21418-41-7; **4c**, 50532-93-9; **5a**, 32278-63-0; **5b**, 69461-76-3; **5c**, 50532-97-3; **6a**, 32278-445-8; **6b**, 50290-40-9; **6c**, 50532-91-7; **8**, 69461-77-4; **9**, 69461-80-9; **10**, 69461-81-0; DMAF, 7542-94-1; DMAD, 762-42-5; DEEM, 87-13-8; dimethyl ethoxymethylenemalonate, 24362-46-7; 2-aminobenzothiazole, 136-95-8; 2-amino-1-methylbenzimidazole, 1622-57-7; 2-aminobenzoxazole, 4570-41-6; 4-oxopyrimido[2,1-*b*]benzothiazole-3-carboxylic acid, 21786-97-0; 4-oxopyrimido[2,1-*b*]benzothiazole-2-carboxylic acid, 69461-82-1; 4-oxopyrimido[2,1-*b*]benzoxazole-3-carboxylic acid, 69461-83-2; 4-oxopyrimido[2,1-*b*]benzoxazole-2-carboxylic acid, 69461-84-3; 10-methyl-4-oxopyrimido[2,1-*b*]benzimidazole-3-carboxylic acid, 50532-94-0; 10-methyl-4-oxopyrimido[2,1-*b*]benzimidazole-2-carboxylic acid, 69461-85-4; 2-oxopyrimido[2,1-*b*]benzothiazole-4-carboxylic acid, 58099-50-6; 2-oxopyrimido[2,1-*b*]benzoxazole-4-carboxylic acid, 69461-86-5; 10-methyl-2-oxopyrimido[2,1-*b*]benzimidazole-4-carboxylic acid, 69461-87-6; 2-[2,2-bis(carbomethoxy)-ethyleneimino]benzoxazole, 69461-88-7.

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Reaction of 2*H*-Benzimidazole-2-thione with Dimethyl Acetylenedicarboxylate

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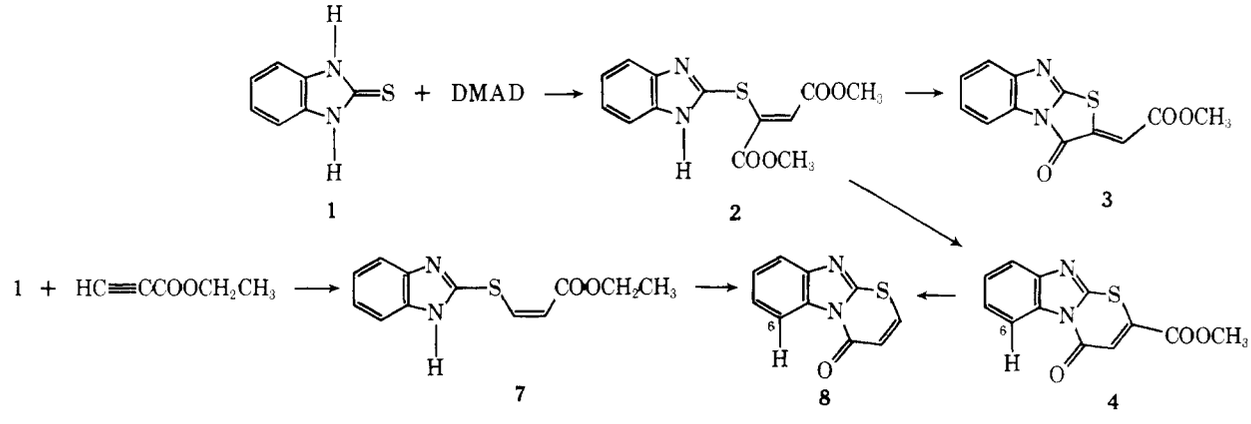
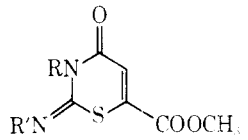
The reaction of dimethyl acetylenedicarboxylate (DMAD) with 2*H*-benzimidazole-2-thione in methanol has been investigated. When run for prolonged reaction times, the exclusive product of this reaction, in high yield, is methyl 4-oxo-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole-2-carboxylate. This is also the exclusive product after short reaction times in the presence of a catalytic amount of sodium methoxide. The structure of the product was confirmed by its hydrolysis and decarboxylation to the same product obtained from the reaction of ethyl propiolate with 2*H*-benzimidazole-2-thione. When reactions with DMAD are run for shorter periods of time in methanol, without added base, mixtures of three products can be obtained. Each of these compounds was isolated and characterized. One of them, 2-(carbomethoxymethylene)-3-oxo-2*H*,3*H*-thiazolo[3,2-*a*]benzimidazole, rearranges in methanol to the isomeric thiazinone, and this rearrangement can be catalyzed by methanolic sodium methoxide.

In the course of a medicinal chemical project in our laboratories, I became interested in the reaction of dimethyl acetylenedicarboxylate (DMAD) with 2*H*-benzimidazole-2-thione. A recent report by McKillop et al.[1] prompts this report since my results differ significantly from those which they have described.

An earlier report by Grinblat and Postovskii indicated that the reaction of DMAD with 2*H*-benzimidazole-2-thione (**1**) in glacial acetic acid yields the thiazolidinone **3**, mp 190–192 °C.[2] Theoretically, several other products of such a reaction are possible, perhaps the most notable possibility being the thiazinone **4**, which might be formed from the presumed intermediate Michael adduct **2** by reaction of the ring nitrogen with the other ester functionality (see Scheme I). It seemed possible that the Russian workers might have actually isolated **4** instead of **3**. The relevant literature, although somewhat confusing, seems to bear out their structural assignment, however. Thus, the reaction of DMAD with N,N′-disubsti-

Scheme I





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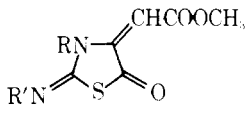


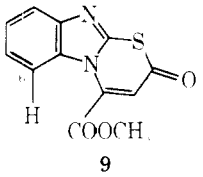
6

tuted thioureas has been variously claimed to yield the thiazinone **5**[3,4] or the thiazolidinone **6**.[5,6] This confusion has recently been settled, however, in favor of the five-membered ring structure **6** on the basis of chemical evidence,[7] X-ray analysis,[8] and ^{13}C NMR spectroscopy by application of C–H spin-coupling constants.[9] Thus, although one would not necessarily expect 2*H*-benzimidazole-2-thione to react as an ordinary N,N′-disubstituted thiourea, the published data suggest that structure **3** could well be correct.

The recent report from the English group gives even better evidence since they isolated the same compound that Grinblat and Postovskii obtained, established its identity with material prepared by an alternative route, and performed an X-ray analysis. Their work unequivocally establishes structure **3** for this compound. In contrast to the Russian workers, however, McKillop et al. reported that the crude reaction product is a mixture containing not only **3**, but also a second compound which they were apparently unable to isolate cleanly. Although they tentatively assigned structure **4** to this compound on the basis of ^1H NMR spectroscopy, their evidence is not unambiguous.

This report describes the isolation and characterization of all three of the compounds **2, 3,** and **4**, the establishment of structure **4** by chemical and spectroscopic methods, and the rearrangement of **3** to **4** in methanol.

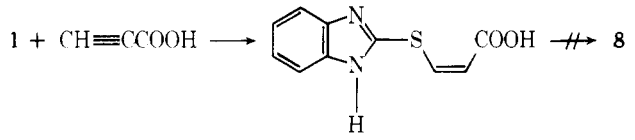
The reaction of 2*H*-benzimidazole-2-thione (**1**) with DMAD in methanol at reflux overnight, or at room temperature for several days, gave good yields (~90%) of a single compound, mp 170–172 °C, for which ^1H NMR, IR, and microanalytical data are consistent for structure **4**. Hydrolysis and thermal decarboxylation of this material gave a compound which is identical with the compound obtained by addition of ethyl propiolate to **1** followed by thermal ring closure (Scheme I). This identity with the ethyl propiolate derived product verifies the presence of the six-membered thiazinone ring system rather than a thiazolidinone system. The 4-one structure of **4** rather than the alternative 2-one structure **9** is indicated by



9

the ^1H NMR spectrum since the position of the C-6 benzo ring proton is shifted downfield from the rest of the aromatic protons, presumably by the proximity of the C-4 carbonyl group which can thus exert a deshielding effect.[10] Subsequent hydrolysis and decarboxylation of the ester cause no appreciable change in the chemical shift of the C-6 proton, indicating that the downfield shift seen in the ester is not due to the carbomethoxy group, as it might be if the actual structure was **9**.

There is a single reference to compound **8** in the literature, a report by Zav'yalova et al. that they prepared the compound by reaction of **1** with propiolic acid.[11] Their compound has a significantly different melting point than mine, and the partial ^1H NMR spectrum which they reported is different. Repetition of their reaction as reported gave a product with a melting point similar to theirs, but whose IR, ^1H NMR, and mass spectral data, as well as its solubility in aqueous sodium bicarbonate, all indicate that the compound is simply the uncyclized acid **10**. Cyclization of this acid to the thiazinone **8**



10

by any of the methods they reported could not be accomplished.

Although prolonged reaction of DMAD and **1** in methanol thus yields only the thiazinone **4**, a closer look at the reaction soon indicated that workup after shorter reaction times can result in mixtures of two or three compounds and that the exact nature of these mixtures varies depending on reaction time and temperature. The ^1H NMR spectra, although quite cluttered in the aromatic region, proved quite useful for analyzing these mixtures since the methoxyl absorbances appeared at distinctly different chemical shifts. One of the compounds in these mixtures was clearly the thiazinone **4**, which had already been isolated and characterized. A second product appeared to be the Michael adduct **2**, with two methoxyl groups.[12] It seemed reasonable that the third compound in the mixtures was the thiazolidinone **3**. By submitting the methanol reactions to workup at various times, reaction products containing various amounts of the three compounds were obtained. Generally, the workup procedure involved simply collecting the precipitated product by filtration, washing with ether, air-drying, and then analyzing by ^1H NMR spectroscopy in $CDCl_3$.

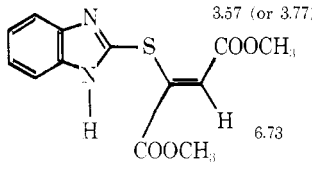
Table I indicates the relative molar percent of each of the three compounds in the products isolated under various conditions. The table also indicates the chemical shifts of the relevant ^1H NMR absorbances which were integrated in order to calculate the molar percentages. The numbers shown in the table were fairly reproducible in different experiments. High pressure liquid chromatography (LC) or TLC analysis of these mixtures proved useless since compound **2** cyclizes to **3** and/or **4** during TLC or LC elution and because **3** and **4** are difficult to separate by these chromatographic methods.

Isolation of each of the apparent intermediates **2** and **3** was of interest. The initial Michael adduct **2** was obtained in modest yields by carefully running the condensation reaction at low temperature and for very short times in methanol. This material was uncontaminated by **3** or **4** according to the ^1H NMR spectrum. That condensation had clearly taken place as expected at the sulfur atom was indicated by the symmetry of the aromatic region of the spectrum. The configuration of **2** which is shown, resulting from trans addition in the Michael reaction, is assumed on the basis of the work of Truce et al.[13] Extension of this assumption to the cyclized product **3** has also been made on the basis of Truce's work and on the basis of the ^{13}C NMR study with thioureas.[9]

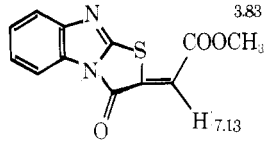
Attempts to find reaction conditions of time, temperature, or solvent which yield only compound **3** were unsuccessful, and an investigation of the reaction in an NMR tube indicated that **3** and **4** are formed simultaneously from **2**. Good yields of mixtures of **3** and **4** were isolated in either methanol or THF, and compound **3** was cleanly separated from **4** by very careful preparative LC, using 1% ethyl acetate in benzene. In this manner a bright yellow compound, mp 190–192 °C, was isolated which is apparently the same product obtained by McKillop et al. and whose structure they have proven conclusively to be **3**.[1]

That **3** can rearrange to **4** in methanol solution was shown by refluxing a sample of purified **3** in methanol overnight, resulting in complete conversion to **4**. Conducting the rearrangement in an NMR tube using deuterated methanol as solvent led to deuterated ester **4**, thus suggesting that the rearrangement involves reversion of **3** to **2** by methanolysis of

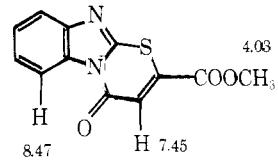
Table I. ^{1}H NMR Analysis of the Reaction of DMAD with 1 in Methanol[a]



2



3



4

reaction time	reaction temp, °C	yield of total product, %	% 2	% 3	% 4
8 min	−1	28	100	0	0
15 min	0	43	80	15	5
1 h	25	84	0	63	37
18 h	25	89	0	40	60
19 h	65	96	0	0	100

[a] Chemical shifts in $CDCl_3$ of relevant absorbances are given in parts per million downfield from Me_4Si (δ).

the amide bond, followed by recyclization with the other ester functionality to give 4.

This rearrangement of 3 to 4 is sensitive to base catalysis, as was demonstrated by adding a trace of CD_3ONa/CD_3OD to a solution of 3 in CD_3OD in an NMR tube. Under these conditions, rearrangement to 4 was complete within a few minutes, compared to several hours without the added base. The overall reaction of 1 with DMAD was then tried on a preparative scale using a catalytic amount of sodium methoxide in methanol. Under these conditions, 4 can be isolated exclusively in good yields after a few minutes at room temperature.

Thus, the reaction of 2*H*-benzimidazole-2-thione with DMAD in methanol leads to good yields of the thiazinone 4 exclusively, and the reaction can be catalyzed by sodium methoxide. In the absence of added base, some thiazolidinone 3 can also be observed and isolated at earlier stages of the reaction, but prolonged reaction times yield only 4. The details of the experimental procedures used by previous workers are not included in their published reports, but it can be presumed that the exclusive formation of 4 was not observed by them because their reactions were either run in different solvents or for shorter times.

Why this system should give results so distinctly different from those obtained with ordinary N,N′-disubstituted thioureas is unclear. The results could be due to enhanced stability of the 6,5,6 ring system because of pseudoaromaticity, to the inherent strain of the 6,5,5 ring system, or to differences in basicity between a benzimidazole and a thiourea. Other similar systems are under investigation in our laboratories in an effort to determine how general these results might be.

Experimental Section

General Comments. Melting points were obtained with a Uni-melt apparatus and are corrected. The IR spectra were obtained, using Nujol mulls, on a Perkin-Elmer Infracord spectrophotometer; ^{1}H NMR spectra were measured with a Varian T-60 spectrometer. High pressure liquid chromatographies were performed using a Waters Associates' Prep LC/System 500 with PrepPAK-500/silica cartridges. Microanalyses were performed by J. H. Gagnon and co-workers in the Central Research Analytical Group, 3M Co.

Dimethyl 2-(2-Benzimidazolylthio)fumarate (2). Dimethyl acetylenedicarboxylate (DMAD; 4.00 g, 28.2 mmol) was added all at once to a solution of 2*H*-benzimidazole-2-thione (1; 4.00 g, 26.7 mmol) in 150 mL of methanol cooled at −4 °C. After 8 min of stirring (−4 to −1 °C), the solid which had precipitated was quickly collected by filtration, washed with ether, and air-dried to give 2.20 g (28%) of 2: melting point changes form at 144 °C, melts 152–172 °C; IR 5.7, 5.8 μm; ^{1}H NMR ($CDCl_3$) δ 7.7–7.0 (m, 4), 6.73 (s, 1), 3.77 (s, 3), 3.57 (s, 3).

Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.4; H, 4.1; N, 9.6. Found: C, 53.1; H, 4.2; N, 9.6.

2-(Carbomethoxymethylene)-3-oxo-2*H*,3*H*-thiazolo[3,2-*a*]benzimidazole (3). A mixture of 1 (3.00 g, 20.0 mmol) and DMAD (3.00 g, 21.1 mmol) was stirred at room temperature overnight in 100 mL of dry THF. The solution was concentrated in vacuo to a solid which was triturated with ether and filtered to yield 3.20 g (62%) of a mixture of 3 and 4 in a ratio of about 2:1 (^{1}H NMR analysis). High pressure liquid chromatography of 1.50 g of this material, using two silica cartridges and eluting with 1% ethyl acetate in benzene, yielded 0.20 g of pure 3, 0.75 g of a mixture of 3 and 4 (~70% 3), and 0.40 g of a second mixture of 3 and 4 (~33% 3). The 70% mixture was rechromatographed in the same manner to yield another 0.19 g of pure 3. The yield of 3 was thus 0.39 g (16% from 1): mp 190–192 °C (lit. mp 192–193[1] (and 190–192 °C[2]); IR 5.70, 5.84, 6.10 (sh), 6.16 μm; ^{1}H NMR ($CDCl_3$) δ 8.1–7.2 (m, 5), 3.83 (s, 3).

Anal. Calcd for $C_{12}H_8N_2O_3S$: C, 55.4; H, 3.1; N. 10.8. Found: C, 55.2; H, 2.9; N, 10.9.

Methyl 4-Oxo-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole-2-carboxylate (4). A solution of DMAD (75.0 g, 0.526 mol) in 200 mL of methanol was added dropwise at room temperature to a suspension of 1 (75.0 g, 0.500 mol) in 1200 mL of methanol. The resulting mixture was refluxed overnight (19 h) and then cooled. The solid was collected by filtration and air-dried to give 125 g (96%) of 4: mp 170–172 °C; IR 5.70, 5.84, 6.26 (w) μm; ^{1}H NMR ($CDCl_3$) δ 8.47 (m, 1), 7.8–7.3 (m, 4), 4.03 (s, 3).

Anal. Calcd for $C_{12}H_8N_2O_3S$: C, 55.4; H, 3.1; N, 10.8. Found: C, 55.2; H, 3.1; N, 10.8.

From 1 with Base Catalysis. DMAD (5.00 g, 35.2 mmol) was added carefully with stirring to a suspension of 1 (5.00 g, 33.3 mmol) in 100 mL of methanol containing sodium methoxide (0.25 mL of a 25% methanol solution, ~1 mmol). After being stirred for 5 min at room temperature and for 5 min at 0 °C, the solid was collected by filtration, washed with ether, and air-dried to give 7.35 g (85%) of 4, mp 171–172 °C. The ^{1}H NMR spectrum of this material is identical with that of the compound derived from 1 in the absence of sodium methoxide and shows the complete absence of 3.

From 3. The ester 3 (50 mg, 1.93 mmol) was refluxed overnight (17 h) in 20 mL of methanol. The mixture was cooled and concentrated in vacuo to 4: 45 mg (90%); mp 168–169 °C. The ^{1}H NMR spectrum of this material is identical with that of the compound derived from 1 and shows the complete absence of 3.

Ethyl 3-(2-Benzimidazolylthio)acrylate (7). A mixture of 1 (14.7 g, 0.098 mol) and ethyl propiolate (10.6 g, 0.108 mol) in 250 mL of ethanol was stirred overnight at room temperature. The solid was collected by filtration and dried in a vacuum oven to give 21.3 g (88%) of 7. An analytical sample was prepared by recrystallization from ethyl acetate/hexane: mp 182–183 °C; IR 3.10, 5.95 μm; ^{1}H NMR (Me_2SO-d_6) δ 8.40 (d, 1, J = 10 Hz), 7.7–7.0 (m, 4), 6.30 (d, 1, J = 10 Hz), 4.22 (q, 2, J = 7 Hz), 1.30 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.0; H, 4.9; N, 11.3. Found: C, 57.9; H, 4.9; N, 11.2.

4-Oxo-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole (8) from 7. The ester 7 (3.00 g, 12 mmol) in 50 mL of diphenyl ether was heated at boiling for 15 min, allowed to cool, and diluted with 300 mL of hexane. The resulting solid was collected by filtration and washed with ether to give 1.23 g of tan solid which was recrystallized (charcoaled) from

ethanol to give 0.61 g (24%) of **8**: mp 167–168 °C; IR 5.84 μm; ^{1}H NMR (Me_2SO-d_6) δ 8.5–8.1 (d superimposed on m, 2, J = 10 Hz), 7.8–7.2 (m, 3), 6.80 (d, 1, J = 10 Hz).

Anal. Calcd for $C_{10}H_{16}N_2OS$: C, 59.4; H, 3.0; N, 13.9. Found: C, 59.5; H, 2.9; N, 14.1.

From 4. A mixture of NaOH (1.65 g, 41.3 mmol) and the ester **4** (10.0 g, 38.5 mmol) in 500 mL of water was heated at about 70 °C for 5 h, during which time most of the solid dissolved. The reaction mixture was cooled and filtered, and the filtrate was acidified with concentrated HCl. The resulting mixture was heated to boiling and then filtered while hot, and the collected solid was washed with water and dried in a vacuum oven to yield 4-oxo-4H-[1,3]thiazino[3,2-a]benzimidazole-2-carboxylic acid: 8.86 g (93%); mp 230–232 °C dec; IR 5.84 μm; ^{1}H NMR (Me_2SO-d_6) δ 8.3 (m, 1), 7.8–7.3 (m, 3), 7.27 (s, 1).

Anal. Calcd for $C_{11}H_6N_2O_3S$: C, 53.6; H, 2.5; N, 11.4. Found: C, 53.1; H, 2.5; N, 11.4.

This acid (5.00 g, 20.3 mmol) was suspended in 125 mL of Dowtherm A, heated to 250 °C, and then allowed to cool. The solution was diluted to 800 mL with hexane and cooled to precipitate a solid which was collected by filtration, washed with ether, and recrystallized from chloroform/hexane to give **8**: 2.35 g (57%; 53% overall); mp 167–168 °C; mixture melting point with the compound obtained from **7** is 167–168 °C; IR 5.84 μm; ^{1}H NMR (Me_2SO-d_6) δ 8.5–8.1 (d superimposed on m, 2, J = 10 Hz), 7.8–7.2 (m, 3), 6.80 (d, 1, J = 10 Hz).

Anal. Calcd for $C_{10}H_6N_2OS$: C, 59.4; H, 3.0; N, 13.9. Found: C, 59.0; H, 3.0; N, 13.7.

Acknowledgment. The author is grateful to Professor R. F. Borch and Dr. C. M. Leir for useful discussions and suggestions.

Registry No.—**1**, 583-39-1; **2**, 69469-78-9; **3**, 69469-79-0; **4**, 68470-82-6; **7**, 69469-80-3; **8**, 55360-92-4; DMAD, 762-42-5; ethyl propiolate, 623-47-2; 4-oxo-4H-[1,3]thiazino[3,2-a]benzimidazole-2-carboxylic acid, 69469-81-4.

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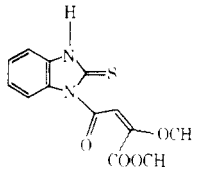
(12) A referee has suggested that structure **2a** is a possible alternative for this compound. This possibility was investigated by running the condensation reaction in CD_3OD rather than CH_3OH since the enol ether of **2a** would be derived from the reaction solvent. The product which was isolated from CD_3OD was identical with that obtained from CH_3OH and shows no evidence in its ^{1}H NMR spectrum of any deuterium incorporation.



2a

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Oxidation of Isoxazolidines with Peroxy Acids. Nitrones and N-Hydroxy-1,3-tetrahydrooxazines

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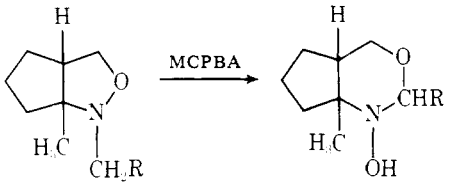
N-Methylisoxazolidines, prepared by 1,3-dipolar cycloadditions of nitrones and olefins, are smoothly converted to N-hydroxy-1,3-tetrahydrooxazines by reaction with m-chloroperbenzoic acid. N-γ-Hydroxypropyl methylene nitrones are proposed intermediates. With N-benzylisoxazolidines, mixtures of 2-phenyl-1,3-tetrahydrooxazines and N-γ-hydroxypropyl C-phenyl nitrones are obtained. The preferred regiochemistry for nitrone formation involves the α-CH of the N-alkyl substituent as opposed to the isoxazolidine C_5-H. This reaction provides a useful supplement to syntheses based on nitrone cycloadditions.

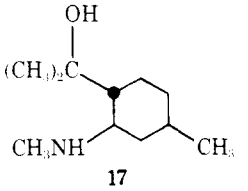
The reaction between nitrones and alkenes is one of the more versatile of 1,3-dipolar cycloaddition reactions, and the intramolecular counterpart can lead to a variety of interesting structures having useful synthetic potential.[1] The product isoxazolidines have, for the most part, been subjected to hydrogenolytic cleavage of the N–O bond, liberating 1,3-amino alcohols. Some years ago we described briefly two examples of the oxidative cleavage of polycyclic isoxazolidines.[2,3] We now report in detail on the scope and most probable mechanism for this useful reaction.



1, R = H
3, R = Ph

2, R = H
4, R = Ph

In a typical case, a solution of *cis*-1,6a-dimethylcyclopent[*c*]isoxazolidine (**1**)[4] in methylene chloride was treated with 1 molar equiv of m-chloroperbenzoic acid during the course of 1 h. After workup, the crystalline *cis*-1-hydroxy-7a-methylcyclopenta[*d*]tetrahydro-1,3-oxazine (**2**) was isolated in ~80% yield. The structure of **2** followed from an exact mass determination, its infrared spectrum (ν_{max} 3580 and 3250



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