Registry No.—**2**, 56411-59-7; **4**, 56411-60-0; **5**, 56411-61-1; **6**, 56411-62-2; **7**, 56411-63-3; **8**, 56411-64-4; **9**, 56411-65-5; *N*-*tert*-butyloxycarbonyl-L-alanine, 15911-69-0; 4-(methylthio)phenol, 1073-72-9; *N*-carbobenzoxy-L-serine 2,4-dinitrophenyl ester, 5249-65-0; *N*-*tert*-butyloxycarbonyl-L-valine, 13734-41-3; *N*-*tert*-butyloxycarbonyl-5-aminovaleric acid, 27219-07-4; *m*-chloroperoxybenzoic acid, 937-14-4.

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Structures of the 1:1:1 Adducts of the "Nitroso–Isonitrile–Isocyanate" Reaction. Possible Intermediacy of a Carbodiimide *N*-Oxide[1]

Carlos J. Wilkerson and Frederick D. Greene*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Reaction of a nitrosoalkane with an isonitrile in the presence of an isocyanate affords 1:1:1 adducts, $RR'R''C_2N_3O_2$. Adducts **1** (R = R′ = R″ = *tert*-butyl) and **2** (R = *tert*-butyl; R′ = R″ = phenyl) are substituted 3-imino-1,2,4-oxadiazolidin-5-ones (C), proved by synthesis from the corresponding carbodiimides. Adducts **3** (R = *tert*-butyl; R′ = isopropyl; R″ = phenyl) and **4** (R = R′ = *tert*-butyl; R″ = phenyl) are assigned as substituted 2-imino-1,3,4-oxadiazolidin-5-ones (D) based on acid-catalyzed conversion to **13a** and **13b** (assigned as 3-amino-1,3,4-oxadiazolin-5-ones) and on base-catalyzed isomerization to substituted 1,3,4-triazolidine-2,5-diones (F, **16a**, **16b**), proved by synthesis. Adduct **5** is assigned as a substituted 3,5-diimino-1,4,2-dioxazolidine (A) on the basis of thermal isomerization to **4** and decomposition to di-*tert*-butyldiaziridinone (**19**, R = R′ = *tert*-butyl) and phenyl isocyanate. The relation of these structures to the course of the "nitroso–isonitrile–isocyanate" reaction is discussed. The results are in good agreement with the earlier suggestion of the intermediacy of a carbodiimide *N*-oxide (from RNO + RNC) and trapping of this species by the isocyanate. Adduct **1** loses carbon dioxide at 150°, affording tri-*tert*-butyldiaziridinimine (**10**), providing a new entry to this novel small-ring heterocyclic system.

Some years ago we described a novel route to a small-ring heterocyclic system: reaction of a nitrosoalkane with an isonitrile to give a diaziridinone (diazacyclopropanone) (Scheme I). Several lines of evidence pointed to an intermediate. In the presence of R″NCO (the best trapping agents were alkyl or aryl isocyanates), no diaziridinone was observed; instead, adducts of composition RNO + R′NC + R″NCO were formed. The rate of disappearance of RNO and R′NC was independent of the concentration of R″NCO. The intermediacy of a carbodiimide *N*-oxide was suggested. Heterocycles of type A and C (Scheme I) seemed the best candidates for the 1:1:1 adducts. In this paper, the structures of several of the adducts are established, both supporting Scheme I and providing some unexpected extensions.

Results

The adducts **1–5** are listed in Table I. Adducts **1–4**, although showing some differences in the infrared carbonyl region, were generally similar in mass spectra (primary fragmentation patterns are loss of carbon dioxide and isobutylene units),[2] in thermal stability (decomposition at 120°), and in sensitivity to acid. Adduct **5**, a much more labile material, differed from **1–4** in the infrared (e.g., compare the similarly substituted **3** vs. **5**), and in mass spectra (loss of R′NCO, no primary loss of carbon dioxide). Thermal decomposition of **5** at 80° afforded a mixture of **4**, diaziridinone, and phenyl isocyanate.[2] Our hypothesis early in the present study was that adducts **1–4** were heterocycles of type C (Scheme I) (3-imino-1,2,4-oxadiazolidin-5-one) and that adduct **5** was of type A (3,5-diimino-1,4,2-dioxazolidine). This hypothesis, shown to be correct for **1** and **2**, facilitated establishment of structure C for these adducts. As will be shown later in the paper, adducts **3** and **4** do *not* possess structure C. Structure A remains the best formulation for **5**.

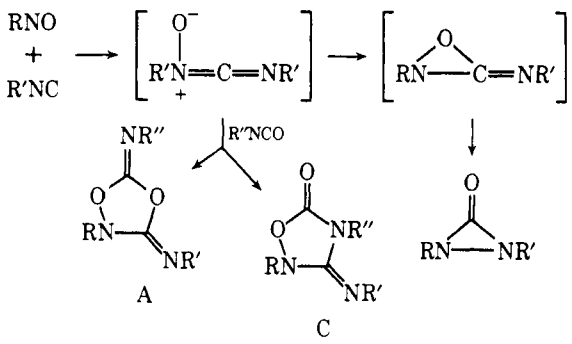
Table I
1:1:1 Adducts, Composition $RR'R''C_2N_3O_2$ (RNO + R′NC + R″NCO)

Compd	R	R′	R″	Ir, cm^{-1}
1	*t*-Bu	*t*-Bu	*t*-Bu	1789, 1700
2[a]	*t*-Bu	C_6H_5	C_6H_5	1804, 1687
3	*t*-Bu	*i*-Pr	C_6H_5	1809, 1717
4	*t*-Bu	*t*-Bu	C_6H_5	1811, 1710
5	*t*-Bu	*t*-Bu	C_6H_5	1775, 1700

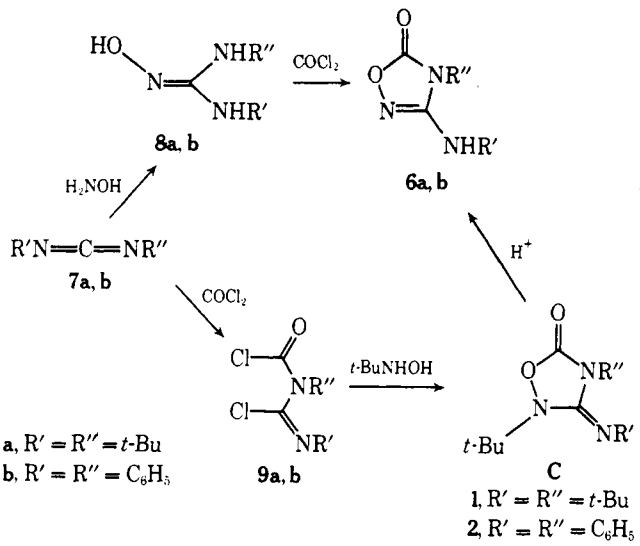
[a] Minor one of three adducts (**2**, **4**, and **5**) isolated from reaction of $(CH_3)_3CNO$, $(CH_3)_3CNC$, and C_6H_5NCO (see ref 2).

Adducts 1 and 2. Concentrated hydrochloric acid effected rapid loss of a *tert*-butyl group. The structures of the new products, **6a** and **6b**, were established by synthesis in high yield from the carbodiimides **7a** and **7b** (Scheme II). Assignment of the endocyclic C=N structure to **6** rather than the tautomeric exocyclic C=N form is based on the

Scheme I



Scheme II



differences in the infrared between 1 and 6 (see Table II). A related synthesis of a compound of type 6 (R′ = R″ = cyclohexyl) has been reported.[3] Syntheses of 1 and 2 were achieved via the phosgene–carbodiimide adducts, 9 (reactive, unstable materials).[4] Ring closure with *tert*-butylhydroxylamine afforded 1 and 2 in low yield (Scheme II).

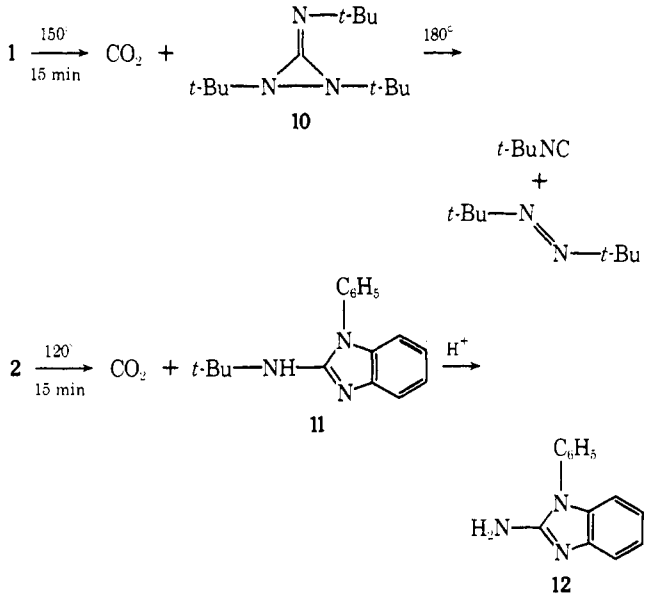
The syntheses of **6a** and **6b** establish the correctness of the direction of addition of the *tert*-butylhydroxylamine shown in Scheme II. Determination of the direction of addition with a less hindered alkylhydroxylamine was not investigated. Synthesis of several compounds of the same heterocyclic system as 1 and 2 (C, R = CH_3; R′ = R″ = cyclohexyl or aryl) has been reported by condensation of CH_3NHOH with the carbodiimide followed by cyclization with $ClCOOCH_3$.[3,5] Hydrolysis (HCl, ethanol) of the compounds in which R = CH_3 resulted in replacement of the imino group by oxygen.[5]

Table II
1:1:1 Adducts and Acid Cleavage Products. Infrared Bands in the Carbonyl Region

Structure found in		Adducts, ir, cm^{-1}		Acid cleavage products ir, cm^{-1}
Scheme II	1	1789, 1700	6a	1768, 1615
Scheme II	2	1804, 1687	6b	1777, 1611
Eq 3[a]	14	1797, 1700	6c[a]	1768, 1605
Scheme VI	3	1809, 1717	13a	1790, 1778, 1660
Scheme VI	4	1811, 1710	13b	1785, [b]1772, 1675
Scheme IV	16a[c]	1778, 1720	18a	1765, 1695

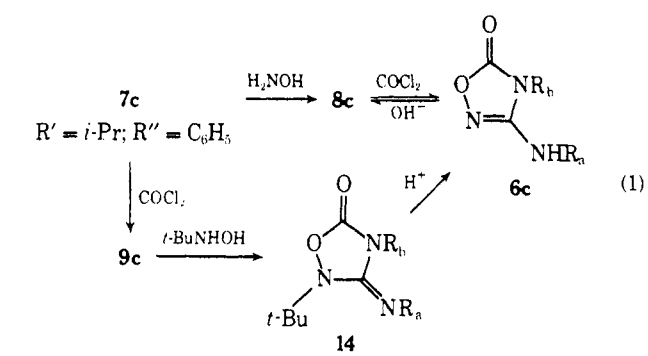
[a] Structure not established. See text. [b] Shoulder. [c] 16b (Scheme IV), 1773(m), 1720 cm^{-1} (vs).

Scheme III



Thermal decomposition of 1 (Scheme III) afforded the novel small-ring heterocycle, tri-*tert*-butyldiaziridinimine (**10**), identical with that described by Quast and Schmitt.[6] Thus, thermolysis of compounds of type 1 provides a new entry to this novel small-ring heterocyclic system. (Further heating of **10** resulted in fragmentation to the azoalkane and *tert*-butyl isonitrile.) Under similar conditions 2 afforded the *tert*-butylaminobenzimidazole **11**, established by acid degradation to **12**, a known compound.[7]

Adducts 3 and 4. These 1:1:1 adducts, like 1 and 2, lost carbon dioxide on heating at 120°, and readily lost a *tert*-butyl group by the action of acid. It seemed probable that they were also of structural type C, although there were differences in the infrared of the acid degradation products, **13a** and **13b**, compared with **6a** and **6b** (e.g., **13a**, 1790, 1778, 1660 cm^{-1}; **6a**, 1768, 1615 cm^{-1}). The infrared differences were not considered compelling because of the possibilities for isomers of C (including syn–anti forms) and for isomers of 6 (endocyclic vs. exocyclic C=N). In the expectation that 3 was similar in structure to 1 and 2, isopropylphenylcarbodiimide **7c** was subjected to the reactions of Scheme II. The reactions of the carbodiimide **7c** with hydroxylamine and with phosgene afforded single products, **8c** and **9c**, each of which was cyclized (eq 1).



(1)

Compound **14** (not isolated in pure form) was related to **6c** by acid-catalyzed loss of isobutylene. The synthetic sequences (eq 1) might afford two isomers of **6c** and of **14** (R_a = *i*-Pr; R_b = C_6H_5; and vice versa).

Unfortunately, only one isomer of **6c** was obtained (from **8c** or from **14**) and that one not identical with **13a**, the acid degradation product of 3 (and correspondingly, **14** was not identical with 3). However, the synthetic compound **6c**

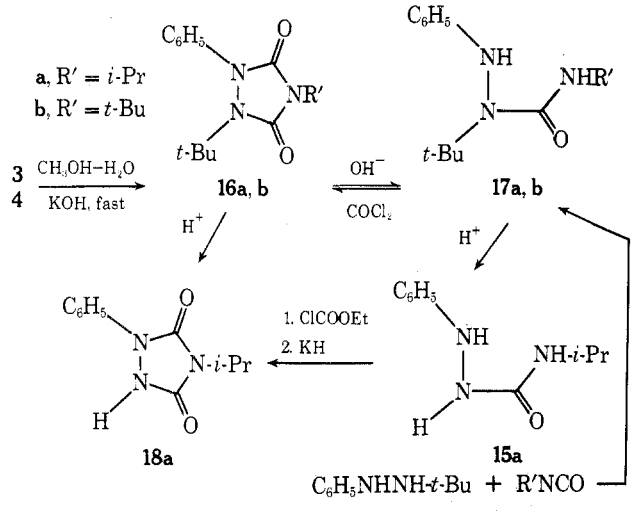
showed greater similarity in the infrared to **6a** and **6b**, the acid degradation products of **1** and **2**, than to **13a** and **13b**, the acid degradation products of **3** and **4**. A further indication that compounds **13a** and **13b** were not of the same structural type as **6a** and **6b** came from alkaline hydrolysis. Compound **6c** was reconverted to the hydroxyguanidine **8c** by base; compound **13a** was converted to semicarbazide **15a**, established by synthesis (eq 2).

$$3 \xrightarrow{H^+} \mathbf{13a} \xrightarrow{OH^-} \underset{\mathbf{15a}}{C_6H_5NHNHCONH\text{-}i\text{-}Pr} \qquad (2)$$

Action of Base on 3 and 4. Treatment of adduct **3** with base effected rapid (3–4 sec), quantitative conversion to an isomer **16a**. Further reaction with base converted **16a** to semicarbazide **17a**. A similar sequence was shown for adduct **4**.

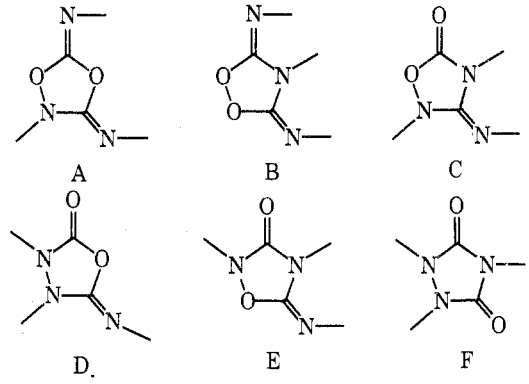
Compounds **16a** and **16b**, the products of base isomerization of **3** and **4**, were more stable to heat and to acid than their precursors. Their conversion by base to the semicarbazides suggested that they might be urazoles, proved by degradation and synthesis of **16a** and **16b** and by synthesis of the semicarbazides **17a** and **17b** (Scheme IV).

Scheme IV



Structures for adducts 3 and 4 may be assigned on the basis of the available physical and chemical data. Compounds **3** and **4** (as well as **1**, **2**, **5**, **16a**, and **16b**) have the composition $RR'R''C_2N_3O_2$, indicating the presence of three rings and/or double bonds. The acid and base degradations of **3** and **4** place one substituent on each of the three nitrogens, ruling out the presence of nitrogen–oxygen or nitrogen–nitrogen double bonds. Each of the two carbons may have a maximum of one double bond, and thus the presence of a ring is required. The infrared spectra strongly indicate the presence of two double bonds (C=N or C=O). Both must be exocyclic to the ring, restricting the ring size to five membered or less. Rings smaller than five membered would require the presence of nitrones or R–N⁻–N⁺(R)=, for which there is no evidence in the infrared. Consequently, only five-membered rings were considered. Lastly, there is no carbon–carbon bond in the products of acid or base degradations of **3** and **4**, strongly suggesting the absence of such a bond in the skeletons of **3** and **4**. Thus, possible systems for **3** and **4** are shown in Scheme V. Principal considerations in the assignment of one of the heterocyclic systems of Scheme V to **3** and **4** are the presence of an N–N bond in the products of base degradations (e.g., conversion of **3** to **17a**)[8] and the thermal (and mass spectral) loss of carbon dioxide.

Scheme V[a]



[a] **Consideration of A (3,5-Diimino-1,4,2-dioxazolidine).** Structure A is assigned to the labile adduct **5** on the basis of the mass spectral data (presence of an M − C_6H_5NCO peak, absence of peaks associated with loss of carbon dioxide), chemical reactions, and possible mode of formation. Compound **5** could only be isolated when the RNO + R′NC + R″NCO reaction was carried out at 40° and worked up after 10% reaction. Heating of **5** at 80° in solution afforded adduct **4**, phenyl isocyanate, and di-*tert*-butyldiaziridinone.[2]

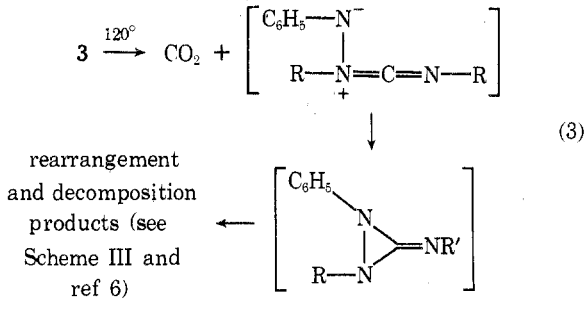
Consideration of B (3,5-Diimino-1,2,4-dioxazolidine). Structure B is rejected on the basis of the loss of carbon dioxide in the thermolysis and mass spectra of **3** and **4**. One might also expect peroxygen species B (unknown) to be of lower thermal stability than that shown by **3**.

Consideration of C (3-Imino-1,2,4-oxadiazolidin-5-one). Structure C has been established by synthesis (Scheme II) for **1** and **2**. Compounds **3** and **4** differ from **1** and **2** toward acid and toward base. In particular, **3** and **4** are converted to semicarbazides **17a** and **17b** by aqueous nonalcoholic base. No satisfactory route exists for the *hydroxide*-catalyzed (see ref 8) conversion of C to these products. Structure C is rejected for **3** and **4** on these grounds.

Consideration of E (5-Imino-1,2,4-oxodiazolidin-3-one). Structure E, like C, is rejected for **3** and **4** on the basis of the lack of a satisfactory route for *hydroxide*-catalyzed (see ref 8) conversion of E to the semicarbazides. Also, the loss of carbon dioxide in the thermolysis and mass spectra of **3** and **4** is hard to reconcile with E.

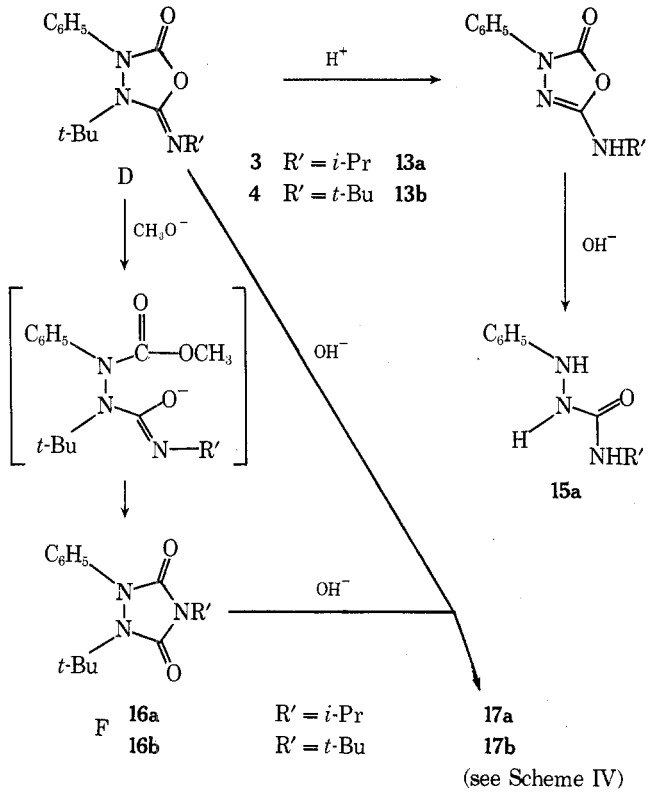
Consideration of F (Urazole, 1,3,4-Triazolidine-2,5-dione). Structure F has been established by synthesis (Scheme IV) for **16a** and **16b**, the products of base-catalyzed isomerization of **3** and **4**, and cannot also be the structure for **3** and **4**.

Compounds **3** and **4** are assigned structure D (2-imino-1,3,4-oxadiazolidin-5-one). It accounts for the chemical and physical data, and is nicely in accord with a reasonable mode of formation of adducts **3** and **4**. A brief indication of the grounds on which systems A, B, C, E, and F are *not* suitable for **3** and **4** is given in Scheme V. Assignment of structure D to **3** and **4** and analysis of the reactions under acidic and basic conditions are shown in Scheme VI. The thermal decomposition of **3** affords carbon dioxide and a mixture of products. It is of interest that **3** is of comparable thermal stability to **1** and **2** although rather different in structure. Possibly, breakdown of **3** may proceed as shown in eq 3.

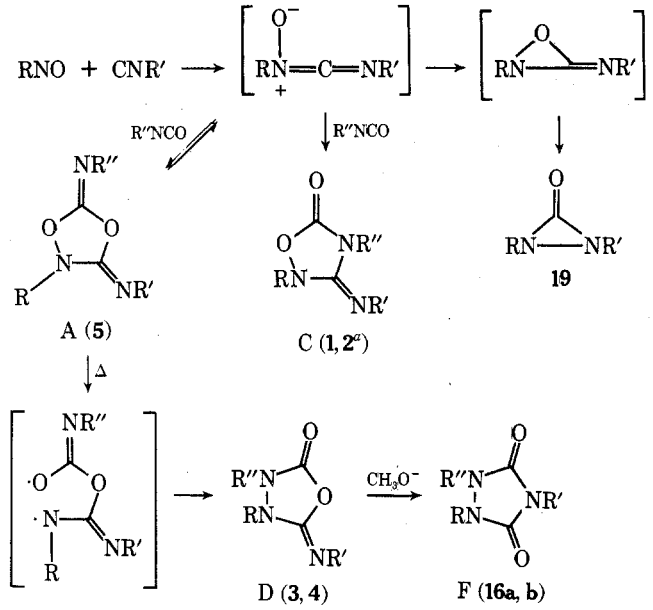


(3)

Scheme VI



Scheme VII



[a] Exact origin of adduct **2** (i.e., origin of C_6H_5NC for this case) is unclear (see Table I, footnote *a*).

An overall summary of the probable modes of formation and interconversion of the different types of adducts is shown in Scheme VII and eq 4. Attention is also directed to the sequence in eq 5.

$$\underset{A}{5} \xrightarrow{80^\circ} \underset{D}{4} \xrightarrow{CH_3O^-} \underset{F}{16b} \xrightarrow{OH^-} 17b \qquad (4)$$

$$R_3C_2N_3O_2 \xrightarrow{150^\circ} R_3CN_3 \xrightarrow{180^\circ} R_2N_2 \xrightarrow{200^\circ} R_2 + N_2 \qquad (5)$$

1 → 10 + CO_2; R_2N_2 → + RH + R(−H); RNC $\xrightarrow{200^\circ}$ RCN

With respect to the "nitroso–isonitrile–isocyanate" reaction, the rigorous establishment of structure C for the 1:1:1 adducts **1** and **2**, and the strong evidence for the sequence leading to structure F (eq 4) provide support for the original suggestion of the intermediacy of a carbodiimide *N*-oxide. In the absence of a trapping agent, this species closes to the oxaziridinimine, which then isomerizes to the diaziridinone.[2,9] The oxaziridinimine could also lead to structures A and C, and cannot be excluded as the trappable intermediate, but it would not appear to be a reactive dipolar species (e.g., compare nitrones and oxaziridines in cycloaddition reactivity).[10]

In the cases examined to date, the reaction of RNO with R′NC in the presence of a trapping agent R″NCO has afforded rather complex mixtures from which the adducts **1–5** were isolated in low yield. Thus it is not possible to say which path predominates, C or A → D. As noted earlier in this paper, the spectral properties of C and D are similar. Distinction between these may be made by the action of alkoxide which effects rapid isomerization of the compounds of type D to F (urazoles), and only slowly reacts with the compounds of type C (affording colored solutions and product mixtures). For R = *tert*-butyl, distinction between C and D may also be made by acidic degradation and infrared analysis. Distinctive bands are summarized in Table II. A third indication may be seen in the mass spectra:[2] adducts **1** and **2** of type C do not show ions of *m/e* R′NCO; adducts **3** and **4** show these ions in 17 and 8% abundance, relative to the base peaks for **3** and **4**. None of the adducts **1–4** shows an ion for M − R″NCO. Adduct **5** (type A) shows ions for both M − R″NCO and for R″NCO.

Experimental Section

General. Infrared spectra have the following notations: vs, very strong; s, strong; m, medium; w, weak; br, broad. Nuclear magnetic resonance spectra (NMR) are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si) with the following notations: s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet; br, broad. Adducts **1–5** were obtained by the literature procedures.[2]

Carbodiimides. Diphenylcarbodiimide was prepared by the method of Hunger in 70% yield: bp 112–114° (1.5 mm) [lit.[11] bp 119° (0.07 mm)]; ir (CCl_4) 2120 (vs), 2090 (sh, s), 1570 (m), 1470 cm^{-1} (m). **Isopropylphenylcarbodiimide** was prepared by the method of Hinton and Webb in 56% yield: bp 63–64° (0.3 mm) [lit.[12] bp 56–57° (0.1 mm)]; ir (CCl_4) 2110 (sh, m), 2120 (vs), 2040 (sh, s), 1590 (s), 1495 cm^{-1} (s). **Di-*tert*-butylcarbodiimide** was prepared by the general procedure of Campbell.[13a] *tert*-Butyl isocyanate (100 g, 1.01 mol) was dissolved in 200 ml of tetralin and 10 g of 1-ethyl-3-methyl-3-phospholene 1-oxide as a catalyst was added and refluxed for 1 week. The di-*tert*-butylcarbodiimide was distilled from the reaction mixture at 80–90 mm and the 105–120° fraction was redistilled on a spinning band column, affording 19.89 g (25% yield) of di-*tert*-butylcarbodiimide as a clear liquid: bp 59° (20 mm) [lit.[13b] bp 58° (15 mm)]; ir (CCl_4) 2970 (s), 2915 (m), 2130 (sh, m), 2095 cm^{-1} (vs).

***N*-Hydroxyguanidines (8a–c).** A solution of hydroxylamine hydrochloride (0.1 g, 1.44 mmol) in 1 ml of ethanol was added to di-*tert*-butylcarbodiimide (0.22 g, 1.44 mmol) in ethanol and stirred overnight. The solvent was removed under high vacuum and the solid residue was dissolved in water. Dropwise addition of a cold concentrated solution of KOH while cooling to 0° afforded a white solid; the solid was extracted into ether and dried over $MgSO_4$. The ether was then removed under reduced pressure affording 0.14 g (43% yield) of ***N*-hydroxy-*N′*,*N″*-di-*tert*-butylguanidine (8a).** It was recrystallized from THF and heptane: mp 117–117.5°; ir (CCl_4) 3609 (w), 3500–2400 (br, m), 2985 (s), 1645 (s), 1225 (m), 1205 (m); NMR ($CDCl_3$) 1.32 (s, 18 H), 3.1 (br, s, 2 H), 4.83 ppm (br, s, 1 H).

Anal. Calcd for $C_9H_{21}N_3O$: C, 57.71; H, 11.30; N, 22.44. Found: C, 57.55; H, 11.35; N, 22.36.

***N*-Hydroxy-*N′*,*N″*-diphenylguanidine (8b)** was prepared by the same procedure in 25% yield: mp 149–151° (lit.[14] mp 151°); ir ($CHCl_3$) 3560 (m), 3380 (s), 3500–2400 (m, broad), 1640 (vs), 1590

(vs), 1480 cm^{-1} (vs); NMR ($CDCl_3$) 3.80 (br, s, 3 H), 6.80–7.43 ppm (br, m, 10 H). ***N*-Hydroxy-*N'*-isopropyl-*N''*-phenylguanidine (8c)** was obtained as white crystals: mp 133–134°; ir (CCl_3H) 3480 (w), 3395 (m), 1650 (vs), 1600 (s), 1500 cm^{-1} (vs); NMR ($CHCl_3$ + D_2O) 1.13 (d, 6 H), 3.58 (sept, 1 H), 6.8–7.5 ppm (m, 5 H).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.2; H, 7.82; N, 21.8. Found: C, 62.34; H, 8.07; N, 21.74.

Phosgene–Carbodiimide Adducts, 9a–c. A phosgene solution (1.25 g, 0.0126 mol) in 10 ml of CH_2Cl_2 was added dropwise under N_2 by means of a cannula to di-*tert*-butylcarbodiimide (1.94 g, 0.0126 mol) in 15 ml of CH_2Cl_2 with stirring and cooling. Removal of the solvent by a stream of N_2 afforded *N,N'*-di-*tert*-butylchloroformamidine-*N*-carbonyl chloride (**9a**) as a yellow oil. The major bands in the ir were similar to those reported in the isopropyl case;[4] ir (CCl_4) 2975 (s), 1760 (vs), 1693 (s), 1395 (m), 1368 (s), 1290 cm^{-1} (s); NMR (CCl_4) 1.52 (s, 9 H), 1.40 ppm (s, 9 H). ***N,N'*-Di-*tert*-butylchloroformamidine-*N*-carbonyl chloride (9a)** was unstable to heat and attempted distillation resulted in decomposition. Compounds **9b** and **9c** were prepared in the same way: **9b,** yellow oil, ir (CCl_4) 1755 (vs), 1660 (vs), 1590 (s), 1487 cm^{-1} (s) (lit.[4] ir 1755, 1660 cm^{-1}); **9c,** a light yellow oil, ir (CCl_4) 1750 (vs), 1660 cm^{-1} (s), NMR (CCl_4) 1.23 (d, 6 H), 3.82 (sept, 1 H), 7.32 ppm (s, 5 H).

Pyrolysis of Adduct 1. A 300-mg sample of compound 1 sealed in a Pyrex tube at 0.4 mm was heated at 150° for 15 min. Upon cooling, a solid separated. The remaining oil was carefully decanted and the solid was washed several times with pentane. A melting point showed the solid to be starting material; ir (CCl_4) of the remaining oil showed absorption at 1790 (vs), 1767 (sh, m), 1697 (m), 1380 (m), 1365 cm^{-1} (s). Gas-liquid partition chromatographic analysis was performed on an Aerograph Model 200, using helium carrier gas and thermal conductivity detectors with the following column: a 1.5 ft × 0.125 in. Teflon tube packed with 20% (w/w) silicone oil SE-30 on a 60–80 mesh Chromosorb P diatomite with a column temperature of 100° and employing a flow rate of 600 ml/min, revealed two peaks with relative areas of 1:13.7 and retention times of 5 and 11.5 min, respectively. The second peak, *N,N',N''*-tri-*tert*-butyldiaziridinimine (**10**), was collected: ir (CCl_4) 2970 (vs), 2900 (sh, w), 2865 (m), 1790 (vs), 1362 cm^{-1} (vs); NMR (CCl_4) 1.08 (s, 9 H), 1.10 (s, 9 H), 1.23 ppm (s, 9 H) [lit.[6] ir 1790 cm^{-1}; NMR (10°, CCl_4) 1.09 (s, 9 H), 1.17 (s, 9 H), 1.25 ppm (s, 9 H)]. Further heating of **10** resulted in decomposition to *tert*-butyl isonitrile and to 2,2'-dimethyl-2,2'-azopropane.

Conversion of Compound 1 to Compound 6a. To a 100-mg sample of compound 1, 1 ml of concentrated HCl was added at room temperature. There was vigorous bubbling, but the solid did not go into solution. After 3 min, the solid was filtered and washed several times with distilled water. The solid was dried (crude mp 114–117°) and recrystallized from THF and heptane, affording compound **6a** as white crystals: mp 116–117°; ir (CCl_4) 3460 (w), 1768 (vs), 1615 (s), 1512 (s), 1390 (m), 1365 cm^{-1} (s); NMR ($CDCl_3$) 1.37 (s, 9 H), 1.67 (s, 9 H), and 3.93 ppm (s, 1 H).

Anal. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.31; H, 8.98; N, 19.70. Found: C, 56.31; H, 9.10; N, 19.78.

Synthesis of 3-*tert*-Butylamino-4-*tert*-butyl-1,2,4-oxadiazolin-5-one (6a). A phosgene solution (0.040 g, 0.48 mmol) in 0.2 ml of CH_2Cl_2 was added slowly by means of a microsyringe to a stirring solution of *N*-hydroxy-*N',N''*-di-*tert*-butylguanidine (**8a,** 0.09 g, 0.484 mmol) in 15 ml of anhydrous ether buffered with 12 drops of triethylamine. After stirring at room temperature for 15 min, the solid was filtered and the ether laver was evaporated to dryness under vacuum. The solid residue was recrystallized from THF and heptane, affording white crystals, mp 116–117°, of **6a,** shown to be identical with the **6a** from acid-catalyzed decomposition of 1 by ir and mixture melting point.

Synthesis of 2,4-Di-*tert*-butyl-3-*tert*-butylimino-1,2,4-oxadiazolidin-5-one (1). A solution of *tert*-butylhydroxylamine[15] (4.45 g, 0.0504 mol) in 25 ml of CH_2Cl_2 was added dropwise under N_2 to a stirred and cooled (0°) solution of *N,N'*-di-*tert*-butylchloroformamidine-*N*-carbonyl chloride (**9a** 3.19 g, 0.0126 mol) in 15 ml of CH_2Cl_2, and left standing overnight at room temperature. The solvent was removed in vacuo and the residual oil was extracted into pentane (only part of it was soluble) and washed with H_2O several times. The pentane layer was dried over $MgSO_4$ and removed in vacuo, affording a clear oil. Upon standing in the refrigerator overnight, part of it crystallized. The crystals were filtered and washed with cold pentane, affording a 10% yield, mp 104–106°, ir identical with that of compound **1,** and a mixture melting point showed no depression.

Pyrolysis of Adduct 2. A 200-mg sample of compound **2** sealed in a Pyrex tube evacuated to 0.04 mm was heated at 120° for 45 min, after which the bubbling had ceased: ir (CCl_4) 3420 (m), 2120 (vw), 1622 cm^{-1} (s). The brown oil crystallized upon standing (10 min). The solid was triturated with a small portion of ether, filtered, and washed two times with pentane. It was crystallized from THF and heptane, affording 1-phenyl-2-(*tert*-butylamino)benzimidazole (**11**) as white crystals: mp 139–141°; ir ($CHCl_3$) 3420 (m), 1622 (s), 1601 (s), 1390 (m), 1368 cm^{-1} (s); NMR ($CDCl_3$) 1.47 (s, 9 H), 4.40 (s, 1 H), and 6.67–7.67 ppm (m, 9 H).

Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.94; H, 7.22; N, 15.84. Found: C, 77.10; H, 7.09; N, 15.77.

Conversion of 1-Phenyl-2-(*tert*-butylamino)benzimidazole (11) to 1-Phenyl-2-aminobenzimidazole (12). 1-Phenyl-2-*tert*-butylaminobenzimidazole (40 mg, 0.151 mmol) was dissolved in 3 ml of concentrated HCl at room temperature and allowed to stand for 2 days. Addition of a cold concentrated solution of KOH with cooling resulted in a white precipitate. The mixture was extracted with ether and dried over $MgSO_4$. The ether was then removed and the yellow solid residue was recrystallized from THF and heptane, affording 7.8 mg (25% yield) of 1-phenyl-2-aminobenzimidazole (**12**) as white crystals: mp 149–151° (lit.[7] mp 151–152°); ir ($CHCl_3$) 3485 (w), 3390 (w), 1630 (s), 1610 (m), 1598 cm^{-1} (m); NMR ($CDCl_3$) 4.92 (br, s, 2 H), 6.20–7.34 ppm (br, m, 9 H).

Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.03. Found: C, 74.74; H, 5.08; N, 19.98.

The compound was converted to the picrate in ethanol. The picrate was recrystallized from ethanol, mp 256° dec (lit.[7] mp 251–253°).

Conversion of Compound 2 to Compound 6b. To a 150-mg sample of compound **2,** 1 ml of concentrated HCl was added at room temperature. The solid appeared to dissolve, the solution turned slightly pink, and a white solid precipitated. The solid was filtered and washed several times with distilled water. It was dried (crude mp 158–161°) and recrystallized from THF and heptane, affording compound **6b** as a white solid: mp 161.5–162°; ir ($CHCl_3$) 3410 (m), 1777 (vs), 1611 cm^{-1} (vs); NMR ($CDCl_3$) 2.87 (s, 1 H), 6.67–8.0 ppm (m, 10 H).

Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.4; H, 4.35; N, 16.6. Found: C, 66.20; H, 4.36; N, 16.50.

Synthesis of 3-Phenylamino-4-phenyl-1,2,4-oxadiazolin-5-one (6b). To a slurry of *N*-hydroxy-*N',N''*-diphenylguanidine (**8b** 0.264 g, 1.14 mmol) in 20 ml of ether, a solution of 340 mg of KOH in 20 ml of water was added. To this stirred and cooled (0°) mixture, a solution of phosgene (114 mg, 1.44 mmol) in 1 ml of CH_2Cl_2 was added dropwise. At the first drop, a visible reaction took place. After addition was complete, the organic layer was separated, dried over $MgSO_4$, and evaporated. The brown solid residue was triturated with ether several times until only a faint yellow color remained. It was then recrystallized from THF and heptane, affording white crystals, mp 160–161°. Ir was identical with that of compound **6b,** and mixture melting point showed no depression.

Synthesis of 2-*tert*-Butyl-4-phenyl-3-phenylimino-1,2,4-oxadiazolidin-5-one (2) was achieved from *tert*-butylhydroxylamine and *N,N''*-diphenylchloroformamidine-*N*-carbonyl chloride (**9b**) by the procedure used to synthesize **1:** mp 102–103°, shown to be identical with the 1:1:1 adduct **2** by ir and mixture melting point.

Synthesis of compound 6c was achieved from *N*-hydroxy-*N'*-isopropyl-*N''*-phenylguanidine (**8c**) and phosgene by the procedure described above for **6b.** Compound **6c** was obtained as white crystals: mp 136–137.5°; ir ($CHCl_3$) 3400 (w), 1768 (vs), 1605 (vs), 1520 cm^{-1} (s); NMR ($CDCl_3$) 1.15 (d, 6 H), 3.35–4 (m 2 H), 7–7.5 ppm (m, 5 H).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.16. Found: C, 60.19; H, 5.87; N, 19.22.

Synthesis of 14 and Acid-Catalyzed Conversion to 6c. A solution of *tert*-butylhydroxylamine[15] (1.8 g, 0.02 mol) in 15 ml of CH_2Cl_2 was added dropwise to a stirred and cooled (0°) solution of *N*-isopropyl-*N'*-phenylchloroformamidine-*N*-carbonyl chloride (**9c,** 1.30 g, 5 mmol) in 20 ml of CH_2Cl_2. The reaction was complete in 1 hr. The solvent was removed in vacuo, and the oily residue was dissolved in pentane. The pentane layer was washed with water several times, dried, and evaporated, affording a clear oil, **14,** ir (CCl_4) 1790 (m), 1755 (m), 1700 cm^{-1} (vs), clearly different from **3.** No further purification was attempted. Treating part of the pentane solution with dilute HCl afforded **6c,** identical with the synthetic material.

Pyrolysis of Adduct 3. A 100-mg sample of compound **3** sealed in a Pyrex tube at 0.4 mm was heated at 120° until no additional gas evolution could be detected (~30 min). Ir of the oily mixture revealed many bands in the carbonyl region, and no attempt was made to separate the components: ir (CCl_4) 1779 (s), 1712 (s), 1660 (vs), 1615 (s), 1595 cm^{-1} (s). Formation of carbon dioxide was established by mass spectral analysis of the gas phase.

Conversion of Adduct 3 to 2-Isopropylamino-4-phenyl-1,3,4-oxadiazolin-5-one (13a). To a 100-mg sample of compound **3**, 1 ml of concentrated HCl was added at room temperature. An oily layer formed and solidified upon standing (3 min). The solid was filtered and washed with distilled water several times. It was recrystallized from THF and heptane, affording compound **13a** (90% yield): mp 104–106°; ir (CCl_4) 3420 (m), 1790 (s), 1778 (s), 1660 cm^{-1} (s); NMR ($CDCl_3$) 1.25 (d, 6 H), 3.72 (sept, 1 H), 4.53 (d, 1 H), 6.90–7.90 ppm (m, 5 H).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 5.9; N, 19.18. Found: C, 60.11; H, 5.95; N, 18.97.

Conversion of Adduct 3 to 1-Isopropyl-3-phenyl-4-*tert*-butyltriazolidine-2,5-dione (16a). Compound **3** (16.6 mg, 0.06 mmol) was dissolved in 2 ml of 20% KOH in ethanol. After 1–2 min, the solution was added to H_2O and extracted with ether three times. The organic layers were combined and dried over $MgSO_4$. The ether was removed in vacuo, affording a solid residue. The solid was recrystallized two times from THF and heptane, affording 13 mg (81% yield) of compound **16a** as white crystals: mp 93–94°; ir (CCl_4) 2975 (m), 1778 (s), 1720 (vs), 1412 (vs), 1385 (s), 1367 cm^{-1} (s); NMR ($CDCl_3$) 1.32 (s, 9 H), 1.43 (d, 6 H), 4.40 (sept, 1 H), 6.55–7.16 ppm (br, m, 5 H).

Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.45; H, 7.69; N, 15.26. Found: C, 65.50; H, 7.57; N, 15.38.

Conversion of Adduct 3 to 4-Isopropyl-1-phenyl-2-*tert*-butylsemicarbazide (17a). Compound **3** (0.10 g, 0.365 mmol) was added to 0.5 g of KOH dissolved in 5 ml of ethanol and heated at 75° for 30 min. The reaction mixture was added to water and extracted with ether several times. The ether layers were combined, dried, and evaporated in vacuo. The resulting solid residue was recrystallized from THF and heptane, affording compound **17a** in 62% yield as white crystals: mp 162– 163.5°; ir ($CHCl_3$) 3418 (m), 2960 (m), 1653 (s), 1595 (s), 1495 (s), 1475 cm^{-1} (s); NMR ($CDCl_3$) 1.07 (d, 6 H), 1.43 (s, 9 H), 4.0 (sept split, 1 H), 3.50–5.91 (br, m, 2 H), 6.35–7.36 ppm (br, m, 5 H).

Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30; N, 16.85. Found: C, 67.40; H, 9.49; N, 16.85.

Subjection of compound **3** to the action of KOH in aqueous dioxane afforded only **17a** with no evidence for **16a** (the *alkoxide* isomerization product of **3**, see above).

***N*-*tert*-Butyl-*N'*-phenylhydrazine.** 1-*tert*-Butyl-2-phenyldiazene[16] (320 mg, 1.95 mmol) in 9 ml of ethanol was hydrogenated with platinum. The mixture was filtered by means of a cannula through a sintered funnel under a N_2 atmosphere and the ethanol was removed in vacuo, affording the hydrazine in nearly quantitative yield as a clear white oil, highly reactive toward air.

4-Isopropyl-1-phenyl-2-*tert*-butylsemicarbazide (17a). To a solution of *N*-*tert*-butyl-*N'*-phenylhydrazine (~300 mg) in 2 ml of $CHCl_3$, an excess of isopropyl isocyanate (340 mg, 4 mmol) was added by means of a syringe through a no-air stopper. The solution was heated to 70° for 2 hr and left at room temperature overnight. The $CHCl_3$ was removed in vacuo and the solid residue was recrystallized from THF and heptane, affording 250 mg (50% yield) of the semicarbazide **17a** as white crystals, mp 162–163°. A mixture melting point with the slower formed product obtained from the base treatment of compound **3** showed no depression and comparison of their ir spectra showed them to be identical.

1-Isopropyl-3-phenyl-4-*tert*-butyltriazolidine-2,5-dione (Urazole 16a). An excess of phosgene was bubbled through a solution of 1-phenyl-2-*tert*-butyl-4-isopropylsemicarbazide (~15 mg) dissolved in 1 ml of CH_2Cl_2. The reaction only went to ⅔ completion shown by NMR. After 4 days, the solvent was removed and the solid residue was digested with hot hexane. The hexane was decanted and left standing, affording urazole **16a** as white crystals, mp 92–94°. A mixture melting point with the first-formed product obtained from base treatment of compound **3**, and comparison of their ir spectra showed them to be identical.

Conversion of 4-Isopropyl-1-phenyl-2-*tert*-butylsemicarbazide (17a) to 4-Isopropyl-1-phenylsemicarbazide (15a). 4-Isopropyl-1-phenyl-2-*tert*-butylsemicarbazide (5 mg) was dissolved in 0.5 ml of concentrated HCl and left overnight at room temperature. The solution was cooled in an ice bath and concentrated KOH was added dropwise until no further precipitate was formed. The solid, 4-isopropyl-1-phenylsemicarbazide (**15a**), was filtered and air dried: mp 143–147° (lit.[17] mp 145–147°); ir ($CHCl_3$) 3498 (m), 2981 (m), 1670 (vs), 1530 (s), 1485 cm^{-1} (s), NMR ($CDCl_3$) 1.10 (d, 6 H), 5.63 (br, s, 2 H), 6.07 (br, s, 1 H), 6.66–7.46 (m, 5 H); shown to be identical with an authentic sample by ir and mixture melting point.

Conversion of 1-Isopropyl-3-phenyl-4-*tert*-butyltriazolidine-2,5-dione (Urazole 16a) to 1-Isopropyl-3-phenyltriazolidine-2,5-dione (Urazole 18a). Urazole **16a** (69.5 mg, 0.244 mmol) was dissolved in 1 ml of concentrated HCl (heating gently) and left overnight at room temperature. It was diluted with 4 ml of H_2O, affording 27 mg (50% yield) of 1-isopropyl-3-phenyltriazolidine-2,5-dione (**18a**) as white crystals: mp 109–111°; ir ($CHCl_3$) 1765 (m), 1695 (vs), 1595 (m), 1495 (m), 1435 cm^{-1} (s); NMR ($CDCl_3$) 1.52 (d, 6 H), 4.40 (sept, 1 H), 7.1–7.62 (m, 6 H).

Anal, Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.16. Found: C, 60.07; H, 5.87; N, 19.22.

1-Isopropyl-3-phenyltriazolidine-2,5-dione (Urazole 18a). To a slurry of 1-phenyl-4-isopropylsemicarbazide (**15a**, 0.69 g, 3.67 mmol) in 20 ml of CH_2Cl_2 was added an excess of ethyl chloroformate. The reaction was monitored by NMR. When the reaction was complete (overnight) the solvent was removed and the solid residue recrystallized from THF and heptane, affording 1-carboethoxy-1-phenyl-4-isopropylsemicarbazide as a light yellow powder: mp 126–128°; ir ($CHCl_3$) 3700–3120 (br, m), 2945 (m), 1715 (s), 1681 (s), 1595 (w), 1518 cm^{-1} (m); NMR ($CDCl_3$) 1.10 (d, 6 H), 1.28 (t, 3 H), 4.27 (q, 2 H), 4.90 (br, s, 1 H), 5.03 (br, s, 1 H), 7.0–7.31 (m, 5 H). A solution of this material (537 mg, 1.27 mmol) in 3 ml of dry DME was added to a slurry of KH (excess) in 5 ml of DME. After the bubbling stopped, the flask was sealed with a no-air stopper and the reaction was heated at 90° for 5 hr. The solvent was removed in vacuo and the solid residue was dissolved in water and filtered. Acidification of the aqueous solution with dilute HCl resulted in a red oil that was extracted into pentane. The pentane layer was dried and removed in vacuo and the solid residue recrystallized from water, affording urazole **18a** in 32% yield, mp 143–147°. A mixture melting point with the compound obtained from the reaction of 1-isopropyl-3-phenyl-4-*tert*-butyltriazolidine-2,5-dione (**16a**) with concentrated HCl showed no depression and comparison of their ir spectra showed them to be identical.

Alkaline hydrolysis of 13a under the conditions described above for **3** → **16a** afforded 4-isopropyl-1-phenylsemicarbazide,[17] shown to be identical with an authentic sample by ir and mixture melting point.

Alkaline hydrolysis of 6c under the above conditions regenerated **8c**, *N*-hydroxy-*N'*-isopropyl-*N''*-phenylguanidine.

Conversion of Adduct 4 to 1,3-Di-*tert*-butyl-4-phenyltriazolidine-2,5-dione (Urazole 16b). Compound **4** (~10 mg) was dissolved in 0.5 ml of methanol and three drops of a concentrated solution of KOH (0.5 g KOH in 0.5 ml of H_2O, 0.5 ml of CH_3OH) were added. The reaction was instantaneous as shown by NMR. The solvent was removed in vacuo and the solid recrystallized from pentane, affording 1,3-di-*tert*-butyl-4-phenyltriazolidine-2,5-dione (**16b**) in 80% yield: mp 119.5–121°; ir (CCl_4) 1773 (m), 1720 (vs), 1595 (w), 1370 cm^{-1} (s); NMR (CCl_4) 1.29 (s, 9 H), 1.59 (s, 9 H), 6.80–7.50 (m, 5 H); shown to be identical by ir and mixture melting point with an authentic sample of urazole **16b** prepared from 1-phenyl-2,4-di-*tert*-butylsemicarbazide and phosgene by the procedure described above for the synthesis of **16a**.

Conversion of Adduct 4 to 2,4-Di-*tert*-butyl-1-phenylsemicarbazide (17b). Compound **4** (~10 mg) was dissolved in 0.5 ml of methanol and 3 drops of a concentrated KOH solution (0.5 g of KOH in 0.5 ml of H_2O, 0.5 ml of CH_3OH) were added. Water was then added until the solution started to turn cloudy. It was heated for 30 min and the methanol removed in vacuo. The solid residue was dissolved in CH_2Cl_2, dried, and evaporated. The solid residue was recrystallized from THF and heptane, affording 1-phenyl-2,4-di-*tert*-butylsemicarbazide (**17b**): mp 172–173°; ir ($CHCl_3$) 3420 (m), 2965 (s), 1660 (vs), 1600 (s), 1500 and 1480 (vs, doublet), 1450 (s), 1388 (m), 1360 cm^{-1} (s); NMR ($CDCl_3$) 1.29 (s, 9 H), 1.31 (s, 9 H), 5.4–5.9 (br, 2 H), 6.65–7.3 (m, 5 H); identical in ir and mixture melting point with an authentic sample prepared from *N*-*tert*-butyl-*N'*-phenylhydrazine and *tert*-butyl isocyanate (see synthesis of **17a**, above).

Acid hydrolysis of 4 under the conditions described above for **3** → **13a** afforded as the first-formed product **13b**, ir (CCl_4) 1785 (sh), 1772 (s), 1675 (m), 1617, 1603 cm^{-1}. Longer exposure to acid effected further changes, loss of the second *tert*-butyl, ir (CCl_4)

1785 (s), 1680 (m), 1660 (s), 1600 cm^{-1}. The product was not characterized further.

Registry No.—**1,** 55871-81-3; **2,** 19656-65-6; **3,** 55871-82-4; **4,** 55871-83-5; **6a,** 55871-84-6; **6b,** 55871-85-7; **6c,** 55871-86-8; **7a,** 691-24-7; **7b,** 622-16-2; **7c,** 14041-89-5; **8a,** 42136-40-3; **8b,** 34362-08-8; **8c,** 55871-87-9; **9a,** 55871-88-0; **9b,** 55871-89-1; **9c,** 55871-90-4; **10,** 22975-87-7; **11,** 55871-91-5; **12,** 43023-11-6; **13a,** 55871-92-6; **13b,** 55871-93-7; **14,** 19656-62-3; **15a,** 55871-94-8; **16a,** 55871-95-9; **16b,** 55871-96-0; **17a,** 55871-97-1; **17b,** 55871-98-2; **18a,** 55871-99-3; 1-carboethoxy-1-phenyl-4-isopropylsemicarbazide, 55872-00-9.

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A *trans*-1,2-*cis*-4,5-Germacradienolide and Other New Germacranolides from *Tithonia* Species[1]

Werner Herz* and Ram P. Sharma

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

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Isolation and structure determination of two new germacranolides, tifruticin (**1a**) and deoxyfruticin (**4a**), from *Tithonia fruticosa* Canby and Rose are described. Deoxyfruticin is the first naturally occurring *trans*-1,2-*cis*-4,5-germacradienolide. Structures were determined by chemical transformations and extensive use of ^1H and ^{13}C NMR spectrometry. Structures are suggested for tirotundin and its ethyl ether, two new germacranolides from *Tithonia rotundifolia* (Mill.) Blake.

As part of our search for secondary metabolites of Compositae with potential biological activity, we have examined collections of *Tithonia fruticosa* Canby and Rose and *Tithonia rotundifolia* (Mill.) Blake (Heliantheae, subtribe Helianthinae). The former yielded two closely related new germacranolides, tifruticin (**1a**) and deoxyfruticin (**4a**). Although only small amounts of these compounds were available, the complete structure and stereochemistry has been elucidated. *T. rotundifolia* afforded the new germacranolide tirotundin and its ethyl ether, for which structures **9a** and **9b** are suggested in preference to **10a** and **10b.**

Trifruticin (**1a**), mp 141°, $C_{20}H_{26}O_7$ (mass spectrum and elemental analysis), $[\alpha]^{22}D$ −22°, was a conjugated γ-lactone (ir bands at 1760 and 1640 cm^{-1}, strong uv end absorption) and had at least one hydroxyl group (ir band at 3400 cm^{-1}). In the ^1H NMR spectrum of **1a,** the proton under the (secondary) hydroxyl group was located at 4.46 ppm by D_2O exchange and by its paramagnetic shift to 5.33 ppm on acetylation of tifruticin to **1b.** In the 270-MHz NMR spectrum of the latter compound, all signals were well separated; hence decoupling experiments on **1b** afforded the full structure of tifruticin.

The NMR spectrum of **1b** (Table I) exhibited the typical two doublets of H_a and H_b in partial structure A at 6.38 and 5.92 ppm. Spin decoupling experiments involving H_a and H_b established the location of the H_c multiplet at 3.22 ppm. Irradiation at the frequency of H_c converted a doublet of doublets at 5.05 ppm to a doublet (J = 10 Hz) and a multiplet at 5.21 ppm was also simplified. Thus H_d and H_e are at 5.05 and 5.21 ppm, respectively, or the reverse. If it be assumed provisionally that the signal at higher field is H_d, as is generally the case, the signal at lower field could be assigned tentatively to a proton on a carbon carrying a conjugated ester function whose presence was indicated by an ir band at 1700 cm^{-1}.

Since the low-resolution mass spectrum of tifruticin displayed diagnostically important peaks at *m/e* 278 (M^+ − 100), 260 (M − 100 − 18), and 83 (base peak), the inference was drawn that a five-carbon ester side chain was present. The nature of the ester (partial structure B) was revealed by the NMR spectrum, which had a vinyl multiplet at 6.20 ppm coupled to a three-proton multiplet at 2.01 ppm and another methyl multiplet at 1.88 ppm, all characteristic of an angeloyl group.

Irradiation at the frequency of H_e (5.21 ppm) affected the H_c multiplet, collapsed a doublet of doublets at 2.22 ppm to a doublet (J = 15 Hz), and affected a partially obscured one-proton signal near 2.00 ppm. Irradiation near 2 ppm collapsed the doublet of doublets at 2.22 ppm to a doublet (J = 6 Hz) and converted the 5.21-ppm multiplet to a triplet, thus demonstrating that H_e was adjacent to a methylene group (H_f). Irradiation at the frequency of H_c (5.05 ppm) collapsed a broadened doublet at 5.52 ppm to a broad singlet. The broadening of this signal (H_g) could be traced to a small coupling with a narrowly split three-proton multiplet at 2.10 ppm. Thus partial structure A could be extended to C, where the symbol ■ represents quaternary carbon.