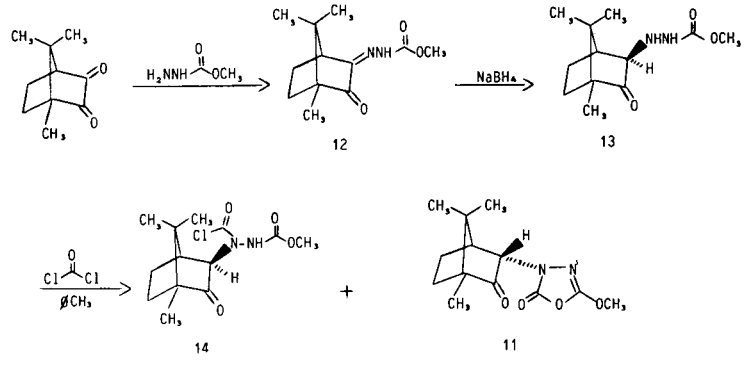
Scheme I



Scheme II



Scheme III



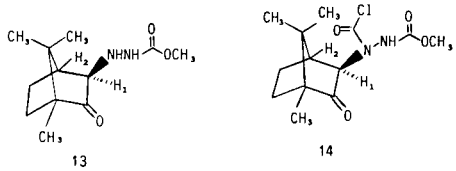
Scheme IV

displacement of the bromine atom by methyl hydrazinocarboxylate in refluxing alcohol.

1,2-Diketones as Starting Materials.

Oxadiazolones with oxo functionality at the β-carbon, such as **11**, **15**, and **16**, were obtained from the appropriate 1,2-diketones. The synthesis of **11** from camphoroquinone is depicted in Scheme IV. Compound **12** was stereoselectively reduced by sodium borohydride to the exo-substituted carbazate **13**. The ^{13}C nmr spectrum of **13** indicated a single isomer; the ^{1}H nmr spectrum was consistent with an exo-isomer. Treatment of **13** with phosgene in toluene at 80° for 3 hours gave an approximately 1:1 mixture of carbamoyl chloride **14** and oxadiazolone **11**. Prolonged heating with excess phosgene did not noticeably change the ratio of **14** *vs.* **11**. This partial spontaneous closure was unexpected since, under similar conditions, only carbamoyl chlorides could be isolated from the corresponding alkyl 3-arylcarbazates [6-8, 13], or alkyl 3-alkylcarbazates as described in Schemes I and III. Oxadiazolone **11** was obtained after a mixture of **14** and **11** was treated with sodium hydride. Transformation of **13** to

oxadiazolone **11** was accomplished in one step by heating compound **13** with phosgene in the presence of powdered sodium carbonate in toluene. The epimerization observed on the formation of **11** has not been studied in detail. The stereochemistry of compounds **13, 14,** and **11** was assigned based on the coupling constants of the methine protein α-to the carbonyl group, as illustrated below.

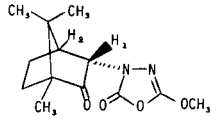


13

H_1: at 3.90 ppm (s)
J_{1-2} = < 1 Hz

14

H_1: at 4.45 ppm (s)
J_{1-2} = < 1 Hz



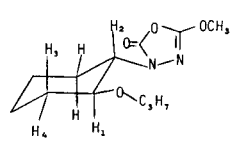
11

H_1: at 4.63 ppm (d)
J_{1-2} = 5 Hz

Figure 1

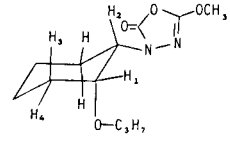
Oxadiazolone **15** was obtained from the methyl carbazate **17** when treated with phosgene in the presence of pyridine (Scheme V). Under similar condition with **18** [14], the formation of an oxadiazolone assumed to be **16** was observed. An ir spectrum indicated the presence of the oxadiazolone moiety (1800, 1660 cm^{-1}) and high resolution mass spectra suggested the molecular formula to be $C_{12}H_{18}N_2O_4$ consistent with the proposed structure [15]. However, its identity could not be fully established due to the presence of numerous minor impurities which were produced due to decomposition. The formation of either **17** or **18** was found to be dependent on the amount of anhydrous hydrochloric acid used in the sodium cyanoborohydride reduction of **19**. With one equivalent of hydrochloric acid, only carbazate **18** was formed and, with excess of hydrochloric acid, carbazate **17** was isolated.

Two isomeric oxadiazolones (**22a**, *trans*-) and (**22b**, *cis*-) were isolated after reacting a mixture of *trans*- and *cis*-carbazates **21** with phosgene (Scheme VI). Hydrogenation of **19** with Palladium on activated carbon to form **20**, followed by reduction with sodium cyanoborohydride led to a mixture of *trans*- and *cis*-isomers of **21**. The stereochemical assignments of these two isomers, **22a** and **22b**, are based on the coupling patterns observed on 250 MHz high-resolution ^1H nmr spectra, as illustrated below. The larger coupling constants between H_1 and H_2 or H_1 and H_3 (8-10 Hz) is consistent with those of **22a** and the smaller



22a

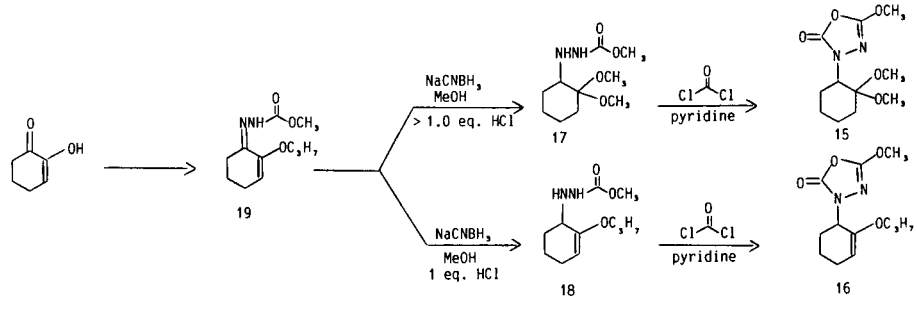
H_1: at δ 3.80 ppm
J_{1-2} = 8-10 Hz
J_{1-3} = 8-10 Hz
J_{1-4} = 2 Hz



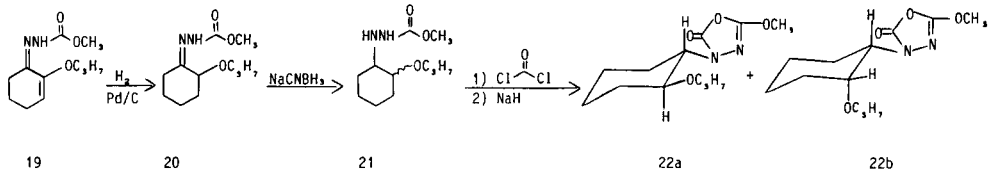
22b

H_1: at δ 3.97 Hz
J_{1-2} = 2 Hz
J_{1-3} = 2 Hz
J_{1-4} = 2 Hz

Figure II



Scheme V

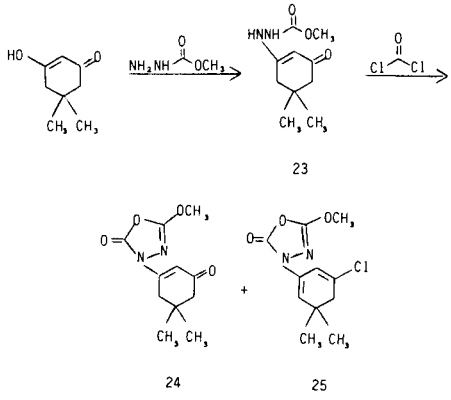


Scheme VI

values (2 Hz) with those of the isomeric compound **22b**.

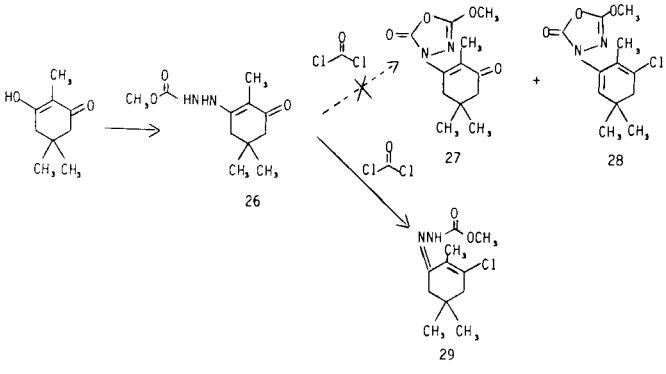
1,3-Diketones as Starting Materials.

Carbazate **23**, which was derived from dimedone and methyl hydrazinocarboxylate, on further reaction with phosgene directly afforded a mixture of two oxadiazolones **24** and **25** in an approximately 1:1 ratio (Scheme VII). No base was necessary to cause the cyclization. Addition of



Scheme VII

powdered sodium carbonate to the reaction of **23** with phosgene had little effect on the ratio of **24** and **25**. When carbazate **26** [16] was treated with phosgene (Scheme VIII), neither oxadiazolone **27** nor **28** was formed. Only compound **29** [17] was produced. The presence of a methyl

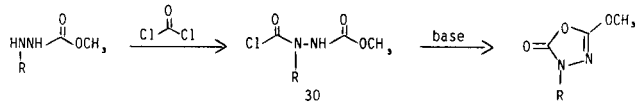


Scheme VIII

group adjacent to the carbazate appears to hinder the cyclization to oxadiazolone.

Discussion.

The rate of oxadiazolone ring formation was effected by the nature of a substituent at the N-3 position. When an enone moiety was present, such as **23**, direct ring cyclization occurred with phosgene within seven hours at 80°. Under similar conditions, when the R substituent in Scheme IX was a less electron withdrawing group such as alkyl (see Scheme I), α-phenylacetate (see Scheme III) or



Scheme IX

aryl [18], only the *N*-chlorocarbamoyl chlorides **30** were isolated. In these cases, bases were required to induce the cyclization. Triethylamine was used to achieve the ring formation of *N*-chlorocarbamoyl chlorides **30** where R groups were aryl [6-18, 13], benzyl [1] and α-phenylacetate (see Scheme III). However, a stronger base was found to be necessary to effect an efficient ring closure of **30** where R = alkyl group (see Scheme I). For example, only 30% of the *N*-carbamoyl chloride **30** with R = neopentyl was converted to oxadiazolone **7c** after stirring with triethylamine at 80° for 18 hours, where sodium hydride gave clean conversion to **7c** at room temperature. A similar type of effect by base (ethyldiisopropylamine *vs.* lithium diisopropylamide) in the cyclization of 2-carbobenzyloxy-1-phenylhydrazinecarbonyl chloride *vs.* 2-carbobenzyloxy-1-α-cumylhydrazinecarbonyl chloride was also observed by Pirkle *et al.* [2]. It may be rationalized that the *N*-chlorocarbamoyl carbon of **30** with R = alkyl groups is less electron-positive than that of its aryl or α-phenylacetate analogs, therefore, sodium hydride is needed to effect ring formation.

The cyclization to the oxadiazolone was also effected by steric factors. After the reaction of the *exo*-substituted carbazate **13** with phosgene followed by base treatment, only the *endo*-oxadiazolone **11** was isolated. The formation of the more hindered *exo*-oxadiazolone was not observed. Another example of steric interaction is demonstrated by comparing the results from the reaction of **23** *vs.* **26** with phosgene. The presence of a methyl group adjacent to the carbazate group of **26** hinders the formation of the corresponding *N*-carbamoyl chloride of **26**.

Conclusion.

During the synthesis of a limited series of the aliphatic oxadiazolones, it was noted that the conditions to effect the cyclization of the *N*-carbamoyl chloride intermediates varied widely depending on the steric and electronic effects on the chlorocarbamoyl moiety. The N-3 substituted 1,3,4-oxadiazol-2-ones described in this paper will allow us to study the spatial, positional, and electronic effects of nearby functionality and structure on the biologically active oxadiazolone ring. The biological results will be described in a separate report.

EXPERIMENTAL

All novel intermediates and oxadiazolones have been characterized by nmr and ir spectral analysis. The melting points are uncorrected. ^{1}H nmr spectra were obtained with a Varian Associated EM-360L spectrometer

using tetramethylsilane as an internal standard. The ^{13}C nmr spectra were recorded at 22.5 MHz with a JEOL FX 90Q fourier transform spectrometer. High resolution ^1H nmr spectra were obtained with a Bruker 250 MHz spectrometer with an Aspect 2000 data system. Microanalyses were performed by Galbraith Laboratories, Inc. Infrared spectra were recorded on a Perkin-Elmer 197 spectrometer. The characteristic ir absorption frequencies of aforedescribed oxadiazolones such as 1820-1790 cm^{-1} (C=O) and 1670-1640 cm^{-1} (C=N) agreed well with the data reported by Hai [3]. Reaction yields reported here have not been optimized.

3-(1-Methyl-2-methoxyethyl)-5-methoxy-1,3,4-oxadiazol-2-one (**7a**).

A solution of methyl 3-(1-methyl-2-methoxyethyl)carbazate [**5a**, 6.0 g, prepared from sodium cyanoborohydride reduction of the product **3a** (derived from methoxyacetone and methyl hydrazinocarboxylate)], phosgene (58.6 g, 12.5% in toluene) and toluene (50 ml) was heated with a dry ice-acetone condenser at 80° for 4 hours. This reaction was then concentrated *in vacuo*. The resultant residue was stirred with sodium hydride (1.63 g, 60% in oil dispersion) and tetrahydrofuran (250 ml) at room temperature for two days. Tetrahydrofuran was removed *in vacuo*. The residue was dissolved with dichloromethane and saturated aqueous ammonium chloride solution. The dichloromethane layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product (4.33 g) was chromatographed on Florisil (100-200 mesh) using a hexane-ethyl acetate gradient elution to give 1.9 g (27%) of light yellow solid of **7a**, mp 46-48°; ir (dichloromethane): 1790, 1655 cm^{-1}; ^{13}C nmr (deuteriochloroform): δ 155.4, 151.2, 73.2, 58.5, 57.1, 50.7 and 14.7 ppm.

Anal. Calcd. for $C_7H_{12}N_2O_4$: C, 44.68; N, 6.43; N, 14.89. Found: C, 44.98; H, 6.58; N, 14.91.

3-(2-Methyl-2-methylthiopropyl)-5-methoxy-1,3,4-oxadiazol-2-one (**7b**).

This compound was prepared according to the procedure used to obtain compound **7a** with sodium carbonate prior to the addition of phosgene; ir (neat): 1800, 1650 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.97 (s, $-OCH_3$, 3H), 3.63 (s, $-CH_2-$, 2H), 2.08 (s, $-SCH_3$, 3H) and 1.37 (s, $-C(CH_3)_2$, 6H) ppm.

Numerous attempts to obtain correct elemental analysis for the tlc purified aldehyde derivatives **7b** and **7c** proved to be unsatisfactory, possibly due to instability.

3-(2,2-Dimethylpropyl)-5-methoxy-1,3,4-oxadiazol-2-one (**7c**).

This compound was prepared from trimethylacetaldehyde (**2c**) according to Scheme I; ir (neat): 1810, 1650 cm^{-1}; ^1H nmr (deuteriochloro form): δ 3.97 (s, OCH_3, 3H), 3.37 (s, $-CH_2-$, 2H) and 0.98 (s, $-C(CH_3)_3$, 9H) ppm.

For elemental analysis results see comment in **7b**.

3-(Dicyclopropylmethyl)-5-methoxy-1,3,4-oxadiazol-2-one (**7d**).

This compound was prepared starting with dicyclopropylketone (**2d**) according to Scheme I, mp 68-70°; ir (dichloromethane): 1795, 1655 cm^{-1}; ^{13}C nmr (deuteriochloroform): δ 155.5, 151.5, 66.1, 57.3, 14.3, 4.3 and 2.4 ppm.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; N, 6.71; N, 13.32. Found: C, 57.26; H, 6.73; N, 13.38.

3-(1-Phenyl-2-methoxyethyl)-5-methoxy-1,3,4-oxadiazol-2-one (**7e**).

This compound was prepared starting with 2-methoxyacetophenone (**2e**) according to Scheme I; ir (dichloromethane): 1800 , 1655 cm^{-1}; ^{13}C nmr (deuteriochloroform): δ 155.6 (s), 151.6 (s), 135.8 (s), 128.7 (d), 128.4 (d), 127.4 (d), 72.1 (t), 58.7 (q), 58.7 (d) and 57.3 (q) ppm.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.59; H, 5.61; N, 11.43.

3-(1-Cyano-1-methyl-2-methoxyethyl)-5-methoxy-1,3,4-oxadiazol-2-one (**6a**).

Excess hydrogen cyanide (generated from sodium cyanide and 50% sulfuric acid) was bubbled into the solution of compound **3a** [with R = CH_3, R_1 = CH_2OCH_3, 9.42 g] and ethanol (294 ml) at -5° for 2 hours and stirred at room temperature overnight. The reaction solution was concentrated and the residue was chromatographed to yield 2.96 g of **4a** (with R = CH_3, R_1 = CH_2OCH_3) as a faint yellow solid, mp 87-90°; ^{13}C nmr (deuteriochloroform): δ 157.7, 120.1 (C≡N), 75.6, 59.6, 58.7, 52.9 and 20.3 ppm. The solution of **4a** (7.04 g), phosgene (89.3 g, 12.5% in toluene) and toluene was heated at 80° for 5 hours. The reaction was concentrated *in vacuo* and the residue was stirred with sodium hydride (1.5 g, 60% in oil dispersion) and tetrahydrofuran (200 ml) at room temperature for two days. Tetrahydrofuran was removed and the residue was partitioned between dichloromethane and saturated ammonium chloride solution. The dichloromethane concentrate was chromatographed to yield oxadiazolone **6a** (1.68 g, 20%) as a colorless oil; ^{13}C nmr (deuteriochloroform): δ 155.4 (s), 149.2 (s), 117.1 (s, -C≡N), 73.8 (t), 59.7 (q), 57.8 (q), 57.3 (s) and 21.2 (q) ppm; ir (dichloromethane): 1810, 1665 cm^{-1}.

Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 45.03; H, 5.18; N, 19.78.

Ethyl α-[3-(5-Methoxy-1,3,4-oxadiazol-2-onyl)](*o*-trifluoromethylphenyl)-acetate (**9d**).

A mixture of *o*-trifluoromethylphenylacetic acid (15.31 g) and thionyl chloride (5.9 ml) was heated at 80° for one hour until the evolution of hydrochloric acid and sulfur dioxide gases had ceased. Bromine (3.76 ml) was then added dropwise to the reaction solution at 80° and stirred at 80° for an additional one hour. After cooling to 0°, a solution of absolute ethanol (100 ml) and triethylamine (7.79 g) was added slowly and the reaction mixture was allowed to stir overnight at room temperature. Methyl hydrazinocarboxylate (6.62 g) and triethylamine (7.79 g) were added to the reaction mixture at room temperature and refluxed for four days. After work-up and chromatography, 5.64 g of a white solid was isolated, mp 98-99°; ir (dichloromethane) 1740 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.8-7.3 (m, aromatic H, 4H), 6.58 (d, J = 5 Hz, 1H), 5.23 (d, J = 3 Hz, 1H), 4.78 (dd, J_1 = 5 Hz, J_2 = 3 Hz, 1H), 4.12 (q, J = 7 Hz, $-OCH_2CH_3$, 2H), 3.70 (s, $-OCH_3$, 3H) and 1.14 (t, J = 7 Hz, $-OCH_2CH_3$, 3H) ppm. The solution of this intermediate (4.2 g), phosgene (4.0 equivalents) and toluene was heated at 70° for four hours. It was concentrated *in vacuo* and the residue was stirred with triethylamine (2.65 g) and dichloromethane (100 ml) at room temperature overnight. The reaction solution was then washed with 1% aqueous hydrochloric acid solution twice, dried over magnesium sulfate, filtered and concentrated. The crude material was chromatographed to yield 1.98 g (44%) of **9d** as a colorless liquid; ir (dichloromethane): 1815, 1760, 1670 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.90-7.50 (m, aromatic H, 4H), 6.2 (s, 1H), 4.29 (q, J = 7 Hz, 2H), 4.0 (s, $-OCH_3$, 3H) and 1.22 (t, J = 7 Hz, 3H) ppm. The non-aromatic carbons of **9d** shown on ^{13}C nmr spectrum (deuteriochloroform): 123.9 (CF_3), 62.7 (t), 57.5 (d), 57.5 (q), 14.0 (q) ppm.

Anal. Calcd. for $C_{14}H_{13}F_3N_2O_5$: C, 48.55; H, 3.78. Found: C, 48.53; H, 3.95.

Ethyl α-[3-(5-Methoxy-1,3,4-oxadiazol-2-onyl)]phenylacetate (**9a**).

This compound was prepared according to Scheme III (73%) yield from **10** with R = H, R_1 = C_2H_5); ^1H nmr (deuteriochloroform): δ 7.7-7.31 (m, aromatic H, 5H), 5.82 (s, methine H, 1H), 4.24 (q, J = 7 Hz, $-OCH_2CH_3$, 2H), 3.89 (s, $-OCH_3$, 3H) and 1.18 (t, J = 7 Hz, $-OCH_2CH_3$, 3H) ppm; ^{13}C nmr (deuteriochloroform): δ 167.8 (s), 155.6 (s), 151.5 (s), 132.9 (s), 129.3 (d), 129.1 (d), 128.7 (d), 62.3 (t), 61.5 (d), 57.5 (q) and 14.1 (q) ppm; ir (dichloromethane): 1805, 1750, 1665 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.10; H, 5.07; N, 10.06. Found: C, 56.02; H, 5.17; N, 9.98.

Ethyl α-[3-(5-Methoxy-1,3,4-oxadiazol-2-onyl)](*o*-fluorophenyl)acetate (**9b**).

This compound was synthesized from *o*-fluorophenylacetic acid according to Scheme III; ^1H nmr (deuteriochloroform): δ 7.70-6.90 (m, aromatic H, 4H), 6.05 (s, 1H), 4.22 (q, J = 7 Hz, 2H), 3.89 (s, OCH_3, 3H) and 1.20 (t, J = 7 Hz, 3H) ppm; ^{13}C nmr (deuteriochloroform): the non-aromatic carbons of **9b**, δ 62.5 (t), 57.5 (q), 55.2 (d) and 14.1 (q) ppm; ir (neat): 1810, 1750, 1660 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}FN_2O_5$: C, 52.70; H, 4.42; N, 9.45. Found: C, 52.63; H, 4.28; N, 9.60.

Ethyl α-[3-(5-Methoxy-1,3,4-oxadiazol-2-onyl)](*p*-fluorophenyl)acetate (**9c**).

This compound was prepared from *p*-fluorophenylacetic acid based on the procedure for the preparation of compound **9d**; ^{1}H nmr (deuteriochloroform): δ 7.58-6.90 (m, aromatic H, 4H), 5.73 (s, 1H), 4.28 (q, J = 7 Hz, 2H), 3.98 (s, -OCH_3, 3H) and 1.28 (t, J = 7 Hz, 3H) ppm; ^{13}C nmr (deuteriochloroform): the non-aromatic carbons on **9c**, δ 62.5 (t), 60.7 (d), 57.5 (q) and 14.1 (q) ppm; ir (neat): 1810, 1755, 1665 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}FN_2O_5$: C, 52.70; H, 4.42; N, 9.45. Found: C, 52.68; H, 4.45; N, 9.63.

Ethyl α-[3-(5-Methoxy-1,3-4-oxadiazol-2-onyl)](*p*-methoxyphenyl)acetate (**9e**).

This compound was prepared starting with *p*-methoxyphenylacetic acid based on Scheme III; ^{1}H nmr (deuteriochloroform): δ 7.42 (d, J = 9 Hz, aromatic H, 2H), 6.94 (d, J = 9 Hz, aromatic H, 2H), 5.72 (s, 1H), 4.28 (q, J = 7 Hz, 2H), 3.97 (s, -OCH_3, 3H), 3.82 (s, -OCH_3, 3H) and 1.24 (t, J = 7 Hz, 3H) ppm; ir (neat): 1800, 1745, 1655 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.08. Found: C, 54.03; H, 5.26; N, 9.30.

Ethyl α-[3-(5-Methoxy-1,3,4-oxadiazol-2-onyl)](2-chloro-6-fluorophenyl)-acetate (**9f**).

This compound was prepared starting with 2-chloro-6-fluorophenyl acetic acid according to Scheme III; ^{1}H nmr (deuteriochloroform): δ 7.50-6.90 (m, aromatic H, 3H), 6.2 (s, 1H), 4.30 (q, J = 7 Hz, 2H), 3.97 (s, -OCH_3, 3H) and 1.28 (t, J = 7 Hz, 3H) ppm; ir (neat): 1810, 1760, 1660 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}ClFN_2O_5$: C, 47.20; H, 3.66; N, 8.50. Found: C, 47.08; H, 3.68; N, 8.57.

3-(α-Camphoryl)-5-methoxy-1,3,4-oxadiazol-2-one (**11**).

A solution of *dl*-camphoroquinone (60.0 g), methyl hydrazinocarboxylate (32.84 g) and methanol (500 ml) was refluxed for three days. Methanol was removed and the residue was dissolved with dichloromethane and water. The dichloromethane was washed with one more portion of water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The yellow solid residue was chromatographed on Florisil using a hexane-ethyl acetate gradient elution to afford 38.3 g of a yellow solid as compound **12**, mp 177-178°. Sodium borohydride (1.62 g) was added to the solution of compound **12** (20.0 g) and methanol (300 ml) at 0° and stirred at room temperature for 3.5 hours and 6*M* potassium hydroxide was added to adjust to *p*H 11. The basic aqueous solution was extracted with dichloromethane several times. The combined dichloromethane extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 17.4 g of a white solid as **13**, mp 158°; ^{13}C nmr of compound **13** (deuteriochloroform): δ 166.3 (s), 155.0 (s), 78.8 (d), 52.9 (q), 49.2 (s), 47.8 (d), 47.5 (s), 33.5 (t), 22.8 (t), 21.3 (q) and 10.6 (q) ppm. The solution of compound **13** (15.0 g), phosgene (148.2 g, 12.5% in toluene) and toluene (100 ml) was heated at 80° with a dry ice-acetone condenser for 3 hours. It was then concentrated *in vacuo* and the residue was stirred with sodium hydride (1.82 g, 60% oil dispersion) and tetrahydrofuran (175 ml) at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue was dissolved with dichloromethane and saturated aqueous ammonium chloride solution. The dichloromethane layer was dried over magnesium sulfate, filtered and concentrated. The yellow oil residue was chromatographed on Florisil to yield 10.3 g (62%) of 3-(α-camphoryl)-5-methoxy-1,3,4-oxadiazol-2(3*H*)-one (**11**) as a white solid, mp 200-205°; ir (dichloromethane): 1800, 1755 (C=O), 1665 cm^{-1}; ^{13}C nmr (deuteriochloroform): δ 210.2 (s), 155.5 (s), 151.8 (s), 61.7 (d), 58.4 (s), 57.4 (q), 48.3 (d), 44.1 (s), 30.7 (t), 20.2 (t), 19.6 (q), 18.8 (q) and 9.5 (q) ppm. The stereochemical assignment was based on the coupling constant between two methine protons (J = 5 Hz at 4.6 ppm) on ^{1}H nmr spectrum.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.59; H, 6.87; N, 10.44.

3-(2,2-Dimethoxycyclohexyl)-5-methoxy-1,3,4-oxadiazol-2-one (**15**).

To a solution of compound **19** (5.0 g, prepared from 2-*n*-propoxycyclohex-2-en-1-one and methyl hydrazinocarboxylate), sodium cyanoborohydride (0.92 g), a catalytic amount of methyl orange and methanol (150 ml) was added enough anhydrous hydrochloric acid/methanol to maintain the reaction solution *p*H <5. After work-up according to the preparation of compound **13**, 4.03 g of carbazate **17** as a yellow oil was obtained; ^{1}H nmr (deuteriochloroform): of **17** indicated the presence of three methoxy groups, δ 3.71 (s, -OCH_3, 3H), 3.31 (s, -OCH_3, 3H) and 3.20 (s, -OCH_3, 3H) ppm; ^{13}C nmr (deuteriochloroform): δ 157.9 (s), 100.6 (s, $C(OCH_3)_2$), 56.9 (d), 52.3 (q), 47.5 (q), 27.7 (t), 25.1 (t), 22.4 (t) and 19.3 (t) ppm. The solution of carbazate **17** (3.33 g), phosgene (22.6 g, 12.5% in toluene), pyridine (6.78 g) and toluene (200 ml) was stirred at room temperature overnight. The reaction mixture was washed with water and the organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was chromatographed on Florisil using a hexane-ethyl acetate gradient elution to give 1.93 g (53%) of a liquid product as compound **15**; ir (neat): 1800, 1660 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.43-4.10 (m, 1H), 4.00 (s, -OCH_3, 3H), 3.23 (s, C-$(OCH_3)_2$, 6H) and 2.30-0.63 (m, 8H) ppm.

Anal. Calcd. for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.02; N, 10.85. Found: C, 51.06; H, 7.03; N, 10.74.

3-[2-(*n*-Propoxy)cyclohexyl]-5-methoxy-1,3,4-oxadiazol-2-one, *trans* (**22a**).

Prepared from methyl carbazate **21** (7.1 g prepared from the sequential reduction of **19** *via* hydrogen/Palladium-carbon, followed by sodium cyanoborohydride) according to the experimental procedure described for the preparation of compound **7a**; 1.43 g of **22a** as a clear liquid was isolated from column chromatography; ir (neat): 1795, 1645 cm^{-1}; ^{13}C nmr (deuteriochloroform): δ 155.5, 151.8, 77.9, 75.7, 70.5, 59.6, 57.2, 30.9, 29.6, 24.7, 24.0, 23.2 and 10.5 ppm.

Anal. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.23; H, 7.87; N, 10.93. Found: C, 56.04; H, 8.06; N, 11.38.

3-[2-(*n*-Propoxy)cyclohexyl]-5-methoxy-1,3,4-oxadiazol-2-one, *cis* (**22b**).

Compound **22b** (1.75 g) as a clear liquid was obtained from column chromatography; ir (neat): 1790, 1655 cm^{-1}; ^{13}C nmr (deuteriochloroform): δ 155.0, 151.4, 75.3, 70.9, 57.2, 57.0, 28.2, 25.3, 24.1, 23.2, 20.2 and 10.6 ppm.

Anal. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.23; H, 7.87; N, 10.93. Found: C, 56.29; H, 7.91; N, 11.40.

3-(5,5-Dimethylcyclohex-1-en-3-onyl)-5-methoxy-1,3,4-oxadiazol-2-one (**24**).

A solution of dimedone (14.67 g), methyl hydrazinocarboxylate (9.42 g) and methanol (300 ml) was refluxed for three days. After work-up, 9 g of compound **23** as a solid was obtained, mp 175-177°; ^{13}C nmr (deuteriochloroform): δ 196.4 (s), 164.5 (s), 156.4 (s), 94.9 (d), 52.2 (q), 50.4 (t), 39.4 (t), 32.6 (s) and 28.0 (q) ppm; ^{1}H nmr (deuteriochloroform/(methyl sulfoxide)-d_6): δ 9.22 (br, -NH, 1H), 8.70 (br, -NH, 1H), 5.10 (s, olefinic H, 1H), 3.68 (s, -OCH_3, 3H), 2.21 (s, -CH_2-, 2H), 2.07 (s, -CH_2-, 2H) and 1.04 (s, $C(CH_3)_2$, 6H) ppm; ir (dichloromethane): 1748, 1610 cm^{-1}. The solution of compound **23** (7.0 g), phosgene (160 g, 12.5% in toluene) and toluene (50 ml) was heated at 80° for 6.5 hours and stirred at room temperature overnight. (Tlc indicated no change effected by overnight stirring at room temperature). The solution was concentrated *in vacuo* to a residual oil and purified by chromatography to afford 0.49 g of a yellow solid as **24**, mp 74-77°; ^{1}H nmr (deuteriochloroform): δ 6.43 (s, olefinic H, 1H), 4.10 (s, -OCH_3, 3H), 2.81 (s, -CH_2-, 2H), 2.28 (s, -CH_2-, 2H) and 1.12 (s, -$C(CH_3)_2$, 6H) ppm; ir (dichloromethane): 1810, 1670, 1660, 1614 cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 54.99; H, 6.04; N, 11.64.

3-(3,3-Dimethyl-5-chloro-1,5-cyclohexadienyl)-5-methoxy-1,3,4-oxadiazol-2-one (**25**).

This compound was isolated from the reaction of the preparation of compound **24**, mp 117-118°; ^{1}H nmr (deuteriochloroform): δ 5.95 (m, olefinic H, 1H), 5.68 (m, olefinic H, 1H), 4.03 (s, -OCH_3, 3H), 3.33 (dd, -CH_2-, 2H) and 1.13 (s, $C(CH_3)_2$, 6H) ppm; ir (dichloromethane): 1795, 1665 cm^{-1}; ei/ms: m/e 256 (M^+, 24), 241 (M^+-CH_3, 100).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.10; N, 10.91. Found: C, 51.39; H, 5.11; N, 10.90.

Acknowledgement.

We thank Edward C. Bailey for the ^{13}C nmr spectra.

REFERENCES AND NOTES

[†] Current address: Burroughs Wellcome Co., Research Triangle Park, NC 27709.

[1] Japanese Patent 59,222,482A (1984) to Mitsubishi Chem Ind KK; *Chem. Abstr.*, **102**, 203975u (1985).

[2] W. H. Pirkle and P. L. Gravel, *J. Org. Chem.*, **41**, 3763 (1976).

[3] S. M. A. Hai, *Pak. J. Sci. Ind. Res.*, **16**, 168 (1973).

[4] S. M. A. Hai and W. Lwowski, *J. Org. Chem.*, **38**, 2442 (1973).

[5] S. M. A. Hai and A. Begum, *Pak. J. Sci. Ind. Res.*, **18**, 15 (1975).

[6] R. Boesch, U. S. Patent 4,076,824 (1978) to Rhone-Poulenc Ind; *Chem. Abstr.*, **85**, 143115g (1976).

[7] R. Boesch, U. S. Patent 4,150,142 (1979) to Philagro; *Chem. Abstr.*, **85**, 143115g (1976).

[8] C. H. Tieman, U. S. Patent 4,302,592 (1981) to Shell Oil Company; *Chem. Abstr.*, **96**, 104254j (1982).

[9] *Org. Synth.*, **58**, 101.

[10] The structure of **8** was determined based on ir and nmr spectral data; ir (chloroform): 1754, 1690 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.77 (s, -OCH_3, 3H), 3.57 (s, -CH_2, 2H) and 1.63 (s, $C(CH_3)_2$, 6H) ppm; ^{13}C nmr (deuteriochloroform): δ 172.5, 155.9, 62.7, 53.2, 46.0 and 29.4 ppm.

[11] E. Schwenk and D. Papa, *J. Am. Chem. Soc.*, **70**, 3626 (1948).

[12] J. P. Berry, A. F. Isbell, and G. E. Hunt, *J. Org. Chem.*, **37**, 4396 (1972).

[13] A. Stern, *J. Prakt. Chem.*, **60**, 235 (1899).

[14] ^{13}C nmr (deuteriochloroform) of **18**: δ 157.9, 152.8, 97.8, 68.2, 57.0, 52.4, 27.2, 23.8, 22.4, 19.5 and 10.7 ppm; ir (dichloromethane): 1728 cm^{-1}.

15] High resolution ms, molecular ion at m/e 254, 254.1265 (Calcd. for $C_{12}H_{18}N_2O_4$, 254.1266).

[16] ^{1}H nmr (deuteriochloroform) of **26**: δ 7.75 (s, -NH, 1H), 6.55 (s, -NH, 1H), 3.73 (s, -OCH_3, 3H), 2.32 (s, -CH_2, 2H), 2.18 (s, -CH_2, 2H), 1.70 (s, CH_3, 3H) and 1.03 (s, $C(CH_3)_2$, 6H) ppm. Prepared from 2-methyldimedon [Ref: M. Sekiya and K. Suzuki, *Chem. Pharm. Bull.*, **19**, 1531 (1971)] and methyl hydrazinocarboxylate.

[17] ^{13}C nmr (deuteriochloroform) of **29**: δ 155.0 (s), 149.4 (s), 136.5 (s), 129.1 (s), 53.0 (q), 47.4 (t), 36.7 (t), 31.6 (s), 28.3 (q) and 13.5 (q) ppm; mp 158-162°; ei/ms: m/e 244 (M^+, 87.3), 229 (M^+-CH_3, 100).

Anal. Calcd. for $C_{11}H_{17}ClN_2O_3$: C, 53.99; H, 7.00; N, 11.45; Cl, 14.49. Found: C, 53.99; H, 6.96; N, 11.31; Cl, 14.29.

[18] Alkyl 3-phenylcarbazates have been reported by K. H. Pilgram [*J. Heterocyclic Chem.*, **19**, 823 (1982)] to cyclize when treated with phosgene in refluxing toluene (7-48 hours) in the absence of bases.