**Table IV—Assay of I in Other Matrixes**

| Sample | GLC Assay | Theoretical |
|---|---|---|
| Ampul solution 1 | 16.2 mg/2 ml[a] | 20 mg/2 ml |
| Ampul solution 2 | 18.4 mg/2 ml[a] | 20 mg/2 ml |
| Ampul solution 3 | 21.2 mg/2 ml | 20 mg/2 ml |
| Premix pellets | 2.53% | 2.5% |
| Premix 1 | 14.8% | 15.0% |
| Premix 2 | 16.1% | 17.3% |
| Premix 3 | 16.4% | 16.5% |
| Premix 4 | 16.2% | 17.3% |
| Mycelial cake 1 | 6.3% | NA[b] |
| Mycelial cake 2 | 6.5% | NA |
| Mycelial cake 3 | 5.0% | NA |
| Mycelial cake 4[c] 1.1% excess | 7.6% | 7.4 |

[a] Decomposition of I in solution was indicated by the presence of an unknown GLC peak. [b] NA = not available. [c] Sample 1 to which had been added 1.1% of active ingredient to get an indication of recovery.

quently, the column temperature was raised to 260° to elute the I or II derivative peaks.

If any retroaldol ketone (known thermal degradation product) is present in the samples, it also would be silylated, resulting in a well-resolved peak suitable for quantitation. Samples of I and II complexes with meglumine were experimentally spiked with known amounts of retroaldol ketone and chromatographed after silylation. When the column temperature was programmed from 100 to 300°, trimethylsilyl derivatives of retroaldol ketone, meglumine, I, and II eluted at retention times of 7.5, 15, 30, and 35 min, respectively, clearly indicating the specificity and capability of the method for the assay of the antibiotic in multicomponent systems.

Furthermore, the I derivative peak area was approximately twice that of the retroaldol ketone when equal concentrations of I were subjected to the GLC–thermolysis method and the silylation procedure. This enhancement in peak response would be an added advantage in the analysis of low levels of I as a trimethylsilyl derivative.

The method presented has been applied to the assay of I in various solid and liquid preparations. It is specific for the antibiotic and does not require any extraction or pretreatment of the samples as in other reported methods.

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[x] To whom inquiries should be directed.


# New Synthesis of 1,4,2-Dioxazoles and Their Pharmacological Properties


**NED D. HEINDEL[*x], WILLIAM P. FIVES[*], and RICHARD A. CARRANO[‡§]**



**Abstract** □ A series of 3-substituted 5-methoxycarbonyl-5-methoxycarbonylmethyl-1,4,2-dioxazoles was prepared by addition of hydroxamic acids to acetylene esters. Eleven of these previously unknown compounds were submitted to general pharmacological screening, and several displayed modest CNS depressant activity.



**Keyphrases** □ 1,4,2-Dioxazoles, substituted—synthesis, general pharmacological screening □ CNS activity—substituted 1,4,2-dioxazoles screened □ Structure-activity relationships—substituted 1,4,2-dioxazoles, general pharmacological screening


Most reported 1,4,2-dioxazoles are derived from the condensation of hydroxamic acids with phosgene (1, 2) or diethylacetals (3). Newer routes include a 1,3-dipolar addition method involving ketones and nitrile oxides (4) and a ring expansion of 2-acyloxaziridines (5). Except for some claims of antifungal activity in the 5-oxo derivatives (6) and of antibacterial potency in 5-benzenesulfonamido-substituted 1,4,2-dioxazoles (7), the possible pharmacological utility of this family of heterocyclics is still unknown.

## CHEMISTRY

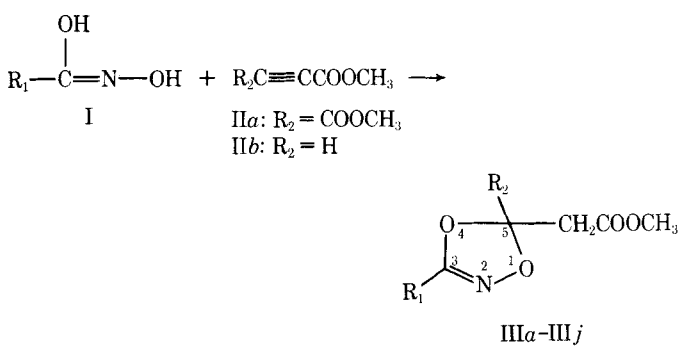
Reports from these laboratories noted the general utility of acetylenic esters in the synthesis of heterocyclic compounds generated by double nucleophilic additions to the same alkyne carbon (8, 9). In a similar fashion, hydroxamic acids, presumably in their enol tautomers (I) (10), reacted with dimethyl acetylenedicarboxylate (II*a*) and/or methyl propiolate (II*b*) (Schemes I and II) to produce high yields of 3-substituted 5-methoxycarbonyl-5-methoxycarbonylmethyl-1,4,2-dioxazoles (III*a*–III*j* and IV, Table I). In view of the paucity of information available on this heterocyclic family and the unique nature of this particular subclass, the general biological responses are now reported.

Available spectral evidence supported the assigned dioxazole structure.

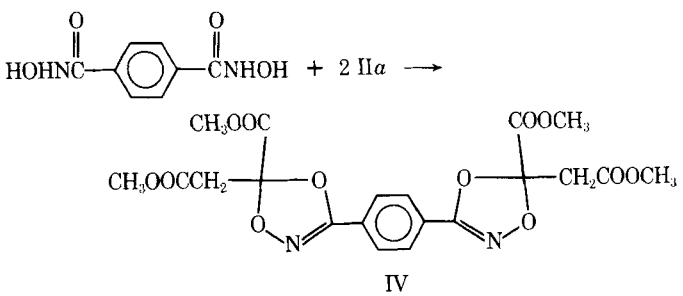
Table I—Physical Data for 1,4,2-Dioxazoles

| Compound | $R_1$ | $R_2$ | Yield, % | Melting Point (Boiling Point/ mm Hg) | $n_D^{21}$ | Formula | Analysis, % Calc. | Found |
|---|---|---|---|---|---|---|---|---|
| III*a* | $C_6H_5$ | $COOCH_3$ | 80 | (154–156°/0.5) | 1.5182 | $C_{13}H_{13}NO_6$ | C 55.91 | 55.81 |
| | | | | | | | H 4.70 | 4.61 |
| | | | | | | | N 5.02 | 4.97 |
| III*b* | *p*-$CH_3OC_6H_4$ | $COOCH_3$ | 90 | 50–51° | — | $C_{14}H_{15}NO_7$ | C 54.37 | 54.65 |
| | | | | | | | H 4.89 | 5.09 |
| | | | | | | | N 4.53 | 4.72 |
| III*c* | *m*-$CH_3OC_6H_4$ | $COOCH_3$ | 66 | (120–121°/0.1) | 1.5221 | $C_{14}H_{15}NO_7$ | C 54.37 | 54.25 |
| | | | | | | | H 4.89 | 4.80 |
| | | | | | | | N 4.53 | 4.37 |
| III*d* | *p*-$BrC_6H_4$ | $COOCH_3$ | 83 | — | 1.5450 | $C_{13}H_{12}BrNO_6$ | C 43.60 | 43.78 |
| | | | | | | | H 3.38 | 3.66 |
| | | | | | | | N 3.91 | 4.01 |
| III*e* | *m*-$NO_2C_6H_4$ | $COOCH_3$ | 45 | (145–148°/0.1) | 1.5337 | $C_{13}H_{12}N_2O_8$ | C 48.15 | 48.29 |
| | | | | | | | H 3.73 | 3.75 |
| | | | | | | | N 8.64 | 8.60 |
| III*f* | $C_6H_{11}$ | $COOCH_3$ | 76 | (123–135°/0.04) | 1.4687 | $C_{13}H_{19}NO_6$ | C 54.73 | 54.58 |
| | | | | | | | H 6.71 | 6.77 |
| | | | | | | | N 4.91 | 4.93 |
| III*g* | $C_6H_5CH_2$ | $COOCH_3$ | 74 | (161–163°/0.3) | — | $C_{14}H_{15}NO_6$ | C 57.33 | 57.22 |
| | | | | | | | H 5.16 | 5.35 |
| | | | | | | | N 4.78 | 4.62 |
| III*h* | $C_6H_5CH_2CH_2$ | $COOCH_3$ | 79 | — | 1.5032 | $C_{15}H_{17}NO_6$ | C 58.63 | 58.56 |
| | | | | | | | H 5.58 | 5.53 |
| | | | | | | | N 4.56 | 4.73 |
| III*i* | $CH_3$ | $COOCH_3$ | 69 | (77–79°/0.07) | — | $C_8H_{11}NO_6$ | C 44.24 | 44.15 |
| | | | | | | | H 5.11 | 5.22 |
| | | | | | | | N 6.45 | 6.45 |
| III*j* | $C_6H_5$ | H | 76 | (134–136°/0.6) | 1.5344 | $C_{11}H_{11}NO_4$ | C 59.72 | 59.94 |
| | | | | | | | H 5.01 | 5.02 |
| | | | | | | | N 6.33 | 6.52 |
| IV | Terephthaloyl compound | | 58 | 112–114° | — | $C_{20}H_{20}N_2O_{12}$ | C 50.00 | 49.94 |
| | | | | | | | H 4.20 | 4.06 |
| | | | | | | | N 5.83 | 5.74 |

In the IR spectrum, all NH and OH absorptions of the starting hydroxamic acid disappeared and the saturated ester carbonyls appeared between 1732 and 1752 $cm^{-1}$. The PMR spectrum revealed the ester methoxys between $\delta$ 3.65 and 3.86 ppm and, more significantly, the pendent methylene group by its characteristic geminally coupled *AB* quartet ($J$ = 17 Hz) at $\delta$ 3.20 ± 0.20 ppm. This appearance of magnetically nonequivalent methylene protons adjacent to an asymmetric center is well known (11). Furthermore, the mass spectra of all 1,4,2-dioxazoles derived from dimethyl acetylenedicarboxylate showed the expected parent ion and fragments at P − 73 (loss of $CH_2COOCH_3$) and P − 59 (loss of $COOCH_3$), clearly indicating the nature of the two ester moieties attached at C-5 of the 1,4,2-dioxazoles.




*Scheme I*




*Scheme II*

In accord with numerous citations in the patent literature claiming pyrolysis of 1,4,2-dioxazoles as a route to isocyanates (12, 13), distillation of the prepared liquid dioxazoles often produced a fraction containing the corresponding isocyanate (absorption at 2250 ± 15 $cm^{-1}$). Two dioxazoles (III*d* and III*h*) suffered such extensive thermal decomposition on refluxing that they could not be distilled. For these two particular materials, an extraction purification procedure was developed which yielded analytically pure product. This technique was also applicable to most other liquid dioxazoles.

Table I reports boiling points for the substances that could be vacuum distilled and refractive indexes for the dioxazoles purified by the extraction method. If an analytically pure product could be obtained by either route, then both boiling points and refractive index values are cited.

## PHARMACOLOGY

**General Rat Screening**—All compounds were tested and the results were analyzed according to the methods described by Malone and Carrano (14) and employed previously (15). Nonfasted albino rats, 180–210 g, were used; injections were made intraperitoneally.

**General Central Nervous System (CNS) Testing in Mice**—Motor function and neurotoxicity were tested at 200 mg/kg ip by measuring the inability of trained animals to walk a rotating wooden rod (28 mm diameter at 6 rpm) for 1 min. Six 18–22-g nonfasted albino mice were used per group; dosing was done intraperitoneally. The animals were tested at 0, 15, 30, 60, 90, 120, 150, and 180 min postinjection.

If there was no neurotoxicity at 200 mg/kg ip, then that dose was used for subsequent work in the antistrychnine, antipentylenetetrazol, antielectroshock, and antioxotremorine tests. In these tests, the experimental drug was injected intraperitoneally into groups of six 18–22-g nonfasted albino mice; at 30 min postinjection, strychnine sulfate (1.1 mg/kg sc), pentylenetetrazol (70 mg/kg sc), oxotremorine (350 μg/kg sc), or a 50-amp, 0.2-sec shock was administered to each animal. The animals were observed for 30 min for tonic extensor seizures in the antistrychnine test and for clonic seizures in the antipentylenetetrazol test. In the antielectroshock test, they were observed for hindlimb tonic extensor seizures. In the antioxotremorine test, tremors were subjectively rated per

animal on a scale of 0–3 and the total response for the entire group was calculated and compared to that of a control group.

In each test, a group of animals receiving 0.9% NaCl (5 ml/kg) was run simultaneously with the experimental groups. In the acetylcholine writhing test, mice were injected orally with the experimental agent; 30 min later, they were challenged with 7.0 mg/kg ip of acetylcholine bromide. The number of animals in the experimental group that elicited a writhing response within 2 min was compared to a control group receiving 0.9% NaCl.

Selected drugs were tested for their ability to inhibit aggression induced in pairs of mice by subjecting them to an interrupted direct current foot shock of 0.8 mamp for 2 min.

**Acute Anti-Inflammatory–Analgesic Testing**—Nonfasted albino rats, 160–180 g, equally divided between sexes were used. The experimental drugs were administered orally. A modified Randall–Selitto (16) method was used; immediately following administration of the drug, 0.1 ml of a 1% carrageenan suspension was injected into the subplantar area of the right hindpaw, and the control foot volume was recorded by volume displacement. The control analgesic response was then estimated by placing the injected paw between two grooved disks, which were slowly forced together *via* air pressure. The amount of pressure required to cause the animal to vocalize or attempt to bite the disks was recorded. The analgesic response was again estimated at 45 min postinjection, and foot volume was measured at 4 hr postinjection. A control group that received 0.9% NaCl in place of the experimental drug was tested simultaneously.

## RESULTS AND DISCUSSION

Table II lists the important observations in the general rat screening. The maximum sublethal dose is the highest dose administered at which no death occurred. Since no doses were made over 1.0 g/kg, the maximum sublethal dose was assumed to be greater than 1.0 g/kg in cases where there was no death at this dosage.

Also presented in Table II are scores that represent the extent of general autonomic nervous system (ANS) and general CNS depressant (CNSD) activity. The absolute values of these ANS and CNSD scores are not comparable. The significant symptomatology of the candidate dioxazoles is given. These data were subjected to a computer-matching operation against a library of 27 reference drugs. The symptomatology and ANS/CNSD scores for the drugs selected for comparison were reported previously (15).

Compounds III*a*, III*g*, and IV produced significant CNS depression in rats. The symptomatology exhibited by these drugs suggests that they have activity similar to tranquilizers, muscle relaxants, anticonvulsants, and other CNS depressants. On the basis of computerized matching, III*g* showed a particular similarity to chlorpromazine and chlordiazepoxide. Apparently, only the dioxazoles with phenyl moieties (lacking polar substituents such as methoxy, nitro, and bromo) attached directly to the hetero ring or in the $\alpha$-position (*i.e.*, III*g*) displayed the depressant activity. The two pendent ester groupings are apparently necessary, since III*a* was one of the most active compounds tested while III*j* gave evidence of only very modest activity. On the basis of the primary rat screening, III*a*, III*g*, and IV were submitted for further evaluation in the CNS battery. The percent protection at the rotarod $ED_{50}$ was evaluated.

Here again the benzyl derivative, III*g*, displayed the highest percentage protection (36%) against shock-induced aggression and did exhibit some antioxotremorine activity (14%). All compounds were tested at a considerably more elevated dose, 200 mg/kg ip, than the comparison drugs, and none was judged sufficiently active to warrant further study. Chlordiazepoxide hydrochloride, for example, at a dose of 32 mg/kg ip, provides 100% protection against shock-induced aggression and 75% protection in the antioxotremorine assay.

Some protection against acetylcholine writhing was observed with III*a* and IV, 33% in both cases, but they were rejected for advanced studies because of the elevated doses required (300 mg/kg po) and the lack of significant anti-inflammatory–analgesic activity in the Randall–Selitto assay (16).

Since both III*i* and III*j* displayed significant scores in the autonomic category of the general rat screen (Table II), they were selected for cardiovascular measurements in the anesthetized cat. Both compounds produced moderate to extreme transient falls in blood pressure at 1–25 mg/kg iv. Heart rate was not affected dramatically. Both drugs produced some potentiation of the responses to norepinephrine, a decrease in the pulse pressure response to isoproterenol, and an inhibition of the response to 1,1-dimethyl-4-phenylpiperazinium iodide. However, none of these actions was considered significant enough to merit further investigation.

Table II—*In Vivo* Rat Screening Data for 1,4,2-Dioxazoles

| Compound[a] | ANS Score | CNSD Score | Significant Symptomatology |
|---|---|---|---|
| III*a* | 0.53 | 4.78 | Decreased body tone, body weight |
| III*b* | 0 | 0 | None |
| III*c* | 2.01 | 1.23 | Miosis, piloerection |
| III*d* | 1.48 | 2.16 | Miosis, piloerection, decreased body tone |
| III*e* | 1.27 | 0 | Miosis, piloerection, decreased body weight, fearfulness |
| III*g*[b] | 1.06 | 11.88 | Decreased motor activity, ataxia, decreased respiratory rate, piloerection, decreased rotarod ability, decreased body tone |
| III*i* | 4.87 | 0.62 | Miosis, decreased body weight |
| III*f* | 0.74 | 2.93 | Decreased motor activity, piloerection, increased body tone |
| III*j* | 4.97 | 0.77 | Miosis |
| IV | 3.70 | 10.49 | Decreased motor activity, ataxia, miosis, piloerection, decreased body weight, decreased body tone, decreased rotarod ability |
| III*h* | 0.42 | 1.08 | Decreased body weight |

[a] The maximum sublethal dose was greater than 1000 mg/kg ip. [b] Similar to chlordiazepoxide and chlorpromazine.

In general, these 1,4,2-dioxazoles were water-insoluble viscous liquids that were difficult to manipulate and administer in the animal studies. Gross necropsy of rats at 48 hr after intraperitoneal injection revealed the presence of some unabsorbed drug in the peritoneal cavity.

## EXPERIMENTAL[1]

**Hydroxamic Acids**—The required hydroxamic acids were either commercially available or prepared from the corresponding ester and hydroxylamine according to published procedures (17–22).

**Compounds III*a*–III*i***—An equimolar mixture of the required hydroxamic acid and dimethyl acetylenedicarboxylate was prepared in anhydrous methanol at a concentration of 100 mmoles/100 ml of solvent. The solution was refluxed for 30–60 min and then allowed to stir at room temperature for 24 hr. Concentration *in vacuo* produced an oil, which solidified in the case of III*b* (recrystallized from methanol, mp 50–51°, 90%) but remained liquid in the other examples. Purification was effected by either fractional vacuum distillation or by the following solvent extraction procedure.

The oily dioxazole was dissolved in a minimum of carbon tetrachloride and washed four times with 50-ml portions of cold distilled water. The carbon tetrachloride layer was dried with magnesium sulfate and evaporated under vacuum with minimal heating to yield the product as a clear oil. Refractive indexes ($n_D^{21}$), yields, and analytical data are given in Table I for those dioxazoles purified by this method. If no refractive index is given, the purification was by vacuum distillation.

**Compound III*j***—A solution of 73.0 mmoles of benzohydroxamic acid and methyl propiolate in 75 ml of methanol was heated at reflux for 24 hr, evaporated *in vacuo*, and purified by the solvent extraction procedure to return a 76% yield. The oil could also be vacuum distilled.

**Compound IV**—A methanol solution of 51.0 mmoles of terephthalohydroxamic acid, 102 mmoles of dimethyl acetylenedicarboxylate, and 200 ml of methanol was stirred at room temperature for 48 hr, during which time a white precipitate appeared. The reaction mixture was filtered, concentrated, and chilled to produce an additional crystal crop; the crude product was recrystallized from methanol to afford 14.2 g (58%) of white microneedles, mp 112–114° (Table I).

[1]Melting points were determined with a Fisher-Johns apparatus and are not corrected. IR spectra were obtained as hydrocarbon mulls or neat on a Perkin-Elmer model 257 spectrophotometer. PMR spectra were determined on a Hitachi Perkin-Elmer model R20A spectrometer in deuterochloroform, using tetramethylsilane as the internal reference.

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§ Present address: Adria Laboratories, Inc., Wilmington, DE 19801.

x To whom inquiries should be directed.


# Plasma Isosorbide Dinitrate Concentrations in Human Subjects after Administration of Standard and Sustained-Release Formulations


**D. F. ASSINDER, L. F. CHASSEAUD[x], and T. TAYLOR**



**Abstract** □ After sublingual administration of 5 mg of isosorbide dinitrate, mean plasma concentrations (± *SD*) peaked (8.9 ± 3.1 ng/ml) at 15 min after dosing and declined with a half-life of 30 min. After oral administration of 5 mg, mean concentrations peaked (3.1 ± 0.7 ng/ml) at 30 min and declined with a half-life of 40 min. After oral administration of 20 mg in a sustained-release tablet, mean concentrations initially peaked (1.4 ± 1.2 ng/ml) at 40 min, declining to 0.9 ± 0.5 ng/ml after 8 hr. Mean concentrations were maintained above half the mean peak level during 10 hr. Because of probable rapid first-pass metabolism, the bioavailability of isosorbide dinitrate after administration of the oral dose of the standard tablet was 58% of that from the sublingual dose, and the bioavailability from the sustained-release tablet was 47% of that from the sublingual dose of the standard tablet. The time course of mean plasma concentration data could be described by a one-compartment model; but a more complex model, taking the pass effect into account, probably is needed for a better description of the pharmacokinetics of isosorbide dinitrate.



**Keyphrases** □ Isosorbide dinitrate—pharmacokinetics, oral and sublingual administration compared, standard and sustained-release tablets compared, humans □ Pharmacokinetics—isosorbide dinitrate, oral and sublingual administration compared, standard and sustained-release tablets compared, humans □ Vasodilators—isosorbide dinitrate, pharmacokinetics, oral and sublingual administration compared, standard and sustained-release tablets compared, humans


The vasodilator isosorbide dinitrate has been in use for many years (1–9), but little has been reported regarding its pharmacokinetics in humans because, in part, of the difficulty in measuring small amounts of the drug in blood. Using a GLC method (10), peak plasma concentrations ranging between 10.5 and 34.5 ng/ml in different subjects were measured at 6 min following a 1.25-mg sublingual dose of isosorbide dinitrate. More detailed studies involving the oral administration of 5.4 mg of $^{14}$C-isosorbide dinitrate (11) showed that peak levels of unchanged drug of about 5 ng/ml could be expected (12). However, higher concentrations of the respective mononitrate metabolites were present (12).

Isosorbide dinitrate and other organic nitrates are rapidly metabolized by the glutathione *S*-transferases (13, 14). From studies in animals, Needleman *et al.* (15) concluded that after oral administration of any one of the various organic nitrates, such as isosorbide dinitrate, essentially