# Cycloaddition Reactions of 2-Ethoxyisobutenylidenecyclopropane and 2,3-Tetramethyleneisobutenylidenecyclopropane

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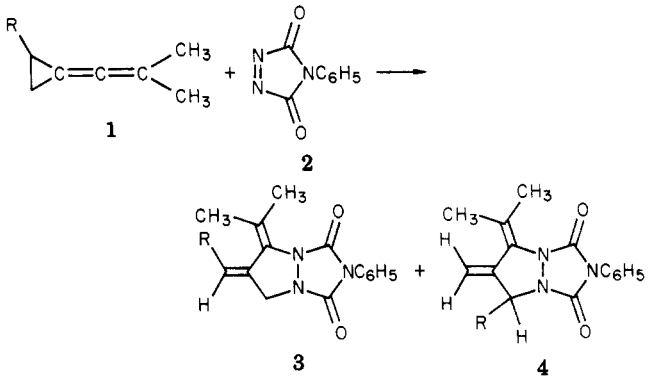
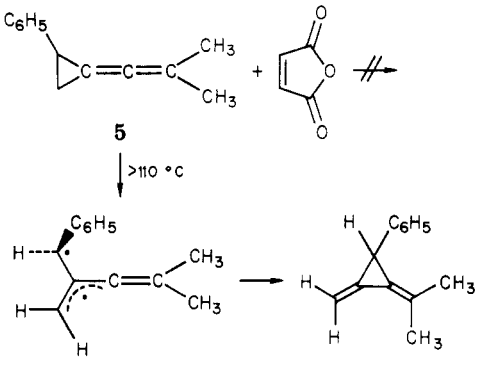
The title compounds (**15** and **6**) were reacted with maleic anhydride and *N*-phenylmaleimide (**7a** and **7b**) in an attempt to derive cycloaddition across the "methylenecyclopropane" portions of **6** and **15** in a manner previously observed with 4-phenyl-1,2,4-triazoline-3,5-dione. Cycloaddition in the desired manner did not occur. Instead, **6** reacted with **7a** and **7b** to give predominantly ene product (which underwent further cycloaddition) along with [2 + 2] cycloaddition across the exocyclic double bond. To a minor extent **6** also underwent [1,3] sigmatropic rearrangement followed by cycloaddition. **15** underwent only sigmatropic rearrangement followed by cycloaddition of the intermediate diene with **7b**. Reasons for the observed differences in reactivity and mode of reaction are discussed on the basis of the effect of the ethoxy group of **15** on the orbital energies as determined by photoelectron spectroscopy and theoretical calculations.

Alkenylidenecyclopropanes (**1**) have been shown to undergo facile cycloaddition with *N*-phenyltriazoline-3,5-dione (**2**) across the "methylenecyclopropane" portion of **1** to form the cycloadducts of structure **3** and **4**[1] (Scheme I). Initial attempts to form five-membered carbocyclic products by cycloaddition of 2-phenylisobutenylidenecyclopropane (**5**) with maleic anhydride met with failure, owing to the rather facile methylenecyclopropane-type rearrangement of **5** at the temperatures required to induce cycloaddition (Scheme II). A later study of this rearrangement reaction showed that it proceeds via a trimethylenemethane-type diradical intermediate[2] and that depriving the intermediate diradical the stabilization afforded by the phenyl group results in systems that are thermally stable. This presented the possibility that formation of five-membered carbocycles could be achieved which might provide a potential synthetic methodology for the preparation of such compounds. Preliminary investigations of such cycloaddition reactions unfortunately have shown that such reactions are superseded by ene [2 + 2] cycloadditions and sigmatropic rearrangement reactions. Although the original objectives have not been achieved, the results derived in this study are of interest in terms of the observed reactivity and the structures of the products formed.

Scheme I



Scheme II



## Results

The reaction of **6** with maleic anhydride (**7a**) at 160 °C in toluene produced a mixture of products (by NMR), which on standing at 25 °C for several days deposited colorless crystals (Scheme I). The crystals were removed by filtration and were recrystallized with great difficulty. NMR and mass spectral data indicated the product to be a 1:2 adduct of **6** with **7a**. The gross structure of the 1:2 adduct was readily derived from its very characteristic NMR spectrum by using decoupling techniques. The NMR spectrum showed no vinyl hydrogen resonance, a single vinyl methyl resonance as a singlet, and isolated AMX and AMXY spin systems (see Experimental Section for details). The NMR data is consistent only with one of the stereoisomers derived from an initial ene-reaction product (**10a**) followed by cycloaddition across the diene portion of **10a**. Assuming that the endo rule holds for the cycloaddition step, the two stereoisomers **11a** and **12a** are possible for the 1:2 adduct in which the isolated AMX and AMXY spin systems are comprised of $H_1$, $H_2$, and $H_3$ and $H_4$, $H_5$, $H_6$, and $H_7$, respectively. A second 1:2 adduct was formed but could not be isolated free of its stereoisomer. Unfortunately, the NMR spectra of **11a** and **12a** (as a mixture of **11a** and **12a**) are very similar, and analysis of long-range shielding effects in the two stereoisomers does not provide a means for distinguishing between the two possibilities.

The remainder of the reaction mixture of **6** with **7a** was subjected to column chromatography, giving a mixture of the 1:1 adducts **8a** and **9a**, a small amount of **14**, and a mixture of the 1:2 adducts **11a** and **12a**. Unfortunately, the mixtures of 1:1 and 1:2 adducts could not be separated sufficiently to isolate pure fractions of the individual isomers, nor could crystallization of any of the isomers be induced. The structures of **8a** and **9a** were assigned by comparison of the pure **8b** and **9b** isolated from the reaction of **6** with *N*-phenylmaleimide (**7b**). The adduct **14** could not be induced to crystallize, and its structure is assigned on the basis of its NMR spectrum which shows

(1) D. J. Pasto and A. F.-T. Chen, *J. Am. Chem. Soc.*, **93**, 2562 (1971); D. J. Pasto, A. F.-T. Chen, and G. Binsch, *ibid.*, **95**, 1553 (1973).
(2) D. J. Pasto, *J. Org. Chem.*, 41, 4012 (1976).

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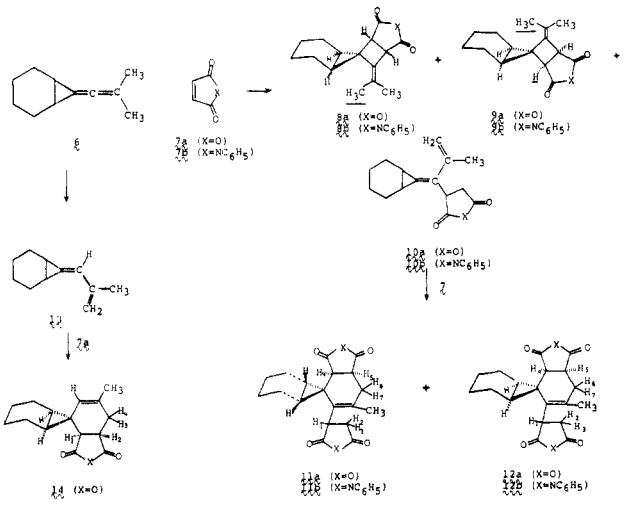
Scheme III



a single vinyl hydrogen resonance at $\delta$ 5.44 as a broadened singlet, a single vinyl methyl doublet at $\delta$ 1.85 ($J$ = 1.6 Hz), and a distinct AMXY system in which the $H_A$ ($H_2$ in **14**) portion is essentially identical in appearance and chemical shift with $H_5$ in **11** and **12**. Adduct **14** must be formed by cycloaddition of **7a** with **13** which must be formed from **6** by a [1,3] sigmatropic rearrangement. Thermal sigmatropic rearrangements of allenes do occur and are currently under investigation in the author's laboratories.[3] Of the products identified, the 1:2 adducts are formed in ~70% yield (~1:2 ratio of **11a** to **12a**, or vice versa), the 1:1 adducts **8a** and **9a** in ~15% yield (~1:4 ratio **8a**:**9a**), and **14** in ~5–10% yield. There appeared to be a couple more very minor products, but these were not present in sufficient quantity to be isolated and identified. There was no evidence for the formation of any of the desired product in which cycloaddition had occurred across the methylenecyclopropane portion of **6**.

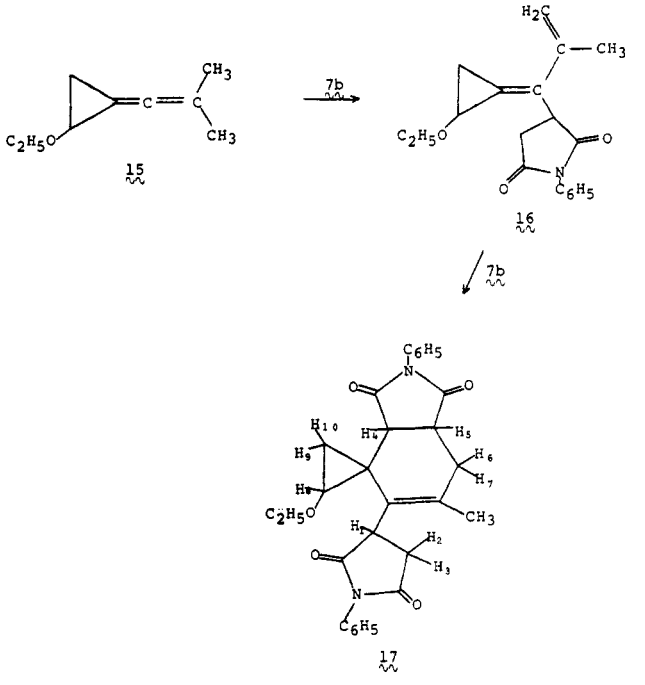
In view of the difficulty in separation and crystallization of the adducts formed from **6** with **7a**, the reaction of **6** with **7b** was carried out. A mixture of products was obtained which could be separated by repeated preparative thin-layer chromatography; the resulting pure fractions (by NMR) proved exceedingly difficult to crystallize. The stereochemistry of the 1:1 adducts **8b** and **9b** is assigned on the basis of the long-range shielding effects of the six-membered ring on the chemical shifts of the underlined methyl and methine hydrogens in **8b** and **9b**. In the minor 1:1 adduct **8b** the methine hydrogen appears at higher field ($\delta$ 2.97 vs. 3.38), while in the major 1:1 adduct **9b** the methyl hydrogens appear at higher field ($\delta$ 1.46 vs. 1.83 or 1.94). Molecular models indicate that the stereochemistry present in the major 1:1 adduct **9b** is that derived by the less sterically hindered approach of **7b** to **6**.

The NMR spectra of the 1:2 adducts **11b** and **12b** are considerably more complex in appearance than is that of the crystalline 1:2 adduct derived from **7a** because of a closer similarity of the chemical shifts of the hydrogens in the AMX and AMXY spin systems. Only subtle differences in chemical shifts are present, and assignment of stereochemistry is not possible.

In the reaction of **6** with **7b** the 1:2 adducts represented an estimated 90% the total products. The formation of a very small amount of a product corresponding to **14** was indicated by the presence of a vinyl resonance at $\delta$ 5.40 in an NMR spectrum of the band comprised mostly of **8b** and **9b**.

(3) D. J. Pasto and M. Haley, unpublished observations.

The reaction of 2-ethoxyisobutenylidenecyclopropane (**15**) with **7b** at 160 °C for 48 h (conditions under which the reaction of **6** with **7b** had gone to completion) resulted in the consumption of only ~40% of the **7b**. Repeated preparative TLC resulted in the isolation of only one crystalline product and an inseparable mixture of the crystalline product and one of its stereoisomers.



The NMR spectrum of the crystalline product showed two distinct AMX and AMXY spin systems (see Experimental Section) consistent only with a 1:2 adduct of general structure **17**. The NMR spectrum of the crude reaction mixture contained two broad singlets at $\delta$ 1.82 and 1.88, representing the vinyl methyl groups in the two stereoisomers of **17**, in a 4:1 ratio. No peaks characteristic of adducts of the general structures **8**, **9**, and **14** could be detected.

## Discussion

The desired mode of cycloaddition of **6** and **15** with **7a** and **7b** was not accomplished; instead, **6** underwent competitive [2 + 2] cycloaddition across the exocyclic double bond to form **8** and **9**, an ene reaction with the remote double bond to form **10** which reacted further to produce **11** and **12**, and [1,3] sigmatropic rearrangement followed by cycloaddition. **15** underwent only a [1,3] sigmatropic rearrangement followed by cycloaddition to form **17**. The difference in reactivity and mode of reaction of **7a** and **7b** compared with that of PTAD (**2**) must be due to the much lower lying LUMO of **2** (the cycloaddition reaction being an alkenylidenecyclopropane HOMO–dienophile LUMO controlled reaction),[4] resulting in a lower activation energy for cycloaddition than for [1,3] sigmatropic rearrangement.

It was hoped that the replacement of the tetramethylene portion of **6** by a $\pi$ electron donating group would result in a strong interaction between the nonbonded-pair AO's on oxygen with the Walsh-type MO's of the ring (i.e., HOMO) to raise the energy of the HOMO of **15** and thus increase its reactivity toward the desired mode of cycloaddition. Such was not the case, the ethoxy system **15** being less reactive in all senses than **6**.

(4) D. J. Pasto, J. K. Borchardt, T. P. Fehlner, H. F. Baney, and M. E. Schwartz, *J. Am. Chem. Soc.*, 98, 526 (1976).

For a better understanding of the reasons for the decrease in reactivity of **15** relative to **6**, photoelectron spectroscopic studies were carried out on **6** and **15**, and theoretical calculations were performed on model systems representing **6** and **15**. The PES IP's of **6** are 8.01 and 8.88 eV ($\nu_{C=C}^{0\rightarrow1}$ = 1280 cm$^{-1}$),[5] and those of **15** are 8.12 and 9.02 eV (oxygen nonbonded-pair IP's are 9.89 and 11.64 eV). STO-3G calculations[6] were carried out on *cis*-2,3-dimethylethenylidenecyclopropane (**18**) and 2-hydroxyethenylidenecyclopropane (**19**).[7] The calculations give energies for the HOMO and the second OMO of **18** of −7.4273 and −8.0941 eV, and of **19** of −7.7590 and −8.3703 eV (oxygen nonbonded-pair energies of −9.3418 and −11.4835 eV). The LUMO,[8] which is involved in the ene reaction, is lowered from 8.0932 eV in **18** to 7.9379 eV in **19**, while the third UMO,[8] which is involved in the desired [$_\pi2_s$ + ($_\pi2_s$ + $_\sigma2_s$)] cycloaddition[4] is *raised* from 14.1992 eV in **18** to 14.6693 eV in **19**. The coefficients of the AO's on oxygen in the HOMO and second OMO are very small, indicating little interaction of the desired type is present in **19** (or **15**). Thus, both the PES and the results of the calculations suggest that the desired cycloaddition and the ene reactions should be slower with **15**, which is consistent with the experimental observations. If the [2 + 2] cycloadditions observed with **6** occur by the recently proposed and discussed [$_\pi2_s$ + ($_\pi2_s$ + $_\pi2_s$)] cycloaddition pathway for allenes,[9] it too should be less favorable with **15**.

## Experimental Section

**Reaction of 6 with Maleic Anhydride (7a).** Into a 5-mL reaction vessel fitted with a pressure seal were placed 1.52 g (15.5 mmol) of **7a**, 2.29 g (15.5 mmol) of **6**, and 1.0 mL of toluene. The sealed vessel was heated in a sand bath at 160 °C for 48 h. When the vessel was allowed to stand at 25 °C, crystals formed which were removed by filtration (0.50 g). The crystalline material was recrystallized from acetone–chloroform mixtures, giving colorless microcrystals: mp 214–218 °C; NMR ($CDCl_3$) $\delta$ 4.35 (dd, $J$ = 10.0 and 8.5 Hz, $H_1$), 3.70 (ddd, $J$ = 9.1, 6.1, and 2.7 Hz, $H_5$), 3.28 (dd, $J$ = 18.6 and 10.0 Hz, $H_2$), 2.72 (d, $J$ = 9.1 Hz, $H_4$), 2.70 (dd, $J$ = 18.6 and 8.5 Hz, $H_3$), 2.51 (dd, $J$ = 6.1 Hz with $J_{gem}$ unassigned, $H_6$), 2.46 (dd, $J$ = 2.7 with $J_{gem}$ unassigned, $H_7$), 1.80 (s, $CH_3$), 2.0–0.9 (m); mass spectrum, exact mass calcd for $C_{19}H_{20}O_6$, $m/e$ 344.126; found, 344.124.

The filtrate from above was dissolved in dichloromethane and applied to a 2 × 30 cm column of silica gel. The column was eluted with dichloromethane–ethyl acetate (10% increase in ethyl acetate every 100 mL) by taking 20-mL fractions. The first few fractions contained unreacted **6**. NMR analysis indicated that fractions 4–17 contained mixtures of **8a**, **9a**, and **14**. These fractions were combined and rechromatographed on silica gel by using cyclohexane–dichloromethane as eluant (10% increase in dichloromethane for every 150 mL). Early fractions contained mixtures of **8a** and **9a** rich in the latter (exact mass calcd for $C_{15}H_{18}O_3$, $m/e$ 246.125; found, 246.129), intermediate fractions were rich in the former, and later fractions contained mixtures of **8a** and **14**. A few milligrams of essentially pure **14** was contained in the final fractions but could not be induced to crystallize. NMR of **14** ($CDCl_3$): $\delta$ 5.44 (br s, vinyl H), 3.46 (ddd, $J$ = 9.6, 6.5, and 2.4 Hz, $H_2$), 2.54 (dd, $J$ = 14.5 and 2.4 Hz, $H_2$ or $H_4$), 2.43 (d, $J$ = 9.6 Hz, $H_1$), 1.85 (d, $J$ = 1.6 Hz, $CH_3$), 2.1–1.0 (m). NMR of **8a** ($CDCl_3$): $\delta$ 4.27 (dm, $J$ = 6.2 Hz with long-range coupling to $CH_3$'s, $H_1$), 3.10 (d, $J$ = 6.2 Hz, $H_2$), 1.86 (d, $J$ = 1.2 Hz, $CH_3$), 1.79 (d, $J$ = 1.8 Hz, $CH_3$), 2.1–1.0 (m). NMR of **9a** ($CDCl_3$): $\delta$ 4.16 (dm, $J$ = 6.2 Hz with long-range coupling to $CH_3$'s, H), 3.50 (d, $J$ = 6.2 Hz, $H_2$), 1.73 (d, $J$ = 1.2 Hz, $CH_3$), 1.47 (d, $J$ = 1.8 Hz, $CH_3$), 2.0–0.9 (m).

Later fractions from the initial column contained mixtures of **11a** and **12a** which varied little in composition. Crystallization could not be induced. The NMR spectra of the fractions showed low-field-resonance patterns similar to those in the NMR of the crystalline material described above, along with methyl resonances at $\delta$ 1.80 and 1.84.

**Reaction of 6 with *N*-Phenylmaleimide 7b.** In the manner described above 1.60 g (11.4 mmol) of **6**, 1.88 g (10.0 mmol) of **7b**, and 2.0 mL of toluene were heated at 160 °C for 30 h. When the mixture cooled, crystals formed which were removed by filtration. Analytical TLC indicated a mixture of adducts to be present in the crystalline material. The crystalline material and filtrate were combined, dissolved in dichloromethane, and subjected to preparative TLC. Development in 85% dichloromethane–ethyl acetate produced two major bands which were mixtures of 1:1 and 1:2 adducts. The bands were removed by acetone extraction. The top band (1:1 adducts) was rechromatographed by using dichloromethane, which gave two very close bands. The bands were removed and the fractions extracted by acetone.

**8b** (minor 1:1 adduct which could not be induced to crystallize): NMR ($CDCl_3$) $\delta$ 7.35 (m, aromatic H's), 4.02 (dm, $J$ = 6.2 Hz with long-range coupling to $CH_3$'s), 2.97 (d, $J$ = 6.2 Hz, $H_2$), 1.92 (d, $J$ = 1.2 Hz, $CH_3$), 1.76 (d, $J$ = 1.8 Hz, $CH_3$), 2.0–1.0 (m); mass spectrum, exact mass calcd for $C_{21}H_{23}NO_2$, $m/e$ 321.173; found, 321.172.

**9b** (major 1:1 adduct): recrystallized from dichloromethane–hexane; mp 139.1–139.8 °C; NMR ($CDCl_3$) $\delta$ 7.35 (m, aromatic H), 4.05 (dm, $J$ = 6.6 Hz with long-range coupling to $CH_3$'s, $H_1$), 3.38 (d, $J$ = 6.6 Hz, $H_2$), 1.77 (d, $J$ = 1.2 Hz, $CH_3$), 1.46 (d, $J$ = 1.8 Hz, $CH_3$), 2.1–1.1 (m); mass spectrum, exact mass calcd for $C_{21}H_{23}NO_2$, $m/e$ 321.173; found, 321.172.

The lower band from the original TLC was rechromatographed by using 25% ethyl acetate–dichloromethane. Two slightly overlapping bands developed, and the upper and lower portions of the bands were removed and extracted with acetone.

**11b (or 12b)**: recrystallized from chloroform–hexane; mp 279.0–280.5 °C; NMR ($CDCl_3$) $\delta$ 7.4 (m, aromatic H), 3.85 (dd, $J$ = 10.0 and 9.2 Hz, $H_1$), 3.33 (ddd, $J$ = 9.4, 6.8, and 2.4 Hz, $H_5$), 3.19 (dd, $J$ = 18.4 and 9.8 Hz), 2.70, 2.46, 2.36, and 2.22 (overlapping multiplets), 1.85 (s, $CH_3$), 2.0–0.9 (m); mass spectrum, exact mass calcd for $C_{31}H_{30}N_2O_4$, $m/e$ 494.217; found, 494.217.

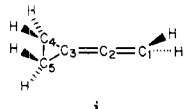
**12b (or 11b).** This compound was recrystallized from chloroform–hexane, giving colorless microcrystals which underwent melting at 110–130 °C with bubbling [apparently entrained hexane (by NMR)]. The crystals were placed on a vacuum line for 24 h and then gave a melting point of 210.0–211.5 °C without evidence of bubbling: NMR ($CDCl_3$) $\delta$ 7.35 (m, aromatic H), 3.89 (dd, $J$ = 10.0 and 7.2 Hz, $H_1$), 3.32 (ddd, $J$ = 9.2, 6.8 and 2.4 Hz, $H_5$), 3.04 (dd, $J$ = 18.4 and 9.6 Hz, $H_2$), 2.74, 2.45, 2.31, and 2.20 (overlapping multiplets), 1.81 (s, $CH_3$), 1.9–0.8 (m); mass spectrum, exact mass calcd for $C_{31}H_{30}N_2O_4$, $m/e$ 494.217; found, 494.220.

**Reaction of 15 with *N*-Phenylmaleimide.** A mixture of 0.80 g (5.8 mm) of **13** and 1.29 g (7.8 mm) of **7b** in 2 mL of toluene was heated at 160 °C for 48 h. Analysis by NMR indicated consumption of ~40% of the **7b**. The toluene was removed under reduced pressure, and the residue was subjected to preparative TLC on silica gel by using dichloromethane as eluant. Only one product band was observed which consisted of a mixture of 2:1

(5) D. J. Pasto, T. P. Fehlner, M. E. Schwartz, and H. F. Baney, *J. Am. Chem. Soc.*, **98**, 530 (1976).

(6) Calculations were carried out by using the GAUSSIAN 70 program package: W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton, and J. A. Pople, *QCPE*, **10**, 236 (1973).

(7) Initial partial geometry optimization calculations were carried out on ethenylidenecyclopropane (i) [not optimized were the $C_1$–H bond lengths (1.082 Å), $C_2$–$C_1$–H bond angles (121.5°), and ring C–H bond lengths (1.909 Å)], giving the following optimized values for the structural parameters: $C_1$–$C_2$, 1.292 Å; $C_2$–$C_3$, 1.271 Å; $C_3$–$C_4$($C_5$), 1.495 Å; ($C_5$)–$C_4$–$C_3$–$C_2$ bond angle, 149.27°; H–$C_4$($C_5$)–$C_3$ bond angle, 115.85°; H–$C_4$–($C_5$)–$C_3$–$C_2$ dihedral angle, 70.42°. The ring hydrogens of i were replaced by two methyls (C–C, 1.52 Å; C–H, 1.09 Å; with tetrahedral geometry) in a staggered conformation for calculation of **18** and by one hydroxyl (C–O, 1.42 Å; H–O, 1.02 Å; H–O–$C_4$, 105°; with anti conformation with respect to the ring) for calculation of **19**.



i

(8) For description of MO's see ref 4.

(9) D. J. Pasto, *J. Am. Chem. Soc.*, **101**, 37 (1979).

adducts. Repeated preparative TLC resulted in the isolation of the major adduct as a difficultly crystallizable material which was recrystallized from chloroform–hexane: mp 273–276 °C; NMR ($CDCl_3$) $\delta$ 0.98 (dd, $J$ = 7.8 and 3.4 Hz, $H_{10}$), 1.17 (t, $J$ = 7.2 Hz, $CH_2CH_3$), 1.62 (dd, $J$ = 7.8 and 6.8 Hz, $H_8$), 1.82 (br s, $=CCH_3$), 2.34 (d, $J$ = 9.2 Hz, $H_4$), 2.63 [d(d), $J$ = 6.0 Hz ($J_{gem}$ not observable), $H_6$], 2.66 (dd, $J$ = 19.0 and 7.2 Hz, $H_3$), 2.69 [d(d), $J$ = 2.6 Hz ($J_{gem}$ not observable), $H_7$], 2.82 (dd, $J$ = 6.8 and 3.4 Hz, $H_9$), 2.99 (dd, $J$ = 19.0 and 9.2 Hz, $H_2$), 3.37 (ddd, $J$ = 9.2, 6.0, and 2.6 Hz, $H_5$), 3.53 (q, $J$ = 7.2 Hz, $OCH_2CH_3$), 3.71 (dd, $J$ = 9.2 and 7.2 Hz, $H_1$), 7.3 (m, aromatic H); mass spectrum, exact mass calcd for $C_{29}H_{28}N_2O_5$, $m/e$ 484.199; found, 484.195.

The NMR spectrum of the crude reaction mixture showed two broad singlets at $\delta$ 1.82 and 1.88 in a ratio of 4:1.

**Acknowledgment.** The authors wish to thank Professor T. Fehlner of our department for running the PES spectra and the Computing Center of the University of Notre Dame for providing computer time.

**Registry No.** 6, 4544-26-7; **7a**, 108-31-6; **7b**, 941-69-5; **8a**, 73261-95-7; **8b**, 73261-96-8; **9a**, 73307-14-9; **9b**, 73306-82-8; **11a/12a**, 73261-97-9; **11b/12b**, 73261-98-0; **14**, 73261-99-1; **15**, 73262-00-7; **17**, 73262-01-8; **18**, 73262-02-9; **19**, 73262-03-0.

# Reactions of Alkylnitrosoureas in Aqueous Solution[1]

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The acid- and base-catalyzed decompositions of *N*-methyl-, *N,N'*-dimethyl-, and *N,N',N'*-trimethyl-*N*-nitrosourea in aqueous solution have been studied. Below pH 2, the *N*-methyl compound undergoes both denitrosation and hydrolysis. The denitrosation yields methylurea and nitrous acid. The hydrolysis yields largely methylamine, nitrogen, and carbon dioxide. The acid-catalyzed denitrosation and hydrolysis of the trimethylnitrosourea are somewhat more rapid than the corresponding reactions of *N*-methyl-*N*-nitrosourea. The denitrosation of this compound yields trimethylurea and nitrous acid. The hydrolysis yields methanol, dimethylamine, nitrogen, and carbon dioxide. The solvent isotope effect, $k_{H_2O}/k_{D_2O}$ = 1.3, and the absence of chloride ion catalysis suggest that the denitrosation reaction proceeds by a rate-determining proton transfer which is followed by the rapid loss of the nitroso group. The results for the hydrolysis reaction are compatible with a formulation in which a hydrate of the nitrosourea is protonated in a rate-determining step to form a tetrahedral intermediate which subsequently decomposes to yield methyldiazonium hydroxide and a carbamic acid derivative. The base-catalyzed reactions of the mono-, di-, and trimethylnitrosoureas are first order in hydroxide ion over a broad pH range. The hydrolysis of *N*-methyl-*N*-nitrosourea yields methanol and derivatives of carbamic acid. Salt effects on the reaction rate are negligible except for the influence of lithium ion. The rate constants for the hydrolysis of the mono- and dimethyl compounds depend upon the buffer concentration at pH 9.5. These constants reach limiting values. The rate constants for the hydrolysis of the trimethyl compound also depend upon the buffer concentration, but a limiting value is not achieved. The solvent isotope effect for the base-catalyzed reaction, the exchange reaction of water-$^{18}O$ with the carbonyl group of the urea, and the fact that *N*-methyl-*N*-nitrosourea is hydrolyzed about $2.2 \times 10^4$ times more rapidly than *N,N',N'*-trimethyl-*N*-nitrosourea suggest that the hydrolysis occurs by a mechanism in which a tetrahedral intermediate is formed. Often, the formation of this intermediate is rate limiting. However, under certain conditions, its decomposition to methyldiazonium hydroxide and a carbamate anion which decompose to form methanol and the other products may be rate determining.

*N*-methyl-*N*-nitrosourea and other *N*-alkyl-*N*-nitrosoureas have been implicated in chemical carcinogenesis.[2] Most workers in this field have focused attention on the alkylation of the nucleic acids by these substances.[3,4] However, the nature of the alkylation reaction is unclear. Uncertainty exists, in part, because the *N*-alkyl-*N*-nitrosoureas have such a rich, diverse chemistry. In early work, Werner found that methylnitrosourea decomposed thermally to give nitrogen, methyl isocyanate, and water.[5] He also found that it reacted with concentrated sodium hydroxide solution to produce diazomethane, with ethoxide ion in ethanol to give diazomethane, sodium cyanate, and water, and with ammonia in ethanol to yield urea, nitrogen, methanol, and some methylurea and dimethylurea[5] (see eq 1–3). Boivin and Boivin subsequently reported that

$$CH_3N(NO)CONH_2 \xrightarrow[KOH]{70\%} CH_2N_2 \quad (1)$$

$$CH_3N(NO)CONH_2 + NaOC_2H_5 \xrightarrow{C_2H_5OH} NaOCN + CH_2N_2 + H_2O \quad (2)$$

$$CH_3N(NO)CONH_2 + NH_3 \xrightarrow{C_2H_5OH} H_2NCONH_2 + N_2 + CH_3OH + CH_3NHCONH_2 \quad (3)$$

methylnitrosourea decomposed in boiling water to give a stoichiometric yield of nitrogen.[6] They also found that *N*-nitroso-*N,N'*-dimethylurea decomposed in a similar manner to give a quantitative yield of nitrogen, methyl isocyanate, and methanol.[6] The nitrosoureas reacted with

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