(1 H, br q, J = 1.2 Hz), 4.70 (1 H, s), 4.15 (1 H, s), 4.10 (2 H, q, J = 7.1 Hz),2.43 (3 H, s), 1.88 (3 H, d, J = 1.2 Hz), 1.22 (3 H, t J = 7.1 Hz); ^{13}C NMR ($CDCl_3$ (DEPT), ppm) 165.2 (s), 159.3 (s), 137.2 (s), 133.1 (s), 128.4 (d), 128.0 (d), 127.9 (d), 114.2 (d), 97.1 (d), 63.7 (d), 59.4 (t), 41.7 (q), 16.1 (q), 14.2 (q).

Trifluoroacetic Acid/$NaCNBH_3$ Reduction of Dihydrooxazine 18c to Dihydrooxazine 19c and 19c′:[6] Figure 3 Results. Dihydrooxazine **18c** (0.036 g, 0.132 mmol) was dissolved in MeOH (2 mL). Bromocresol green was added until a blue color was retained. Trifluoroacetic acid (2 N, MeOH) was added dropwise until the solution turned yellow. $NaCNBH_3$ (0.009 g, 0.145 mmol) was added and the reaction stirred 2 h at room temperature. Trifluoroacetic acid (2 N) was added periodically as needed to maintain a yellow color. The reaction was pounred into $CHCl_3$ (10 mL) and washed with 1 N KOH (2 × 10 mL) and the organic layer dried (K_2CO_3). The solvent was removed under reduced pressure to leave oxazine **19c** as a mixture of two diastereomers, which were separated by silica gel chromatography using 5:4 hexane/EtOAc.

19c: 0.007 g, 0.025 mmol, 19%; oil, analytical TLC (silica gel F254), 5:2 hexane/EtOAc, R_f 0.12; MS, m/e, exact mass calcd for $C_{16}H_{21}O_3N$ 275.1516, found 275.1519, error 1 ppm; IR ($CHCl_3$, cm^{-1}) C=C 1620, C=O 1710; 200-MHz NMR ($CDCl_3$, ppm) 7.36 (5 H, br s), 4.62–4.55 (1 H, m), 4.53 (1 H, d, J = 1.5 Hz), 4.13–3.96 (2 H, m), 3.80 (1 H, d, J = 1.5 Hz), 2.82 (1 H, dd, J = 12.6, 5.0 Hz), 2.68 (1 H, dd, J = 12.6, 3.5 Hz), 2.10 (3 H, s), 1.51 (3 H, d, J = 6.5 Hz), 1.16 (3 H, t, J = 7.1 Hz).

19c′: 0.011 g, 0.039 mmol, 30%; oil, analytical TLC (silica gel F254), 5:2 hexane/EtOAc, R_f 0.17; MS, m/e, exact mass calcd for $C_{16}H_{21}O_3N$ 275.1516, found 275.152, error 1.4 ppm; IR ($CHCl_3$, cm^{-1}) C=O 1700, C=C 1630; 200-MHz NMR ($CDCl_3$, ppm) 7.36 (5 H, br s), 4.37 (1 H, d, J = 1.5 Hz), 4.32–4.31 (1 H, m), 4.10–3.98 (2 H, m), 3.61 (1 H, br d, J = 1.5 Hz), 2.97 (1 H, dd, J = 12.0, 2.6 Hz), 2.33 (1 H, dd, J = 12.0, 10.9 Hz), 2.02 (3 H, s), 1.39 (3 H, d, J = 6.2 Hz), 1.17 (3 H, t, J = 7.0 Hz).

Trimethylsilyl Ethyl Sulfide/CsF Addition to Oxazolium Salts: DMAD-Trapping Products 5a and 5d. General Experimental Procedure. Methyl triflate (0.028 mL, 0.249 mmol) was added to a solution of the oxazole (0.226 mmol) in 2 mL of acetonitrile. After the mixture was stirred for 2 h at room temperature, trimethylsilyl ethyl sulfide[18] (0.070 mL, 0.452 mmol) and DMAD (0.139 mL, 1.13 mmol) were added, and the mixture was transferred by cannula to anhydrous cesium fluoride (0.069 g, 0.452 mmol) in acetonitrile (4 mL). The mixture was stirred overnight, the solvent was removed under reduced pressure and the crude residue purified on a silica gel column to yield the pyrrole.

1. 2,5-Diphenyl-oxazole (6a). Pyrrole 5a: 0.024 g, 0.063 mmol, 28%.

2. 2-Methyl-5-phenyloxazole (6d). Pyrrole 5d: 0.018 g, 0.057 mmol, 25%.

Trimethylsilyl Ethyl Sulfide Addition to 2-Phenyl-5-methyloxazole: Ethyl Propiolate Trapping. Pyrrole 15c. The procedure was carried out as described above except that ethyl propiolate (0.116 mL, 0.113 mmol) was used as the trap. After the mixture was stirred overnight, the solvent was removed under reduced pressure and the crude residue purified on a silica gel column to yield **pyrrole 15c**: 0.006 g, 0.023 mmol, 10%.

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Registry No. 5a, 102537-10-0; **5b**, 102537-12-2; **5c**, 102537-11-1; **5d**, 102537-14-4; **5e**, 102537-13-3; **5f**, 113379-75-2; **5g**, 113379-76-3; **6a**, 92-71-7; **6b**, 25755-93-5; **6c**, 5221-67-0; **6d**, 3969-09-3; **6e**, 32595-70-3; **6f**, 1006-68-4; **6g**, 15031-12-6; **7**, 113379-77-4; **8**, 113379-78-5; **9**, 113379-79-6; **10**, 113379-80-9; **11**, 11403-28-4; **13**, 113379-81-0; **14**, 113379-82-1; **15a**, 113379-83-2; **15b**, 113379-84-3; **15c**, 113379-85-4; **15e**, 113379-86-5; **15f**, 113379-87-6; **15g**, 113379-88-7; **16b**, 113379-89-8; **16e**, 68384-84-9; **17a**, 113403-29-5; **17c**, 113379-90-1; **18a**, 113379-91-2; **18c**, 113379-92-3; **19c**, 113379-93-4; **19c′**, 113379-94-5; DMAD, 762-42-5; H_2C=$CHCO_2Me$, 96-33-3; HC≡CCO_2Me, 922-67-8; HC≡CCO_2Et, 623-47-2; HC(CN)=$CHCO_2Et$, 18228-28-9; 1-methyl-2(or 5)-cyano-3-(ethoxycarbonyl)pyrrole, 113379-97-8; 2-phenyl-3,5-dimethyloxazolium salt, 113379-95-6; 3-methyl-5-phenyloxazolium salt, 113379-96-7.

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A Comparison of 4-Oxazoline and 2-Acylaziridine Routes to Azomethine Ylides

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Pyrolysis of aziridines **6** or **7** affords azomethine ylides, which can also be generated from 3-methyl-2,5-diphenyl-4-oxazoline (**1a**) at room temperature. Attempts to trap the thermally generated ylide with dimethyl acetylenedicarboxylate afford increasing amounts of the unusual enamine product **9** as the temperature decreases. The aziridine-derived dipoles (**2a** or **3a** vs **4a** or **5a**) cannot be trapped prior to equilibration. Similar results are obtained from the aziridines **16**/**17**, but in this case, dipole isomers can be intercepted by *N*-phenylmaleimide in xylene solution. The 2,3-dimethyl-5-methoxy-4-oxazoline derived dipole **2b** probably does not equilibrate, but its 2 + 3 cycloadducts correspond to the major products formed by aziridine pyrolysis under equilibrating conditions.

We have recently described a versatile method for generation of stabilized azomethine ylides from the controlled reduction of *N*-methyloxazolium salts.[1] The intermediate 4-oxazolines **1** open spontaneously to the ylides **2** (Figure 1), which can be trapped in 2 + 3 cycloaddition reactions.

Trapping of the intuitively predicted S-dipole geometry **2** was eventually confirmed on the basis of the X-ray structure determination of an acrylate adduct.[2] However, the crystalline adduct was obtained relatively late in the study, and a variety of other stereochemical correlations

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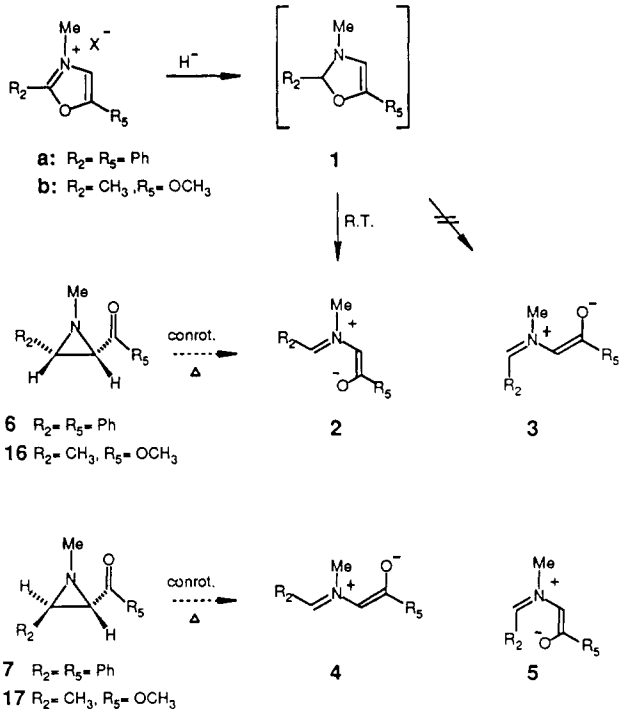

Figure 1.

had been considered. In particular, we were interested to know whether **2** interconverts with geometrical isomers **3–5** and whether pyrolysis of *N*-methylaziridines might provide selective access to the same or to other dipole isomers.[3,4]

Conrotatory ring opening of a *cis*-aziridine **6** should produce the *S*-dipoles **2a** or **3a**.[3,4] If the dipoles can be trapped faster than they equilibrate with **4a** or **5a**, then acetylenic dipolarophiles should give the same 2 + 3 adducts from **6** as from the corresponding oxazoline **1a**. The situation would be more complex with olefinic dipolarophiles CH_2=CHX because an additional asymmetric center is formed in the product. However, each isomeric S-dipole **2** or **3** might produce a unique ratio of exo:endo adducts, and it may be possible to differentiate between the *S*-dipole isomers.

Experiments were initiated to determine whether the azomethine ylides from the *cis*- and *trans*-aziridines **6** and **7**[5] could be intercepted without equilibration (Figure 2). Under the usual conditions of azomethine ylide generation from aziridines **6** or **7** (100 °C or above), dimethyl acetylenedicarboxylate (DMAD) adducts were formed efficiently. However, the initially formed 3-pyrroline did not survive. Instead, a mixture of 2-pyrrolines and the aromatized pyrrole was formed. Attempts to avoid these complications by decreasing the reaction temperature eventually allowed isolation of the 3-pyrroline, but a new complication became apparent. Thus, heating the *trans*-aziridine **7** with DMAD at 60 °C produced the 3-pyrroline **8** (7%)[1] together with an acyclic isomer having the enamine structure **9** according to extensive NMR evidence. At higher temperatures, the ratio of **9** to cycloadducts decreased, but the 3-pyrroline **8** was converted to 2-pyrrolines **10** and the pyrrole **11**.[1] The unexpected side reaction at

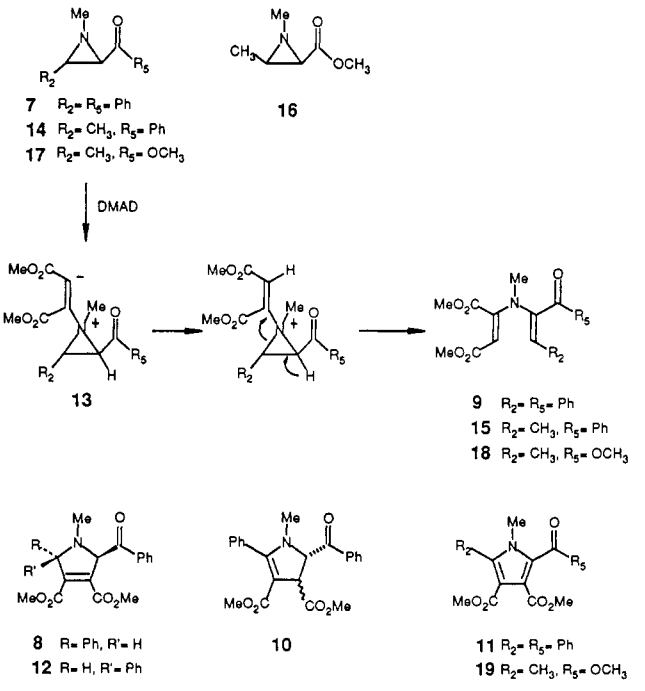

Figure 2.

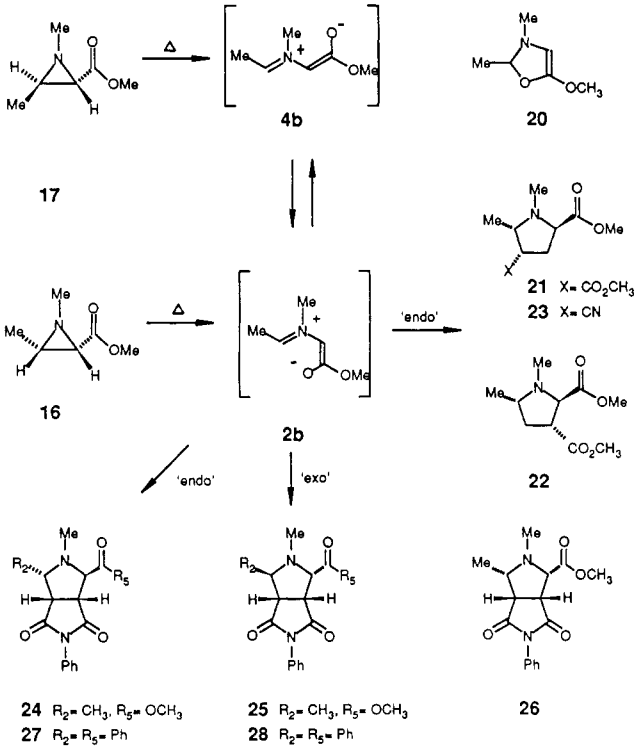

Figure 3.

low temperatures tends to obscure the fate of the azomethine ylide, but the results suggest that at 60 °C, aziridine **7** affords an equilibrated ylide. Conrotatory aziridine ring opening to W (**4**) or U (**5**) dipoles should lead to the *cis*-3-pyrroline **12**,[3,4] but the observed product is the trans isomer **8**, which corresponds to trapping of the *S*-dipole.

The above argument implies that **9** is not derived from an azomethine ylide pathway. This was confirmed by an experiment at room temperature which gave only **9** but no cycloaddition products. Since **9** is not formed when dipole **2a** is generated at room temperature from the oxazoline **1a**,[1] the mechanism must involve DMAD interaction with

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the intact aziridine. As shown in Figure 2, nucleophilic attack by aziridine nitrogen followed by C–N cleavage in **13** explains the observed result. The remarkable temperature effect that strongly favors azomethine ylide adducts at higher temperatures can be interpreted qualitatively as originating from a strongly unfavorable activation entropy term for the (presumed) rate-determining step from **7** to **13**. This process involves greater charge separation (and therefore, more solvation) than does the aziridine to azomethine ylide conversion, and the combination of a bimolecular mechanism and greater solvent ordering should result in a substantial, negative $T\Delta S^*$ contribution to the free energy of activation.

The reactions of DMAD with two other *N*-methylaziridine systems were examined briefly to determine whether the anomalous pathway leading to acyclic enamines could be avoided. However, aziridine **14**[6] gave enamine **15** and no 2 + 3 cycloadducts with DMAD over the temperature range of 60–100 °C. The ester-substituted aziridine **16**[7] likewise reacted with DMAD at 60 °C to afford the enamine **18** (97%). At higher temperatures, 2 + 3 cycloadducts did form, but the 3-pyrrolines did not survive the thermal reaction conditions. As before, a mixture of 2-pyrrolines and the pyrrole **19** was obtained (ca. 1:1 **18**:**19** after DDQ aromatization[1]) and the stereochemistry of the initial adducts could not be established.

From the above findings, it became obvious that DMAD was not a suitable trapping agent for the study of isomeric dipoles derived from *N*-methylaziridines. The undesired side reaction leading to acyclic enamines has not been reported in the case of *N*-arylaziridines[3,4] nor has it interfered with *N*-cyclohexyl, *N*-isopropyl, or *N*-benzyl analogues.[2,8,9] The *N*-methylaziridines are more capable of the nucleophilic addition pathway due to a combination of steric and electronic factors, and this complication precludes a practical result with DMAD.

An earlier report had described the 2 + 3 cycloaddition of dipoles generated from the aziridines **16** or **17** with acrylonitrile.[10] We were encouraged by the claim that dipole isomers had been intercepted prior to equilibration. Since we had been able to trap the corresponding dipole from the oxazoline **20** with methyl acrylate,[11] a meaningful comparison between the two methods of azomethine ylide generation was possible.

The oxazoline route forms the adduct **21** with a trace of **22** as already reported.[1,11] Heating the *cis*-aziridine **16** with methyl acrylate at 140 °C afforded the same adducts in a 8.6:1 ratio. However, an experiment performed by starting from the *trans*-aziridine **17** gave essentially the same product mixture. No new isomers were detected, and equilibration of dipole isomers clearly must have been fast compared to the rate of trapping. In view of this result, we looked more closely at the literature data for the acrylonitrile adducts of **16** and **17**.[10] The reported (60 MHz) spectra for the two "isomeric" products are quite similar, and it seemed possible that the adducts differed in contaminants rather than in structure. In our hands,

Table I

entry	azir	solvent	azir conc, M	yields,[a] % 24	25	26
a	**16**	xylene	0.1	82	17	0
b	**17**	xylene	0.1	25	6	55
c	**17**	xylene	0.01	48	16	11
d	**16**	acetonitrile	0.1	51	26	16
e	**17**	acetonitrile	0.1	54	27	15
f	*b*	acetonitrile	0.03	42	36	0

[a] All yields represent isolated yields. [b] Results obtained from the oxazoline method for azomethine ylide generation.

Table II

entry[a]	azir	azir conc, M	solvent	temp, C	27:28
a	**6**	0.1	benzene	75	18:1
b	**7**	0.1	benzene	75	20:1
c	**6**	0.1	acetonitrile	75	3.3:1
d[b]	**6**	0.1	acetonitrile	75	4.2:1
e	**6**	0.01	acetonitrile	75	2.9:1
f	**6**	0.5	acetonitrile	75	4.9:1
g	**7**	0.03	acetontrile	60	3.2:1
h	**6**	0.1	glyme	70	>50:1
i	**6**	0.1	chloroform	60	>50:1
j	*c*	0.03	acetonitrile	25	3:1
k	*c*	0.03	chloroform	25	>50:1

[a] All reactions used 1.1 equiv of *N*-phenylmaleimide except where noted. [b] 5.0 equiv *N*-phenylmaleimide used. [c] Results obtained from the oxazoline method for azomethine ylide generation.

the pyrolysis of **16** or **17** in the presence of acrylonitrile gave the same major adduct **23** in both cases, and essentially identical 16:1 major:minor product ratios. The same major product was also obtained from the oxazoline **20** in the presence of acrylonirile. It must be concluded that at 140 °C, neither methyl acrylate nor acrylonitrile can intercept the intermediate dipoles **2b–5b** before they equilibrate. At lower temperature, the rate of aziridine opening in this system became too slow for a practical comparison.

Complete dipole equilibration was also observed when **16** or **17** were heated at 140 °C with the more reactive trapping agent *N*-phenylmaleimide in acetonitrile. Three adducts were obtained in a ratio of 3.6:1.8:1 from either precursor (Table I, entries d and e). On the basis of extensive precedent,[1,9] the major products were assigned structures **24** and **25**. The same two adducts **24** and **25** are formed when **2b** is generated by the oxazoline method at room temperature, although the ratio is different (Table I, entry f).[1] This change in stereochemistry reflects differing preferences for the maximum overlap ("endo" vs "exo") transition states for 2 + 3 cycloaddition with S-dipole **2b** from the oxazoline route. The minor isomer **26** from aziridine pyrolysis is not formed from the oxazoline, and the cis stereochemistry at C_2,C_5 indicates that **26** is derived from the W-dipole **4b**. Similar results were obtained from **17** in xylene (140 °C) at a reactant concentration of 0.01 M. However, at higher concentrations in the nonpolar solvent, each aziridine yielded a distinct product ratio. At 0.1 M concentration, **16** gave only the products **24** and **25** derived from the S-dipoles. Significant dipole equilibration occurred starting from the *trans*-aziridine **17**, but the adduct **26** corresponding to the trapping of dipoles formed by conrotatory ring opening predominated by a ratio of 2.3:1 (Table I).

There are substantial differences between acrylate and maleimide dipolarophiles. Acrylate reacts with a strong preference for the "endo" transition state, as does acrylonitrile. *N*-Phenylmaleimide is more easily diverted from the "endo" (maximum overlap) pathway, presumably due to its greater steric demands. Nevertheless, the maleimide

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(11) Reference 1 reports the ethyl analogue, and the same result is obtained from 1,2-dimethyl-5-methoxy-4-oxazoline (ref 2).

is the more effective dipolarophile with respect to dipole trapping prior to equilibration at 140 °C. Similar results have been reported for the related *N*-cyclohexyl- or *N*-isopropyl-2-arylaziridinecarboxylates by Woller and Cromwell at 80 °C.[9]

Successful interception of dipole isomers **2b** and **4b** from ester-substituted aziridines **16** and **17** encouraged a similar series of experiments with the benzoyl analogues **6** and **7**. Remarkable solvent effects were observed on the ratio of "exo" vs "endo" transition states (Table II), but no hint of stereospecific dipole trapping was detected despite extensive effort. Either **6** or **7** gave the same mixture of products **27** and **28**, depending on solvent. Very similar ratios of **27** and **28** were obtained at room temperature using the oxazoline route to the dipole **2a**. Inspection of Table II indicates that temperature differences are less important than the effect of solvent on product ratios. Since both **27** and **28** correspond to trapping of S-dipoles, it is conceivable that there is a rapid and reversible equilibrium between the dipoles **2a–5a** in all of the experiments in Table II and that the S-dipoles are most reactive.[12,13] We are inclined to believe this generalization for the aziridine case, but there is no reason to invoke equilibration of the oxazoline-derived dipole since it is formed in the reactive S-dipole geometry **2a** from the start and does not form adducts derived from **4a** or **5a**. In any event, it is clear that the *N*-methyl phenacyl dipoles **2a–5a** are exceptionally susceptible to equilibration.

The ester-substituted analogues **2b–5b** can also equilibrate readily, but here the isomeric dipoles **2b** or **3b** and **4b** can be trapped with relatively little interconversion in the nonpolar solvent xylene. The evidence is consistent with equilibration via rotation about the enolate C–N bond.[3,4] Enhanced equilibration in acetonitrile is reasonable since the "orthogonal" dipole transition state for the interconversion of **2** and **4** would enjoy less interaction between opposite charges and would benefit from better solvation. The faster equilibration in the series **2a–5a** vs **2b–5b** is consistent with the bond rotation process due to the improved stability of the phenacyl enolate relative to the ester enolate subunit. Increased dipole interconversion relative to the *N*-arylaziridine series is also in accord with the favorable electronic effect of *N*-alkyl vs *N*-aryl on positive dipole nitrogen. Facile equilibration in other *N*-alkylaziridine systems has been noted earlier for an *N*-isopropyl analogue of **16**/**17**,[8,9] and the apparent literature contradiction in the case of **16**/**17** is resolved in favor of dipole equilibration. In the original study, a control experiment demonstrated that **16** and **17** do not interconvert upon heating.[10] This observation by itself does not rule out dipole equilibration because the isomeric dipoles are not obliged to reclose to aziridines faster than they decompose. Another possible complication is reclosure to the 4-oxazoline **1**.[14,15] Thus, dipoles **2** or **5** have the necessary geometry for electrocyclic ring closure to **1**, and interconversion is possible in principle by ring opening of **1**. The relative importance of 4-oxazoline formation has not been determined in the present study, but it has been established for certain 2-acyl-*N*-*tert*-alkylaziridines.[14,15]

In conclusion, it is demonstrated that benzoyl-stabilized dipoles **2a–5a** are especially sensitive to interconversion. All attempts at stereospecific trapping of these dipoles have failed. The ester-stabilized analogues **2b–5b** are more resistant to equilibration and can be intercepted with predominant retention of geometry in the low dielectric solvent xylene. However, the equilibration process is difficult to avoid in the present case as well as in previous studies.[8,9] In all of the *N*-alkylaziridine examples, dipole equilibration favors cycloaddition via the S-dipoles **2** or **3** (or their enolate *E*,*Z*-isomers).

The similarity of product ratios from the 4-oxazoline and the aziridine methods raises the prospect that even the oxazoline-derived dipole equilibrates. This possibility cannot be ruled out for **2a–5a**, but it is unlikely in the case of **2b–5b**. The **b** series dipoles can be trapped with predominant retention at 140 °C. If equilibration occurs during the room temperature conversion of **1b** to **2b**, this would have to involve a low-temperature (presumably, catalytic) mechanism which does not function in the aziridine pyrolysis. A more plausible scenario is that aziridine pyrolysis under equilibrating conditions (acetonitrile, 140 °C) generates one or more dipoles including **2** and that **2** drains off selectively to products because it is more reactive. The differences in "exo":"endo" ratios for the S-dipole-derived products **24** and **25** may be due to the temperature differences (140 °C for the aziridines; 20 °C for the oxazoline) or they may reflect contributions from more than one S-dipole at the higher temperature.[12]

Since the oxazoline method appears to produce the same dipole under kinetic control which is favored from aziridine pyrolysis under thermodynamic control, the stereochemical advantages will be largely due to the lower reaction temperature. This results in improved selectivity in a number of examples[1] and in greater potential for azomethine ylide applications to stereocontrolled synthesis. So far, no method is known that allows effective interception of the *N*-alkyl dipoles in the W-geometry **4** although there are some cases where this pathway is observed.[9] The oxazoline procedure also has the advantage that it avoids side reactions such as the conversion of *N*-methylaziridines to enamine products **9** or **18** with DMAD, and it provides access to a greater variety of azomethine ylides.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were obtained on a Bruker WP200 200 MHz, WP270 270 MHz, or AM500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to solvent peak ($CDCl_3$ 7.24 ppm, CD_3CN 1.93 ppm and acetone-d_6 2.09). Infrared spectra (IR) were recorded by using a Beckman Acculab 7 or a Mattson FT IR spectrometer and calibrated with a polystyrene peak (1601.8 cm^{-1}). Mass spectra were obtained on an MS-80 high-resolution mass spectrometer. Melting points were obtained on a hot stage microscope apparatus and are not corrected.

Column chromatography was performed by using Kieselgel 60 flash silica gel. Solvents were dried as follows: diethyl ether (Et_2O), dioxane, tetrahydrofuran (THF), and glyme (dimethoxyethane) were distilled from sodium/benzophenone; halocarbons and hydrocarbons were distilled from calcium hydride; hexane and EtOAc for silica gel chromatography was flash distilled prior to use; acetonitrile was distilled first from CaH_2 then from P_2O_5. All reagents that are not referenced were obtained from Aldrich. All aziridines were made by the literature procedures referenced in the text.

Anhydrous reactions were carried out under a N_2 atmosphere. Anhydrous cesium fluoride was prepared by flame-drying under vacuum taking care not to fuse the salt.

Thermolysis of *cis*-1-Methyl-2-benzoyl-3-phenylaziridine (6) and *trans*-1-Methyl-2-benzoyl-3-phenylaziridine (7) in the Presence of DMAD: Pyrrolines 8 and 10, Pyrrole 11, and Enamine 9. The aziridine was dissolved in the appropriate solvent, DMAD was added, and the reaction was stirred at the

(12) The formation of enolate *E*,*Z* isomers is implicit in all cases of dipole equilibration via enolate C–N bond rotation mecanisms; each isomer may react via a unique exo:endo ratio.

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corresponding temperature and time (see subsequent entries). Aliquots were removed by pipet, the solvent was removed (rotary evaporator), and the crude residue was analyzed by NMR. The products consisted of 2-pyrrolines **10** and pyrrole **11**, which were identical with the products observed in the reduction of 2,5-diphenyl-3-methyloxazolium salt in the presence of DMAD.[1] Also isolated in some cases was the enamine **9**.

Enamine 9 (For isolation see entry d): oil, separated on flash silica gel Kieselgel 60, 5:2 hexane–EtOAc, R_f 0.19; MS, *m/e*, exact mass calcd for $C_{22}H_{21}O_5N_1$ 379.1414, found 379.141, error 1.1 ppm; IR ($CDCl_3$, cm^{-1}) C=O 1750, C=O 1710, C=O 1676; 200-MHz NMR ($CDCl_3$, ppm) 7.9–7.83 (2 H, m), 7.43–7.17 (8 H, m), 6.87 (1 H, s), 5.03 (1 H, s), 3.7 (3 H, s), 3.63 (3 H, s), 2.93 (3 H, s).

Experimental Conditions. 1. Entry a: Aziridine **6** (0.05 g, 0.21 mmol) and DMAD (0.032 mL, 0.262 mmol) in toluene (0.4 mL) at 100 °C for 14 h. The reaction products were isolated by silica gel chromatography (5:1 hexane–EtOAc) to yield pyrrole **11** (47%) and pyrroline **10** (54%).

2. Entry b: Aziridine **7** (0.0124 g, 0.052 mmol) and DMAD (0.007 mL, 0.063 mmol) in benzene (0.5 mL) at 60 °C. An aliquot taken after 2 h showed the formation of pyrroline **8** (7%) and enamine **9** (74%) (yields are based on consumed aziridine).

3. Entry c: Aziridine **6** (0.05 g, 0.21 mmol) and DMAD (0.029 mL, 0.23 mmol) in benzene (2.1 mL) at ambient temperature for 24 h. An aliquot showed enamine **9** (10%) (yield based on consumed aziridine).

4. Entry d: Aziridine **6** (0.05 g, 0.21 mmol) and DMAD (0.029 mL, 0.23 mmol) neat at ambient temperature for 24 h. The product was purified by silica gel chromatography (5:1 hexane–EtOAc) to yield the enamine **9** (100%).

Thermolysis of *cis*-1,3-Dimethyl-2-benzoylaziridine (14) in the Presence of DMAD: Enamine 15. The aziridine (0.050 g, 0.285 mmol) was dissolved in 2.8 mL benzene, and DMAD (0.071 mL, 0.571 mmol) was added. The reaction was heated at 60 °C for 5 h, and the solvent was removed (rotary evaporator). Purification of the residue on a silica gel column yielded the oily yellow enamine **15** (0.083 g, 0.262 mmol, 92%). The same product was observed when the reaction was performed at 100 °C for 2 h.

Enamine 15: oil, separated on flash silica gel Kieselgel 60, 5:2 hexane–EtOAc, R_f 0.21; MS, *m/e*, exact mass calcd for $C_{17}H_{19}O_5N_1$ 317.1258, found 317.1266, error 2.5 ppm; IR ($CDCl_3$, cm^{-1}) C=O 1740; C=O 1695; 270-MHz NMR ($CDCl_3$, ppm) 7.93–7.88 (2 H, m), 7.59–7.4 (3 H, m), 6.15 (1 H, q, J = 7.5 Hz), 4.86 (1 H, s), 3.8 (3 H, s), 3.63 (3 H, s), 2.83 (3 H, s), 1.76 (3 H, d, J = 7.5 Hz).

Thermolysis of *cis*-1-Methyl-2-carbomethoxy-3-methylaziridine (16) in the Presence of DMAD: Enamine 18. The aziridine (0.025 g, 0.212 mmol) was dissolved in 2 mL benzene, and DMAD (0.026 mL, 0.212 mmol) was added. The reaction was heated at 60 °C for 12 h, and the solvent was removed (rotary evaporator). Purification of the residue on a silica gel column yielded enamine **18** (0.051 g, 0.187 mmol, 97%) as an oil.

Enamine 18: oil, analytical TLC (silica gel F254), 5:4 hexane–EtOAc, R_f 0.35; MS, *m/e*, exact mass calcd for $C_{12}H_{17}O_6N_1$ 271.1051, found 271.1058, error 2.6 ppm; IR ($CHCl_3$, cm^{-1}) C=O 1750, C=O 1740, C=O 1732, C=O 1690, C=C—N 1580; 270-MHz NMR ($CDCl_3$, ppm) 6.36 (1 H, q, J = 7.5 Hz), 4.69 (1 H, s), 3.78 (3 H, s), 3.75 (3 H, s), 3.61 (3 H, s), 2.91 (3 H, s), 2.07 (3 H, d, J = 7.5 Hz).

Thermolysis of *cis*-Aziridine 16 in the Presence of DMAD: Enamine 18 and Pyrrole 19. The aziridine (0.025 g, 0.212 mmol) was dissolved in 2 mL of benzene, and DMAD (0.026 mL, 0.212 mmol) was added. The reaction was heated at 130 °C for 12 h and then 2,3-dichloro-5,6-dicyano-1,4-benzophenone (DDQ; 0.048 g, 0.212 mmol) was added, and the reaction was stirred at room temperature for 12 h. The reaction mixture was poured into ethyl acetate (10 mL) and extracted with 1 M KOH (3 × 10 mL). The organic layer was dried (MgSO4) and the solvent removed (rotary evaporator) to leave the pyrrole **19** (0.026 g, 0.098 mmol, 51%) and the enamine **18** (0.025 g, 0.092 mmol, 48%), which were purified by silica gel chromatography (5:2 hexane–EtOAc).

Pyrrole 19: oil, analytical TLC (silica gel F254), 5:4 hexane–EtOAc, R_f 0.28; MS, *m/e*, exact mass calcd for $C_{12}H_{15}O_6N_1$ 269.0895, found 269.0897, error 0.7 ppm; IR (CH_2Cl_2, cm^{-1}): C=O 1710, C=O 1720; 270-MHz NMR ($CDCl_3$, ppm) 3.88 (3 H, s), 3.82 (3 H, s), 3.79 (3 H, s), 3.77 (3 H, s), 2.52 (3 H, s).

Thermolysis of *cis*-Aziridine 16 or *trans*-1-Methyl-2-carbomethoxy-3-methylaziridine (17) in the Presence of Methyl Acrylate: Pyrrolidine 21. This procedure was carried out as described by Gelas-Mialhe et al.[10] The aziridine (0.050 mL, 0.387 mmol) was dissolved in xylene (4 mL), and methyl acrylate (0.07 mL, 0.774 mmol) was added. The reaction was refluxed for 8 h. Removal of the solvent (rotary evaporator) left a residue, which was purified on a silica gel column (5:2 hexane–EtOAc) to yield pyrrolidine **21** (0.071 g, 0.332 mmol, 86%). Also isolated was a small amount of a product (ca. 10%) which in a previous study was identified as the regioisomer **22**, but this compound was not characterized further in the present experiment. The use of either aziridine **16** or **17** led to the same result.

Pyrrolidine 21: oil, analytical TLC (silica gel F254), 5:2 hexane–EtOAc, R_f 0.21; MS, *m/e*, exact mass calcd for $C_{10}H_{17}O_4N_1$ 215.1153, found 215.1153, error 0 ppm; IR ($CDCl_3$, cm^{-1}) C=O 1738, C=O 1725; 270-MHz NMR ($CDCl_3$, ppm) 3.68–3.58 (1 H, m), 3.67 (3 H, s), 3.66 (3 H, s), 3.44 (1 H, dq, J = 8.8, 6.4 Hz), 3.28 (1 H, q, J = 8.8 Hz), 2.53 (1 H, dt, J = 13.1, 8.8 Hz), 2.34 (3 H, s), 2.00 (1 H, ddd, J = 13.1, 8.8, 3.2 Hz), 0.89 (3 H, d, J = 6.4 Hz).

Thermolysis of *cis*-Aziridine 16 or *trans*-Aziridine 17 in the Presence of Acrylonitrile: Pyrrolidine 23. This procedure was carried out as described by Gelas-Mialhe et al.[10] The aziridine (0.050 mL, 0.387 mmol) was dissolved in xylene (4 mL) and acrylonitrile (0.051 mL, 0.774 mmol) was added. The reaction was refluxed for 8 h. Removal of the solvent (rotary evaporator) left a residue, which was purified on a silica gel column (5:4 hexane–EtOAc) to yield pyrrolidine **23** (0.056 g, 0.31 mmol, 80%). Also isolated was a small amount of a product (ca. 5%), which in a previous study was identified as the regioisomer, but this compound was not characterized further in the present experiment. The use of either the aziridine **16** or **17** led to the same result.

Pyrrolidine 23: oil, analytical TLC (silica gel F254), 5:4 hexane–EtOAc, R_f 0.23; MS, *m/e*, exact mass calcd for $C_9H_{14}O_2N_2$ 182.1052, found 182.1049, error 1.6 ppm; IR (CH_2Cl_2, cm^{-1}) C=O 1730, CN 2200; 270-MHz NMR ($CDCl_3$, ppm) 3.71 (1 H, dd, J = 8.3, 3.3 Hz), 3.68 (3 H, s), 3.32–3.23 (2 H, m), 2.38–2.28 (2 H, m), 2.35 (3 H, s), 1.21 (3 H, d, J = 6.2 Hz).

Alkylation, Reduction, and Acrylonitrile-Trapping [2 + 3] of 2-Methyl-5-methoxyoxazole: Pyrrolidine 23. Methyl triflate (0.028 mL, 0.249 mmol) was added to a solution of the oxazole (0.023 mL, 0.226 mmol) in 2 mL of acetonitrile. After the mixture was stirred for 2 h at room temperature, phenylsilane (distilled from CaH_2; 0.049 mL, 0.339 mmol) and acrylonitrile (0.045 mL, 0.678 mmol) were added, and the mixture was transferred by cannula to anhydrous cesium fluoride (0.069 g, 0.452 mmol) in acetonitrile (4 mL). After vigorous stirring for 2 h at ambient temperature, the solvent was removed (rotary evaporator), and the resulting residue was passed through a plug of silica gel (5:4 hexane–EtOAc). Examination of the crude oil by NMR revealed the presence of the pyrrolidine **23** as the predominant product.

Thermolysis of *cis*-Aziridine 16 and *trans*-Aziridine 17 in Acetonitrile in the Presence of *N*-Phenylmaleimide: Table I Results. Pyrrolidines 24, 25, and 26. The aziridine **16** (0.05 g, 0.387 mmol) was dissolved in acetonitrile (4 mL), and *N*-phenylmaleimide (0.074 g, 0.426 mmol) was added. The mixture was transferred to a sealed tube and heated for 8 h at 140 °C. Removal of the solvent and silica gel chromatography (5:2 hexane–EtOAc) gave the product pyrrolidines **24** (0.06 g, 0.198 mmol, 51%), **25** (0.03 g, 0.099 mmol, 26%), and **26** (0.019 g, 0.063 mmol, 16%). The use of the trans aziridine **17** led to the isolation of pyrrolidines **24** (0.063 g, 0.208 mmol, 54%), **25** (0.029 g, 0.096 mmol, 27%), and **26** (0.018 g, 0.056 mmol, 15%). Pyrrolidines **24** and **25** were identical with products obtained from the reduction of 2,3-dimethyl-5-methoxyoxazolium salt in the presence of *N*-phenylmaleimide.[1]

Pyrrolidine 26: solid, mp 143–145 °C (hexane); MS, *m/e*, exact mass calcd for $C_{16}H_{18}O_4N_2$ 302.1262, found 302.1277, error 4.9 ppm; IR ($CHCl_3$, cm^{-1}) C=O 1720, C=O 1750; 270-MHz NMR ($CDCl_3$, ppm) 7.43–7.30 (3 H, m), 7.26–7.20 (2 H, m), 3.76 (3 H, s), 3.51 (1 H, t, J = 7.9 Hz), 3.22 (1 H, t, J = 7.9 Hz), 3.21 (1 H, d, J = 7.9 Hz), 2.58 (1 H, dq, J = 7.9, 6.7 Hz), 2.27 (3 H, s), 1.32 (3 H, d, J = 6.7 Hz).

Thermolysis of *cis*- and *trans*-Aziridines 16 and 17 in Xylene in the Presence of *N*-Phenylmaleimide: Table I Results. Pyrrolidines 24, 25, and 26. The aziridine 17 (0.05 g, 0.387 mmol) was dissolved in acetonitrile (4 mL), and *N*-phenylmaleimide (0.074 g, 0.426 mmol) was added. The mixture was refluxed for 8 h at 140 °C. Removal of the solvent and silica gel chromatography (5:2 hexane–EtOAc) left the product pyrrolidines **24** (0.029 g, 0.096 mmol, 25%), **25** (0.007 g, 0.023 mmol, 6%), and **26** (0.064 g, 0.212 mmol, 55%). Performing the above reaction in 40 mL of xylene ([0.01]) led to pyrrolidines **24** (0.056 g, 0.185 mmol, 48%), **25** (0.019 g, 0.062 mmol, 16%), and **26** (0.013 g, 0.042 mmol, 11%). Carrying out the reaction with *cis*-aziridine **16** led to pyrrolidines **24** (82%) and **25** (17%).

Thermolysis of *cis*-Aziridine 6 and *trans*-Aziridine 7 in the Presence of *N*-Phenylmaleimide: Table II Results. Pyrrolidines 27 and 28. The aziridine (0.050 g, 0.210 mmol) was dissolved in 2 mL of benzene, and *N*-phenylmaleimide (0.019 g, 0.21 mmol) was added. The reaction was heated for 2 h, the solvent was removed, and the crude reaction mixture was analyzed by NMR to obtain the pyrrolidine **27**:**28** ratios. These compounds are identical with those prepared from the reduction of 2,5-diphenyl-3-methyloxazolium salt in the presence of *N*-phenylmaleimide.[1] The reactions were performed under various reaction conditions including changes in solvent, temperature, and number of equivalents of *N*-phenylmaleimide (see Table II for specifics). The use of either aziridine **6** or **7** led to the same product ratio.

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Registry No. **6**, 6476-40-0; **7**, 7570-81-2; **8**, 102537-09-7; **9**, 113405-17-7; **10** (isomer 1), 113405-16-6; **10** (isomer 2), 113405-27-9; **11**, 102537-10-0; **14**, 55829-81-7; **15**, 113405-18-8; **16**, 113472-72-3; **17**, 34856-91-2; **18**, 113405-19-9; **19**, 113405-20-2; **21**, 113405-21-3; **22**, 113405-22-4; **23**, 113405-23-5; **24**, 113405-24-6; **25**, 113472-73-4; **26**, 113472-74-5; **27**, 113405-25-7; **28**, 113472-75-6; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; 2-methyl-5-methoxyoxazole, 53878-74-3; *N*-phenylmaleimide, 941-69-5; 2,3-dihydro-3-methyl-2,5-diphenyloxazole, 113405-26-8.

Oxidative Transformations of Minor Components of Nucleic Acids. An Anomalous Reaction Course of Oxidation of N^6,N^6-Dialkyladenosines and Related Compounds with *m*-Chloroperoxybenzoic Acid[1]

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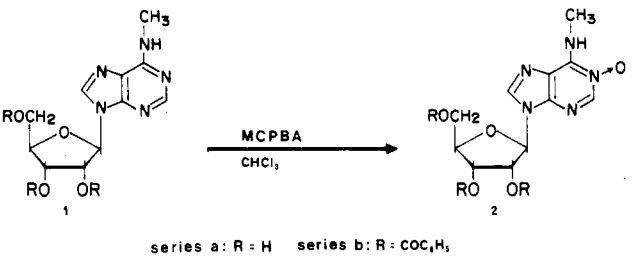
Oxidation of N^6-methyladenosine (**1a**) or the corresponding tribenzoate **1b** with *m*-chloroperoxybenzoic acid gave N^1-oxides **2a** and **2b** whereas N^6,N^6-dimethyladenosine tribenzoate (**3a**) afforded 2′,3′,5′-tri-*O*-benzoylinosine (**4a**) and N^6-methyl-N^6-formyl derivative **5**. The N^6,N^6-diethyladenosine **3b** and piperidine derivative **3c** yielded only **4a**, but N^6,N^6-dibenzyl compound **3d** was not oxidized. *N*,*N*-Dimethyl-2,4-dinitroaniline (**6a**) was oxidized with *m*-chloroperoxybenzoic acid to give *N*-methyl-*N*-formyl derivative **7a**, *N*-methyl-2,4-dinitroaniline (**8a**), *N*-oxide **10a**, and only traces of 2,4-dinitrophenol (**9a**). By contrast, 2-(dimethylamino)-5-nitropyridine (**6b**) afforded 5-nitro-2-pyridone (**9b**) and N-demethylated N^1-oxide **11**. 2-(Dimethylamino)pyridine (**6c**) and 2-(methylamino)-5-nitropyridine (**8b**) gave the respective N^2- and N^1-oxides **10c** and **11**. The reaction of 6-chloropurine nucleosides **15a** and **15b** with *N*,*N*-dimethylhydroxylamine gave inosine **4a** or **4b** accompanied by a smaller amount of **3a** or **3e**. 2,4-Dinitrofluorobenzene (**16**) afforded *O*-(2,4-dinitrophenyl)-*N*,*N*-dimethylhydroxylamine (**17**). Mass spectra of compounds **10a**, **10c**, and **17** provided evidence for Meisenheimer rearrangement and subsequent cyclic transformation. The *N*-oxide **10a** and hydroxylamino derivative **17** gave 2,4-dinitrophenol (**9a**), and N^2-oxide **10c** afforded fragments belonging to 2-pyridone (**9c**). Compound **17** is thermally stable whereas *N*-oxide **10a** yielded at 100 °C a mixture of **8a**, **8b**, **9a**, and **17**.

Introduction

Oxidation of nucleic acids and their components with organic peracids has been the subject of many studies.[2-4] It was established that pyrimidine and purine units such as cytosine, adenine, and guanine are transformed to the corresponding N^3- and N^1-oxides at both monomeric and polymeric levels. Little attention has been paid to similar reactions with minor components of nucleic acids, particularly *N*-methyl nucleosides. Previously, we have investigated oxidation with ruthenium tetraoxide[5] and bromine in phosphate buffer[6] of N^6,N^6-dimethyladenosine,

Scheme I



which occurs as a part of 16S and 18S ribosomal RNA and whose heterocyclic moiety is also found in the antibiotic puromycin. Both reactions led to a selective N-monodemethylation of N^6,N^6-dimethyladenine residue. By contrast, oxidation of protected N^6,N^6-dialkyladenosines with $KMnO_4$ was less selective and led to a significant

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